

行政院衛生署 96 年度委託研究計畫

成果報告

計畫名稱： **cytokines 和肝癌放射治療相關疲倦之間
的角色**

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**本研究報告僅供參考，不代表本署意見

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摘要

放射治療導致的疲倦是很常有之早期及慢性的副作用。據研究報導，多達80% 病人於治療中有早期發生之疲倦，而有多達30% 於治療後仍有慢性疲倦副作用。至今放射治療導致疲倦的原因仍不十分清楚，許多的相關研究也提出放射治療的程度、放射治療的長短、放射治療的癌症部位、及使用合併治療的模式等都有不同的影響。疲倦比疼痛、性生活、癌症本身及治療模式都更嚴重影響生活品質。而造成疲倦之原因包括有貧血、體重減輕、發燒、疼痛及感染等，以及和上述原因相關之Cytokines、如IL-1、IL-2、TNF- α 及interferon 等。

1. 在先前試驗中，我們對45 位肝癌病人，符合收案標準進行每天2Gy劑量、每週5天共50Gy 之立體定位放射治療（沒有併用其他治療）進行實驗，結果顯示疲倦的程度、疲倦的時間長短及疲倦對生活之影響和放射治療累積劑量有顯著相關。

2. 本實驗共收集20例患者，但僅檢測13位癌症病人血液適合檢測。檢測結果患者cytokines濃度(IL-1b、IL-2、IL-6、IL-8、IL-10、IL-12、TNF)，較正常人血清濃度高出1.5到6.5倍。顯示Cytokines 和許多體內器官及互相反應是造成癌症病人疲倦可能原因。

3. 本實驗針對肝癌病人於6週治療內每週檢測病人血液中Cytokines濃度(IL-1b、IL-2、IL-6、IL-8、IL-10、IL-12、TNF)，同時以林佳靜教授發展之台灣版簡明疲憊量表（BFI-Taiwan Form）來檢定疲倦的程度。病人Cytokines 濃度普遍比正常血清高，其中有部分病人的Cytokines 濃度變化與疲倦有相關性；但因Cytokines 濃度受到全身各器官與生理的影響，大多數病人Cytokines 濃度僅較高於正常血清但其變化與疲倦的關係不高。

本實驗顯示Cytokines IL-2, IL-6, IL-8 濃度與疲倦具有正相關，但因Cytokines 濃度受到全身各器官與生理的影響，機制與相應方法仍需進一步了解。

關鍵詞：Cytokines、疲倦、放射治療、肝癌

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英文摘要

Radiation therapy induced fatigue is a common early and chronic side effect, reported in up to 80% and 30% of patients during radiation therapy and at follow-up visit, respectively. The etiology of radiation therapy induced fatigue are still not understood, and in many studies the degree and time course of fatigue was shown to depend on site of tumor and treatment modalities. Fatigue is the major affect of quality of life more than pain, sexual dysfunction and other cancer or treatment related symptoms. Factor contributing to fatigue including anemia, weight loss, fever, pain, medication and infection; and their natural nataghists , such as IL-1, Il-2, TNF- α and interferon.

In our preliminary data, 45 hepatoma patients undergoing stereotactic radiotherapy(2 Gy/ day, 5 fractions/ week, total of 50 Gy) were shown that their fatigue intensity, fatigue duration and fatigue interference were significantly increased during treatment course.

There are 7 cytokines(IL-1b、IL-2、IL-6、IL-8、IL-10、IL-12、TNF) of 20 cancer sera were analyzed and their concentration is 1.5 to 6.5 times higher than normal sera. This shows that radiotherapy-induced fatigue may correlate the changes of level of cytokines, besides duration of treatment or time-dose factor in radiotherapy is also an important factor.

The cytokines(IL-1b、IL-2、IL-6、IL-8、IL-10、IL-12、TNF) of sera from hepatoma cancer patients were analyzed during the 6 weeks of radiotherapy, and Brief Fatigue Inventory- Taiwan Form (BFI) was used to score of fatigue in cancer patients receiving radiotherapy. The cytokines concentration of patient sera were higher than normal sera. Some changes of cytokines concentration positively related to the scale of fatigue.

The alteration of cytokines concentrations in these 13 samples might be affected by many factors that could not be manipulated by this experiment. However the data show that there are correlation between IL-2, IL-6, IL-8 and fatigue. Since fatigue is one of the most common long-term radiotherapy side effects, numerous patients continue to seek information. This study need further investigation to identify the correlation of the fatigue and cytokines and the mechanism of cytokines to fatigue.

Key Words: Cytokines, Fatigue, Radiation therapy, Hepatoma

前言

Many cytokines have been cloned and administered to patients. [1] (Figure 1) Several of these cytokines produce fatigue, malaise, fever, weight loss, and night sweats. For example, interferon produces neurasthenia, a neurologic fatigue suggestive of frontal lobe changes. This fatigue manifests as loss of motivation. [2] Varieties of distressing symptoms debilitate cancer patients and contribute to their profound fatigue. These symptoms include malaise, B-symptoms (weight loss, fever, and sweats), pruritus, pain, depression, and loss of appetite. These symptoms may predate the diagnosis of cancer or they may be the first harbinger of relapse. Some of these symptoms can also be induced by therapeutic intervention or infection, but many are intrinsic to cancer. Regardless of the underlying cause, cytokines are crucial contributors to many of these symptoms (Table 1), and most of the symptoms correlate or combine with fatigue, that means “symptoms cluster”.

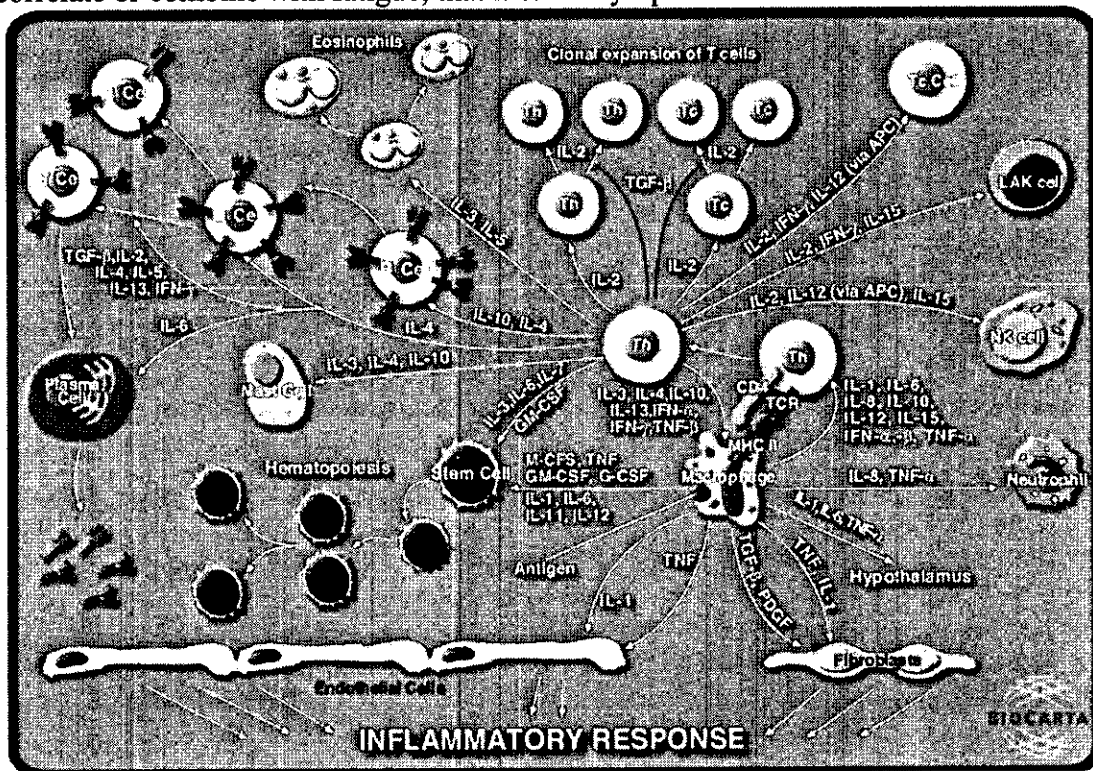


Figure 1. Pathway of Cytokines. Contributed By Glenn Croston, PhD

TABLE 1
Cancer-Related Fatigue: Contributing Factors

Contributing factors	Cytokines deregulated
Anemia	Erythropoietin IL-1 IL-6
Weight loss	TNF IL-1 IL-6 Interferon
Fever	Leukemia inhibitory factor IL-1 IL-6 Interferon
Infection	TNF IL-1 IL-6 IL-10
Depression	Interferon Interferon

IL: interleukin; TNF: tumor necrosis factor.

It is possible that fatigue in cancer patients can be ameliorated by soluble receptors, receptor antagonists, or other cytokine inhibitors. It is because cytokines also enhance the growth of cancer cells and disturb immunosurveillance, cytokine antagonists may have antitumor effects.

Radiotherapy has been reported to induce “early fatigue”(occurring during treatment or shortly after) in up to 80% of patients. [4,5,6] This early fatigue is often accompanied by loss of appetite, nausea and vomiting and constitutes Acute Radiation Sickness. In about 30% of cases it can last long after the completion of treatment (chronic fatigue). [4,5,6]

Since about 50% of cancer patients receive either curative or palliative radiation therapy during the course of their disease, one can easily assess that up to 40% of all oncological patients will suffer from radiotherapy-induced fatigue. Such high prevalence of this symptom warrants its good understanding by all medical and nursing staff dealing with the cancer patients. The real prevalence of radiotherapy-related fatigue is not well know. (Table 2) [7]

There are only few studies comparing the levels of fatigue in cancer patients undergoing radiotherapy and in general population or patients treated with other modalities. For example, in the breast cancer patients higher fatigue level has been observed in the women treated with chemotherapy or chemotherapy and irradiation when compared to women treated with surgery with or without radiotherapy. [8] However, these differences in fatigue levels in breast cancer patients were not significant in the multifactorial analysis. [8]

Definitely, the studies including patients receiving irradiation for being diseases could elucidate the prevalence and etiology or radiotherapy-related fatigue. However, even large series do not report any data on fatigue, which can partially be explained

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by lower radiotherapy doses and smaller fields employed for such treatment. [9]
Knowledge on the therapeutic options in management of radiotherapy-induced fatigue is still limited, however a few randomized studies have been recently published. Significant reduction in fatigue, tension, depression and anger was observed in the out-patients undergoing curative or palliative radiotherapy assigned randomly to relaxation therapy when compared to the control conditions. [9]

Since fatigue is one of the most common long-term radiotherapy side effects, numerous patients continue to seek information. [10] This study related the cytokines , especially IL-6, with fatigue.

TABLE 2. [7]

Potential causes of radiotherapy-related fatigue in cancer patients

Biochemical factors

Serum interleukins

Reverse triiodothyronine

Decline in neuromuscular efficiency

Physical factors

Pulse change with orthostatic stress

Psychological disturbances

Stress

Sleep disturbances

Depression

Anxiety

Radiotherapy complications

Myelosuppression

Diarrhea

Malnutrition

Dehydration

Electrolyte disorders

Dyspnea

Nausea/vomiting

Hormonal or immune insufficiency

Change in weight

Concomitant or pre_ious therapies

Chemotherapy

Hormonotherapy

Biologic response modifiers (for example, interferone)

Surgery

Pharmacological therapy (for example, analgesics)

Co-existing morbidities

Pain

Myelosuppression

Anemia

Infection

Malnutrition

Dehydration

Electrolyte disorders

Concomitant diseases (for example, heart or renal insufficiency)

Immobilation (functional disability)

The goal of this exploratory study is to assess changes in the levels of cytokines

in the plasma during radiotherapy for hepatoma patients and correlate these changes with subjective symptom of fatigue. Hepatocellular carcinoma is a common malignancy in Taiwan. Recently, stereotactic radiotherapy is one of the new treatment modality for this disease[11]. However, there still do not have study focused on the changes of fatigue level in patients receiving this treatment. Our hypothesis was that radiotherapy induces the release of cytokines which in turn contribute to acute and transient flu-like side effects. At baseline, all subjects had measurable level of IL-1B, IL-12, TNF, IL-10, IL-6, IL-8, IL-2 in the serum. Then the baseline levels of cytokines were compared with cumulative radiation dose.

As shown in Figure 2 [13] there are several potential targets for therapeutic interventions of fatigue. Novel interventions that target cytokines and other potential mediators (especially interventions for which the mechanisms of action are understood and can be monitored.)

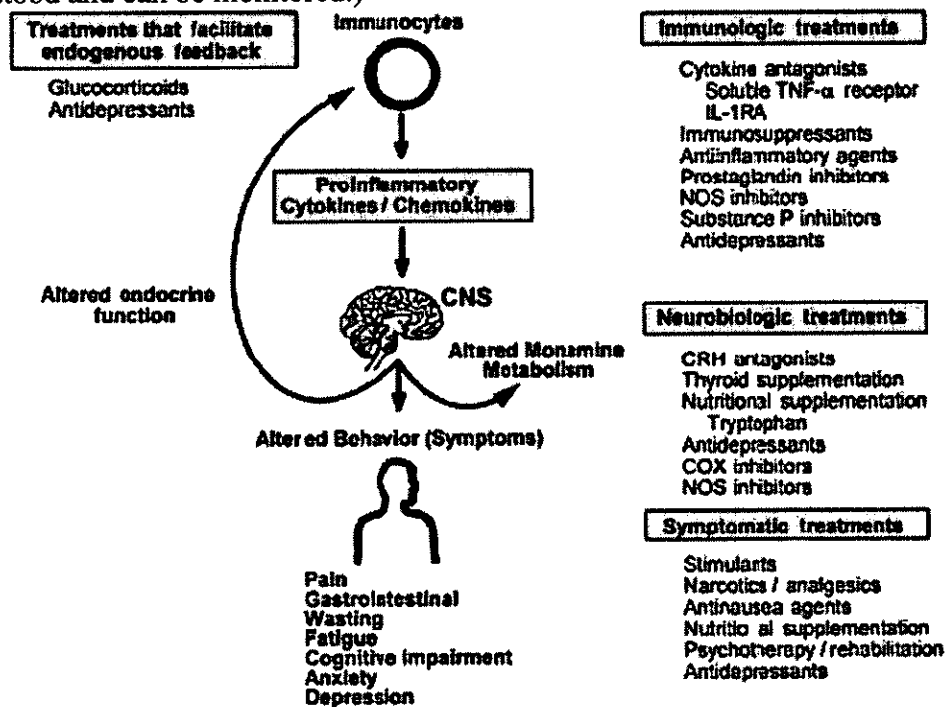


Figure 2. Treatment strategies for cancer-related symptoms. Sites for the implementation of treatments directed at the sickness response circuit are shown. (1) Immunologic treatments (such as soluble receptors of TNF- α and IL-1 receptor antagonists) that are designed to inhibit cytokine signaling directly, or treatments that block downstream mediators of inflammation, including prostaglandins, nitric oxide, and substance P; (2) neurobiologic treatments that target central nervous system (CNS) mediators of behavioral alterations including the monoamines and corticotropin-releasing hormone (CRH); (3) symptomatic treatments (such as narcotics for alleviation of pain, stimulants to combat fatigue, antidepressants for relief from depression) that address the ultimate manifestations of upstream mediators; and (4) treatments designed to take advantage of the normal endogenous feedback circuits that limit sickness responses in settings such as viral illness. CNS: central nervous system; CRH: corticotropin-releasing hormone; COX: cyclooxygenase; NOS: nitric oxide synthase. Figure after A. H. Miller. [13]

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It may become possible to apply new and existing medications to immunologic and neurobiologic targets, rather than to specific symptoms. Therapeutic interventions that target cytokines and their receptors are highly promising candidates for suppressing and perhaps even protecting against the development of cancer-related symptoms. Challenges to developing such therapies will include ensuring that the therapies do not exacerbate the cancer by weakening the patients' immunologic surveillance for cancer cells and that they do not increase the likelihood of problematic infections.

Researchers have proposed that 1 possible explanation for the development of fatigue in cancer patients is the increased secretion of proinflammatory cytokines in response to both the disease itself and the treatment. proinflammatory cytokines-interleukins, interferon, or tumor necrosis factor-are proteins that mediate cell-to-cell communication. [14] Herskind and others [15] reported that they are released in greater amounts in patients with cancer as part of the host response to the tumor, in response to tissue doseage, or due to depletion of immune-cell subsets associated with treatment for the disease. Fatigue is also one of the most common symptoms of cancer radiotherapy, with the level of fatigue influenced by the daseage of radiotherapy.

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材料與方法

Specific Aim: Correlation between changes in symptoms of fatigue during radiotherapy and changes in cytokines level.

Materials and methods:

Study Population

The study population consisted of Hepatoma patients who received stereotactic radiation therapy (50Gy, 2 Gy/fraction, 5days/week). Other inclusion criteria were that the patients gave informed consent, had the ability to understand, speak, and read Chinese, and understood the purpose of the study as well as the testing procedures involved. The exclusion criteria were evidence of dementia or a known history of psychiatric disorder.

Study variables and Instruments

Hepatoma for stereotactic radiotherapy protocol:

1. Trial Eligibility: Tumor criteria
 - . Unresectable primary hepatocellular carcinoma
 - . Post-TAE failure
 - . PV thrombosis
 - . Tumor diameter >6 cm combined with TAE
2. Trial Eligibility: Patient criteria
 - . Acceptable bleeding tendency (PT and PTT increase < 2.5x10)
 - . Liver cirrhotic Child A-B

3. Definition of Liver Volume

Karnofsky performance scale >60

Estimated life span \geq 6 months

Adequate bone marrow function (total granulocytes >1,500/ μ L; platelets >4 x 10⁴)

Adequate liver function (GOT and GPT increase <5x10)

Total liver volume: The liver parenchyma excluding gall bladder, IVC, porta hepatis

Planned treated volume: Determined from dose planning distribution, \geq 30-Gy liver volume minus tumor volume

Fatigue & The Brief Fatigue Inventory

Fatigue was measured with a Brief Fatigue Inventory-Taiwan Form (BFI).

The Brief Fatigue Inventory (Mendoza, Wang, Cleeland, et al., 1999) (BFI) was developed in the Pain Research Group by Charles S. Cleeland, Ph.D to measure fatigue in cancer populations and to determine how much the disease and

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treatment influence fatigue. It consists of 9 items on a single page. Fatigue and its interference are measured on numeric scales from 0-10. There are four items that describe patient fatigue at its WORST, LEAST, USUAL and NOW during the normal waking hours, with 0 being “no fatigue”, and 10 being fatigue “as bad as you can imagine”. Seven items describe how much fatigue has interfered with different aspects of the patient’s life during the past 24 hours. These items include general activity, mood, waking ability, normal work (includes both work outside the home and housework), relations with other people, ability to think clearly, and enjoyment of life. The interference is measured with 0 being “does not interfere”, and 10 being “completely interferes”. The instrument also uses descriptors for fatigue, ‘weariness’ and ‘exhaustion.’

The validation of BFI was modeled on the work of the Pain Research Group in developing and validating the Brief Pain Inventory (BPI), a measure that has been used to assess the severity and interference of cancer pain in various cancer populations in both clinical and research settings. A unique feature of the work on the BPI has been to develop ranges of scores on the 0-10 scale for pain that correspond to what is typically meant by mild, moderate or severe (Serlin, Mendoza, Nakamura, Edwards, Cleeland, et al., 1995). The mild category on the BPI is 1-4, moderate is 5-6, and severe is 7 or greater. We also found range scores in fatigue severity in our work with the BFI. Severity ratings could be thought of as forming two groups, “severe” and “non-severe”, and that, similar to the BPI, patients rating their worst fatigue at 7 or greater are considered to have “severe” fatigue. This similar range for fatigue enhances the performance of both epidemiologic and clinical studies of fatigue.

In this study, the Vigor and Fatigue subscales of the POMS are selected for the validation packet. The Vigor and Fatigue subscales have been shown to demonstrate good internal consistency (K-R20=0.89 and 0.94, respectively), adequate test-retest reliability ($r=0.65$ and 0.66 , respectively, over an average 20-day period), and good construct validity in multiple empirical investigations. The information on factors that may influence fatigue scores for this individual group of patients will be collected in the checklist which includes patient demographic, disease, and treatment information, and laboratory test results.

Cytokines (IL-1B, IL-12, TNF, IL-10, IL-6, IL-8, IL-2)

Peripheral venous blood samples were drawn into sterile endotoxin-free blood collection tubes. The tubes were centrifuged for 20 mins at 3000 rpm at 4°C. The plasma samples were frozen at -70°C until the analyses were performed. Plasma levels of IL-1B, IL-12, TNF, IL-10, IL-6, IL-8, IL-2 were determined by an ELISA procedure using recombinant proteins to construct a standard curve.

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All potential participants received verbal and written information and gave verbal consent. The data were collected before start of radiotherapy, two weeks interval during radiotherapy. Finally, cytokines were measured 1 week after the completed radiotherapy. Patients completed the BFI at baseline (i.e., before radiotherapy treatment began) in a private room at the hospital. They completed the questionnaire after 2 weeks and 4 weeks when they were visiting the radiation unit. Blood samples to be used for analysis of cytokine and hemoglobin levels were taken the same day as the fatigue measurements in connection with the participants' visits to the hospital.

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結果

A preliminary data were collected from December 2001 to May 2002. A total of 45 eligible subjects were recruited from two teaching hospitals in Taipei. Five patients were excluded due to expire or dropout from this study. Forty eligible patients finished the seven weeks study. Fatigues index were evaluated by questionnaire of Fatigue Symptom Inventory (FSI) which measured the fatigue intensity, fatigue duration and fatigue interference weekly. Hb, Ht, WBC and Platelet were measured weekly for 7 weeks. Besides, AST, ALT and albumin blood index were measured one week before radiation therapy and at week 2, week 4 and week 6 during treatment. Data were analyzed by SPSS computer program.

All the subjects in this study had mild fatigue in the beginning of the treatment. Their fatigue intensity, fatigue duration and fatigue interference were significantly increased from pre-treatment to the 5th week except the 3rd week. The peak level of fatigue occurred in the 5th week and it decreased since the 6th week ($p < 0.01$)(Fig. 2). Blood Hb, Ht, WBC and platelet level descended gradually to abnormal along with treatment ($p < 0.05$), but the blood AST and ALT level rise along with the treatment. Though the blood albumin level decreased, it was in normal range. No significant correlations between fatigue level and laboratory data were found.

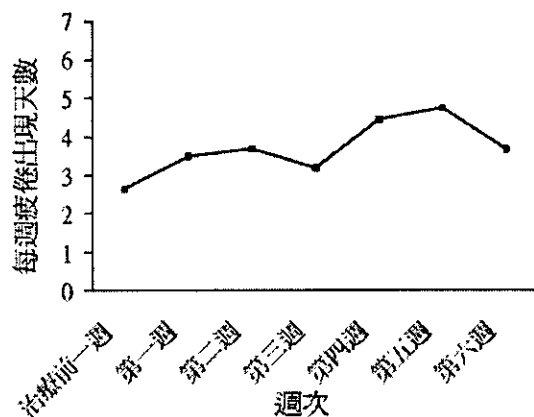


Figure 3. Days of fatigue during radiation therapy

Fatigue was a commonly experienced problem in hepatocellular cancer patients receiving stereotactic radiotherapy. Part of the hematology study data change during treatment. The results of this study can provide the clinical personnel information about the change of fatigue level in hepatocellular cancer patients receiving stereotactic radiotherapy.

For the status of the patients had the symptom of fatigue, the time course was shown in Fig.4. Patients started to had the fatigue symptom worse than the baseline immediately after treatment and reached the peak at 5th week after treatment.

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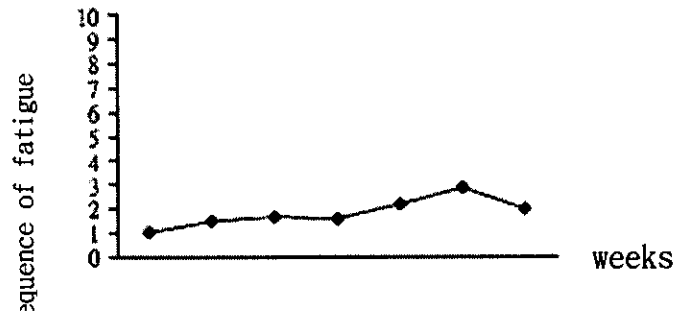


Fig. 4. Time course of the fatigue symptom.

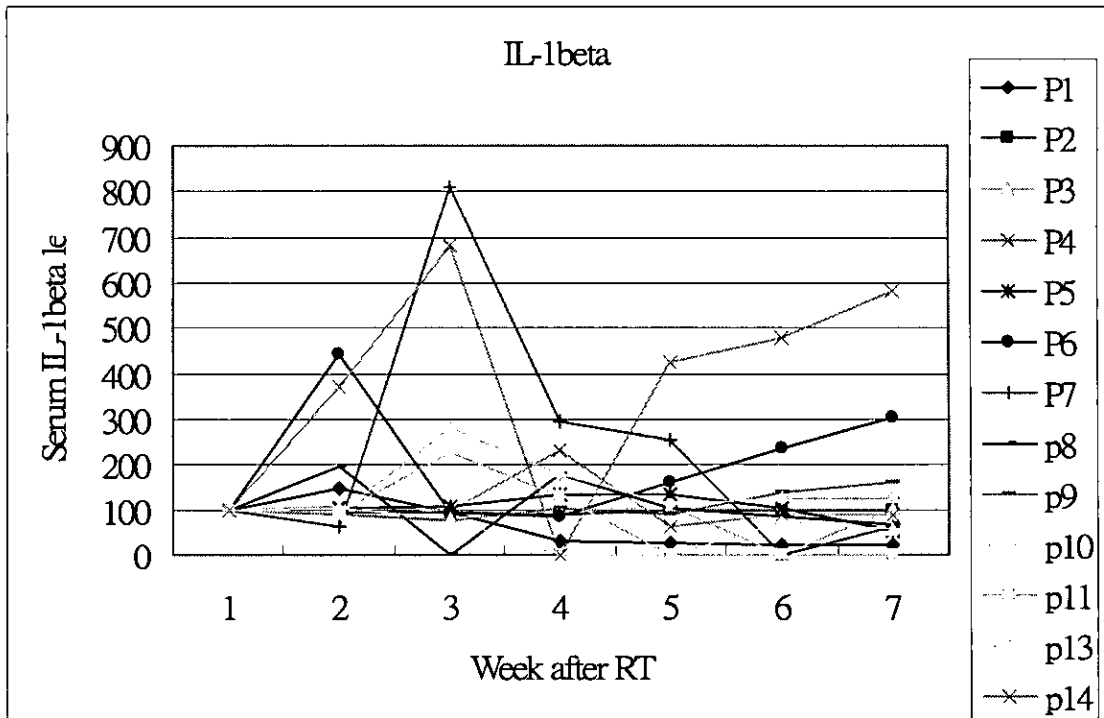
There are 7 cytokines(IL-1b、IL-2、IL-6、IL-8、IL-10、IL-12、TNF) of 20 cancer sera were analyzed but only 13 samples were suitable for analyses. Their concentration is 1.5 to 6.5 times higher than normal sera. This shows that radiotherapy-induced fatigue may correlate the changes of level of cytokines, besides duration of treatment or time-dose factor in radiotherapy is also an important factor.

The cytokines(IL-1b、IL-2、IL-6、IL-8、IL-10、IL-12、TNF) of sera from hepatoma cancer patients were analyzed during the 6 weeks of radiotherapy, and Brief Fatigue Inventory- Taiwan Form (BFI) was used to score of fatigue in cancer patients receiving radiotherapy. The cytokines concentration of patient sera were higher than normal sera. Some changes of cytokines concentration positively related to the scale of fatigue.

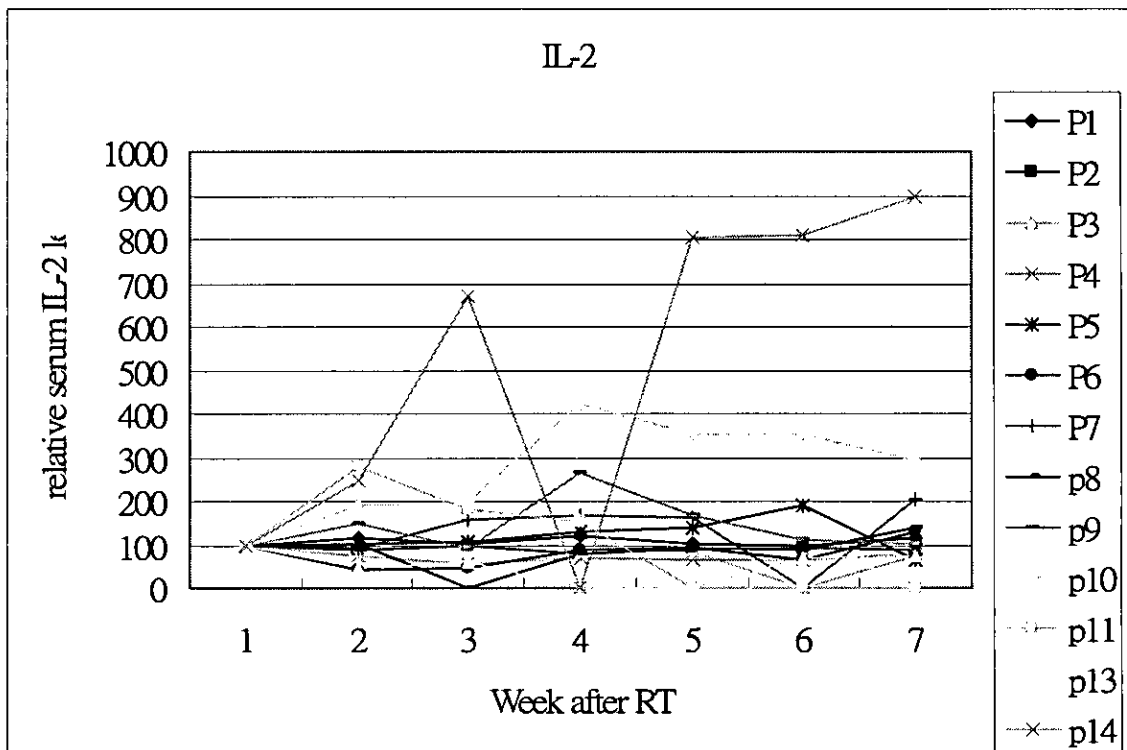
The alteration of cytokines concentrations in these 13 samples might be affected by many factors that could not be manipulated by this experiment.

Fig 5 The concentration of 7 kinds of cytokines in liver cancer sera in 6 weeks after radiation-therapy treated.

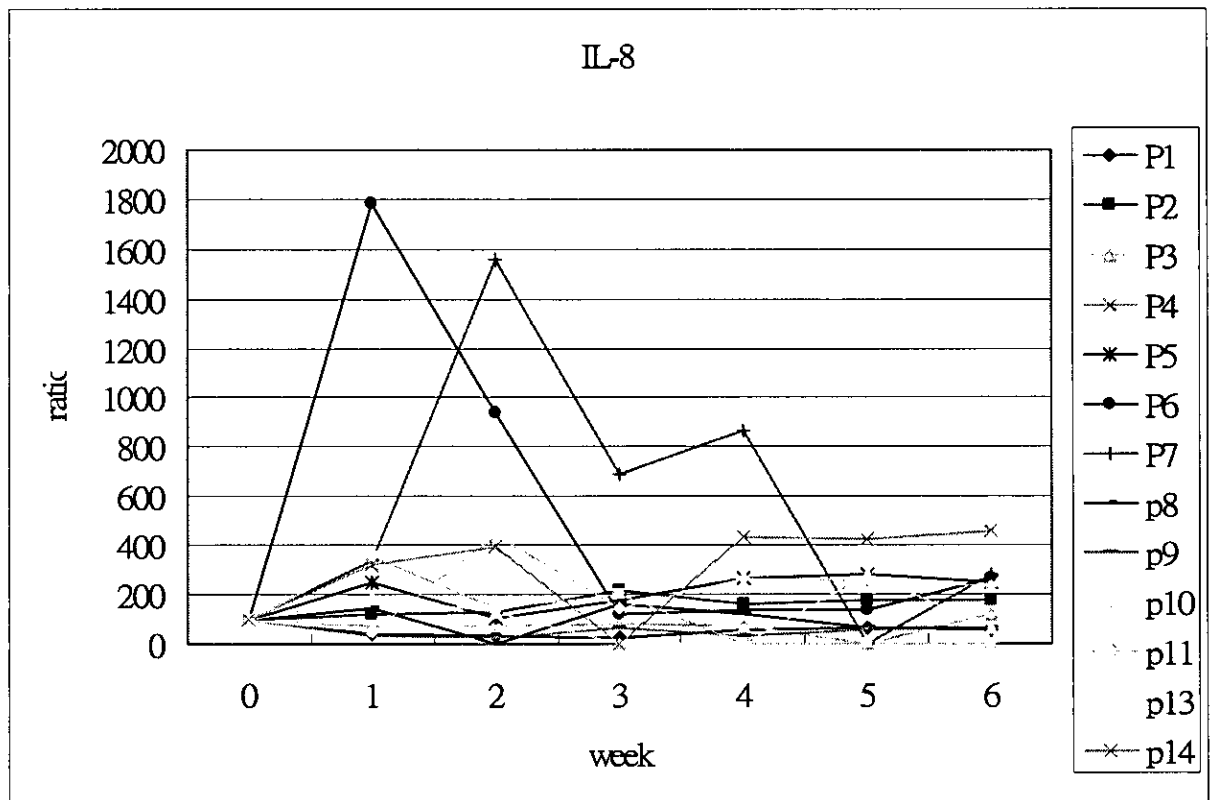
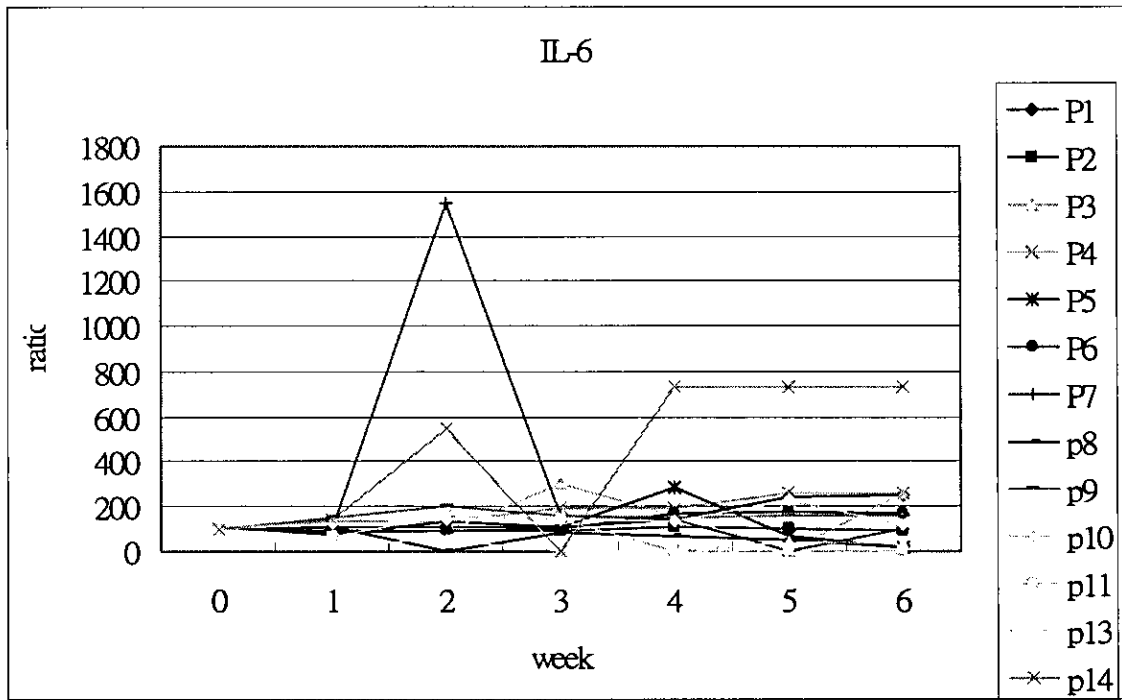
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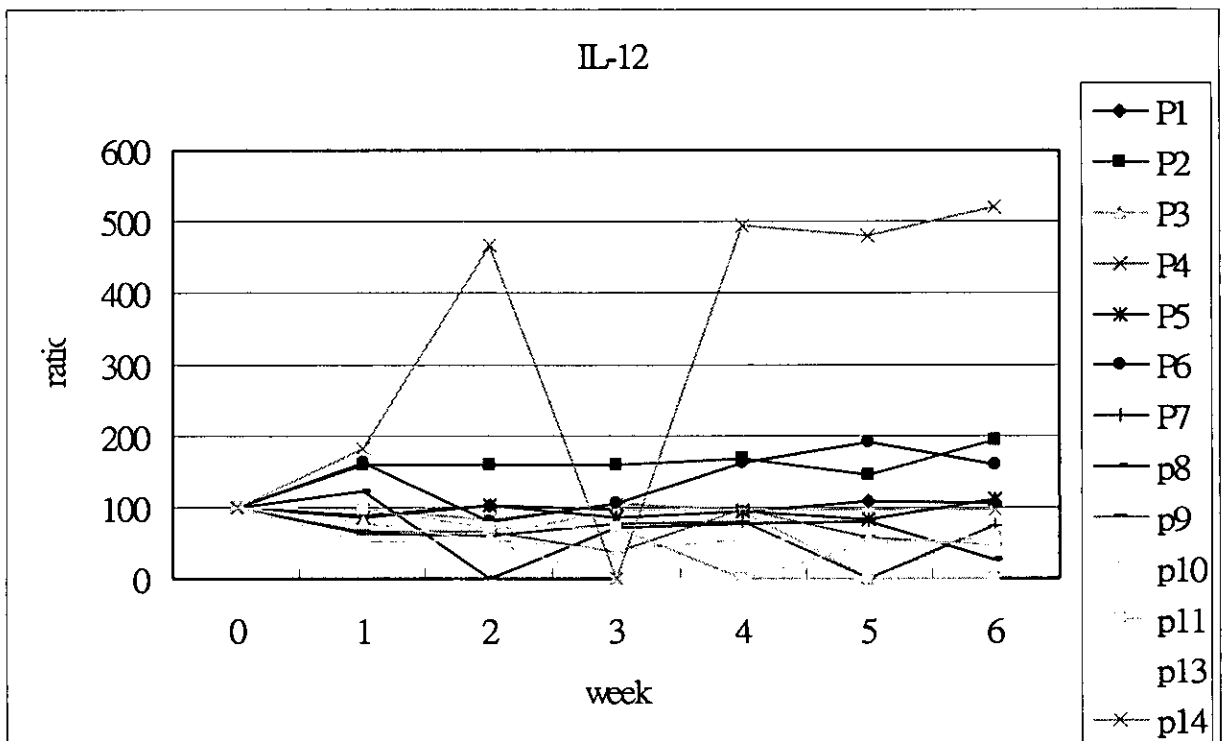
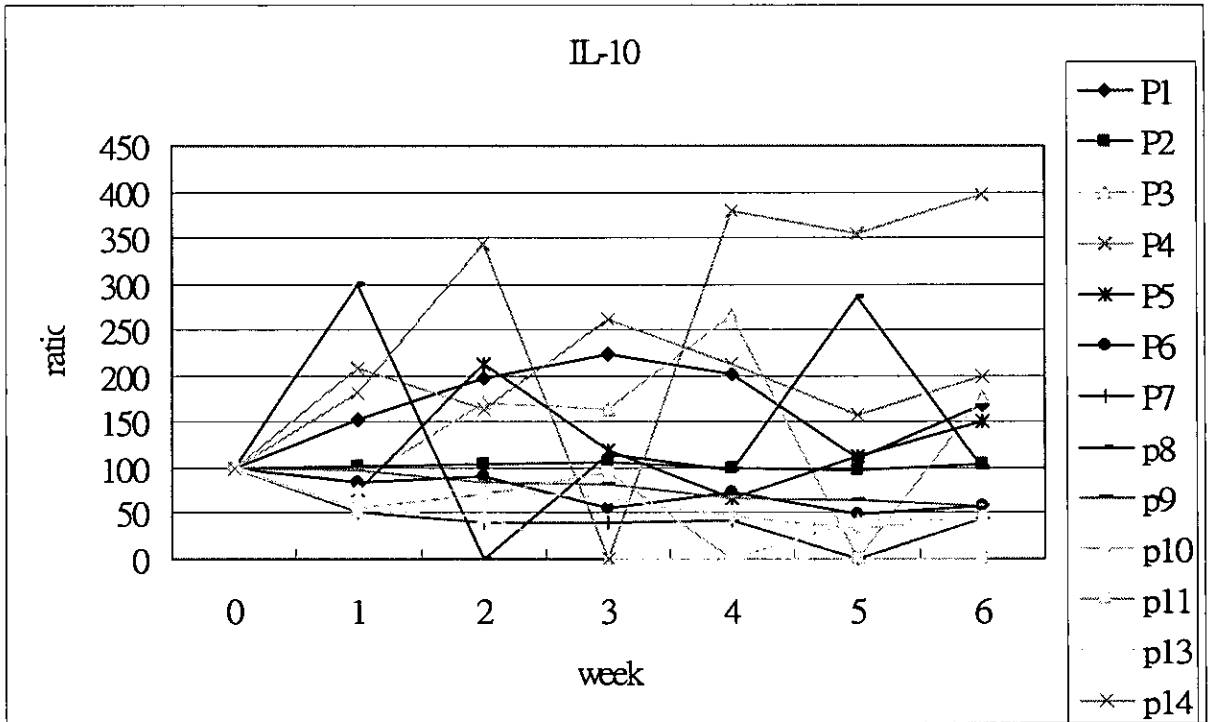
P1 – P14 are patient number.



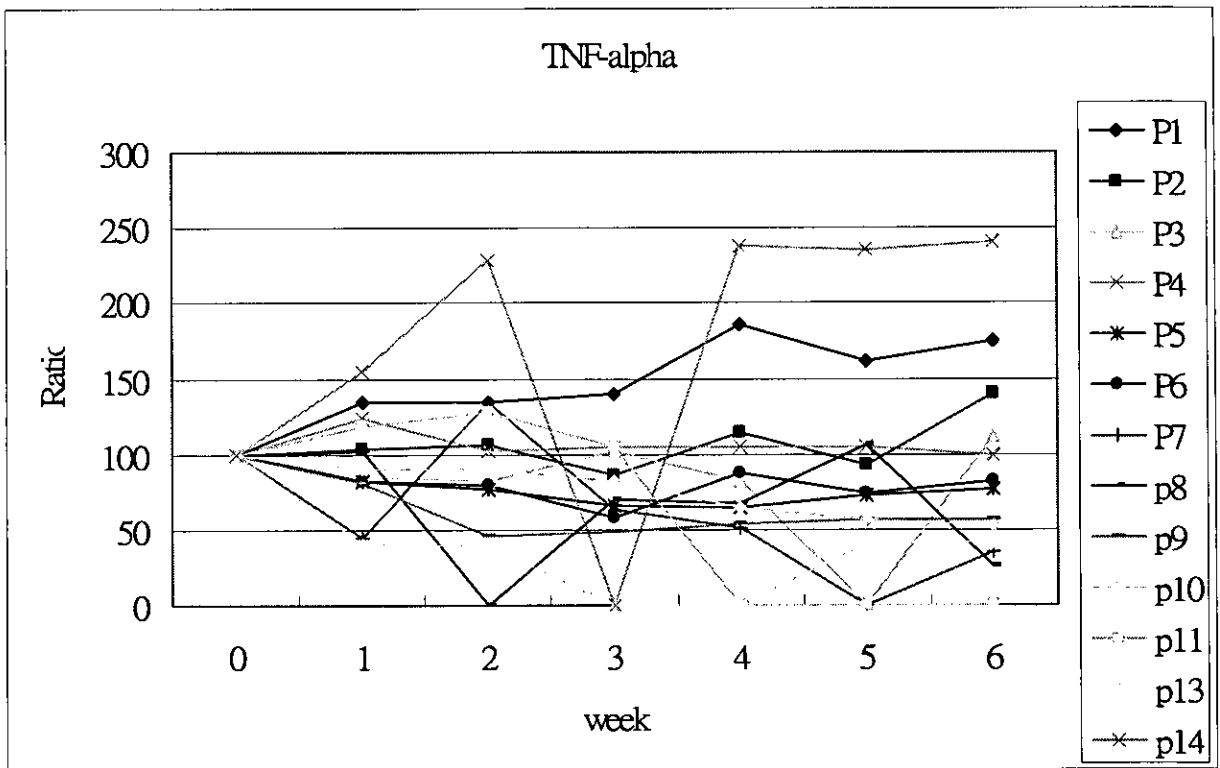
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討論

1. The average concentration of 7 kinds of cytokine of cancer samples is higher than normal samples

Table 3. The average concentration (ng/ml) of 7 kinds of cytokine in sera of normal and 40 cancer samples.

	IL-1b	IL-2	IL-6	IL-8	IL-10	IL-12	TNF
Normal	36.7±2.6	12.2±20.	102.8±53.1	18.7±25.6	406.4±75.3	400.1±41.5	111±6.7
cancer	121.5±113.	65.2±112	655.7±733.4	122.4±146.0	1059.6±56	636.9±473.	351.1±336.
factor	3.3±3.0	5.3±9.2	6.3±7.1	6.5±7.8	2.6±1.3	1.5±1.1	3.1±3.0

The concentration of 7 kinds of cytokines of cancer sera is 1.5 to 6.5 times higher than normal sera as shown in table 1, though the derivation is quite large. However, this implies some connection between cytokines and fatigue of cancer patient.

2. The change of cytokines of 13 liver cancer sera after radiation treated in 6 weeks
The concentration of 7 kinds of cytokines in liver cancer sera in 6 weeks were shown in fig 1. The patient H13 shows the concentration of 7 cytokines raised greatly at second week and sustained to sixth week and Brief Fatigue Inventory- Taiwan Form (BFI) also shows the same change. The connection between fatigue and IL-8, IL-10 and IL-1b of sample H06 and H08 also shows the trend.

3. The cytokines concentrations change of these 13 sample might be affected by many factors that could not control by this experiment. However the data show that there are close correlation between cytokines and fatigue. We are planning to use more cancer sera to investigate this correlation and using cell lines under well experiment control to study the relationship of cytokines and radiation therapy. Since fatigue is one of the most common long-term radiotherapy side effects, numerous patients continue to seek information. Thus , support and guidance provided by healthcare givers are essential.

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結論與建議

From the data measured for the irradiated hepatoma patients, the results did not show closely correlation between the severity of fatigue and the elevation of particular cytokines. It can be caused by the results of complex in vivo condition and the difference between microenvironment in the liver and the serum that we collected from the systemic blood. Other possible reasons included the sensitivity of the tests and the techniques of individual technician who did the tests. However, these result show the correlation of cytokines and fatigue, but more investigation need to be done to find out the mechanism of cytokines on fatigue.

參考文獻

1. Tomoda A, Joudoi T, Rabab el-M, Matsumoto T, Park TH, Miike T. Cytokine production and modulation: comparison of patients with chronic fatigue syndrome and normal controls. *Psychiatry Res.* 2005 Mar 30;134(1):101-4.
2. Moutschen, M., Triffaux, J.M., Demonty, J., Legros, J.J., Lefebvre, P.J., 1994. Pathogenic tracks in fatigue syndrome. *Acta Clinica Belgica* 49, 274– 289.
3. Kurzrock R, Talpaz M. Cytokines and their receptors. Norwell, MA: Kluwer Publishers, 1995.
4. Razelle Kurzrock, M.D.. Cancer-related fatigue: new directions for research. *Cancer Supp* 2001:Vol. 92, No.6: 1684-1688
5. Smets EM, Visser MR, Willems-Groot AF, Garssen B, Schuster-Uitterhoeve AL, de Haes JC. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. *Br J Cancer* 1998;78:907–12.
6. Hickok JT, Morrow GR, McDonald S, Bellg AJ. Frequency and correlates of fatigue in lung cancer patients receiving radiation therapy: implications for management. *J Pain Symptom Manage* 1996;11:370–7
7. Smets EM, Visser MR, Willems-Groot AF, et al. Fatigue and radiotherapy: (A) experience in patients undergoing treatment. *Br J Cancer* 1998;78:899–906
8. Barbara Alicja JF, Hugo RM, Roberto O. Radiotherapy-related fatigue. *Critical Reviews in Oncology/Hematology* 2002,41,1181-7.
9. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: Occurrence,correlates, and impact on quality of life. *J Clin Oncol* 2000;18:743–53.
10. Wenkel E, Thornton AF, Finkelstein D, et al. Benign meningioma: partially resected, biopsied, and recurrent intracranial tumors treated with combined proton and photon radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;48:1363–70.
11. Walker BL, Nail LM, Larsen L, Magill J, Schwartz A. Concerns, affect, and cognitive disruption following completion of radiation treatment for localized breast or prostate cancer. *Oncol Nurs Forum* 1996;23:1181–7.
12. Ya-li H, Yeur-Hur L. Jeng-fong,Chiou. The changes of fatigue and its correlates in liver cancer patients receiving stereotactic radiotherapy. *Therapeut radial Oncol.*, 2003,10(4), 57-64
13. Greenberg DB, Gray JL, Mannix CM, Eisenthal S, Carey ..Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer. *J Pain symptom Manage* 1993, 8(4):196-200.
14. Charles S.C, Gary J.B, Robert D. et. al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism ? *Cancer* :2003, Vol. 97, No.11, 2919-25
15. Kurzrock R. The role of cytokines in cancer-related fatigue.*Cancer* 2001, 92: 1684-8.
16. Herskind C, Bamberg M, Rodemann HP.The role of cytokines in the development of normal-tissue reactions after radiotherapy. *Strahlenther Onkol* 1998,174(Suppl 3):12-5.
17. Lavey RS. Clinical trial experience using erythropoietin during radiation therapy. *Strahlenther Onkol* 1998;174(suppl 4):24–30.
18. Okuyama T, Akechi T, Kugaya A, et al. Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale. *Support Care Cancer* 2000;8:215–22.
19. Lelli G, Angelelli B, Giambiasi ME, et al. The anabolic affect of high dose

計畫編號：

- Medroxyprogesterone acetate in oncology. *Pharmacol Res Commun* 1983;15:561–568.
20. Cavalli F, Goldhirsch A, Jungi F, et al. Randomized trial of low-versus high-dose Medroxyprogesterone acetate in the induction treatment of postmenopausal patients with advanced breast cancer. *J Clin Oncol* 1984;2:414–419.
 21. Ottery FD, Walsh D, Strawford A. Pharmacologic management of anorexia/cachexia. *Sem Oncol* 1998;25:35–44.
 22. Koretz RL. Parenteral nutrition: is it oncologically logical? *J Clin Oncol* 1984; 2:534–538.
 23. Wang W, Lonroth C, Svanberg E, Lundholm K. Cytokine and cyclooxygenase-2 protein in brain areas of tumor-bearing mice with prostanoid-related anorexia. *Cancer Res* 2001;61:4707–4715.
 24. Innui A. Cancer anorexia-cachexia syndrome: are neuropeptides the key? *Cancer Res* 1999;59:4493–4501.
 25. Hellerstein MK, Meydani SN, Meydani M, et al. Interleukin-1-induced anorexia in the rat. Influence of prostaglandins. *J Clin Invest* 1989;84:228–235.
 26. Sergeev VG, Akmaev IG. Effects of vagotomy and bacterial lipopolysaccharide on food intake and expression of cyclooxygenase-2 mRNA in rat brain vessels. *Bull Exp Biol Med* 2000;129:553–555.
 27. Tisdale M. Protein loss in cancer cachexia. *Science* 2000;289:2293–2294.
 28. Lang I, Zielinski CC, Templ H, Spona J, Geyer G. Medroxyprogesterone acetate lowers plasma corticotropin and cortisol but does not suppress anterior pituitary responsiveness to human corticotropin releasing factor. *Cancer* 1990;66:1949–53
 29. Gagnon B, Bruera E. A review of the drug treatment of cachexia associated with cancer. *Drug* 1998;55:675–88
 30. Ganz PA, Bower JE. Cancer related fatigue: a focus on breast cancer and Hodgkin's disease survivors. *Acta Oncol.* 2007;46(4):474–9.
 31. Mantovani G, maccio A, Esu S, et al. Medroxyprogesterone acetate reduces the in vitro production of cytokines and serotonin involved in anorexia/ cachexia and emesis by peripheral blood mononuclear cells of cancer patients. *EUR J Cancer* 1997;33:602–607
 32. Wratten C, Kilmurray J, Nash S, Seldon M, Hamilton CS, O'Brien PC, Denham JW. Fatigue during breast radiotherapy and its relationship to biological factors. *Int J Radiat Oncol Biol Phys.* 2004 May 1;59(1):160–7.

計畫編號：

受獎人投入工作時間說明

邱仲峰醫師、兼任、96年1-12月投入時間30%(約80個工作天)

工作內容：

1. 病患篩選與溝通(約5工作天)。
2. 實驗設計與實驗室準備(約10工作天)。
3. 檢測病人血中7種Cytokines之變化，找出不同Cytokines和疲倦程度及放射劑量間的相關性(約40工作天)。
4. 使用台灣版簡明疲憊量表 Brief Fatigue Inventory- Taiwan Form 記錄劑量累積和疲倦程度之相關(約5工作天)。
5. 評估符合收案條件中之肝癌病人只接受立體定位放射治療中，劑量累積和疲倦程度之相關(約10工作天)。
6. 數據整理分析與論文投稿撰寫(約10工作天)。

臨床試驗/研究案件統計表

經費來源	PI 自行設計	廠商設計
人才獎勵計畫	1	
廠商委託	1	1
總計案件數	2	1