Human Papillomavirus Infection Following Radiation Therapy or Concurrent Chemoradiation for Invasive Cervical Cancer

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Objective: *To determine the prevalence of Human Papillomavirus (HPV) infection in patients with invasive cervical cancer after treatment by concurrent chemoradiation therapy.*
Material and Method: *Cervicovaginal mucous samples were collected from fifty-five patients with invasive cervical cancer two months after treatment completion and tested for HPV genotypes.*
Results: *Of the 55 patients, 31 (56.36%) were found to be positive for HPV among these 25(45.46%) were positive for high-risk HPV. The most common high-risk HPV found was type 16 which accounted for 35.48 % (11/31) of cases. Other high-risk HPV found were types 18 (16.13%), 52 (16.13%) and 58 (12.90%). Follow-up time for patients were 3 to 22 months with mean follow-up of 13 months. In patients positive for high-risk HPV, 24.00% (6/25) were found to have persistent or recurrent disease. While 30 patients negative for high-risk HPV, 3.33% (1/30) were found to have persistent or recurrent disease.*
Conclusion: *The prevalence of HPV infection in cervical cancer patients with positive high-risk HPV after treatment by radiation or concurrent chemoradiation seems to be a risk factor for persistent and recurrent disease. Testing for high-risk HPV may be a useful modality for follow-up of these patients.*

Keywords: *Human papillomavirus (HPV), Radiation therapy, Concurrent chemoradiation, Invasive cervical cancer*

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Cervical cancer is the second most common cancer in women worldwide[1]. Approximately 80 % of cases occur in developing countries[2]. Over the last two decades the incidence of invasive cervical cancer has decreased, largely due to secondary prevention by cytological screening, however stage-specific cervical cancer death rate has not changed. Treatment aims for cervical cancer patients are directed toward curative intent, long-term survival and good quality of life.

Oncogenic or high-risk human papillomavirus (HPV) is associated with 99.7% of cervical cancer[3], of which, HPV 16 and 18 are the most common types accounting for 70%[4] of cases. Previous studies have demonstrated a correlation between pre-treatment status of HPV infection and prognosis in patients treated with radiation therapy[5,6]. Information regarding status of HPV infection post-treatment by radiation or chemo-radiation is limited[7]. The objective of the present study was to determine the prevalence and prognostic significance of HPV infection in cervical cancer patients after treatment by radiation or concurrent chemo-radiation.

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Material and Method

Approved from the Institutional Review Board, Royal Thai Army Medical Department and then informed consents were obtained from fifty five patients with histologically confirmed cervical cancer, FIGO (International Federation of Gynecology and Obstetrics) stage Ia or greater, diagnosed and treated

with radiation or concurrent chemoradiation at the Gynecologic Oncology Unit, Phramongkutklao Hospital during March 2006 to December 2007. Immunosuppressed patients were excluded. Cervical cytology (Pap smear) and HPV test of cervicovaginal mucous by polymerase chain reaction (PCR) assay were performed at the scheduled follow-up visit two months after completion of treatment. The results were summarized in term of frequency and percentage, mean and standard deviation (SD) with range.

Results

Characteristics of 55 patients are shown in Table 1, age at diagnosis ranged from 30 to 88 years (mean, 52). Histologic cell types of 78.18% were squamous cell carcinoma, 18.18% were adenocarcinoma and 3.64 % were other cell carcinoma.

Majority had stage III disease. Only one patient had sexual intercourse before HPV DNA examination in follow-up visit two months after completion of treatment. Follow-up time for patients in the present study was 3 to 22 months with the mean of 13 months.

Eighteen of high-risk and non high-risk HPV genotypes were detected in the present study (Table 2), including high-risk HPV types 16, 18, 33, 39, 52, 53, 56 and 58 respectively. HPV 45 was not detected.

Fig. 1 shows that of 55 patients, 31 (56.36%) were found to be HPV positive and 11 (20.0%) had multiple types of HPV. Among these 25 (45.46%) were positive for high-risk HPV. The most common high-risk HPV found was type 16 which accounted for 11 of 31 (35.48%) of cases. Other high-risk HPV found were types 18 (16.13%), 52 (16.13%) and 58 (12.90%). Six of twenty-five patients (24.00%) with positive high-risk HPV were found to have persistent or recurrent disease, whereas, only 1/30 (3.33%) in negative high-risk HPV patients developed persistent or recurrent disease (Table 3). One patient having sexual intercourse before HPV DNA examination in the follow-up period was found negative for HPV DNA detected.

Table 1. Characteristics of the patients (n = 55)

Characteristics	Number (%)
Age (years)	
30-40	9 (16.36)
41-50	25 (45.46)
51-60	10 (18.18)
> 61	11 (20.0)
Range 30-88	
Mean 51.62	
Disease stage	
II	25 (45.46)
III	28 (50.91)
IV	2 (3.63)
Follow-up (months)	
< 6	7 (12.73)
6-12	18 (32.72)
13-18	23 (41.82)
> 18	7 (12.73)
Range (3-22)	
Mean (13)	

Discussion

HPV DNA is regarded to be a reliable marker of cervical cancer because HPV is involved in the pathogenesis of the disease[8-10] and HPV DNA is found in most cervical cancers[11,12]. To date, rare information

Table 2. HPV DNA genotypes detected

Type	Number detected (%)
High-risk HPV	
16	11 (35.5)
18	5 (16.1)
33	1 (3.2)
39	1 (3.2)
52	5 (16.1)
53	1 (3.2)
56	1 (3.2)
58	4 (12.9)
Total	29
Non high-risk HPV	
6	1 (3.2)
54	2 (6.5)
55	1 (3.2)
61	1 (3.2)
62	3 (9.7)
66	2 (6.5)
70	1 (3.2)
71	1 (3.2)
72	3 (9.7)
84	1 (3.2)
Total	16

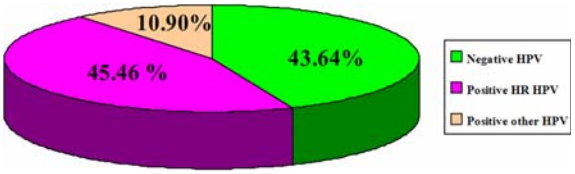

Fig. 1 Prevalence of HPV DNA detected

Table 3. Association between status of disease and HPV DNA detected

Persistent or recurrent	Positive	Negative	Total
HPV DNA detected			
Positive	6	25	31
Negative	1	23	24
Total	7	48	55

is available concerning a natural history of HPV infection in cervical carcinoma managed with radiation therapy[7].

Previous studies examined HPV infection only before radiotherapy, that is, they assessed a possible correlation between a pre-treatment status of HPV infection and a prognosis in patients treated with radiation therapy[5,6,13]. The most crucial possibility that should be kept in mind is the persistence of clinically or microscopically undetectable disease in the cervix and/or parametrium in patients with HPV infection persisting after complete response. HPV infection persisting patients were at an extremely high-risk of local recurrence with the rate of approximately 5 times in comparison with HPV infection cleared patients[7]. Thus, the high local recurrence rate in these patients most likely reflects the persistence of viable carcinoma cells.

The presented data demonstrated that cervical cancer patients who were positive for high-risk HPV post-treatment by radiation or chemoradiation therapy had higher rate of persistent and recurrent disease.

In conclusion, the prevalence of HPV infection in cervical cancer patients with positive high-risk HPV after treatment by radiation or concurrent chemoradiation are at risk for persistent and recurrent disease thus HPV testing may be useful for prediction of persistent or recurrent disease after treatment.

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Potential conflicts of interest

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การติดเชื้อไวรัสฮิวแมนแป็บปิโลมาในผู้ป่วยมะเร็งปากมดลูกระยะลุกลามภายหลังการรักษาด้วยรังสีรักษาหรือการฉายรังสีร่วมกับการให้เคมีบำบัด

สุทธิดา อินทรบุหรั่น, เยาวนา ธนะพัฒน์, กรรณิกา ตาตะนันทน์, กนธีร์ สังขวาสี, กุศทินญ์ บูรณะวิทย์, สยมพร โกมลภิส, พนิดา จารุเวฬ

วัตถุประสงค์*: เพื่อหาอุบัติการณ์ของการติดเชื้อไวรัสฮิวแมนแป็บปิโลมาในผู้ป่วยมะเร็งปากมดลูกระยะลุกลามภายหลังการรักษาด้วยรังสีรักษา หรือการฉายรังสีร่วมกับการให้เคมีบำบัด*

วัสดุและวิธีการ*: เก็บตัวอย่างสารคัดหลั่งในช่องคลอดและบริเวณปากมดลูกของผู้ป่วยมะเร็งปากมดลูก ระยะลุกลาม จำนวน 55 ราย ที่ได้รับการคัดเลือกแล้ว และนัดตรวจติดตามหลังจากสิ้นสุดการรักษา 2 เดือน เพื่อส่งตรวจหาการติดเชื้อไวรัสฮิวแมนแป็บปิโลมาโดยใช้ polymerase chain reaction amplification ของ DNA หา linear array HPV genotyping test*

ผลการศึกษา*: จากการศึกษาการเก็บตัวอย่างสารคัดหลั่งในช่องคลอดและบริเวณปากมดลูกของผู้ป่วยมะเร็งปากมดลูกระยะลุกลาม จำนวน 55 ราย พบว่าร้อยละ 56.36 (31/55) ตรวจพบมีการติดเชื้อไวรัสฮิวแมนแป็บปิโลมาและร้อยละ 45.46 (25/55) เป็นชนิดความเสี่ยงสูง โดยไวรัสฮิวแมนแป็บปิโลมาชนิด 16 พบบ่อยที่สุดคือร้อยละ 35.48 (11/31) สำหรับชนิดความเสี่ยงสูงชนิดอื่นที่พบคือชนิด 18, 52 และ 58 เป็นร้อยละ 16.13, 16.13 และ 12.90 ตามลำดับ โดยการตรวจติดตามหลังจากสิ้นสุดการรักษาตั้งแต่ 3 ถึง 22 เดือน มีระยะเวลาเฉลี่ยที่ 13 เดือน ในกลุ่มผู้ป่วยที่ตรวจพบเชื้อไวรัสฮิวแมนแป็บปิโลมาชนิดความเสี่ยงสูง 6 ราย ใน 25 ราย คิดเป็น ร้อยละ 24.00 จะมีโรคคงอยู่หรือมีการกลับเป็นซ้ำ ในทางกลับกันในกลุ่มผู้ป่วยมีโรคคงอยู่หรือมีการกลับเป็นซ้ำจำนวนเพียง 1 ใน 30 ราย คิดเป็นร้อยละ 3.33 ที่ตรวจไม่พบเชื้อไวรัสฮิวแมนแป็บปิโลมาชนิดความเสี่ยงสูง*

สรุป*: ผู้ป่วยมะเร็งปากมดลูกระยะลุกลาม ที่ตรวจพบมีการติดเชื้อไวรัสฮิวแมนแป็บปิโลมาชนิดความเสี่ยงสูงภายหลังการรักษาด้วยรังสีรักษา หรือการฉายรังสีร่วมกับการให้เคมีบำบัด พบมีความเสี่ยงสำหรับการคงอยู่หรือมีการกลับเป็นซ้ำของโรคมะเร็งปากมดลูก*