

## **Fatigue in Cancer Patients Receiving Radical Anti -Cancer Treatments**

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### **Abstract**

*Side effects from anti-cancer treatments remain inevitable. Cancer related fatigue (CRF) is a distressing effect experienced by many cancer patients, however, it remains a side effect that is under-reported and under treated. The aim of the study was to explore the prevalence and general patterns of fatigue in patients diagnosed with various types of cancers. In addition, the study explored whether tumour site and different multi-modal combinations of treatment, influenced fatigue levels. A survey, using a self-developed questionnaire, was conducted in three oncology centres in Gauteng, South Africa. Results showed that 80% of the participants experienced fatigue at the end of treatment, irrespective of the diagnosis. Moreover, various patterns for CRF were noted, with the type of cancer and anti- cancer treatments received, influencing fatigue levels. It is therefore imperative that CRF be reported and managed, to ensure a better quality of life (QoL) for all cancer patients.*

**Keywords:** cancer; fatigue; prevalence; anti- cancer treatment

Cancer remains a lifetime health problem in spite of the advances made in the field of oncology. Although multimodal treatments (a combination of various types of anti-cancer treatments) are commonly administered to improve local control and survival rates, cancer and the side effects of the treatment received, remains problematic (Wang, Janjan, Guo, Johnson, Engstrom, Crane, Mendoza & Cleeland, 2001). Furthermore, patients who receive multimodal treatments may be at greater risk of experiencing severe side effects as more tissue becomes targeted with each modality used (Bomford & Kunkler, 2003; Irvine, Vincent, Graydon, Bubela & Thompson, 1994).

While considerable improvements have been made in the detection and control of side effects such as pain, nausea and vomiting, cancer related fatigue (CRF) remains a major concern for both the patient and health professional. Approximately 70%-100% of cancer patients experience CRF (Ahlberg, Ekman & Gaston-Johansson, 2005; National Comprehensive Cancer Network (NCCN), 2009). Prevalence rates for CRF have been correlated with the type of cancer and the modality used to administer treatment. It has also been noted that CRF could be experienced from the onset of treatment, during or after treatment, irrespective of the stage of disease (Irvine, Vincent, Graydon & Bubela, 1998).

It is important to note that CRF can threaten the success of anti-cancer treatments. If under reported or inadequately managed, it could result in failure to complete the prescribed treatment due to the extreme exhaustion experienced. An interruption in the treatment schedule could lead to a decrease in survival rates (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre & Morrow, 2007).

Radical anti-cancer treatments should therefore not only be aimed at cure, but should include a concern for the individual's quality of life. CRF should therefore be identified, documented and managed accordingly for all cancer patients.

Conceptualizing fatigue can be a difficult task as it is a symptom that is frequently experienced in the general population. A better understanding of CRF is hence required and may only be achieved if one is able to distinguish CRF from normal fatigue. Fatigue in the general population is usually relieved after having "a good night's sleep." Contrary to this, fatigue experienced by the cancer patient lasts longer, is more intense and stressful and is not easily relieved by rest (Van Weert, Hoekstra-Weebers, Otter, Postema, Sanderman & Van der Schans, 2006; Wu & McSweeney, 2006). For the purpose of this study then, CRF was defined as "a distressing persistent subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (NCCN, 2009).

#### Problem statement

In South Africa, the incidence of cancer seems to be escalating, which has been attributed to lifestyle changes. Statistics suggest that at least one in six South African men and one in seven South African women will develop a form of cancer (Cancer in South Africa, n.d., para.1). CRF occurring as a result of anti-cancer treatments has received little attention in the South African radiotherapy setting. In South Africa, patients generally tend to present with more advanced stages of disease as opposed to patients in developed countries, yet these patients still receive radical anti-cancer treatment schedules. Consequently results obtained in international fatigue studies may not be applicable to the South African setting, as international fatigue studies relate to early stages of disease where the volume of tissue treated may well be smaller than that in radical treatment schedules administered in a South African setting. Quality of life in the cancer patient is severely disturbed by fatigue. Therefore the question that arises from the problem statement is "What is the prevalence and general fatigue patterns in a South African cancer population during a course of radical anti-cancer treatment". Furthermore does the tumour site influence the level of fatigue experienced and do different multi-modal combinations of treatment result in varying fatigue levels?

#### Research objective

The objective was to explore the prevalence and general patterns (frequency, extent and severity) of fatigue in patients diagnosed with various types of cancers, during a radical course of anti-cancer treatment. For the purpose of this study, radical anti-cancer treatment refers to patients who received any one of the following treatment combinations: radiotherapy alone or surgery and radiotherapy or chemotherapy and radiotherapy or surgery, chemotherapy and radiotherapy. A further objective of the study was to assess if the tumour site and different treatment combinations, influenced fatigue levels.

#### **Methodology**

A survey was used. This method allowed for the characteristics of the sample to be obtained and addressed specific research questions (Burns & Grove, 2005; Pallant, 2009). Comparisons could therefore be made between the fatigue levels experienced and the variables selected (type of treatment received and tumour site). Findings of the current study could further be compared to those cited in the literature reviewed.

#### Population and sampling

The population consisted of both male and female patients diagnosed with either lung, cervix, breast, rectum, prostate or head and neck cancers who completed a radical course of radiation therapy at one of three oncology centres in Gauteng who consented to participate in the study. A total of 60 questionnaires was distributed to each oncology centre. The following specific inclusion criteria were applied:

- Patients treated with curative intent using any one of the following treatment combinations: radiotherapy alone; surgery and radiotherapy; chemotherapy and radiotherapy or surgery, chemotherapy and radiotherapy
- The total radiation dose  $\geq 50$  Gray (Gy).
- Age > 18 years.
- Performance status of ECOG  $\leq 3$
- Signed informed consent.

A purposive sampling method was used to select participants that met with the inclusion criteria. In total a sample of 180 participants was achieved. However seven of the 180 returned questionnaires were excluded from the sample. Two participants received a dose of less than 50Gy and five were excluded due to half of the questionnaire being inadequately completed.

### **Data Collection and Analysis**

Data collection tools such as the Brief Fatigue Inventory(BFI; Cronbach  $\alpha = 0.96$ ) was initially considered for use. However, due to the fact that the BFI scale was limited to assessing the severity and impact of fatigue only over the past 24 hours, contrary to the study's objective which focused on the fatigue experienced over a complete radical course of treatment, it could not be utilized.

A self-developed questionnaire was thus designed in consultation with a statistician and was constructed in line with the objectives of the study. The questionnaire allowed for the following information to be obtained: medical data of the patient, demographical data and information with regards to the extent, frequency and severity of fatigue experienced during treatment and variables that may have influenced the level of fatigue. Research assistants were utilized to assist with the facilitation of the research process.

Reliability and validity of the questionnaire was tested by means of a pilot study to assess whether any amendments were necessary before the actual data was scheduled to be collected. The questionnaire allowed relevant information to be captured in a systematic and structured manner, thus relationships between the selected variables would be measurable. All participants from the pilot study were excluded from the research study. Validity of the research process could further be substantiated as specific inclusion criteria were set for the sample population of the study. The research assistants appointed were qualified therapy radiographers and were therefore able to ensure that the sample required was obtained correctly. The questionnaire was completed by the research participants on the last day of their radiotherapy treatment, as radiotherapy was the common denominator in the treatments received, and was the modality that was administered last when multi-modal treatment was given. The researcher then collected the questionnaires on an adhoc basis until the required sample of 180 completed questionnaires was obtained.

The Statistical Package for Social Science (SPSS), version15, was used to analyze the data. Descriptive statistics was used to describe the sample characteristics (percentage, mean, standard deviation) and address the research questions. Inferential statistics were used to draw conclusions with regards to the comparisons made between the different cancer groups and the treatment received.

Normality of the data was ascertained through the Kolmogorov-Smirnov test (Pallant, 2009). One-way ANOVA tests were used when more than two groups were explored and showed whether or not the means of the various groups were significantly different from one another. An F ratio was calculated which illustrated the variance between groups divided by the variance within the groups. Post hoc Scheffe tests were further conducted to determine if the differences between groups could be identified. The Pearson correlation was calculated to explore the strength of the relationship between variables. The level of significance for all tests was at the .05 level.

### **Ethical Considerations**

Permission to conduct the study was obtained from the three designated oncology treatment centers in Gauteng. Ethical clearance was sought and approval given from the University of Johannesburg's Faculty of Health Sciences Research Ethics Committee (42/07) and the University of the Witwatersrand Human Research Ethics Committee (R14/49).

Questionnaires included in the study were coded using numbers only, thus ensuring the confidentiality and anonymity of the participants in the study. In addition, the researcher used colour coding to differentiate between participants according to the centre at which they received their treatment. Although the researcher used this method, at no time was the name of the centre disclosed in the results.

### **Findings**

The majority of the participants were females (74.6%; n=129) and presented with breast cancer (n=80; 46,2%). Most participants received multimodal treatment (n=132; 7%). The mean age was 54 years, with the youngest participant 21 years of age and the oldest 87 years. The characteristics of the participants are shown in Table "1" (n=173).

For the purpose of statistical analysis, the six tumour sites were grouped as follows: group 1-breast cancer patients; group 2- prostate cancer patients; group 3- cervical cancer patient and group 4- other (included lung, head and neck and rectal cancer patients)

### **Patterns of Fatigue**

The results presented in this section answers the first research question and provides an overview of the prevalence and general fatigue patterns among the population surveyed. Participants who did not complete this section of the questionnaire (n=20) were excluded from the analysis. The Pearson's correlation test illustrated a positive relationship between the extent of fatigue experienced and the duration of radiation therapy ( $r = 0.74$ ,  $n = 153$ ,  $p < 0.05$ ), indicating that fatigue levels increased as treatment progressed in this population. The mean for the extent of fatigue experienced during radiotherapy was 3.16 (n=153) reflecting high fatigue levels and 1.88 (n=153) reflecting low fatigue levels at the end of the treatment.

In addition to exploring the extent of fatigue, the frequency of fatigue experienced during treatment was recorded. The prostate and "other" group reported to be more often fatigued than the breast and cervical cancer groups. As a result, the age of the respective groups were taken into consideration to assess if a correlation could be made. The mean age for each of the groups was as follows: breast = 51 years, cervix = 50 years, prostate = 63 years and other = 59 years. The results could therefore possibly be explained by the lower mean age of the breast and cervix groups. Younger patients are most likely able to cope better with the demands of radical treatment protocols than older patients.

### **Tumour Site**

This section answers the second research question. The ANOVA test showed no significant differences between fatigue and the tumour sites both during and at the end of treatment, at the 0.05 level ( $p = 0.389$  during treatment and  $p = 0.120$  at the end of treatment).

Furthermore, participants were asked to indicate at which point during their course of treatment, they experienced the most fatigue (severity). Results indicated that for all four groups, the highest score was observed towards the end of treatment. It appeared though, that the prostate and "other" group experienced higher scores compared to the breast and cervix group in this category. Figure "1" shows the mean scores for the various groups. Interestingly, both the breast and cervix groups experienced high fatigue scores throughout treatment.

### **Type of Treatment Received**

This section answers the third research question. The ANOVA test showed no significant differences between the groups during treatment,  $p = 0.140$ . Contrary to this, a significant difference was found when the test was performed at the end of treatment,  $p = 0.022$ . The post hoc Scheffe test was used to assess where the differences occurred. Results of the test are shown in Table "2".

The extent of fatigue in patients who received surgery, chemotherapy and radiotherapy was found to be higher relative to the other three groups  $p = 0.046$ . In addition, although no significant result was obtained, it was noted that severe fatigue was mostly experienced towards the end of the course of radiotherapy for each of the respective treatment groups.

The study found no statistical difference between the frequency of fatigue and the type of treatment ( $p = 0.983$ ). However Figure "2" illustrates that participants who received surgery and radiation were less often fatigued when compared to the other three groups.

## **Discussion**

### **Prevalence and Patterns of Fatigue**

Fatigue has been recognized as the most common side effect that cancer patients experience (Hofman, Morrow, Roscoe, Hickok, Mustian, Moore, Wade & Fitch, 2004; Stone, Richardson, Ream, Smith, Kerr & Kearney; 2000). In addition, it has been noted that CRF differs from the fatigue experienced in normal healthy individuals (Irvine et al., 1994). The findings of this study revealed that as many as 80% of the participants experienced fatigue during their course of treatment, irrespective of the diagnosis. These scores appear to be in line with the prevalence rates of fatigue cited in other literature studies, i.e. 30% - 90% during the course of treatment (Breitbart, Cella, Groopman, Horning, Itri, Johnson, Miaskowski, Scherr, Portenoy & Vogelzang, 2000; Cella, Davis, Breitbart & Curt, 2001; Hofman et al., 2007; Van Weert et al., 2006 ; Wang et al., 2001).

With regards to the patterns of fatigue, it was found that the severity of fatigue increased over the course of treatment. These findings concur with those cited by Ahlberg et al. (2005), Irvine et al. (1994), Prue, Allen and Gracey (2010) and Wang et al. (2001). Wang et al.(2001) reported that 67% of their sample population experienced an increase in fatigue during radiotherapy, whilst 31% experienced their worst fatigue at the end of treatment. Conversely, Hickock, Roscoe, Morrow, Mustian, Okunieff and Bole (2005) noted significant increases in the frequency and severity of fatigue after the third week of radiotherapy treatment (without concurrent chemotherapy), in patients with different types of cancer. Janaki, Kadam, Mukesh, Nirmala, Ponni, Ramesh & Rajeev (2010) further indicated that patients report a degree of fatigue before the onset of treatment and therefore researchers are of the opinion that baseline fatigue may contribute to the fatigue experienced within the first two weeks of treatment. An increase in fatigue scores during radiotherapy treatment could moreover be attributed to the side effects experienced, as these effects generally start at the beginning of the third week of treatment (Wang et al., 2001).

While many participants in the current study reported to be more fatigued towards the end of treatment, the mean score obtained for the extent of fatigue immediately post treatment was slightly lower than the score obtained during treatment. In a meta-analysis conducted by Jacobsen and Thors (2003), similar patterns were observed when various end points were used post treatment, i.e. from three to fourteen months post treatment. Although the results of the current study may seem contradictory in that patients reported more fatigue towards the end of treatment and then reported to be less fatigued immediately upon completing treatment, when examining the results from a different perspective, a decline in fatigue scores may well be accounted for by the fact that at this stage, side effects of treatment are experienced to a smaller degree, as appropriate management strategies are utilized, thus reducing fatigue levels. In addition, patients are more likely to have settled into a daily routine, thus reducing anxiety levels and hence fatigue.

### **Factors Influencing Levels of Fatigue**

In view of the fact that a trend was found between the extent of fatigue and progression of treatment, factors such as the tumour site and type of treatment received were statistically explored to establish whether they contributed to the fatigue levels. These two variables were specifically selected as they were identified by Dagnelie et al. (2007), Hickok et al. (2005) and Hofman et al. (2007), as being aetiological factors of fatigue. Results showed that participants who received surgery, chemotherapy and radiation therapy, were more frequently fatigued and subsequently reported higher levels of fatigue relative to those who received chemotherapy and radiation therapy, or surgery and radiation therapy, or radiation therapy alone. Multimodal treatments generally exacerbate side effects, thus increasing fatigue (Prue et al., 2006). Therefore results obtained in the study could be attributed to the management of the patients, since the sample of this study comprised to a large extent of breast and cervix cancer patients, where multimodal treatment regimes are often used to improve local control. For this study, then, it may be deduced that the type of treatment participants received did impact on the frequency of fatigue experienced during the course of radiotherapy, and seem to be comparable with the results obtained by Van Weert et al. (2006).

No significant correlation was found between the tumour site and extent of fatigue both during and after treatment in the current study. The results were contrary to the findings by Hickok et al. (2005), but in line with those of Irvine et al. (1998) who studied the pattern of fatigue longitudinally in a sample comprising of breast, prostate, lymphoma and ovarian cancer patients. Data indicated that the prostate patients and the participants marked as “other” reported to be more often fatigued, and experienced more fatigue towards the end of radiation therapy compared to the breast and cervical cancer participants. This could be ascribed to the difference found in the mean ages between the groups. Alternatively the treatment technique used i.e. whole pelvis radiotherapy, could have had an influence on the results. Conversely, comparable results would have then been expected for the cervix cancer participants as these patients have similar pelvic volumes treated.

In summary, various levels of CRF can be experienced by cancer patients during a course of radical radiotherapy. Although aetiological factors were not a focus of this research study, it seems that there are factors such as the type of treatment administered that can influence the extent, frequency and severity of CRF.

### **Limitations of the Study**

The study made use of a self-developed questionnaire. The use of a more reliable and validated questionnaire could have produced a different outcome. In addition, the study did not exclude patients with other co-morbidities or patients on concurrent medications that could have influenced fatigue levels.

Many patients received chemotherapy, however it was not clear whether the intensity of the chemotherapy had any impact. More disease related and treatment details need to be recorded in the future. The current study did not assess baseline fatigue which could have influenced the results of the study. Although the sample was representative of the centres selected, this clearly is not representative of the entire target population.

### **Conclusion and Recommendations**

CRF is a symptom that is generally experienced in cancer patients, irrespective of the diagnosis or type of treatment received. The study confirmed the prevalence of fatigue in cancer patients after receiving a radical course of radiation therapy, administered either as a definitive form of treatment, or in combination with other anti-cancer treatments. In addition, results confirmed that the patterns for CRF were similar to those cited in the literature.

Qualitative as well as quantitative longitudinal studies should however be conducted throughout oncology centres in South Africa to obtain a more accurate overview of CRF in cancer patients. The study should be replicated using validated multidimensional assessment tools since CRF is subjective in nature. Future fatigue studies should take “baseline” fatigue into account, as research has indicated that this may contribute to increase fatigue levels in cancer patients. Patients should additionally be encouraged to write self-reports on when their fatigue levels increase and which factors are responsible for a rise in their fatigue levels. Research should be undertaken with particular reference to the aetiological factors of CRF in order for this side effect to be effectively managed.

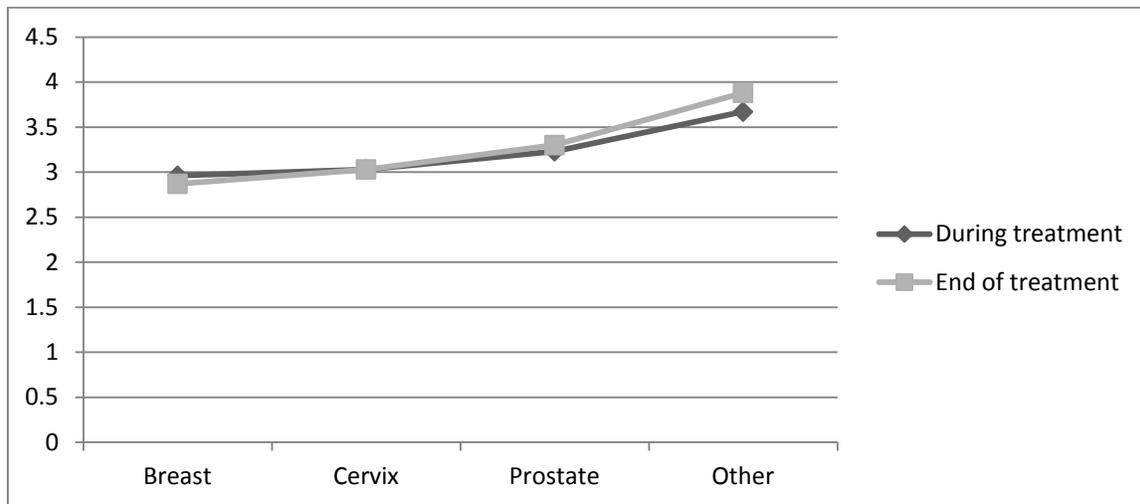
As healthcare providers we should become more aware of this side effect, offer the guidance and support that cancer patients seek from the onset of diagnosis, as all patients have the right to a good health service. Health professionals should not only focus on aim of the treatment, but also, on the quality of life of cancer patients.

**Table 1: Characteristics of the Study Population (n=173)**

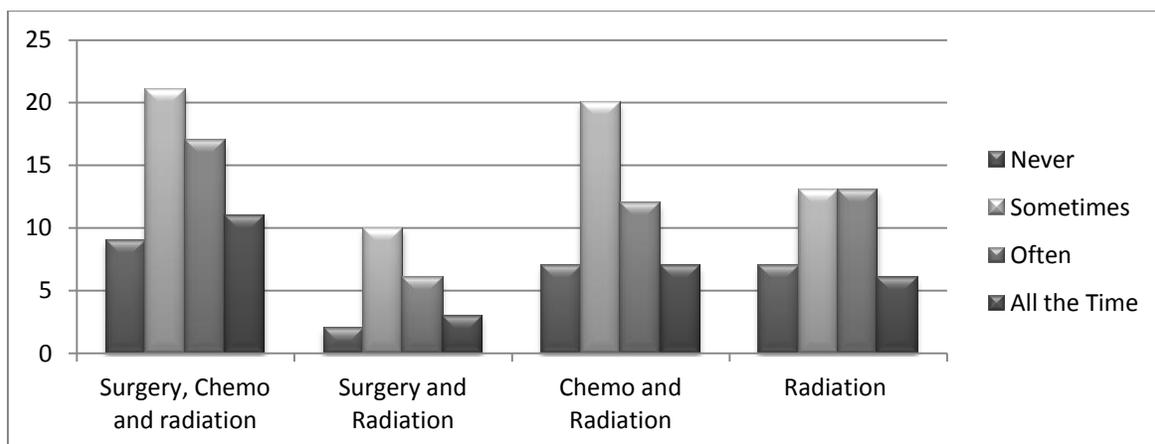
	%	n
<b>Tumour site</b>		
Lung	5.2	9
Breast	46.2	80
Cervix	21.4	37
Rectum	2.9	5
Prostate	16.2	28
Head and neck	8.1	14
<b>Gender</b>		
Male	25.4	44
female	74.6	129
<b>Type of treatment</b>		
Surgery, chemotherapy and radiation therapy	34.1	59
Surgery and radiation therapy	12.7	22
Chemotherapy and radiation therapy	29.5	51
Radiation therapy only	23.7	41
<b>Age</b>		
21-30 years	2.9	5
31-40	15.0	26
41-50	17.9	31
51-60	30.0	52
61-70	28.9	50
71-80	4.6	8
81-90	0.6	1
<b>Total</b>	100%	173

**Table 2: Post Hoc Scheffe Test For Extent of Fatigue at the End of Treatment vs. Type of Treatment**

Multiple comparisons						
(I)	(J)	Mean difference (I-J)	Std. error	Sig.	95% confidence interval	
					Upper bound	Lower bound
Surgery, chemo and radiation	Surgery and radiation	0.524	0.433	0.692	-0.70	1.75
	<b>Chemo and radiation</b>	<b>1.007(*)</b>	<b>0.352</b>	<b>0.046</b>	<b>0.01</b>	<b>2.00</b>
	Radiation only	0.881	0.365	0.125	-0.15	1.91
Surgery and radiation	Surgery, chemo and radiation	-0.524	0.433	0.692	-1.75	0.70
	Chemo and radiation	0.483	0.446	0.759	-0.78	1.74
	Radiation only	0.357	0.456	0.893	-0.93	1.65
Chemo and radiation	<b>Surgery, chemo and radiation</b>	<b>-1.007(*)</b>	<b>0.352</b>	<b>0.046</b>	<b>-2.00</b>	<b>-0.01</b>
	Surgery and radiation	-0.483	0.446	0.759	-1.74	0.78
	Radiation only	-0.126	0.379	0.991	-1.20	0.95
Radiation only	Surgery, chemo and radiation	-0.881	0.365	0.125	-1.91	0.15
	Surgery and radiation	-0.357	0.456	0.893	-1.65	0.93
	Chemo and radiation	0.126	0.379	0.991	-0.95	1.20



**Figure 1: Extent of Fatigue During and at the End of Treatment for the Four Groups**



**Figure 2: Frequency of Fatigue versus Types of Treatment (N = 164)**

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