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The Experience of Pain and Anxiety in Cervical Cancer Patients Undergoing Multiple Fraction High-Dose Rate Brachytherapy: A Prospective Observational Study

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Abstract

Purpose: To evaluate the anxiety and pain levels of cervical cancer patients undergoing intracavitary multifraction high-dose rate (HDR) brachytherapy, as part of a process to develop guidelines for quality patient-centered care. **Methods:** Cervical cancer patients (n = 31) undergoingmultiple fraction HDR brachytherapy treatment at the National Institute of Oncology in Rabat (Morocco) completed ratings of pain and anxiety intensity using 11-point verbal analog scales, at 6 key time points over 2 brachytherapy insertion procedures and 4 brachytherapy fractions. Women were evaluated for psychological status at baseline before starting the brachytherapy process using the Hospital Anxiety and Depression Scale (HADS). Scores were grouped as follows: 0 - 7 = normal, 8 - 10 = borderline, 11 - 21 = abnormal. Factors that could affect anxiety levels such as education level, relationship status, number of pregnancies and prior surgical history were documented. **Results:** Between July and August 2020, 31 women with a median age of 49.6 years were evaluated (range: 27 - 70). The HADS score identified depression in 5 patients (16.1%) and anxiety in 12 patients (38.7%). Throughout both treatment procedures, anticipatory anxiety was reported, with a maximum intensity in the operating room during spinal anesthesia (3.23 ± 1.7) and during applicator insertion (2.97 ± 2.4). Moderate-to-severe anxiety scores were reported in 25.8% and 22.6% of patients respectively. Level of education showed a significant correlation with anxiety scores ($p = 0.027$). Pain increased significantly during the procedure ($p < 0.001$). Bed-rest restriction applicator in situ (4.42 ±

1.4) and applicator removal (4.74 ± 1.5) turned out to be the most painful parts of the procedure. No correlation was found between pain and anxiety levels. **Conclusion:** Intracavitary multifraction high-dose rate brachytherapy is associated with mild to moderate levels of pain and anxiety, although a subset of patients reported more severe symptoms and may require additional medical and psychological support, with particular emphasis on bed-rest duration and applicator removal. The development of effective interventions (both pharmacological and non-pharmacological) is needed to improve women's experiences of brachytherapy for locally advanced cervical cancer.

Keywords

Cervical Cancer, Brachytherapy, High-Dose Rate, Pain, Anxiety

1. Introduction

Cervical cancer is a major cause of female mortality throughout the world and the second cancer in women in Morocco [1]. The standard of care for women diagnosed with locally advanced disease is external beam radiation and concurrent chemotherapy followed by intracavitary brachytherapy. Widely acknowledged advantage of high-dose rate (HDR) brachytherapy over external-beam radiation therapy is dose escalation focally in the tumor, resulting in better sparing of normal tissues [2]. However, brachytherapy is an invasive procedure that can cause a wide range of physical, emotional and psychosocial difficulties. Pain and anxiety have been reported as primary concerns for patients with gynecologic cancers undergoing HDR brachytherapy [3]. However, almost no research has been published on the degree to which these symptoms are experienced by cervical cancer patients during HDR brachytherapy [4].

A better understanding of the unique experiences of this particular group of patients could help healthcare professionals to provide better emotional support and appropriate pain management protocols to meet their needs.

We conducted a pilot study to examine the tolerability of multiple fraction intracavitary high-dose rate (HDR) brachytherapy in cervical cancer patients, specifically to prospectively assess the levels and trajectory of anxiety and pain, in order to identify areas in which improvement is required.

2. Methods

This is a prospective observational study conducted between June and August 2020 at the Brachytherapy Department of the National Institute of Oncology, Ibn Sina Teaching Hospital of Rabat, Morocco.

The Ethics Review Committee approval was obtained for this study.

Eligible women scheduled for HDR brachytherapy were approached with the study information by a radiation oncologist, and were given the opportunity to participate in the study. Informed consent was obtained for patients wishing to

participate.

Eligibility criteria:

- Age ≥ 18 years.
- Histologically proven cervical cancer (FIGO Stages I-IVA).
- Completion of a course of concurrent chemoradiation with curative intent at our institution.
- Referral for intracavitary (tandem applicator with either ring or ovoids) brachytherapy.

Exclusion criteria:

- Inability to communicate or to understand scores because of speech, language or cognitive impairment.
- Psychiatric diagnosis currently being treated.

No patients had to be excluded based on those criteria.

In our institution, applicator placement is completed in the operating room (OR) under spinal anesthesia. Subsequent analgesia consists of intravenous paracetamol and oral anti-inflammatory analgesics as needed for the duration of the treatment planning and delivery. Antidiarrheals and antiemetics are provided based on patient assessment.

After CT-guided brachytherapy planning, patients are treated to a total dose of 28 Gy in four fractions of 7 Gy. Two fractions of HDR brachytherapy are delivered with each applicator insertion, with one overnight stay, then repeated a week later. Between two fractions, patients are hospitalizedand required to complete full bed-rest in a supine position in order to keep the applicators in situ overnight. The average time between the insertion and removal of the applicator is 24 hours and the waiting time on bed-rest between two fractions is 20 hours.

The psychological state of the patients was assessed before starting brachytherapy using the Hospital anxiety and depression scale (*HADS*). Scores were grouped as follows: 0 - 7 = normal, 8 - 10 = borderline, 11 - 21 = abnormal.

A prospective assessment of pain and anxiety levels was completed by the same radiation oncologist using the patients' scoring on a visual analog scale (VAS) (**Figure 1**).

The VAS uses a 11-point scale ranging from 0 (no symptom) to 10 (worst possible symptom).

Using the pain-VAS scoring system, 0 is considered no pain, 1 - 3 is considered mild, 4 - 6 is moderate to severe, 7 - 9 is very severe and 10 is categorized

Figure 1. Visual analog scale.

as worst possible pain.

Using the anxiety-VAS scoring system, 0 is considered "balanced mood", 1 - 3 is considered "mild fear and worry", 4 - 6 is "moderate to severe worry and physical agitation", 7 - 9 is "very severe and strong agitation" and 10 is categorized as "out-of-control behavior and agitation".

Ratings of pain and anxiety were completed at 6 key time points, and at each insertion:

- Time 1: Baseline assessment;
- Time 2: During anesthesia in the OR;
- Time 3: Patient lying in a gynecological position during the insertion procedure;
- Time 4: Right before HDR treatment in the bunker;
- Time 5: On bed rest, applicator *in situ*;
- Time 6: Immediately after removal of the applicator.

The CT imaging, dose calculations, and planning occurred between time points 3 and 4.

Descriptive analysis was used to describe the patient population and anxiety and pain scores.

Data regarding age, relationship status, level of education, number of pregnancies and surgical history were documented.

The primary outcome variables were the VAS pain and anxiety scores. Means (with standard deviation) and percentages are reported to describe the central tendency and dispersion of scores.

Two-tailed student's t-tests were used to test for significance of differences between the first and second insertion mean scores.

The raw scores were then grouped into two categories: 0 - 3, mild symptoms; 4 or more, moderate-to-severe symptoms.

Baseline pain and anxiety score groups were compared with each time score groups using the McNemar's test.

Univariate analysis of variance was used to explore correlations between anxiety and pain levels and the following variables: relationship status, education level, number of pregnancies, surgery history.

Chi-square test was used to explore a correlation between pain and anxiety levels at each time point.

A p value of 0.05 or less was considered statistically significant.

All analyses were conducted using the SPSS® Statistics software application (version 20, IBM®, U.S.A.).

3. Results

From June to August 2020, 31 cervical cancer patients requiring HDR brachytherapy with uterine (tandem) and vaginal (ring/ovoid) applicators were recruited.

Patient ranged in age from 27 and 70 years (median 49.6 years). Sixteen

women were in pre-menopause and 15 women were in menopause. The median number of pregnancies was four (range 1 - 8), and 23 women (74.2%) had at least three children. Eleven patients had a surgical history. Five were divorced or separated at the time of collection, 5 were widows, while the remaining 21 were married. Twenty participants had never been to school, 4 received primary schooling, 5 completed secondary schooling and 2 completed their tertiary education.

Table 1 summarizes patient demographics and characteristics.

The HADS questionnaire identified depression in 5 patients (16.1%) and anxiety in 12 patients (38.7%) (Table 2).

At baseline measurement, before initiating HDR brachytherapy, 26 patients (83.9%) reported mild anxiety and moderate or severe anxiety was identified in 5 patients (16.1%).

Anxiety levels were similar at baseline before the second insertion procedure, with 25 patients (80.6%) and 6 patients (19.4%) reporting mild versus moderate

Table 1. Patients characteristics.

Characteristics	Value (n)	Percentage %
Relationship status		
Divorced	4	12.9
Separated	1	3.2
Married	21	67.7
Widow	5	16.1
Number of pregnancies		
<4	15	48.4
4 or more	16	51.6
Level of education		
Illiterate	20	64.5
Primary schooling	4	12.9
Secondary schooling	5	16.1
Tertiary education	2	6.5
Occupation		
Employed	9	29.0
Housewife/Unemployed	22	71.0
ECOS performance status		
0	17	54.8
1	14	45.2
Surgical history		
Yes	20	64.5
No	11	35.5

or severe anxiety respectively (Table 3).

Throughout the first insertion, anxiety mean scores were the highest before the procedure in the OR during spinal anesthesia (3.23 ± 1.7) and during the insertion procedure (2.97 ± 2.4), with 25.8% and 22.6% of patients reporting moderate to severe anxiety respectively. A resolution of anxiety occurred when leaving the operating room (1.26 ± 1.1), to increase again at bed-rest overnight and upon removal of the applicator (2.48 ± 1.8 and 3.10 ± 1.7 respectively) (Table 3 and Table 4).

During the second insertion, the proportion of patients reporting moderate or severe anxiety remained high during times 1 to 3, however anxiety levels declined

Table 2. Hospital-anxiety-and-depression-scale results in cervical cancer patients before brachytherapy.

HADS score group	Anxiety n (%)	Depression n (%)
Normal (0 - 7)	13 (41.9)	19 (61.3)
Borderline (8 - 10)	6 (19.4)	7 (22.6)
Abnormal (11 - 21)	12 (38.7)	5 (16.1)

Table 3. Anxiety group scores reported by patients over the two brachytherapy insertions.

	First insertion		Second insertion	
	Anxiety Group scores n, (%)			
Time	Mild	Moderate or severe	Mild	Moderate or severe
1	26 (83.9)	5 (16.1)	25 (80.6)	6 (19.4)
2	23 (74.2)	8 (25.8)	24 (77.4)	7 (22.6)
3	24 (77.4)	7 (22.6)	26 (83.9)	5 (16.1)
4	31 (100)	0	31 (100)	0
5	27 (87.1)	4 (12.9)	31 (100)	0
6	23 (74.2)	8 (25.8)	26 (83.9)	5 (16.1)

Table 4. Mean visual analog scores for anxiety during HDR brachytherapy for cervical cancer.

	First insertion		Second insertion	
Time	Median	Range	Median	Range
1	2.39 ± 1.9	0 - 8	2.13 ± 1.8	0 - 6
2	3.23 ± 1.7	1 - 8	3.06 ± 1.9	1 - 10
3	2.97 ± 2.4	0 - 10	2.81 ± 1.3	2 - 6
4	1.26 ± 1.1	0 - 4	0.48 ± 0.62	0 - 2
5	2.48 ± 1.8	0 - 8	0.42 ± 0.62	0 - 2
6	3.10 ± 1.7	0 - 7	2.97 ± 1.3	0 - 6

at times 4 and 5. The difference in the percentage of patients reporting moderate or severe anxiety between time 1 and times 4 and 5 (19.4% vs 0%) was statistically significant (p 0.031).

In comparison with the first insertion, a significant decrease in anxiety mean scores was observed at time 5 during the second insertion ($p < 0.001$) (Table 5).

Level of education showed a significant correlation with anxiety scores ($p = 0.027$). Relationship status, number of pregnancies or having ever had a surgery showed no significant correlation with anxiety.

Anesthesia was found to be effective in preventing pain during applicator insertion in the operating room (0.61 ± 1.9). Levels of pain started to increase gradually from time 3, as the anesthesia wore off and persisted for hours after the procedure. Pain scores were the highest at times 5 and 6, after patients were transferred to their room (4.42 ± 1.4), as complete bed-rest restriction with the applicator in situ overnight was described as the most uncomfortable experience. Removal of the applicator was equally painful (4.74 ± 1.5) (Table 6). The difference in the percentage of patients reporting moderate or severe pain between time 1 (0%) and times 5 (48.4%) and 6 (64, 5%) respectively, was statistically

Table 5. Comparative analysis of anxiety mean scores between the first and second insertion.

Anxiety	T-Test					t	p value
	Mean	Standard Deviation	Standard Error mean	95% Confidence interval of the difference			
				Lower	Upper		
A1.1 - A2.1	0.258	1.413	0.254	−0.260	0.777	1.017	0.317
A1.2 - A2.2	0.161	1.293	0.232	−0.313	0.636	0.694	0.493
A1.3 - A2.3	0.161	1.614	0.290	−0.431	0.753	0.556	0.582
A1.4 - A2.4	0.774	0.920	0.165	0.437	1.112	4.683	**0.000**
A1.5 - A2.5	2.065	1.750	0.314	1.423	2.706	6.569	**0.000**
A1.6 - A2.6	2.677	1.777	0.319	2.025	3.329	8.387	0.324

Table 6. Mean visual analog scores for pain during HDR brachytherapy for cervical cancer.

	First insertion		Second insertion	
Time	Median	Range	Median	Range
1	0.0 ± 0.0	0	0.03 ± 0.1	0 - 1
2	0.55 ± 0.9	0 - 3	0.61 ± 1.5	0 - 8
3	0.61 ± 1.9	0 - 10	0.32 ± 1.1	0 - 6
4	2.61 ± 1.2	0 - 5	2.58 ± 1.7	0 - 5
5	4.42 ± 1.4	2 - 7	4.52 ± 1.5	2 - 9
6	4.74 ± 1.5	2 - 8	4.32 ± 1.6	2 - 8

Table 7. Pain group scores reported by patients over the two brachytherapy insertions.

	First insertion		Second insertion	
	Pain Group scores n, (%)			
Time	Mild	Moderate or severe	Mild	Moderate or severe
1	31 (100)	0	31 (100)	0
2	31 (100)	0	30 (96.8)	1 (3.2)
3	30 (96.8)	1 (3.2)	30 (96.8)	1 (3.2)
4	28 (90.3)	3 (9.7)	29 (93.5)	2 (6.5)
5	16 (51.6)	15 (48.4)	21 (67.7)	10 (32.3)
6	11 (74.2)	20 (64.6)	19 (61.3)	12 (38.7)

Table 8. Comparative analysis of pain mean scores between the first and second insertion.

Pain	T-Test					t	p value
	Mean	Standard Deviation	Standard Error mean	95% Confidence interval of the difference			
				Lower	Upper		
P1.1 - P2.1	−0.032	0.180	0.032	−0.098	0.034	−1.000	0.325
P1.2 - P2.2	−0.065	1.788	0.321	−0.720	0.591	−0.201	0.842
P1.3 - P2.3	0.290	2.341	0.420	−0.568	1.149	0.691	0.495
P1.4 - P2.4	0.032	1.110	0.199	−0.375	0.439	0.162	0.873
P1.5 - P2.5	−0.097	1.446	0.260	−0.627	0.434	−0.373	0.712
P1.6 - P2.6	0.419	1.628	0.292	−0.178	1.017	1.434	0.162

significant ($p < 0.001$) (Table 7). Pain levels and trajectory remained similar week to week over the two treatment procedures, with no significant difference in mean pain scores (Table 8).

Education level, relationship status, number of pregnancies or surgery history showed no significant correlation with pain scores.

Comparative analysis of pain and anxiety group scores at each time point did not identify a significant correlation between pain and anxiety levels.

4. Discussion

International guidelines for brachytherapy treatment of locally advanced cervical mainly focus on treatment planning and dose reporting. There is little or no mention of the delivery of clinical aspects relating to patient experience, psychological repercussions and any impact on quality of life after treatment [5] [6] [7]. At present, there is little data on methods to improve the patients experience with respect to pain and anxiety.

The HADS questionnaire screened unknown depression and anxiety in 16.1% and 38.7% patients, respectively, which underlines the importance of evaluating the psychological state of our patients in order to provide appropriate care.

In this study, we examined patient reports of pain and anxiety during multi-fraction HDR brachytherapy. To our knowledge, this is the first study to assess pain and anxiety levels and trajectories in cervical cancer patients undergoing HDR brachytherapy in Morocco. Although treatment was relatively well tolerated by most patients, up to 25% and 64% experienced moderate or severe anxiety and pain respectively.

Women in our study feared the procedure before receiving the first treatment and even after having had one, with no significant difference in anxiety levels before starting the second insertion procedure compared to the first insertion.

Our results are consistent with the literature. In a recent systematic literature review, nine of ten studies regarding psychological issues reported that brachytherapy caused anxiety and distress for most women [4]. Rollison and Strang described anticipatory anxiety before brachytherapy procedures in 17 of 20 patients, although these scores were not quantified [8]. Likewise, E. Wiebe *et al*. reported the highest mean anxiety scores before the brachytherapy procedure [9]. In a study with patients undergoing HDR brachytherapy with conscious sedation, pretreatment distress was scored at 2.55 versus a mean score of 2.39 in our population [10].

Some studies reported that anxiety levels were not reduced prior to subsequent insertions, concluding that women did not adapt [4] [11]. However, our results differ in part since we observed a significant decrease in anxiety between the first and second procedure, after leaving the operating room and during the waiting time on bed-red (time 5), perhaps because of reassurance and support by medical staff. Another reason may be that women showed the ability to adjust to this known experience, with a sense of helplessness and resilience.

Sparse data exist on the possible factors influencing anxiety levels. In 146 women treated for gynecological malignancies using intracavitary brachytherapy, Kamer *et al*. found anxiety significantly lower for married or widowed women and those with two or more children [12]. In our sample, marital status and number of pregnancies was not related to anxiety levels. However, education level showed a significant correlation with anxiety scores, as illiterate women exhibited lower levels of anxiety.

Available studies indicate that pain is the most frequently reported stressful experience during gynecological brachytherapy [4]. According to Kwekkeboom, Dendaas, Straub *et al*. women diagnosed with cancer experience varying degrees of pain during brachytherapy [4]. In addition, Rollison and Strang found more than half (13 of 20) of the patients in their study experienced moderate to severe pain during this procedure [8].

In our sample, pain increased significantly after insertion to reach the highest point during bed-rest applicator in situ and applicator removal. These findings

suggest that spinalanesthesia was effective to alleviate the pain during the insertion procedure. However, the nonopioid analgesics received afterwards were not sufficient for pain management for the duration of the insertion. This argues in favor of revising pain management protocols, with particular emphasis on bed-rest duration and applicator removal.

The complexity of image-guided brachytherapy to achieve a highly conformal individual plan increases planning time thereby increasing the time from applicator insertion to treatment delivery.

To date, there is no consensus on the most effective analgesia in published recommendations for high-dose rate (HDR). For intracavitary brachytherapy applicators that remain in situ over several hours, approaches to analgesia vary between centers. Oral or intravenous/subcutaneous opioids and oral transmucosal fentanyl citrate have been reported in the literature and may provide options for pain control at identified points in the procedure likely to cause higher pain, such as transfers for imaging, bed confinement or applicator removal [4] [13].

Besides drug options, effects of non-pharmacological interventions were examined in two studies. Relaxation and guided imagery and a music relaxation video showed significant benefits for women undergoing long duration brachytherapy procedures. They were found to be simple, effective, non-invasive and cheap [14] [15].

Our study has limitations. A simple study with a small sample size focusing on women treated in the public healthcare sector might not be representative of patients in different healthcare settings or from different cultural backgrounds. Further research is needed to gain a deeper understanding of this phenomenon.

5. Conclusions

High-dose rate uterovaginal brachytherapy for cervical cancer experience mild to moderate levels of pain and anxiety. Level of education showed a significant correlation with anxiety scores.

There is a need for better pain management strategies, patient information and support and the development of non-pharmacological interventions to improve experiences, particularly for the group of patients who experience more severe pain or anxiety.

Further studies should be carried out to define patient-centered recommendations and provide quality care to this group of women.

Competing Interests

The authors declare no competing interests.

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