Section: Radiation Oncology

Original Research Article

RETROSPECTIVE ANALYSIS ON THE IMPACT OF TREATMENT TIME ON SURVIVAL IN SQUAMOUS CELL CARCINOMA OF CERVIX

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Received : 20/03/2023
Received in revised form : 14/04/2023
Accepted : 26/04/2023

Keywords:
Effect of treatment duration, Survival, Pelvic control, Carcinoma cervix.

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DOI: 10.47009/jamp.2023.5.3.38

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (3); 173-177

Abstract

Background: Carcinoma cervix is the 4th most common cancer globally and 2nd most common in India. The study aims to analyse the impact of overall treatment time (OTT) on survival outcomes and pelvic control of early and locally advanced cervical cancer patients treated with Definitive chemoradiation or Radical radiation. **Materials and Methods:** 868 cervical cancer patients were registered from January 2014 to December 2015, in which 347 patients were planned for either definitive chemoradiation or Radical radiation (RT). Of that, 132 early and locally advanced carcinoma cervix patients who completed protocol treatment [Pelvic EBRT (45 -50 GY /25#) + Intra-cavitary Brachytherapy (14 -16 GY/2#) + Parametrial boost] with or without weekly cisplatin at our hospital were included. Overall treatment time is defined as the time start of pelvic EBRT to the end of the last fraction of PM boost. **Result:** The median age of presentation was 50 years, and most patients were in stages IIB and III. The median overall treatment time (OTT) was 80 days, and 65.9% of patients completed the protocol treatment within this timeframe. Patients who completed treatment within 80 days had a higher 3-year and 5-year all-stage survival rate than those who took longer than 80 days. All-stage 5-year pelvic control rates were also better in patients who completed treatment within 80 days. Waiting time for intracavitary brachytherapy was the major factor influencing delay in OTT. Treatment-related toxicities and co-morbidities were other factors that contributed to the delay in treatment time. **Conclusion:** Prolongation of overall treatment time impacted 5-year overall survival and pelvic control. Efforts must be taken to complete radiation treatment as early as possible.

INTRODUCTION

Carcinoma cervix is the 4th most common cancer globally and the 2nd most common cancer in India among females.[1] Around 40 – 45 % of patients present with locally advanced stage in developing countries, mainly because of the prevalence of HPV infection and unawareness of the vaccination and screening programs. Radiation therapy provides an excellent survival rate with a five-year disease-specific survival and Local control rate of 90% and 98%, respectively. Currently, Chemo-irradiation remains the standard of care for the management of cervical carcinoma. FIGO stage I B3-IVA based on several phase III RCT trials showing a 30-50% decrease in risk of death compared to radiation alone and meta-analysis showing 6% improvement in 5-year overall survival with chemo-irradiation.[2,3] Local control/Pelvic control mainly depends upon the ability of radiation to eradicate the clonogenic tumor cells. During radiation, changes in radio sensitivity (due to changes in tumor oxygenation) and tumor repopulation may increase the tumor clonogenic cell survival. Prolongation of treatment time is a major factor leading to clonogenic cell survival due to accelerating repopulation, subsequently leading to poor outcomes.[4] Recent trial evaluating tumor repopulation remodelling has shown that accelerated repopulation in cervical cancer cells occurs approximately at 19 days of radiation treatment (11 -22 days).[5]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Many trials have shown that overall treatment time impacts tumor control rate, 0.3–1.6% and 1-2% loss of local control per day of prolonged cervical and Head & Neck cancer treatment, respectively.[6] So, Overall treatment time should be less than eight weeks, including brachytherapy (< 56 days) in carcinoma cervix and less than seven weeks in Head and neck cancer.[7,8]

The study aims to analyse the impact of overall treatment time (OTT) in locally advanced cervical cancer FIGO stage IB2 –III patients treated with Definitive chemo-irradiation or Radical irradiation in our institute to local control rate, disease-free survival and overall survival.

MATERIALS AND METHODS

Our study retrospectively looked into the records of histologically proven squamous cell carcinoma of cervix FIGO IB2 –III in the year 2014- 2015, who received Protocol treatment [concurrent chemo-irradiation or Radical irradiation alone (due to medical reasons) followed by brachytherapy then followed by parametrial boost] were included.

Patients with histology other than squamous, post-hysterectomy status, and patients who had not completed the protocol treatment were excluded.

Radiotherapy consists of pelvic External beam radiation (EBRT), intracavitary brachytherapy, and parametrial boost. Pelvic EBRT was delivered using CLINAC 2100CD by a conventional technique using two fields (AP/PA) or a 3D conformal radiotherapy technique using four fields (AP/PA/RL/LL). EBRT Prescription dose ranged from 45-50 GY (1.8 – 2.0 GY /#) / 5 # per week.

Patients receiving chemo-irradiation were given chemotherapy after the first fraction of radiotherapy. The chemotherapy regimen is cisplatin 40 mg/m2 weekly for six cycles. Concurrent chemotherapy was withheld if a patient developed any toxicity, such as raised RFT or decreased Hb, RBC, or WBC count and restarted if/once the patient's condition improved. Patients with pre-existing renal disease, poor performance status, and other co-morbidities received Radical radiotherapy alone without chemotherapy.

After completing pelvic EBRT, the patient received HDR intra-cavitary brachytherapy (BT) using MicroSelectron HDR remote after loading system (Nucleotron, Netherlands). Dose was prescribed to point A, to a total dose is 16-14 Gy/8-7 GY/# were delivered in two fractions.

After ICBT, a parametrial boost was done using a midline shield block in AP and PA fields to provide an adequate dose to the lateral parametrium. Dose and fractionation for PM boost depends upon the cumulative dose received from Pelvic EBRT and point B dose from ICBT to the lateral parametrium. It varies for each patient (3-5#). During treatment, weekly blood investigations and Local examinations were done to assess the toxicity of radiation and chemotherapy.

Data Collection

Information such as initial presentation, associated co-morbidity, clinical examination findings, and imaging details was collected from the patient's medical record and details. Regarding the radiotherapy, Informations such as the technique used, date of initiation of pelvic EBRT and treatment break during treatment were collected from radiotherapy records. Other relevant information, such as follow-up details and the patient's current status, was collected through medical records and phone calls. Duration in treatment was defined as EBRT time (ET) from the start of the first fraction of pelvic EBRT to the last fraction of pelvic EBRT (EBRT – BT time), defined as the interval between the completion of pelvic EBRT & Start of Brachytherapy. Overall treatment time (OTT) is from the start of 1st fraction of pelvic EBRT to last fraction of parametrial boost. Outcomes such as OS and pelvic control rate were measured from the completion date of protocol treatment to death from any cause/ last date of follow-up and to the date of first radiographic/pathological evidence of recurrence, respectively.

RESULTS

In our study period 2014- 2015, 347 carcinoma cervix patients were planned for radiotherapy. Out of these, 132 patients who completed protocol treatment were included in the study. The median age of the patient in the study was 50 yrs (28-70 years). All carcinoma cervix were squamous cell carcinoma with predominantly moderately differentiated (65.9%). Several patients in each stage, IB2, IIA, IIB, and III, were 24 (18.2%), 13(9.8 %),50 (37.8 %), and 45 (34.2 %), respectively. Ninety-four patients (71.2%) received chemotherapy in our study population. The median time to complete pelvic EBRT (EBRT time) was 42 days (38 – 45 days), and for Overall treatment time (OTT), it was 80 days (58 - 110 days). There was the median time interval between pelvic EBRT, and brachytherapy was 21 days (9 – 48 days)

Eighty-seven patients (65.9 %) in our study completed protocol treatment within 80 days. The Overall 3-year and 5-year all-stage survivals were 75.86% & 58.62% for OTT < 80 days and 57.7% & 26.6 % for OTT > 80 days, respectively. All-stage 5-year pelvic control rates were 58.62 % and 22.2 % for OTT < 80 days and > 80 days, respectively.

Table 1: Distribution of parameters, chemotherapy details and treatment duration.

Parameter		Percentage (median/ range)
Age		50 years (28 – 70 years)
Histology (grade)	Grade 1	15 (11.3%)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

	Grade 2	87 (65.9%)
	Grade 3	30 (22.7%)
FIGO Stage	IB2	24 (18.2 %)
	IIA	13 (9.8%)
	IIB	50 (37.8%)
	III	45 (34.2 %)
Chemotherapy details		
Number of Patients who received chemotherapy	Yes	94 (71.2%)
	No	38 (28.8%)
Percentage of pt received chemo stage-wise distribution	IB2	18 (74%)
	IIA	11 (84.6%)
	IIB	33 (66%)
	III	32 (71.1%)
Treatment duration		
EBRT time		42 days (38 – 45 days)
EBRT – BT time		21 days (9 – 48 days)
Overall Treatment time		80 days (58 – 110 days)

Table 2: Overall treatment time < 80 and > 80 days

PARAMETER		Overall treatment time < 80 days (n-87)		Overall treatment time >80 days (n-45)	
		No	Percentage	No	Percentage
Stage wise distribution	IB2 (n-24)	16	66.6%	8	33.3%
	IIA (n-13)	9	69.2%	4	30.7%
	IIB (n-50)	35	70%	15	30%
	III (n-45)	27	60%	18	40%
3-year Overall survival	IB2 (n-18)	13	54.1%	5	20.8%
	IIA (n-10)	9	69.2%	1	7.6%
	IIB (n-37)	26	52%	11	22%
	III (n-27)	18	40%	9	20%
5-year Overall survival	IB2 (n-15)	12	50%	3	12.5%
	IIA (n-8)	7	53.8%	1	7.6%
	IIB (n-25)	20	40%	5	10%
	III (n-15)	13	28.8%	2	4.4%
5-year pelvic control	IB2 (n-14)	11	45.8 %	3	12.5%
	IIA (n-7)	6	46%	1	7.6%
	IIB (n-21)	17	34%	4	8%
	III (n-15)	12	26.6%	1	2.2%

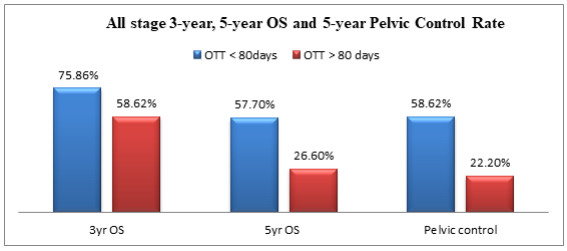

Figure 1: All stage 3-year, 5-year OS and 5-year Pelvic Control Rate

In our study, the Major factor influencing OTT delay was the time for intra-cavitary brachytherapy and logistics problems. Despite > 95% of patients completing pelvic EBRT within 42 days, many patients had an increase in OTT due to the delay in the brachytherapy. Other factors influencing delay in treatment time were treatment-related toxicities & co-morbidities to a lesser extent.

DISCUSSION

The concept of the time factor in clinical fractionated radiotherapy became popularized after the results published by Withers et al.[9] on his evaluation of overall treatment time in squamous cell carcinoma of head and neck cancer. He showed that for treatment time longer than 44 days, the repopulation of tumor cells would be equivalent to a loss of 0.6Gy/day. Thus, a greater dose is required to compensate for increased overall treatment time.

During radiotherapy, accelerated repopulation of clonogenic tumor cells occurs as a response to radiation-induced injury and loss of tumor volume. Apart from the accelerated proliferation of clonogenic tumor cells, other implicated Mechanisms, such as increasing fraction of hypoxic tumor cells and increased long repair half-times during radiation, are responsible for poor outcomes associated with increased treatment duration. Following this, many studies were started evaluating the impact of OTT in cervical cancer in the definitive radiation Era. A study by Fyles et al,[10] showed that in cervical carcinoma patients treated with irradiation alone, if the treatment duration prolonged beyond 30 days, it will result in approximately 1% per day loss in Local control.

Some studies also reported a correlation between the FIGO stage of cervical carcinoma and the prolongation of treatment time with its impact on pelvic control and survival. Keane et al,[11] reported a loss of tumor control by 1.2% per day for stages III and IV, while for stages I and II, loss of pelvic control is 0.7% per day. Similarly, a study by Lanciano et al,[12] it was shown that FIGO stage III had significant loss in pelvic control and survival with prolongation of OTT compared with FIGO stages I and II. But in a study by Petereit et al,[13] the

ISSN (O): 2687-5365; ISSN (P): 2753-6556

OS decreases by 0.6% per day and pelvic control by 0.7% per day for each additional day of treatment beyond 55 days for all stages of the disease. In our study, the stage-wise correlation between pelvic control and OTT were IB2 (45.8% vs 12.5%), IIA (46% vs 7.6%), IIB (34% vs 8%) and III (28.8% and 4.4%) for OTT < 80 days and > 80 days respectively. While Chen et al,[14] reported poor pelvic control and 5-year cause-specific survival in patients with overall treatment time > 63 days. All these trials were done in older days when definitive radiation was the standard of care.

In the era of concurrent chemo irradiation (CCRT), the effect of overall treatment time in cervical carcinoma was controversial. According to Shaverdian et al,[15] the prolongation of treatment time in the concurrent chemo-irradiation Group has no adverse effect on treatment efficacy compared to RT alone group. They attributed that this difference may be due to the inhibition of accelerated repopulation. An increase in the biologically effective dose of RT due to sensitization by concurrent chemotherapy. In another retrospective analysis, Monk et al,[16] showed women receiving CCRT according to the GOG 165 protocol, a treatment delay (> 8 weeks) was associated with worse PFS and OS. Similarly, a study by Lin SM et al,[17] showed no significant association between more advanced stages and longer treatment duration among the patients receiving CCRT. In contrast, FIGO I-IIB patients had significant CSS disadvantages among patients with OTT > 56 days. While another study by Song et al,[18] in a similar CCRT setting reported that prolonged OTT impacted pelvic control, with increased 3-year pelvic failure rate (OTT > 56 days vs. ≤ 56 days: 26% vs. 9%; p = 0.04). But there is no associated increase in DF or DSM with increased treatment duration.

A Data-Derived Treatment Duration Goal for Cervical Cancer study by Hong et al,[19] showed that 5-year OS were 65%, 63%, 58% and 52% for treatment time < 56 days, 57 to 64, 65 to 70 days and > 71 days respectively. In our study, the 5-year OS was 58.62 % in OTT < 80 days and 26.6% in OTT > 80 days, similar to ours.

Our study has many limitations, such as a small number of patients, irregular follow-up of patients, the nature of the study being retrospective, resulting in many confounders, the influence of concurrent chemoradiation, co-morbidity, Anaemia was not accounted for in our study and consequently, OS were calculated based on last day of follow up visit.

We observed that the reason for increased overall treatment time in our study population might be attributed to our institute is situated in a peripheral location, with most cases being from a village-based population and from distant places, who have limited awareness & compliance to the treatment.

Another major reason for our study's overall treatment time is the increased waiting time for brachytherapy (a gap between EBRT (external beam radiotherapy) and ICBT). Socio & financial problem of the patient and logistic issues of transportation remains the another main reason for non-compliance and brachytherapy default, leading to increased treatment time and poor pelvic control. This drawback can be overcome by Interspacing brachytherapy with EBRT (in selected patients) by significantly reducing the treatment duration. Maintaining haemoglobin levels (>10gm/dl) during treatment to improve local control and using higher conformal techniques to reduce toxicity, thus reducing treatment interruption, were the other options to reduce the prolongation of treatment time.

CONCLUSION

Prolongation of overall treatment impacted survival and local control in our study population. Other factors such as FIGO stage of disease, use of chemotherapy, and patient age also influence the outcome in carcinoma cervix. Even though our study used an OTT of 80 days for stratification, efforts must be taken to complete the treatment as early as possible or within 56 days. Even in Early carcinoma cervix increase in OTT lead to a decrease in OS and poor local tumor control. Measures must be taken to protract the treatment duration, such as Interspacing brachytherapy during radiation.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556