
PALLIATIVE TREATMENT OF ADVANCED CERVICAL CANCER WITH RADIOTHERAPY AND THAI HERBAL MEDICINE AS SUPPORTIVE REMEDY

Montien PESEE M.D¹ Wichit KIRDPON Ph.D² Sukachart KIRDPON M.D³
Anucha PUAPAIROJ M.D⁴ Pongsiri PRATHNADI M.D⁵

ABSTRACT

OBJECTIVE: To evaluate the supportive effect of Thai herbal medicine, Vilac Plus (G716/45) on standard radiotherapy in comparison with historic control from the literature reports the results of treatment in stage IIIB-IV cervical cancer.

PATIENTS AND METHODS: During the period of March 2003 to June 2005. Thirty patients in advanced cervical cancer stage IIIB-IV with poor performance status were treated by palliative radiotherapy in adjuvant with the Thai herbal tonic solution (Vilac Plus G716/45) daily dose 15-30 ml orally tid, pc as an additional supportive remedy.

RESULTS: Thirty cases of patients in advanced cervical cancer stage IIIB-IV with poor performance status, the median age in stage IIIB, IVA, IVB were 50 years (range 41-73 years), 50.5 years (45 years, 58 years), 69 years (67 years, 71 years) respectively. The analysis were being categorized and performed on stages IIIB, IVA, IVA with bladder cancer and IVB reporting in corresponding number of cases/total subject (percentage) were 25/30 (83.33%), 2/30 (6.67%), 1/30 (3.33%) and 2/30 (6.67%) respectively. The median tumor size for stages IIIB, IVA and IVB were 5 cm (range 2-10 cm), 5 cm (4,6 cm) and 4 cm (2, 6 cm) respectively. The pathological identification had been classified to be squamous cell carcinomas 21/30 (70.00%), adenocarcinomas 7/30 (23.33%), small cell carcinoma 1/30 case (3.33%) and clinically staging IIIB 1/30 case (3.33%). The median time interval between teletherapy and brachytherapy was 22 days (range 7-41 days). Eventually, 84% of the stage IIIB cases were undergone by prolonged gap of more than 2 weeks of time interval between teletherapy and brachytherapy while the rest of the case (16%) received the optimal time gap of treatments. The initial complete response and partial response after 4-6 weeks of radiotherapy were 84% and 16 % respectively. The patterns of failure in stage IIIB revealed in 16 % with residual pelvic diseases (< 6 months), 4% with local pelvic recurrence (> 6 months) and 4% with distant metastases. Median follow-up period in stage IIIB was 22 months (range 2-48 months). Low radiation complications were noted, the severe radiation proctitis (grade 3) was found to

¹ Division of Radiotherapy, Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand 40002

² Division of Nuclear Medicine, Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand 40002

³ Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Thailand 40002

⁴ Department of Pathology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand 40002

⁵ Department of Surgery, Faculty of Medicine, Chiang Mai University, Thailand 50000

be 3.33%. It was notable results in the declined BUN/Cr level in cervical cancer patients with underlying renal insufficiency/chronic renal failure patients treated by palliative radiotherapy and Thai herbal tonic solution as an additional supportive remedy had been observed in 2 cases of stage IIIB and 1 case of stage IVA with neither surgical intervention nor hemodialysis.

CONCLUSION: Our preliminary study in the treatment of advanced cases of Ca. Cervix with palliative radiotherapy and Thai herbal medicine had shown the evidence of initial complete regression of tumour with disappearance of foul smell discharge as high as 84 % with low rate of local pelvic recurrence, low distant metastases and low rate of radiation complication. However, the study has a limitation on the number of cases and a short follow up period. Moreover, this treatment modality had shown the benefit on the declination of BUN/Cr level in some cases of those locally advanced stages III B-IV in chronic renal failure caused by chronic ureteric obstruction due to lateral spreading of the cancer pressing on both ureters, without neither surgical intervention nor hemodialysis. The declined BUN/Cr levels were the consequence of the relief of pressure effect on the ureters by the decreasing of the tumour volumes. Palliative radiotherapy with Thai herbal tonic as supportive remedy was safe, cost effective, in addition to the benefit of improval of quality of life without the toxicity of herbal medicine. Therefore, this combination of palliative radiotherapy together with Thai Herbal Medicine would be the alternative option for the palliative treatment of advanced cancer cases with poor performance status or in locally advanced cancer cases. Further studies of increasing number of cases with longer follow up period including multicenters studies should be performed in order to confirm this findings with statistical significant conclusion.

Key words : Advanced cervical carcinoma, palliative radiotherapy, Thai herbal medicine.
BUN/Cr = Blood Urca Nitrogen/Creatinine

INTRODUCTION

Carcinoma of the uterine cervix had been recognized to be the major problem of malignant diseases in developing countries particularly in Thai women with an estimated 5,593 new cases in 1990. It was the most common malignancy prevalence in women. In Thailand, the estimated national age-standardized incidence was 23.4: 100,000 which was quite typical comparing to other developing countries in south and southeast Asia, and only a little less than the areas of the world at highest risk (Latin America, the Caribbean, sub-Saharan Africa).¹⁻² In Thailand, the incidence was highest in Chiang Mai (age standardized incidence rates(ASR) was 29.7 per 100,000 followed by KhonKaen , the ASR was 23.9 per 100,000).¹⁻² The risk factors of the cervical cancer was known to be related to human papilloma virus infection, etc.¹⁻² Most of the patients were found to be in advanced stages burdened with large tumor

volume at the first visit.³⁻⁷ At these advanced stages of diseases, radiotherapy remained the most general treatment available for controlling inoperable tumors as the palliative treatment. The large tumors volume burden in addition to the advanced stages rendered the consequence of radioresistant tumors that beings the contributing factors on the limitation to achieve the effectiveness of radiation therapy. Currently, the new gold standard is concomitant chemoradiation for dealing with locally advanced cervical carcinoma.⁸ But some of our patients were inaccessible to concurrent chemoradiation for the reasons of poor performance status, aging, obstructive uropathy, associated with underlying diseases such as chronic renal failure, etc. Therefore, another alternative approach for the resolution was using Thai herbal medicine (Vilac Plus G716/45) as supportive remedy. The Thai herbal tonic (Vilac Plus G716/45) was proven

to have no acute oral toxicity in animal study.¹⁰ No traces of prednisolone and dexametasone were detected.¹¹ An In Vitro study, the Vilac Plus(G716/45) presented an important antioxidant capacity.¹² The recipe of the ingredients of the Thai herbal tonic solution (Vilac Plus G716/45) was consisting of three edible plants, the whole part of mushroom namely *Ganoderma lucidum*, *Houttuynia cordata thunb* (leaves) and the roots of *Boesenbergia Pandurata Holtt* (Kra chai) which were found to be effective anti-tumor activities.¹³⁻¹⁴

OBJECTIVE

To evaluate the supportive effect of Thai herbal medicine, Vilac Plus (G716/45) on standard radiotherapy compare with historic control from the literature reports in advanced stage IIIB-IV cervical cancer. This study was performed at Radiotherapy Division, Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand 40002.

PATIENTS AND METHODS

During the period of March 2003 to June 2005. Thirty patients in advanced cervical cancer stage IIIB-IV with poor performance status were treated by palliative radiotherapy in adjuvant with the Thai herbal tonic solution (Vilac Plus G716/45) daily dose 15-30 ml orally tid, pc, as an supportive remedy. The evaluation parameters before staging were complete history, physical examinations as well as pelvic and rectal examination, routine laboratory investigations, chest X-ray, excretory urography, cystoscopy and proctoscopy. The staging of the diseases had been classified by the tumor clinic committee of gynecologists and radiotherapists according to FIGO recommendations.⁸ **Inclusion criteria** were: (1) advanced stages IIIB-IV cervical cancer; (2) poor performance status; (3) minimal response of the tumors after radiotherapy 30-40 Gy /3-4 weeks; (4) evidence of other underlying diseases; (5) advanced cervical cancer with other malignancies (two malignancies); (6) the informed of consent had been signed by the patients. **Exclusion criteria** was:

(1) The patients refused this treatment modality. This project was approved by the Human Ethics Committee of Khon Kaen University (HE 480745).

Definition of treatment failure was classified into residual disease and recurrent disease. The residual disease was defined as the present of persistent tumors which were noted 1-6 months after complete treatment while recurrence disease was defined as reappearance of the disease after a complete remission more than 6 months after complete treatment.

Grading of complications was defined according to Perez, et al.⁹

Radiotherapy technique: The treatment planning was done by two-paralleled opposing fields AP-PA with telecobalt-60 or linear accelerator (6 MV). The position for radiotherapy treatment was preferably to be supine. The prescribed dose of teletherapy was 5000 cGy/25 fractions, five fractions per week. Field margins were: anterior and posterior fields 15*15 cms; upper limit: L4-L5; lower limit: the superior two-thirds of the vagina. Brachytherapy was performed by using high dose rate Ir-192 about 2-4 weeks after teletherapy with doses ranges between 500-600 cGy/fraction to point A for 4-5 fractions, once weekly. The point A. dose was about 8600 cGy. The aim of using this tonic solution was to provide the better well-being condition for the patients, and to enhance the radiotherapeutic effects. The herbal tonic had the positive enhance effect on increasing appetite that may contribute the indirect effect on better nutritional status of the patients, and the better result of radiation therapy was the expected outcome.

RESULTS

During the period of March 2003 to June 2005, Thirty patients in advanced cervical cancer stage IIIB-IV with poor performance status were treated by palliative radiotherapy in adjuvant with the Thai herbal tonic solution (Vilac Plus G716/45) daily dose 15-30 ml orally tid,pc, as an supportive remedy. The following results were obtained in accordance with table 1-9.

1. Age distribution.

The median age in stage IIIB, IVA, IVB were 50 years (range 41-73 years), 50.5 years (45 years, 58 years), 69 years (67 years, 71 years) respectively. There was one case, age 29 years with two primary cancer, stage IVA cervical cancer with bladder cancer. (Table 1)

2. Stage of diseases.

The staging of the diseases had been classified by the tumor clinic committee of gynecologists and radiotherapists according to FIGO recommendations. (8) There were stage IIIB, stage IVA, stage IVA with bladder cancer and stage IVB were 25/30 cases (83.33%), 2/30 cases (6.67%), 1/30 case (3.33%) and 2/30 cases (6.67%) respectively. (Table 1)

3. Median tumor size (range) in cm.

The median tumor size for stage IIIB, IVA and stage IVB were 5 cms (range 2-10 cms), 5 cms (4,6 cms) and 4 cms (2,6 cms) respectively. (Table 1)

4. Pathology

The pathological diagnoses were squamous cell carcinomas 70.00% (21/30), adenocarcinomas 23.33% (7/30), small cell carcinoma 3.33% (1 case) and clinically staging IIIB 3.33% (1 case) (Table 1). The pathology of stage IIIB which developed pulmonary metastasis at 10 months after complete treatment was adenocarcinoma, poorly differentiated, while in stage IVB the pulmonary metastases presented at the initial diagnosis. The pathological diagnoses were squamous cell carcinoma, non keratinized and papillary adenocarcinoma, moderately differentiated.

5. Underlying diseases of the patients were diabetes mellitus, hypertension, renal insufficiency, chronic renal failure and HIV. (Table 1)

6. Time interval between teletherapy and brachytherapy.

The median time interval between teletherapy and brachytherapy were 22 days (range 7-41 days). There were 84% having prolonged time interval between teletherapy and brachytherapy, more than 2 weeks in stage IIIB while 16% having optimal time gap of treatment.

7. The initial complete response and partial response after 4-6 weeks of radiotherapy were 84% and 16% respectively. (Table 3)

8. It was observed that 93.33% (28/30) of cervical cancer patients, had been found to have clinical improvement according to Karnofsky's performance status (more than 80%). (Table 4-5)

9. Patterns of failure, in stage IIIB, it was found that that 16% having residual pelvic disease (< 6 months), 4% having local pelvic recurrence (> 6 months) and 4% having distant metastasis. Median follow-up period was 22 months (range 2-48 months). (Table 6 and 1)

10. Low radiation complications were noted while the severe radiation proctitis (G3) was found to be 3.33% and mild radiation proctitis and cystitis were 33.33%. (Table 7)

11. The onset time of the patients who develop severe radiation proctitis G3 was 9 months. (Table 8)

12. The declined BUN/Cr level in cervical cancer patients with underlying renal insufficiency/chronic renal failure patients treated by palliative radiotherapy with Thai herbal tonic solution as an supportive remedy had been observed in 3 cases (stage IIIB 2 cases and stage IVA 1 case) by neither surgical intervention nor hemodialysis. (Table 9)

Table 1 Patient Characteristics

Patient characteristics	
Gender (Female)	Total 30 cases
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Age in years	
Median (range)	
Stage IIIB	50.0 (41-73)
Stage IVA	51.5 (45,58)
Stage IVA * with bladder cancer	29
Stage IVB	69.0 (67,71)
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Stage of diseases	
Stage IIIB	25/30 cases (83.33%)
Stage IVA	2/30 cases (6.67%)
Stage IVA * with bladder cancer	1/30 case (3.33%)
Stage IVB	2/30 cases (6.67%)
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Median tumor size (range) in cms.	
Stage IIIB	5(2-10) cms
Stage IVA	5(4-6) cms
Stage IVA with bladder cancer	7.0 cms
Stage IVB	4(2-6) cms
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Median follow-up period (range) in months	
Stage IIIB	22 (2- 48)
Stage IVA	32.5 (17,48)
Stage IVA with bladder cancer	18
Stage IVB	9.5 (4,15)
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Pathology	
Squamous cell carcinomas	2 cases
Squamous cell carcinomas, non keratinized *	18 cases
Squamous cell carcinoma , keratinized	1 case
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Total squamous cell carcinoma group	21/30 (70.00%)
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Adenocarcinomas	3 cases
Adenocarcinomas, moderately differentiated	2 cases
Papillary adenocarcinoma, moderately differentiated	1 case
Adenocarcinoma, poorly differentiated	1 case
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Total adenocarcinoma group	7/30(23.33%)
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Neuroendocrine group	
Small cell carcinoma	1 case(3.33%)
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Clinically advanced cervical cancer stage IIIB (Tumor size 5*5cm with frozen pelvis)	1case (3.33%)
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Underlying diseases of the patients	
Stage IIIB with HIV	1 case
Stage IIIB with DM	1 case
Stage IIIB with DM +CRF	1 case
Stage IIIB with CRF	1 case
Stage IIIB with HT+CRF	1 case
Stage IVA with CRF	1 case
Stage IVB with DM+HT+CRF	1 case
Stage IVB with DM+HT	1 case

Time interval between teletherapy and brachytherapy	
Median (range) days	
Stage IIIB	22(7-41)

DM = Diabetes mellitus
 HT = Hypertention
 CRF = Chronic renal failure

Table 2 Time interval between teletherapy and brachytherapy (days).

Stage	Time interval (days)	No. of cases (%)
Stage IIIB	1-14	4 (16%)
	15-30	16 (64%)
	31-45	5 (20%)

Stage IVA	16,54	1,1

Stage IVA*	17	1

Stage IVB	16,35	1,1

* Stage IVA 1 case revealed both squamous cell carcinoma, non keratinized and transitional cell carcinoma.gr I/III of bladder.

Table 3 Initial complete response rate (CR) and partial response rate (PR) after 4-6 weeks of radiotherapy.

Stages	Initial response rate (cases)	%
Stage IIIB	CR=21/25	84%
	PR=4/25	16%
Stage IVA	CR=1/3	33.33%
	PR=1/3	33.33%
Stage IVA*	PR=1/3	33.33%
Stage IVB	CR=1/2 (local)	50%
Stage IVB	PR=1/2 (local)	50%

* **Stage IVA** 1 case revealed both squamous cell carcinoma, non keratinized and transitional cell CA.gr.I/III of bladder.

Table 4 Subjective response after 4-6 weeks of radiotherapy.

Subjective response	cases	%
Clinical improvement	30/30	100

Table 5 Karnofsky's performance status (KPS) after radiotherapy

KPS	cases	%
70 %	2/30	6.67
80-85%	6/30	20
90%	10/30	33.33
100%	12/30	40

Table 6 Patterns of failure: residual disease (<6 months) & recurrence disease (>6 months)

Stage	Residual disease (<6months)	Recurrence disease (>6months)	
		Pelvic recurrence	Distant metastases
Stage IIIB	4/25 (16%)	1/25 (4%)	1/25 (4%)
Stage IVA	-	-	1 /2case
Stage IVA with bladder cancer	Pelvic +Distant metastases 1 case		
Stage IVB	Pelvic +Distant metastases 1 case		

Table 7 Radiation complications

Radiation complication	No. of cases	%
Radiation proctitis G1	8/30	13.33
Radiation cystitis G1	2/30	6.37
Total proctitis+cystitis G1	10/30	33.33
Radiation proctitis G3	1/30	3.33

Table 8 Onset time to develop radiation complications after complete treatment.

	Onset (months)	No. of cases
Stage IIIB (grade 1)	7-12	3
	13-18	4
	19-25	1
	40-46	1

Stage IIIB (grade 3)	9	1

StageIV (grade 1)	14	1

Table 9 The declined BUN/Cr level in cervical cancer patients with underlying renal insufficiency / chronic renal failure patients treated by palliative radiotherapy and Thai herbal tonic solution as supportive remedy.

Stage	BUN/Cr mg/dl (Before)	BUN/Cr mg/dl (After)
IIIB	51/3.5 (01/12/03)	38.2/2.6 (11/07/05)
IIIB	167/24 (27/02/04)	32.6/3.4 (03/05/05)
IVA	112/1.2 (24/03/03)	13.3/0.9 (01/09/03)

BUN = Blood urea nitrogen
Cr = Creatinine

DISCUSSION

The ten years retrospective study in our institute had been reported on 1,180 cervical cancer cases who had been treated by radiotherapy.¹⁵ The analysis results demonstrated that the factors influencing survival of cervical cancer patients were staging, hemoglobin level, time interval between external and intracavitary radiation and fractionation of brachytherapy. The stage III group was found to be 1.65 fold mortality risk over stage I group. The patients with low hemoglobin level less than 10 g/dl demonstrated a 1.85 fold mortality risk over the high hemoglobin over than 12 g/dl. The time interval between external and intracavitary radiation more than 28 days was associated with 2.28 fold mortality risk over the duration of less than one day. The two fractionations of brachytherapy was associated with

0.25 fold mortality risk over the one fractionation. The overall 5-year survival rate in this study revealed 62.5% and median survival was more than 10 years.¹⁵ The other reports revealed the overall 5 year survival rate of 412 cervical cancer patients in all stages were found to be 51.2% and 39 % in stage IIIB while the 5 year actuarial survival rates for small size tumor less than 2 cm in diameter and tumor size larger than 2 cm in diameter were 74% and 56% respectively.³⁻⁴ The treatment failures with radiotherapy alone were found to be statistically significance correlated with staging, tumor size and time interval between teletherapy and brachytherapy had been reported by Pese M. et al.³ According to the pathology 5 year actuarial survival rate of squamous cell carcinoma and adenocarcinoma were 51 % and 58 % respectively.³

In radiation complication aspects which had been reported that 39.6 % of 412 cases developed radiation proctitis, 2.7% with radiation cystitis, 3.9 % combined radiation proctitis with cystitis, 0.7 % with recto- vaginal fistula and 1 ileal perforation, occurred during a second course of palliative treatment for lumbar metastasis, causing death had been reported by Boonvisuth V. et al.¹⁶ From the literature reviews of 212 cases of stage III cervical cancer patients treated with radiotherapy alone had been reported that the incidences of pelvic recurrence, pelvic recurrence plus distant metastases, total pelvic recurrence and distant metastases only were 14.6%, 21.2%, 35.8% and 18.4% respectively.¹⁷ The other reports of the incidences of local pelvic recurrence, recurrence outside the pelvis and metastatic failure in stage III cervical cancer patients treated with radiotherapy alone were 12.0% -13.6%, 24.0%, and 15.8% respectively.¹⁸⁻¹⁹ In radiation complication aspects which had been reported by Perez CA, et al. that 9.2 % of 271 stages III cervical cancer cases treated with radiotherapy alone developed grade 2 and 10.7% of grade 3 radiation complication.⁹ The absolute 5 year survival rates of 515 cases in stage IIIB and 104 cases in stages IVA and IVB disease treated with radiotherapy alone were 52.2%, 24.1% and 13.3% respectively. The patterns and severity degree of complications were reported as grade 3 and 4 where the complications involved in 4.1% for rectosigmoid colon, 1.2% for bladder, and 1.1% for small intestine in accordance to the report by Arai T, et al.²⁰ Perez CA .et al reported of 1054 cervical cancer patients that the controlling of the tumor in the pelvis was crucial to the survival of the patients in all stages. The results of complete tumor regression within 30 days after completion of radiation therapy had not only substantialling lower number of pelvic recurrence but also fewer distant metastases.²¹ The high incidence of distant metastases had been found in stage III-IV.²¹ Pelvic tumor control of stages III-IVA cervical cancer patients treated with concurrent chemoradiation and radiotherapy alone were 62% and 59% respectively had been reported by Perez, et al.²² The incidence of pelvic failure in concurrent chemoradiation and radiotherapy alone were 41% and 39% while the combined pelvic failure plus

distant metastases were 24% and 19% respectively. In addition, the distant metastases only in concurrent chemoradiation and radiotherapy alone were 29% and 11% respectively.²² In another study of locally advanced stage III-IV cervical cancer treated with combination chemotherapy followed by surgery or radiotherapy revealed complete response was 10.6% and complete response plus partial response were 66% and median survival was 88 weeks had been reported by Kirsten F, et al.²³ The complete response rates and the rates of pelvic recurrence in advanced cervical cancer treated stage IIIB -IVA with chemotherapy (CMT) plus radiation (RT) compared with radiotherapy alone (RT) were found to be 53% (CMT+RT) / 57%(RT) and 60%(CMT+RT) / 47% (RT) respectively while the rates of distant metastases were 19% (CMT+RT) / 35% (RT) respectively had been reported by Sundfor K, et al²⁴ The complete response and partial response in advanced stages III-IVA treated with chemotherapy plus radiotherapy were found to be 53% had been reported by Symonds RT, et al.²⁵ The complete response and partial response in advanced stages IIIB treated with chemotherapy plus radiotherapy were found to be 62.5% had been reported by Lara PC, et al.²⁶ The four randomized trial of neoadjuvant chemotherapy and irradiation in stage IIB-III cervical cancer patients were found to be 30-85% of the response rates and none of the studies showed an advantage to pelvic control or survival had been reported by Thomas GM.²⁷

Our cervical cancer patients in this study demonstrated having several poor factors such as advanced stage IIIB-IV, large tumor size (median 5 cm, range 2-10 cm.), prolonged time interval between teletherapy and brachytherapy 84 % of cases and associated with poor performance status with or without underlying diseases in table 1. The remarkable of the results of this treatment modality revealed the evidences of:-

1. High initial complete response rate 84% in the stage IIIB-IV locally advanced cervical cancer
2. Low local pelvic recurrence (4%)

3. Low distant metastases (4%) had been observed. The mild radiation complications had been found 33.33%, the moderate radiation complication had not been detected and severe complication was found to be 3.33%. In comparison with historical controls as evidenced in local control and distant metastases had been improved by this modality therapy. Moreover, it had been observed on the benefit with declined BUN/Cr level in some cases of those locally advanced stage IIIB-IV cervical cancer cases with underlying renal insufficiency/chronic renal failure by neither surgical intervention nor hemodialysis. The evidence of declined BUN/Cr level had been observed by this treatment modality in 1 advanced lung cancer case who had underlying chronic renal failure as in our previous report.²⁸ However, the study had limitation on number of cases and follow-up period (median follow-up period in the stage IIIB was 22 months, range 2-48 months while the stage IVA was 32.5 months, 1 case was 17 months and 1 case was 48 months).

The noteworthy results of this modality therapy were remarkable evidences in the aspects of high initial complete response of the local control of the tumor in contrary to the low distant metastases, low local pelvic recurrence and low radiation complications were observed. Some of them being improved their underlying diseases of renal insufficiency/chronic renal failure. The declined BUN/Cr levels were the consequence of the relief pressure effect on the KUB system by the decreased tumor volume. Therefore the better ability excretory function of kidney had been observed. It seems to be better well being of those patients in the holistic performance status.

The pharmaceutical aspects considerations and explanations should be emphasizing on the "supportive remedy" actions of Vilac Plus® which had been used as adjuvant to the standard radiation therapy compare to the relevance historic control in articles reviewing with other modalities of treatments. The ingredients of the Vilac Plus® tonic consisting of anti-tumor mushroom, LingZhi (*Ganoderma lucidum*), *Houttuynia cordata*, *Thunb* and *Boesenbergia*

pandurata Holtt (Krachai). The tonic preparation accomplished by fermentation by using *Lactobacillus casei* spp. (Genebank Reg. No. AF 320255) and *Lactobacillus plantarum* spp. (Genebank Reg. No. AF 320256). An invitro analysis of the Vilac Plus® tonic had been reported by Kirial International Laboratories, France. This analysis reported,¹² the overall antioxidant potency of all ingredients in the mixture of Vilac Plus® which being concurrently bioavailable in the subcellular level represented by the whole blood sample assessment. This was the key and crucial evidence for scientific explanation upon the mechanism and pharmacological action of our clinical studies. The promising supportive adjuvants actions contributed from each composition of the 4 ingredients in Vilac Plus® including the microorganism used in the fermentation proceedings that should be recognized as the "probiotics" which is one key component in the biotechnology procedure of production. The probiotic action and role on cancer therapy could be summarized as follows^{31,32}

1. Antitumor and antimetastatic effects³² by induction or stimulation the synthesis of several cytokines which had been known to be the immunomodulating factor. The small molecular weight cytokines such as IFN-gamma, IL-1 beta and TNF alpha. being one of the enhancement transfer factor to work effectively.
2. Immunomodulation enhancement through the heat-killed lysate in the tonic (Vilac Plus®) that resulting in the delayed or inhibit the process of distance metastases in various cell type of cancers³¹ such as colon, liver, lung uterine, cervix and mammary cancers.

The herbal ingredients was world recognition mushroom, Ling Zhi (*Ganoderma lucidum*) or Reishi, where it had been mentioned as sacred mushroom which had been found the 119 different terpenoids, about 80 of which biologically active.^{34,35} The role to be the supportive action in cancer treatment was immunomodulation anticancer by protection DNA damage through its powerful antioxidant mechanism by inhibition of tumor necrosis factor (TNF). There were a number of reports that had mentioned the benefit on various cancers.^{36,37}

The other herbs were the edible plants (*Houttuynia cordata Thunb* and the root of *Boesenbergia Pandurata Holtt* (Krachai).³⁷ The role to contribute as supportive remedy was phytosterols in addition to their characteristic of one of the essential antiproliferative of cancer cells such as flavonoids and volatile oil which the strongest one that present this action was linolool.³⁸ The study had been shown this effective action on various cancers and the best of action was found to be on cervical carcinoma.³⁸ The co-operative actions of these herbs were reported to be the "interferon-inducing herb" that may contribute some important role to play on antitumor-antiviral activity through the "interferon" molecule.^{39,40}

However the outcome of the support remedy by using Vilac Plus® as an adjuvant to standard therapy were very promising in the aspect of the benefit of cost-effectiveness model of cancer therapy. This should be one option of the multimodalities model of treatment that might be useful in the developing countries where the high technology or expensive chemotherapy even concurrent chemotherapy were inaccessible.

In summary, the best strategy approaches to fight with cancer should be achieve only in the holistic considerations. Therefore, this modality would provide the effective local controls, prevent distant metastases and strengthening of the host immunity then encouraging result could be observed.

CONCLUSION

Palliative radiotherapy was the standard treatment for poor performance status, advanced cervical cancer patients with or without underlying diseases. Radiation therapy alone had been reported of disappointing outcome as the results of pelvic failure, paraaortic nodes failure and also distant metastases. Our preliminary study revealed that palliative radiotherapy with Thai herbal medicine (Vilac plus G 716/45) demonstrated of having high initial complete

response rate of 84% with low local pelvic recurrence, low distant metastases and low radiation complication. However, the study had limitation on number of cases and follow-up period. Surprisingly, it had been unexpectedly finding that these treatment modality having benefit on declined BUN/Cr level in some cases of those locally advanced stage IIIB-IV cervical cancer cases with underlying renal insufficiency/chronic renal failure with neither surgical intervention nor hemodialysis. The declined BUN/Cr levels were the consequence of the relief pressure effect on the KUB system by the decreased tumor volume. Nevertheless, palliative radiotherapy with Thai herbal tonic as supportive remedy was safe, cost effective and benefit in the aspect of quality of life by the evidence of high initial complete response rate with poor performance status who could not undergo concurrent chemoradiation. Therefore, this modality would be the alternative option for the palliative cancer cases or one of the multimodality in locally advanced cervical cancer. Further studies deep in details by increasing number of cases, longer follow-up period including multicenter studies are necessary to affirm with statistically significant conclusion, especially in the aspects of the benefit of declined BUN/Cr level in those who have locally advanced cervical cases with underlying renal insufficiency/chronic renal failure which are very interesting topics for developing country.

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REFERENCES

1. Vatanasapt V, Martin N, Sriplung H, et al. Cancer in Thailand. 1988-1991. Khonkaen: Siriphan Press, 1993:68-69.
2. Vatanasapt V, Martin N, Sriplung H, et al. Cancer incidence in Thailand. 1988- 1991. Cancer Epidemiology, Biomarkers & Prevention 1995; 4 :475-483.
3. Pesee M, Tangvoraphonkchai V, Boonvisuth V, et al. Radiotherapy alone in the treatment of carcinoma of the uterine cervix in Srinagarind Hospital: Analysis of treatment failure. Thai J Radiol. 1989;26(1):67-70.
4. Pesee M, Tangvoraphonkchai V, Reamsiri T, et al. Low dose rate brachytherapy Caesium -137 afterloading in the treatment of carcinoma of uterine cervix in Srinagarind hospital: Analysis of a actuarial survival rate. Thai J Radiol. 1995;1(3):125-30.
5. Tungsubutra K, Pesi M, Tangvoraphonkchai V. Problems in treatment of cancer in the rural areas and the remedies. In Mould RF, Tungsubutra K, eds. Diagnosis and treatment of carcinoma of the cervix in developing areas. Bristol and Boston: Adam Hilger 1985; 219-22.
6. Tungsubutra K, Tangvoraphonkchai V, Pesi M. Cancer epidemiology in Thailand. In Mould RF, Tungsubutra K, eds. Diagnosis and treatment of carcinoma of the cervix in developing areas. Bristol and Boston: Adam Hilger 1985; 187-90
7. Tangvoraphonkchai V, Pesee M, Boonvisuth V, et al. Tumor registry: An overview of problems shooting in radiotherapy. Thai J Radiol 1989; 26(1): 95-8.
8. Chao K.S.C , Perez CA, Bradym LW, eds. Uterine Cervix in Textbook of Radiation Oncology. Management Decisions. Lippincott Williams & Wilkins, Philadelphia. 2002;489-509.
9. Perez CA, Breaux S, Bedwinek JM, et al. Radiation Therapy Alone in the Treatment of Carcinoma of the Uterine cervix. II. Analysis of Complication. Cancer 1984;54:235-246.
10. Suntornanasat T, Banchonglikitkul C, Klungsupaya P, et al. Acute oral toxicity test Herbal tonic solution (G716/45). An analytical report. Thailand Institute of Scientific and Technological Research. September 2003,1-8.
11. Amadi Pirasahid P, Suntornanasat T, Analytical report on Herbal tonic solution. (G716/45). An analytical report. Thailand Institute of Scientific and Technological Research. September 2004,1-3.
12. Durand Phillippe, Prost Michel. In Vitro study of Vilac Plus analysis. Kirial International laboratories KRL Test (SPIRAL-No. Patent FR 2. 642. 526), 3 rue des Mardors 21560 COUTERNON, France. July 2006,1-4.
13. Lee S-S, Wei Y-H, Chen C-F, et al. Anti -tumor effects of polysaccharides of Ganoderma lucidum. Proc Int Symposium Ganoderma Sci, Auckland, 27-29 April, 2001, 1-6
14. Murakami A, Jiwajinda S, Koshimizu k, et al. Screening for in vitro anti-tumor promoting activities of edible plant from Thailand. Cancer Letters 1995; 95: 139-14
15. Pomros P, Sriamporn S, Tangvoraphonkchai V, et al. Factors Affectng Survival of Cervical Cancer Patients Treated at the Radiation Unit of Srinarind Hospital, Khon Kaen University, Thailand. Asian Pacific Journal of Cancer Prevention 2007; 8: 297-300
16. Boonvisuth V, Pesee M, Tangvophonchai V, et al. Radiotherapy alone in the treatment of carcinoma of the uterine cervix in Srinagarind Hospital: Analysis of Complication. Thai J Radiol. 1989; 26(2): 139-146.
17. Perez CA, Breaux S, Madoc-Jones H et al. Radiation therapy alone in the treatment of carcinoma of uterine cervix. I. Analysis of tumor recurrence. Cancer 1983; 51: 1393-1402
18. Kataoka M, Kawamura M, Nishiyama Y, Hamada K, Hamamoto K, Matsu-Ura S. Results of the combination of external-beam and high-dose-rate intracavitary irradiation for patients with cervical carcinoma. Gynecol Oncol 1992; 44: 48-52.

19. Khoo-Tan HS, Chua EJ. Radical radiotherapy for carcinoma of the uterine cervix using high dose rate brachytherapy--a preliminary report. *Ann Acad Med Singapore* 1996; 25: 367-70.
20. Arai T, Nakano T, Morita S, et al. High dose rate remote afterloading intracavitary radiation therapy for cancer of the uterine cervix. A 20-year experience. *Cancer* 1992; 69:175-180.
21. Perez CA, Kuske RR, Camel HM, et al. Analysis of pelvic tumor control and impact on survival in carcinoma of the uterine cervix treated with radiation therapy alone. *Int J Radiat Oncol Bio Phys* 1988; 14: 613-621.
22. Perez CA, et al Uterine cervix in textbook of principles and practice of radiation oncology, third edition. Perez CA, Brady LW, eds. Lippincott-Raven publishers. New York. 1997: 1806-1808.
23. Kirsten F, Atkinson Kh, Coppelsen JVM, et al. Combination chemotherapy followed by surgery or radiotherapy in patients with locally advanced cervical cancer. *Br. J Obstet Gynaecol* 1987; 94: 583-588.
24. Sundfor K, Trope CG, Hogberg T, et al. Radiotherapy and neoadjuvant chemotherapy for cervical cancer. A randomized multicenter study of sequential cisplatin and 5-fluorouracil and radiotherapy in advanced cervical carcinoma stage IIIB and IVA. *Cancer* 1996; 77: 2371-2378.
25. Symonds RP, Burnett RA, Habeshew T, et al. The prognostic value of chemotherapy given before radiotherapy in advanced cancer of cervix. *Br J Cancer* 1989; 59: 473-475.
26. Lara PC, Garcia Puche JL, Pedraza V. Cisplatin- ifosfamide as neoadjuvant chemotherapy in stage IIIB cervical uterine squamous cell carcinoma. *Cancer chemother Pharmacol* 1990; 26: 36-38.
27. Thomas GM. Is neoadjuvant chemotherapy a useful strategy for the treatment of stage IB cervix cancer [Editorial]. *Gynecol Oncol* 1993; 49: 153-155.
28. Pesee M, Kirdpon W, Puapairoj A, et al. Palliative treatment of advanced lung cancer with radiotherapy and Thai herbal medicine as supportive remedy. *The Asean J of Riology* 2006; 12(3): 149-176.
29. Pesee M, Kirdpon W, Puapairoj A, et al. Palliative treatment of advanced subependymal oligodendroglioma with radiotherapy and Thai herbal medicine as supportive remedy. *The Asean J of Riology* 2006;12(3):135-148.
30. Takagi A, Matsuzaki T, Sato M, et al. Enhancement of natural killer cytotoxicity delayed murine carcinogenesis by a probiotic microorganism. *Carcinogenesis* 2001 ; 22(4): 599-605.
31. Takagi M. Immunomodulation by treatment with *Lactobacillus casei* strain shirota. *Int J Food Microbiol* 1998; 41(2): 33-40.
32. Salminen S, Isolauri E, Salminen E. Probiotics and stabilization of the gut mucosal barrier. *Asia Pacific J Clin Nutr* 1996; 5(1): 53-56
33. Wasser SP. Review of Medicinal Mushrooms Advances: Good news from old allies. *Herbalgram* 2002; 56: 28-33
34. Kim HW, Kim BK. Biomedicinal triterpenoids of *Ganoderma lucidum* (*Aphyllophoromycetidae*). *Int J of Med Mushroom* 1999; 1:121-38.
35. Van der Hem LG, Ling Zhi-8. Studies of a new immuno modulating agent. *Trasplantation*. 1995; 60: 438-443.
36. Wang SY. Anti-tumor effect of *Ganoderma Lucidum* is mediated by cytokines released from activated macrophages and T-lymphocytes. *Int J Cancer* 1997;70:699-705.
37. Murakami A, Kondo A, Nakamura Y, et al. Possible antitumor Promoting and identification of Active Constituent Cardomoin of *Boesenbergia Pandurata*. *Biosci Biotech Biochem* 1993; 57 (11): 1971-3.
38. Cherng JM, Shieh DE, Chiang W, et al. Chemopreventive effects of minor dietary constituents in common foods on human cancer cells. *Bioscience, Biotechnology and Biochemistry* 2007; 71(6): 1500-1504

39. Morita N, Hayashi K, Fujita A, et al. Extraction of antiviral substances from *Houttuynia cordata* Thunb. *Chemical abstract* 1995; 123: 93249j.
40. Hayashi K, Kamiya M, Hayashi T. Virucidal effects of the steam distillate from *Houttuynia cordata* and its components on HSV-1, influenza virus and HIV. *Plant Med.* 1995; 61 (3): 237-41