RESEARCH ARTICLE

Age and Survival of Cervical Cancer Patients with Bone Metastasis

Adisak Nartthanarung[1], Kamolrat Thanapprapasr[2], Umaporn Udomsubpayakul[3], Duangmani Thanapprapasr[4,5]*

Abstract

Background: To determine survival times of cervical cancer patients with bone metastasis related to the effect of age at the time of cervical cancer diagnosis, we performed the retrospectively analytical study. Methods: A total of 68 cervical cancer patients with bone metastasis were treated at a single hospital, during January 1998 to December 2010. Fifty-two medical records were identified and collected, the remaining sixteen medical records were not found. Main outcome measures were patient characteristics, clinical information, duration from cervical cancer diagnosis to bone metastasis diagnosis, survival time after bone metastasis and overall survival time. Results: Among fifty-two cervical cancer patients with bone metastasis, there were 13 patients who were less than 45 years old, and 39 patients were 45 years old or more at the time of cervical cancer diagnosis. The younger group had less median overall survival than the older group, with a statistically significant difference (21 months, 95% CI 19.93-22.06; 34 months, 95% CI 23.27-44.72, p = 0.021). However, they were comparable in the duration from cervical cancer diagnosis to bone metastasis diagnosis and the survival time after bone metastasis. Conclusion: Young patients with bone metastasis aged less than 45 years old at the time of cervical cancer diagnosis have a poorer prognosis than the elderly patients. Impact: To improve survival and quality of life, more intensive and novel multimodal treatments at the time of cervical cancer diagnosis should be considered in patients less than forty-five years, who can tolerate the side effects better.

Keywords: Cervical cancer - bone metastasis - age - survival

Asian Pac J Cancer Prev, **15 (19)**, 8401-8404

Introduction

According to the global cancer incidences 2012, cervical cancer is the fourth most common cancer in women after breast, colorectal and lung cancers (Ferlay et al., 2012). Less developed regions have reported that their cervical cancer incidences and mortalities have still been more expanding than more developed regions. It is still a major problem, while it is preventable. Unfortunately, patients with cervical cancer who develop bone metastasis have been found to have poor prognoses. Even though few patients who were diagnosed with the incidences of 1.1-8.3%, the median overall survival was only 23 months (Thanapprapasr et al., 2010). The retrospective report showed characteristics of the patients with bone metastasis with the median age of 49 years (range, 27-76 years) (Thanapprapasr et al., 2010).

Risks of developing cervical cancer and bone metastasis were focused upon and detailed. Oncogenic Human Papilloma Virus infection is now accepted to be the cause of cervical cancer. Younger women seem to have higher risk from the infection. Therefore, we evaluated patients who were diagnosed bone metastasis from cervical cancer at a single tertiary hospital during 1998-2010. The age at the time of cervical cancer diagnosis was determined and critically interpreted on the detail of patient profiles, clinical characteristic of bone metastasis and survival outcomes. Herein, the data from medical records have been examined and discussed in this study. The primary aim was to determine survival of cervical cancer patients with bone metastasis related with the effect of age at the time of cervical cancer diagnosis.

Materials and Methods

After the research proposal was approved by the Ramathibodi Hospital Ethics Committee, we collected the clinical data from patients' medical records. With this cross-sectional study, 68 cervical cancer patients with bone metastasis were treated at Ramathibodi hospital,

*[1]Musculoskeletal Oncology Unit, Department of Orthopaedics, [3]Section of Clinical Epidemiology and Biostatistics, [4]Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, [5]Samitivej Sukhumvit Hospital, Bangkok, Thailand [2]National Metal and Materials Technology Center (MTEC), National Science and Technology Development Agency (NSTDA), Pathumthani, Thailand *For correspondence: dmngynonc@gmail.com*

Bangkok, Thailand, during January 1998 - December 2010. Patient characteristics: International Federation of Gynecology and Obstetrics (FIGO) staging, histology, primary treatment; clinical information of bone metastasis: symptoms and signs, investigations, number of bone metastasis, sites of bone metastasis and treatment; duration from cervical cancer diagnosis to bone metastasis diagnosis, survival time after bone metastasis and overall survival time were the main outcomes.

Data records were analyzed using descriptive statistics and Pearson Chi-square test where appropriate, with $p<0.05$ considered statistically significant. All analyses were performed with StataCorp. 2011, Stata: release 12 (Statistical Software, College Station, TX: StataCorp LP).

Results

A total of 68 cervical cancer patients with bone metastasis during January 1998 - December 2010 were identified, and 16 medical records were data loss or unfound. The data of 52 medical records were collected and analyzed. There were 13 patients who were aged less than 45 years, and 39 patients who were aged 45 years or more at the time of cervical cancer diagnosis.

Most patients were FIGO staging classification in stage II and III, in both age groups respectively. Squamous cell carcinoma is the most common histologic type, followed by adenocarcinoma, adenosquamous cell carcinoma and small cell carcinoma. Radiation therapy and concurrent chemoradiation therapy were the treatments for cervical cancer, as shown in Table 1.

Clinical bone metastases between the younger and the older groups were not statistically different. Most patients had pain on their affected bones. Clinicians frequently used skeletal scintigraphy, imaging and/or tissue biopsy as diagnostic and investigative tools. The majority of patients had multiple bone metastases. Extra-pelvic bone metastasis was common. Radiation therapy, chemotherapy, surgery and supportive care were the treatments after bone metastasis in both groups. (Table 2) With these results' findings, patient characteristics and clinical information between the younger group and the older group were not statistically different.

In survival analysis, the younger group had less median overall survival than the older group with statistically significant difference (21 months, 95% CI 19.93-22.06 for the younger group and 34 months, 95% CI 23.3-44.72 for the older group, p=0.021), (Figure 1). The duration from cervical cancer diagnosis to bone metastasis diagnosis (younger group 16 months, 95% CI 12.47-19.52 and older group 26 months, 95% CI 14.08-37.91, p=0.072) and the median survival after bone metastasis diagnosis (younger group 4 months, 95% CI 2.88-5.11 and older group 7 months, 95% CI 5.30-8.69, p=0.228) were comparable as shown in Figure 2 and Figure 3.

Table 1. Clinicopathological Characteristics

Characteristics	Number of patients N (%) Age <45	Age ≥45	p-value
FIGO1 stage			
I	0 (0)	4 (10.26)	0.157
II	9 (69.23)	15 (38.46)	
III	4 (30.77)	15 (38.46)	
IV	0 (0)	5 (12.82)	
Histology			
Squamous cell carcinoma	9 (69.23)	32 (82.05)	0.747
Adenocarcinoma	2 (15.38)	5 (12.82)	
Adenosquamous cell carcinoma	1 (7.69)	1 (2.56)	
Small cell carcinoma	1 (7.69)	1 (2.56)	
Primary treatment			
RT2	8 (61.54)	22 (56.41)	0.923
CCRT3	4 (30.77)	11 (28.21)	
RT followed by TAH4	1 (7.69)	2 (5.12)	
Radical hysterectomy with pelvic lymphadenectomy	0 (0)	3 (7.70)	
Chemotherapy	0 (0)	1 (2.56)	

Table 2. Characteristics of Bone Metastasis

Characteristics	Number of patients N (%) Age <45	Age ≥45	p-value
Symptoms and signs			
Pain	11 (84.62)	37 (94.88)	0.56
Painless	2 (15.38)	2 (5.12)	
Investigations			
Skeletal scintigraphy	5 (38.46)	19 (48.72)	0.894
Tissue biopsy	3 (23.07)	7 (17.94)	
CT1 scan or MRI2	4 (30.77)	9 (23.08)	
Plain radiograph	1 (7.69)	4 (10.26)	
No. of bone metastasis			
Single	3 (23.07)	14 (35.90)	0.506
Multiple	10 (76.93)	25 (64.10)	
Sites of bone metastasis			
Pelvic bone	1 (7.69)	5 (12.82)	0.76
Extra pelvic bone	11 (84.62)	29 (74.36)	
Both	1 (7.69)	5 (12.82)	
Treatment			
RT3	3 (23.07)	2 (5.12)	0.091
Supportive care	2 (15.38)	17 (43.59)	
RT and Chemotherapy	3 (23.07)	4 (10.26)	
Surgery with or without RT	2 (15.38)	11 (28.21)	
Chemotherapy	3 (23.07)	5 (12.82)	

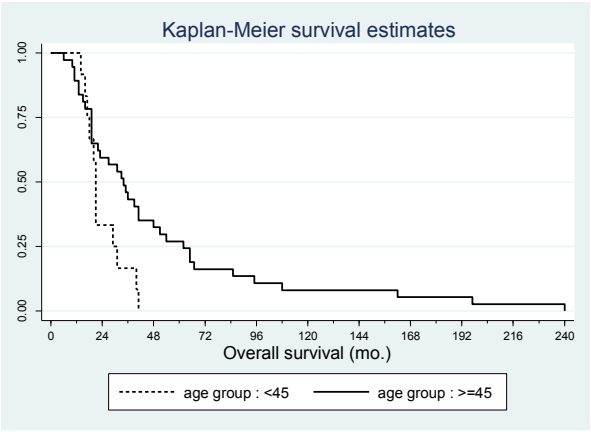

Figure 1. Kaplan-Meier survival analysis showing overall survival of the 13 patients age less than 45; and 39 patients age 45 or over at the time of cervical cancer diagnosis. The median overall survival in younger group 21 months, 95%CI 19.93-22.06, and in older group 34 months, 95%CI 23.27-44.72, p=0.021.

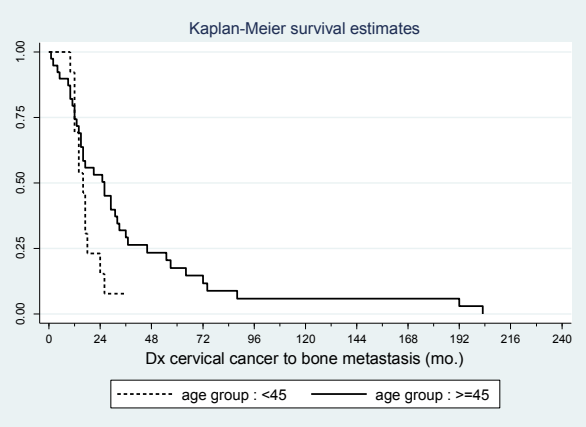

Figure 2. Kaplan-Meier survival analysis showing interval from diagnosed cervical cancer to bone metastasis of the 13 patients age less than 45; and 39 patients age 45 or over at the time of cervical cancer diagnosis. The median duration from cervical cancer diagnosis to bone metastasis diagnosis in younger group 16 months, 95%CI 12.47-19.52, and in older group 26 months, 95%CI 14.08-37.91, p=0.072.

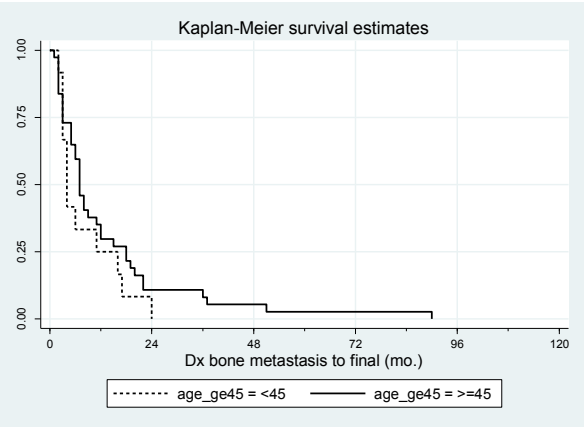

Figure 3. Kaplan-Meier survival analysis showing survival after diagnosis of bone metastasis of the 13 patients age less than 45; and 39 patients age 45 or over at the time of cervical cancer diagnosis. The median survival after bone metastasis in younger group 4 months, 95%CI 2.88-5.11, and in older group 7 months, 95%CI 5.30-8.69, p=0.228

Discussion

The incidence of cervical cancer increased worldwide from 2002 to 2012 (Ferlay et al., 2012; Parkin et al., 2005). More than half million patients were diagnosed with cervical cancer in the year 2012. Over half of these died because of their cancer annually. It is 12% of all women cancers, and estimated world age-standardized rates over 30 per 100,000 women in some regions. Although for many decades cervical cancer screening has been given attention, the cancer burdens are still major problems in less developed regions accounting for 85% in 2012. It remains the most common female cancer in Eastern and Middle Africa regions. In 2012, it was reported that 87% of cervical cancer death occur in the less developed regions (Ferlay et al., 2012).

By examination of age, cervical cancer was diagnosed beginning at the age of 20 to more than 85 years in various races and the peak started at age 40-50 (Schiffman et al., 2007). The annual incidence among women age 25-34 years was 7 per 100,000 women in the US, (Wang et al., 2004). World report in 2012 shows estimated incidence at age 15-39 years of 8.2 per 100,000 women and at age 40-44 years of 28.4 per 100,000 women (Ferlay et al., 2012). In Thailand, there were 23.3 per 100,000 women at age 35 and 36.4 per 100,000 women at age 40, compared to 50.0 per 100,000 women at age 45, (Khuhaprema et al., 2012). There are also increased age specific incidence rates in Korean women at age 30-34 from 12.4 per 100,000 women in 2009 to 12.9 per 100,000 women in 2010, and age 35-39 from 15.1 per 100,000 women in 2009 to 16.3 per 100,000 women in 2010(Seol et al., 2014). There seems to be high incidences of cervical cancer among young women.

In our study, we found that the FIGO stages, histology, primary treatments and clinical characteristics including symptoms and signs, investigations, numbers, sites and treatments of their bone metastasis were similar among young age and old age groups. Prior treatment efforts on cervical cancer with bone metastasis have been speculated (Nartthanarung and Thanapprapasr, 2010). These factors did not appear to be an independent predictor of outcomes in our results. Prognostic factors of pathological characteristics in patients who received surgical treatment were revealed in some studies (Khunamornpong et al., 2013; Khunamornpong et al., 2013).

We defined the ages which were significantly different survivals. Surprisingly, we found that patients age less than 45 had shorter overall survival than the others. Further study should be compared with our observed results. The human papilloma virus is linked to most cervical cancer (Schiffman et al., 2007). It is proposed that Human Papilloma virus (HPV) infection of the cervix may be involved and related to our results.

As the most common sexually transmitted infection, Human Papilloma virus (HPV) infection occurs as a large peak following sexual initiation which begins at approximately age 15-25 years. High risk HPV types persist and progress to cancer within 10-15 years later, frequently starting at age 40-50 years. Out of 17 high-risk types among 110 types of HPV, HPV type 16 causes 50% and type 18 causes 20% of cervical cancers. The majority of the patients (89-92%) were aged under 45 ,who had HPV 16/18 infected tumors, which were more than the older patients (73-78%), (Carozzi et al., 2010). This is consistent with an international study which observed a decreasing proportion of HPV16/18-positive cancers with increasing age, (de Sanjose et al., 2013). In 10.2% of invasive cancers, in which coinfections were observed, HPV 16 was involved in the highest rate of coinfections along with other HPV types (77%), (Carozzi et al., 2010). Populations at high risk, such as early lifetime sexual contacts, multiple lifetime sexual partners, cigarette smoking habits, immunocompromised hosts and history of sexually transmitted diseases, have multiple high risk HPV type infections and develop cervical cancer at early age. The report shows links among early age at first

intercourse and early age of diagnosis (Edelstein et al., 2009). Vaccine against HPV 16/18 may highly recommend for women under age of 45. More than 15% prevalence of smoking habits among women age less than 40 was revealed in 2004 and these have continued to increase, (Connolly et al., 2011).

With aggressive features of HPV 16 and multiple coinfections with other HPV types in young high risk women, invasion and metastasis over the bones has been observed. These may consistently explain the poorer prognosis for younger age patients less than 45 compared with older age patients with bone metastasis. Since data on age and cervical cancer with bone metastasis is limited, our study may be the first to look exclusively at these patients. Prior study has noted the importance of age which appears to influence treatment received by patients with cervical cancer, (Roque et al., 2013). Novel molecular therapy may be needed for further study for these groups of patients besides more intensive contemporary treatments, (Coleman, 2008; Thanapprapasr et al., 2012; Chao et al., 2014).

However, with a small sample size of cervical cancer with bone metastasis patients, caution must be applied, as the findings might not be transferable to all cervical cancer patients who do not diagnosed with bone metastasis.

Cervical cancer appears to be the most common gynecologic malignancy in developing countries, and the number of younger age patients seems to increase. Further investigations for cervical cancer should be carried out in all age groups, and also in the younger age under 45 with focus on bone metastasis from the cancer. It is valuable to consider many aspects of prevention, early diagnosis, novel therapy and quality of life in the young cervical cancer patients.

In conclusion, young patients with bone metastasis age less than 45 years at the time of cervical cancer diagnosis had poorer prognosis than older patients. To improve survival time and quality of life, more intensive and novel multimodal treatments at the time of cervical cancer diagnosis in the young patients who can tolerate the side effects should be considered.

Acknowledgements

Thanks are given to Pakkapol Nartthanarung and Thanapat Nartthanarung, Kasetsart University Laboratory School Center of Educational Research and Development, International Program, Bangkok, Thailand, for assisting in manuscript preparation. We also thank Stephen John Pinder, a native speaking medical proofreader for language revision.

References

Carozzi FM, Tornesello ML, Burroni E, et al (2010). Prevalence of human papillomavirus types in high-grade cervical intraepithelial neoplasia and cancer in Italy. *Cancer Epidemiol Biomarkers Prev*, **19**, 2389-400.

Chao A, Lin CT, Lai CH (2014). Updates in Systemic Treatment for Metastatic Cervical Cancer. *Curr Treat Options Oncol*, **15**, 1-13.

Coleman RL (2008). The Gynecologic Oncology Group's role in the treatment of recurrent cervix cancer: current clinical trials. *Gynecol Oncol*, **110**, 77-80.

Connolly GN, Behm I, Osaki Y, et al (2011). The impact of menthol cigarettes on smoking initiation among non-smoking young females in Japan. *Int J Environ Res Public Health*, **8**, 1-14.

de Sanjose S, Wheeler CM, Quint WG, et al (2013). Age-specific occurrence of HPV16- and HPV18-related cervical cancer. *Cancer Epidemiol Biomarkers Prev*, **22**, 1313-8.

Edelstein ZR, Madeleine MM, Hughes JP, et al (2009). Age of diagnosis of squamous cell cervical carcinoma and early sexual experience. *Cancer Epidemiol Biomarkers Prev*, **18**, 1070-6.

Ferlay J, Ervik M, Dikshit R, et al (2012). GLOBOCAN v1.0.

Khuhaprema T, A P, Sriplung H, Wiangnon S, S Y S S (2012). Cervix uteri. In: Cancer in Thailand 2004-2006, vol. VI, 1st edn (eds Khuhaprema T, Attasara P, Sriplung H, Wiangnon S, Sumitsawan Y & Sangrajrang S), pp. 45-48. Bangkok Medical Publisher, Bangkok, Thailand.

Khunamornpong S, Settakorn J, Sukpan K, et al (2013). Prognostic value of pathological characteristics of invasive margins in early-stage squamous cell carcinomas of the uterine cervix. *Asian Pac J Cancer Prev*, **14**, 5165-9.

Khunamornpong S, Lekawanvijit S, Settakorn J, et al (2013). Prognostic model in patients with early-stage squamous cell carcinomas of the uterine cervix: A combination of invasive margin pathological characteristics and lymphovascular space invasion. *Asian Pac J Cancer Prev*, **14**, 6935-40.

Nartthanarung A, Thanapprapasr D (2010). Comparison of outcomes for patients with cervical cancer who developed bone metastasis after the primary treatment with concurrent chemoradiation versus radiation therapy alone. *Int J Gynecol Cancer*, **20**, 1386-90.

Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Roque DR, Cronin B, Robison K, et al (2013). The effects of age on treatment and outcomes in women with stages IB1-IIB cervical cancer. *J Geriatr Oncol*, **4**, 374-81.

Schiffman M, Castle PE, Jeronimo J, et al (2007). Human papillomavirus and cervical cancer. *Lancet*, **370**, 890-907.

Seol HJ, Ki KD, Lee JM (2014). Epidemiologic characteristics of cervical cancer in Korean women. *J Gynecol Oncol*, **25**, 70-4.

Thanapprapasr D, Hu W, Sood AK, et al (2012). Moving beyond VEGF for anti-angiogenesis strategies in gynecologic cancer. *Curr Pharm Des*, **18**, 2713-9.

Thanapprapasr D, Nartthanarung A, Likittanasombut P, et al (2010). Bone metastasis in cervical cancer patients over a 10-year period. *Int J Gynecol Cancer,* **20**, 373-8.

Wang SS, Sherman ME, Hildesheim A, et al (2004). Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. *Cancer*, **100**, 1035-44.