LAPORAN AKHIR PROJEK PENYELIDIKAN
R & D JANGKA PENDEK

"CORRELATION OF CANCER TREATMENT RELATED FATIGUE WITH BIOCHEMICAL & HORMONAL PROFILE A PROSPECTIVE STUDY"

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Geran Jangka Pendek IRPA
NO 304/PPSP/6131233

UNIVERSITI SAINS MALAYSIA

JABATAN PERUBATAN NUKLEAR, RADIOTERAPI & ONKOLOGI
DEPARTMENT OF NUCLEAR MEDICINE, RADIOTHERAPHY & ONCOLOGY

23 Disember 2004

Puan Latifah Abdul Latif,
Penolong Pendaftar,
Pejabat Pengurusan & Kreativiti Penyelidikan,
Canselori,
Universiti Sains Malaysia,
11800 Pulau Pinang.

Puan,

Penghantaran Laporan Akhir Projek Jangka Pendek
(No Geran: 304/PPSP/6131233)

Saya telah menjalankan kajian bertajuk "Correlation of Cancer Treatment Related Fatigue (CTRF) With Biochemical & Hormonal Profile. A Prospective Study" dari tahun 2002-2004. Kajian tersebut telah selesai dijalankan. Oleh yang demikian bersama-sama ini saya sertakan salinan laporan kajian tersebut untuk tindakan pihak puan selanjutnya.

Sekian, terima kasih.

Yang benar,

.....

Dr. Biswa Mohan Biswal
Penyelaras Projek.

s.k En. Halim Othman
Pegawai Sains
Penyelidikan & Pembangunan, PPSP

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Laporan Akhir Projek Penyelidikan Jangka Pendek

1) Nama Penyelidik: Biswa Mohan Biswal

Nama Penyelidik-Penyelidik Lain (Jika berkaitan) : N. Kumaraswamy
Mallik Mumtaz

2) Pusat Pengajian/Pusat/Unit : Jabatan Perubatan Nuklear, Radioterapi & Onkologi, Pusat Pengajian Sains Perubatan

3) Tajuk Projek: Correlation of Cancer Treatment Related Fatigue with Biochemical & Hormonal Profile. A Prospective Study.

4) (a) Penemuan Projek/Abstrak

(Perlu disediakan makluman di antara 100 – 200 perkataan di dalam Bahasa Malaysia dan Bahasa Inggeris. Ini kemudiannya akan dimuatkan ke dalam Laporan Tahunan Bahagian Penyelidikan & Pembangunan sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti).

Background: Cancer treatment using chemotherapy or radiotherapy results in considerable cancer treatment related fatigue. Fatigue can induce significant stress causing hormonal alteration through hypothalamic pituitary axis leading to change in the internal milleu. We evaluated hormonal and biochemical profile to find out a putative correlation. *Materials & Method:* Fifty two histopathology documented cases of cancer patients were subjected to Pipers Fatigue Score (PFS) and blood test for hormone and other biochemical parameters before and after radiotherapy and chemotherapy treatment. Human growth hormone, adenocorticotrophic hormone, thyroid stimulating hormone and serum free cortisol level were evaluated along with routine biochemical analysis before and after anticancer treatment. The individual fatigue score were compared with individual hormone levels and other biochemical parameters. *Results:* Fifty two cancer patients planned for anticancer therapy completed initial pretreatment evaluation however post treatment assessment was not possible in 8 cases as they died during therapy. There were 20 males and 32 females in the study with a median age of 50 years (range15-78 years). The stage distribution was as stage-I (12%), stage-II (17%), stage-III (44%) and stage-IV (26%).The primary cancer were in breast (19%), sarcomas (9%), head and neck (19%), gynecological (19%) and miscellaneous sites (14%). The individual fatigue score were behavioral severity (26.6%), affective meaning (28%), sensory (22.2%), cognitive mood (8.8%) and total score (22.2%) respectively. There were significant rise in the fatigue score following chemotherapy and radiotherapy. The serum human growth hormone and cortisol were positively correlated whereas serum TSH level was negatively correlated with fatigue. *Conclusions*: Cancer treatment related fatigue is a multidimensional event that affect stress hormonal milieu. The human growth hormone and corticotrophins were affected among cancer patients suffering from cancer treatment related fatigue. Probably this finding may help to improve therapeutic intervention in the management fatigue in cancer

(b) Senaraikan Kata Kunci yang digunakan di dalam abstrak:

Bahasa Malaysia	Bahasa Inggeris
Keletihan	Fatigue
Hormon	Hormone
Barah/ Kanser	Cancer
Kimoterapi	Chemotherapy
Radioterapi	Radiotherapy
Berkaitan Rawatan	Treatment Related

5) Output Dan Faedah Projek

(a) Penerbitan (termasuk laporan/kertas seminar)
(Sila nyatakan jenis, tajuk, pengarang, tahun terbitan dan di mana telah diterbit/dibentangkan).

In this research we found a statistical correlation between significant cancer fatigue with serum cortisol and serum growth hormone levels. This is probably the first research in the realm of cancer fatigue to findout a putative correlation between fatigue related stress to hypothalamopituitary-axis.

(b) Faedah-Faedah Lain Seperti Perkembangan Produk, Prospek Komersialisasi Dan Pendaftaran Paten.
(Jika ada dan jika perlu, sila guna kertas berasingan)

Nil

(c) Latihan Gunatenaga Manusia

i) Pelajar Siswazah: Nil

ii) Pelajar Prasiswazah: Nil

iii) Lain-Lain : RA -1

6. Peralatan Yang Telah Dibeli:

1) Digital Video Camera (Panasonic-WV-DS65)

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T/TANGAN PENGERUSI
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PUSAT PENGAJIAN

Professor Zahidi Azhar Mohd. Hussin
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MANUSKRIP

CORRELATION OF CANCER TREATMENT RELATED FATIGUE WITH BIOCHEMICAL & HORMONAL PROFILE A PROSPECTIVE STUDY

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Abstract

Background: Cancer treatment using chemotherapy or radiotherapy results in considerable cancer treatment related fatigue. Fatigue can induce significant stress causing hormonal alteration through hypothalamic pituitary axis leading to change in the internal milleu. We evaluated hormonal and biochemical profile to find out a putative correlation. *Materials & Method:* Fifty two histopathology documented cases of cancer patients were subjected to Pipers Fatigue Score (PFS) and blood test for hormone and other biochemical parameters before and after radiotherapy and chemotherapy treatment. Human growth hormone, adenocorticotrophic hormone, thyroid stimulating hormone and serum free cortisol level were evaluated along with routine biochemical analysis before and after anticancer treatment. The individual fatigue score were compared with individual hormone levels and other biochemical parameters. *Results:* Fifty two cancer patients planned for anticancer therapy completed initial pretreatment evaluation however post treatment assessment was not possible in 8 cases as they died during therapy. There were 20 males and 32 females in the study with a median age of 50 years (range15-78 years). The stage distribution was as stage-I (12%), stage-II (17%), stage-III (44%) and stage-IV (26%).The primary cancer were in breast (19%), sarcomas (9%), head and neck (19%), gynecological (19%) and miscellaneous sites (14%). The individual fatigue score were behavioral severity (26.6%), affective meaning (28%), sensory (22.2%), cognitive mood (8.8%) and total score (22.2%) respectively. There were significant rise in the fatigue score following chemotherapy and radiotherapy. The serum human growth hormone and cortisol were positively correlated whereas serum TSH level was negatively correlated with fatigue. *Conclusions*: Cancer treatment related fatigue is a multidimensional event that affect stress hormonal milieu. The human growth hormone and corticotrophins were affected among cancer patients suffering from cancer treatment related fatigue. Probably this finding may help to improve therapeutic intervention in the management fatigue in cancer

Key words: Fatigue, hormone, cancer, chemotherapy, radiotherapy, treatment related

Introduction

Fatigue is a debilitating symptom complex affecting cancer patients.[1] The sum of fatigue is a combination of psychological, physical, behavioral and biochemical event.[1] The fatigue is influenced by co-morbid pre-existing psychological history, massive disease load, progressive anemia and cancer treatment itself. Relation of anemia and fatigue is an well-established fact and studied extensively in the literature.[2] However, cancer treatments like surgery, radiation therapy, immunotherapy and chemotherapy etc aggravate the fatigue syndrome, leading to poor quality of life and low compliance to anti-cancer treatment.[3] This cancer treatment related fatigue (CTRF) is currently being emphasized in the literature.[4-5] Every cancer treatment modality has got its own magnitude of fatigue. Chemotherapy and immunotherapy (interferon) results in significant fatigue, however radiotherapy induces moderate degree of fatigue.[6] The importance of fatigue is very recently realized in the medical community. Very few oncologists feel that fatigue is a problem to be thought of, whereas very few cancer patients think that it is not a symptom to be discussed with treating doctor. However the fatigue is a real problem for the cancer patients. Many patients consider fatigue is more bothering than cancer pain.

Though cancer fatigue has been emphasized much in the palliative care and psycho-oncology research scenario, very few studies are available today on the pathogenesis and patho-physiology of cancer fatigue.[7] So far, low hemoglobin level related fatigue has been explained well, however correlation between biochemical and hormonal factors with CTRF is not available in the literature. Here we tried to correlate cancer treatment related fatigue using Piper's fatigue scale with stress related hormones and conventional biochemical profile.

Materials and Methods

Tissue diagnosis confirmed cancer patients planned for chemotherapy and radiotherapy were considered for this study. The patients were pooled from the Radiotherapy & Oncology clinics of University Science Malaysia Hospital. A written consent was obtained to enroll in to the study. There was a strict selection criteria imposed to enter in

to the study. Patients with positive tissue diagnosis of cancer, age between 10-80 years, willing to participate voluntarily in this study were selected in this study. However patients with prior radiotherapy or chemotherapy, patients suffering from brain tumor, co-morbid psychological distress, interferon medication etc were excluded to participate. The full medical record, age, gender, type of cancer, stage of cancer, intention of treatment were recorded. A blood sample was obtained to check full blood count, liver and renal chemistry, growth hormone (GH), adenocorticotrophin hormone (ACTH), thyroid stimulating hormone (TSH), and free serum cortisol. Besides blood tests, patients were subjected to Pipers Fatigue Scale consisted of 22 questions.[8] There are four components of PFS containing questions i.e. behavioral severity (6-items), affective meaning (5-items), cognitive/mood (6-items) and sensory (5-items). Each question is graduated in to 10 levels and patients were asked to grade their feeling. The PFS questionnaire was validated in local language (Bahasa Melayu) and found to be equivocal. A WHO quality of life questionnaire was also recorded to evaluate quality of life of the patients. Then the patients were subjected to chemotherapy or radiotherapy treatment. The chemotherapy consisted of multiagent intravenous cytotoxic agents given at frequent intervals. Radiotherapy consisted of percutaneous external beam radiotherapy delivered by either a 6 MV or a10 MV linear accelerator. The patients were again evaluated towards the end of therapy where we expect maximum therapy related fatigue. Similar questionnaire and blood samples were obtained for comparison. At the end of study the fatigue score was compared between pre and post treatment score and correlation of fatigue score with individual stress hormone levels. We used SPSS 11.1 version software to analyze the data using the correlation method.

Results

A total of 52 cancer patients have completed this study. The first assessment and blood test could be done in 52 patients but second assessment was possible in 44 cases as 8 patients died during their treatment. There were 20 males and 32 females with a median age of 50 years (15-78 years)(Figure-1a, 1b)(Table-1). Thirty five (35) patients received chemotherapy, 17 patients received radiotherapy while 4 patients received both chemotherapy and radiotherapy. The primary cancers were distributed in head & neck region (19%), breast (19%), gynecological (19%), musculoskeletal system (29%), and

Table-1. Patients Profile

Total number of case (n=52)		
Age	Minimum	15
	Maximum	78
	Median	50
Sex	Male	20
	Female	32
Stage	I	12%
	II	17%
	III	44%
	IV	27%
Disease	Sarcomas	29%
	Head & Neck	19%
	Breast	19%
	Gynecology	19%
	Miscellaneous	14%

Table-3. Fatigue Score

Fatigue Score	**1**	**2**	**3**	**4**	**Total**
Chemotherapy + Radiotherapy					
Before (%)	26.6	33.3	22.2	8.88	22.8
After (%)	35.5	35.5	31.1	24.4	24.4
Pure Radiotherapy					
Before (%)	20	23.3	16.6	0	13.3
After (%)	26.6	33.3	26.6	23.3	23.3
Chemotherapy					
Before (%)	40	53.3	33.3	26.6	40
After (%)	53.3	40	40	26.6	26.6

Table 2. Showing correlation of PFS fatigue score with hormones

Hormon-Fatique	N	Person Correlation	P. Value	Spearmen's	P. Value
HGH_FAG 1	52	.384**	0.005	.439**	0.001
HGH_ FAG 2	52	.399**	0.003	.496**	0
HGH_ FAG 3	52	.363**	0.008	.380**	0.005
HGH_FAG 4	52	.283*	0.042	0.285	0.041
total	52	0.402	0.003	0.484	0
HGH_ FBG 1	44	0.175	0.208	0.424	0.124
HGH_FBG 2	44	0.237	0.122	0.56	0.09
HGH_FBG 3	44	0.82	-0.03	0.932	0.013
HGH_FBG 4	44	0.598	0.083	0.847	0.3
total	44	0.345	0.146	0.369	0.139
HGH_FDG 1	44	0.638	-0.073	0.985	0.003
HGH_FDG 2	44	0.914	0.017	0.593	-0.083
HGH_FDG 3	44	0.267	0.171	0.433	-0.121
HGH_FDG 4	44	0.893	0.021	0.582	0.085
total	44	0.532	0.097	0.615	-0.078
ACTH_FAG 1	52	0.983	0.003	0.902	-0.018
ACTH_FAG 2	52	0.803	-0.035	0.559	0.083
ACTH_FAG 3	52	0.759	0.044	0.375	0.126
ACTH_FAG 4	52	0.215	0.175	0.858	0.025
total	52	0.971	0.005	0.733	0.049
ACTH_FBG1	45	0.637	-0.072	0.947	-0.01
ACTH_FBG2	45	0.25	-0.175	0.542	-0.093
ACTH_FBG 3	45	0.623	-0.075	0.952	0.009
ACTH_FBG 4	45	0.525	-0.097	0.635	-0.073
total	44	0.83	-0.033	0.463	0.114
ACTH_FDG1	44	0.433	0.121	0.371	0.013
ACTH_FDG 2	44	0.948	0.01	0.535	0.096
ACTH_FDG 3	44	0.799	0.04	0.284	0.165
ACTH_FDG 4	44	0.893	-0.021	0.582	0.085
total	44	0.197	0.198	0.764	0.047
TSH_FAG 1	52	0.265	0.057	0.538	0.087
TSH_ FAG 2	52	0.185	0.187	0.391	-0.121
TSH_FAG 3	52	0.466	0.103	0.911	0.016
TSH_FAG 4	52	0.781	0.04	0.361	0.129
total	52	0.159	0.198	0.951	0.009
TSH_FBG 1	44	0.348	-0.145	0.134	-0.229
TSH_FBG 2	44	0.255	-0.175	0.181	-0.205
TSH_FBG 3	44	0.274	-0.169	0.175	-0.208
TSH_FBG 4	44	0.948	-0.01	0.666	-0.067
total	44	0.36	-0.141	0.176	-0.208
TSH_FDG 1	44	0.764	0.047	0.197	0.198
TSH_FDG 2	44	0.528	0.098	0.778	0.004
TSH_FDG 3	44	0.226	-0.186	0.315	-0.155
TSH_FDG 4	44	0.923	-0.015	0.504	0.103
total	44	0.7	-0.06	0.985	-0.003
CORT_FAG 1	52	0.251	0.162	0.45	0.107
CORT_FAG 2	52	0.3	0.146	0.573	0.08
CORT_FAG 3	52	0.282	0.152	0.398	0.12
CORT_FAG 4	52	0.171	0.193	0.178	0.19
total	52	0.202	0.18	0.41	0.117
CORT_FBG 1	44	0.022	.346*	0.017	.357*
CORT_FBG 2	44	0.078	0.268	0.208	0.194
CORT_FBG 3	44	0.005	.414**	0.021	.347**
CORT_FBG 4	44	0.002	.457**	0.008	.397**
total	44	0.007	.400**	0.037	.316*
CORT_FDG 1	44	0.789	-0.041	0.422	0.124
CORT_FDG 2	44	0.529	-0.097	0.788	-0.042
CORT_FDG 3	44	0.993	-0.001	0.203	0.196
CORT_FDG 4	44	0.65	0.07	0.266	0.172
total	44	0.845	-0.03	0.405	0.129

Figure 1a.

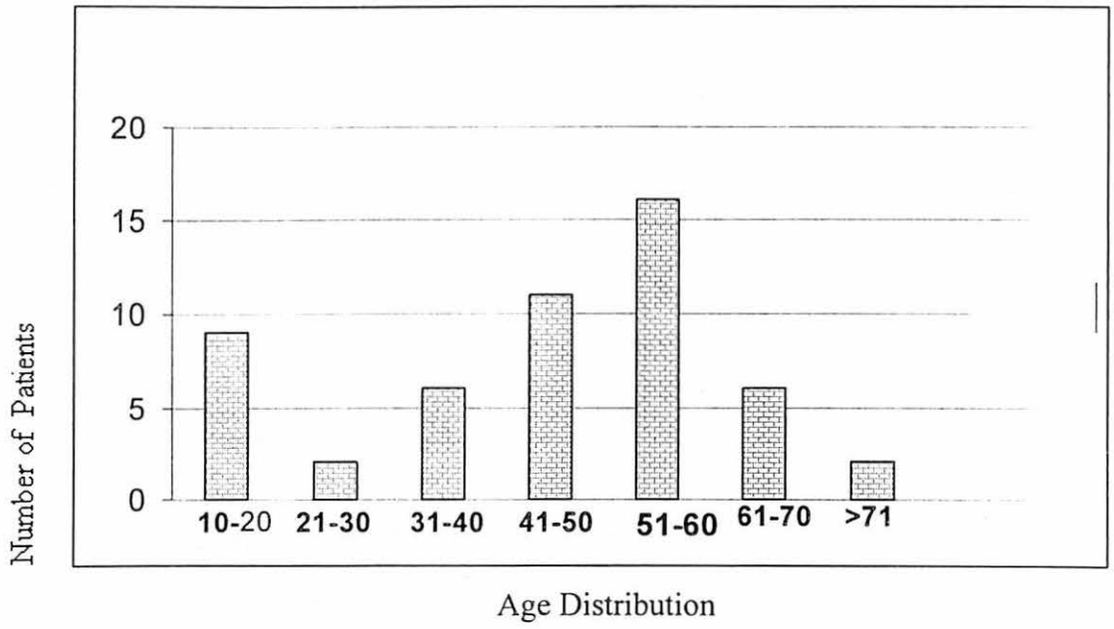


Figure 1b.

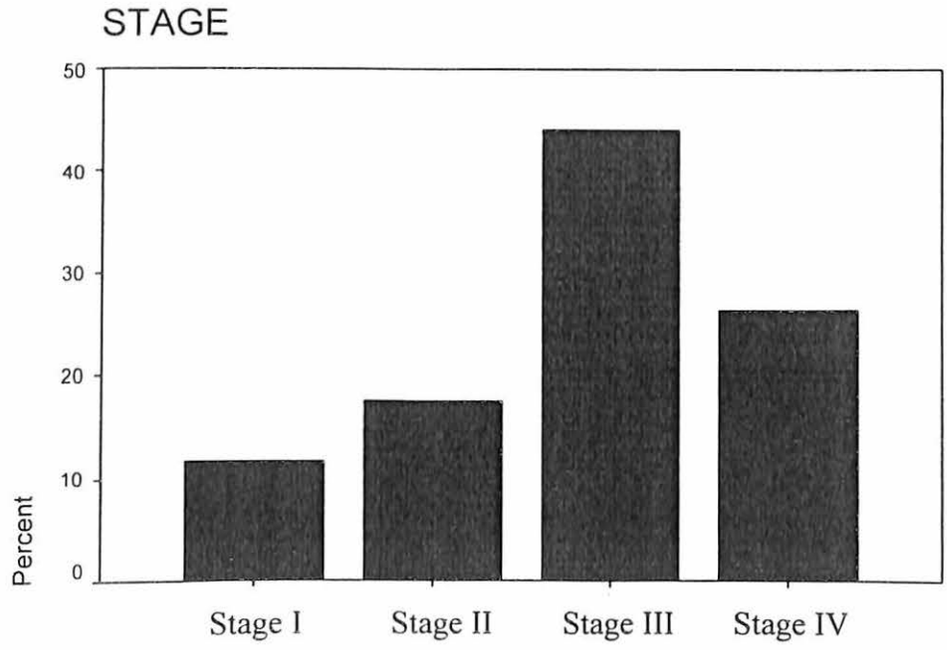


Figure 1c.

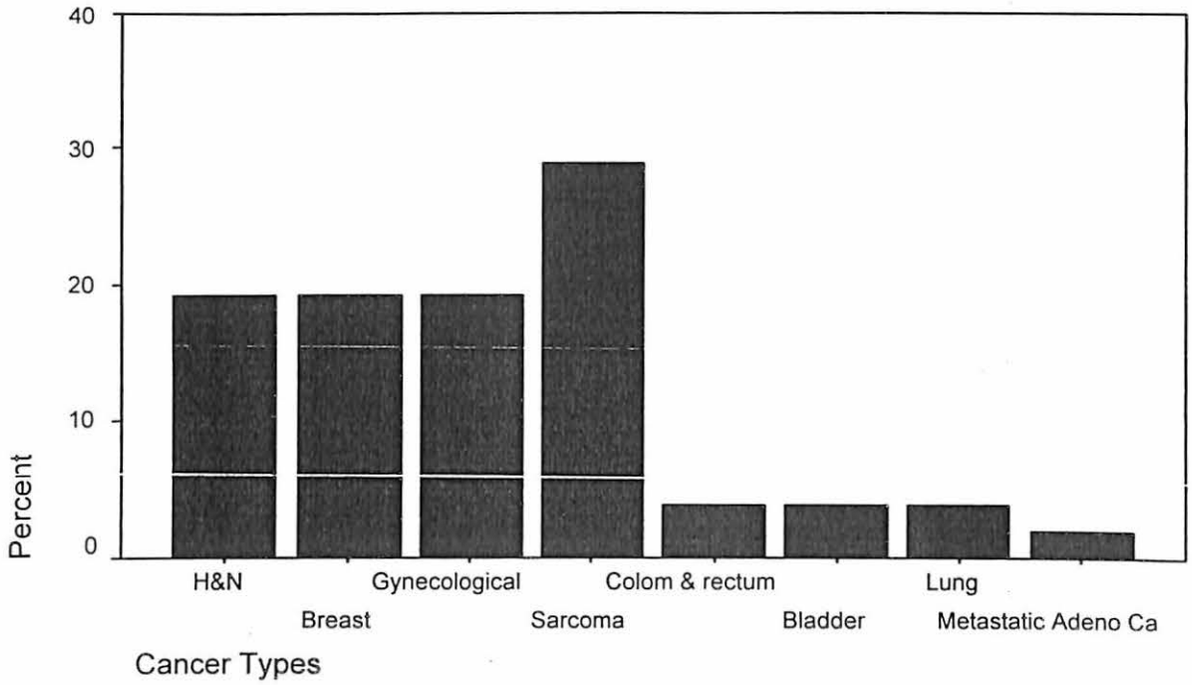
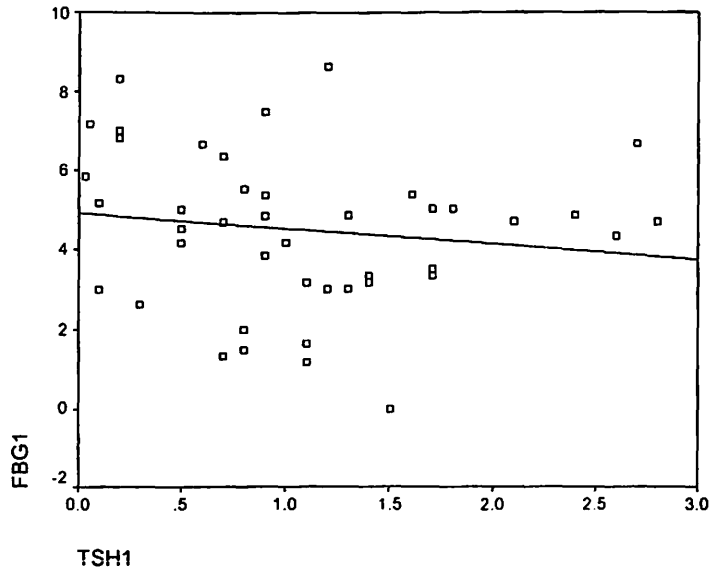
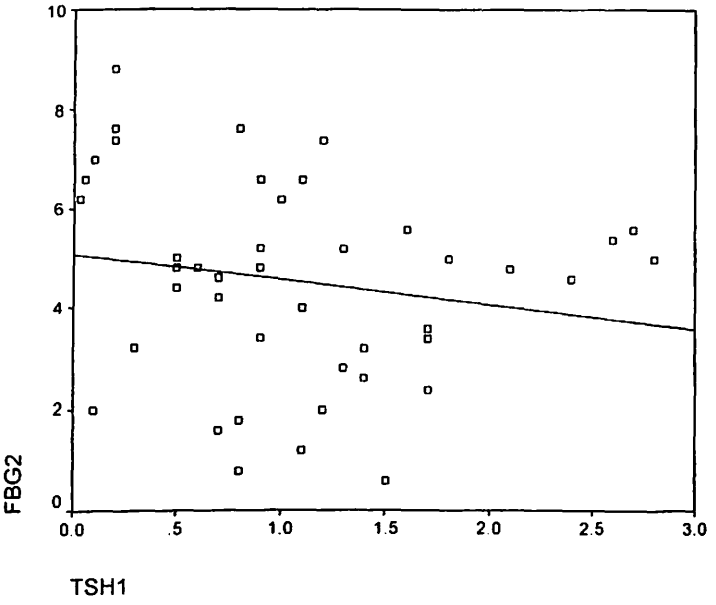

40
30
20
10
0
Percent
H&N
Breast
Gynecological
Sarcoma
Colom & rectum
Bladder
Lung
Metastatic Adeno Ca
Cancer Types

Figure 2a.



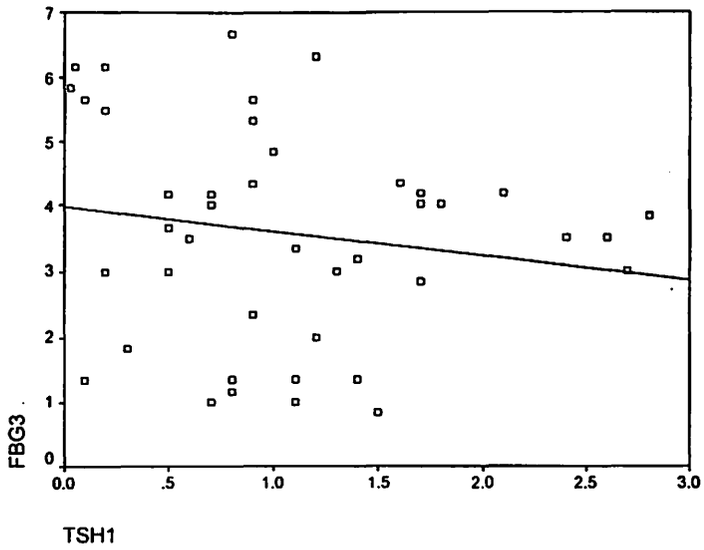
Correlation between TSH levels with Fatigue Score(1)

Figure 2b.



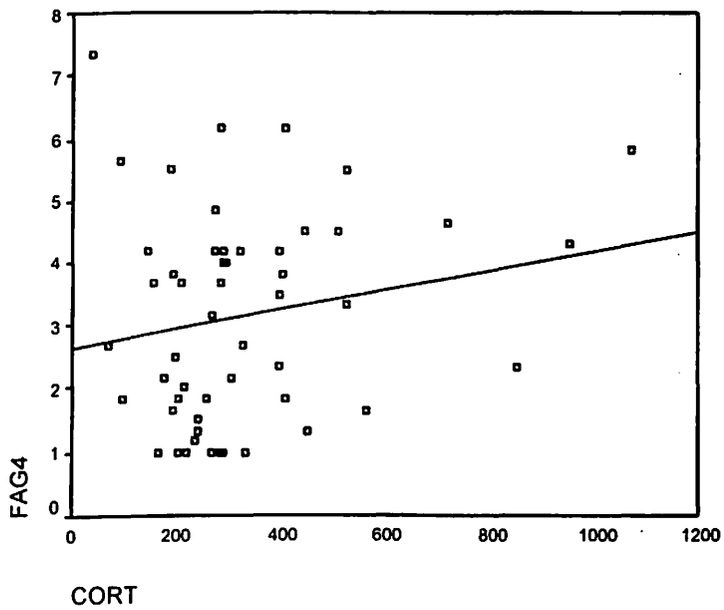
Correlation between TSH levels with Fatigue Score (2)

Figure 2c.



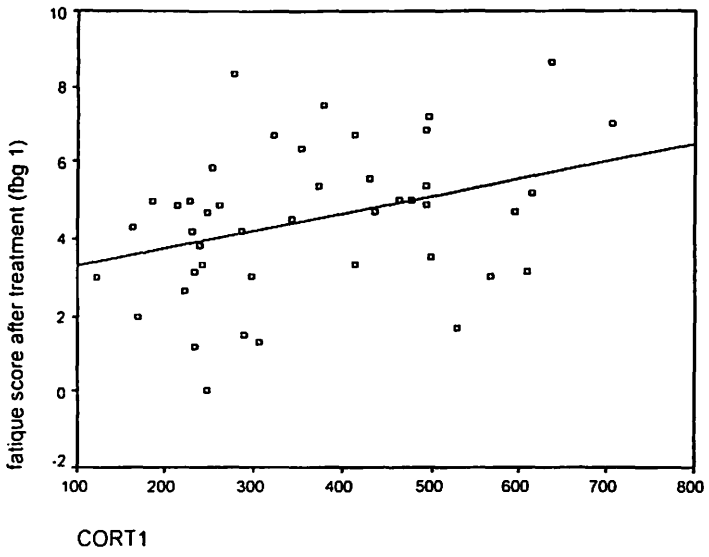
Correlation between TSH levels with Fatigue Score (3)

Figure 2d.



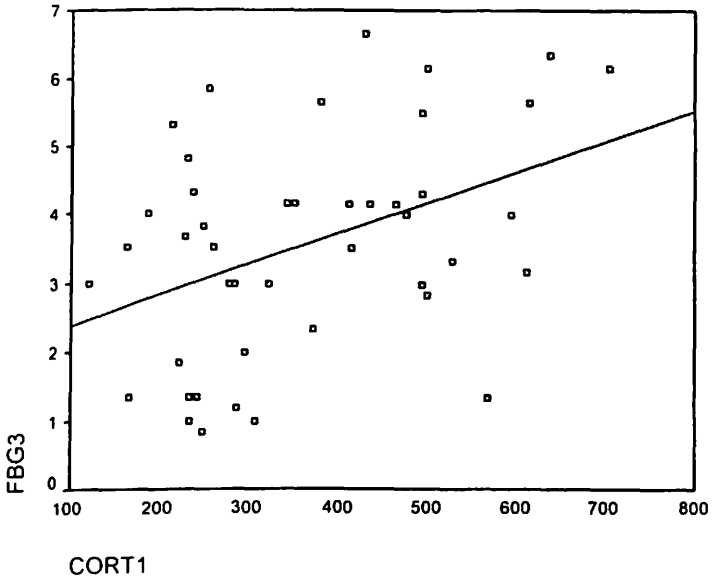
Correlation between serum cortisol level and fatigue score(4)

Figure 2e.



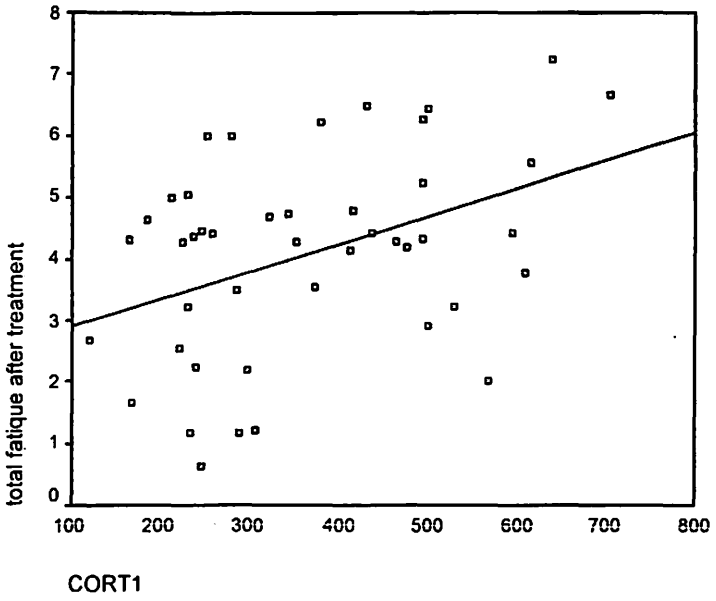
Correlation between serum cortisol level and fatigue score(5)

Figure 2f.



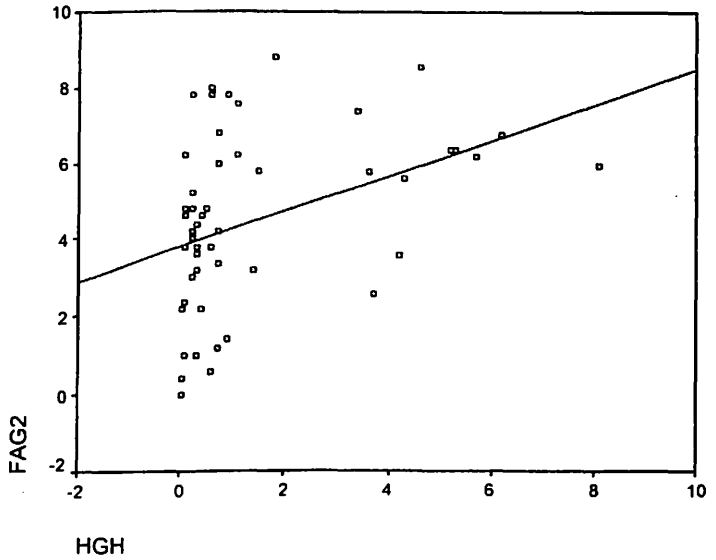
Correlation between serum cortisol level and fatigue score (6)

Figure 2g.



Correlation between serum cortisol level and fatigue score (7)

Figure 2h.



Correlation between serum cortisol level and fatigue score (8)

other miscellaneous sites (14%)(Figure-1c). The evaluation of hematological and biochemical parameters did not yield any correlate. Hormone analysis revealed significant correlation between CTRF and human growth hormone (HGH) (Pearson correlation 0.399), cortisol (Pearson correlation 0.414) and thyroid stimulating hormones (TSH). The former parameters (HGH & cortisol) were positively correlated however the later (TSH) parameter was negatively correlated (Pearson correlation -0.145) with CTRF (Figure-2)(Table-2). The fatigue score before treatment behavioral severity (26.6%), affective meaning (28%), sensory (22.2%), cognitive mood (8.8%) and total score (22.2%). Following treatment the fatigue score changed to behavioral severity (35.5%), affective meaning (35.5%), sensory (31.1%), cognitive mood (24.4%) and total fatigue score (24.4%)(Table-3).

Discussion

Fatigue is the one of the most common symptom encountered amongst cancer patients before, during and after cancer therapy. Fatigue exists in 14 to 96% of patients, particularly among individuals undergoing anti-cancer treatment.[9] Fatigue is difficult to describe and patients express it in a variety of ways, using terms such as tiredness, weakness, exhausted, weary, worn out, heavy or slow. Likewise health professionals too have problem to describe fatigue as asthenia, lassitude, prostration, exercise intolerance, lack of energy and weakness.

Defining fatigue has challenged clinicians and researchers alike for many years. Generally fatigue may be defined as a condition characterized by distress and decreased functional status related to decrease in energy. The specific manifestations may be physical, mental or emotional. For clinical and research purpose, it is useful to distinguish significant cancer related fatigue from other kinds of fatigue to plan specific management guidelines.

Acute fatigue is normal or expected tiredness characterized by localized intermittent symptoms, rapid onset and for short duration. Whereas rest will completely restore a healthy individual to a normal level of functioning, this restorative capacity is diminished in the presence of neoplastic disease. Chronic fatigue described as prolonged,

debilitating fatigue that is persistent or relapsing, lasting weeks, and not anticipated to end soon. This illness is sometimes diagnosed in general medical population. Although a variety of treatment and disease related factors might contribute to the development of fatigue, the biochemical, physiological, psychological, and behavioral mechanism of this symptom complex are poorly understood. There is no standard of care for the assessment or treatment of fatigue in patients suffering from cancer.

For many people diagnosed with cancer, fatigue may become a critical issue in their lives. Fatigue may influence one's well-being, daily performance, activities of daily living, relationship with family and compliance to treatment.

The exact mechanism of fatigue that cause or promote fatigue in patients with cancer is unknown. It is likely that many different mechanisms may play role in its pathogenesis. Various models have been proposed for the study of fatigue.[10] Prolonged stress that produces a stress response may be used as a model for fatigue. Peoples with fatigue frequently suffers from extreme stress over a long period of time, causing them to expend energy and experience a high level of fatigue. In contrast, one study demonstrated that energy requirements vary in peoples with cancer. This suggests that the factors other than energy requirements contribute to fatigue.

A neurophysiologic model has been proposed to study fatigue.[10] This model has both central and peripheral components. The central component consists of the psyche/brain and spinal cord. The peripheral system consists of peripheral nerves, muscle sarcolemma, transverse tubular system, calcium release, actin/myosin interaction, cross bridge tension and heat and force /power output. Impairment of the central component causes lack of motivation, impaired spinal cord transmission and exhaustion or malformation of brain cells in the hypothalamic region. Damage to the peripheral component can cause impaired peripheral nerve function in transmission at the neuromuscular junction, thereby affecting fibre activation. Both types of damage may play a role in the chronic fatigue. The central mechanism may be the key to explaining the extreme fatigue of biotherapy treated patients. It remains to be established whether potentially neurotoxic chemotherapeutic regimens cause fatigue through this mechanism. Further many individuals with cancer may be concurrently receiving

analgesics, hypnotics, anti-depressants, anti-emetics and anticonvulsants, because many of these drugs act on the CNS, they can significantly compound this problem.

Another perspective in the study of fatigue focuses on the reduction in skeletal muscle protein stores that may result from endogenous tumor necrosis factor (NTF) or from TNF administered as antineoplastic therapy. This muscle wasting would require individuals to exert an unusually high amount of energy to generate adequate contractile force during exercise performance or during extended period of sitting or standing.

The pathophysiological mechanism of fatigue is still in research phase. There are very few evidences in the literature related to is pathophysiology. The role of anemia in the development of fatigue and low quality of life is well established in randomized controlled trials. Low haemoglobin level leading to decreased oxygen transport thus decreasing cellular metabolism and thus development of fatigue. Further chronic fatigue syndrome may affect hypothalamic pituitary adrenal axis.[11] However the neuroendocrine response in depression and chronic fatigue syndrome is contradictory.[12] In the above study of 15 depression and10 fatigued patients, the baseline circulating cortisol level were found to have raised among depressed and lowest among chronic fatigue syndrome in our study of 52 patients the cortisol level was raised in cancer treatment related fatigue. Probably the cancer related psychological stress might have stimulated cortisol level in the blood.

Influence of the human growth hormone has been known to be related to the growth and well being and cognitive function in human beings. In a study the effects of HGH on the central nervous system activity, vigilance and sleepiness was studied among HGH deficient patients. In this study there were some improvement in the sleep quality, and mood.[13] In our study we found raise in the HGH level among patients with high fatigue score. Again the raise in the HGH might be related to the stress related cancer itself or due to cancer treatment with chemotherapy and radiotherapy.

Low thyroxine levels leading to hypothyroid syndrome. Hypothyroid patients develop low energy level and easy fatiguability. In contrast, the thyroid stimulating hormone is raised as an inhibitory mechanism. In our analysis we found an inverse correlation between TSH level and cancer treatment related fatigue.

In conclusion the correlation of hormone level in cancer treatment related fatigue is a very complex issue. This syndrome is multifactorial and involve multiple hormones. In our study we found a low level correlation between increased CTRF with HGH and cortisol but a negative relation with TSH. Our finding could help in the understanding of the pathophysiology of fatigue at the hypothalamo-pituitary and adrenal axis, thereby help in the management of fatigue. However further study on the other hormones are necessary to unreveal the alteration of hormonal milleu in response to fatigue.

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LAPORAN AKHIR PROJEK PENYELIDIKAN
R & D JANGKA PENDEK

"CORRELATION OF CANCER TREATMENT RELATED FATIGUE WITH BIOCHEMICAL & HORMONAL PROFILE A PROSPECTIVE STUDY"

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CORRELATION OF CANCER TREATMENT RELATED FATIGUE WITH BIOCHEMICAL & HORMONAL PROFILE A PROSPECTIVE STUDY

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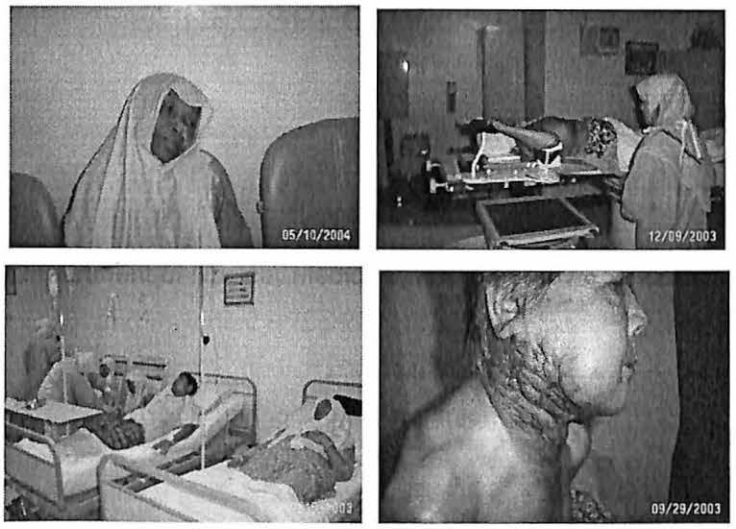

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Abstract

Background: Cancer treatment using chemotherapy or radiotherapy results in considerable cancer treatment related fatigue. Fatigue can induce significant stress causing hormonal alteration through hypothalamic pituitary axis leading to change in the internal milleu. We evaluated hormonal and biochemical profile to find out a putative correlation. *Materials & Method:* Fifty two histopathology documented cases of cancer patients were subjected to Pipers Fatigue Score (PFS) and blood test for hormone and other biochemical parameters before and after radiotherapy and chemotherapy treatment. Human growth hormone, adenocorticotrophic hormone, thyroid stimulating hormone and serum free cortisol level were evaluated along with routine biochemical analysis before and after anticancer treatment. The individual fatigue score were compared with individual hormone levels and other biochemical parameters. *Results:* Fifty two cancer patients planned for anticancer therapy completed initial pretreatment evaluation however post treatment assessment was not possible in 8 cases as they died during therapy. There were 20 males and 32 females in the study with a median age of 50 years (range15-78 years). The stage distribution was as stage-I (12%), stage-II (17%), stage-III (44%) and stage-IV (26%).The primary cancer were in breast (19%), sarcomas (9%), head and neck (19%), gynecological (19%) and miscellaneous sites (14%). The individual fatigue score were behavioral severity (26.6%), affective meaning (28%), sensory (22.2%), cognitive mood (8.8%) and total score (22.2%) respectively. There were significant rise in the fatigue score following chemotherapy and radiotherapy. The serum human growth hormone and cortisol were positively correlated whereas serum TSH level was negatively correlated with fatigue. *Conclusions*: Cancer treatment related fatigue is a multidimensional event that affect stress hormonal milieu. The human growth hormone and corticotrophins were affected among cancer patients suffering from cancer treatment related fatigue. Probably this finding may help to improve therapeutic intervention in the management fatigue in cancer

Key words: Fatigue, hormone, cancer, chemotherapy, radiotherapy, treatment related

Introduction

Fatigue is a debilitating symptom complex affecting cancer patients.[1] The sum of fatigue is a combination of psychological, physical, behavioral and biochemical event.[1] The fatigue is influenced by co-morbid pre-existing psychological history, massive disease load, progressive anemia and cancer treatment itself. Relation of anemia and fatigue is an well-established fact and studied extensively in the literature.[2] However, cancer treatments like surgery, radiation therapy, immunotherapy and chemotherapy etc aggravate the fatigue syndrome, leading to poor quality of life and low compliance to anti-cancer treatment.[3] This cancer treatment related fatigue (CTRF) is currently being emphasized in the literature.[4-5] Every cancer treatment modality has got its own magnitude of fatigue. Chemotherapy and immunotherapy (interferon) results in significant fatigue, however radiotherapy induces moderate degree of fatigue.[6] The importance of fatigue is very recently realized in the medical community. Very few oncologists feel that fatigue is a problem to be thought of, whereas very few cancer patients think that it is not a symptom to be discussed with treating doctor. However the fatigue is a real problem for the cancer patients. Many patients consider fatigue is more bothering than cancer pain.

Though cancer fatigue has been emphasized much in the palliative care and psycho-oncology research scenario, very few studies are available today on the pathogenesis and patho-physiology of cancer fatigue.[7] So far, low hemoglobin level related fatigue has been explained well, however correlation between biochemical and hormonal factors with CTRF is not available in the literature. Here we tried to correlate cancer treatment related fatigue using Piper's fatigue scale with stress related hormones and conventional biochemical profile.

Materials and Methods

Tissue diagnosis confirmed cancer patients planned for chemotherapy and radiotherapy were considered for this study. The patients were pooled from the Radiotherapy & Oncology clinics of University Science Malaysia Hospital. A written consent was obtained to enroll in to the study. There was a strict selection criteria imposed to enter in

to the study. Patients with positive tissue diagnosis of cancer, age between 10-80 years, willing to participate voluntarily in this study were selected in this study. However patients with prior radiotherapy or chemotherapy, patients suffering from brain tumor, co-morbid psychological distress, interferon medication etc were excluded to participate. The full medical record, age, gender, type of cancer, stage of cancer, intention of treatment were recorded. A blood sample was obtained to check full blood count, liver and renal chemistry, growth hormone (GH), adenocorticotrophin hormone (ACTH), thyroid stimulating hormone (TSH), and free serum cortisol. Besides blood tests, patients were subjected to Pipers Fatigue Scale consisted of 22 questions.[8] There are four components of PFS containing questions i.e. behavioral severity (6-items), affective meaning (5-items), cognitive/mood (6-items) and sensory (5-items). Each question is graduated in to 10 levels and patients were asked to grade their feeling. The PFS questionnaire was validated in local language (Bahasa Melayu) and found to be equivocal. A WHO quality of life questionnaire was also recorded to evaluate quality of life of the patients. Then the patients were subjected to chemotherapy or radiotherapy treatment. The chemotherapy consisted of multiagent intravenous cytotoxic agents given at frequent intervals. Radiotherapy consisted of percutaneous external beam radiotherapy delivered by either a 6 MV or a10 MV linear accelerator. The patients were again evaluated towards the end of therapy where we expect maximum therapy related fatigue. Similar questionnaire and blood samples were obtained for comparison. At the end of study the fatigue score was compared between pre and post treatment score and correlation of fatigue score with individual stress hormone levels. We used SPSS 11.1 version software to analyze the data using the correlation method.

Results

A total of 52 cancer patients have completed this study. The first assessment and blood test could be done in 52 patients but second assessment was possible in 44 cases as 8 patients died during their treatment. There were 20 males and 32 females with a median age of 50 years (15-78 years)(Figure-1a, 1b)(Table-1). Thirty five (35) patients received chemotherapy, 17 patients received radiotherapy while 4 patients received both chemotherapy and radiotherapy. The primary cancers were distributed in head & neck region (19%), breast (19%), gynecological (19%), musculoskeletal system (29%), and

Table-1. Patients Profile

Total number of case (n=52)		
Age	Minimum	15
	Maximum	78
	Median	50
Sex	Male	20
	Female	32
Stage	I	12%
	II	17%
	III	44%
	IV	27%
Disease	Sarcomas	29%
	Head & Neck	19%
	Breast	19%
	Gynecology	19%
	Miscellaneous	14%

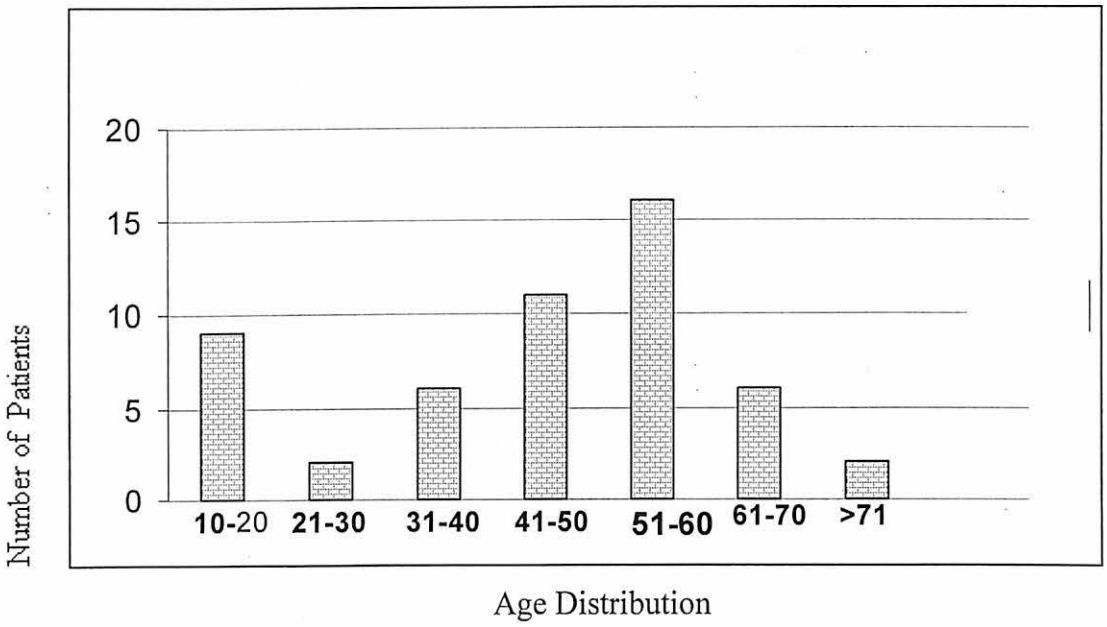
Table-3. Fatigue Score

Fatigue Score	**1**	**2**	**3**	**4**	**Total**
Chemotherapy + Radiotherapy					
Before (%)	26.6	33.3	22.2	8.88	22.8
After (%)	35.5	35.5	31.1	24.4	24.4
Pure Radiotherapy					
Before (%)	20	23.3	16.6	0	13.3
After (%)	26.6	33.3	26.6	23.3	23.3
Chemotherapy					
Before (%)	40	53.3	33.3	26.6	40
After (%)	53.3	40	40	26.6	26.6

Table 2. Showing correlation of PFS fatigue score with hormones

Hormon-Fatique	N	Person Correlation	P. Value	Spearmen's	P. Value
HGH_FAG 1	52	.384**	0.005	.439**	0.001
HGH_ FAG 2	52	.399**	0.003	.496**	0
HGH_ FAG 3	52	.363**	0.008	.380**	0.005
HGH_FAG 4	52	.283*	0.042	0.285	0.041
total	52	0.402	0.003	0.484	0
HGH_ FBG 1	44	0.175	0.208	0.424	0.124
HGH_FBG 2	44	0.237	0.122	0.56	0.09
HGH_FBG 3	44	0.82	-0.03	0.932	0.013
HGH_FBG 4	44	0.598	0.083	0.847	0.3
total	44	0.345	0.146	0.369	0.139
HGH_FDG 1	44	0.638	-0.073	0.985	0.003
HGH_FDG 2	44	0.914	0.017	0.593	-0.083
HGH_FDG 3	44	0.267	0.171	0.433	-0.121
HGH_FDG 4	44	0.893	0.021	0.582	0.085
total	44	0.532	0.097	0.615	-0.078
ACTH_FAG 1	52	0.983	0.003	0.902	-0.018
ACTH_FAG 2	52	0.803	-0.035	0.559	0.083
ACTH_FAG 3	52	0.759	0.044	0.375	0.126
ACTH_FAG 4	52	0.215	0.175	0.858	0.025
total	52	0.971	0.005	0.733	0.049
ACTH_FBG1	45	0.637	-0.072	0.947	-0.01
ACTH_FBG2	45	0.25	-0.175	0.542	-0.093
ACTH_FBG 3	45	0.623	-0.075	0.952	0.009
ACTH_FBG 4	45	0.525	-0.097	0.635	-0.073
total	44	0.83	-0.033	0.463	0.114
ACTH_FDG1	44	0.433	0.121	0.371	0.013
ACTH_FDG 2	44	0.948	0.01	0.535	0.096
ACTH_FDG 3	44	0.799	0.04	0.284	0.165
ACTH_FDG 4	44	0.893	-0.021	0.582	0.085
total	44	0.197	0.198	0.764	0.047
TSH_FAG 1	52	0.265	0.057	0.538	0.087
TSH_ FAG 2	52	0.185	0.187	0.391	-0.121
TSH_FAG 3	52	0.466	0.103	0.911	0.016
TSH_FAG 4	52	0.781	0.04	0.361	0.129
total	52	0.159	0.198	0.951	0.009
TSH_FBG 1	44	0.348	-0.145	0.134	-0.229
TSH_FBG 2	44	0.255	-0.175	0.181	-0.205
TSH_FBG 3	44	0.274	-0.169	0.175	-0.208
TSH_FBG 4	44	0.948	-0.01	0.666	-0.067
total	44	0.36	-0.141	0.176	-0.208
TSH_FDG 1	44	0.764	0.047	0.197	0.198
TSH_FDG 2	44	0.528	0.098	0.778	0.004
TSH_FDG 3	44	0.226	-0.186	0.315	-0.155
TSH_FDG 4	44	0.923	-0.015	0.504	0.103
total	44	0.7	-0.06	0.985	-0.003
CORT_FAG 1	52	0.251	0.162	0.45	0.107
CORT_FAG 2	52	0.3	0.146	0.573	0.08
CORT_FAG 3	52	0.282	0.152	0.398	0.12
CORT_FAG 4	52	0.171	0.193	0.178	0.19
total	52	0.202	0.18	0.41	0.117
CORT_FBG 1	44	0.022	.346*	0.017	.357*
CORT_FBG 2	44	0.078	0.268	0.208	0.194
CORT_FBG 3	44	0.005	.414**	0.021	.347**
CORT_FBG 4	44	0.002	.457**	0.008	.397**
total	44	0.007	.400**	0.037	.316*
CORT_FDG 1	44	0.789	-0.041	0.422	0.124
CORT_FDG 2	44	0.529	-0.097	0.788	-0.042
CORT_FDG 3	44	0.993	-0.001	0.203	0.196
CORT_FDG 4	44	0.65	0.07	0.266	0.172
total	44	0.845	-0.03	0.405	0.129

Figure 1a.



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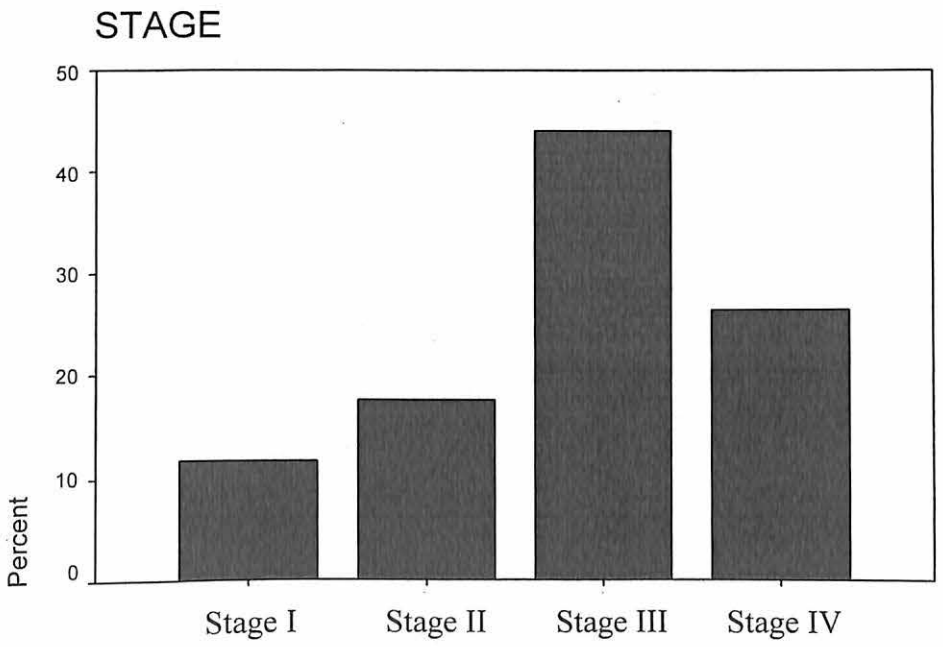

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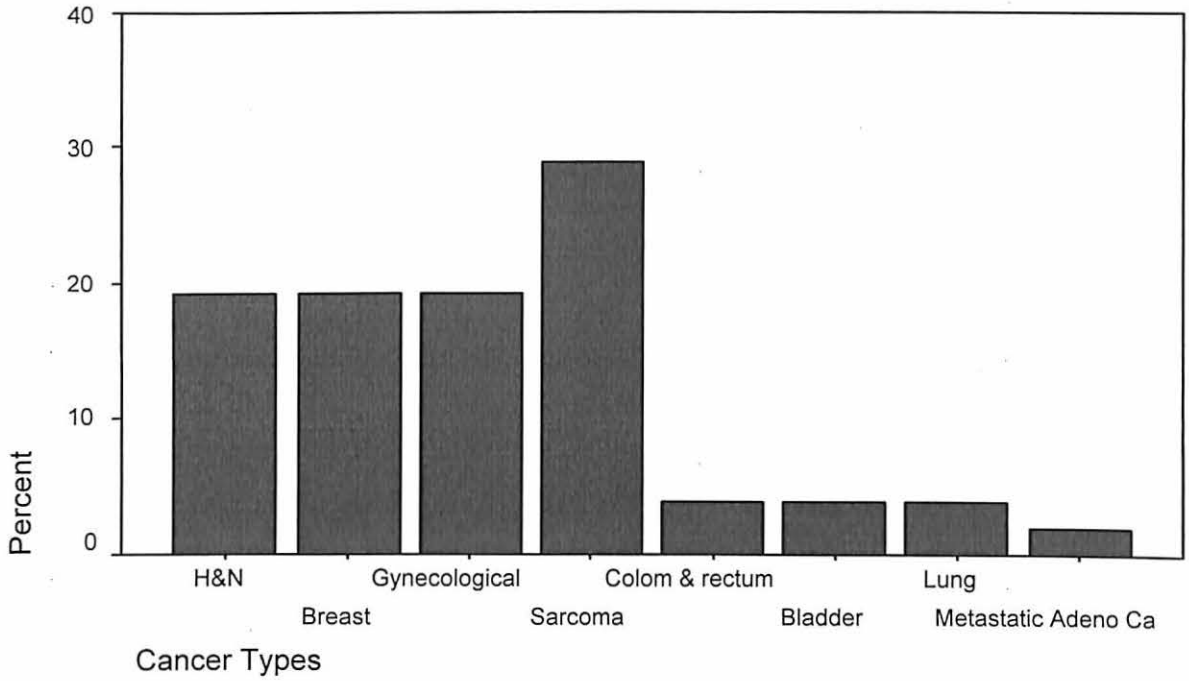
40
30
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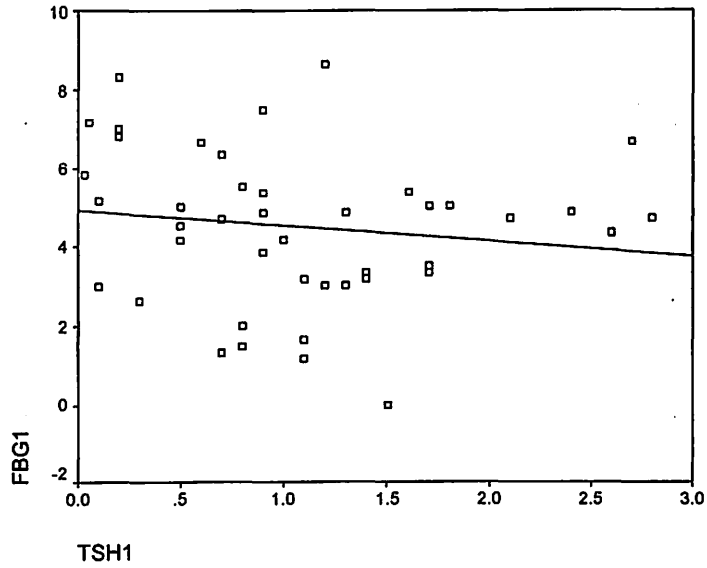
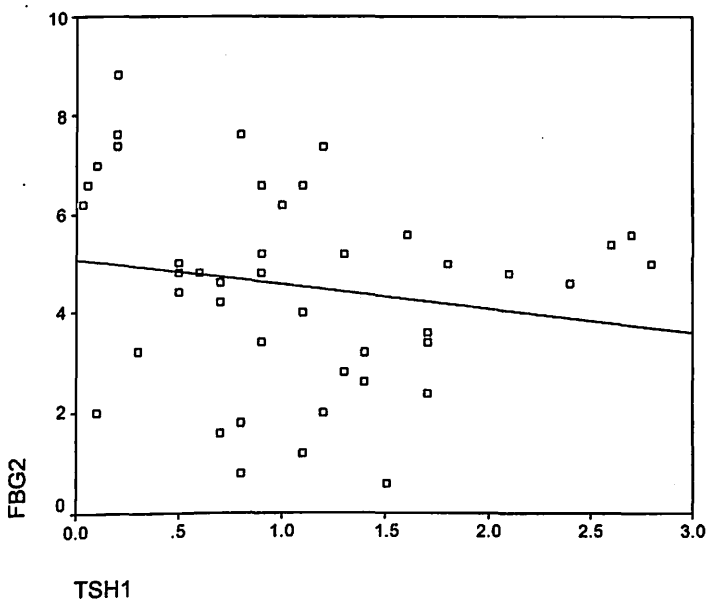
Cancer Types

Figure 2a.



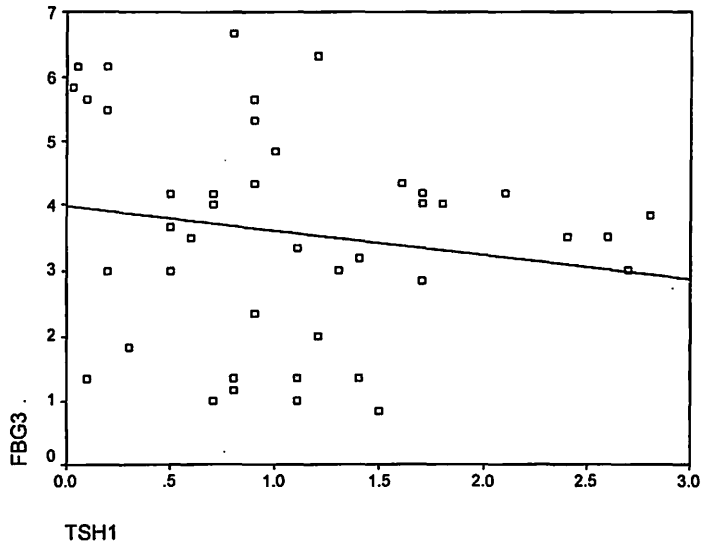
Correlation between TSH levels with Fatigue Score(1)

Figure 2b.



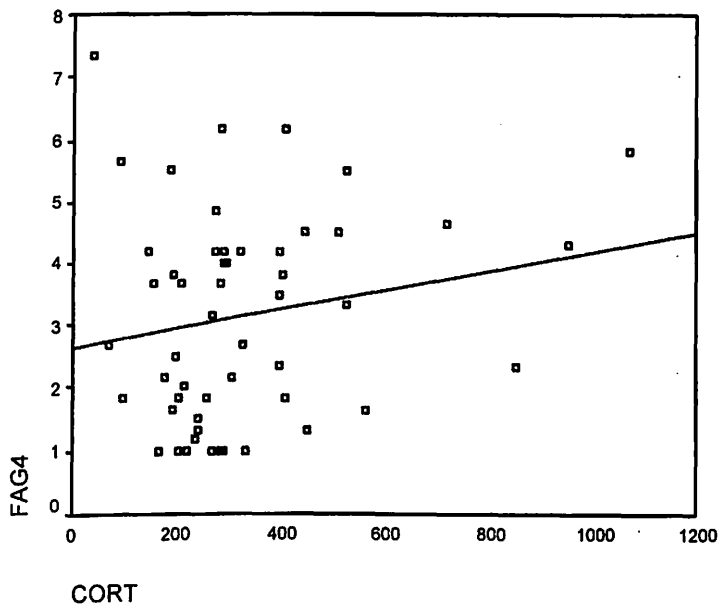
Correlation between TSH levels with Fatigue Score (2)

Figure 2c.



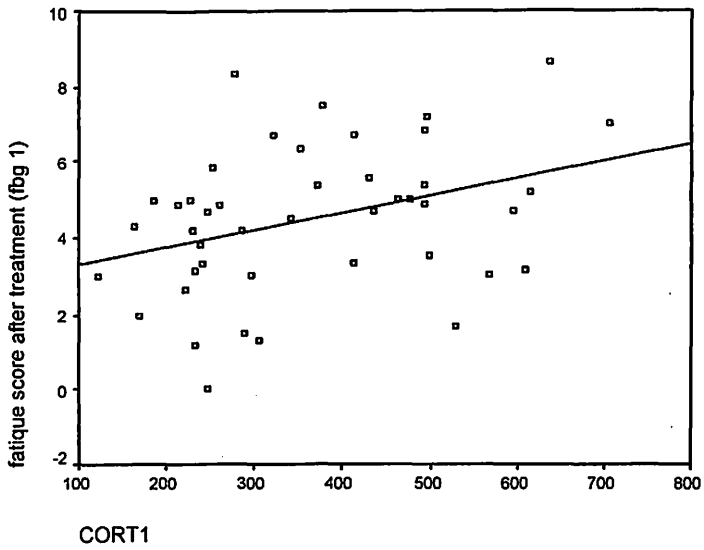
Correlation between TSH levels with Fatigue Score (3)

Figure 2d.



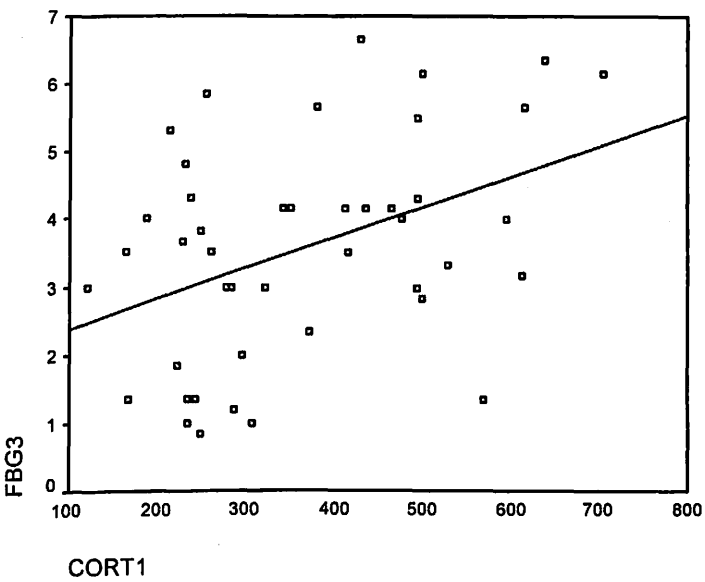
Correlation between serum cortisol level and fatigue score(4)

Figure 2e.



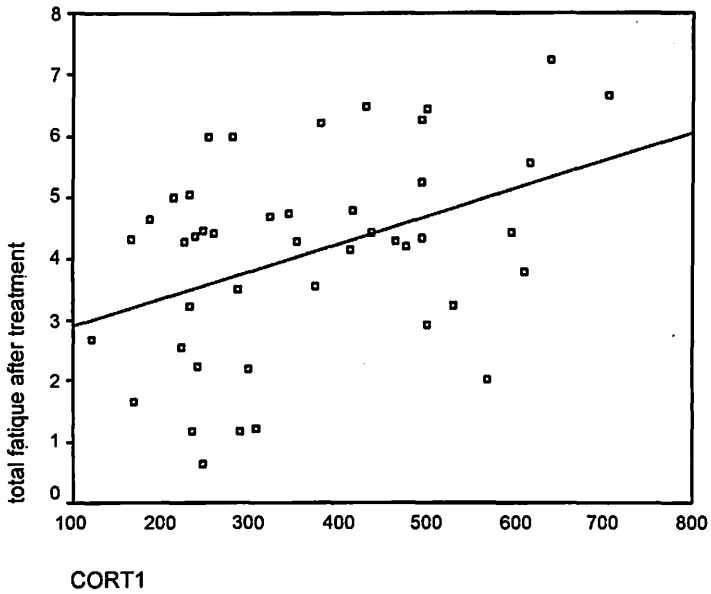
Correlation between serum cortisol level and fatigue score(5)

Figure 2f.



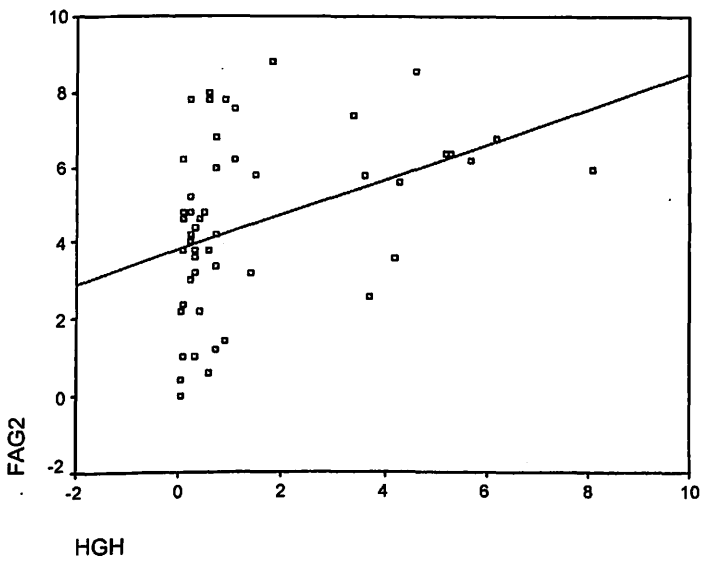
Correlation between serum cortisol level and fatigue score (6)

Figure 2g.



Correlation between serum cortisol level and fatigue score (7)

Figure 2h.



Correlation between serum cortisol level and fatigue score (8)

other miscellaneous sites (14%)(Figure-1c). The evaluation of hematological and biochemical parameters did not yield any correlate. Hormone analysis revealed significant correlation between CTRF and human growth hormone (HGH) (Pearson correlation 0.399), cortisol (Pearson correlation 0.414) and thyroid stimulating hormones (TSH). The former parameters (HGH & cortisol) were positively correlated however the later (TSH) parameter was negatively correlated (Pearson correlation -0.145) with CTRF (Figure-2)(Table-2). The fatigue score before treatment behavioral severity (26.6%), affective meaning (28%), sensory (22.2%), cognitive mood (8.8%) and total score (22.2%). Following treatment the fatigue score changed to behavioral severity (35.5%), affective meaning (35.5%), sensory (31.1%), cognitive mood (24.4%) and total fatigue score (24.4%)(Table-3).

Discussion

Fatigue is the one of the most common symptom encountered amongst cancer patients before, during and after cancer therapy. Fatigue exists in 14 to 96% of patients, particularly among individuals undergoing anti-cancer treatment.[9] Fatigue is difficult to describe and patients express it in a variety of ways, using terms such as tiredness, weakness, exhausted, weary, worn out, heavy or slow. Likewise health professionals too have problem to describe fatigue as asthenia, lassitude, prostration, exercise intolerance, lack of energy and weakness.

Defining fatigue has challenged clinicians and researchers alike for many years. Generally fatigue may be defined as a condition characterized by distress and decreased functional status related to decrease in energy. The specific manifestations may be physical, mental or emotional. For clinical and research purpose, it is useful to distinguish significant cancer related fatigue from other kinds of fatigue to plan specific management guidelines.

Acute fatigue is normal or expected tiredness characterized by localized intermittent symptoms, rapid onset and for short duration. Whereas rest will completely restore a healthy individual to a normal level of functioning, this restorative capacity is diminished in the presence of neoplastic disease. Chronic fatigue described as prolonged,

debilitating fatigue that is persistent or relapsing, lasting weeks, and not anticipated to end soon. This illness is sometimes diagnosed in general medical population. Although a variety of treatment and disease related factors might contribute to the development of fatigue, the biochemical, physiological, psychological, and behavioral mechanism of this symptom complex are poorly understood. There is no standard of care for the assessment or treatment of fatigue in patients suffering from cancer.

For many people diagnosed with cancer, fatigue may become a critical issue in their lives. Fatigue may influence one's well-being, daily performance, activities of daily living, relationship with family and compliance to treatment.

The exact mechanism of fatigue that cause or promote fatigue in patients with cancer is unknown. It is likely that many different mechanisms may play role in its pathogenesis. Various models have been proposed for the study of fatigue.[10] Prolonged stress that produces a stress response may be used as a model for fatigue. Peoples with fatigue frequently suffers from extreme stress over a long period of time, causing them to expend energy and experience a high level of fatigue. In contrast, one study demonstrated that energy requirements vary in peoples with cancer. This suggests that the factors other than energy requirements contribute to fatigue.

A neurophysiologic model has been proposed to study fatigue.[10] This model has both central and peripheral components. The central component consists of the psyche/brain and spinal cord. The peripheral system consists of peripheral nerves, muscle sarcolemma, transverse tubular system, calcium release, actin/myosin interaction, cross bridge tension and heat and force /power output. Impairment of the central component causes lack of motivation, impaired spinal cord transmission and exhaustion or malformation of brain cells in the hypothalamic region. Damage to the peripheral component can cause impaired peripheral nerve function in transmission at the neuromuscular junction, thereby affecting fibre activation. Both types of damage may play a role in the chronic fatigue. The central mechanism may be the key to explaining the extreme fatigue of biotherapy treated patients. It remains to be established whether potentially neurotoxic chemotherapeutic regimens cause fatigue through this mechanism. Further many individuals with cancer may be concurrently receiving

analgesics, hypnotics, anti-depressants, anti-emetics and anticonvulsants, because many of these drugs act on the CNS, they can significantly compound this problem.

Another perspective in the study of fatigue focuses on the reduction in skeletal muscle protein stores that may result from endogenous tumor necrosis factor (NTF) or from TNF administered as antineoplastic therapy. This muscle wasting would require individuals to exert an unusually high amount of energy to generate adequate contractile force during exercise performance or during extended period of sitting or standing.

The pathophysiological mechanism of fatigue is still in research phase. There are very few evidences in the literature related to is pathophysiology. The role of anemia in the development of fatigue and low quality of life is well established in randomized controlled trials. Low haemoglobin level leading to decreased oxygen transport thus decreasing cellular metabolism and thus development of fatigue. Further chronic fatigue syndrome may affect hypothalamic pituitary adrenal axis.[11] However the neuroendocrine response in depression and chronic fatigue syndrome is contradictory.[12] In the above study of 15 depression and10 fatigued patients, the baseline circulating cortisol level were found to have raised among depressed and lowest among chronic fatigue syndrome in our study of 52 patients the cortisol level was raised in cancer treatment related fatigue. Probably the cancer related psychological stress might have stimulated cortisol level in the blood.

Influence of the human growth hormone has been known to be related to the growth and well being and cognitive function in human beings. In a study the effects of HGH on the central nervous system activity, vigilance and sleepiness was studied among HGH deficient patients. In this study there were some improvement in the sleep quality, and mood.[13] In our study we found raise in the HGH level among patients with high fatigue score. Again the raise in the HGH might be related to the stress related cancer itself or due to cancer treatment with chemotherapy and radiotherapy.

Low thyroxine levels leading to hypothyroid syndrome. Hypothyroid patients develop low energy level and easy fatiguability. In contrast, the thyroid stimulating hormone is raised as an inhibitory mechanism. In our analysis we found an inverse correlation between TSH level and cancer treatment related fatigue.

In conclusion the correlation of hormone level in cancer treatment related fatigue is a very complex issue. This syndrome is multifactorial and involve multiple hormones. In our study we found a low level correlation between increased CTRF with HGH and cortisol but a negative relation with TSH. Our finding could help in the understanding of the pathophysiology of fatigue at the hypothalamo-pituitary and adrenal axis, thereby help in the management of fatigue. However further study on the other hormones are necessary to unreveal the alteration of hormonal milleu in response to fatigue.

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Annexure I

BORANG MAKLUMAT DAN KEIZINAN PESAKIT

Hubungan CTRF (Penat atau lesu disebabkan oleh rawatan radioterapi,kimoterapi imunoterapi atau pembedahan) dengan biokimia dan profil/ bentuk hormon – satu kajian perspektif.

Pengenalan

Anda dijemput secara sukarela untuk mengambil bahagian dalam projek penyelidikan ini berkenaan kajian (CRTF). Rawatan barah, sama ada radioterapi, kimoterapi, imunoterapi atau pembedahan boleh menyebabkan keletihan yang ketara. Gejala keletihan ini amat menganggu bagi pesakit barah kerana membawa kepada ketidakseimbangan rawatan kanser sebenar dan kuantiti hidup yang buruk. Sindrom keletihan adalah tanda penyakit psikologi dan fizikal. Pengesanan keletihan dan rawatan yang tepat pada masanya boleh mengelakkan gejala yang melemahkan ini. Dalam penyelidikan ini kita akan lihat jika had biokimia dan hormon mempengaruhi perkembangan CTRF, supaya doktor yang merawat anda boleh merawat anda sebelum gejala keletihan anda menjadikan anda lebih sakit. Jika anda mengambil bahagian, anda akan menerima satu salinan borang ini untuk rekod atau simpanan anda. Penyertaan anda dalam penyelidikan ini hanyalah semasa rawatan antibarah anda iaitu pada permulaan dan penghujung rawatan.

TUJUAN PENYELIDIKAN

Tujuan penyelidikan ini ialah untuk mengetahui sebarang hubung kait antara CTRF dengan had biokimia dan hormon pesakit.

KELAYAKAN UNTUK PENYERTAAN

Doktor yang mengendalikan penyelidikan ini atau wakil dalam penyelidikan ini akan memaklumkan kepada anda mengenai prosedur penyelidikan ini dan kelayakan untuk menyertai kajian ini. Adalah penting anda bercakap benar sepenuhnya dengan doctor anda dan kakitangan mengenai sejarah kesihatan anda. Anda tidak patut menyertai kajian ini jika anda tidak memenuhi semua kelayakan yang disebut di bawah.

1. Anda mestilah didiognosis menghidap barah.
2. Anda sukarela mahu menyertai.
3. Anda tidak menghidap sebarang penyakit psikiatrik.
4. Sanggup menandatangani keizinan bertulis untuk menyertai kajian
5. Berumur antara 15-71 tahun
6. Status pelaksanaan atau pencapaian ECOG kurang daripada 3 (Taraf)

Anda tidak boleh menyertai kajian ini jika anda mempunyai perkara berikut:

1. Sejarah penyakit psikiatrik yang lampau atau sekarang.
2. Pesakit-pesakit dengan tahap hemoglobin kurang dari 10 gm/dl
3. Pesakit medical yang mengerikan atau melemahkan
4. Pesakit-pesakit hipotiroid
5. Pesakit-pesakit tumor otak
6. Pesakit-pesakit yang tidak memahami kandungan soal selidik.

PROSEDUR KAJIAN

Jika anda bersetuju menyertai penyelidikan ini, semasa lawatan pertama anda ke klinik radioterapi dan ongkologi. Kami akan mencatat rekod kesihatan anda daripada rekod hospital . Satu soal selidik khas disediakan untuk mendapatkan maklumat mengenai keletihan, Anda digalakkan menjawab soalan-soalan tersebut atau pembantu penyelidik kami akan menbantu anda menjawabnya dengan betul. Sampel darah akan diambil pada hari temubual atau sebelum memulakan rawatan antibarah sebenar. Contohnya kimoterapi dan radioterapi untuk menguji fungsi hati, fungsi buah pinggan, kiraan darah, pertumbuhan hormon, hormon rangsangan tirod, hormon adrenocarticotrophin, dan tahap kortisol dalam darah anda. Prosedur sama akan diulang selepas selesai kimoterapi atau radioterapi.

RISIKO YANG ADA.

Tiada risiko tertentu yang dijangkakan kerana kajian ini pada asasnya adalah soal selidik sahaja.

MELAPORKAN KEADAAN KESIHATAAN

Jika anda mengalami keadaan yang teruk semasa kajian, pastikan anda menghubungi Dr. Biswa Mohan Biswa (09-7651700 ext 3102) untuk bantuan semasa waktu pejabat.

PENYERTAAN DALAM KAJIAN INI

Penyertaan anda dalam kajian ini adalah sukarela. Anda boleh menolak daripada menyertai kajian ini atau anda boleh berhenti menyertai kajian ini pada bila-bila masa, tanpa sebarang denda atau kehilangan faedah yang berhak anda terima. Penyertaan anda juga boleh diberhentikan oleh doktor penyelidik tanpa keizinan anda.

FAEDAH KEMUNGKINAN

Dengan menyertai kajian ini, anda dapat mengetahui markah keletihan anda jika anda mahu.

BAYARAN PENYELIDIKAN

Penyelidik tidak di bayar dari geran penyelidik untuk mengendalikan kajian ini. Walau bagaimanapun setiap pesakit akan dibayar insentif RM 20.00 untuk berkerjasama dalam kajian ini.

PENYERTAAN

Jika anda mempunyai sebarang pertanyaan mengenai kajian ini , sila hubungi Dr. Biwa Mohan Biswal di jabatan Perubatan Nuklear,Radioterapi dan Onkologi, Hospital Universiti Sains Malaysia atau menulis email di alamat biswa@kb.usm.my atau telefon di nombor 09-7651700 (ext 3102)

MAKLUMAT ANDA DI RAHSIAKAN

Maklumat perubatan anda akan dirahsiakan oleh doktor penyelidik dan kakitangan dan tidak akan diumumkan, kecuali dikehendaki oleh undang-undang. Data yang diambil dari kajian ini tidak mengenalkan anda sebagai individu tapi boleh disiarkan. Rekod perubatan asal anda mungkin disemak oleh jawatankuasa etika perubatan, jawatankuasa penyelidik atau pihak berkuasa berkanun untuk tujuan pengesahan penyelidikan. Maklumat perubatan anda mungkin disimpan dan diproses oleh komputer. Dengan menandatangani borang keizinan ini, anda memberi kuasa untuk penyemakan rekod, penyimpanan maklumat dan pemindahan data yang diterangkan di atas.

TANDATANGAN

Untuk berhak menyertai kajian ini, anda atau wakil yang sah mestilah menandatangani dan menulis tarikh di muka surat yang ditetapkan (lihat lampiran 1)

Borang Keizinan Pesakit
Lampiran 1
Halaman Tandatangan

Untuk menyertai kajian ini, anda atau wakil sah anda mesti menandatangani mukasurat ini.

Dengan menandatangani mukasurat ini, saya mengesahkan yang berikut:

- O Saya telah membaca semua maklumat dalam Borang Maklumat dan Keizinan Pesakit ini **termasuk apa-apa maklumat berkaitan risiko yang ada dalam kajian** dan saya telahpun diberi masa yang mencukupi untuk mempertimbangkan maklumat tersebut.
- O Semua soalan-soalan saya telah dijawab dengan memuaskan
- O Saya, secara sukarela, bersetuju menyertai kajian penyelidikan ini, mematuhi segala prosedur kajian dan memberi maklumat yang diperlukan kepada doktor, para jururawat dan juga kakitangan lain yang berkaitan apabila diminta.
- O Saya boleh menamatkan penyertaan saya dalam kajian ini pada bila-bila masa.
- O Saya telahpun menerima satu salinan Borang Maklumat dan Keizinan Pesakit untuk simpanan peribadi saya.

Nama Pesakit (Ditera atau Ditaip)	**Nama Singkatan** dan **Nombor Pesakit**
No. Kad Pengenalan Pesakit (baru)	**No. K/P (lama)**
Tandatangan Pesakit atau Wakil Sah	**Tarikh** (ddMMyy) (tambahkan masa jika sesuai)
Nama Individu yang Mengendalikan Perbincangan Keizinan (Ditera atau Ditaip)	
Tandatangan Individu Mengendalikan Perbincangan Keizinan	**Tarikh** (ddMMyy)
Nama Saksi dan **Tanda Tangan**	**Tarikh** (ddMMyy)

Annexure II

I.D.nombor

Tentang anda

Sebelum anda bermula kami ingin anda menjawab beberapa soalan am mengenai diri anda : dengan membulatkan jawapan yang betul atau mengisi tempat kosong yang di sediakan.

Apakah jantina anda? Lelaki Perempuan

Bilakah tarikh lahir anda ? ---------- / ---------- / ----------
Hari Bulan Tahun

Apakah tahap pendidikan tertinggi yang anda terima ?
Tiada langsung
Sekolah Rendah
Sekolah Menengah
Peringkat Tinggi / kolej/ Universiti

Apakah status perkahwinan anda
Bujang Berpisah
Kahwin Bercerai
Hidup Berasama Duda/Balu

Adakah anda sekarang ini sakit ?
Jika ada yang kena dengan kesihatan anda apakah ia ---------- sakit/ masalah lain

Arahan

Penilaian ini bertanyakan perasaan anda mengenai kualiti kehidupan, kesihatan dan perkara lain dalam kehidupan anda. **Sila jawab semua soalan**. Jika anda tidak pasti mengenai jawapan kepada sesuatu soalan, **sila pilih salah satu yang anda rasakan sesuai**. Ia selalunya respon pertama anda.

Sila beri perhatian kepada standard harapan kegembiraan dan keperihatinan anda. Kami mahu anda fikir mengenai kehidupan **anda sepanjang dua minggu lepas**. Sebagai contoh berfikir mengenai dua minggu lepas, terdapat soalan yang mungkin bertanya :

	Adakah anda mendapat jenis sokongan yang anda kehendaki daripada orang lain	Tiada langsung	Tidak banyak	Sederhana	Banyak	Sepenuhnya
		1	2	3	4	5

Anda dikehendaki membulatkan nombor yang paling sesuai menunjukkan kekerapan sokongan yang anda terima dari orang lain sepanjang dua minggu lepas. Jadi anda akan membulatkan nombor empat jika andamendapat banyak sokongan daripada orang lain.

	Adakah anda mendapat jenis sokongan yang anda kehendaki daripada orang lain	Tiada langsung	Tidak banyak	Sederhana	Banyak	Sepenuhnya
		1	2	3	4	5

Anda akan membulatkan nombor satu jika anda tidak mendapat langsung sokongan yang anda perlukan daripada orang lain selama dua minggu lepas

Sila baca setiap soalan, nilai perasaan anda dan bulatkan nombor di skala yang menunjukkan jawapan terbaik kepada anda.

		Sangat Teruk	Teruk	Teruk Tapi tidak teruk	Baik	Sangat baik
1(G1)	Bagaimanakah anda menilai quality hidup anda	1	2	3	4	5

		Sangat tidak berpuas hati	Tidak puas hati	Tidak puas dan tidak rasa tidak puas	Puas hati	Sangat puas hati
2(G4)	Adakah anda berpuas hati dengan kesihatan anda	1	2	3	4	5

Soalan-soalan berikut menanyakan sebanyak mana anda mengalami perkara-perkara tertentu sepanjang dua minggu lalu.

		Tidak menganggu langsung	Sedikit	Jumlah yang sederhana	Sangat menganggu	Teruk
3(F1.4)	Sehingga setakat manakah anda merasa kesakitan fizikal menghalang anda melakukan apa yang perlu anda lakukan?	1	2	3	4	5
4(F11.3)	Berapa banyak anda memerlukan rawatan perubatan dalam kehidupan seharian?	1	2	3	4	5
5(F4.1)	Sebanyak manakah anda menikmati kehidupan anda?	1	2	3	4	5
6(F24.2)	Sehingga setakat manakah anda rasa hidup anda bermakna?	1	2	3	4	5

		Tidak menganggu langsung	Sedikit	Jumlah yang sederhana	Sangat menganggu	Teruk
7(F5.3)	Berapa banyak anda boleh menumpukan perhatian ?	1	2	3	4	5
8(F16.1)	Adakah anda berasa selamat dalam kehidupan seharian ?	1	2	3	4	5
9(F22.1)	Bagaimana kesihatan persekitaran fizikal anda ?	1	2	3	4	5

Soalan ini bertanya sebanyak manakah anda mengalami atau berkeupayaan melakukan perkara-perkara tertentu sepanjang dua minggu lepas.

		Tidak ada langsung	Sedikit	Sederhana	Kebanyakan	Sepenuhn
10(F2.1)	Adakah anda mempunyai cukup tenaga dalam kehidupan seharian anda?	1	2	3	4	5
11(F7.1)	Adakah anda dapat menerima penampilan diri/fizikal anda?	1	2	3	4	5
12(F18.1)	Adakah anda mempunyai cukup wang dalam memenuhi kehendak awak?	1	2	3	4	5
13(F20.1)	Adakah mudah untuk mendapatkan maklumat yang anda perlukan dalam kehidupan sehari-harian ?	1	2	3	4	5
14(F21.1)	Sejauh manakah anda mempunyai peluang untuk aktiviti masa lapang anda?	1	2	3	4	5

		Sangat teruk	Teruk	Tidak teruk dan tidak bagus	Baik	Sangat baik
15(F9.1)	Sebaik manakah anda boleh bergerak	1	2	3	4	5

Soalan-soalan berikut menghendaki anda menyatakan sebaik atau sepuas mana anda rasakan mengenai pelbagai aspek kehidupan anda sepanjang dua minggu lalu.

		Sangat tidak puas hati	Tidak puas hati	Tidak puas dan tidak rasa tidak puas	Puas hati	Sangat puas hati
16(F3.3)	Adakah awak berpuas hati dengan tidur awak	1	2	3	4	5
17(F10.3)	Adakah anda berpuas hati dengan kemampuan anda untuk menjalankan aktiviti harian anda?	1	2	3	4	5
18(F12.4)	Adakah anda berpuas hati dengan kapisiti pekerjaan anda?	1	2	3	4	5
19(F6.3)	Sejauh manakah anda berpuas hati dengan diri anda?	1	2	3	4	5
20(F13.3)	Sejauh manakah nada berpuas hati dengan hubungan peribadi anda?	1	2	3	4	5
21(F15.3)	Sejauh manakah nada berpuas hati dengan kehidupan seksual anda?	1	2	3	4	5
22(F14.4)	Sejauh manakah anda berpuas hati dengan sokongan yang anda dapati dari kawan-kawan anda?	1	2	3	4	5
23(F17.3)	Sejauh manakah anda berpuas hati dengan tempat tinggal anda?	1	2	3	4	5
24(F19.3)	Sejauh manakah anda berpuas hati dengan kemudahan anda mendapatkan khidmat kesihatan?	1	2	3	4	5
25(F23.3)	Sejauh manakah anda berpuas hati dengan kenderaan anda?	1	2	3	4	5

Soalan berikut merujuk kepada sekerap mana anda merasai atau mengalami perkara tertentu sepanjang dua minggu lepas.

		Tidak pernah	Jarang-jarang	Agak selalu	Kerap kali	Sentiasa
26(F8.1)	Sekerap manakah anda mempunyai perasaan negatif seperti kemurungan, sedihdan rungsing?	1	2	3	4	5

Adakah seseorang menolong anda untuk mengisi borang ini.....

Berapa lama anda mengambil masa untuk mengisi borang ini?.....

Adakah anda mempunyai apa-apa komen mengenai penilaian ini?

.....

.....

TERIMA KASIH DI ATAS BANTUAN ANDA

Annexure III

SKALA KELETIHAN PIPER (PFS)

Arahan: Ramai orang akan mengalami satu perasaan letih/penat yang keterlaluan atau lebih dari biasa apabila mereka sakit, menerima rawatan atau sedang sembuh dari sakit atau rawatan. Perasaan ini biasanya tidak dapat dikurangkan samada dengan tidur yang cukup atau dengan berihat. Ada orang mengenali gejala in sebagai "fatig" atau keletihan untuk membezakannya dengan perasaan letih yang biasa.

Untuk setiap soalan berikutnya, sila tandakan √ pada angka yang terbaik yang mengambarkan keletihan yang anda alami pada masa ini atau pada hari ini. Jika anda tidak mengalami keletihan itu sekarang atau pada hari ini, tandakan pada "0" untuk menandakan respons anda. Terima kasih!

1. Berapa lamakah anda telah mengalami keletihan?

   0 1. tidak pernah.
   0 2. beberpa minit
   0 3. beberapa jam
   0 4. beberapa hari
   0 5. beberapa minggu
   0 6. beberapa bulan
   0 7. lain-lain (sila nyatakan) _____

2. Setakat manakah keletihan yang anda alami sekarang menyebabkan anda merana?

Tiada									Teramat banyak	
0	1	2	3	4	5	6	7	8	9	10

3. Setakat manakah keletihan yang anda alami sekarang mengganggu keupayaan anda untuk menyelesaikan kerja anda?

Tiada									Teramat banyak	
0	1	2	3	4	5	6	7	8	9	10

4. Setakat manakah keletihan yang anda alami sekarang mengganggu keupayaan anda untuk bergaul dengan sahabat-sahabat anda?

Tiada									Teramat banyak	
0	1	2	3	4	5	6	7	8	9	10

5. Setakat manakah keletihan yang anda alami sekarang mengganggu keupayaan anda dalam melakukan aktiviti seksual?

Tiada									Teramat banyak	
0	1	2	3	4	5	6	7	8	9	10

6. Setakat manakah keletihan yang anda alami sekarang mengganggu keupayaan anda melibatkan diri dengan aktiviti yang anda gemar?

Tiada — Teramat banyak

0 1 2 3 4 5 6 7 8 9 10

7. Bagaimanakah anda menggambarkan tahap kekuatan atau teruknya keletihan yang anda alami sekarang?

Ringan — Sangat teruk

0 1 2 3 4 5 6 7 8 9 10

8. Setakat manakah anda menggambarkan keletihan yang anda alami sekarang sebagai:

Menyenangkan — Tidak menyenangkan

0 1 2 3 4 5 6 7 8 9 10

9. Setakat manakah anda menggambarkan keletihan yang anda alami sekarang sebagai:

Boleh diterima — Tidak boleh diterima

0 1 2 3 4 5 6 7 8 9 10

10. Setakat manakah anda menggambarkan keletihan yang anda alami sekarang sebagai:

Melindungi — Memudaratkan

0 1 2 3 4 5 6 7 8 9 10

11. Setakat manakah anda menggambarkan keletihan yang anda alami sekarang sebagai:

Positif — Negatif

0 1 2 3 4 5 6 7 8 9 10

12. Setakat manakah anda menggambarkan keletihan yang anda alami sekarang sebagai:

Biasa — Luar biasa

0 1 2 3 4 5 6 7 8 9 10

13. Setakat manakah perasaan anda sekarang:

Kuat — Lemah

0 1 2 3 4 5 6 7 8 9 10

14. Setakat manakah anda sekarang berasa:

Sedar/Jaga — Mengantuk

0 1 2 3 4 5 6 7 8 9 10

15. Setakat mana perasaan anda sekarang:

Bersemangat — Tidak bermaya

0 1 2 3 4 5 6 7 8 9 10

16. Setakat manakah anda sekarang berasa:

Segar — Lesu

0 1 2 3 4 5 6 7 8 9 10

17. Setakat mana perasaan anda sekarang:

Bertenaga — Tidak bertenaga

0 1 2 3 4 5 6 7 8 9 10

18. Setakat mana perasaan anda sekarang:

Sabar — Tidak sabar

0 1 2 3 4 5 6 7 8 9 10

19. Setakat mana perasaan anda sekarang:

Tenang — Tegang

0 1 2 3 4 5 6 7 8 9 10

20. Setakat mana perasaan anda sekarang:

Sangat gembira — Sedih

0 1 2 3 4 5 6 7 8 9 10

21. Setakat mana anda sekarang:

Boleh menumpukan perhatian — Tidak boleh menumpukan perhatian

0 1 2 3 4 5 6 7 8 9 10

22. Setakat mana anda sekarang mempunyai:

Daya ingatan yang baik — Daya ingatan yang tidak baik

0 1 2 3 4 5 6 7 8 9 10

23. Setakat mana anda sekarang:

Boleh berfikir dengan jelas — Tidak boleh berfikir dengan jelas

0 1 2 3 4 5 6 7 8 9 10

24. Secara keseluruhannya, apakah yang anda percaya banyak menyumbang atau menyebabkan keletihan anda?

_____

_____

25. Secara keseluruhannya, perkara terbaik yang anda telah temui untuk melegakan keletihan anda adalah:

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_____

26. Adakah anda ingin menambah perkara lain yang boleh mengambarkan keletihan anda dengan lebih baik kepada kami?

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_____

27. Adakah anda mengalami sebarang gejala lain sekrang ini?

Sila huraikan:

_____

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P05/1250: Hormone levels in radiotherapy treatment related fatigue

Biswa M Biswal, Gulam S Mallik, Universiti Sains Malaysia, Malaysia

Introduction: Radiotherapy is known to cause debilitating treatment related fatigue. Fatigue in general is a conglomeration of psychological, physical, hematological and unknown factors influencing the internal milieu of the cancer patient. Radiotherapy can add stress at the cellular and somatic level to aggravate further fatigue in cancer patients undergoing radiotherapy. Stress related hormones might be mediating in the development of fatigue.

Materials and Methods: This is an ongoing prospective study to evaluate if the hormonal profile related to stress is influenced by radiotherapy treatment related fatigue. The study was conducted from September 2002 onwards in the division of Radiotherapy & Oncology of our Medical School. Previously untreated patients with histopathology proof of malignancy requiring external beam radiotherapy were considered for this study. Selection criteria were applied to exclude other causes of fatigue. Initial fatigue score was obtained using Pipers Fatigue Score questionnaire containing 23 questions, subsequently final fatigue score was obtained at the end of radiotherapy. Blood samples were obtained to estimate the levels of ACTH, TSH, HGH, and cortisol on the final assessment. The hormone levels were compared with resultant post radiotherapy fatigue score.

Results: At the time of reporting 50 patients were evaluable for the study. The total significant fatigue score was observed among 12 (24%) patients. The individual debilitating fatigue score were behavioral severity 14 (28%), affective meaning 14(28%), Sensory 13 (26%) and cognitive mood 10 (20%) respectively. From the analysis of hormonal profile, growth hormone level > 1 ng/mL and TSH <0.03 appears to be associated with high fatigue score (though statistically not significant); whereas there was no correlation with ACTH and serum cortisol level.

Conclusions: In our prospective study severe radiotherapy treatment related fatigue was found among our patient population. Low levels of TSH and high levels of GH appear to be associated with significant fatigue.

Keywords: Radiotherapy, treatment related fatigue, hormone profile, and correlation

P05/1251: A randomised trial of preoperative radiotherapy for stage T3 adenocarcinoma of rectum (TROG 01.04): a progress report

Sam Ngan, Richard Fisher, Michael J McKay, B McClure, Peter MacCallum Cancer Centre, Australia; Bryan H Burmeister, D Schache, Princess Alexandra Hospital, Australia; David Joseph, Sir Charles Gairdner Hospital, Perth, Australia; M Solomon, Royal Prince Alfred Hospital, Australia; Stephen P Ackland, Mater Hospital, Newcastle, Australia; D Goldstein, Prince of Wales Hospital, Australia; S McLachlan, St Vincent's Hospital, Australia; H Dhillon, NHMRC Clinical Trials Centre, Australia; P Thompson, Auckland Hospital, New Zealand

Purpose: To provide a progress report of the conduct of the randomised trial TROG 01.04.

Methods: This is a randomised Australian and New Zealand multi-centre trial of preoperative radiotherapy for rectal cancer currently being conducted under the auspices of Trans-Tasman Radiation Oncology Group, Australasian Gastrointestinal Trials Group, Colorectal Surgical Society of Australasia, and Royal Australasian College of Surgeons.

The trial comprises two studies, each with its own main objective. These objectives are, in patients with T3 clinically resectable carcinoma of the rectum, to demonstrate that (Study 1) the local recurrence rate in patients treated with a long course (LC) of pre-operative radiotherapy with continuous infusion 5-FU is lower than that in patients treated with a short course (SC) of pre-operative radiotherapy with early surgery; and (Study 2) the local recurrence rate in patients given pre-operative radiotherapy and chemotherapy is lower than that in patients treated with initial surgery.

Results: Over 150 patients have been accrued from 21 centres in the first 21 months. All patients were enrolled on Study 1, SC versus LC pre-operative radiotherapy. Study 2 has enrolled no patients in 15 months and has been discontinued. There was no obvious difference in rates of serious adverse events of SC and LC. An Independent Data Monitoring Committee is monitoring these and other aspects of the trial.

Conclusions: The trial of SC versus LC is progressing well: such a trial is clearly feasible in Australia and New Zealand. It is however not feasible to compare initial surgery with preoperative radiotherapy.

UNIVERSITI SAINS MALAYSIA
JABATAN BENDAHARI
KUMPULAN WANG PENYELIDIKAN GERAN USM(304)
PENYATA PERBELANJAAN SEHINGGA 30 NOVEMBER 2004

Jumlah Geran:	RM	19,904.00	Ketua Projek:	DR. BISWA MOHAN BISWAL
Peruntukan 2002 (Tahun 1)	RM	0.00	Tajuk Projek:	Correlation of Cancer Treatment l Related Fatigue (CTRF) with Biochemical and Hormonal Profile. A Prospective Study
Peruntukan 2003 (Tahun 2)	RM	0.00		
Peruntukan 2004 (Tahun 3)	RM	0.00	Tempoh:	15 Julai 02- 14 Apr 04
			No.Akaun:	304/PPSP/6131233

Kwg	Akaun	PTJ	Projek	Donor	Peruntukan Projek	Perbelanjaan T'kumpul Hingga Tahun Lalu	Peruntukan Semasa	Tanggungan Semasa	Bayaran Tahun Semasa	Belanja Tahun Semasa	Baki Projek
304	11000	PPSP	6131233		5,234.00	7,861.58	(2,627.58)	-	756.90	756.90	(3,384.48)
304	14000	PPSP	6131233		-	-	-	-	259.77	259.77	(259.77)
304	15000	PPSP	6131233		-	-	-	-	-	-	-
304	21000	PPSP	6131233		870.00	395.80	474.20	-	-	-	474.20
304	22000	PPSP	6131233		-	-	-	-		-	-
304	23000	PPSP	6131233		300.00	181.80	118.20	-	-	-	118.20
304	24000	PPSP	6131233		-	-	-	-	-	-	-
304	25000	PPSP	6131233		-	-	-	-	-	-	-
304	26000	PPSP	6131233		-	-	-	-	-	-	-
304	27000	PPSP	6131233		3,000.00	722.10	2,277.90	-	4,534.55	4,534.55	(2,256.65)
304	28000	PPSP	6131233		-	-	-	-	-	-	-
304	29000	PPSP	6131233		10,500.00	1,020.20	9,479.80	-	380.00	380.00	9,099.80
304	32000	PPSP	6131233		-	-	-	-	-	-	-
304	35000	PPSP	6131233		-	-	-	-	2,810.00	2,810.00	(2,810.00)
304	42000	PPSP	6131233		-	-	-	-		-	-
					19,904.00	10,181.48	9,722.52	-	8,741.22	8,741.22	981.30