The Treatment Outcome of Adenocarcinoma of Uterine Cervix at Phramongkutklao Hospital

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***Objective**: To determine the survival rate of patients with adenocarcinoma of the cervix after completing treatment at Phramongkutklao Hospital.*

***Material and Method:** Retrospective review of medical records of 229 patients with adenocarcinoma of the cervix who had completed treatment at Phramongkutklao Hospital between October 1991 to September 2006.*

***Results:** Overall 2, 5 and 10-year survival for patients with adenocarcinoma of the cervix was 78.9%, 70.1% and 67.0%, respectively. The 5-year survival rates for stages I, II, III and IV were 94.6%, 76.1%, 49.2% and 0, respectively. Five-year survival of patients with locally advanced adenocarcinoma of the cervix treated with concurrent chemoradiation was comparable to that of patients treated with radiation alone (64.0 vs. 62.4%). Survival of group treated by radiation plus surgery was not significantly different to the group recieved radiation alone. There have been no serious complications from the treatments.*

***Conclusion:** Survival of patients with adenocarcinoma of the cervix shows a direct correlation with stage. The survival for each treatment modality was comparable. Adjuvant hysterectomy after radiation in adenocarcinoma of the cervix stage IIB and IIIB did not improve long term survival.*

***Keywords:** Adenocarcinoma, Cervical cancer, Survival*

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Cancer of the uterine cervix is the most common cancer in Thai women[1] with age-standardized incidence rates of 19.5 per 100,000 in 2005[2]. Since the introduction of Papaniculaou smear for cervical cancer screening, the incidence of squamous cell carcinoma has markedly decreased recently in many developed countries[3,4]. On the other hand, several studies described increase incidence of the adenocarcinoma from 4-7 %[5-8] to 15-27%[9-13], resulting in increase proportion of adenocarcinoma[13,14]. The reason for this phenomenon is not known. Some researchers believe that it is related to the difficulty in detecting adenocarcinoma lesion in screening test because of the lesion usually originated inside of the cervical cannel[15].

Some authors have reported a poorer prognosis for adenocarcinoma compare to squamous cell carcinoma[16-18], whereas others have shown no difference[7,19,20]. Some reports suggest that one of the factor attributed to poor prognosis is that adenocarcinoma is relatively radioresistant[21]. Simple hysterectomy after radiation was advocated from some reports to improve survival and local control of the disease especially in patients with bulky lesions[5,6,8,22,23]. Conversely, other reports indicated that radiation therapy alone was adequate[7,18,24]. After 1999, five major reports showed that treatment with concurrent chemoradiation reduced risk of death from cervical cancer by about 30-50%[25-29]. Since then, concurrent chemoradiation has become standard treatment for locally advanced cervical cancer. However, most of the patients in the concurrent chemoradiation studies were squamous cell type. It has been extensively debated as to whether or not the best treatment for adenocarcinoma is the same as for squamous cell carcinoma because of data limited. This retrospective study was performed to explore the clinical manifestation, treatment patterns and outcomes of patients with adenocarcinoma of the

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cervix treated at Phramongkutklao Hospital, with priority made to the 5 year survival of this disease.

Material and Method

Patients with histology confirmed primary adenocarcinoma of the uterine cervix that completed treatment at the Gynecologic Oncology unit, Phramongkutklao Hospital from October 1, 1991 to September 30, 2006 and with adequate medical records for date of diagnosis, date of death or last follow, clinical history, treatment and treatment outcome, were eligible. The staging process was clinically evaluated by an experienced gynecologic oncologist and radiotherapist according to the International Federation of Obstetrics and Gynecologic (FIGO) staging system.

Treatment of all cervical cancer patients follows the clinical practice guidelines for cervical cancer treatment at the Department of Obstetrics and Gynecology Phramongkutklao Hospital. This guideline has been used until 1996 and revised in 2000. Although there have new treatment methods during period of time but the principle of treatment have not been changed. Early stages of cervical cancer (stages IA-IIA) were managed primarily with surgery or radiotherapy if the patient is unsuitable for surgery. Patients with locally advanced cervical cancer (stages IIB-IVA) were treated with radiation therapy that consisted of whole pelvic radiation and intracavitary insertions for a total of approximately 7,500-8,500 cGy at point A. Concurrent chemoradiation was optional treatment in locally advanced disease before 1999 but became standard treatment thereafter. Combine radiation therapy and simple hysterectomy was performed in selected cases. Stage IVB patients were treated with systemic chemotherapy or palliative treatment.

Follow-up examinations took place at the Gynecologic Oncology Unit. Patients were scheduled to return for follow-up every 2-3 month during the first two years and every 6 months thereafter. Follow-up data, such as date of last visit, toxicity from treatment, disease status at last clinic visit, and disease status at time of last contact were noted.

Medical records were reviewed for demographic information, treatment provided, toxicity and disease status at last clinic visit. Those patients who lost to follow-up were contacted by phone or mail to identify their current status. Date and caused of death were collected from medical records or death certificates issued by the Ministry of Interior. Toxicity was assessed using World Health Organization (WHO) and Radiation Therapy Oncology Group (RTOG) criteria.

Time to recurrence was defined as the time interval from date of diagnosis to date of disease recurrence of the patients who were complete disappearance of all disease on radiographic and physical examination for a minimum of 4 weeks or complete response. The survival time was defined as the time interval from date of diagnosis to date of death from any cause or to the last follow-up date. Survival data were estimated using the Kaplan-Meier method and were compared among subsets by the log-rank test. The demographic data were presented by using mean, median and percent.

Results

During study period, 229 patients were enrolled in the study. Thirty-five patients were excluded, 21 patients due to incomplete treatment, 14 patients had other histological subtypes or insufficient data to evaluate survival. Thus, a total of 194 patients were reviewed. Five patients listed as having incidental cervical cancer were found with invasive cervical cancer following simple hysterectomy. These 5 cases were excluded from survival analysis because their primary treatment did not follow standard protocol. One hundred and eighty nine patients were evaluated for survival analysis. Patient age was between 24 to 81 years, with a median age of 47. Most patients had exhibited abnormal vaginal bleeding (34%), with tumor size < 4 cm (24.7%) and well histological grading (43%) as shown in Table 1. The number of patients treated with surgery, radiation alone, concurrent chemoradiation and chemotherapy in each stage is listed in Table 2. Thirty-two patients in stages IA-IIA were treated with surgery; surgery consisted of radical hysterectomy with pelvic lymphadenectomy in 29 patients, simple hysterectomy in 2 patients and modified radical hysterectomy with pelvic lymphadenectomy in 1 patient. Among the remainder of stages IA-IIA, 10 patients were treated with radiation and 1 patient with stage IIA received concurrent chemoradiation. Most of the patients with locally advanced disease were stage IIB (82 patients, 42.2%) followed by stage IIIB (59 patients, 30.4%) and stage IVA (3 patients, 1.5%). The majority of these patients were treated with radiation alone (93 patients, 47.9%) followed by concurrent chemoradiation (51 patients, 26.3%).

The 2, 5 and 10 year survival rates for all stages were 78.9%, 70.1% and 67.0%, respectively. The

Table 1. Characteristics of the patients

Characteristics	Number of patients	Percent of patients
Parity		
Nulliparity	15	7.7
1	9	4.6
2	28	14.4
> 2	33	17.0
Unknown	109	56.1
Initial clinical presentation		
Abnormal bleeding	67	34.5
Vaginal discharge	15	7.7
Pain	9	4.6
Mass	3	1.5
Combine	3	1.5
No symptom	8	4.1
Unknown	89	45.9
Tumor size (cm)		
≤ 4	53	27.3
> 4	36	18.5
Unknown	100	45.9
Tumor type		
Exophytic	48	27.4
Endophytic	12	6.1
Ulcerative	9	4.6
Unknown	125	64.4
Histologic grading		
Well	85	43.8
Moderately	32	16.4
Poorly	28	14.4
Unknown	49	25.2

Table 2. Adenocarcinoma of cervix: Number of patients treated with surgery, radiation alone, concurrent chemoradiation and chemotherapy by stage

Stage	No. (%) n = 194	Treatment			
		Sx	RT	RT+ CT	CT
IA	3 (1.5)	3	-	-	-
IB	34 (17.5)	27	7	-	-
IIA	6 (3.0)	2	3	1	-
IIB	82 (42.2)	-	62	20	-
IIIA	0	-	-	-	-
IIIB	59 (30.4)	-	28	31	-
IVA	3 (1.5)	-	3	-	-
IVB	2 (1.0)	-	-	-	2
Incident	5 (2.5)	-	-	-	-

Surgery (Sx), Radiation alone (RT), Concurrent chemoradiation (RT + CT), Chemotherapy (CT)

survival of 189 patients with adenocarcinoma of cervix according to FIGO stages are shown in Table 3. Kaplan-Meier survival curves of each stage are displayed in Fig. 1. No stage IV patients survived up to five years. There were sixty-three deaths, 51 of these patients died due to cervical cancer. There was no treatment-related death. The 10 year cancer-specific survival for stage I, II, III and IV were 97.4%, 75.9%, 49% and 0, respectively. The prognostic factors that significantly associated with survival were histological grading and tumor size. Patients with well differentiate grade of adenocarcinoma had a better survival than moderate and poorly differentiate grade ($p = 0.014$, HR 2.856 95% CI (1.739-3.974)). After comparing survival to size of primary tumor in 89 of 189 patients who have record about tumor size, patients with tumor size < 4 cm had a significantly better survival than those with tumor size > 4 cm ($p = 0.012$), as presented in Fig. 2.

In the early stage, all of stage IA patients

Table 3. Adenocarcinoma of cervix: 2, 5 and 10 year survival rate of by stage

Stage	No.	2 year		5 year		10 year	
		No.	SR (%)	No.	SR (%)	No.	SR (%)
I	37	36	97.3	35	94.6	34	91.9
II	88	77	87.5	67	76.1	63	71.6
III	59	34	57.6	29	49.2	28	41.5
IV	5	1	20.0	0	0	0	0

Survival rate (SR)

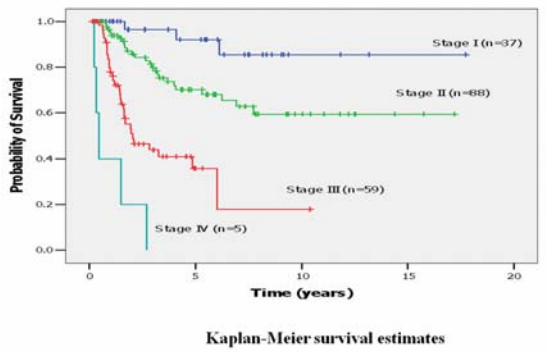

Fig. 1 Adenocarcinoma of cervix: survival of stage I, II, III and IV in 189 patients

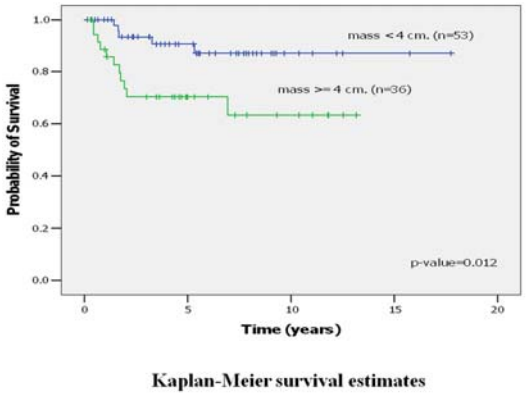

Fig. 2 Adenocarcinoma of cervix: Overall survival curve by tumor size in 89 patients

treated with surgery alone survived more than 10 years. Two- , five- and ten-year survival of stage IB-IIA were not different between the surgery and the radiation group ($p \geq 0.05$). None of patients in the surgical group received postoperative radiation. Difference in survival of locally advanced stages between the two treatment groups (radiation alone and concurrent chemoradiation) was not statistically significant ($p \geq 0.05$), shown in Table 4. In stage IIB and IIIB, among one hundred and fifty-five patients treated with radiation alone or concurrent chemoradiation, 47 patients (42 patients with stage IIB and 5 patients with stage IIIB) had simple hysterectomy performed 4-6 weeks subsequent to radiation treatment. Residual disease was found in 18 patients (38.3%). There was no significant difference in 2, 5 and 10 year survival between radiation group (radiation alone or concurrent chemoradiation) and combined radiation plus surgery group ($p > 0.05$), shown in Table 5.

A hundred and fifty-eight patients were complete response. Twenty-three patients recurred; only one patient in the early stage had recurred after primary surgery treatment, 17 patients of radiation or concurrent chemoradiation therapy recurred and 5 patients recurred after radiation plus surgery. There is no difference of recurrent rate between the group of radiation and radiation plus surgery. The median time to recurrence was 17 months. Recurrent rate by stage of disease is shown in Table 6.

In this study, 41 patients were loss follow-up. All of them were complete response after initial treatment. The median age of loss follow-up patients was 47 years old. Patients with early stage disease, 11 patients loss follow-up (8 after surgery and 3 after radiation therapy). Thirty patients of locally advanced disease were loss follow-up (17 after radiation therapy, 2 after concurrent chemoradiation and 11 after radiation plus surgery).

There were neither treatment-related deaths nor serious complications found in this study. Fourteen patients of the radiation group had grade 1 or 2 hematologic toxicities. Twenty-two patients had grade

Table 4. Adenocarcinoma of cervix: 2, 5 and 10 year survival rate of each treatment modalities in stage IB-IIA (Early stages) and stage IIB-IVA (Locally advanced stages)

Stage	Treatment	No.	Survival rate (%)			p-value*
			2 year	5 year	10 year	
IB-IIA	Sx	29	96.5	96.5	93.1	> 0.05
	RT or RT + CT	11	100.0	90.9	90.9	
IIB-IVA	RT	93	75.3	62.4	58.1	> 0.05
	RT + CT	51	72.0	64.0	62.0	

Surgery (Sx), Radiation alone (RT), Concurrent chemoradiation (RT + CT), *p > 0.05 = not significant

Table 5. Adenocarcinoma of cervix: compared 2, 5 and 10 year survival rate between radiation group (radiation alone or concurrent chemoradiation) and combined radiation plus surgery group with stage IIB and IIIB

Stage	Treatment	No.	Survival rate (%)			p-value*
			2 year	5 year	10 year	
IIB	RT or RT + CT	40	78.38	70.27	64.86	> 0.05
	RT or RT + CT plus Sx	42	90.48	73.81	73.8	
IIIB	RT or RT + CT	54	53.85	50.00	50.00	> 0.05
	RT or RT + CT plus Sx	5	60.00	60.00	40.00	

Radiation alone or concurrent chemoradiation (RT or RT + CT), Combined radiation or concurrent chemoradiation plus surgery (RT or RT+CT plus Sx), *p > 0.05 = not significant

Table 6. Adenocarcinoma of cervix: recurrent rate by stage and treatment modalities of 158 patients who were complete response

Stage	No. of patients (%)	No. of CR patients		
		Sx (n = 32)	RT or RT+CT (n = 79)	RT or RT+CT plus Sx (n = 47)
IA	0	-	-	-
IB	2 (8.4)	1	1	-
IIA	1 (4.3)	-	1	-
IIB	10 (43.6)	-	6	4
IIIA	0	-	-	-
IIIB	9 (39.1)	-	8	1
IVA	1 (4.3)	-	1	-
IVB	0	-	-	-
Total	23	1 (3.1%)	17 (21.5%)	5 (10.6%)

Radiation alone or concurrent chemoradiation (RT or RT + CT), Combined radiation or concurrent chemoradiation plus surgery (RT or RT + CT plus Sx), Complete response (CR)

Table 7. Adenocarcinoma of cervix: Grading of toxicity from radiation therapy

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematology					
Hemoglobin	147	6	2	-	-
WBC	149	1	5	-	-
Platelet	155	-	-	-	-
Non hematology					
Nausea	154	2	-	-	-
Vomiting	153	2	1	-	-
LFT	153	-	2	-	-
Azotemia	152	2	1	-	-
Radiation cystitis	149	4	2	-	-
Radiation proctitis	148	5	1	-	-

Table 8. Adenocarcinoma of cervix: Grading of toxicity by treatment modality

Treatment	No.	Hematologic		Non hematologic	
		Grade 1-2 (%)	Grade 3-4 (%)	Grade 1-2 (%)	Grade 3-4 (%)
Sx	32	-	-	-	-
RT	103	4 (3.8)	-	9 (8.7)	-
RT + CT	52	10 (19.2)	-	11 (21.1)	-
CT	2	1 (50)	-	1 (50)	-

Surgery (Sx), Radiation alone (RT), Concurrent chemoradiation (RT + CT), Chemotherapy (CT)

1 or 2 non-hematologic toxicities, as shown in Table 7. All of the radiation cystitis and proctitis occurred within 5 year after completion of treatment. No serious complication was found in all treatments modality, presented in Table 8. Both hematologic and non hematologic toxicity were increase in the concurrent chemoradiation when compare with radiation therapy alone. The record of intra- and post-operative complication in radiation plus surgery is not found.

Discussion

The incidence of squamous cell carcinoma, adenocarcinoma and other cell type of the cervix treated at the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Phramongkutklao Hospital during 1991-2000, account for 81.7%, 16.7% and 2%[30].

In our study, the mean age at diagnosis was 47 years, which is similar to the range of 47-52.4 years reported in the literature[6,16-18,22,30,31] and not significantly different from the mean age of patients with squamous lesions treated at this institution over the same period[30]. The volume of primary tumor is an extremely important prognostic factor. Berek et al[22] found that there is an apparent decrease in survival with increasing lesion size in all treatment groups. Other investigators have supported this finding[18,24,31]. Our study show similar result, with survival decreasing in group of tumor larger than 4 cm. However, sizes of primary lesions are not recorded for 100 patients.

Five-year cumulative probability of survival by FIGO stages I, II, III and IV in this study was compared with other studies, as shown in Table 9. The 5-year survival rates for stage II and III patients were higher than some reports[6,16,17,22] but similar to that reported by Goodman et al[32] Five-year survival of adenocarcinoma lesion in this study was comparable to 5-year survival of squamous cell carcinoma reported previously in this institute[30,33]. This result similar with the finding of several investigators who have shown no difference in outcome[7,19,20].

Table 9. Adenocarcinoma of cervix: Five-year cumulative probability of survival by stages

FIGO Stage	5 year survival rate (%)			
	I	II	III	IV
Rutledge[6]	a 100 b 81.8	a 52.4 b 43.3	a - b 28.8	0
Peter[15]	84	50	9	29
Hopkins[16]	60	47	8	0
Berek[22]	81.4	57.2	28	0
Goodman[32]	82	90	38	0
Phramongkutklao	94.6	76.1	49.2	0

After 1999, concurrent chemoradiation became standard treatment in locally advanced cervical cancer because many reports showed this treatment reduce risk of death from cervical cancer about by 30-50% compared to radiation alone[25-29,35]. Moris et al[27] and Eilel et al[35] studied patients with stages IIB-IVA, and although they reported improvement in survival with concurrent chemoradiation, only 24 (6.8%) of their patients were adenocarcinoma subtype. In this study which reviewed only adenocarcinoma of cervix, we found no statistically significant difference in survival and recurrence rate between the radiation alone and concurrent chemoradiation group. The result is different from other studies probably due to this study observed only adenocarcinoma lesions.

In the early stages, both definitive radiation and radical operation are accepted treatment for stage IB and IIA because both treatment methods are comparable with respect to survival[34]. In this study, the survival of adenocarcinoma of the cervix stages IB-IIA with radical surgery was shown to be similar to survival of patients who were treated with radiation.

Major discrepancies exist among conclusions regarding adjuvant hysterectomy subsequent to radiation. The use of adjuvant hysterectomy in the management of adenocarcinoma also has been controversial. Some reports showed higher local control rates among patients treated with radiation plus surgery. Rutletdge et al[6] did not show advantage of combined radiation plus surgery in stage I disease comparing to radiation alone but there was an apparent benefit in bulky stage I, stage II and III, including a lower central recurrence rate and increased survival compared with radiation alone. Berek et al[22] showed that with adenocarcinoma of the cervix stage I lesions smaller than 2 cm, whether the survival was similar whether the treatment was with radical surgery, radiation alone or combined radiation plus surgery; however, with increasing tumor size or in stage II, improved survival and local control of disease was obtained with radical surgery or combined radiation plus surgery. Prempree et al[31] suggested that early stage adenocarcinoma of the cervix, stage I (lesion smaller than 4 cm) can be treated effectively by radiation alone or radical hysterectomy with comparable results. With lesions larger than 4 cm, disease beyond stage I, uterine enlargement and poorly differentiation, treatment should be combined radiation plus surgery. However, Grigsby et al[24] observed comparable survival in patients treated with radiation alone and combined radiation plus surgery. Weiner et al[25] reported that combined therapy for stage I and II patients did not improve survival but did increase the complication rate. Eifel et al[18] also found no advantage with combine radiation plus surgery over radiation alone. According to the treatment reviewed, combined radiation and surgery was performed only on patients with stages IIB and IIIB, we found that adjuvant hysterectomy did not improved survival for these stages, although this treatment decreased recurrence rate with no serious complications occurred. However, this study is limited by retrospective analysis; in that extant data do not always indicate why surgery was either used or omitted for individual patients. A well controlled prospective study comparing these therapies is essential to further clarify the issues.

In summary, this study shows that survival of patients with adenocarcinoma of cervix correlated with stage of disease and tumor size, but not with treatment modalities. In stages IB to IIA, there was no significant difference in survival between radical surgery and radiation alone. For stage IIB to IVA, concurrent chemoradiation had no advantage over radiation alone. Adjuvant hysterectomy subsequent to radiation did not improve survival in patients stage IIB and IIIB.

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ผลของการรักษามะเร็งปากมดลูกชนิดอะดิโน ในโรงพยาบาลพระมงกุฎเกล้า

กฤษณมน ฤทธิภาชัย, กุศทินญ์ บูรณะวิทย์, เยาวนา ธนะพัฒน์

วัตถุประสงค์*: เพื่อศึกษาอัตราการมีชีวิตรอดใน 5 ปี (5 year survival rate) ของมะเร็งปากมดลูกชนิดอะโนที่รับการรักษาในโรงพยาบาลพระมงกุฎเกล้า*

วัสดุและวิธีการ*: เก็บรวบรวมข้อมูลจากเวชระเบียนของผู้ป่วยมะเร็งปากมดลูกชนิดอะดีโนทั้งหมด จำนวน 229 ราย ที่มารับการรักษาจนเสร็จสิ้นที่หน่วยมะเร็งนรีเวช กองสูตินรีเวชกรรม โรงพยาบาลพระมงกุฎเกล้า ตั้งแต่ 1 ตุลาคม พ.ศ. 2534 ถึง วันที่ 30 กันยายน พ.ศ. 2549*

ผลการศึกษา*: ผู้ป่วยมะเร็งปากมดลูกชนิดอะดิโนโดยรวมมีอัตราการรอดชีวิตที่ 2, 5 และ 10 ปี เท่ากับร้อยละ 78.9, 70.1 และ 67.0 ตามลำดับ อัตราการอดชีวิตที่ 5 ปี ของระยะที่ I, II, III และ IV เท่ากับร้อยละ 94.6, 76.1, 49.2 และ 0 ตามลำดับ ในกลุ่มมะเร็งระยะลุกลามเฉพาะที่ (IIB ถึง IVA) เมื่อได้รับรังสีรักษาร่วมกับเคมีบำบัด และรังสีรักษาเพียงอย่างเดียวอัตราการมีชีวิตรอดที่ 5 ปี เท่ากับร้อยละ 64 และ 62.4 ตามลำดับ การผ่าตัดหลังจากได้รับรังสีรักษาไม่ช่วยเพิ่มอัตราการมีชีวิตรอดในผู้ป่วยระยะ IIB และ IIIB ไม่พบภาวะแทรกซ้อนที่รุนแรงในแต่ละวิธีการรักษา*

สรุป*: อัตราการรอดชีวิตของมะเร็งปากมดลูกชนิดอะดิโนขึ้นกับระยะของโรค ผลของการรักษาในแต่ละวิธีใกล้เคียงกันทั้งในกลุ่มมะเร็งระยะแรก (I ถึง IIA) และระยะลุกลามเฉพาะที่ (IIB ถึง IVA) และการผ่าตัดหลังจากได้รับรังสีรักษาไม่ช่วยเพิ่มอัตราการมีชีวิตรอดในผู้ป่วยระยะที่ IIB และ IIIB*