

RESEARCH ARTICLE

Palliative Treatment of Advanced Cervical Cancer with Radiotherapy and Thai Herbal Medicine as Supportive Remedy - Analysis of Survival

Montien Pesee^{1*}, Wichit Kirdpon², Anucha Puapairoj³, Sukachart Kirdpon⁴, Pongsiri Prathnadi⁵

Abstract

Background: To evaluate outcomes using a Thai herbal medicine, Vilac Plus (G716/45) with standard radiotherapy in comparison with historic controls from literature reports of the results of treatment in stage IIIB cervical cancer. **Materials and Methods:** Between March 2003 and June 2005, thirty patients with advanced cervical cancer stage IIIB-IV who had a poor performance status were treated by palliative radiotherapy along with an adjuvant daily dose of 15-30 ml of Thai herbal tonic solution (Vilac Plus G716/45) administered orally three times after meals as an additional supportive therapy. The results were analyzed from the aspect of the overall survival rates with curves estimated by the Kaplan-Meier method. **Results:** The median follow-up time for stage IIIB was 4.2 years with a range of 7.9 months – 6.1 years. The overall 1, 3, and 5 year survival rates for stage IIIB were 88%, 60% and 52%. **Conclusions:** The overall 5 year survival rate for stage IIIB with a poor performance status was 52% when compared with 34-54.8% for historic controls. The combined complementary palliative radiotherapy (CCPR) had low rates of radiation morbidity. It was a simple technique and feasible for developing countries. The pilot study was limited by the small number of patients and further research will be necessary to assess interrelated and confounding factors in treatment of cervical cancer patients.

Keywords: Advanced cervical carcinoma - palliative radiotherapy - Thai herbal medicine - *Lactobacillus casei*

Asian Pacific J Cancer Prev, 14 (3), 1593-1596

Introduction

Advanced carcinoma of the uterine cervix has been recognized to be the major malignant diseases problem in the developing countries and is a particular problem in Thai women (Sriamporn et al., 2004). For these advanced stages of disease, radiotherapy remains the most general treatment available for controlling inoperable tumors as the palliative treatment. The large tumors volume burden in addition to the advanced stage when presented plus the complication of radioresistant tumors were contributing factors to the ability to achieve effectiveness of radiation therapy. Currently, the new gold standard is concomitant chemoradiation for dealing with locally advanced cervical carcinoma (Thomas., 2000., Green et al., 2001; Toita et al., 2012). In addition, The advanced sophisticated radiation techniques such as 3D conformal radiotherapy, intensity modulated radiation therapy (IMRT) along with advanced imaging applications have increased in usage for locally advanced cervical cancer (Petsuksiri et al., 2012). Some of the patients were inaccessible to concurrent chemoradiation because of poor performance status,

age, obstructive uropathy, or associated with underlying diseases such as chronic renal failure.

The reports of antioxidants combined with therapeutic modalities revealed the enhancement of the therapeutic effects of chemotherapy and/or radiotherapy, a decrease in side effects, protection of normal tissues and also increased survival (Simone et al., 2007). Most of the studies demonstrated evidences of a synergistic effect of antioxidants and radiotherapy and decreased adverse effects of the therapy (Moss, 2007). Based on this rationale, another alternative approach was tried using Thai herbal medicine (Vilac Plus G716/45) as supportive remedy. The Thai herbal tonic (Vilac Plus G716/45) are healthy tonic for all persons (sick or well) and it has been registered as a tonic, available without prescription by the Thai food and drug council. It was proven to have no acute oral toxicity in animal studies (Suntornntanasat et al., 2003). No traces of prednisolone or dexamethasone were detected (Amadi, 2004). In an *in vitro* study, the Vilac Plus (G716/45) demonstrated an important antioxidant capacity (Phillippe et al., 2006). The recipe of the ingredients of the Thai herbal tonic solution (Vilac Plus G716/45) consisted

¹Division of Radiotherapy, ²Division of Nuclear Medicine, Department of Radiology, ³Department of Pathology, Srinagarind Hospital, ⁴Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, ⁵Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand *For correspondence: pmonti@kku.ac.th

of three edible plants, the whole part of mushroom namely *Ganoderma lucidum*, leaves of *Houttuynia cordata thunb* and the roots of *Boesenbergia Pandurata Holtt* (Kra chai) which were found to have effective antitumor activities (Murakami et al., 1995; Wang et al., 1997).

The current authors therefore conducted a follow-up study to determine whether palliative treatment in advanced uterine cervical cancer using palliative radiotherapy and the Thai herbal medicine as supportive therapy, now designated as combined complementary palliative radiotherapy (CCPR) between March 2003 and June 2006 improved the survival rate.

Objectives

To evaluate the outcomes based on survival parameters of advanced stage IIIB cervical cancer by using CCPR in comparison with historic controls from the literature.

Materials and Methods

This study was performed at the Radiotherapy Division, Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand 40002. Between March 2003 and June 2006, thirty patients in advanced cervical cancer stage IIIB-IV with poor performance status were treated by palliative radiotherapy along with the Thai herbal tonic solution (Vilac Plus G716/45) at a daily dose of 15-30 ml orally three times after meals as a supportive remedy. The staging of the diseases was classified by the tumor clinic committee of gynecologists and radiation oncologists according to the International Federation of Gynecologists and Obstetricians (FIGO) recommendations (International Federation of Gynecologists and Obstetricians, 1995). This project was approved by the Human Ethics Committee of Khon Kaen University (HE 480745).

The inclusion criteria were: (1) advanced stages IIIB-IV cervical cancer; (2) poor performance status; (3) minimal response of the tumors after radiotherapy 30-40Gy /3-4 weeks; (4) evidence of other underlying diseases; (5) advanced cervical cancer along with another malignancy; (6) informed of consent signed by the patients. The sole exclusion criterium was that the patients refused this treatment modality. All patients were followed until date of death or lost to follow - up.

Analysis: The results were analyzed for survival rates. The survival curve was estimated by the Kaplan -Meier method.

Radiotherapy: All patients were treated with a Linear accelerator (LINAC) 6 MV. The prescribed dose of teletherapy was 50 Gy/25 fractions, five fractions per week to the whole pelvis through AP and PA 15x15 cm² or a 16x16 cm 2port. In addition, the parametrial boosts of 200 cGy for 3-5 days after the completion of brachytherapy were used to treat stage IIIB patients with massive tumors at the parametrium.

Brachytherapy was performed by using high dose rate Ir-192 about 2-4 weeks after completion of teletherapy with doses range between 500-600 cGy/ fraction to point A for 4-5 fractions, once weekly fractionation. The point A dose was about 86 Gy.

Table 1. Patient Characteristics (Pesee et al., 2007)

Gender (Female)	Total 30 cases
Age in years	Median (range)
Stage IIIB(25 cases)	50 (41-73)
Stage IVA-IVB (5 cases)	45 (29-71)
Stage of diseases	
Stage IIIB	25/30 cases (83.33%)
Stage IVA -IVB	5/30 cases (16.67%)
Median tumor size	Median (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
Follow -up time	Median follow- up time (range)
Stage IIIB	4.2 years, (7.9 months-6.1years)
Pathology	
Squamous cell carcinomas	21/30 cases (70.00%)
Adenocarcinomas	7/30 cases (23.33%)
Small cell carcinoma	1 case (3.33%)
Clinically advanced cervical cancer stage IIIB 1case (3.33%) (Tumor size 5x5cm with frozen pelvis)	
Underlying diseases of the patients (HIV,DM,HT,CRF)	
Stage IIIB with HIV, DM, HT, CRF	5 cases (16.67%)
Stage IVA- IVB with DM,HT,CRF	3 cases (10.0%)
Time interval between completion of teletherapy and brachytherapy	Median (range) days
Stage IIIB	22 (7-41)

*One stage IVA case revealed both squamous cell carcinoma, non keratinized and transitional cell carcinoma.gr I/III of bladder. DM=Diabetes mellitus, HT=Hypertention, CRF=Chronic renal failure

Table 2. The Overall 1, 3, and 5 Year Survival Rates of Stage IIIB Cervical Cancer (Kaplan-Meier survival estimate)

Follow -up time (years)	Overall survival rates (%)	95% Cont. Int.
1	88	0.67-0.96
3	60	0.38-0.76
5	52	0.31-0.69

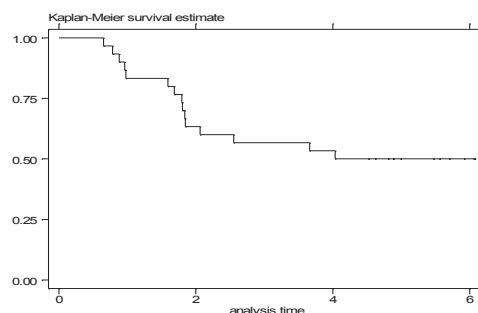


Figure 1. The Survival Curve of Stage IIIB Cervical Cancer

Results

Thirty cases of patients in advanced cervical cancer stage IIIB-IV with a poor performance status were treated using CCPR. The overall 1, 3, and 5 year survival rates for stage IIIB were 88 %, 60% and 52%. The following results are summarized in accordance with Tables 1-2 and Figure 1.

Discussion

Radiotherapy remains the most general treatment available for controlling inoperable tumors (Bermudez et al., 2010). The factors influencing overall survival are tumor size, staging, hemoglobin level, interval between external- intracavitary radiation and radiotherapy

fractionations (Pomros et al., 2007). The overall 5 year survival rate of stage IIIB cervical cancer by using CCPR was 52% when compared with 34-54.8% of historic controls (Arai et al, 1992; Lorvidhaya et al., 2000; Rose et al., 2007; Wong et al., 2003; Pesee et al., 2010). In addition, the overall 3 year survival rate of 3D conformal radiotherapy with or without chemotherapy plus image (MRI) guided adaptive intracavitary brachytherapy was 45% for stage IIIB cervical cancer (Potter et al., 2011). The incidence of radiation proctitis, grade 1, grade 2 and grade 3 by using CCPR were 13.30%, 0% and 3.33%. The radiation cystitis grade 1, grade 2 and grade 3 by using CCPR were 6.36%, 0%, 3.33% (Pesee et al., 2007). Some cervical cancer patients with underlying diseases of renal insufficiency/chronic renal failure improved their level of blood urea nitrogen (BUN) / creatinine (Cr) ratio by using CCPR (Pesee et al., 2007).

The enhancing effect of Vilac Plus® on radiotherapy to prolong the survival of these patients may be explained under the principle that antioxidants have an antitumor effect and offer normal tissue protection. The Vilac Plus® tonic revealed antioxidant activity (Phillippe et al., 2006) being bioavailable at the subcellular level. The hypothesis of radical- scavenging activity of the tonic against excess free radicals of the radiotherapy may be explained by specific protection against DNA of normal cells. This is the key and crucial evidence for the possible scientific explanation of the mechanism and pharmacological action of CCPR, therefore, further research will be needed to test this hypothesis. The ingredients of the Vilac Plus® tonic consisting of antitumor mushroom, LingZhi (*Ganoderma lucidum*), *Houttuynia cordata Thunb* and *Boesenbergia pandurata Holtt* (Krachai) were used as adjuvant therapy. The tonic was prepared by fermentation using *Lactobacillus casei* spp. (Genebank Reg. No. AF 320255) and *Lactobacillus plantarum* spp. (Genebank Reg. No. AF 320256). The promising supportive adjuvant actions contributed from the composition of the 3 ingredients in Vilac Plus® plus the microorganism used in the fermentation that should be recognized as a probiotic is a key component in the biotechnological production. The herbal ingredients of the mushroom, widely recognized in world literature, Ling Zhi (*Ganoderma lucidum*) or Reishi, has been found to contain 119 different terpenoids, about 80 of which biologically active (Van der Hem 1995; Kim et al., 1999). The possibility to have a supportive role in cancer treatment appears to be immunomodulation by protection DNA damage of normal cells through its powerful antioxidant mechanism and inhibition of tumor necrosis factor (TNF). There are a number of reports that have mentioned the benefit of this mushroom on various cancers (Wang et al., 1997; Sliva, 2003; Wu et al., 2006). The other herbs are the edible plants, *Houttuynia cordata thunb* (Hayashi et al., 1995) and the root of *Boesenbergia pandurata Holtt* (Murakami et al., 1995). The role to contribute as supportive therapy is perhaps because of the presence of phytosterols such as flavonoids and volatile oil, of which the strongest one is linalool, that have essential antiproliferative activity on cancer cells (Cherng et al., 2007; Banjerdpongchai et al., 2011). The co-operative actions of these herbs are reported to be as

“interferon-inducing herbs” that may contribute some important role to play as antitumor - antiviral activity through the interferon molecule (Hayashi et al., 1995; Chang et al., 2001).

The *Lactobacillus plantarum*, *Lactobacillus casei*, antioxidants actions on the possible role in cancer therapy might be summarized as follows: 1) The antioxidants combined with therapeutic modalities produce enhancement of the therapeutic effects of chemotherapy and/or radiotherapy, decrease side effects, protect normal tissues and therefore increase survival (Moss, 2007; Simone et al., 2007). 2) Heat- killed *Lactobacillus plantarum* L-137 demonstrated an antitumor effect in tumor-bearing mice (Murosaki et al., 2000). 3) Antitumor and antimetastatic effects by induction or stimulation of the synthesis of several cytokines that have been known to be an immunomodulation factors. The small molecule weight cytokines such as IFN-gamma IL-1 beta and TNF alpha being some of the enhancement transfer factors to work effectively has been reported (Matsuzaki., 1998). 4) Immunomodulation enhancement through LC 9018, a biologic response modifier prepared from heat-killed *Lactobacillus casei* YIT9018 that results in the delayed or inhibited process of metastases in various cell types of cancers and the delayed process of cancer recurrences have been reported (Okawa et al., 1993; Matsuzaki, 1998). 5) The clinical reports of LC9018 as an adjuvant with radiotherapy demonstrated an enhancement of tumor regression, prolonged survival and relapse – free survival compared with radiotherapy alone (Okawa et al., 1993).

To demonstrate the potential advantages of integrating complementary therapies into cancer care, future areas of research will need to include improvement of the following aspects, such as access for patients, symptom control for patients, assessment of patient well-being, patient satisfaction, and cost effectiveness (Barnett, 2001).

In conclusion, the overall 5 year survival rate for stage IIIB with poor performance status was 52% compared with 34-54.8% of historic controls. The CCPR demonstrated low rates of radiation morbidity. It was a simple feasible technique, and could be the alternative option for the palliative cancer cases with poor performance status for developing countries. The pilot study was limited by the small number of patients. The treatment of cancer patients has many interrelated and confounding factors that have to be sorted out and further research will be necessary.

Acknowledgements

We would like to express our deep appreciation to Mr.Supot Kamsa-ard, Cancer Unit for statistical analysis. and to Emeritus Professor Dr. James A. Will, Department of Pathobiology, School of Veterinary Medicine and Animal Science, College of Agriculture and Life Sciences, University of Wisconsin, Madison, Wisconsin, for his valuable comments and critical reviews of the manuscript. Appreciations acknowledgement for kind contribution from Lanna Probiotic Company Limited, Thailand, particularly Mr.Suriya Vichitchot who provided the herbal tonic products for clinical trial. The authors declare that there is no conflict of interest regarding this research.

References

- Arai T, Nakano T, Morita S, et al (1992). High dose rate remote afterloading intracavitary radiation therapy for cancer of the uterine cervix. A 20-year experience. *Cancer*, **69**, 175-80.
- Amadi PP, Suntornanatsat T (2004). Analytical report on herbal tonic solution.(G716/45). An analytical report. Thailand Institute of Scientific and Technological Research, 1-3.
- Barnett M (2001). Overview of complementary therapies in cancer care. In: Textbook of Integrated Cancer Care. Holistic, complementary, and Creative approaches. Barraclough J, ed. New York : Oxford University Press 1-17.
- Bermudez RS, Huang K, Hsu IC (2010). Cervical cancer. In: Handbook of evidence-based radiation oncology, second edition. Hansen EK, Roach III M, eds. New York: Springer, 499-512.
- Banjerdpongchai R, Kongtawelert P (2011). Ethanolic extract of fermented thumb induced human leukemic HL-60 and Molt-4 Cell apoptosis via oxidative stress and mitochondrial pathway. *Asian Pac J Cancer Prev*, **12**, 2871-4.
- Cherng JM, Shieh DE, Chiang W, et al (2007). Chemopreventive effects of minor dietary constituents in common foods on human cancer cells. *Bioscience, Biotechnology and Biochemistry*, **71**, 1500-4.
- Chang JS, Chiang LC, Chen CC, et al (2001). Antileukemic activity of *bidens pilosa* L, var. minor (Blume) Sherff and *Houttuynia cordata* Thunb. *Am J Clin Med*, **29**, 303-12.
- Green JA, Kirwan JM, Tierney JF, et al (2001). Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet*, **358**, 781-6.
- Hayashi K, Kamiya M, Hayashi T (1995). Virucidal effects of the steam distillate from *Houttuynia cordata* and its components on HSV-1, influenza virus and HIV. *Planta Med*, **61**, 237-41.
- International Federation of Gynecologists and Obstetricians (1995). Staging announcement: FIGO staging of gynecologic cancers: cervical and vulva. *Int J Gynecol Cancer*, **5**, 319.
- Kim HW, Kim BK (1999). Biomedicinal triterpenoids of *Ganoderma lucidum* (Aphyllophoromycetidae). *Int J Med Mushroom*, **1**, 121-38.
- Lorvidhaya V, Tonusin A, Changwiwit W, et al (2000). High dose rate afterloading brachytherapy in carcinomas of the cervix: an experience of 1992 patients. *Int J Radiat Oncol Biol Phys*, **46**, 1185-91.
- Murosaki S, Muroyama K, Yamamoto Y, et al (2000). Antitumor effect of heat-killed *Lactobacillus plantarum* L-137 through restoration of impaired interleukin-12 production in tumor-bearing mice. *Cancer Immunother*, **49**, 157-64.
- Moss RW (2007). Do antioxidants interfere with radiation therapy for cancer. *Integr Cancer Ther*, **6**, 281-92.
- Murakami A, Jiwajinda S, Koshimizu K, et al (1995). Screening for in vitro anti-tumor promoting activities of edible plant from Thailand. *Cancer Letters*, **95**, 139-14.
- Matsuzaki T (1998). Immunomodulation by treatment with *Lactobacillus casei* strain shirota. *Int J Food Microbiol*, **41**, 133-40.
- Okawa T, Niibe H, Arai T, et al (1993). Effect of LC 9018 combined with radiation therapy on carcinoma of the uterine cervix. A phase III, multicenter, randomized, controlled study. *Cancer*, **72**, 1949-54.
- Phillippe D, Michel P (2006). 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, 1-4.
- Petsuksiri J, Jaishuen A, Pattaranutaporn P, et al (2012). Advanced imaging applications for locally advanced cervical cancer. *Asian Pac J Cancer Prev*, **13**, 1713-8.
- Pesee M, Kirdpon W, Puapairoj A, et al (2007). Palliative treatment of advanced cervical cancer with radiotherapy and Thai herbal medicine as supportive remedy. *Asean J Radiology*, **13**, 171-84.
- Pesee M, Krusun S, Padoongcharoen P (2010). High dose rate Cobalt-60 afterloading intracavitary therapy of the uterine cervical carcinoma in Srinagarind hospital, Analysis of survival. *Asian Pac J Cancer Prev*, **11**, 1469-71.
- Pomros P, Sriamporn S, Tangvoraphonkchai V, et al (2007). Factors affecting survival of cervical cancer patients treated at the radiation unit of srinagarind hospital, Khon Kaen university, Thailand. *Asian Pac J Cancer Prev*, **8**, 297-300.
- Potter R, Georg P, Dimopoulos JCA, et al (2011). Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol*, **100**, 116-23.
- Rose PG, Ali S, Watkins E, et al (2007). Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a gynecology group study. *J Clin Oncol*, **25**, 2804-10.
- Sriamporn S, Swaminathan R, Parkin DM, et al (2004). Loss-adjusted survival of cervix cancer in Khon Kaen, Northeast Thailand. *Bri J Cancer*, **91**, 106-10.
- Simone CB 2nd, Simone NL, Simone V, et al (2007). Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, part 1. *Altern Ther Health Med*, **13**, 22-8.
- Suntornanatsat T, Banchonglikitkul C, Klungsupaya P, et al (2003). Acute oral toxicity test herbal tonic solution (G716/45). An analytical report. Thailand Institute of Scientific and Technological Research, 1-8.
- Sliva D (2003). *Ganoderma lucidum* (Reishi) in cancer treatment. *Integr Cancer Ther*, **2**, 358-64.
- Thomas MG (2000). Concurrent chemotherapy and radiation for locally advanced cervical cancer: the new standard of care. *Seminar in Radiation Oncology*, **10**, 44-50.
- Toita T, Kitagawa R, Hamano T, et al (2012). Feasibility and acute toxicity of concurrent chemoradiotherapy (CCRT) with high-dose rate intracavitary brachytherapy (HDR-ICBT) and 40-mg/m² weekly cisplatin for Japanese patients with cervical cancer: results of a multi-institutional phase 2 study (JGOG). *Int J Gynecol Cancer*, **22**, 1420-6.
- Van der Hem LG (1995). Ling Zhi-8. Studies of a new immuno modulating agent. *Transplantation*, **60**, 438-43.
- Wang SY (1997). Anti-tumor effect of *Ganoderma lucidum* is mediated by cytokines released from activated macrophages and T-lymphocytes. *Int J Cancer*, **70**, 699-705.
- Wong F CS, Tung SY, Leung TW, et al (2003). Treatment results of high-dose-rate remote afterloading brachytherapy for cervical cancer and retrospective comparison of two regimens. *Int J Radiation Oncology Biol Phys*, **55**, 1254-64.
- Wu QP, Xie YZ, Li SZ, et al (2006). Tumor cell adhesion and integrin expression affected by *Ganoderma lucidum*. *Enzyme Microbial Technol*, **40**, 32-41.