

## RESEARCH COMMUNICATION

# Factors Affecting Survival of Cervical Cancer Patients Treated at the Radiation Unit of Srinagarind Hospital, Khon Kaen University, Thailand

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### Abstract

This retrospective longitudinal study aimed to evaluate factors for survival of cervical cancer patients treated with radiation therapy. Information was retrieved from the medical records of 1,180 cervical cancer patients and pathologic material was reviewed to confirm the diagnosis of those treated with radiation therapy at Srinagarind Hospital, Khon Kaen University between 1 January 1994 and 31 December 1999. The patients were followed up until December 31, 2004, with current vital status determined through the hospital-based registry, the population-based cancer registry of Khon Kaen Province, the civil registration database, the Ministry of Interior and by mail. Data were analysed with the Kaplan-Meier, Log-rank test and Cox proportion hazard models. The mortality rate was 70 per 1,000 person-years with an overall 5-year survival of 62.5%. Median survival was >10 years. From multivariate analyses, the factors that statistically affected survival of cervical cancer patients included stage (p-value<0.001), hemoglobin level (p-value<0.001), interval between external and intracavitary radiation (p-value<0.001) and fractionation (p-value=0.024). Stage III was associated with a 1.65-fold mortality risk compared with stage I (95% CI=1.05-2.59). Patients with a low hemoglobin level ( $\leq 10$  g./dl.) demonstrated a 1.85-fold mortality risk compared with patients a value  $>12$  g./dl. (95% CI=1.40-2.44). An interval between external and intracavitary radiation  $>28$  days was associated with 2.28-fold mortality risk compared with a duration of  $<1$  day (95% CI= 1.40-2.44). The fractionation 2 fraction was associated with 0.25-fold mortality risk compared with 1 fraction (95% CI=0.07-0.96). Future prospective trials should be undertaken to confirm the validity of these factors and to elucidate their therapeutic implications.

**Key Words:** Cervical cancer - radiation treatment - survival

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### Introduction

Cancer of the cervix uteri is an important public health problem worldwide with the overall incidence of 16.2 per 100,000. The incidence is higher in developing than developed countries (19.1 v 10.3 per 100 000) (Globocan, 2002). Cervical cancer is the most common cancer in Thai women, the incidence is 19.8 per 100,000 with a mortality of 8.4 per 100 000 (Globocan, 2002). In Khon Kaen province which is in the northeastern part of Thailand, the average incidence during 1998-2000 was 16.6 per 100,000 (Sriplung et al., 2003). The Cancer Unit at Srinagarind Hospital, Khon Kaen, reported that in 2003 there were 346 cervical cancer patients receiving treatment, accounting for 8.2 % of the total cancers at the hospital (Cancer Unit, 2004). The major cause of cervical cancer is human papillomavirus (Walboomers et al., 1999). Radiation is one of the effective treatment modalities, alone or in combination with other therapies (Marcial et al., 1993). Lorvidhaya et al (2000) found the overall 5

years survival after radiotherapy for cervical cancer to 68.2%, values being 86.3, 81.1, 73.0, 50.3, 47.8 and 7.8% for stages IB, IIA, IIB, IIIA, IIIB and IVA respectively. Ruangsanam (1998) reported 5 years survival of stage IB cervical cancer was 62%, Kapp et al. (1998) reported cervical cancer was 94% and Eifel et al. (1994) reported that survival of cervical cancer with stage IB1 was 89.6% and IB2 73%. Differences in survival may due to many factors such as age (Brun et al., 2003; Wong et al., 2003), cell type (Thomas et al., 1995), staging (Sriamporn et al., 2004; Serur et al., 1995), tumor size (Kapp et al., 1998) and treatment (Chen et al., 2003).

The study of survival in cervical cancer with radiotherapy is rather low. At Srinagarind Hospital, during 2002-2004 reported that 74.5% of all cervical cancer received radiotherapy (Cancer unit, 2005; Cancer unit, 2004; Cancer unit, 2003). Pesee et al. (1989) studied in this hospital found 51.2% of cervical cancer patients survived 5 years after radiotherapy. In this study we studied the factors influence to survival of cervical cancer

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received treatment at the Srinagarind Hospital; age, cell type, staging, tumor size, Hemoglobin level, and treatment which will help for planning the effective treatment modality and prognostic diseases.

### Patients and Methods

This longitudinal study was conducted by retrospective collecting data to study factors influencing survival of cervical cancer patients receiving radiotherapy at Srinagarind Hospital from January 1, 1993 to December 31, 1999. All cases were histological confirmed and those undergoing hysterectomy were excluded. There were 1,180 subjects eligible for the study. Independent variables were age, cell type, staging, tumor size, hemoglobin level, radiation, and external and intracavitary radiation and fractionation.

The starting point of survival time is the date of receiving radiation until date of death with cancer (Failed) or censored date; patients still survive at the end of the study or lost to follow-up.

Data were retrospectively collected from medical records and radiation records during December 2005 and February 2006. Patient current vital status was determined

**Table 1. Factors Affecting Survival of Cervical Cancer Patients Treated at the Radiation Unit of Srinagarind Hospital, from Univariate Analysis**

Variables	Subjects	Crude HR	95%CI	p-value
<b>Cell type</b>				
SCC	991	1.00	-	0.186
Adenocarcinoma	178	1.12	0.88-1.42	
Others	11	0.39	0.10-1.57	
<b>Staging</b>				
I	92	1.00	-	<0.001
II	410	1.20	0.79-1.83	
III	657	2.20	1.47-3.28	
IV	16	3.70	1.73-7.91	
<b>Tumor size (cm.)</b>				
<4	658	1.00	-	<0.001
>4	392	1.49	1.23-1.80	
<b>Hemoglobin level (g./dl.)</b>				
>12	356	1.00	-	<0.001
11.1-12	266	1.27	0.97-1.66	
10.1-11	245	1.68	1.29-2.19	
≤ 10	300	2.28	1.79-2.90	
<b>Total dose of radiation (cGy.)</b>				
< 6,000	296	1.00	-	0.004
6,000-6,500	529	1.00	0.80-1.24	
6,501-7,000	328	0.80	0.62-1.02	
> 7,000	27	2.19	1.30-3.68	
<b>Dose of radiation at A (cGy.)</b>				
< 6,000	46	1.00	-	0.003
6,000-7,000	511	0.60	0.40-0.92	
7,001-8,000	595	0.57	0.37-0.86	
> 8,000	27	1.33	0.70-2.50	
<b>Duration of radiotherapy (day)</b>				
< 63	340	1.00	-	<0.001
63-84	357	1.87	1.45-2.42	
> 84	483	2.45	1.93-3.11	
<b>Duration between external and intracavitary radiation (days)</b>				
< 1	207	1.00	-	<0.001
1-28	531	1.62	1.20-2.17	
> 28	442	2.45	1.83-3.28	

through the hospital-based registry, the population-based cancer registry of Khon Kaen province, the civil registration database, and the Ministry of Interior. For the remaining unknown status a follow-up was done by sending a reply-paid postcard inquiring about the current status. If no reply was received, a second postcard was sent. The final response rate was 57%.

### Analytical methods

Data were analysed with the Kaplan-Meier, Log-rank test and Cox proportion hazard models. Univariate analysis was applied for each variable, then statistically significant variables were entered into a multivariate analysis.

### Results

The mean age of the patients was 50 years, 50.5% were involved in agriculture, 63.8% had 1-5 children. Most tumors were squamous cell carcinomas, 55.7% stage III, 53.6% with a tumor size 1-4 cm. At the end of the study, 41.5% were surviving, 52.7 had died, and 5.8% had an unknown status.

Survival with reference to various factors is shown in Figures 1-9. Factors effecting survival from the univariate analysis and multivariate analysis are shown in Tables 1 and 2. The final factors that were statistically affected survival of cervical cancer patients from the multivariate analysis were stage, hemoglobin level, interval between external and intracavitary radiation and fractionation.

**Table 2. Factors Affecting Survival of Cervical Cancer Patients Treated at the Radiation Unit of Srinagarind Hospital, from the Multivariate Analysis**

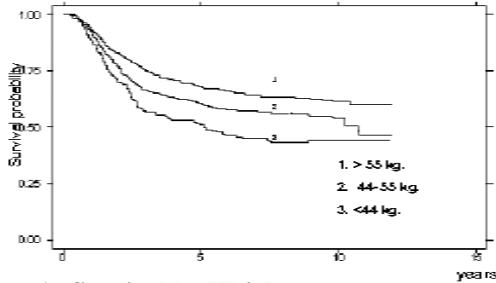
Variable	Crude HR	Adjusted HR	95% CI	p-value
<b>Staging</b>				
I	1.00	1.00	-	<0.001
II	1.20	0.96	0.60-1.53	
III	2.20	1.65	1.05-2.59	
IV	3.70	2.10	0.87-5.08	
<b>Tumor size (cm.)</b>				
≤ 4	1.00	1.00	-	<0.001
> 4	1.49	0.79	0.51-1.24	
<b>Hemoglobin level (g./dl.)</b>				
> 12	1.00	1.00	-	<0.001
11.1-12	1.27	1.24	0.92-1.66	
10.1-11	1.68	1.44	1.08-1.93	
≤ 10	2.28	1.85	1.40-2.44	
<b>Duration between external and intracavitary radiation (days)</b>				
< 1	1.00	1.00	-	<0.001
1-28	1.62	1.55	1.11-2.16	
> 28	2.45	2.28	1.64-3.17	
<b>Fractionation</b>				
1	1.00	1.00	-	0.024
2	0.55	0.25	0.07-0.96	
3	0.58	0.34	0.09-1.28	
4	0.55	0.41	0.11-1.54	
5	1.16	0.63	0.15-2.63	
<b>Tumor size and total dose of radiation (cGy.)</b>				
< 6,000	1.00	1.00	-	<0.001
6,000-6,500	-	0.90	0.55-1.51	
6,501-7,000	-	0.89	0.48-1.56	
> 7,000	-	2.03	0.89-4.64	

**Discussion**

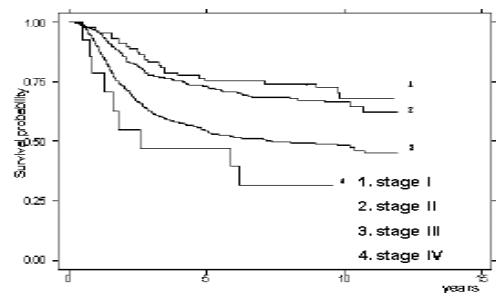
The characteristics of the study subjects regarding age, occupation, education, cell type, hemoglobin level were similar to the findings in other studies (Ruangsam, 1998; Shingleton et al., 1995; Sriamporn et al., 1995; Lorvidhaya et al., 2000; Okkan et al., 2003; Wong et al., 2003). The average of overall of duration of radiation at 85 days was

higher than with Chen et al (2003) who reported only 63 days. This may due to the patients did not follow the appointment or the machine was under repair. The unknown status (lost to follow-up) was very small compared to Sriamporn et al (2004) (5% as opposed to 27%). Keele University (2005) has suggested that if the lost follow-up rate should be less than 15% for appropriate results . The overall 5-year survival rate in this study was 62.5%, median >10 years, similar to Ruangsam (1998) and Kapp et al (1998), but different from Lorvidhaya et al (2000) and Sakurai et al (2000) who reported slightly longer survival.

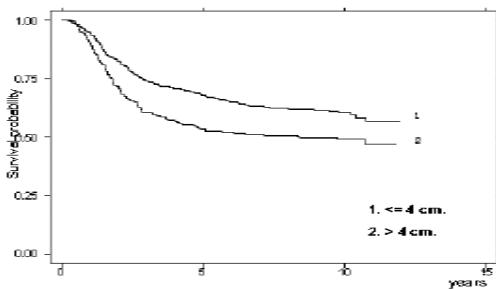
After control for confounding factors, stage, hemoglobin level, duration between external and intracavitary radiation, and fractionation were significantly associated with the risk of mortality of cervical cancer patients undergoing radiotherapy. Patients with stages IV, III and II had 2.10, 1.65 and 0.96 fold the risk of death of those with stage I, similar to earlier findings (Ruangsam,



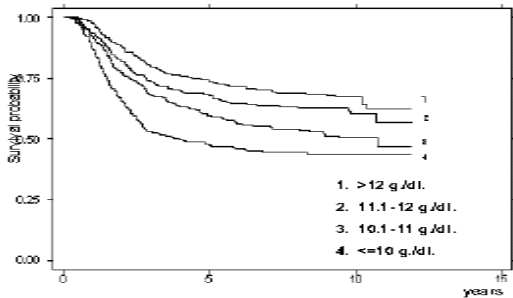
**Figure 1. Survival by Weight**



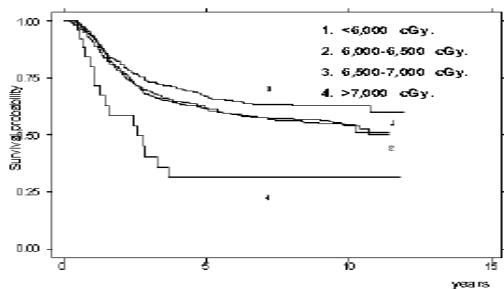
**Figure 2. Survival by Stage**



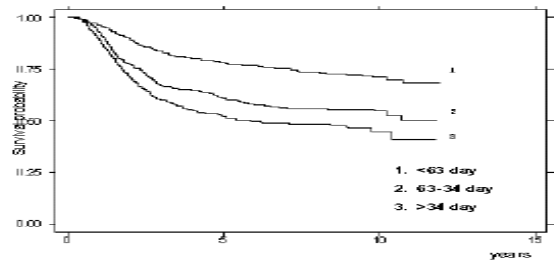
**Figure 3. Survival by Tumor Size**



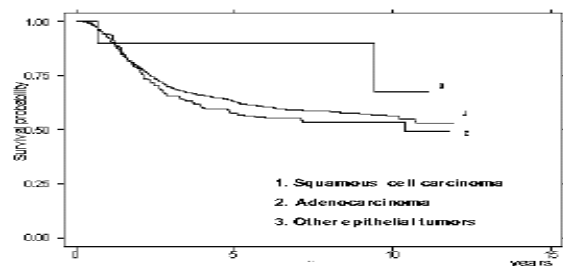
**Figure 4. Survival by Hemoglobin Level**



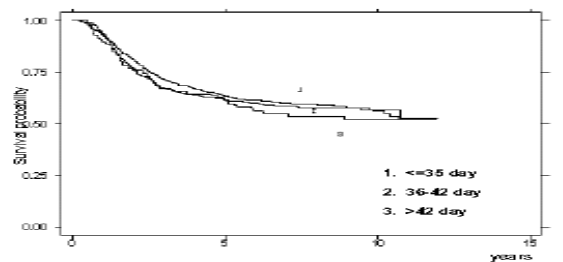
**Figure 5. Survival by Total Dose of Radiation**



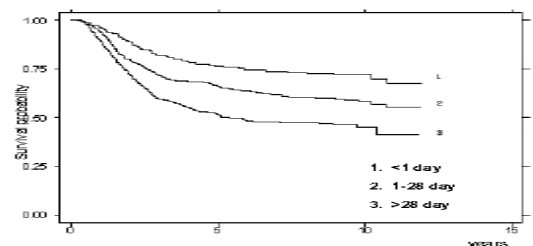
**Figure 6. Survival by Duration of Radiation**



**Figure 7. Survival by Cell Type**



**Figure 8. Survival by Days of Radiation**



**Figure 9. Survival by Time between External and Intracavitary Radiation**

1998; Okkan et al., 2003; Wong et al., 2003; Shingleton et al., 1995).

An association with hemoglobin level was also found by Wang et al (2004) and Kapp et al (1998). Tangvoraphonkchai (1987) described good response to radiotherapy in cervical cancer patients with an average hemoglobin level of 11.33% but a poor response with an average hemoglobin level of 10.24%.

A longer duration between external and intracavitary radiation was associated with failure of radiotherapy, presumably due to growth in the intermittent period (Pesee et al., 1989). Overall the tumor size was associated with risk to death, in line with the studies of Okkan et al (2003) and Kapp et al (1998), especially when combining the tumor size and total dose of radiation.

In conclusion, the findings from this study suggested that early detection and treatment for cervical cancer are necessary following an effective referral system. A study on quality of life in cervical cancer patients with radiotherapy is recommended for future study.

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## References

Tangvoraphonkchai V (1987). Factors affecting the response to radiation treatment in cervical cancer. *Thai Cancer J*, **1**, 11-5.

Ruangsanam O (1998). Survival of cervical cancer in Thailand Master degree thesis (Public Health). Bangkok: Graduate school, Mahidol University.

Brun J-L, Stoven CD, Trouette R, Lopez M, Chene G, Hocke C (2003). Survival and prognosis of women with invasive cervical cancer according to age. *Gynecol Oncol*, **91**, 395-401.

Cancer Unit Khon Kaen University (2003). Tumor Registry 2002. Khon Kaen: faculty of medicine Srinagarind hospital Khon Kaen University.

Cancer Unit Khon Kaen University (2004). Tumor Registry 2003. Khon Kaen: Faculty of Medicine Srinagarind Hospital Khon Kaen University.

Cancer Unit Khon Kaen University (2005). Tumor Registry 2004. Khon Kaen: Faculty of Medicine Srinagarind Hospital Khon Kaen University.

Chen SW, Liang JA, Yang SN, Ko HL, Lin FJ (2003). The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. *Radiother Oncol*, **67**, 69-76.

Eifel PJ, Morris M, Wharton JT, Oswald MJ (1994). The influence of tumor size and morphology on the outcome of

patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. *Int J Radiation Oncol Biol Phys*, **29**, 9-16.

Globocan 2002. Cancer incidence, mortality and prevalence worldwide [cited 2005 June 30]. Available from: <http://www-dep.iarc.fr/>

Kapp KS, Stuecklschweiger GF, Kapp DS, et al (1998). Prognostic factors in patients with carcinoma of the uterine cervix treated with external beam irradiation and IR-192 high-dose-rate brachytherapy. *Int J Radiation Oncol Biol Phys*, **42**, 531-40.

Keele University. An introduction to critical appraisal training notes. [online] 2005 [cited 2005 June 30]. Available from: <http://www.keele.ac.uk/depts/li/hl>

Lorvidhaya V, Tonusin A, Changwiwit W, et al (2000). High-dose-rate afterloading brachytherapy in carcinoma of the cervix: an experience of 1992 patients. *Int J Radiation Oncol Biol Phys*, **46**, 1185-91.

Marcial VA, Marcial LV (1993). Radiation therapy of cervical cancer. *Cancer*, **71**, 1438-45.

Okkan S, Atkovar G, Sahinher I, et al (2003). Results and complications of high dose rate and low dose rate brachytherapy in carcinoma of the cervix: cerrahpsa experience. *Radiother Oncol*, **67**, 97-105.

Pesee M, Tangvoraphonkchai V, Boonvisuth V, Kirdpon W (1989). Radiotherapy alone in treatment of carcinoma of uterine cervix in Srinagarind hospital: analysis of treatment failure. *Thai J Radiol*, **26**, 67-70.

Sakurai H, Mitsuhashi N, Takahashi M, et al (2000). Radiation therapy for elderly patient with squamous cell carcinoma of the uterine cervix. *Gynecol Oncol*, **77**, 116-20.

Serur E, Fruchter RG, Maiman M, et al (1995). Age, substance, abuse and survival of patients with cervical carcinoma. *Cancer*, **75**, 2530-8.

Shingleton HM, Bell MC, Fregen A, et al (1995). Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma of the cervix?. *Cancer*, **76**, 1948-55.

Sriampron S, Roger JB, Sankaranarayanan R, Kamsa-ad S, Parkin DM, Vatanasapt V (1995). Cancer survival in Khon Kaen province, Thailand. *Int J Cancer*, **61**, 296-300.

Sriampron S, Swaminathan R, Parkin DM, Kamsa-ard S, Hakama M (2004). Loss-adjusted survival of cervix cancer in Khon Kaen, Northeast Thailand. *Br J Cancer*, **91**, 106-10.

Sriplung H, Sontipong S, Matin N, Wiangnon S, Vootiprux V, Cheirsilpa A, et al (2003). Cancer in Thailand 1995-1997. Bangkok: [n.p].

Thomas WW, Unger ER, Johnson PR, et al (1995). Cervical cancer survival in a high risk urban population. *Cancer*, **76**, 2518-23.

Walboomers JM, Jacobs MV, Manos MM, et al (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*, **189**, 12-9.

Wang CJ, Huang EY, Sun LM, et al (2004). Clinical comparison of two linear-quadratic model-based isoeffect fractionation schemes of high-dose-rate intracavitary brachytherapy for cervical cancer. *Int J Radiation Oncol Biol Phys*, **59**, 179-89.

Wong FC, 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 Oncol Biol Phys*, **55**, 1254-64.