

行政院國家科學委員會專題研究計畫 成果報告

Cytokines 和癌症放射治療相關疲倦之間的角色：以肝癌
放射治療中的病人為經驗

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 期中進度報告

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The Role of Cytokines in Cancer Radiotherapy-Related Fatigue: Experience
in Hepatoma Patients Undergoing Treatment

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中文摘要：

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. 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. 本實驗檢測癌症病人血液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-6 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，但因本實驗已終止，而無法以更多癌症病人血清樣品進行Cytokines 濃度變化的測量。因此本計劃已有的結果將列舉於下面，以方便其它臨床上之研究，並對醫療工作人員及家人來照顧疲倦病人有一些幫助。

關鍵詞：Cytokines、疲倦、放射治療、肝癌

(二) 計畫英文摘要。(五百字以內)

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 nataghist, such as IL-1, IL-2, TNF- α and interferon.

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 40 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.

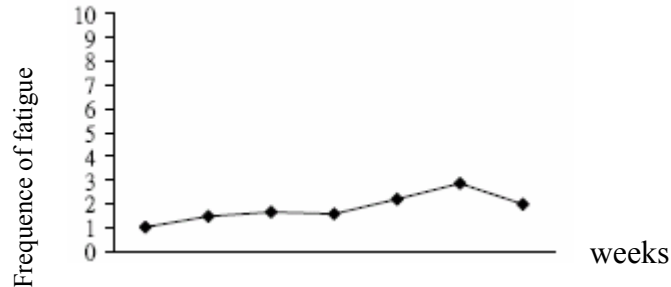
The alteration of cytokines concentrations in these 13 samples might be affected by many factors that could not be manipulated by this experiment. However the data show that there are close correlation between IL-6 and fatigue. However,. Since fatigue is one of the most common long-term radiotherapy side effects, numerous patients continue to seek information. However, this project was terminated, the results of the current experiment will be listed in this summary to help other researchers to identify the correlation of the fatigue and cytokines.

Key Words: Cytokines, Fatigue, Radiation therapy, Hepatoma

Results:

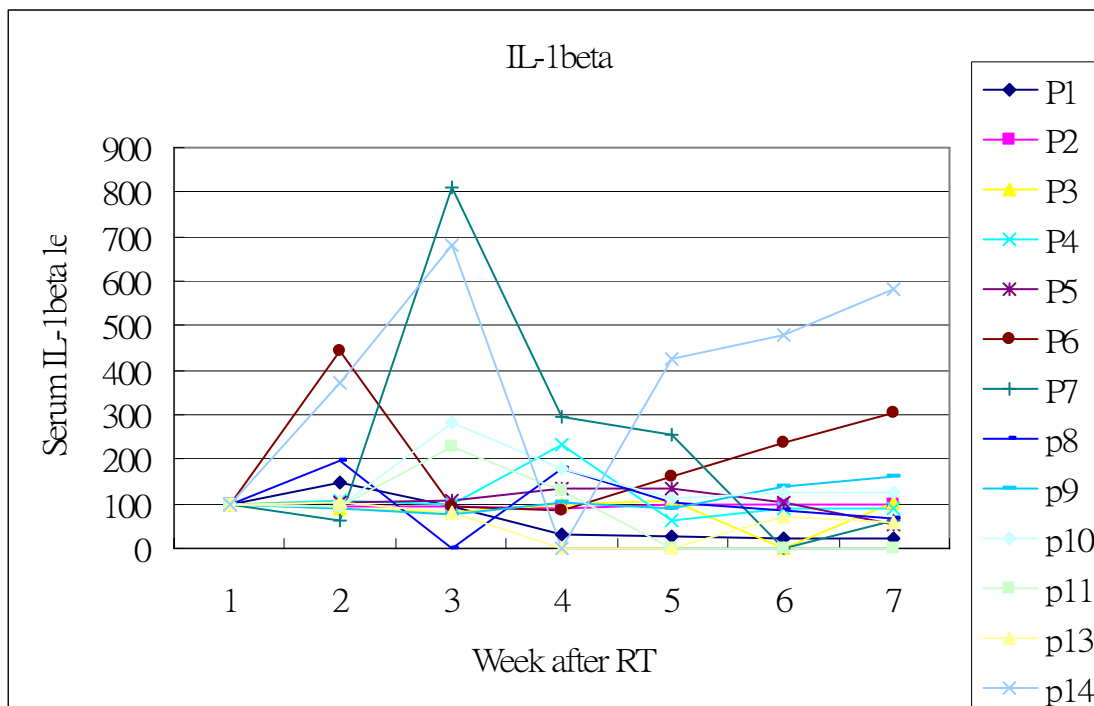
For the status of the patients had the symptom of fatigue, The time course was listed in Fig.1. Patients started to had the fatigue symptom worse than the baseline immediately after treatment and reached the peak at 5th week after treatment.

Fig. 1. Time course of the fatigue symptom.



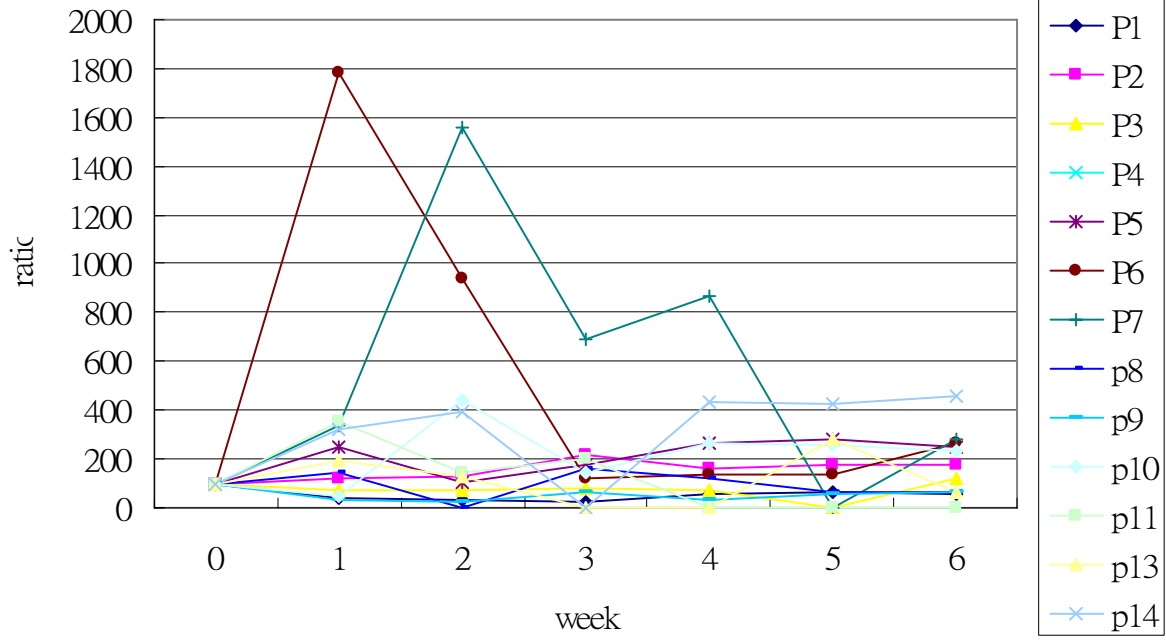
The results of each cytokines of each patient during the treatment of the hepatoma.

Fig 2 The concentration of 7 kinds of cytokines in liver cancer sera in 6 weeks after radiation-therapy treated.

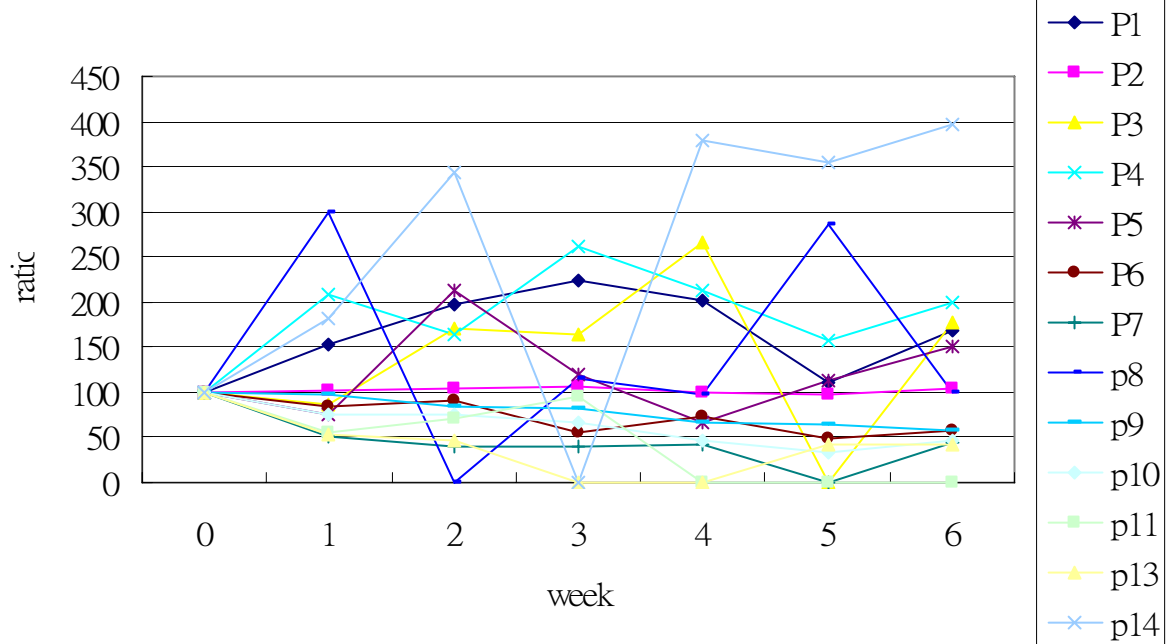


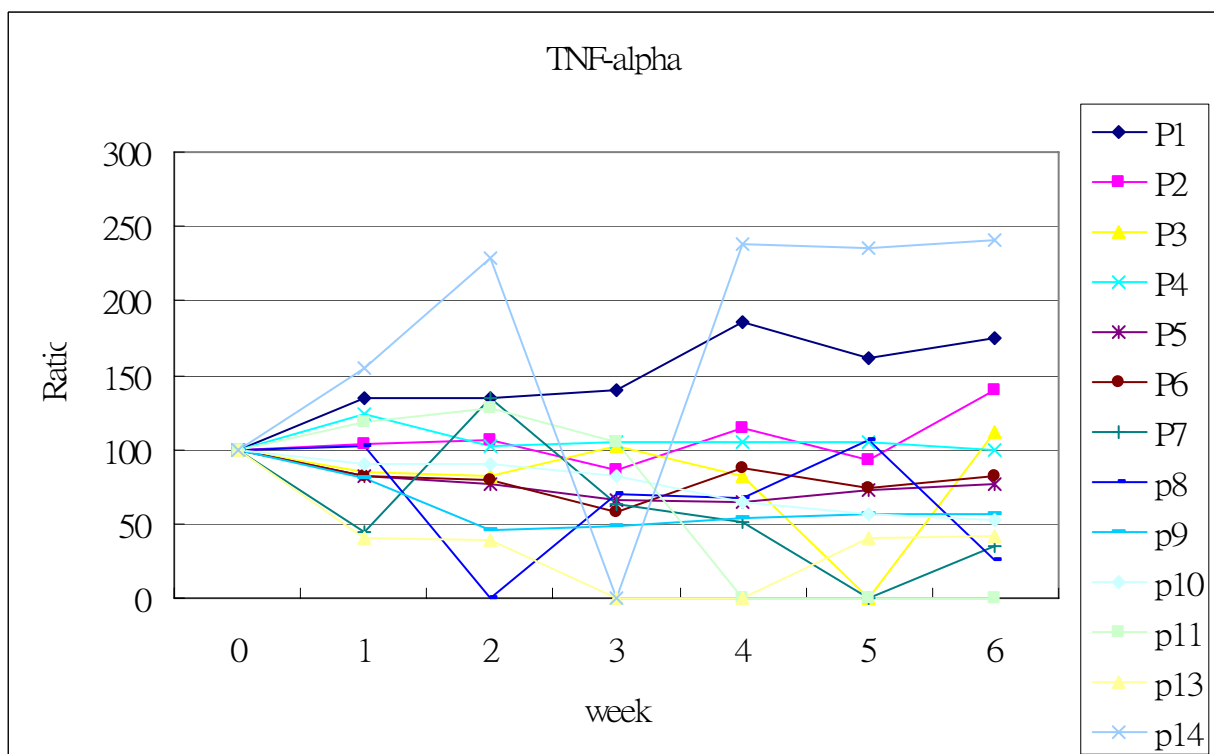
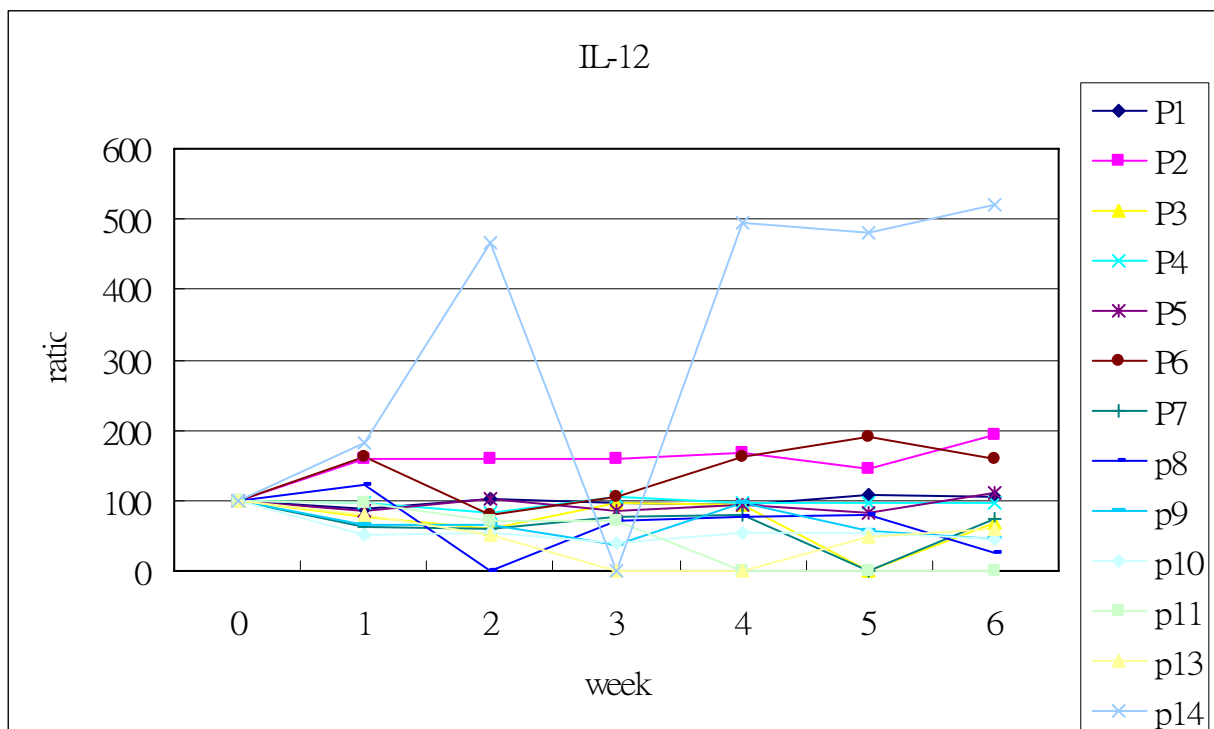
P1 – P14 are patient number.

IL-8



IL-10





Summary

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

Table 1. 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±20.6 | 102.8±53.1 | 18.7±25.6 | 406.4±75.3 | 400.1±41.5 | 111±6.7 |
| cancer | 121.5±113.2 | 65.2±112 | 655.7±733.4 | 122.4±146.0 | 1059.6±564.5 | 636.9±473.1 | 351.1±336.3 |

| | | | | | | | |
|--------|---------|---------|---------|---------|---------|---------|---------|
| 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.

Conclusion

From the our data measured for the irradiated hepatoma patients, the data did not show 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 Imicroenvironment 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.

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