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Original Research Article

Survival outcomes in carcinoma cervix with contemporary radiation therapy: an insight

Himanshu Srivastava^{1*}, Tejas Kalyanpur², Harnoor Singh Pruthi³, Preety Negi¹

¹Department of Radiation Oncology, Capitol Hospital, Jalandhar, Punjab, India

²Department of Radiology, Capitol Hospital, Jalandhar, Punjab, India

³Department of Cardiology, Capitol Hospital, Jalandhar, Punjab, India

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*Correspondence:

Dr. Himanshu Srivastava,

E-mail: himanshu.srv1803@gmail.com

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ABSTRACT

Background: Concurrent chemoradiation therapy (CCRT) followed by brachytherapy is the standard of care treatment for locally advanced cervical cancer (stage IB3-IVA disease). The present study aimed to evaluate the success achieved by CCRT followed by computed tomography (CT)-based brachytherapy in patients with locally advanced carcinoma cervix in a tertiary care center.

Methods: This was a prospectively conducted retrospective observational study of patients with cervical carcinoma, treated at Capitol Hospital, Jalandhar, Punjab, from January 2018 to December 2021. Data were captured from the electronic medical records of the hospital. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier curve. The survival analysis was assessed by the patient's age, tumor stage, histology, and overall treatment duration.

Results: This study included 129 patients treated with CRT followed by CT-based brachytherapy. The median follow-up was 30 months (range 8-67 months). The 2-year OS and DFS were 83.5% and 80.2%, respectively. On univariate analysis, the factors associated with better survival were histology, and treatment duration, although not statistically significant.

Conclusions: Our treatment results with definitive CCRT followed by CT-based brachytherapy for locally advanced cervical carcinoma are comparable to the published literature. The prognostic factors such as tumor histology and treatment duration (<65 days) influenced patient survival, with squamous cell carcinoma, and completion of the treatment within 65 days resulted in better survival rates.

Keywords: Cervix uteri, Disease-free survival, Prognosis, Standard of care, Survival analysis

INTRODUCTION

According to the GLOBOCAN 2020 database, cervical cancer has been recognized as the fourth most common cancer among women globally. Worldwide, 604000 new cases and 342000 deaths have been estimated to be due to carcinoma cervix, mainly in low- and middle-income countries.¹ A substantial difference in the incidence and mortality of cervical cancer among developing and developed countries has been acclaimed. The reason for this variation is delay in diagnosis, lack of effective

screening, and the paucity of treatment facilities.² In India, cervical cancer accounts for 9.4% of all cancers, and 18.3% of new cases in 2020.³

Radiation therapy is an imperative component for the treatment of cervical cancer. Multiple randomized clinical trials have demonstrated significant improvement in OS and progression-free survival with definitive CCRT as the standard of care for the International Federation of Gynaecology and Obstetrics (FIGO) stage IB-IVA disease.⁴⁻⁸ This treatment resulted in 5-year overall and

progression-free survival of 66% and 58%, respectively.⁹ Brachytherapy forms an integral part of the radical treatment in addition to CCRT for locally advanced carcinoma cervix. Several studies have reported improved OS and reduced local recurrence with intracavitary brachytherapy in these patients.^{10,11}

With the recent technological advancements, brachytherapy has evolved from 2-dimensional to 3-dimensional treatment planning. Three-dimensional image-guided brachytherapy (IGBT) planning relies on 3D imaging modalities either CT or magnetic resonance imaging (MRI). Using these techniques, individualized treatment plans can be generated in comparison to the 2-dimensional point-based brachytherapy. The GEC-ESTRO recommended a dose of >85 Gy delivered in <50 days to the high-risk clinical target volume to achieve an approximate 10% increase in local control, disease-specific survival, and OS compared to the control group.¹² This study was conducted to describe the clinicopathological characteristics and 2-year survival outcomes of patients with cervical carcinoma treated with definitive CCRT followed by CT-based image-guided intracavitary brachytherapy at a tertiary care center.

Aim

This study aimed to describe the clinicopathological characteristics and 2-year survival outcomes of patients with cervical carcinoma treated with definitive CRT followed by CT-based image-guided intracavitary brachytherapy at a tertiary care center in north India.

METHODS

Patients

A retrospective review was conducted using electronic medical records data from the department of radiation oncology at Capitol Hospital, Jalandhar, Punjab. Between 2018-2021, a total of 251 patients with histopathological diagnoses of carcinoma cervix were registered. Among these, 129 patients were found to have completed the planned CCRT followed by brachytherapy treatment and were considered eligible to be enrolled in this study. The patients who were lost to follow-up were contacted telephonically. The patients with incomplete clinical data, those who underwent upfront surgery, those with metastatic or recurrent disease on presentation, and those who received part of the treatment from some other hospitals were excluded.

Institutional review board approval was obtained to conduct this study. Detailed patient demographic, tumor- and treatment-related details were retrieved from medical records and managed as per privacy regulations. All these patients were treated with intensity-modulated radiation therapy (IMRT) technique with TrueBeam 6-MV linear accelerator.

Treatment planning

For all cervical cancer patients planned for treatment with definitive CRT, the following radiation treatment protocol was followed.

CT simulation

Patients were instructed to take laxatives 1 day before planning CT scan. They are given oral and intravenous contrast to delineate normal structures such as small bowel and blood vessels. Urografin contrast was given as 20 ml dissolved in 1 liter of water to be taken 1 hour before CT scan. Rectal contrast is given by dissolving 20 ml of urografin in 50 ml of normal saline. The bladder was comfortably full throughout the simulation process. Similar bladder and rectal protocols were followed before treating all patients. During CT simulation, the patient was made to lie supine with immobilization using the thermoplastic cast. CT scan was performed extending from T10-T11 interspace to half of the femur and a slice thickness of 3 mm using a 64-slice Philips Brilliance Big Bore CT simulator. These images were transferred to the Eclipse treatment planning system Varian associates, Palo Alto, CA, USA workstation.

Contouring

The target volume was outlined in the planning CT scan by the consultant radiation oncologist on the axial slices of the planning CT scan based on the radiation therapy oncology group (RTOG) guidelines.¹³

CTV-primary components

The clinical target volume (CTV-primary) consisted of the gross tumor volume of the primary tumor (GTV-primary), uterine cervix, uterine corpus, parametrium, vagina, and ovaries.

Definitions for each component of the CTV-primary

GTV-primary

The GTV-primary included gross disease visible on an MRI T2-weighted image and disease detected by clinical examination.

Vagina

During CT simulation, a vaginal marker was placed at the lowermost extent of vaginal disease. Paravaginal tissue along with the vaginal wall were included. The caudal border was determined individually based on the MRI findings and clinical examination according to the RTOG guidelines. Minimal or no vaginal extension: include upper half of the vagina. Upper vaginal involvement: include the upper 2/3rd of the vagina. Extensive vaginal involvement: include the entire vagina.

Parametrium

Parametrium was considered as the adipose tissue between the cervix and pelvic wall and the linear structures running laterally including vessels, nerves, and fibrous structures. The cranial border was taken as corresponding to the beginning of the true pelvis. The contouring was done anteriorly up to the level of the posterior border of the bladder in the central region. Peripherally, it extended to the anterior end of the lateral pelvic bony wall. Posteriorly, the contouring was done from the anterior part (semicircular) of the mesorectal fascia. Laterally, the parametrium was contoured till the lateral pelvic wall, up to the medial edge of the internal obturator muscle. The caudal border was marked at the medial border of the levator ani or at the pelvic floor.

Ovaries

Ovaries visible on CT were included within the CTV primary.

CTV nodal delineation

As per the guidelines by Taylor et al, blood vessels were taken as representatives for delineating regional lymph nodes involved in carcinoma cervix.¹⁴ We contoured common iliac vessels from aortic bifurcation.

For common iliac nodes, CTV was drawn 7-mm anterior and medial to the vessels. The CTV was extended posterolaterally to the psoas muscle and vertebral body. A 7-mm margin was used around internal iliac vessels to contour internal iliac lymph nodes. The anterior border was extended by 17 mm along the iliopsoas muscle to include the external iliac lymph nodes including the lateral group. The obturator nodes were contoured by joining the external and internal iliac regions. A 10-mm strip over the sacral prominence connecting the common iliac contours included the pre-sacral lymph nodes.

Organs at risk (OARs) delineation

The structures identified as OARs were the rectum, bladder, and small intestine. These structures were contoured on the CT image of each slice as per the RTOG guidelines. The dose constraints of the OARs including bladder, rectum, and small bowel were according to the quantitative analysis of normal tissue effects in the clinic (QUANTEC) guidelines.¹⁵ The medical physicist then planned the radiation treatment using Eclipse version 13.5. The treatment plans were evaluated by the consultant radiation oncologist. The final treatment plan was executed on the patient.

Prescribed radiation dose

All patients received external beam radiation therapy to a dose of 50.4 Gy in 28 fractions followed by a gap of 1 week. These patients were then taken for intracavitary

brachytherapy with either 9 Gy in 2 fractions or 7.5 Gy in 3 fractions.

Concurrent chemotherapy

All these patients received concurrent chemotherapy with injection cisplatin 40 mg/m² intravenously once every week.

Brachytherapy

All these patients were treated with IGBT using a high-dose rate Ir192 remote afterloading system (microselectron, Elekta). IGBT was delivered based on CT images with a 1.25 mm slice thickness with inserted applicators. The dose to point A was prescribed as per the Manchester system.

Follow-up

All these patients were followed in the radiation therapy clinic 2 months after the completion of treatment, and then every 3 months for the first 2 years, every 6 months in the third year, and yearly following that. During each visit, all these patients were examined clinically. Imaging either positron emission tomography-computed tomography or magnetic resonance imaging scan was performed as and when required. The patient was considered disease-free if there was no evidence of disease by clinical examination and imaging. Local or nodal recurrence was determined radiologically or clinically followed by biopsy.

Treatment endpoints

OS was defined as the duration between the completion of treatment and the date of patient death or last follow-up visit (censored). DFS was defined as the time between the completion of treatment and the date of any event either recurrence, metastasis, or second primary. The OS and DFS were plotted with the Kaplan-Meier graph.

Statistical analysis

Data were described in terms of range; mean±standard deviation (±SD), median (IQR), frequencies (number of cases), and relative frequencies (percentages) as appropriate. For comparing categorical data, the Chi-square test was performed, and Fisher exact test was used when the expected frequency was less than 5. Kaplan-Meier curves for OS and DFS were plotted. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21.0 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

RESULTS

Clinicopathological characteristics showed that most patients were 51-70 years old constituting 59.7%. The

median age was 55 years, with only 6.2% of the patients being under 40 years. The majority of the patients (87.6%) had squamous cell carcinoma followed by 10.9% of patients with adenocarcinoma. The most common presentation was discharge or bleeding per vaginum in 64.3% of patients. Performance status was assessed based

on the Eastern Cooperative Oncology Group scale. This score assessment revealed that 55.8% of the patients could perform light or sedentary work. Out of 129 patients, 113 (87.6%) patients had squamous cell carcinoma followed by 12.4% of patients with other histologies (Table 1).

Table 1: Patient and tumor characteristic.

Characteristics	Number of patients (%)
Age (in years)	
31-40	8 (6.2)
41-50	35 (27.1)
51-60	43 (33.3)
61-70	34 (26.4)
>71	9 (6.9)
Presenting symptoms	
Discharge/bleeding per vaginum	83 (64.3)
Abdominal pain	15 (11.6)
Others	43 (33.3)
Menstrual status	
Premenopausal	23 (17.8)
Perimenopausal	36 (27.9)
Postmenopausal	70 (54.3)
ECOG performance status	
0	6 (4.7)
1	72 (55.8)
2	51 (39.5)
Histopathology	
Squamous cell carcinoma	113 (87.6)
Adenocarcinoma	14 (10.9)
Others	2 (1.6)
Clinical stage	
IIB	53 (41.1)
IIIA	15 (11.6)
IIIB	52 (40.3)
IVA	9 (6.9)

Table 2: Treatment details.

Duration of EBRT	
Range	35-45 days
Median	38 days
The time interval between EBRT and brachytherapy	
Range	5-25 days
Median	11 days
The time interval between fractions of brachytherapy	
Range	5-7 days
Median	6 days
Overall treatment time (EBRT+BT)	
Range	50-87 days
Median	64 days
Chemotherapy cycles	
<4 cycles	15 (11.6%)
4-6 cycles	114 (88.4%)

All patients completed the planned doses of definitive EBRT with concurrent chemotherapy with weekly cisplatin followed by intracavitary brachytherapy (Table 2).

The first follow-up was carried out at 6-8 weeks following completion of treatment and this period varied from 5 months to 2 years, with a median follow-up of 30 months (range 8-67 months). Radiological response assessment at 2 months revealed complete response in 96.9% of the patients, partial response in 3.1% and none showed stable or progressive disease overall survival (OS).

Status of patients at last follow-up

During follow-up, 89 (68.9%) patients were disease-free, 9 (6.9%) patients developed locoregional recurrence, 7 (5.4%) patients progressed to develop distant metastasis, and 5 (3.9%) patients developed histopathological proven second primary malignancy. Fifteen (11.6%) patients including those lost to follow-up were taken as expired. Four (3.1%) patients had residual disease for which they received systemic chemotherapy. Locoregional control was reported to be 93% in these patients, irrespective of the stage of the disease. Mean DFS and OS were 31.8 and 33.1 months respectively. The 2-year OS and DFS were 80.2% and 83.5% respectively (Figures 1 and 2).

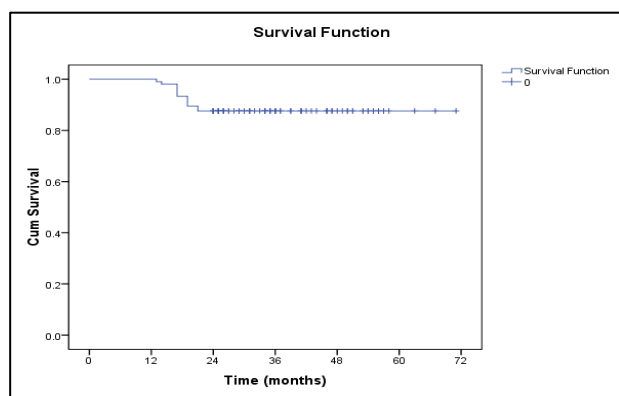


Figure 1: Kaplan-Meier analysis for overall survival.

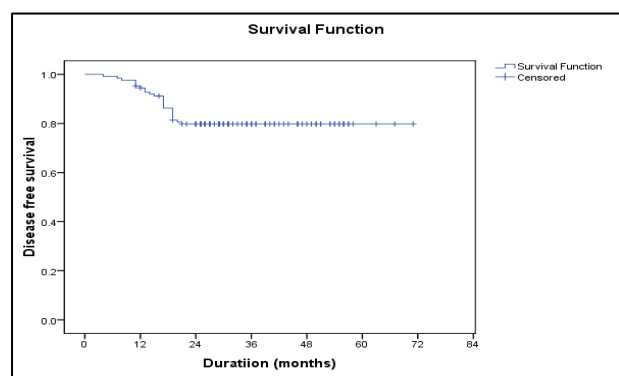


Figure 2: Kaplan-Meier analysis for disease-free survival.

DISCUSSION

Cervical cancer is an example of the global disparity as it ranks second among women in developing countries and ranks tenth among developed countries.¹⁶ The reported age-standardized incidence of cervical cancer has been 13.3 cases per 1 lakh women-years (95% CI 13.3-13.3) and a mortality rate of 7.2 deaths per 1 lakh women-years (95% CI 7.2-7.3).¹ In India, an estimated 123,907 new cervical cancer cases are diagnosed with a mortality of 77,348 cases.¹⁷

Despite a noticeable fall in the global pattern of cervical cancer, it remains a major challenge to the healthcare system in India. The median age at presentation in our study was 55 years. Most of our patients were in the age group of 51-60 years (33.3%) similar to as reported by Mehrotra et al. where a significant increase in the incidence of cervical cancer after 45 years with a peak at 55 years of age has been reported.³

We found a significantly high percentage of patients (94.4%) presenting with locally advanced disease. This finding is in concordance with other single institutional studies.^{18,19} Low awareness of symptoms, poor access to superior oncology-related healthcare services, and minimal effective screening programs for cervical cancer in our country could be the primary reasons for this finding.²⁰

CCRT (external beam radiation therapy with concurrent platinum-based chemotherapy followed by brachytherapy) is the standard of care treatment for locally advanced cervical cancer (stage IB3-IVA disease).²¹ BT is an integral component of treatment for cervical cancer due to its special characteristics of rapid dose fall-off and close treatment distance. As to survival, our study revealed similar survival rates, corresponding to the literature. Our data on survival analysis showed DFS and OS to be 80.2% and 83.5%, respectively. In 2018, an audit on 339 patients of locally advanced carcinoma cervix (stage IB-IIIB) published 3-year local control, DFS, and OS of 94.1%, 83.3%, and 82.7%, respectively. For stage III-IVA disease, the rates were 85.1%, 60.7%, and 69.6%, respectively.²² Contrary to this, varying survival rates have been published. In a recent publication by Jeevanrajan et al stagewise observed 5-year survival rates were reported to be 64%, 50%, 37%, and 17.5% for stage I, stage II, stage III, and stage IV, respectively.²³

We assessed various factors such as the age of the patient, tumor stage, histology, and treatment duration determining the survival outcomes. We found no statistically significant difference between survival rates according to age and tumor stage. A thorough literature search revealed contradictory results regarding older age as an independent prognostic factor in carcinoma cervix. Quinn et al have reported worse survival in elderly carcinoma cervix patients, independent of other factors such as associated comorbidities, histology, and stage of the disease.²⁴

Studies on the prognostic significance of adenocarcinoma in cervical cancer after treatment with CRT are limited with conflicting results.^{25,26} On a similar ground, a retrospective study was carried out on stage IB-IVA carcinoma cervix patients and assessed the treatment outcomes according to the histological subtypes. The authors reported the 3-year OS, DFS, pelvic control, and distant control rates in the squamous cell carcinoma group and adenocarcinoma group to be 85.2% and 75.4% ($p=0.005$), 77.5% and 57.3% ($p<0.001$), 89% and 74% ($p=0.001$), and 86% and 74.4% ($p=0.011$), respectively. On multivariate analysis, histology was found to be an independent factor of OS ($p=0.003$), DFS ($p<0.001$), pelvic control ($p=0.002$), and distant control ($p=0.003$). This histological survival difference persisted regardless of RT alone or concurrent CRT.²⁷ We noted that patients with squamous cell carcinoma histology had better survival than those with adenocarcinoma, although it was not statistically significant ($p=0.31$).

Several studies highlighted the importance of overall treatment duration in the RT-alone era. These studies demonstrated that prolonged treatment duration was associated with worse locoregional progression and OS.²⁸ Similar findings were reported for patients treated with CRT.²⁹ This focuses on completing the CRT treatment in cervical cancer within a short time, preferably ranging from 55-65 days.^{30,31} It has been put forward that a decline in OS by 0.6% per day is expected for each additional day of treatment beyond 6-8 weeks.³² The negative impact of prolonged radiation treatment duration does not preclude the addition of concurrent chemotherapy to radiation therapy in both early and locally advanced cervical cancer.³³ An interesting finding of our study was that the patients who completed the planned treatment of CRT followed by intracavitary BT in <65 days had better survival, though statistically non-significant ($p=0.18$).

The key strength of our work resides in providing an overview of treatment impact on survival and prognostic factors affecting survival in locally advanced carcinoma cervix with standard EBRT and CT-based brachytherapy. We acknowledge the limitations of our study as the retrospective nature of the collected data due to which the details regarding CRT-related acute or late toxicities could not be retrieved. Further prospective studies with larger sample sizes should be conducted to assess long-term survival analysis in locally advanced carcinoma cervix.

CONCLUSION

Our findings show that the results of treatment with definitive CCRT followed by CT-based brachytherapy provide good overall and disease-free survival for patients with locally advanced cervical carcinoma. This study suggests focusing on timely detection and prevention strategies as an important prerequisite to procure better outcomes. Our study highlights that traditional prognostic factors such as histology and treatment duration are well-

defined and appear to be the most important prognostic factors for survival.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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