

Combined Kampo with radiation therapy prolongs survival in patients with cervical cancer

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Abstract

We conducted a retrospective study on therapeutic effects of Kampo therapy for the prolongation of life in patients with uterine cervical cancer. Our subjects in this study were 174 patients with newly diagnosed cervical cancer who were admitted to the Tokushima University Hospital between 1976 and 1998, and who were treated with radiotherapy with concomitant Kampo therapy. Outcome was studied for a total of 92 patients (43 patients in Stage IIb and 49 patients in Stage IIIb) who were followed up for at least 5 years after treatment. For historical controls, we selected 120 patients treated during the same period in our department who did not receive concomitant Kampo treatment (63 patients in Stage IIb and 57 patients in Stage IIIb). Patients were treated with standard radiation therapy. Some patients were also treated with chemotherapy or immunotherapy. The Kampo formulations used were Tsumura Kampo granulated extracts. Almost all patients began this regimen during radiation therapy and continued to follow it for several years, up to 20 years in some cases. The 5-year survival rate for the 92 patients given concomitant Kampo therapy was 75.6 %, in comparison to 65.6 % for the 120 patients not receiving Kampo treatment. 10-year survival rates for these groups were 65.9 % and 49.1 % respectively ($p=0.0102982$). Among patients in Stage IIIb, the 5-year survival rate was 68.4 % among the 49 patients who given concomitant Kampo therapy and 48.4 % among the 57 patients who did not receive Kampo treatment, and the 10-year survival rates were 59.7 % and 38.3 % respectively ($p=0.00803624$). This study shows that concomitant Kampo therapy significantly extended the survival of patients with uterine cervical cancer.

Key words concomitant Kampo therapy, radiation therapy, life-prolonging effect, cancer of uterine cervix.

Abbreviations Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang), 補中益氣湯; Juzen-taiho-to (Shi-Quan-Da-Bu-Tang), 十全大補湯; Ninjin-yoei-to (Ren-Shen-Yang-Rong-Tang), 人參養榮湯; QOL, quality of life; Yin and Yang, 陰陽.

Introduction

Kampo was first introduced in the treatment of cancer in the late 4th Century. In modern times, Kampo applications for cancer therapy were developed by trial and error because of dissatisfaction with Western medicine in dealing with problems such as the side effects of radiation therapy and various types of general malaise. However, routine treatment pro-

duced results which were better than expected.^{1,2)} This led to rising expectations for the "Oriental mysteries" of Kampo. As increasing numbers of reports are now becoming available on cancer radiation therapy, ranging from basic research to clinical studies,³⁻⁹⁾ my colleagues and I decided to do a retrospective study of the life-prolonging effects of concomitant treatment with traditional Chinese medicine in combination with Western medicine.

We based our study on patients with cancer of the

uterine cervix. Results are reported below.

Materials and Methods

Our subjects in this study were 174 patients with cervical cancer who were admitted to the Radiology Department of the University of Tokushima School of Medicine Hospital during the 23-year period between 1976 and 1998, and who were treated primarily with radiotherapy with concomitant Kampo therapy (Table I). Most of these cancers were in Stage IIb or IIIb.

Outcome was studied for a total of 92 patients (43 patients in Stage IIb and 49 patients in Stage IIIb) who were followed up for at least 5 years. For historical controls, we selected 120 patients treated during the same period in our department who did not receive concomitant Kampo treatment (63 patients in Stage IIb and 57 patients in Stage IIIb).

Patients were treated with standard radiation therapy consisting of low-dose-rate intracavitary

irradiation with cesium 137 and x-ray teletherapy by linear accelerator at 6 MV.¹⁰⁾ Some patients were also treated with chemotherapy or immunotherapy.¹¹⁾

The Kampo formulations used were Tsumura Kampo granulated extracts, given at a dose of 7.5–9.0 g/day, 30 minutes before meals, in a small quantity of hot water. Almost all patients began this regimen during radiation therapy and continued to follow it for several years, up to 20 years in some cases. Typical Kampo formulations were constitution-builders such as Juzen-taiho-to (Shi-Quan-Da-Bu-Tang), Ninjin-yoei-to (Ren-Shen-Yang-Rong-Tang), and Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang), with usage designated as traditional diagnosis ("Sho") for both Wazai and Shazai type formulations (Table I).

Outcome was evaluated statistically, applying the Kaplan-Meier test for survival rate, the Logrank test to determine significant difference, and the Cox Proportional Hazard Model for multivariate analysis.

Results

Stratified by disease stage, the 5-year survival rate was 80.7 % for the 106 patients with cervical cancer in Stage IIb (43 patients given concomitant Kampo therapy and 63 patients not receiving Kampo treatment), and 57.4 % for the 106 patients in Stage IIIb (49 patients given concomitant Kampo therapy and 57 patients not receiving Kampo treatment). The 10-year survival rates for these groups were 63.6 % and 47.8 % respectively ($p=0.0131004$) (Fig. 1).

By treatment method, the 5-year survival rate for the 92 patients given concomitant Kampo therapy was 75.6 %, in comparison to 65.6 % for the 120 patients not receiving Kampo treatment. Ten-year survival rates for these groups were 65.9 % and 49.1 % respectively ($p=0.0102982$) (Fig. 2). When results were compared by disease stage, the 5-year survival rate was 83.7 % among the 43 patients in Stage IIb who given concomitant Kampo therapy and 78.9% among the 63 patients in Stage IIb who did not receive Kampo treatment. The 10-year survival rates among these two groups were 72.7% and 57.9% respectively ($p=0.1721434$) (Fig. 3). Among patients in Stage IIIb, the 5-year survival rate was 68.4% among the 49 patients who given concomitant Kampo therapy and

Table I Patient characteristics

Number of cases		174 cases
Age (years)	34 ~ 92	
	Mean 67	
	30 ≤	1
	40 ≤	11
	50 ≤	29
	60 ≤	45
	70 ≤	67
	80 ≤	20
	90 ≤	1
	Stage	
	I	12
	II	65
	III	67
	IV	30
Traditional medicine		
	Juzen-taiho-to	59 (34.0 %)
	Hachimi-jio-gan	30 (17.2 %)
	Ninjin-yoei-to	22 (12.6 %)
	Sairei-to	20 (11.5 %)
	Hochu-ekki-to	11 (6.3 %)
	Sho-saiko-to	9 (5.2 %)
	Dai-saiko-to	3 (1.7 %)
	Other	20 (11.5 %)

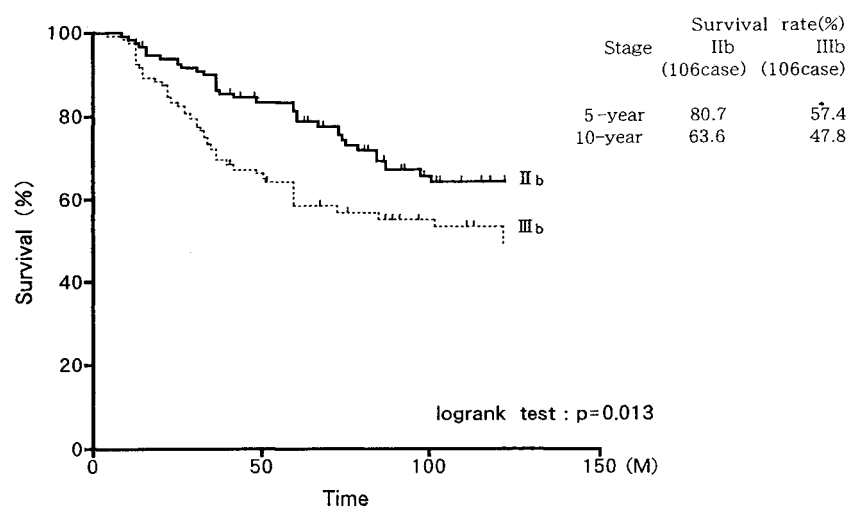


Fig. 1 Cumulative survival curve for cervical cancer (Stage IIb, IIIb)

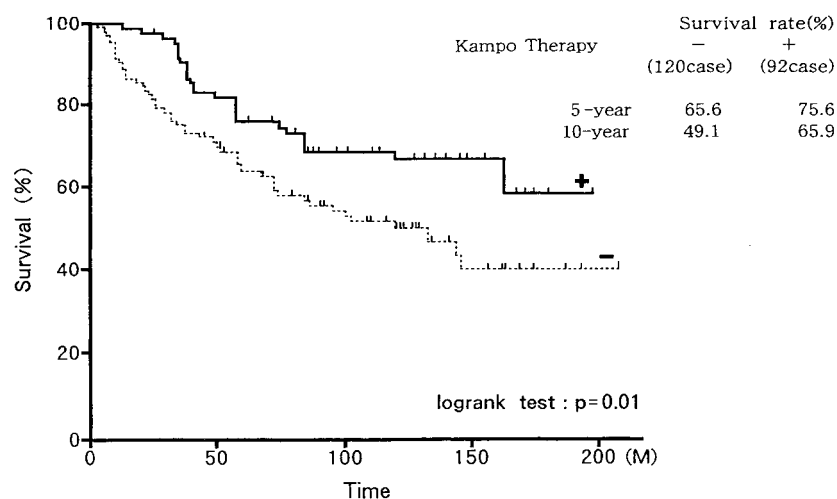


Fig. 2 Cumulative survival curve for cervical cancer (Stage IIb+IIIb)

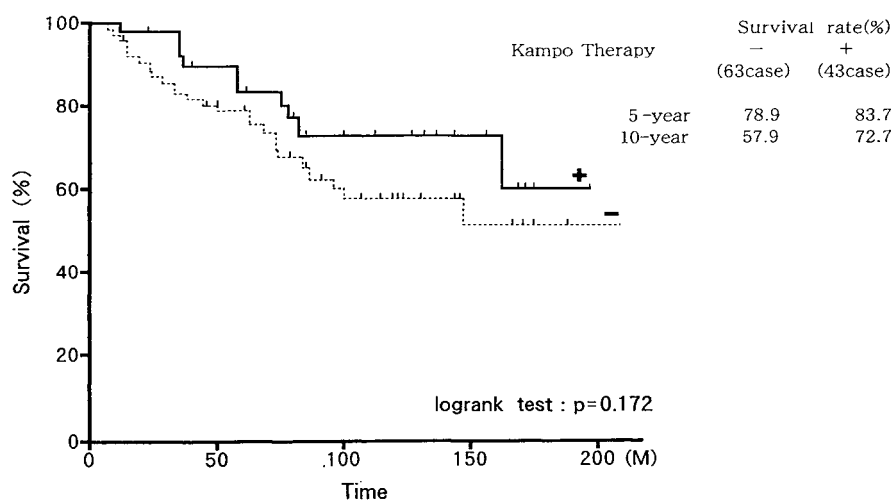


Fig. 3 Cumulative survival curve for cervical cancer (Stage IIb)

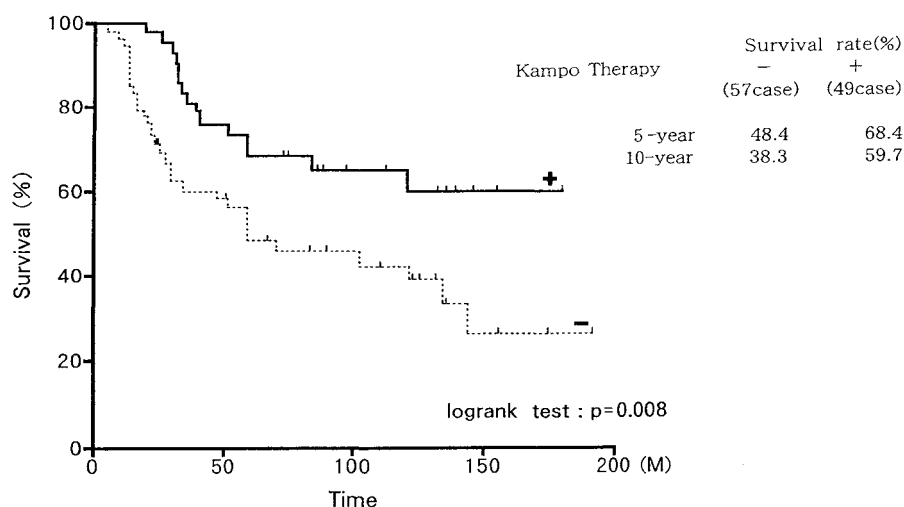


Fig. 4 Cumulative survival curve for cervical cancer (Stage IIb)

48.4% among the 57 patients who did not receive Kampo treatment. The 10-year survival rates were 59.7% and 38.3% respectively ($p=0.00803624$) (Fig. 4).

Multivariate analysis of prognostic indicators, including treatment method, was performed in all cases. Results showed the major prognostic indicators to be clinical stage of disease ($p=0.0137901$) and Kampo therapy ($p=0.0007952$). No other factors were found to be prognostic indicators, including concomitant chemotherapy ($p=0.2514115$), concomitant immunotherapy ($p=0.2931284$), ongoing chemotherapy ($p=0.6365786$), or ongoing immunotherapy ($p=0.7542801$).

Discussion

In recent years, dramatic advances in molecular biology have made it possible to analyze complex physioprotective systems at the molecular level. It is now important that we utilize this technology both in accurately assessing Kampo medicine from the viewpoint of modern science and also in developing new clinical applications for these products.

Chinese medicine has its roots in Chinese philosophy, so that it differs profoundly from Western medicine. Theories incorporating the principles of Yin and Yang and the Five Elements present a type of universalism in which everything is considered in relationship to everything else. The world represents one

universe. Each human body is also a universe, containing within it the smaller universe of the organs including the heart, kidneys, and liver. Everything has both a Yin and a Yang aspect, and these aspects repeatedly oppose and are integrated with each other, so that the universe operates through cycles of growth and decay, according to the natural philosophy presented by the Book of Divination.

Western medicine has its basis in science. Its orientation is mechanical, statistical, and dualistic, with emphasis on local pathophysiology, and the therapeutic focus is on the elimination of pathologic factors. Chinese medicine has its basis in universalism, and is humanistic, individualized, and monistic in its approach. The therapeutic focus is primarily on the functioning of the body, to increase the body's natural healing powers against outside factors. This treatment system also has as its objective the multifaceted regulation and optimization of physiologic functions.

An integration of traditional Chinese medicine with Western medicine began to be practiced in Japan from the 1950s. This new form of medicine, which combined the rich legacy of thousands of years of Chinese medical practice with the penetrating insights of modern Western medicine, began to develop rapidly beginning in the 1980s. Previous to that, my colleagues and I had already theorized that a new form of cancer treatment could be developed based on this integration of Chinese and Western medical theory. Such

treatment would utilize the powerful tools of Western medicine, such as surgery, radiation, and anticancer drugs, to directly combat cancer, but these treatments would be combined with restorative techniques specific to Chinese medicine which would replenish lost vitality and build up the natural healing powers of the body. There would also be concomitant use of BRM and other similar tools from Western medicine. By utilizing the strengths of both Chinese and Western medicine, this treatment method should provide optimal cancer therapy.

Our many years of experience with Kampo therapy indicates that it is inappropriate to evaluate these products on the same scale as used to measure the clinical effectiveness of Western medicine. However, progress has been made in recent years on immunologic analysis of cancer patients,⁹⁾ and the present report provides information on survival rates.

Gradually, we are approaching the point where objective evaluation will be possible.

Results from the cases of cervical cancer in this study showed a 5-year survival rate of 80.7% for Stage IIb and 57.4% for Stage IIIb, with 10-year survival rates of 63.6% and 47.8% respectively. These results are comparable to those obtained at other hospitals (Table II).¹²⁾

Initially, we began the concomitant administration of Kampo with the objective of reducing side effects and improving the quality of life (QOL) of patients undergoing radiation and chemotherapy. However, our analysis of these patients showed that Kampo therapy also provided life-prolonging effects. Our study showed a significantly greater 5-year survival rate (65.6%→75.6%) and 10-year survival rate (49.1%→65.9%) with concomitant Kampo therapy ($p=0.0102982$). Also, the statistically significant dif-

Table II Results of radiotherapy for cervical cancer in Japan^a

Reporter, institution	Year	No. of cases	5-year cumulative survival rate						Late complication rate more than grade 2			
			IB	II	(IIA	IIB)	III	IVA	All	Rectum	Bladder	Small intestine
<i>Treatment with low-dose-rate intracavitary irradiation :</i>												
OKAWA et al. Tokyo W.C.H.	1987	98	82	77			53	29	12.2			
AKINE et al. Nat. C.C.	1988	142	82		75	56				40	11.5	0.5
NARIMATSU et al. Nat. Sapporo H.	1992	231	70	67			46	22		10	3	
ARAI et al. N.I.R.S.	1992	77	83		74	47	34	29		18	8	0.4
TAKEKAWA et al. Tokushima Univ.	1993	280	77	71	74	70	54	33	8.6			
TESHIMA et al. Osaka Univ.	1993	89	89	73			45			5		
KATO and MORITA Aichi C.C.	1993	214	89	70	79	60	50			6.5	0.5	0
<i>Treatment with high-dose-rate intracavitary irradiation :</i>												
KOGA et al. Miyazaki Univ	1987	34	85	68					3.7			
TESHIMA et al. Osaka A.D.C.	1987	105		69			61	29		7.6	5.7	1.0
ARAI et al. N.I.R.S.	1992	403	88		77	67	52	24		10.6	6.7	2.9
KATAOKA et al. Ehime Univ.	1992	140	72		89	69	64	17		20.7		
KIKUCHI et al. Asahikawa Univ.	1992		80	74			63					
ITO et al. Keio Univ.	1992	291	84	71			47	12		13.6	0.8	

^aCompiled in part from proceedings of congresses held in Japan and from personal communications.

ference produced by concomitant Kampo therapy was noticeably greater in patients with more advanced cancer (Stage IIb) than with less advanced cancer (Stage I). Stage IIb patients showed an improvement in 5-year survival rate of 48.4%→68.4% and in 10-year survival rate of 38.3%→59.7% ($p=0.00803624$).

Recently various forms of chemotherapy have been tested in conjunction with radiation therapy with the objective of prolonging survival in patients with advanced cervical cancer.^{13,14)} However, although these methods increase the local control rate of cancer treatment, they do little to prolong survival, and their use is reportedly accompanied by a higher incidence of side effects. Multivariate analysis on the patients in this study showed that concomitant chemotherapy was not a significant prognostic indicator of prolonged survival. Concomitant Kampo therapy, however, did emerge as a significant prognostic indicator ($p=0.0007952$).

We feel sure that further clinical research will result in the development of new applications for Kampo formulations, and that an integration of Chinese and Western medicine will prove beneficial in the treatment of cancer in the 21st Century.

Conclusion

Modern cancer treatment, which involves surgery, radiation, and chemotherapy, inflicts great suffering and requires stoic endurance on the part of the patient. Chinese medicine was introduced into cancer therapy to improve patient QOL, but has also been found therapeutically useful in itself. The results of our study indicate that concomitant Kampo therapy has a significant positive effect on survival time.

We expect that cancer treatment in the 21st Century will maximize the patient's own natural healing abilities, and that concepts will be changed and further efforts will be made to decrease the difficulties of cancer therapy for the patient.

和文抄録

漢方治療の延命効果について、子宮頸癌症例を基に retrospective に検討した。1976～1998 年の 23 年間に徳島大学医学部放射線科にて放射線治療に漢方を併用した

174 例の子宮頸癌新鮮症例のうち、5 年以上経過観察が出来た 92 例 (IIb : 43 例, IIIb : 49 例) を対象として予後につき検討した。ヒストリカルコントロールとして、同時期の漢方非併用治療 120 例 (IIb : 63 例, IIIb : 57 例) をあてた。放射線治療は低線量率小線源による腔内照射と 6MVX 線による外部照射を用いた標準的放射線治療を施行した。一部の症例には化学療法や免疫療法の併用も施行した。漢方方剤は、ツムラ漢方製剤エキス顆粒として 1 日 7.5～9.0 g, 食前 30 分に微温湯で服用させた。殆どの症例は放射線治療中より開始して、数年～20 年間継続投与されている。使用方剤は、十全大補湯, 人參養榮湯, 補中益気湯等の補剤が中心である。5 年, 10 年生存率は, 漢方併用群 (92 例) と非併用群 (120 例) はそれぞれ 75.6 %, 65.9 % と 65.6 %, 49.1 % で ($P=0.0102982$) あった。このうち IIIb 期では, 5 年, 10 年生存率は, 漢方併用群 (49 例) と非併用群 (57 例) はそれぞれ 68.4 %, 59.7 % と 48.4 %, 38.3 % で ($P=0.00803624$) あった。更に, 治療法による予後因子を多変量解析で検討すると, 漢方治療が ($P=0.0007952$) 因子としてあがった。今回の検討では, 子宮頸癌の予後を大きく延ばす結果を得た。今後は, 更に症例数を蓄積し, 何が延命に寄与しているかを究明していきたい。

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