



Evaluation of Three- and Five-Year Disease-Free Survival in Patients With Cervical Cancer With Spinal Cord Metastasis Under Treatment With External Radiotherapy + Brachytherapy

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Abstract

Objectives: In developing countries, treatment of cervical cancer with metastasis to the spinal cord is generally associated with failure and reduced patient survival due to the lack of appropriate facilities. Oncologists are using a variety of methods to prolong patient survival. In the present study, we aimed to estimate the three- and five-year disease-free survival of patients with cervical cancer and spinal cord metastasis, treated with external radiotherapy + brachytherapy (i.e., internal radiotherapy).

Materials and Methods: This descriptive cross-sectional study was performed over a period of ten years (2010-20) in the brachytherapy ward of Shahid Madani Hospital (Tabriz, Iran). Overall, 200 patients with cervical cancer and spinal cord metastasis who were candidates for external radiotherapy + brachytherapy were recruited by the census sampling method. The variables that were likely to affect survival were recorded and analyzed using the Koch survival test and relevant descriptive and inferential statistics in SPSS version 23 software.

Results: The patients' overall survival was 43.12 ± 1.44 months; 78 patients (39%) survived until the end of the third year, and 49 (24.5%) lived till the end of the fifth year. Also, the pathological diagnosis ($P=0.013$ - $P=0.015$), disease stage ($P=0.014$ - $P=0.018$), the length of the treatment area ($P=0.026$ - $P=0.044$), and undergoing chemotherapy ($P=0.001$ - $P=0.002$) were significantly associated with the survival of the patients who completed the treatment course.

Conclusions: Chemotherapy, advanced disease, and greater length of the treatment area reduced three- and five-year survival in the patients with cervical cancer and spinal cord metastasis who underwent brachytherapy.

Keywords: Survival rate, Radiotherapy, Brachytherapy, Cervical cancer, Spinal cord

Introduction

Cervical cancer is the second leading cause of cancer in less developed countries and the third leading cause of cancer in women worldwide (1,2). Currently, most patients with cervical cancer in developing countries refer at advanced stages. Concomitant chemoradiotherapy is recommended as the standard treatment for advanced cervical cancer; nevertheless, radiotherapy facilities are inadequate in developing countries (3-5). Neoadjuvant chemotherapy can be used for the patients who have been waiting long for radiotherapy. Again, in developing countries such as Iran, there is a delay in the availability of novel therapeutic methods, so using conventional strategies is more common (6-8).

In developing countries such as Iran, radiotherapy is the method of choice for most women diagnosed with cervical cancer (9-11). Nevertheless, different methods are used to increase the chances of survival in these patients, such as using higher radiotherapy doses, different photon energies, different doses of brachytherapy, etc. It is clear;

however, that combination therapy is the best strategy to treat advanced cervical cancer with metastasis to the spinal cord. In this regard, combined use of external radiotherapy (with external beams), brachytherapy, and chemotherapy can result in plausible outcomes (12-14).

In developing countries, treatment of cervical cancer with metastasis to the spinal cord is generally associated with failure and reduced patient survival due to the lack of appropriate facilities. oncologists are using a variety of methods to prolong patient survival. Given that no similar study was found in the text search, in the present study, we aimed to estimate the three- and five-year disease-free survival of patients with cervical cancer and spinal cord metastasis, treated with external radiotherapy + brachytherapy (i.e., internal radiotherapy).

Materials and Methods

Study Design

The present study was a cross-sectional descriptive study performed over a period of 10 years from the beginning

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Key Messages

- ▶ Three- and five-year survival following cervical cancer depends on several factors
- ▶ Spinal metastasis in cervical cancer leads to high mortality
- ▶ Brachytherapy can be effective in increasing patient survival
- ▶ The larger the area undergoing radiotherapy, the lower the patient survival

of 2010 to the end of 2020 in the brachytherapy ward of Shahid Madani Hospital (Tabriz University of Medical Sciences). The minimum sample size, based on the results of a study by Hosseini et al (15) and considering three- and five-year survival rates of 65% and 32%, respectively, an alpha level of 0.05, and the study power of 80% equal was estimated as 55 using a sample size calculation formula. To increase the validity of the data, the census sampling method was used, and finally 200 patients were included in the study.

Inclusion and Exclusion Criteria

Inclusion criteria were the confirmed diagnosis of cervical cancer by a pathologist, spinal cord metastasis, referral by a specialist for radiotherapy, being candidate for external radiotherapy and brachytherapy according to a radiotherapist, and consent to participate in the study. Exclusion criteria were previous radiotherapy, Breastfeeding, history of hormone therapy, evidence of improvement during the past six months, a history of neuropathic pain following radiotherapy, a history of uncontrollable and therapy-resistant nausea during radiotherapy, irregular referrals for radiotherapy, the port catheter infections that could lead to death, sepsis, and diagnosis of the autoimmune diseases that could significantly compromise immune system function and increase the risk of mortality before radiotherapy.

Study Protocol

The information of all the patients fulfilling the inclusion and exclusion criteria, referred to the radiotherapist for external radiotherapy and brachytherapy, was recorded over a period of 10 years. These data included age, tumor location, pathological features, tumor histological type, tumor stage, type of treatment, radiotherapy dose, treatment area size, the number of radiotherapy sessions, and three- and five-year survival rates. Patients were regularly followed up, and their post-treatment three- and five-year survival rates were recorded every three months after examination by a radiotherapist. During examination, the patients' responses to treatment were assessed, and those who had no clinical problems were considered as recovered, but in patients with recurrence, the first appointment after this event was designated as the end of the disease-free period. The complete and incomplete clinical responses were determined by

a radiotherapist at the end of the last treatment session based on the presence or absence of cervical lesions.

Statistical Analysis

The collected information was initially checked and validated by two of the main researchers in terms of readability and authenticity and then delivered to a statistician. The data was entered in SPSS version 23 statistical software. Three- and five-year survival rates were determined, and their associations with tumor size, histological type, and stage, as well as radiotherapy dose, and chemotherapy were assessed. To identify factors with possible effects on patient survival, univariate rank log analysis and finally multivariate cox regression analysis were performed. The independent sample *t* test was also used, and the *P* value for all comparisons was considered to be significant at the <0.05 threshold.

Results

The mean age of the participants at the beginning of the study was 53.81 ± 5.29 years with the minimum and maximum ages of 24 and 84 years, respectively. Most of the patients were diagnosed with adenosquamous cell carcinoma ($n = 38$, 19%) and the IIIB stage ($n = 54$, 27%). The largest length of the treatment area was 14-16 cm ($n = 80$, 40%). Photon X9 was used in 83 (41.5%), and the dose of brachytherapy ranged from 2201 to 2600 in 98 patients. The total dose of radiotherapy ranged from 6001 to 7000 in 88 patients (44%), and 119 (59.5%) patients received chemotherapy concomitantly. The patients' demographic characteristics have been presented in Table 1.

The overall survival rate of the patients was 43.12 ± 1.44 months. Also, 78 patients (39%) survived until the end of the third year, and 49 patients (24.5%) lived to the end of the fifth year (Figure 1). There were no significant correlations between age and three-year ($r = -0.119$) or five-year ($r = 0.120$) survival rates, indicating that age had no impact on patient survival.

The pathological diagnosis had no significant correlations with three-year ($r = 0.115$) or five-year ($r = 0.066$) survival rates. On the other hand, three-year survival had a statistically significant inverse correlation with disease stage ($r = -0.693$); however, the inverse correlation of five-year survival ($r = -0.163$) with disease stage was statistically insignificant. Also, there was a significant inverse correlation between the length of the treatment area and both three-year ($r = -0.559$) and five-year ($r = -0.501$) survival rates. The type of the irradiated beam was not significantly associated with five-year ($r = 0.101$) and three-year ($r = 0.125$) survival. Also, the dose of brachytherapy was not significantly correlated with three-year ($r = 0.112$) or five-year ($r = 0.098$) survival. Moreover, external radiotherapy dose did not significantly affect three-year ($r = 0.079$) and five-year ($r = 0.091$) survival rates. The total radiotherapy dose

Table 1. The Demographic and Baseline Information of Participants

Variable		No. (%)
Age (y)	<40	14 (7)
	41-50	26 (13)
	51-60	70 (35)
	61-70	62 (31)
	>70	28 (14)
Pathological diagnosis	SCC	112 (56)
	Adenocarcinoma	28 (14)
	Adenosquamous cell carcinoma	38 (19)
	Undifferentiated carcinoma	22 (11)
Stage	IB	20 (10)
	IIA	32 (16)
	IIB	44 (22)
	IIIA	50 (25)
	IIIB	54 (27)
Length of the treatment area(cm)	<10	10 (5)
	11-13	36 (18)
	14-16	80 (40)
	17-19	61 (30.5)
	>20	13 (6.5)
Photon energy	Cobalt 60	41 (20.5)
	X9	83 (41.5)
	X18	76 (38)
Dose of brachytherapy	<1800	25 (12.5)
	1801-2200	49 (24.5)
	2201-2600	98 (49)
	2601-3000	20 (10)
	>3000	8 (4)
External radiotherapy dose	<5000	118 (59)
	>5000	82 (41)
Total dose of radiotherapy	<6000	23 (11.5)
	6001-7000	88 (44)
	7001-8000	73 (36.5)
	>8000	16 (8)
Simultaneous chemotherapy	Yes	81 (40.5)
	No	119 (59.5)
Clinical response	Full	60 (30)
	Incomplete	140 (70)

showed an inverse non-significant correlation with three-year ($r = -0.110$) and five-year ($r = -0.141$) survival. The combination of chemotherapy and radiotherapy adversely and significantly affected both three-year ($r = -0.789$) and five-year ($r = -0.551$) survival. Finally, there were no significant correlations between the clinical response and neither three-year ($r = 0.211$) nor five-year ($r = 0.105$) survival (Table 2).

The mean of disease-free survival was 33.1 ± 42.28 months (95% CI: 11.43-27.36) in the patients who underwent radiotherapy (internal + external) plus chemotherapy and 51.2 ± 63.69 months (95% CI: 27.16-48.55) in patients who did not use chemotherapy along with radiotherapy (internal +external) (Figure 2).

Regardless of completing the treatment course or not, the variables of pathological diagnosis, disease stage, the length of the treatment area, and receiving chemotherapy were significantly associated with three- and five-year

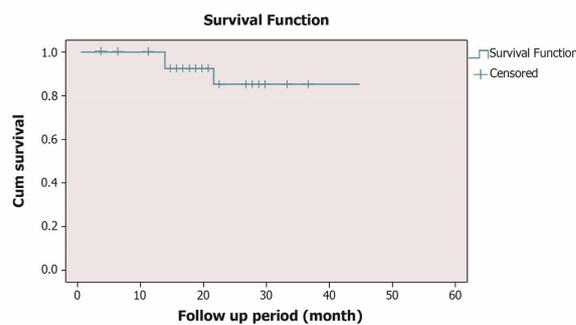


Figure 1. The curves of the participants' overall survival.

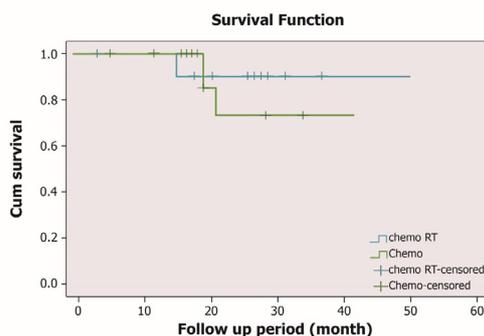


Figure 2. The survival Curves of the Patients Undergoing Radiotherapy With and Without Chemotherapy.

survival rates, decreasing the survival rate in patients with a complete treatment course (Table 3).

Discussion

The aim of this 10-year study was to evaluate the three- and five-year disease-free survival rates in patients with cervical cancer and spinal cord metastasis, undergoing treatment with external radiotherapy plus brachytherapy. The study of disease-free rates in cancers that have metastasized to different parts of the body has been performed in very limited studies; However, our study, which examined the rate of disease-free survival in patients with breast cancer and spinal metastasis, is the first study in this field and therefore could pave the way for further research. Our results showed that there were non-significant improvements in the overall survival and disease-free survival of the patients receiving radiotherapy compared to those receiving radiotherapy (external and brachytherapy) plus chemotherapy. The prevalence of complete pathological responses was higher in patients with high-grade and larger tumors; however, this observation was not statistically significant. Age had no impact on the rate of response to radiotherapy (16-20). The preferred treatment approach in patients with cervical cancer is to use a single therapeutic method instead of combination therapies, which mainly consists of radiotherapy with or without concomitant chemotherapy at either early or

Table 2. The Participants' Therapeutic Responses Based on Three- and Five-year Survival Rates

Variable		Three-year survival (n=78)	Five-year survival (n=49)
Age (y)	<40	20 (25.64%)	11 (22.44%)
	41-50	25 (32.05%)	19 (38.77%)
	51-60	22 (28.20%)	11 (22.44%)
	61-70	8 (10.25%)	8 (16.32%)
	>70	28 (35.89%)	0 (0%)
Pathological diagnosis	SCC	41 (52.56%)	20 (40.8%)
	Adenocarcinoma	10 (12.82 %)	11 (22.44%)
	Adenosquamous Cell carcinoma	20 (25.64%)	8 (16.32%)
	Undifferentiated carcinoma	10 (12.82 %)	10 (20.4%)
Stage	IB	3 (3.84%)	5 (10.2%)
	IIA	29 (37.17%)	21 (42.85%)
	IIB	19 (24.35%)	15 (30.61%)
	IIIA	16 (20.51%)	6 (12.24%)
	IIIB	11 (14.10%)	2 (4.08%)
Length of the treatment area (cm)	<10	7 (8.97%)	5 (10.2%)
	11-13	21 (26.92%)	21 (42.85%)
	14-16	25 (32.05%)	15 (30.61%)
	17-19	20 (25.64%)	7 (14.29%)
	>20	5 (6.41%)	1 (2.04%)
Photon energy	Cobalt 60	21 (26.92%)	15 (30.61%)
	X9	40 (51.28%)	20 (40.8%)
	X18	17 (21.79%)	15 (30.61%)
Dose of brachytherapy	<1800	9 (11.53%)	5 (10.2%)
	1801-2200	19 (24.35%)	19 (38.77%)
	2201-2600	28 (35.89%)	15 (30.61%)
	2601-3000	17 (21.79%)	10 (20.4%)
	>3000	21 (26.92%)	0 (0%)
External radiotherapy dose	<5000	51 (65.38%)	33 (67.35%)
	>5000	27 (34.62%)	16 (32.65%)
Total dose of radiotherapy	<6000	11 (14.10%)	8 (16.33%)
	6001-7000	32 (41.02%)	17 (34.69%)
	7001-8000	28 (35.89%)	18 (36.73%)
	>8000	7 (8.97%)	6 (12.24%)
Simultaneous chemotherapy	Yes	19 (24.35%)	15 (30.62%)
	No	59 (75.64%)	34 (69.38%)
Clinical response	Full	51 (65.38%)	11 (22.45%)
	Incomplete	27 (34.62%)	38 (77.55%)

Table 3. The Factors Affecting Three-Year and Five-Year Survival Based on Treatment Response Rates

Variable	Three-Year Survival (N=78)		Five-Year Survival (N=49)	
	Full response (n=51)	Incomplete response (n=27)	Full response (n=11)	Incomplete response (n=38)
	<i>P</i> Value ^a		<i>P</i> Value ^a	
Pathological diagnosis	0.013		0.015	
Stage	0.014		0.018	
Length of the treatment area (cm)	0.026		0.044	
Simultaneous chemotherapy	0.001		0.002	

^a Multivariate regression.

advanced (selectively) disease stages. Young people, due to their tendency to maintain pregnancy, are more likely to have surgery, despite the possible need for adjuvant radiotherapy, which is not possible in the case of large tumors. Adjuvant radiotherapy in the patients who are applicable for surgery may help to shrink tumor size and improve response, based on tumor characteristics (21-23).

Also, neoadjuvant chemotherapy in patients with cervical cancer can eradicate micrometastases, prevent tumor neovascularization, and reduce hypoxic cells (24-26).

There are no valid assessments regarding the role of neoadjuvant chemotherapy plus surgery as the definitive treatment for patients with cervical cancer versus chemoradiotherapy. In the recent decade, two randomized

phase three clinical trials compared chemoradiotherapy with neoadjuvant chemotherapy plus surgery. In one of the studies, which has been published recently, Gupta et al in 2018 (27) compared 5-year disease-free survival and overall disease-free survival in the cervical cancer patients undergoing either neoadjuvant chemotherapy plus surgery or chemotherapy plus radiotherapy, showing a non-significant higher 5-year disease-free survival in the former group.

Suggestions for Further Research

Considering the pathology diagnosis, disease grade, and the size of the treatment area, it is recommended to apply brachytherapy to increase the survival of patients with metastatic cervical cancer. It is also suggested that different brachytherapy protocols, with or without surgery and chemotherapy, be evaluated in future studies.

Study Limitations

The limitations of this study were the small sample size, performing chemotherapy by different specialists, and not assessing complications during treatment, which could affect patients' outcomes. However, the main strength of this study was using 10-year experiences of performing brachytherapy in northwestern Iran.

Conclusions

Chemotherapy, advanced disease grade, and increase in the length of the treatment area reduced three- and five-year survival in the patients with cervical cancer and spinal cord metastasis undergoing brachytherapy.

Authors' Contribution

SC: Study design and data analysis; FM: Data collection and data analysis; AN: Article writing and submission and data analysis.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

Researchers adhered to the ethical standards of the Helsinki Declaration. Treatments were chosen based on patients' clinical conditions to increase their survival, and no compulsion or additional costs were imposed on them or on insurance companies. Patients' consent was a priority in all the procedures. The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences (Ethic No: IR.TBZMED.REC.1397.374).

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