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ORIGINAL ARTICLE

Treatment Outcomes and Patterns of Failure in Elderly Patients with Cervical Cancer Treated with Definitive Radiotherapy

Gautam SARMA, Luri BORAH, Jyotiman NATH, Mouchumee BHATTACHARYYA, Partha Pratim MEDHI, Apurba Kumar KALITA

Department of Radiation Oncology, Dr. Bhubaneswar Borooah Cancer Institute, Guwahati, Assam-*India*

OBJECTIVE

The incidence of cervical cancer among older women is increasing. The treatment outcome in these patients is affected byvarious patient and tumor-related factors. In this study, we retrospectively investigated the survival outcomes, treatment-related toxicity, and patterns of failures for elderly patients (≥75 years old) with cervical cancer treated with definitive radiotherapy.

METHODS

Twenty-three patient's fulfilling inclusion and exclusion criteria were analyzed. The survival was studied using the Kaplan-Meir method, and its relation with different clinicopathologic parameters was compared.

RESULTS

After a median follow-up time of 46 months (range 3-93), the overall survival for the entire cohort of patients at 5 years and 7 years were 54.9% and 43.9%, respectively, and the disease-free survival at 3 years and 5 years were 66.3% and 45.9% respectively. Patients receiving total radiation dose (EqD2) more than 80 Gy achieved statistically significant improved survival than those receiving lower doses (p=0.04). Grade III acute toxicity was experienced by 2 patients (8.7%) with diarrhea and one patient (4.3%) with dermatitis, but no grade IV acute toxicity was recorded. Two patients (8.7%) developed rectal bleeding as late toxicity. At the end of follow-up, 11 patients (47.8%) experienced a relapse. Distant metastasis to the lung was the most common type of failure.

CONCLUSION

Definitive radiotherapy is safe and well-tolerated by elderly patients with cervix cancer with an acceptable degree of toxicities.

Keywords: Cancer; cervix; chemotherapy; elderly; radiotherapy.

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Introduction

Cervical cancer is the fourth most common malignancy in women and remains one of the leading causes of cancer-related morbidity worldwide. In India, it is the second most common cancer in women.[1,2] The incidence and mortality due to cervical cancer is declining in developed countries. This is primarily due

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Dr. Jyotiman NATH
Department of Radiation Oncology,
Dr. Bhubaneswar Borooah Cancer Institute,
Guwahati, Assam-*India*
E-mail: jyotimannath@gmail.com

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to the increase of knowledge that persistent human papillomavirus (HPV) infection is the leading cause of cervical cancer, resulting in the development of prophylactic vaccines. However, it is still a significant health problem in developing countries due to the lack of routine screening and introduction of vaccination programs.[3,4]

Cervical cancer demonstrates a bimodal age distribution, with peaks between 30 to 39 years and 60 to 69 years. Data from various hospital-based cancer registries (HBCR) of India reports the mean age of presentation ranging between 50 and 56.7 years. Patients above 65 years of age account for around 15% of these HBCRs. With the increase in life expectancy of the population, the incidence of cervical cancer among elderly women is increasing.[5,6] Elderly patients are heterogeneous to comorbidities, performance status, access to healthcare and motivation towards screening programs, etc. These factors contribute to the delayed diagnosis and compromised treatment of this age group?. Moreover, various reports have demonstrated that elderly women often present with more advanced staged disease and receive less aggressive treatment.[7,8]

There are conflicting reports on the impact of age on treatment outcome in cervical cancer. Many studies have reported age to be a prognostic factor in cervix cancer.[9-12] Some studies have shown a similar prognosis of cervical cancer in old and young women, while few demonstrated that younger age is an unfavorable prognostic factor.[13,14] However, there are kinds of literature which reported younger patients might have improved outcome and old age is a poor prognostic factor.[15-17]

In this study, we retrospectively analyzed the survival outcomes, treatment-related toxicity, and patterns of failures for elderly women (≥75 years) with cervical cancer treated with definitive radiotherapy (RT) with or without concurrent chemotherapy (CCRT).

Materials and Methods

Patient Selection and Assessment

Cervical cancer patients treated between 2011 and 2015 in our institute were retrospectively reviewed. The inclusion criteria were as follows: age 75 years or more, histologically proven carcinoma of the cervix, patients treated with definitive radiotherapy, no prior history of surgery, chemotherapy or radiation for carcinoma cervix, and no evidence of distant metastasis. Patients treated with palliative radiotherapy were excluded from the study. Twenty-three patients (n=23) fulfilling inclusion and exclusion criteria were included in the analysis.

The patients were staged according to the International Federation of Gynaecology and Obstetrics (FIGO-2009) staging system.[18] The findings of clinical examination notes, chest roentgenography, intravenous pyelography, cystoscopy, and proctoscopy were used for staging. Patients' baseline Eastern Cooperative Oncology Group (ECOG) performance status and comorbidities were also recorded.

Treatment

All the patients received Radiotherapy with curative intent. The patients received external beam radiotherapy (EBRT) with a conventional technique. Patients were treated in a supine position using a thermoplastic pelvic mould for immobilization. X-Ray simulation was done in Simulix Evolution (Nucletron) conventional simulator for treatment planning. EBRT was delivered using the four-field box technique with 6 MV photons in Elekta Precise digital linear accelerator (LA) and Siemens Primus LA. EBRT dose ranged between 46-50 Gy in 2Gy daily fractions. Three patients received concurrent chemotherapy with weekly inj Carboplatin AUC 2 for 5 cycles.

EBRT was followed by high dose rate (HDR) intracavitary brachytherapy (ICBT) in Microselectron HDR (Nucletron, The Netherlands) using a 192-Iridium remote afterloading unit. Two patients did not receive brachytherapy as they defaulted after EBRT and one patient received EBRT boost as brachytherapy could not be performed because of the stenosed vagina. Treatment planning for HDR-ICBT was performed using PLATO Brachytherapy Planning System version 3.2 (Nucletron, The Netherlands). Evaluation of the rectal and bladder dose was performed according to ICRU Report 38.[19] The dose of brachytherapy was either 700cGy or 750 cGy to point A for 2 to 4 fractions.

Follow-up

After completion of treatment, the patients were followed up by both gynecological and radiation oncologists. A gynecological examination was performed in each follow-up. Radiological investigations like computed tomography (CT) or magnetic resonance imaging (MRI) were performed as and when necessary.

Both acute and late treatment-related toxicities were evaluated using medical records and CTC-AE

version 4.0. Toxicities occurring within 90 days of the start of treatment were defined as acute, and those that occurred after 90 days persisted beyond 90 days of start of treatment were coined as late.

Statistical Analysis

Baseline variables were depicted as numbers (Percentage). Kaplan Meir's method was used to evaluate the survival rate, and the log-rank test was used to compare the survival among groups, and the t-test was used to compare two means. P<0.05 is considered as statistically significant at 95% confidence interval. All data were analyzed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA).

Results

Patient Characteristics and Treatment

During the period 2011 to 2015, a total of 23 patients were eligible for the analysis. The baseline patient characteristics are depicted in Table 1. The median age was 77 years (range 75-85). The majority of the patients (19 patients, 82.6%) had squamous cell carcinoma. Two patients (8.7%) had adenocarcinoma; one patient (4.3%) had adenosquamous and one patient (4.3%) had small cell carcinoma histology. The FIGO stage of the patients ranged from IB2 to IVA. Stage IIB was most common (10 patients; 43.5%) followed by IIIB (8 patients; 34.8%), IVA (3 patients; 13%) and IB292 patients; 8.7%) respectively. Twelve patients (52.2%) had medical comorbidities like diabetes or hypertension or both.

Table 1 Baseline patient characteristics

Patient characteristics	Number of patients (Total n=23)	Percentage
Age		
Median (Range)	77(75-85)	
75-80 years	16	69.6%
>80 years	7	30.4%
PS (ECOG)		
0 to 1	14	60.9%
2 to 3	9	39.1%
Stage(FIGO)		
IB2	2	8.7%
IIB	10	43.5%
IIIB	8	34.8%
IVA	3	13.0%
Histology		
Squamous cell carcinoma	19	82.6%
Adenocarcinoma	2	8.7%
Adeno Squamous	1	4.3%
Small cell	1	4.3%
Medical co-morbidity		
Yes	12	52.2%
No	11	47.8%

PS: Performance Score; (ECOG): Performance Score (Eastern Cooperative Oncology Group).

The patients received EBRT by a conventional treatment planning to a dose ranging from 46 to 50 Gy in 2Gy daily fractions with the four-field box technique. Twenty patients (86.9%) received HDR-ICBT. The brachytherapy dose was either 7 Gy or 7.5 Gy per fraction for 2-4 fractions. One patient received an external beam boost of 14 Gy in 7 fractions as brachytherapy could not be planned due to stenosed vagina and two patients (8.7%) defaulted and did not receive brachytherapy. Total brachytherapy dose (EqD2) was more than 30 Gy in 10 patients (43.5%) and less than 30 Gy in another 10 patients (43.5%). The overall duration of radiotherapy ranged from 42 to 70 days, with a median of 55 days. Fourteen patients (60.9%) completed their entire course of treatment in less than 8 weeks. Only three patients (13%) received concurrent chemotherapy with weekly inj Carboplatin AUC 2 for 5 cycles.

Survival

The median follow-up time was 46 months (range 3-93). At the end, nine patients (39.1%) were alive. The overall survival (OS) for the entire cohort of patients at 5 years and 7 years was 54.9% and 43.9% respectively and the disease-free survival (DFS) at 3 years and 5 years were 66.3% and 45.9%, respectively (Fig. 1).

The univariate analysis of various patient and treatment parameters influencing OS and DFS are shown in Table 2. The OS at 5 years and 7 years for the patients with pre-treatment ECOG score 0-1 are superior to those with score 2-3, but the statistical difference only reached borderline significance (p=0.06). The patients of stage IB2-IIB had superior 5-year OS and DFS (66.7% and 46.3%) than of stage IIIB-IVA (41.6% and 44.4%); p=0.12 and 0.54 respectively. The patients of squamous cell carcinoma histology had statistically significant improved OS and DFS (Fig. 2) (p=0.009 and p<0.001 respectively).

The median total radiation dose (EqD2, 2 Gy equivalent dose) including, EBRT and ICBT of the patients was 79.75Gy (range 50-85.67). Nine patients (39.1%) received more than 80 Gy. The OS at 5 years of the pa-

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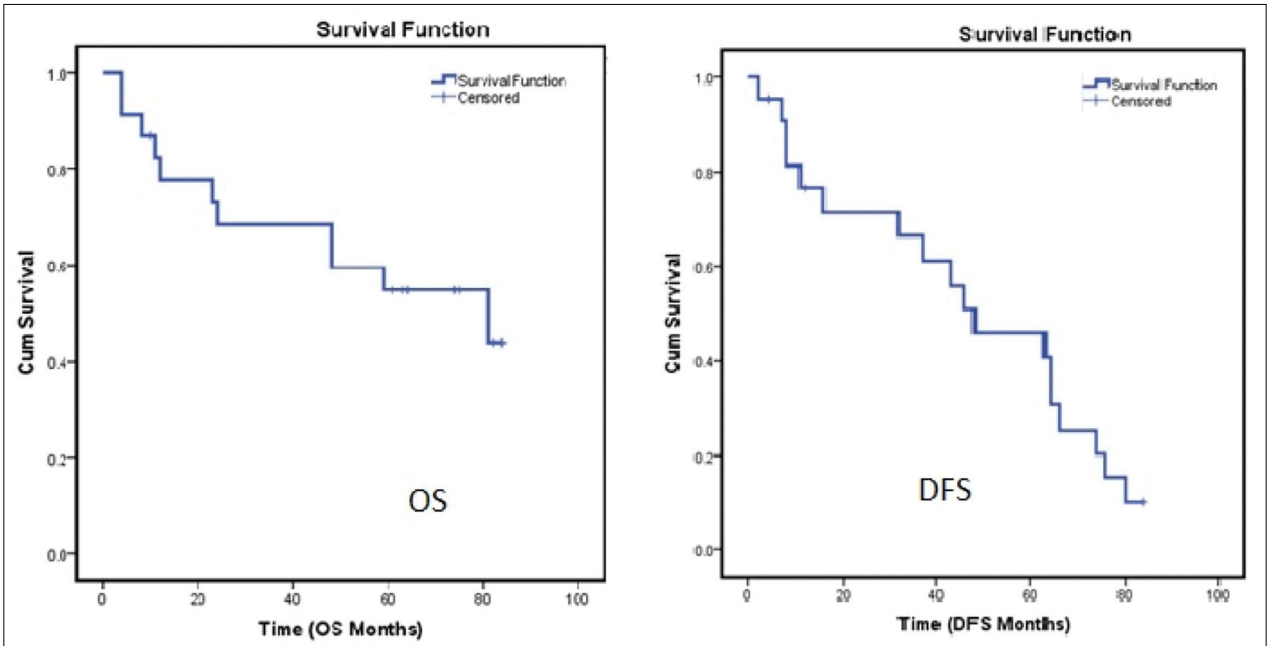


Fig. 1. Overall survival and disease-specific survival (OS and DSS) rates for all patients using the Kaplan–Meier method.

Table 2 Comparison of survival among various patient and treatment-related factors

Variable	No. of patients (%)	Overall survival (OS)			Disease-free survival (DFS)		
		5 Yrs (%)	7 Yrs (%)	p	3Yrs (%)	5 Yrs (%)	p
PS							
0 to 1	14 (60.9%)	69.2	51.9	0.06*	64.3	42.9	0.6
2 to 3	9 (39.1%)	33.3	33.3		71.4	53.6	
Stage							
IB2-IIB	12 (52.2%)	66.7	66.7	0.12	64.8	46.3	0.5
IIIB-IVA	11 (47.8%)	41.6	27.7		66.7	44.4	
Histopathology							
SCC	19 (82.6%)	63.2	50.5	0.009*	81.6	56.5	<0.001*
Others	4 (17.4%)	0	0		0	0	
Total ICRT dose (EqD2)							
Less than 30Gy	10 (43.5%)	40	40	0.2	46.7	23.3	0.1
30 Gy or more	10 (43.5%)	78.8	52.5		80	60	
Not taken	3 (13.0%)	33.3	33.3		100	100	
Total radiation dose (EqD2)							
Less than 80 Gy	14 (60.9%)	35.7	35.7	0.04*	48.2	28.9	0.3
80 Gy or more	9 (39.1%)	87.5	58.3		88.9	66.7	
Total treatment duration (Days)							
56 or less	14 (60.9%)	62.3	62.3	0.2	76	59.1	0.03*
More than 56	9 (39.1%)	44	0		53.3	26.7	
Concurrent chemotherapy							
Yes	3 (13%)	66.7	66.7	0.5	33	0	0.04*
No	20 (87%)	53.1	42.5		72	54	

*Statistically significant. PS: Performance Score; SCC: Squamous Cell Carcinoma; ICRT: Intracacitary Radiotherapy.

tients receiving more than 80 Gy was superior to those receiving lesser doses (87.5% vs 35.5% respectively; p=0.04) Figure 2. The patients completing the entire course of treatment, within 8 weeks had improved OS and DFS at 5 years (62.3% and 59.1% respectively) in comparison to those taking longer treatment time (44% and 26.7% respectively); p=0.2 and 0.03 respectively (Fig. 2). The three patients who received concurrent chemotherapy had improvement of OS at 5 years than the others (66.7% vs 53.1%) but the difference is not statistically significant(p=0.5). However, no benefit was observed in terms of DFS in these patients receiving concurrent chemotherapy with Carboplatin.

Treatment-Related Acute and Chronic Toxicities

The acute and chronic treatment-related toxicities are shown in Table 3. Thirteen patients (56.2%) experienced acute gastrointestinal toxicity. Grade III acute toxicity was experienced by two patients (8.7%) with diarrhea and one patient (4.3%) with dermatitis, but no grade IV acute toxicity was recorded. The patients experiencing grade II-III diarrhea were managed conservatively with intravenous fluid and anti-diarrheal agents. Ten patients (43.5%) developed grade II dermatitis and only one patient (4.3%) developed grade III dermatitis. Grade I and II anemia were recorded in 8 (34.8%) and 4 (17.4%) patients respectively during treatment.

Two patients (8.7%) developed late rectal bleeding due to proctitis for which they had to undergo argon plasma photocoagulation. Only one patient (4.3%) within the entire cohort developed grade II lymphedema of the bilateral lower limbs. Eleven patients (47.8%) developed varying grades of vaginal stricture including one patient (4.3%) with grade III. One patient (4.3%) developed grade II cystitis and presented with moderate haematuria.

Patterns of Failure

Failure was defined as either recurrence of disease or persistent disease following radiotherapy. The failure was classified as 1. Locoregional: a residual or recurrent disease at cervix or uterus and/or pelvic failures below L5–S1 level including nodal, parametrial, and vaginal; 2. Distant: systemic spread, supraclavicular, and/or inguinal spread; 3. PA nodes above L5–S1.

The patterns of failure are shown in Table 4. At the end of follow-up, 11 patients (47.8%) experienced a relapse. The details of various patterns of failure are shown in Table 4. Four patients (17.4%) had residual disease after treatment. The most common failure was distant metastases. Five patients (21.7%) had isolated

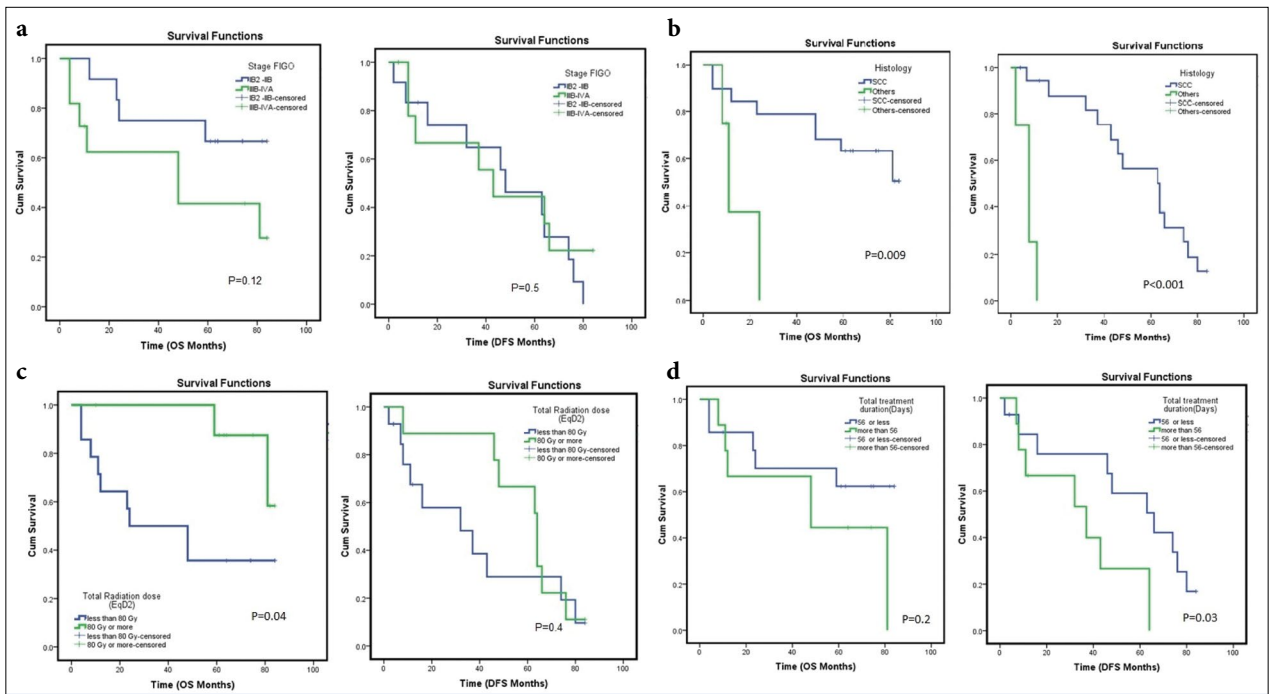


Fig. 2. Comparison of OS and DFS among (a) FIGO stages (b) Histology, SCC vs. Others (c) total radiation dose, <80 Gy vs. >80 Gy (d) total treatment duration, ≤56 days vs. >56 days.

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Table 3 Acute and chronic treatment-related toxicities

	Acute (%)		Chronic (%)
Gastrointestinal (Diarrhoea)		Gastrointestinal (Rectal bleeding)	
NO	10 (43.5)	Grade 2	2 (8.7)
Grade I	7 (30.4)		
Gr II	4 (17.4)	Lymphedema	
Grade III	2 (8.7)	Grade 2	1 (4.3)
Dermatitis			
Grade I	12 (52.2)		
Gr II	10 (43.5)	Vaginal stenosis	
Grade III	1 (4.3)	No	12 (52.2)
Genitourinary (Urinary frequency)		Grade I	7 (30.4)
Grade I	5 (21.7)	Grade II	3 (13)
Grade II	2 (8.7)	Grade III	1(4.3)
Haematological			
Grade I	8 (34.8)	Genitourinary (Cystitis)	
Grade II	4 (17.4)	Grade 2	1 (4.3)

Table 4 Comparison of failure with various parameters

Treatment relapse	Total patients (23)	Total dose (EqD2) (Mean±SD)	Total treatment duration (Mean±SD)	Stage IB2-IIB (n=12), (%)	Stage IIIB-IVA (n=11), (%)
No	12	79.88±6.55	55.58±4.80	8 (34.8)	4 (17.4)
Yes	11	73.46±12.66	56.55±7.2	4 (17.4)	7 (30.4)
P value	0.1	0.7	0.1		
Relapse/failure					
No relapse	12 (52.2%)				
Relapse/failure	11 (47.8%)				
Type of failure/relapse					
Loco regional (LR)	2 (8.7%)				
Distant Mets	5 (21.7%)				
LR+Distant Mets	2 (8.7%)				
LR+Abdominal (PAN)	2 (8.7%)				
Types of Distant failure					
Lung	4 (17.4%)				
Bone	3 (13%)				

PAN: Para-aortic node; SD: Standard deviation

distant metastases and two patients (8.7%) had distant metastases with locoregional failure. Among the distant metastases, lung metastases were most common (4 patients, 17.4%) followed by bone metastases (3 patients, 13%). Two patients (8.7%) developed para-aortic lymph nodes during the follow-up.

The patients who had failure received a lower mean total radiation dose (EqD2) in comparison to those without any relapse (73.46±12.66 Vs 79.88±6.55; p=0.1). Patients with stage IIIB-IVA (7 patients, 30.4%) experienced more failure than those with stage IB2-IIB disease (4 patients, 17.4%); but the difference is not statistically significant (p=0.1).

Discussion

It is an inconclusive issue that whether the treatment outcomes of elderly patients with cervical cancer are poorer than their younger counterparts. Multiple retrospective series have shown mixed results in terms of treatment outcome and toxicity.[20-23]

In this study, we retrospectively reviewed the treatment outcome, toxicity, and patterns of failure of cervi-

cal cancer patients of 75 years or older treated with definitive radiotherapy. The age of 75 years or older was selected based on the definition of "elderly" published in various cancer literature. [7,24-26]

The most relevant studies and guidelines recommend that the women with early-stage disease (FIGO stage IA-IB1/IIA1) are treated with surgery and those with locally advanced disease (FIGO stage IB2/ IIA2-IVA) with a combination of radiotherapy and chemotherapy. But older patients are less likely to receive all types of standard treatments compared with the younger ones. Possible reasons include concerns regarding co-existing medical co-morbidities, lack of access to care, increased toxicity, and physician or patient preference. Various literature have reported that elderly patients have treated less aggressively. [8,27-30]

Definitive radiotherapy is being considered as one of the primary treatment modality for elderly patients with cervical cancer. But compared to young patients, few elderly cervical cancer patients receive concurrent chemotherapy when treated with definitive radiotherapy.[31]

Despite the disparities in treatment, recent studies have demonstrated that elderly women tolerate pelvic radiotherapy and brachytherapy well. It was reported that elderly patients get equivalent survival to young patients when treated with definitive RT. A propensity-matched score analysis in Taiwan by Wang Y et al. showed no significant differences in cancer-specific survival, local and distant failure rates between the elderly group (≥75 years), and young group (<60 years), although OS was inferior in the elderly. The 5-year OS in the elderly group was 49.2%.[32]

Another retrospective analysis by Yoshida K et al. evaluated survival outcomes in 40 Japanese women of age 75 years or more reported 3-year overall and disease-specific survival of 58% and 80%, respectively.[33] In the current study, the 5-year OS was 54.9% and DFS at 3 years and 5 years were 66.3% and 45.9% respectively.

Table 5 shows various published literature evaluating the treatment outcome of elderly

Table 5 Treatment outcome of elderly patients with cervix cancer treated with definitive Radiotherapy with or without chemotherapy from various published literature

Study	Study design	Age group	Number of patients	Median age (Range)	Treatment Modalities	Median follow-up (Range)	Outcome
Yoshida K et al.[33]	Retrospective analysis	≥75 years	40	78 years (75–89)	Definitive RT ±CCT	20 months (1–85)	3 year OS 58% 3 year DSS 80%
Ying Gao et al.[36]	Retrospective analysis	<65 years ≥65 Year	52 107	49.2 years (21–78)	Definitive RT ±CCT	36.5 months	<65 years: OS 73.1%, DFS 71.2% ≥65 Year: OS 72.9%, DFS 67.3%
Hideyuki Sakurai et al.[37]	Retrospective analysis	<70 years 70-79 years ≥80 years	215 124 41		Definitive RT ±CCT		<70 years: 5 years OS 58% 70-79 years: 5 Year OS 50% ≥80 years: 5 Years OS 33%
Ming Yin Lin et al.[38]	Retrospective analysis	≥75 years	126	Mean 81.5 (SD 4.6)	Definitive RT ±CCT Adjuvant RT ±CCT Palliative RT	37 months (10.5 to 71.1)	3 and 5 year: OS 52.7%, 41.2% for entire cohort
Wang W et al.[34]	Retrospective analysis	≥70 years (70-88)	73	74 years	Definitive RT ±CCT	32.4 months (4.8–118.8)	The 3-year OS 64.9%, The 3-year DFS 66.5% for the entire cohort
Wang W et al.[22]	Retrospective analysis	Young <60 Old >70	991 70	49 (23-59) 74 (70-88)	Definitive RT ±CCT	30.2 months (1.9-93.0)	<60 years: 3 Year OS, DFS 86.5%, 74.6% >70 years: 3 year OS, DFS 73.9%, 75.4%
Present study*	Retrospective analysis	75 years or more	23	77 years (75-85)	Definitive RT ±CCT	46 months (3-93)	OS at 5 years and 7 years 54.9% and 43.9% DFS at 3 years and 5 years 66.3% and 45.9%

*Results of the present study, CCT: Concurrent chemotherapy; OS: Overall Survival; DSS: disease-specific survival; DFS: Disease-free survival.

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patients with cervical cancer treated with definitive radiotherapy with or without concurrent chemotherapy. The outcome of our study is also comparable to these published reports.

Similar to other reports, there was a preponderance of advanced-stage tumors in the present cohort at diagnosis. But the acute and late treatment-related toxicities are less frequent as compared to other published literature. It may be because only three patients received concurrent chemotherapy with inj Carboplatin in this study.

Wang W et al. retrospectively analyzed elderly cervical cancer patients (≥70 years old) treated with definitive RT with or without concurrent chemotherapy. The 3-year OS of patients receiving RT and CCRT was 54.3% and 83.1%, DFS was 57.6% and 83.3% respectively. Out of 73 eligible patients; 15.1% had a locoregional failure, 12.3% experienced distant metastasis, and 5.5% had a locoregional failure and distant metastasis.[34] In our study, only three patients received concurrent chemotherapy with inj Carboplatin. The 5-year OS of the patients receiving CCRT was superior to those treated with radiotherapy alone but we got a contrasting result in DFS showing DFS of the CCRT group is inferior to only RT group. This conflict of the result may be due to the low sample size and the fact that only three patients received concurrent chemotherapy. In the present study, distant metastatic failure was higher (21.7%). The lung was the most common site of distant metastasis (17.4%). Patients with stage IIIB-IVA experienced more relapse than those of stage IB-IIB.

The national comprehensive cancer network (NCCN) recommends that the entire treatment time for cervical cancer should be less than 8 weeks.[35] The median treatment duration for the entire cohort of this study was 55 days (42-70 days). The patients completing treatment within 8 weeks have a superior OS and DFS.

Limitations

The current study has many limitations. Firstly, it is a retrospective study and the study population is heterogeneous. Further, the sample size was small and the EBRT in our patients was delivered with a conventional technique. None of the patients received Cisplatin-based concurrent chemotherapy. Therefore, further research in elderly patients with cervical cancer in a prospective design with a larger sample size needs to be done.

Conclusion

The number of elderly patients with cervical cancer is increasing and definitive radiotherapy gives good treatment outcomes with acceptable toxicity. However, caution should be taken when more aggressive treatment modalities like CCRT are used. In our study, good survival outcome with acceptable early and late treatment-related toxicity was observed. It can be concluded that definitive radiotherapy is well tolerated by elderly patients and should be considered whenever feasible.

Peer-review: Externally peer-reviewed.

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval: The study was approved by Institutional Ethics Commitee; BBCI Medical Ethics Committee (Registration No: ECR/1040/Inst/AS/2018), vide approval letter Ref No. BBCI-TMC/Misc-01/MEC/71/2019 Date 27th July 2019.

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