PREVALENCE OF FATIGUE AMONG CANCER PATIENTS UNDERGOING EXTERNAL RADIOTHERAPY

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Abstract. Between July 1999 to November 2000, 115 patients undergoing radiotherapy were evaluated for the development of treatment-related fatigue, using a modified Piper's fatigue scale. The above scale determines 4 dimensions of fatigue *ie* behavioral severity (6 items), affective meaning (5 items), sensory (5 items), and cognitive mood (6 items). Radiotherapy was delivered to the head and neck, breast, pelvis, and miscellaneous sub-sites. The area of the radiation field ranged from 25 to 480 cm^2 (median 156 cm^2). Forty-three percent of patients experienced significant fatigue, which altered their work environment. The individual components of fatigue were behavioral severity 25%, affective meaning 21%, sensory 18%, and cognitive mood 16%. Significant radiotherapy-related fatigue was higher in patients treated with advanced-stage disease, large radiotherapy field area, and low pre-radiotherapy hemoglobin level.

INTRODUCTION

Radiation therapy is an important treatment modality for the management of cancer, where a precise and homogenous dose of ionizing radiation is delivered to the tumor. During exposure to radiation, the body experiences stress at the cellular and psychological levels. Often radiotherapy-related fatigue goes unnoticed and undiscovered, due to underestimation of its manifestation. Under-reporting of treatment-related fatigue is due to lack of communication on the part of the patient, as well as the treating oncologist. Three out of four patients undergoing anticancer treatment suffer from debilitating fatigue at least every week (Servaes *et al*, 2002). The causes of cancer fatigue are manifold, ranging from anemia, the advanced cancer itself, lack of mobility, depression, stress, mutilating surgery, chemotherapy, and radiotherapy.

Recently cancer fatigue has been highlighted as an important symptom of cancer that concerns patients (Portenoy, 2000). In an optimistic report, cancer fatigue was found to affect 76% of patients (Curt, 2000). Two-thirds of patients experienced disturbance in their everyday lives due to fatigue (Vogelzang *et al*, 1997). Recent acceptance of cancer-related fatigue, through diagnosable clinical manifestation in the 10th revision of the International Classification of Disease (ICD-10) should assist and ensure standardized diagnoses in research settings and clinical practice (Cella *et al*, 1998; Portenoy and Itri, 1999).

Very few studies are currently available to support the existence of cancer fatigue. Stone *et al* (2000), from Royal Marsden Hospital, investigated 227 cancer patients to determine the prevalence and severity of fatigue compared with the fatigue of 98 normal persons as controls. Their team observed a 15% incidence of severe fatigue amongst newly-diagnosed prostate cancer cases, 16% among newly-diagnosed breast cancer patients, and 50% among inoperable non-small-cell lung cancer patients. The highest incidence of fatigue was observed among patients undergoing inpatient palliative care.

Radiotherapy-related fatigue has been explored only recently. So far, proper evaluation of fatigue has been done for prostate cancer with small exposure volumes of radiation (Monga *et al*, 1999). However, the incidence of fatigue in advanced cancers, where large field sizes are used, has not yet been studied. Earlier reports on radiotherapy fatigue syndrome were insufficient to evaluate the magnitude of cancer-treatment-re-

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lated fatigue (Kobashi-Schoot *et al*, 1985; Greenberg *et al*, 1992; Vozelzang *et al*, 1997).

There are about 10-assessment scoring systems or inventories available for the evaluation of fatigue and many are under development to challenge the existing ones. The most popular assessment scales are Pipers' Fatigue Scale (PFS), Functional Assessment of Cancer Therapy measuring system (FACT), Memorial Symptom Assessment Scale, Pearson-Byars Fatigue Feeling Checklist, etc (Greenberg, 1998). A fatigue assessment questionnaire should be simple, usable in a clinical setting and comparable with other scales. Many fatigue scales are complicated and difficult to use in a busy clinical setting. Piper's modified version of the visual analog scale is a simple and useful tool to evaluate four distinct dimensions of fatigue (Piper *et al*, 1998). The present paper focuses on the utility of Piper's Fatigue Scale (PFS) to evaluate the incidence of radiotherapy-related fatigue.

MATERIALS AND METHODS

This study was conducted in the Division of Radiotherapy and Oncology of the Hospital University Sains Malaysia from July 1999 to July 2001. Informed consent was provided by the patients participating in the present study.

Sample selection

Patients with histopathological evidence of cancers were considered for the present study. As part of routine practice, all patients requiring radiotherapy were subjected to full blood counts, liver and kidney chemistry, and chest radiograph. In patients with advanced-stage cancer, special radiolography, tumor markers, and nuclear radionuclide studies were performed. The patient's performance status was evaluated using the European Cooperative Oncology Group (ECOG) system and patients with scores <1 were included in the study. Patients who received prior chemotherapy, and who had other co-morbid medical illnesses, were excluded from the study. The tumors were staged using the UICC-TNM staging system. In cases of anemia, blood transfusions were administered to raise hemoglobin levels above 10 g/dl, before starting radiotherapy.

Radiotherapy details

Radiotherapy was delivered by a 6 MV linear accelerator. The radiotherapy was delivered from Saturday to Wednesday every week, as Thursday and Fridays were weekends in the locality. The radical dose schedule was 70 Gy in 35 fractions over 7-weeks, preoperative dose 50 Gy 25 fractions over 5 weeks, postoperative dose of 56 Gy 28 fractions over 6 weeks, and palliative dose of 30 Gy in 10 fractions over a 2-week period. During radiotherapy, the fields were altered in phases to exclude sensitive viscera from the radiation field at respective threshold doses using the shrinking-field technique. The patients were assessed weekly to evaluate treatment response, psychological alterations and radiotherapy-related complications.

Fatigue evaluation

We used a 22-question Piper's Modified Fatigue Scale (Piper *et al*, 1998). This questionnaire contained four dimensions *ie* behavioral severity (6-items), affective meaning (5-items), sensory (5-items), and cognitive mood (6-items). Each item was rated on a 0 to 10 scale. The sum total of each dimension was assessed jointly and separately. Fatigue scores >5.5 were considered significant. Fatigue assessment was done towards the end of the fractionated course of radiotherapy.

Statistical analysis

The data were analyzed using Microsoft Excel software. The mean, median, and modes of each parameter, were determined. The above data were compared with the radiotherapy-related individual parameters using chi-square.

RESULTS

One hundred and fifteen patients completed the questionnaire, comprised of 53 males and 62 females. The median age of the patient population was 48 years. The primary tumors were distributed in the head and neck (33%), breast (15%), pelvis (22%), brain and spine (8%) and other sites (25%). Forty-four out of 115 cases (67%) were stage III and IV cancers (Table 1). The total radiation dose varied from 30 to 70 Gy with a median dose of 45 Gy. The area of radiation exposure ranged from 25 to 480 cm^2, with a median of 156 cm^2. According to the Piper's Fatigue Score results, 43% of our study population suffered from significant fatigue. The four dimensions of fatigue were: behavioral severity 25%, affective mean-

Table 1
Sample characteristics.

Total number of patients	115	
Male: Female ratio	53:62	
Primary site of cancer	Head and Neck	35 (30%)
	Breast	16 (15%)
	Pelvis	26 (22%)
	Brain and spine 26 (22%)	
	Miscellaneous 29 (25%)	
Age distribution	Median [48 years (range 7-90)]	
Stage distribution	I (6%), II (27%), III (25%), IV (42%)	
Radiation field size	25-352 cm^2 (median 156 cm^2)	
Radiation dose	30-70 Gy (median 45 Gy)	
Duration of fatigue	Months 17 (14%)	
	Weeks 09 (7%)	
	Hours 27 (23%)	
	Days 20 (17%)	
	Minutes 13 (11%)	
	No fatigue 14 (12%)	

ing 21%, sensory 18%, and cognitive mood 16% (Table 2). Patients with higher stage disease, large radiation field area, and low initial hemoglobin level at diagnosis, were associated with higher fatigue (Table 3).

DISCUSSION

Fatigue in cancer is a conglomeration of physical, psychological, and biological disturbances that brings about debilitating illness. This symptom is often overlooked, under-recognized, least understood and under-treated in the clinical practice of oncology (Vogelzang *et al*, 1997; Cella *et al*, 1998). In our study, we encountered significant fatigue among 43% of patients. Cancer-related fatigue differs from other fatigue in that it is sudden, overwhelming, and not relieved by rest. Cancer-treatment-related fatigue (CTRF) affects

Table 2
Distribution of significant fatigue scores according to individual components.

Parameters	Score-6	Score-7	Score-8	Score-9	Score-10	Total (%)
Behavioral	15	06	05	00	03	29 (25)
Affective	18	04	01	01	00	24 (21)
Sensory	16	05	00	00	00	21 (18)
Cognitive	10	07	01	01	00	19 (16)

Table 3
Factors influencing radiotherapy-induced fatigue scores.

Variables	Behavioral	Affective	Sensory	Cognitive	Combined	p-value	Total	p-value
Field area								
<100 cm^2	13/35	8/35	8/35	3/35	37/35	<0.03	6/35	NS
>100 cm^2	22/75	19/75	12/75	7/75	59/75		8/75	
Hemoglobin								
>10 g%	9/45	11/45	8/45	2/45	30/45	<0.05	4/45	NS
<10 g%	22/71	15/71	13/71	8/71	58/71		10/71	
Stage								
I and II	6/32	3/32	3/32	3/32	16/32	<0.00	1/32	<0.05
III and IV	19/46	15/46	12/46	5/46	59/46		8/46	
Chemotherapy								
No prior chemotherapy	30/96	20/96	19/96	12/96	70/96	NS	13/96	NS
Prior chemotherapy	4/19	5/19	3/19	1/19	13/19		1/19	
Primary site						Percent		Percent
CNS	1/10	0/10	0/10	0/10	1/10	10	1/10	10
Breast	4/17	1/17	2/17	0/17	7/17	41	2/17	11
Pelvis	6/26	4/26	2/26	0/26	12/26	46	1/26	4
Head and neck	13/32	10/32	9/32	4/32	33/32	103	7/32	21

mood, emotions, activity and treatment. Fatigue is also associated with a wide range of symptoms consistent with psychological impairment, including lack of motivation, depression, and disturbance of mood and cognition. Fatigue in cancer may be due to the cancer itself, the course of disease, anticancer treatment, stress coping with cancer, travel to hospital, anemia hormone therapy, depression, pre-existing mental and physical make up and lack of exercise (Dimeo *et al*, 1997; Portenoy and Itri, 1999; Furst and Ahsberg, 2001). Immunotherapy using interferons also causes significant fatigue (Dean *et al*, 1995). Multi-agent or single agent chemotherapy is known to cause CTRF. In fact, 75-100% patients undergoing chemotherapy experience fatigue (Curt, 2000). The high prevalence rate of fatigue in cancer patients may be due in part to the evolution of more intensive treatment strategies, like dose-intense chemotherapy or concurrent chemoradiotherapy.

Quantification of fatigue is a difficult task for the oncologist. Lack of scientific literature on fatigue is one of the major barriers to improved management. Early efforts to study fatigue were complicated and difficult to implement. While there are numerous fatigue scales described in the literature, very few are currently used to estimate fatigue and some are in the process of development (Portenoy, 2000). The most popular fatigue scales are Piper's Fatigue Score (PFS), Hospital Anxiety Depression Scale (HADS), Symptom Distress Scale (SDS), Memorial Symptom Assessment Scale (MSAS), and the Functional Assessment of Cancer Therapy (FACT) (Greenberg, 1998; Portonoy and Itri, 1999). Past studies on cancer-treatment-related fatigue were better assessed with Piper's Fatigue Scale. Hence we used the recently modified version of Piper's Fatigue Scale in our study (Kobashi-Schoot *et al*, 1985). The scale is composed of 4 components of fatigue, and is easy to follow. It is better to follow one well-accepted fatigue scale than to use multiple scales for assessment. Krishnasamy (2000) emphasized the need to understand fatigue scales before using it in practice. Recent research has thrown light on the correlates of cancer fatigue, like depression, dyspnea, and insomnia, which accounts for 46% of variance in fatigue (Okuyama *et al*, 2000).

Irvine *et al* (1994) studied fatigue among 57 patients undergoing radiotherapy, and 47 patients undergoing chemotherapy. The above fatigue scores were compared with fatigue scores detected from 53 normal volunteers. Significant fatigue was noticed on the 5th to 6th week of fractionated radiotherapy and after the 14th day of systemic chemotherapy. In general, a mean fatigue score of 61% was observed after cancer treatment.

In a prospective study from the USA, 419 cancer patients were evaluated for fatigue by a nationwide telephone interview. A significant incidence of debilitating fatigue was observed among 78% of cancer patients during the course of their disease and treatment. Thirty-two percent of patients experienced fatigue daily, and 32% reported fatigue significantly affected their daily routine. About 80% of oncologists believe fatigue is overlooked or under-treated, and most patients (74%) consider fatigue a symptom to be endured (Vogezang *et al*, 1997).

Treatments like systemic chemotherapy, immunotherapy, and radiotherapy are known to enhance fatigue. Cytotoxic drugs cause cellular lysis and release toxic substances leading to systemic effects of fatigue (Portenoy and Itri, 1999; Broeckel *et al*, 1998). Most chemotherapy protocols are associated with fatigue. Recently, a report showed development of fatigue on long-term use of hormones in prostate cancer patients (Stone *et al*, 2000).

The literature on the impact of ionizing radiation on fatigue is scarce. Ionizing radiation causes cytoplasmic and nuclear damage in direct and indirect mechanisms, the most common event being sub-lethal and potentially lethal damage. These radiation-related stress factors release toxins, leading to the development of fatigue. Lethargy follows brain irradiation as grade II toxicities and hepatic irradiation lead to lassitude. Almost all patients receiving lung irradiation experience fatigue, at first intermittent, but continuous by the end of the 3rd week (Haylock and Hart, 1979). It is worse in the latter part of the day, and naps are of some help. The incidence of fatigue is proportionate to the radiation field size. Patients undergoing magna-field radiotherapy for bone marrow transplantation or palliation extensive bone metastasis experience significant fatigue. The above symptoms are also observed among patients undergoing total axial nodal irradiation for lymphoma. The incidence of fatigue is comparatively less among patients undergoing limited field radiotherapy, like carcinoma of the glottic larynx. During localized irradiation, the tendency to fatigue increases after 4 weeks and then plateaus (Portenoy, 2000). The tendency to sleep increases in the latter part of treatment (Irvine *et al,* 1994).

The site of irradiation also affects the intensity of fatigue. Irradiation of the epigastrium in gastrointestinal tract cancers and thoracic irradiation in non-small-cell lung cancer induces more significant fatigue than skin cancer or extremity cancers. In our study, irradiation of the head and neck sites showed higher fatigue scores than chest wall irradiation in breast cancer patients. Further, the dose per fraction and stage of disease was also related to the magnitude of fatigue.

In conclusion, fatigue is prevalent among cancer patients undergoing external radiotherapy. Early discovery of fatigue symptoms and evaluation can pick up patients for therapeutic intervention. Radiation oncologists must be aware of this problem among their patients and be well-versed with their prompt detection and management. Proper management of cancer-treatment-related fatigue could help improve radiotherapy compliance.

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