International Journal of Research and Review
Vol. 9; Issue: 11; November 2022
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Brachytherapy's Clinical-Imagery Correlates and Tumor's Reduction Outputs Among Patients with Cervical Cancer

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DOI: https://doi.org/10.52403/ijrr.20221166

ABSTRACT

Aim: The aim of this study was to investigate the clinical-imagery correlates of cervical cancer before and after brachytherapy, as well as the effects of tumor reduction resulting from the use of this radiation therapy.
Methods: A prospective case series study was conducted during 2009-2012 in the University Hospital Center: "Mother Teresa", Oncology Service. Sampling technique included 202 consecutive women diagnosed with cervical cancer, presented at the hospital and met the study protocol's inclusion criteria. The instrument used for cervical cancer imaging data was Computerized Tomography, which was used at different times, after applying the respective doses of brachytherapy. The paired t-test was used to estimate the differences between two variables for the same subject, such as imaging data after applying three doses of brachytherapy.
Results: In terms of the distribution of signs and symptoms in cervical cancer patients, 27.2% of them had pain in the lower back, 33.2% referred for pain during sex, 6.4% had vaginal bleeding during sex, 24.8% referred changes to the vaginal discharge, and 30.2% had blood in urine. Only 5.8% of the patients have performed brachytherapy without combined forms of chemo-radiotherapy, since most of the patients (51%) were in stage 2 of cancer. The reductions of the mean tumor sizes in different application of brachytherapy doses such as (dose 3 vs. dose vs. dose 1 vs. before application) were 9.6%, 4.93% and 4.93%, respectively. All these reduction's results (obtained after paired t-tests) were statistically significant, $p<0.001$.
Conclusions: It is important to be aware of the clinical, imaging and anatomopathological characteristics of cervical cancer that are used to diagnose and treat this disease. The application of brachytherapy with or without external beam radiation therapy leads to a gradual reduction size of about 5 to 10% after each dose, until the tumour mass might fully diminished.

Keywords: Brachytherapy, cervical cancer, radiation therapy, tumor reduction

BACKGROUND

The type of brachytherapy usually used to treat cervical cancer is known as intracavital brachytherapy and it is a crucial component of treatment for cervical cancer patients (1). Brachytherapy is a form of radiotherapy that involves the precise placement of radioactive sources directly in or adjacent to the tumour (2). A reduction in the use of brachytherapy has been associated with negative impacts on survival in the age of modern EBRT techniques (3). Physicians in the United States reported some training in brachytherapy for cervical cancer during residency, which could have been reflected in moderate percentages of patients receiving brachytherapy (4). Most participants acknowledged the symptoms of cervical cancer, including menstrual bleeding, postmenopausal bleeding, and aggressive vaginal discharge (5). According

to current estimates in Albania, 133 women are diagnosed with cervical cancer each year and since 2009, many patients are treated with brachytherapy following EBRT radiotherapy treatment (6,7). Brachytherapy was found to be a highly effective and safe treatment, offering a good alternative to surgical removal of the prostate, breast and cervix (8). The aim of this study was to study the clinical correlations-imagery of cervical cancer pre- and post-brachytherapy, as well as the effects of tumour reduction due to the use of this radiation therapy.

METHODS

A prospective case series study was conducted during 2009-2012 in the University Hospital Center: "Mother Teresa", Oncology Service. The sample size of the study was 202 females diagnosed with cervical cancer. Sampling technique included consecutive women presented at the hospital and met the criteria below. Inclusion criteria for individuals participating in the study were: a) Patients diagnosed with cervical cancer stages (1B2-4) b) Patients eligible for brachytherapy c) Given informed consent. Clinical and imagery variables were collected during the period of the study. A clinical-questionnaire was used for obtaining clinical data. On the other side, the instrument used for cervical cancer imaging data was Computerized Tomography, which was used at different times, after applying the respective doses of brachytherapy. The socio-demographic information was also collected.

Descriptive statistics were used to report frequencies and percentages. The paired t-test was used to estimate the differences between two variables for the same subject, such as imaging data after applying three doses of brachytherapy**.** In all cases, a P-value ≤ 0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS, version 26.0) and Microsoft Office Excel 2007 were used for all the statistical analyses. All participants in the study were informed about the purpose and objectives of the study. Confidentiality, privacy and voluntary of participation were assured.

RESULTS

The average age of cervical cancer patients was 54.5 ± 9.5. The clinical characteristics of the patients are given in table 1. 31.2 % and 9.9% of the study population, referred they had high blood pressure and diabetes, respectively. In terms of the distribution of signs and symptoms in cervical cancer patients, 27.2% of them had pain in the lower back, 33.2% referred for pain during sex, 6.4% had vaginal bleeding during sex, 24.8% referred changes to the vaginal discharge, and 30.2% had blood in urine. (Table 1)

Table 1: Distribution of symptoms of cervical cancer patients

Clinical variables	N (%)
High blood pressure	
No	139 (68.8)
Yes	63 (31.2)
Diabetes	
No	182 (90.1)
Yes	20 (9.9)
Pain in the lower back	
No	147 (72.8)
Yes	55 (27.2)
Pain during sex	
No	135 (66.8)
Yes	67 (33.2)
Vaginal bleeding during sex	
No	189 (93.6)
Yes	13 (6.4)
Change to the vaginal discharge	
No	152 (75.2)
Yes	50 (24.8)
Blood in urine	
No	141 (69.8)
Yes	61 (30.2)

The Table 2's results showed that tumors <4 cm were more common than tumors >4 cm (58.4% vs. 41.6%). As for the stages of cervical cancer, in our sample patients in stage 2 prevailed with 51%, and then, patients in stage 3, 4 and 1B2, (20.3% vs. 18.8% vs. 9.9%). Almost 93% of the women underwent Pap smear test, with 49% of them resulted positive. 40.1% of the patients underwent surgery (with/without combined radio-chemotherapy), while 59.9% of them have performed one of the forms of chemo-radiotherapy. Only 5.8% of them have performed brachytherapy without combined forms of chemo-radiotherapy. In terms of the severity of side effects reported after brachytherapy, most patients referred to mild effects (42.1%). (Table 2)

Table 2: Distribution of cancer characteristics and treatment's modalities

Cancer variables	N (%)
Tumor Size	
<4 cm	119 (58.4)
>4cm	84 (41.6)
Stages of cervical cancer	
1B2	20 (9.9)
2	103 (51.0)
3	41 (20.3)
4	38 (18.8)
Treatment	
Surgery (with/without combined radio-chemotherapy)	81 (40.1)
Radio-chemotherapy	121 (59.9)
EBRT+Brachytherapy	114 (94.2)
Brachytherapy	7 (5.8)
PAP test	
No	16 (7.9)
Negative	87 (43.1)
Positive	99 (49.0)
Side effects of brachytherapy	
Mild	85 (42.1)
Moderate	45 (22.3)
Severe	45 (22.3)
Very severe	27 (13.4)

Table 3 showed results from paired t tests in different time of application of brachytherapy doses. The mean of tumor reduction size before brachytherapy was 28.3% (±10.0) compared to mean of tumor reduction size after dose 1 of brachytherapy 23.4% (±10.2). This reduction 4.93%, 95% CI (4.56-5.30) was statistically significant t (200)=26.2, p<0.001. The mean of tumor reduction size after dose 2 of brachytherapy 18.4% (±10.0). This reduction 4.93%, 95% CI (4.84-5.01) was statistically significant t (200)=114.0, p<0.001. The mean of tumor reduction size after dose 3 of brachytherapy 8.8% (±9.5). This reduction 9.60%, 95% CI (9.35-9.86) was statistically significant t (200)=74.5, p<0.001. (Table 3)

Table 3: Results from paired t tests in different time of application of brachytherapy doses

		Paired Differences					**t**	**df**	**Sig. (2-tailed)**
		Mean	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**				
					Lower	**Upper**			
Pair 1	Tumor reduction (TR) before brachytherapy (BTH) – TR after dose 1 of BTH	4.925	2.668	.188	4.554	5.296	26.171	200	.000
Pair 2	TR after dose 1 of BTH - TR after dose 2 of BTH	4.925	.608	.043	4.841	5.010	114.891	200	.000
Pair 3	TR after dose 2 of BTH - TR after dose 3 of BTH	9.602	1.828	.129	9.348	9.856	74.479	200	.000

DISCUSSION

The most common clinical presentation among patients suffering from cervical cancer is vaginal contact bleeding (9). Even our study found that a significant portion of patients reported pain and bleeding during sexual contact. However, the same symptoms apart from sexual contact, such as pelvic pain and hematuria, are often reported, perhaps due to under-reporting by stigmatized women of their sexual inter-courses. About 10% of the patients had diabetes, good news, given that the results of a systematic review suggest that diabetes is an important predictive factor for cervical cancer prognosis (10). In a case-control study in the USA, 45% of women with cervical cancer had hypertension, while 39.8% of controls had hypertension, also referring to the study conclusion of a possible association between metabolic syndrome and hypertension (11). Thus, 31.2% of the patients in our study reported having hypertension, but the confounding effect of age should be taken into account. In terms of tumour size and staging, our results showed similar reports only in the literature, with predominance of tumors under 4 cm and stage 2 (12). The diagnostic accuracy of positive high-risk Pap smear test is satisfactory (13). 49% of our contingent had tested positive after performing the test. Surgery and radiotherapy are equally effective in cases of early onset lower-volume disease (14). Thus, approximately 40% of patients underwent surgery, while most of them underwent EBMRT, brachytherapy and concomitant chemotherapy (mainly cisplatin). This treatment scheme targeted patients with later stages 1B2-4. During the treatment periods, the radiation oncologists performed pelvic examinations, blood tests and CT once a week, after each brachytherapy doses. Overall local control rate of the combined therapy is reported to be around 95% (15). Shrinkage of the tumor mass was evident stage by stage in our study, although it cannot be concluded only for the "pure" effect of brachytherapy, thus not considering the effect of EBRT in many cases. In terms of the severity of side effects reported after brachytherapy, most patients referred to mild effects, without excluding that a significant part of them reported severe side effects.

This study may have some limitations, such as the potential selection bias of the case series and the possible informational bias, due to CT interpretation by a radiologist (without further control).

CONCLUSIONS

It is important to be aware of the clinical, imaging and anatomopathological characteristics of cervical cancer that are used to diagnose and treat this disease. The application of brachytherapy with or without external beam radiation therapy leads to a gradual reduction size of about 5 to 10% after each dose, until the tumour mass might fully diminished.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Enes Hafizi, Helidon Nina, Aldo Shpuza et.al. Brachytherapy's clinical-imagery correlates and tumor's reduction outputs among patients with cervical cancer. *International Journal of Research and Review*. 2022; 9(11): 502-506.
DOI: *https://doi.org/10.52403/ijrr.20221166*

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