PROGNOSTIC FACTORS OF CERVICAL CENCER STAGE IB TREATED WITH RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY AT RAMATHIBODI HOSPITAL: A MULTIVARIATE ANALYSIS

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The survival outcomes, overall and relapse-free survival, of stage IB cervical cancer patients treated with radical hysterectomy and pelvic lymphadenectomy at Ramathibodi Hospital were evaluated. Data of 273 patients who underwent the surgery from January, 1969 to December, 1995 were analysed. The 5-year overall and relapse-free survival rates were 89.2 and 87.5 per cent. The recurrence and death rates were 8.8 and 6.3 per cent. The median time of follow up was 50 months. The 5-year overall and relapse-free survivals were compared among the age, weight, three cell types, grades of differentiation, clinical tumor size, surgical margins, pelvic node metastasis, parametrial tumor involvement, blood transfusion and estimated amount of blood loss. In univariate, only pelvic node metastasis is associated with a difference in 5-year survival rates, both overall and relapse-free survivals. After Cox proportional hazards model was used, pelvic node metastasis remained on independent prognostic factor for overall survival. The hazard ratio for pelvic node metastasis is 6.42 (95% confidence interval 2.32 to 17.79, P<0.001). For relapse-free survival, pelvic node metastasis and surgical margins involvement are the only independent prognostic factors. The hazard ratio for pelvic node metastasis is 4.73 (95% confidence interval 1.84 to 12.11, P=0.001) and for surgical margins involvement is 19.59 (95% confidence interval 2.15 to 178.6, P=0.008). These prognostic factors should be considered in patient counseling and treatment planning.

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ฉัฐพงศ์ อิศรางกูร ณ อยุธยา : การศึกษาปัจจัยในการพยากรณ์โรค โดยวิธี MULTIVARIATE ในผู้ป่วยมะเร็งปากมดลูก ระยะ IB ที่รับการรักษาโดยการผ่าตัดมดลูกแบบ Radical และเลาะต่อมน้ำเหลืองในอุ้งเชิงกราน (PROGNOSTIC FACTORS OF CERVICAL CANCER STAGE IB TREATED WITH RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY AT RAMATHIBODI HOSPITAL : A MULTIVARIATE ANALYSIS). คณะกรรมการควบคุมวิทยานิพนธ์ : กำแหง จาตุรจินดา, M.B., Ch.B., ประทักษ์ โอประเสริฐสวัสดิ์, ว.ว. สูตินรีเวช, อมรรัตน์ โพธิ์พรรค, Ph.D., มัณฑนา ธนะไชย, ว.ว. รังสีรักษา. 76 หน้า. ISBN 974-664-065-8

การศึกษาการรอดชีพและการไม่กลับเป็นซ้ำ ในผู้ป่วยมะเร็งปากมดลูกระยะ IB ซึ่งรับการผ่าตัดมดลูกชนิด radical ร่วมกับการเลาะต่อมน้ำเหลืองอุ้งเชิงกราน ที่โรงพยาบาลรามาธิบดี ระหว่างมกราคม 2512 ถึง ธันวาคม 2538 มีผู้ป่วยที่นำข้อมูลมาวิเคราะห์ 273 ราย พบว่า มีอัตรารอดชีพ 5 ปี และอัตราการไม่กลับเป็นซ้ำ (relapse-free survival) 5 ปี ร้อยละ 89.2 และ 87.5 อัตราการกลับเป็นซ้ำของมะเร็ง และอัตราตายพบร้อยละ 8.8 และ 6.3 ระยะเวลาเฉลี่ยในการศึกษาติดตาม 50 เดือน การศึกษาปัจจัยที่เกี่ยวข้องกับการรอดชีพและการไม่กลับเป็นซ้ำ โดยวิธี univariate พบว่า การกระจายของมะเร็งไปต่อมน้ำเหลืองในอุ้งเชิงกรานเป็นปัจจัยสำคัญ เมื่อวิเคราะห์โดยวิธีของ Cox proportional hazards model พบว่า การกระจายของมะเร็งไปต่อมน้ำเหลืองในอุ้งเชิงกรานเป็นปัจจัยในการพยากรณ์การรอดชีพ โดยมี hazard ratio 6.42 (95% confidence interval 2.32 ถึง 17.79, P < 0.001) ส่วนการศึกษาการไม่กลับเป็นซ้ำ พบปัจจัยที่เกี่ยวข้องในการไม่กลับเป็นซ้ำ คือ การแพร่กระจายของมะเร็งไปยังต่อมน้ำเหลืองในอุ้งเชิงกราน โดยมี hazard ratio 4.73% (95% confidence interval 1.84 ถึง 12.11, P=0.001) และการพบมะเร็งที่ขอบแผลผ่าตัด โดยมี hazard ratio 19.59 (95% confidence interval 2.15 ถึง 178.6, P=0.008). การพิจารณาเลือกแนวทางการรักษาผู้ป่วยในระยะนี้ จึงควรคำนึงถึงปัจจัยในการพยากรณ์โรคเหล่านี้ด้วย

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CHAPTER I

INTRODUCTION

Cervical cancer is one of the most common cancers occuring in women as well as an important cause of death in women worldwide. It is the major cause of death in women due to cancer (1). From 1913 to 1981, 476, 747 cases of carcinoma of cervix were reported (2). Recently, an estimated 15,000 cases of invasive and 55,000 of in situ cervical cancer were diagnosed in the United States in 1994. The average annual age-adjusted incidence for invasive cervical cancer in all SEER areas was 8.3 per 100,000 woman for 1991, with a corresponding age-adjusted mortality rate of 2.9. The overall 5-year survival rate for cervical cancer is 67 per cent, with the rate rising to 90 per cent for cancers diagnosed at early stages. It is estimated that 4,800 women died from cervical cancer in 1995 (3). Despite the considerable effort and costly healthcare resources expended on women who have abnormal Pap smears, the total contribution of cervical cancer to cancer-related morbidity may be the largest of any neoplastic process.

Cervical cancer is also one of the important cancer in Thailand. The age-standardized incidence rate of cervical cancer patient were reported to be 29.7, 23.9, 20.9 and 18.5 per 100,000 population in Chiangmai, Khonkaen, Bangkok and Songkla, respectively. The mortality rate of cervical cancer in Thailand in 1987 was 0.68 per 100,000 population per year (4). The result of treatment of early stage is

much more better than late stages. The clinical staging system was recommended by FIGO (The International Federation of Gynecology and Obstetrics) in the year 1995 (5, Appendix I). In Ramathibodi Hospital, cervical cancer is still marked first of all cancers and of the female cancer (6). From 1992 to 1996, 1,043 cases of cervical cancer were diagnosed. The distribution of stage I, II, III and IV were 11, 44.8, 32.6 and 1.6 per cent. The 5-year survival rate of stage I, II and III were 88, 64 and 38 per cent were reported in 1987 (7).

Although the causative agents of cervical cancer are not known, many factors were found to be risk factors of cervical cancer: host factors (immune response, genetic abnormalities, sexual behavior, reproductive factors), some agents (human papilloma virus, herpes simplex virus) and environmental factors (cigarette smoking, oral contraceptives) (8).

Cervical cancer is believed to result from the progression of milder epithelial abnormalities called dysplasia or cervical intraepithelial neoplasia (CIN). A new cytologic classification system, the Bethesda System, combines similar diagnosis into broad categories, including low-grade and high-grade squamous intraepithelial lesions (9). Support for a continuum of disease is provided by the observation that cervical dysplasia is most often diagnosed among women in their 20s, carcinoma in situ in women 25 to 35 years old, and invasive cancer after the age of 40. Although many cases of CIN tend to regress spontaneously, particular the milder grades, there is definite tendency for progression overtime in average of 5 to 10 years.

Because of the presumed continuum of cervical disease from CIN to invasive cancer, the exfoliative cytology or the Pap smear, is a sensitive and relatively

inexpensive technique for detecting cervical cancer and its precursors, and can have profound effects as morbidity and mortality. The eradication of precursors lesions has preceded significant declines in cervical cancer incidence and mortality in areas where screening has been widespread and prolonged. The rates of cervical cancer have not declined in regions or countries with limited screening programs, such as Thailand and other developing countries. The treatment of cervical cancer is still the important health problem in Thailand.

Cervical cancer metastasizes systematically along the lymphatic of the pelvis that derive from the cervix. The first to be involved will be the lymph nodes of the pelvis, the parametric, the obturator fossa, the internal and external iliac vessels. Lymph nodes in the presacral space and along the common iliac vessels and the para-aortic area usually follow. A direct embolic spread to para-aortic nodes may be possible, but is not likely. In addition to lymph nodes metastases, cervical cancer can spread by direct extension laterally to the parametrium and anteriorly into the muscularis of bladder or rectum.

The FIGO staging system is based on clinical evaluation (inspection, palpation, colposcopy, cysto-proctoscopy, roentgenographic examination of the chest, kidneys, and skeleton, and other imaging techniques if necessary). If disease appears to be confined to the cervix, primary treatment will be surgery. For stage IB cervical cancer (ie. clinical lesion confined to the cervix), the treatment of choice is surgery, using the radical hysterectomy with pelvic lymphadenectomy.

When cure rates of surgical and radiation treatment for FIGO stage IB cancer of the cervix are compared, the survival rates are almost identical. In a collected series,

reported by Delgado, 83.4 per cent 5-year survival after radical surgery (2,600 patients) and 85.5 per cent 5-year survival after radiation therapy (1995 patients) were found (10). Apart from survival, there are other advantages of surgical treatment for healthy patients will FIGO stage IB. Although irradiation could be selected for all patients, major bladder and bowel damage occurs in 2 per cent to 6 per cent and chronic bladder dysfunction has been reported in 23 per cent to 44 per cent (11). Bladder dysfunction after radical hysterectomy was reported only 12 per cent in Ramathibodi Hospital (12). Symptomatic irradiation cystitis or proctitis may occur months or years after treatment and persist for long period of time. Bladder and rectal fistulas after radiation are difficult to correct surgically because the enarteritis associated with therapy reduces blood supply to the pelvic tissues and impedes healing after surgery. The vaginal complication and sexual problems associated with radiation therapy should also be concerned especially in the young healthy and sexually active women. Another benefit of surgical treatment is ovarian conservation. Metastases to ovaries are rare (less than 1 per cent) with early stage of squamous tumors, although somewhat higher in adenocarcinoma patients. With a surgical approach, the extent of tumor can be established; the vagina is left without major changes in caliber or elasticity and the removal of the tumor offers a psychological advantage to the patient that the tumor is "out". The complications of surgical treatment usually occur early in postoperative period and are correctable, whereas those from irradiation may appear later and generally are more difficult to remedy. Operative deaths from surgery are rare. At Ramathibodi Hospital, there was no death from the surgery of 148 patients during 1969 to 1982 (12).

At Ramathibodi Hospital, the patients younger than 65 years old and healthy are often offered surgery, radical hysterectomy with pelvic lymphadenectomy, as primary treatment. The obese, the diabetic, and the woman with cardiac or other major health problems ordinarily receives primary radiation therapy. Post operative radiation therapy is commonly given to patients with pelvic nodes metastases, surgical margin not free from tumor and parametrial involvement of tumor, although there is no established data that such adjunctive irradiation improves survival.

Five-year survival rates of these surgically treated early invasive cervical cancer of stage IB are 82 to 97 per cent overall and in the range of 10 to 50 per cent when metastasis to lymph nodes are documented (13). The recurrent rates are 3 to 21 per cent in patients without lymph node metastases and 27 to 78 per cent in those with lymph node metastases.

In Ramathibodi Hospital, the patients of cervical cancer stage IB treated with radical hysterectomy and pelvic lymphadenectomy in the period of the year 1969-1988 developed recurrence 11.5 per cent (14). The distance metastases was found in 33 per cent. The central and side wall recurrent were 19 and 48 per cent, respectively. The survival rate was about 50 per cent at the end of third year. The median time from recurrence to death was 24 months (range from 12-65 months). Most of the recurrent cases (86 per cent) were diagnosed within 3 years after surgery.

Rationale of the study

Despite the early stage of IB of cervical cancer, the conventional treatment with radical hysterectomy and pelvic lymphadenectomy still led to the recurrent rate of

11.5 per cent and most of recurrent cases progress to death within limited time. Increasing interest has been directed towards identifying factors that either indicate an increase risk of recurrence or decrease survival. If the risk factors can be identified accurately, adjunctive therapeutic regimens may be developed for patients who had increased risk for recurrence and death from disease.

There were still inconsistent findings about the prognostic factors influencing survival. Those which have been reported include the followings:

1. Demographic factors: age, thrombocytosis, weight.

2. Histopathological factors: clinical lesion size, surgical margin, parametrial involvement, pelvic lymph nodes metastases, cell types and degree of differentiation, lymph vascular space tumor invasion, microvascular density, inflammatory stromal reaction, cytokeratin, CEA (cellular embryonic antigen), and SCCAg (squamous cell carcinoma antigen).

3. Treatment factors: peri-operative blood transfusion.

In Thailand, from Medline searched, during recent ten-years period, there is a report of prognostic factors of cervical cancer stage IB treated by radical hysterectomy and pelvic lymphadenectomy from Ramathibodi Hospital. By univariate analysis, some of the prognostic factors for recurrence were studied. One hundred and sixty-four cases were analysed and lesion size more than 3 cm was the only factor found to have statistical significant increased relative risk of recurrence (RR 4.17, 95% CI 1.33, 13.08) (14). Some of the reported prognostic factors were not included

in the study. The multivariate analysis of these factors may show more informations

for further management of the patients of cervical cancer in stage IB.

CHAPTER II

LITERATURE REVIEW

The objectives of this study are to identify the survival and prognostic factors associated with survival outcomes in stage IB cervical cancer patients treated with radical hysterectomy and pelvic lymphadenectomy, the following literature review will focus on

1. The survival outcomes.

2. The prognostic factors associated with survival outcomes.

The literature review was performed by Medline searching during the period from 1987 to 1999 and an additional search from library. There were 179 reports associated with cervical cancer stage IB. The reports of prognostic factors were reviewed, only the significant factors which are available in Ramathibodi Hospital are presented in this review.

The survival outcome

Of the overall survival, the event of interest is death from cervical cancer after treatment of radical hysterectomy and pelvic lymphadencetomy. The overall survival time is defined as the time from the date of surgery until the death or the date known to be alive at the last follow up.

The overall 5-year survival rate reported during 1976 to 1999 varied from 72.8 per cent to 98.4 per cent (15-27) the summary of the results of studies are shown in Table 2-1. Bhamarapravati et al, in 1988, reported the result of treatment of stage IB cervical cancer patients with radical hysterectomy from Ramathibodi Hospital with 5-year survival 88.9 per cent which was similar to the previous reported in 1976 (12, 28). Survival rates in patients whose tumor are confined to the cervix (stage IB) have remained relatively constant in the past few years.

Table 2-1 Overall 5-year survival for stage IB cervical carcinoma treated with radical hysterectomy and pelvic lymphadenectomy

Study	Country	Year	Patients (N)	Overall 5-yr Survival (%)	Reference
Morley, et al	U.S.A	1976	149	91.3	15
Zander, et al	Germany	1981	749	84.5	16
Noguchi, et al	Japan	1987	191	85.3	17
Carenza, et al	Italy	1988	105	85.7	18
Fuller, et al	U.S.A	1989	285	86.0	19
Lee, et al	R.O.C.	1989	237	86.1	20
Monaghan, et al	Netherlands	1990	494	83.0	21
Alvarez, et al	U.S.A	1991	401	85.0	22
Burghardt, et al	Austria	1992	443	83.4	23
Massi, et al	Italy	1993	211	75.8	24
Finan, et al	U.S.A	1996	181	72.8	25
Lai, et al	Taiwan	1999	891	98.4	26
Magrina, et al	U.S.A	1999	56	94.6	27

When metastases to pelvic lymph nodes are documented, the 5-year survival rates were reported to decrease to the range of 38 to 51 per cent (29-32)..

Of the relapse-free survival, the event of interest is the first recurrence of disease. The relapse-free survival time is the time from the date of treatment until the date of first recurrence of disease or the date known to be relapse-free at the last follow up.

The relapse-free or disease-free survival rates of stage IB cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy ranged from 74 to 80 per cent (33, 34).

The prognostic factor

1. Age

According to some reports, carcinoma of the cervix has the same prognosis in younger and older patients (35, 36). Poka et al reported no significant difference in 5-year survival rate between cervical cancer patients under and over 35 year old (37). Serur et al, using the cut point of age under and over 50 years, stated that there were no significant difference in age-related survival in cervical cancer patients (38). Others have observed decreased survival in women younger than 35 or 40 years, who have a greater frequency of poorly differentiated cancer (39, 40). From multivariate studies, age was not the significant independent prognostic factor in stage IB cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy (41, 42).

2. Body weight

Cervical carcinoma patients stage IB treated with radical hysterectomy with a low body mass, as indicated by low BMI (body mass index) or a high PI (ponderal index), were found to have poor survival (43). A multivariate logistic regression analysis was found the predictor of complications was para-aortic lymph node dissection. The obese women underwent radical hysterectomy have no greater risk of surgical complications (43).

3. Clinical tumor size

Many published reports have related survival to lesion size. Five and ten-year survival were excellent for lesion up to 2 cm in diameter, whereas larger lesion result in survival similar to that of the patients with stage II disease (22). As tumors increase in size, the node metastases rates also increase (44). Three reports have demonstrated the size of cervical tumor in relation to the incidence of pelvic lymph nodes metastases, the rate of recurrence and survival (19, 45, 46). All of these authors used the criteria (less than 4 cm) as compared with 4 cm or larger. The weighted data showed 15 per cent positive nodes, 6 per cent of recurrence, 84 per cent of 5-year survival rates in cases with tumor size less than 4 cm as statistical significant compared with 38 per cent, 80 per cent and 56 per cent in cases with tumor size equal or more than 4 cm. Five-year survival rate decreased from 84 per cent in patients with tumor less than 4 cm to 56 per cent in patients with larger than 4 cm (19). The linear regression analysis, corrected for pelvic lymph nodes metastases, found the risk of recurrence with increasing size of tumor persisting.

Recent study of GOG (Gynecologic Oncology Group), by using proportional hazard modeling showed increasing of adjusted relative risk of death from 2.3 to 4.3 when gross tumor size increased from 3 to 8 cm (47). In this study, the cut point of less than 4 cm and equal or more than 4 cm were used according to the new FIGO staging of the carcinoma of cervix in 1995 (Appendix 1).

In 1991, Chang et al reported the results of univariate analysis that bulky tumor size was found to bear the greatest risk of tumor recurrence. Six of 15 patients (40 per cent) with a diameter of more than 4 cm recurred (48).

In 1992, Kamura et al found that longitudinal tumor diameter, histologic subtype and pelvic lymph nodes metastases were identified as independent and significant prognostic factors by multivariate analysis (49).

In 1996, in order to identify a statistic combination of independent pathological and clinical features that best predict 5-year disease free survival (DFS) in patients with early stage cervical carcinoma treated by radical hysterectomy, Sevin et al, showed that, rank by degree of significance, depth of tumor invasion, tumor size, lymph vascular space involvement, lymph nodes metastasis, tumor volumn and clinical stage were significant in predicting survival by univariate analysis. By multivariate analysis, depth of tumor invasion, lymph vascular space involvement and lymph nodes metastasis remained significant prognostic factors (50).

The impact of the new staging system for IB1 and IB2 cervical cancer was determined in 1996. The study with multivariate stepwise logistical regression analysis indicated that the new staging system (using cut point of tumor size 4 cm or more) did not have an independent impact on survival (25).

Other multivariate analysis studies found tumor size remained the significant prognostic factor after adjusted for other confounding factors (51-54).

4. Pelvic lymph nodes metastases

Metastatic disease to pelvic nodes has a significant impact on the chance of 5 and 10-year survival (Table 2-2) (44). With negative parametrium and negative pelvic lymph nodes, the survival rate (regardless of lesion size) is excellent (90 per cent to

98 per cent), whereas with positive parametrium and pelvic nodes metastases, the survival rate fell by about half.

Table 2-2 Surgically treated stage IB carcinoma* : overall 5-year survival and survival by pelvic status

Study	Country	Year	Patients (N)	Negative Nodes (%)	Positive Nodes (%)	Overall (%)
Morley, et al	U.S.A.	1976	149	96.0	55.0	91.3
Zander, et al	Germany	1981	747	90.1	68.8	84.5
Noguchi, et al	Japan	1987	191	90.6	59.4	85.3
Barber	U.S.A.	1988	273	83.4	50.0	78.8
Carenza, et al	Italy	1988	105	91.0	56.2	85.7
Fuller, et al	U.S.A.	1989	285	94.0	54.0	86.0
Kenter, et al	Netherlands	1989	178	94.0	65.0	87.0
Lee, et al	R.O.C.	1989	237	87.7	73.1	86.1
Monaghan, et al	Netherlands	1990	494	91.4	50.5	83.0
Hopkins, et al	U.S.A.	1991	213	93.0	61.0	89.0
Alvarez, et al	U.S.A.	1991	401	88.0	53.0	85.0
Burghardt, et al	Austria	1992	443	-	-	83.4
Massi, et al	Italy	1993	211	85.0	45.0	75.8
Hepp	U.S.A.	1993	183	92.5	63.9	86.9

* Predominantly squamous cell.

The size of the largest metastases node was also shown to be a prognostic factor in the study of Inoue et al (55).

5. Surgical margins

The survival of patients after radical hysterectomy depends on adequate tumor excision. Tumor extension near or to the surgical margins predicts central recurrence (56). Extension to the anterior margin of resection (i.e., deep invasion to or into bladder muscularis) is a finding on some surgical specimens after radical

hysterectomy. If the anterior margin are considered suspicious intraoperatively, the operation should be abandoned.

Determining the result of post operative radiotherapy for clinical stage IB cervical cancer with evidence of microscopic involvement of surgical margin, parametrium and/or lymph nodes metastases, the low 5-year survival rate of 50 per cent was found in the group of microscopic parametrial involvement compared to the rate of 75 per cent in the group of vaginal cuff involvement (57).

6. Parametrial involvement

The risk of parametrial involvement varies by stage. Extracervical extension of tumor may occur in a direct extension manner, a dissociated manner or in parametrial nodes. Some gynecologists strongly believed that continuous cancer spread into parametrial tissue is rare (58). The late stage tumor arises by expansion of the primary tumor and by confluence of multiple isolated foci in the parametrium. The parametrium contains lymph nodes and only by special assessment of specimen is one able to appreciate the number, the size and the location of such nodes. These nodes often small, may be detected through out the parametrium. When the parametrium is invaded, the incidence of pelvic nodes involvement rises three to five times (44); the risk of multiple positive pelvic nodes rises sixfold (55); and vascular invasion in the vessel-rich parametrium probably increases, with its attendant effect on survival (23). Parametrial involvement was shown by multivariate analysis to be risk factor of recurrence (48) and independent prognostic factor for relapse-free survival (59).

7. Cell type

The prognosis of adenosquamous carcinoma of the cervix compared to the other cell types is a controversial issue. Survival rates varies widely among published series, with some studies found prognosis to be worse and other to be equal (60). Report from a GOG study of 813 patients showed no significant difference between cell types in crude comparison of relapse-free survival but there was a different in overall survival with shorter survival in the adenosquamous cell type. After adjusted for lymph vascular space invasion, performance status and depth of tumor invasion, survival remained worse for patients with adenosquamous cancer when compared to squamous and adenocarcinoma (47).

Others studies reported adenocarcinoma was associated with significant shorter relapse-free interval (59) and was the independent prognostic factor after analysis with multivariate method (49, 59, 61).

8. Degree of differentiation

An assessment of prognostic factors using univariate analysis found poorly differentiated tumor is the risk factor of tumor recurrence (48).

9. Perioperative blood transfusion

Since the initial reports linking blood transfusion to improved cadaveric renal transplant survival more than 400 publications, including several randomized, controlled studies, have demonstrated a beneficial immune suppressive effect of pretransplant blood transfusion on graft survival. Based on these data, Gantt

hypothesized that patients with malignant neoplasms who receive perioperative blood transfusion might be at increased risk for tumor recurrence (62).

The mechanism of transfusion induced immuno-suppression is thought to be multifactorical, including an increase in the number and activity of suppressor T lymphocytes, a decrease in natural killer-cell activity, an impairment of lymphocyte blastogenesis, and a stimulation of anti-idiotype antibody production (63). The cellular components of transfused blood are largely response for the immunomodulatory effects of transfusion, particularly in renal transplantation; however, other components, including plasma protein fractions, may also impair immune function (64).

The nonspecific immunosuppressive effect of blood transfusion provides a theoretical basis for the hypothesis that transfusion associated with cancer surgery might adversely affect prognosis. Unfortunately, studies investigating this hypothesis have usually been retrospective and have not controlled for prognostic variables such as tumor volume, which maker their interpretation difficult. Nevertheless, many such studies, particularly those involving patients with soft tissue sarcomas, colorectal cancers, and lung cancers, have consistently reported that perioperative blood transfusion is associated with a worsened prognosis.

Relatively few clinical data exist that address the impact of blood transfusion on survival among women with cervical cancer. One study of 126 patients with stage IB cervical carcinoma treated with radical hysterectomy and pelvic lymphadenectomy and found to have negative nodes and clear surgical margins, reported four times as many recurrence with perioperative transfusion than without (14.7 versus 3.4 per

cent) (65). The lack of confirmation by other investigators (66, 67) call into question the validity of these data.

Morris and coworkers (68) reported a retrospective evaluation of 302 patients with stage IB cervical cancer undergoing radical hysterectomy on whom perioperative blood transfusion were given. Transfusion rate was 81 per cent with a mean of 2.6 units (range 1-18 units). Transfused patients differed significantly from the non-transfused in that they had larger tumors, more frequent lymph vascular space involvement, longer procedures, and greater estimated blood loss. There was no different in relapse-free survival or calculated projected survival between the transfused and non-transfused groups. After controlling for node metastasis and tumor size (which were independent poor prognosticators), the number of blood transfusions was not predictive of recurrence or survival.

Monk et al. (69) reported 5-year survival rates of 86 per cent for transfused group compared with 84 per cent in non-transfused group, which was non-significant different. After controlling for age, cell type, stage, depth of invasion, nodal involvement, and use of adjuvant radiation, blood transfusion still did not adversity influence survival.

Azuma et al. (70) found the overall 5-year survival rate was significantly higher in non-transfused group than in those with transfusion, regardless of post-operative irradiation theory status.

Recently, Wolterbeck et al. (71) given the transfusion rate of 66 per cent, found that transfused patients had more blood loss, longer surgical time and lower

haemoglobin levels. The reported overall 5-year survival rates was 81 per cent for transfused group and 84 per cent for the non-transfused group, a non-significant different. The 5-year relapse-free survival rates were also comparable without statistical significant.

One large review of 374 patients found the transfusion rate of 80 per cent and the characteristics of the transfused group were more common in microscopic parametrial disease and larger tumor lesions (72). Follow-up analysis revealed no difference between the two groups in recurrence or survival. Multivariate analysis found only grade, depth of invasion and nodal status as independent predictors of recurrence and survival. The overall survival and relapse-free survival were not different.

CHAPTER III

MATERIALS AND METHODS

General objective

To study the survival time and to explore the factors associated with survival in cervical cancer patients stage IB treated with radical hysterectomy at Ramathibodi Hospital.

Research questions

1. What is the survival of stage IB cervical cancer patients treated with radical hysterectomy and pelvic lymphadenectomy at Ramathibodi Hospital?

2. What are the potential factors associated with survival in these patients?

Research objectives

1. To identify the survival from time of treatment to death (overall survival) in stage IB cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy.

2. To identify the survival from time of treatment to the first recurrence (relapse-free survival) in stage IB cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy.

3. To explore the potential factors associated with the two survival outcomes.

Design and methods

Type of study:

Historical cohort, descriptive study.

Place:

Ramathibodi Hospital, Mahidol University.

Inclusion criteria:

All patients who were histologically diagnosed as invasive cervical cancer and were stage IB by clinical staging system of FIGO (Appendix 1) and received surgical treatment with radical hysterectomy and pelvic lymphadenectomy in Ramathibodi Hospital from January 1969 to December 1995.

Exclusion criteria:

Patients without histological proven of invasive cervical cancer will be excluded from the study.

Study variables and operating definitions:

1. Overall survival time:

The event of interest is death from any causes. The overall survival time is the time from the date of treatment until the date of death or the date known to be alive at

the last follow up. Patients will be considered as censored cases in survival analysis if they were alive on the date at last follow up.

2. Relapse-free survival time:

The event of interest is the first recurrence of disease. The relapse-free survival time is the time from the date of treatment until the date of first recurrence of disease or the date known to be relapse-free at the last follow up. Patients will be considered as censored cases in survival analysis if they were relapse-free on the date at last follow up.

3. Staging:

FIGO staging system is used in classifying patients into clinical stage IB (Appendix 1). Gynecologic oncologists at tumor clinic were the doctors who decided whether the patients were in stage IB.

4. Clinical lesions size:

The clinical lesion size were subjectively estimated by the gynecologic oncologists who were assigned to perform surgery for those patients before the operation.

5. Age:

The completed year of life will be considered for age.

6. Cell type:

Cell types were coded according to official pathological reports of the radical hysterectomy surgical specimens.

7. Pelvic lymph nodes metastases:

Pelvic lymph nodes metastases are evidenced by pathological reports of tumor cells metastases to pelvic lymph nodes groups.

8. Degree of differentiation:

The degree of differentiation are coded according to official pathological reports of degree of differentiation. These are classified as poorly, moderately and well-differentiated.

9. Surgical margin:

The surgical margins are defined as free of disease for pathological report of no microscopic tumor cells at the surgical margin and are not free if pathological reports showed tumor cells at or near surgical margins.

10. Parametrial involvement:

The parametrial involvement is defined when pathological report of malignant tumor cells infiltrated of parametrium area.

11. Weight:

The weight in kilogram of the patient at the date of surgery will be considered for weight.

12. Estimated blood loss:

The estimated blood loss are defined as blood loss during the operation estimated by surgeons or anesthesiologists. The maximum amount will be considered. This is reported in millilitres by combination of measurement of blood in the suction bottle and weighing the gauze swabs postoperatively.

13. Perioperative blood transfusion:

The perioperative blood transfusions are the blood transfusions given during the operation and 48 hours after the operation.

14. Radical hysterectomy

Radical hysterectomy consists removal of cervix, uterus and a resection of the parametrial tissues to the pelvic wall with complete dissection of the ureters from their beds and mobilization of the bladder and the rectum to allow for more extensive removal of the tissues. A vaginal cuff of at least 2 to 3 cm is always include in the procedure.

Follow up periods

Patients were followed from the date of surgery until the last follow up date or at the end of study (December 31st, 1999).

Conceptual framework

The conceptual framework of the study variables is as followed. The survival outcomes are affected from demographic, histopathological factors.

```
┌─────────────────────────────┐
│   DEMOGRAPHIC VARIABLES     │
│        age, weight          │
└─────────────────────────────┘
                │
                ↓
┌─────────────────────────────┐        ┌──────────────────────────────────┐
│   OVERALL SURVIVAL          │        │     SURGICAL VARIABLES           │
│   RELAPSE-FREE SURVIVAL     │ ←───── │ blood transfusion, estimated blood loss │
└─────────────────────────────┘        │   surgeon*, surgical time*       │
                ↑                       └──────────────────────────────────┘
┌─────────────────────────────┐
│ HISTOPATHOLOGICAL VARIABLES │
│  • Clinical lesion size     │
│  • Surgical margins         │
│  • Parametrial involvement  │
│  • Pelvic nodes metastases  │
│  • Cell types               │
│  • Human papilloma virus*   │
│  • Degree of differentiation│
│  • Thrombocytosis           │
└─────────────────────────────┘
```
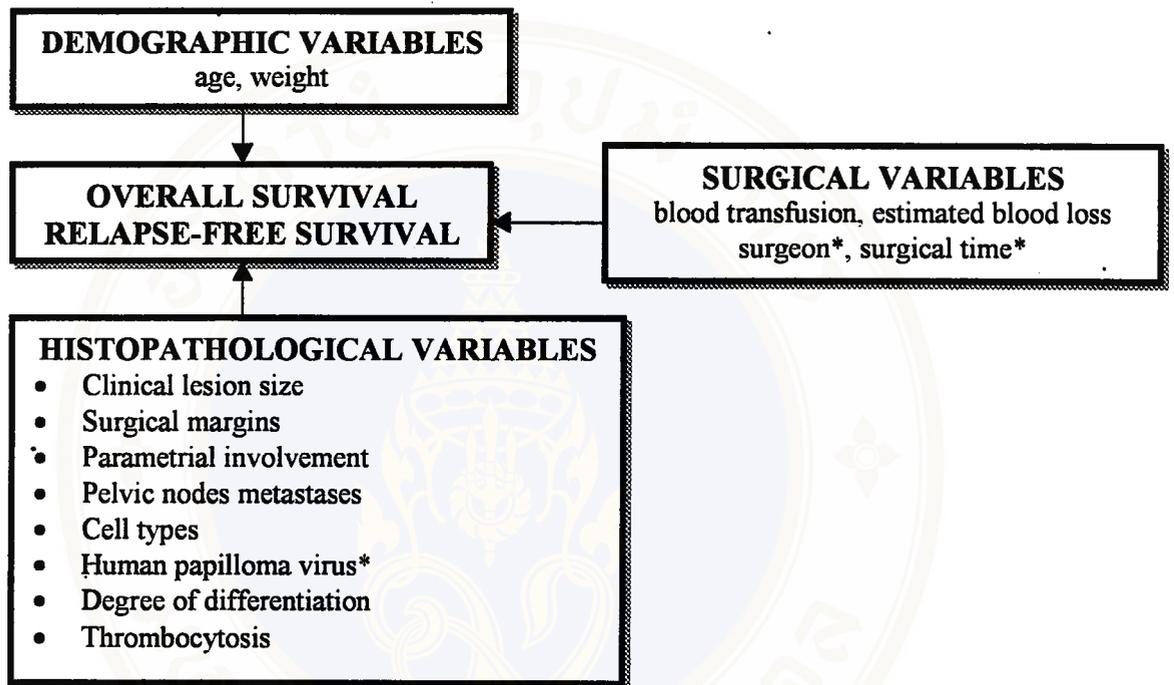
* = not available in this report

Sample size estimation

With assumptions that hazard rate (Δ) is constant over time and follow up periods are so long that all patients should be followed until their death, the incidence density is the estimate of the hazard under exponential survival function. The sample size estimation is calculated by the formula (73).

$$E = \left\langle \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)\left(1 + C\Delta\right)}{1 - \Delta} \right\rangle^2 / C$$

$$n = \frac{\left(1 + C\right)E}{C\left(1 - \pi_t\right) + \left(1 - \pi_c\right)}$$

$$\Delta = \frac{\ell n \pi_t}{\ell n \pi_c}$$

π_t = proportion of events during the follow up time t in treatment group

π_c = proportion of events during the follow up time t in controlled group

In this study, the main interested prognostic factor is the pelvic node metastasis and the outcome event is death. The follow up time period is 5-year interval.

π_t = death rate in patients with no pelvic node metastasis during the 5-year period of follow up

= 0.10   ----------------- (69)

π_c = death rate in patients with pelvic node metastasis during the 5-year period of follow up

= 0.37   ----------------- (69)

$\Delta \quad = \quad$ expected hazard ratio

$$= \quad \frac{\ell n \pi_t}{\ell n \pi_c} = \frac{\ell n(0.10)}{\ell n(0.37)}$$

$$= \quad 2.36$$

$\alpha \quad = \quad 0.05, \quad \beta = 0.10$

$C \quad = \quad \dfrac{\text{number of patients with no metastasis}}{\text{number of patients with node metastasis}}$

$$= \quad \frac{25}{106} \quad = \quad 0.24 \qquad \text{-----------------(74)}$$

so $E \quad = \quad \left\langle \dfrac{(1.96 + 1.28)(1 + 0.24 * 2.36)}{1 - 2.36} \right\rangle^2 / 0.24$

$$= \quad 60$$

$n \quad = \quad \dfrac{(1 + 0.24)60}{0.24(1 - 0.10) + (1 - 0.37)} = \dfrac{74.4}{(0.22) + (0.63)}$

$$= \quad \frac{74.4}{0.840} = 88.5$$

The calculated sample size is 89 cases, with the probability of sampling of patients with pelvic nodes metastasis is 0.24. The sample size for small and large tumor size patients will be 69 and 20 cases.

Data collection and management

Data were collected from the hospital and gynecological unit's records. The data were recorded, coded and entered into the data record form (Appendix 2). Data entry was performed by STATA version 5.0 and programmed twice to eliminate key-punch errors. The two files were checked for the accuracy and consistency. Data analysis was performed using STATA version 5.0.

Data analysis

Univariate analysis:

1. Discrete variables were described by proportion and confidence interval.

2. Continuous variables were described by mean or median when appropriate.

3. Kaplan-Meier survival function were used to estimated survival time (75).

Bivariate analysis:

1. Comparisons of discrete variables by comparison of proportion using Chi-square or Fisher's exact test, when appropriate.

2. Comparison of continuous variables by using independent t-test.

3. Comparison of survival curves by log-rank test.

Multivariable analysis:

1. Cox's proportional hazard model were used for analysis of factors that may associate with survival (77).

2. Hazard ratio will be used to show the strength of the associations.

Ethical consideration

The study have no contact with the patients and the data are retrieved from medical records without knowing the patient's names, so there will be no risk or benefit for individual patients. The contact to get permission of individual patients to use his/her information on medical records are not possible. However the data is processed in collective, not individual manner, therefore there will not be any effect on confidentiality issue.

CHAPTER IV

RESULTS

From January 1967 to December 1995, 290 women with cervical cancer FIGO stage IB had a radical hysterectomy with bilateral lymphadenectomy as a primary treatment at Ramathibodi Hospital. There were 273 patients (94 per cent) available for analysis due to the absence of some records. The operations were performed by Magara technique by gynecologic oncologists (76).

After surgery 17 patients (6.2 per cent) had adjuvant radiotherapy because of pelvic lymph nodes metastasis, microscopic extension of tumor cells into the parametria and/or surgical margin. Post operative whole pelvic irradiation (Cobalt 60, 4,500-6,000 centigrays in 5-6 weeks) and vaginal ovoid 2,160-2,820 mg-hr. The patients were follow up every 3 months for the first 2 years and every 6 months thereafter. After treatment, all evaluable patients were followed up at the department until December 30, 1999. The median time of follow up was 49.6 months (range, 0.3-192.3 months).

The mean age was 40.9 years (range, 24-64 years). The body weight ranged from 32 to 76 kg with mean body weight of 53.0 kg. The clinical tumor sizes, which were estimated by inspection and palpation varied from the diameter of 0.5 to 4.5 cm with mean diameter of 2.0 cm. The mean intraoperative estimated blood loss and mean perioperative blood transfusions were 1,339 ml (range, 700 to 8,000 ml) and 2.58

units (range, 0 to 17 units), respectively. The perioperative blood transfusion rate was 83.9 per cent. The number of lymph nodes removed range from 19 to 23 lymph nodes with mean of 20.9 nodes.

The microscopic extension of tumor cells into the parametria and surgical margins were found 0.37 per cent (1 case) and 0.7 per cent (2 cases), respectively the pelvic lymph nodes metastasis rate was 5.5 per cent (15 cases).

The clinical tumor size, using cut point of less than or equal 3 cm in diameter and more than 3 cm in diameter was not found to be associated with the potential prognostic factors : such as pelvic lymph nodes metastasis, surgical margins tumor involvement, grade of cellular differentiation, parametrial tumor involvement, estimated blood loss and present of perioperative blood transfusions, are shown in Table 4-1.

Table 4-1   The associations of clinical tumor size and some prognostic factors

Prognostic factors	Clinical tumor size (n)		P-value
	≤ 3 cm	> 3 cm	
Pelvic nodes metastases			
No	255	3	1.00*
Yes	15	0	
Surgical margins			
Free	268	3	1.00*
Not free	2	0	
Grade of differentiation			
Well differentiation	168	1	0.201*
Moderately differentiation	66	2	
Poorly differentiation	36	0	
Parametrial involvement			
No	269	3	1.00*
Yes	1	0	
Blood transfusion			
No	44	0	1.00*
Yes	226	3	
Estimated blood loss			
≤ 1,000 ml	79	1	1.00*
> 1,000 ml	191	2	

* = Fisher exact test

For the continuous variables of age, body weight clinical tumor size and estimated blood loss, cut points were used to transform the data into categlory variables. The data for age was subclassified into 2 groups: ≤35 years and >35 years according to previous report from literature review (37). The body weight was analysed for 2 groups : ≤ 50 kg and > 50 kg. The clinical tumor size was initially subclassified into 2 groups : diameter of ≤4 cm and >4 cm, according to FIGO staging, IB1 and IB2. After preliminary analysis, the tumor size of more than 4 cm was scarcely found. The cut point of tumor size was therefore reduced to ≤3 cm and > 3 cm in diameter. The cut point of ≤1,000 ml and > 1,000 ml was used for estimated blood loss.

Outcome : overall survival (OS)

The characteristic of dead and survived groups were not different in terms of the potential prognostic factors, except for pelvic lymph nodes metastasis (P < 0.001) (Table 4-2).

Table 4-2   Characteristics of patients who survived and died

Prognostic factors	Number of patient		P-value
	Survived	Dead (%)	
Age (yr)			
≤ 35	59	5 (7.8)	1.00
> 35	191	18 (8.6)	
Weight (kg)			
≤ 50	77	6 (7.2)	0.638
> 50	173	17 (9.0)	
Cell type			
Squamous	182	17 (8.5)	0.350*
Adenocarcinoma	59	4 (6.4)	
Others	9	2 (18.2)	

Table 4-2   Characteristics of patients who survived and died (Cont'd)

Prognostic factors	Number of patient		P-value
	Survived	Dead (%)	
Grade of differentiation			
Well differentiation	155	14 (8.3)	0.371*
Moderate differentiation	64	4 (5.9)	
Poorly differentiation	31	5 (13.9)	
Tumor size (cm)			
≤ 3	247	23 (8.5)	1.00*
> 3	3	0 (0)	
Surgical margin			
Free	249	22 (8.1)	0.162*
Not free	1	1 (50)	
Pelvic nodes metastasis			
No	242	16 (6.2)	<0.001
Yes	8	7 (46.7)	
Parametrial involvement			
No	249	23 (8.5)	1.00*
Yes	1	0 (0)	
Blood transfusion			
No	41	3 (6.8)	1.00*
Yes	209	20 (8.7)	
Estimated blood loss (ml)			
≤ 1,000	75	5 (6.3)	0.405
> 1,000	175	18 (9.3)	

* = Fisher exact test

Figure 4-1 shows overall survival of all patients. Twenty-three patients were followed up to death, given the death rate of 8.4 per cent. The overall 5-yr survival rate was 89.16 per cent (95% CI 83.16 to 93.11).

Kaplan-Meier survival estimate
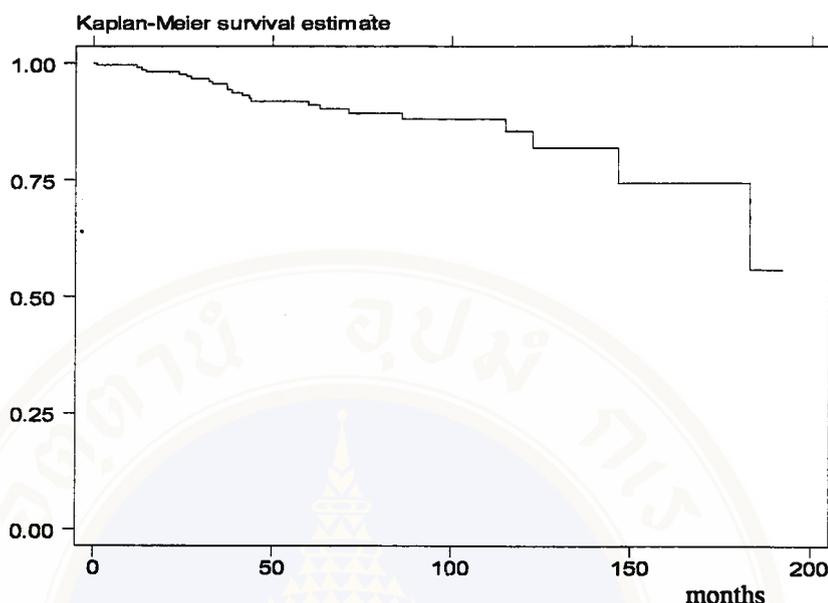
Figure 4-1   Overall survival curve (months) of all patients

In univariate analysis, age, weight, cell type, grade of differentiation, clinical tumor size, surgical margin, parametrial involvement, blood transfusion and estimated blood loss had no significance for overall survival. Only pelvic nodes metastasis was the significant prognostic factor for overall survival (Table 4-3).

Table 4-3   Overall survival of stage IB cervical cancer patients treated with radical hysterectomy

Prognostic factors	Median survival months	5-yr survival %	95% CI	P-value
Age (yr)				
≤ 35	122.7	92.5	78.0-97.6	0.703
> 35	146.3	88.1	80.8-92.8	
Weight (kg)				
≤ 50	182.9	90.1	77.1-95.9	0.509
> 50	NE	88.1	81.1-93.4	
Cell type				
Squamous	182.9	87.7	79.8-92.6	0.211
Adenocarcinoma	NE	95.7	83.8-98.9	
Others	NE	76.1	32.3-93.6	

Table 4-3   Overall survival of stage IB cervical cancer patients treated with radical hysterectomy (Cont'd)

Prognostic factors	Median survival months	5-yr Survival %	95% CI	P-value
Grade of differentiation				
Well	>182.9	88.6	80.1-93.6	0.438
Moderately	>122.7	93.6	81.0-97.9	
Poorly	>122.7	83.5	61.1-93.6	
Tumor size (cm)				
≤ 3	146.5	89.1	83.0-93.0	0.651
> 3	NE	100	NE	
Surgical margin				
Free	>146.5	89.9	84.1-93.7	0.142
Not free	63.1	50.0	0.6-91.0	
Pelvic nodes metastasis				
No	>182.1	91.4	85.5-94.9	<0.001
Yes	146.5	64.5	34.5-83.4	
Parametrial involvement				
No	>146.5	89.1	83.1-93.1	0.690
Yes	NE	100.0	NE	
Blood transfusion				
No	NE	89.5	70.6-96.5	0.977
Yes	>146.5	89.2	82.6-93.5	
Estimated blood loss (ml)				
No	NE	89.5	76.2-95.6	0.821
Yes	>146.5	89.2	81.9-93.7	

NE = Not evaluable

Figure 4-2 shows comparison of overall survival curves of patients with age ≤35 years and >35 years. The Log-rank test for equality of survivor function showed no significant difference.

Kaplan-Meier survival estimates,

Figure 4-2   Comparison of overall survival curves of patients with age ≤35 years and >35 years

Figure 4-3 shows comparison of overall survival curves of patients with weight ≤ 50 kg and >50 kg. The Log-rank test for equality of survivor function showed no significant difference.

Kaplan-Meier survival estimates

Figure 4-3   Comparison of overall survival curves of patients with weight ≤50 kg and >50 kg

Figure 4-4 shows comparison of overall survival curves of patients with three

cell types. The Log-rank test for equality of survivor function showed no significant

difference.

Kaplan-Meier survival estimates
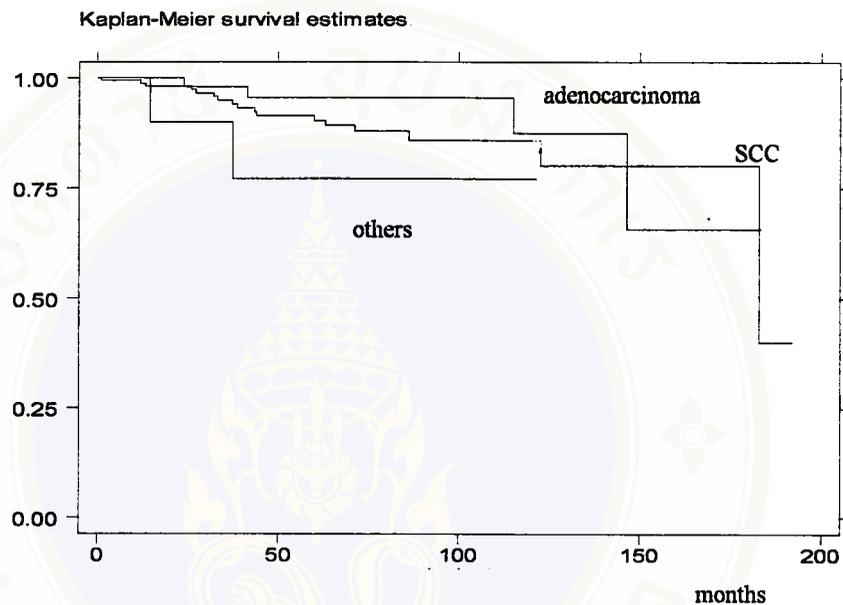
Figure 4-4   Comparison of overall survival curves of patients with three cell types

Figure 4-5 shows comparison of overall survival curves of patients with three

degrees of differentiation. The Log-rank test for equality of survivor function showed

no significant difference.

Kaplan-Meier survival estimates

Figure 4-5   Comparison of overall survival curves of patients with three degrees of differentiation

Figure 4-6 shows comparison of overall survival curves of patients with tumor size ≤3 cm and >3 cm. The Log-rank test for equality of survivor function showed no significant difference.
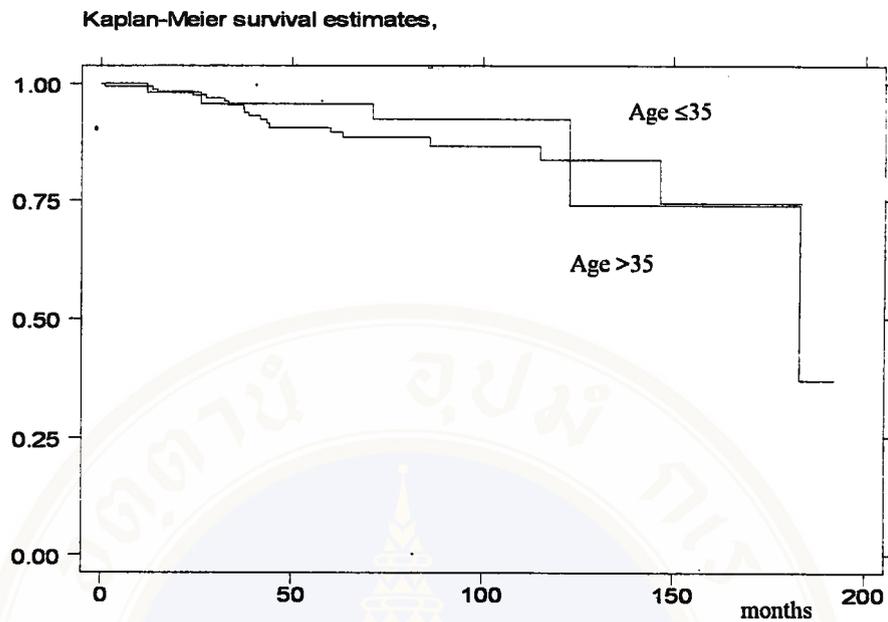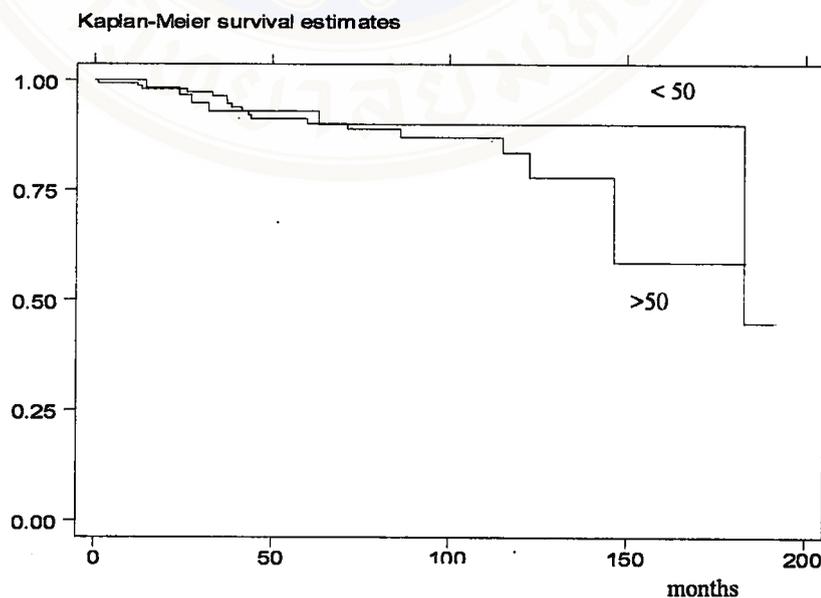
Kaplan-Meier survival estimates,
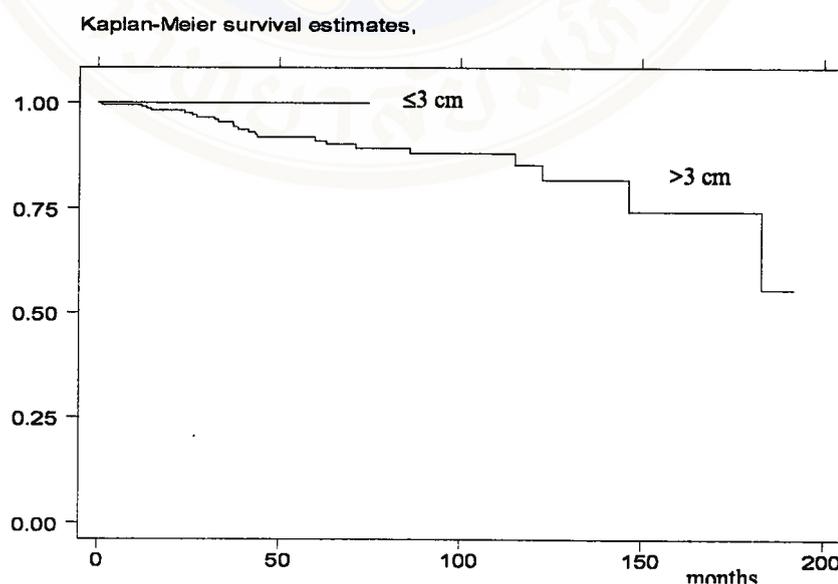
Figure 4-6   Comparison of overall survival curves of patients with tumor size ≤3 cm and >3 cm

Figure 4-7 shows comparison of overall survival curves of patients with free and not free surgical margins. The Log-rank test for equality of survivor function showed no significant difference.

Kaplan-Meier survival estimates,
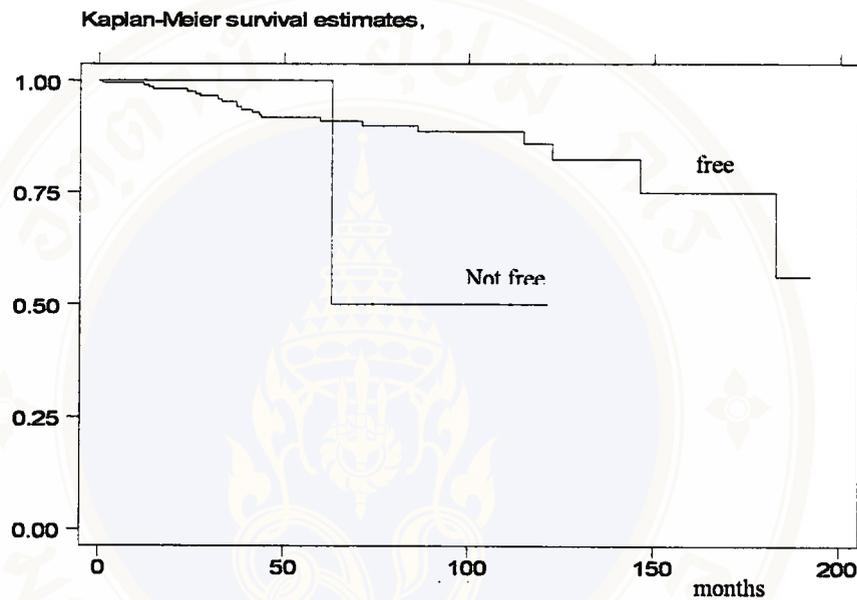
Figure 4-7   Comparison of overall survival curves of patients with free and not free surgical margins

Figure 4-8 shows comparison of overall survival curves of patients with no and present of pelvic nodes metastasis. The Log-rank test for equality of survivor function showed significant difference.

Kaplan-Meier survival estimates
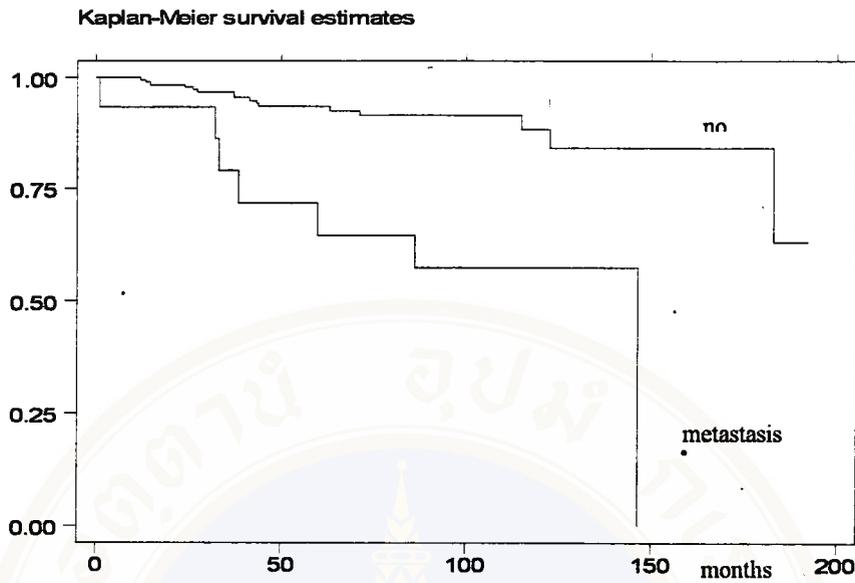
Figure 4-8   Comparison of overall survival curves of patients with no and present of pelvic nodes metastasis

Figure 4-9 shows comparison of overall survival curves of patients with no and presence of parametrial involvement. The Log-rank test for equality of survivor function showed no significant difference.

Kaplan-Meier survival estimates
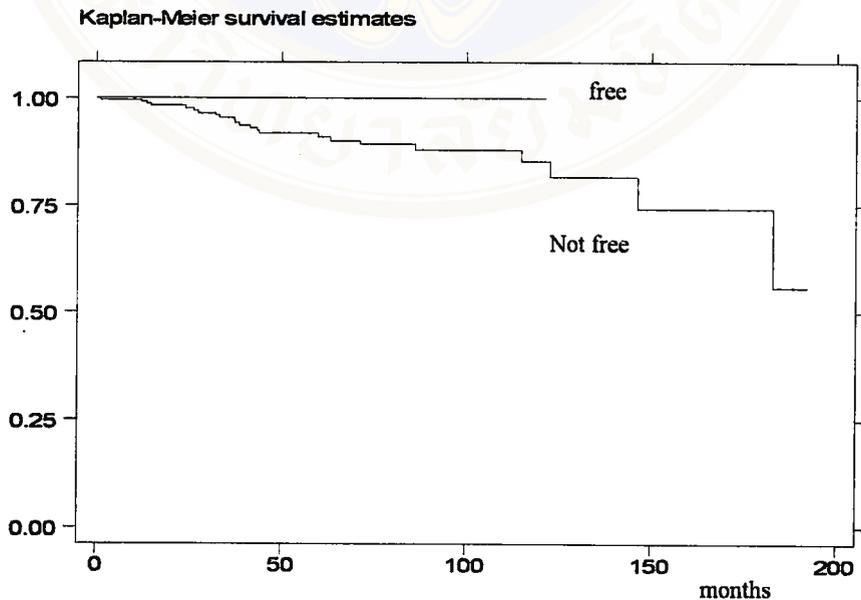
Figure 4-9   Comparison of overall survival curves of patients with no and present of parametrial involvement

Figure 4-10 shows comparison of overall survival curves of patients with and without blood transfusion. The Log-rank test for equality of survivor function showed no significant difference.
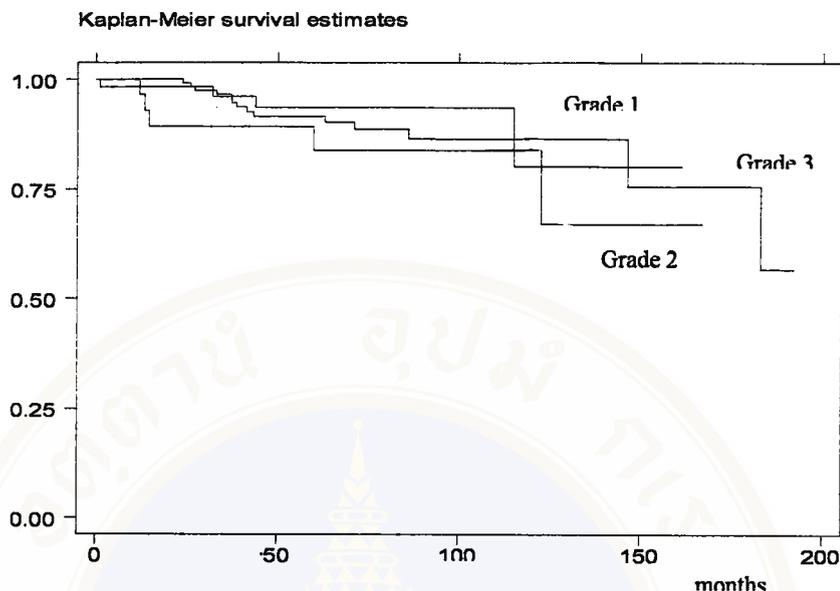

Kaplan-Meier survival estimates
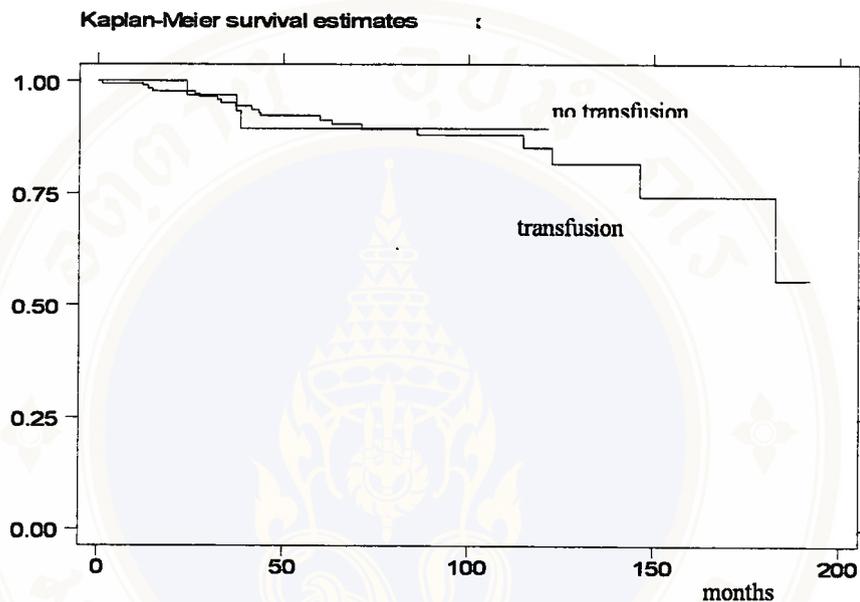
Figure 4-10   Comparison of overall survival curves of patients with and without blood transfusion

Figure 4-11 shows comparison of overall survival curves of patients with estimated blood loss ≤1,000 and >1,000 ml. The Log-rank test for equality of survivor function showed no significant difference.
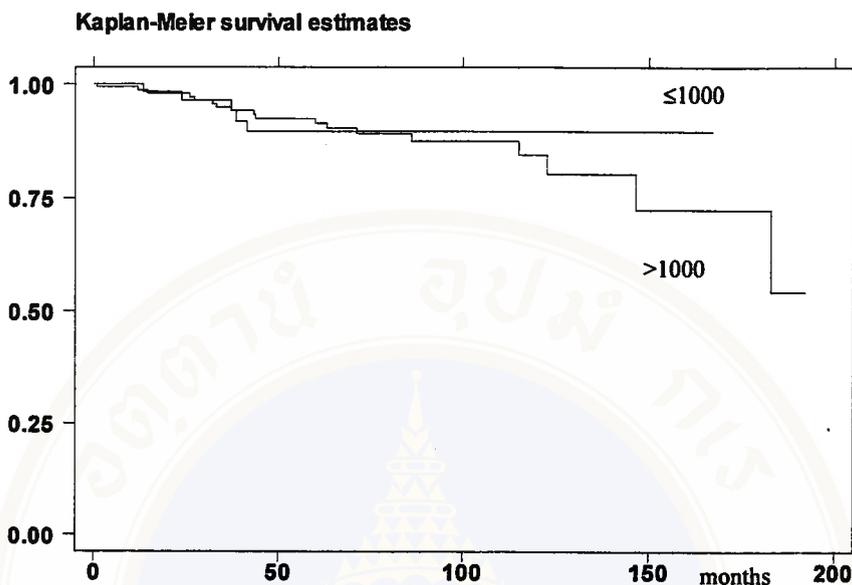
Figure 4-11   Comparison of overall survival curves of patients with estimated blood loss ≤1,000 and >1,000 ml

In univariate analysis, the hazard ratio of pelvic node metastasis were found statistical significant only, as shown in Table 4-4.

Table 4-4   Hazard ratio and 95 per cent confidence interval of the prognostic factors (univariate analysis, overall survival)

Prognostic factors	Hazard ratio (HR)	95% CI	P-value
Age (≤35 yr.*)	1.21	0.44-3.30	0.703
Weight (≤50 kg*)	1.37	0.53-3.53	0.511
Cell type (squamous*)	0.98	0.46-2.08	0.950
Grade (well differentiate*)	1.24	0.72-2.12	0.774
Tumor size (≤3 cm*)	1.24×10^{-14}	-	1.000
Surgical margins (free*)	4.03	0.54-30.24	0.176
Pelvic nodes metastasis (no*)	5.48	2.22-13.55	<0.001
Parametrial involvement (no*)	1.68×10^{-15}	-	1.000
Blood transfusion (no*)	0.98	0.29-3.37	0.977
Estimated blood loss (≤1000ml*)	1.22	0.41-3.06	0.821

* = reference group in analysis

The hazard ratio of main interested prognostic factors, which was pelvic nodes involvement, was 5.48 (95% CI, 2.22 to 13.55). After adjusting for each potential confounder, the adjusted hazard ratios for pelvic nodes metastasis were minimally changed and did not show confounding effect (i.e. confounding index <1.15) as shown in Table 4-5.

Table 4-5   Hazard ratios (HR) of pelvic nodes metastasis (PNM) adjusted for each potential confounder and confounding index

Adjusted factors	Adjusted HR of PNM	Confounding Index
Age	5.47	1.00
Weight	5.58	1.02
Cell type	5.56	1.01
Grade	5.39	1.02
Tumor size	5.43	1.01
Surgical margins	5.26	1.04
Parametrial involvement	6.00	1.09
Blood transfusion	5.48	1.00
Estimated blood loss	5.76	1.05

Because all of the studied prognostic factors are clinically significant, they were all calculated in Cox multivariate analysis (77). Evaluated in Cox's proportional hazards model, pelvic nodes metastasis was highly significant (P < 0.001, hazard ratio (HR) = 6.42, 95% confidence interval 2.32 to 17.79) as well as surgical margins (P = 0.01, HR = 18.66, 95% confidence interval 1.94 to 179.37), while none of other factors obtained significance, as shown in Table 4-6.

Table 4-6   Hazard ratios (HR) of prognostic factor, Cox proportional hazards model

Prognostic factors	HR (95% CI)	P-value
Age	0.99 (0.35-2.75)	0.978
Weight	1.11 (0.37-3.33)	0.852
Cell type	1.12 (0.50-2.48)	0.784
Grade	1.23 (0.70-2.16)	0.466
Tumor size	2.14×10^{-18} (0)	1.000
Surgical margins	18.66 (1.94-179.37)	0.011*
Pelvic nodes metastasis	6.42 (2.32-17.79)	<0.001*
Parametrial involvement	1.86×10^{-20} (0)	1.000
Blood transfusion	1.09 (0.30-4.03)	0.893
Estimated blood loss	0.74 (0.24-2.28)	0.603

* = Statistically significant

The most important assumption of the Cox proportional hazards model is that the hazard ratio is proportional over time. If the hazard of dying of pelvic nodes metastasis in the dead group was 6.42 times the rate as for the survived group (HR = 6.42), the proportional hazards assumption implied that this ratio is the same at any point on the time scale. The test of proportional hazards implemented in this study is based on the generalization by Gambsch and Therneau (78). The null hypothesis of zero slope in appropriate regression was tested, which was equivalent to testing that the log hazard ratio function is constant over time. The Table 4-7 showed both covariate-specific and global tests. There were no evidence that the proportional hazards assumption had been violated.

Table 4-7   **Tests for proportional hazards assumption in details and global tests**

	Rho	χ^2	Prob > χ^2
Age	-0.16598	0.54	0.4634
Weight	0.23146	1.68	0.1943
Tumor size	0.29506	0.00	1.0000
Cell type	-0.16698	1.03	0.3105
Grade	-0.22229	1.52	0.2176
Surgical margin	0.25357	1.39	0.2387
Parametrial involvement	-0.16057	0.00	1.0000
PNM	-0.04804	0.06	0.8029
Blood transfusion	-0.03506	0.02	0.8807
Estimated blood loss	0.07119	0.10	0.7578
Global test	**5.11**	**10**	**0.8835**

Outcome : relapse-free survival (RFS)

The characteristic of dead and survived groups were not different in terms of the potential prognostic factors, except for pelvic lymph nodes metastasis (P < 0.001) (Table 4-8).

Table 4-8   **Characteristic of patients who had no recurrence and recurrence after treatment of stage IB cervical cancer with radical hysterectomy**

Prognostic factors	Number of patient		P-value
	No recurrence	Recurrence	
Age (yr)			
≤ 35	58	6 (9.4)	0.711
> 35	186	23 (11.0)	
Weight (kg)			
≤ 50	76	7 (8.4)	0.438
> 50	168	22 (11.6)	
Cell type			
Squamous	178	21 (10.6)	0.158
Adenocarcinoma	58	5 (7.9)	
Others	8	3 (27.3)	

Table 4-8   Characteristic of patients who had no recurrence and recurrence after treatment of stage IB cervical cancer with radical hysterectomy (Cont'd)

Prognostic factors	Number of patient		P-value
	No recurrence	Recurrence	
Grade of differentiation			
Well differentiation	153	16 (9.5)	0.443
Moderate differentiation	61	7 (10.3)	
Poorly differentiation	30	6 (16.7)	
Tumor size (cm)			
≤ 3	241	29 (10.7)	1.00
> 3	3	0 (0)	
Surgical margin			
Free	243	28 (10.3)	0.202
Not free	1	1 (50.0)	
Pelvic nodes metastasis			
No	236	22 (8.5)	<0.001*
Yes	8	7 (46.7)	
Parametrial involvement			
No	243	29 (10.7)	1.00
Yes	1	0 (0)	
Blood transfusion			
No	39	5 (11.4)	0.862
Yes	205	24 (10.5)	
Estimated blood loss (ml)			
No	72	8 (10.0)	0.830
Yes	172	21 (10.9)	

* = Statistically significant

Figure 4-12 shows relapse-free survival curve of all patients. Twenty-nine patients were followed up to recurrent, given the recurrent rate of 10.6 per cent. The 5-yr relapse-free survival rate was 87.71 per cent (95% CI 81.83 to 91.78).

Kaplan-Meier survival estimate
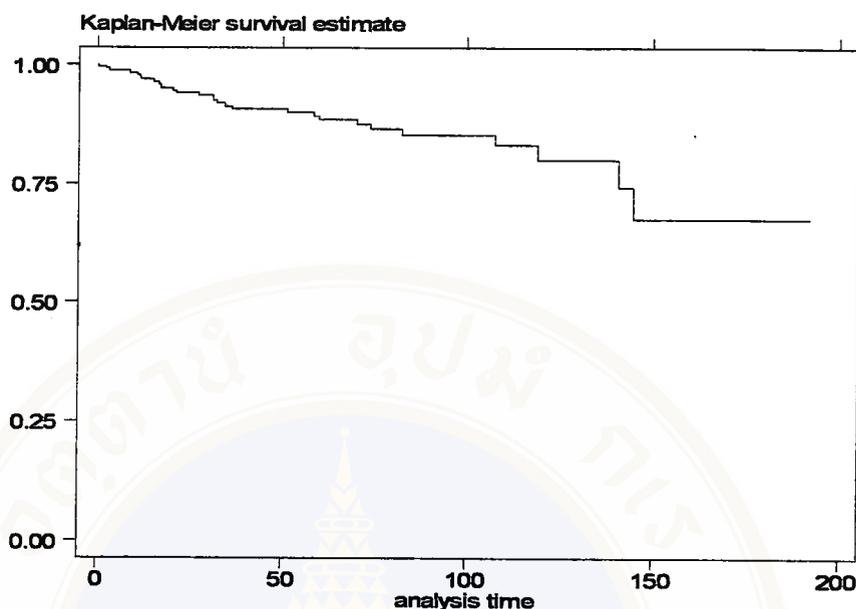
Figure 4-12   Relapse-free survival curve of all patients

In univariate analysis, age, weight, cell type, grade of differentiation, clinical tumor size, surgical margin parametrial involvement, blood transfusion and estimated blood loss all were not significant for relapse-free survival. Only pelvic nodes metastasis was the significant prognostic factor for relapse-free survival (Table 4-9).

Table 4-9   Relapse-free survival of stage IB cervical cancer patients treated with radical hysterectomy

Prognostic factors	Median survival (months)	5-yr relapse-free Survival (%)	95% CI	P-value
Age (yr)				
≤ 35	144.9	91.7	78.6-97.0	0.663
> 35	>140.8	86.4	79.3-91.2	
Weight (kg)				
≤ 50	>144.9	91.3	80.0-96.4	0.315
> 50	>140.8	86.2	78.7-91.2	
Cell type				
Squamous	>144.9	86.7	79.1-91.7	0.105
Adenocarcinoma	>140.8	94.0	82.5-98.0	
Others	>31.2	69.2	31.5-89.0	

Table 4-9   Relapse-free survival of stage IB cervical cancer patients treated
with radical hysterectomy (Cont'd)

Prognostic factors	Median survival (months)	5-yr relapse-free Survival (%)	95% CI	P-value
Grade of differentiation				
Well	>144.8	89.3	81.6-93.9	0.591
Moderately	NE	86.7	72.3-93.9	
Poorly	>119	82.4	61.6-92.5	
Tumor size (cm)				
≤ 3	>140.8	87.6	81.7-91.7	0.613
> 3	NE	100.0	NE	
Surgical margin				
Free	>140.8	88.3	82.5-92.3	0.247
Not free	58.5	50.0	0.6-91.0	
Pelvic nodes metastasis				
No	NE	89.7	83.9-93.5	0.004*
Yes	140.8	64.5	34.5-83.4	
Parametrial involvement				
No	>140.8	87.6	81.7-91.7	0.636
Yes	NE	100.0	NE	
Blood transfusion				
No	NE	84.7	67.0-93.4	0.577
Yes	>140.8	88.5	82.0-92.7	
Estimated blood loss (ml)				
No	NE	86.2	74.1-92.9	0.750
Yes	>140.8	88.5	81.4-93.1	

NE = Not evaluable

* = Statistically significant

Figure 4-13 shows comparison of relapse-free survival curves of patients with

age ≤35 years and >35 years. The Log-rank test for equality of survivor function

showed no significant difference.

Kaplan-Meier survival estimates,

Figure 4-13   Comparison of relapse-free survival curves of patients with age ≤ 35 years and >35 years

Figure 4-14 shows comparison of relapse-free survival curves of patients with weight ≤50 kg and >50 kg. The Log-rank test for equality of survivor function showed no significant difference.

Kaplan-Meier survival estimates,

Figure 4-14   Comparison of relapse-free survival curves of patients with weight ≤50 kg and >50 kg

Figure 4-15 shows comparison of relapse-free survival curves of patients with three cell types. The Log-rank test for equality of survivor function showed no significant difference.
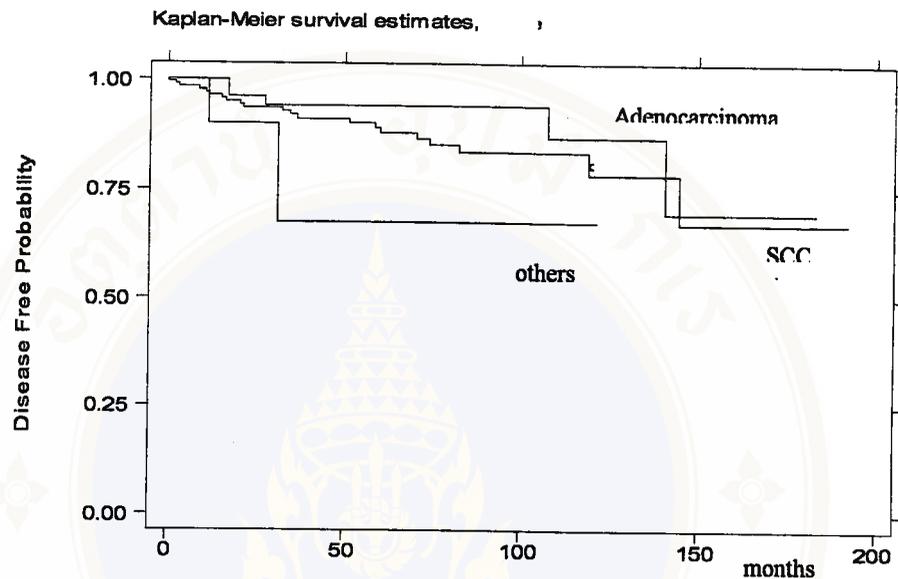
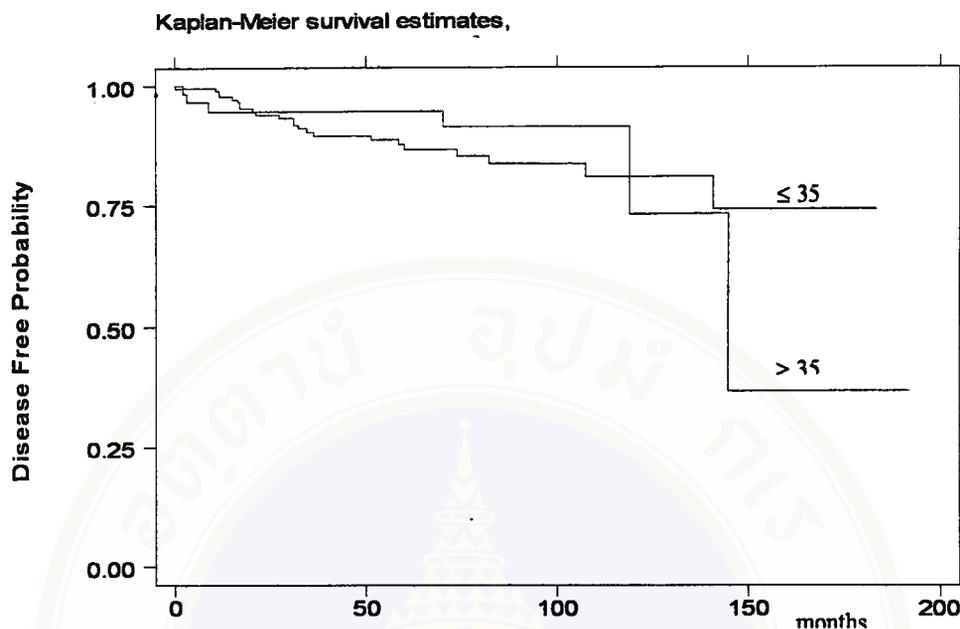**Figure 4-15   Comparison of relapse-free survival curves of patients with three cell types**

Figure 4-16 shows comparison of relapse-free survival curves of patients with three degrees of differentiation. The Log-rank test for equality of survivor function showed no significant difference.

Kaplan-Meier survival estimates,
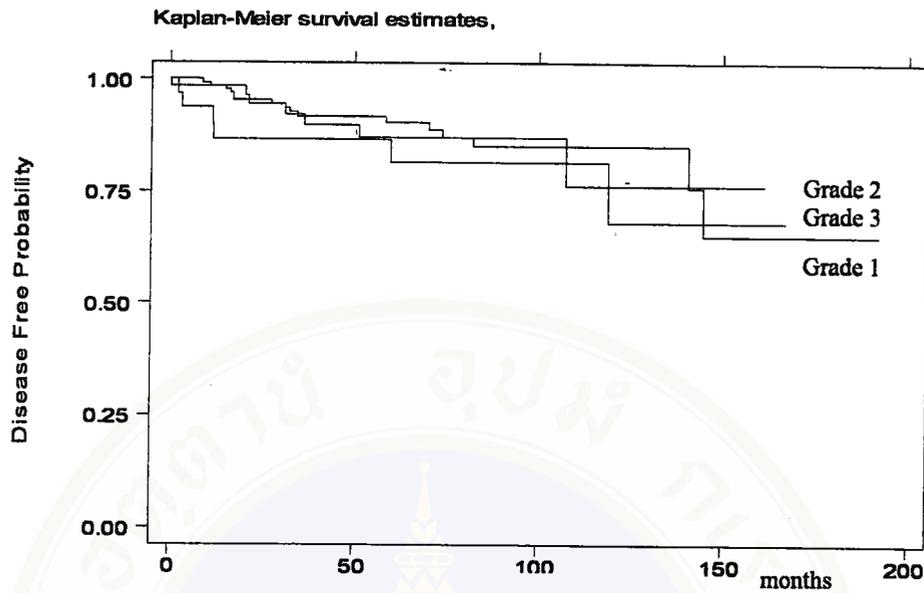
Figure 4-16   Comparison of relapse-free survival curves of patients with three degrees of differentiation

Figure 4-17 shows comparison of relapse-free survival curves of patients with tumor size ≤3 cm and >3 cm. The Log-rank test for equality of survivor function showed no significant difference.
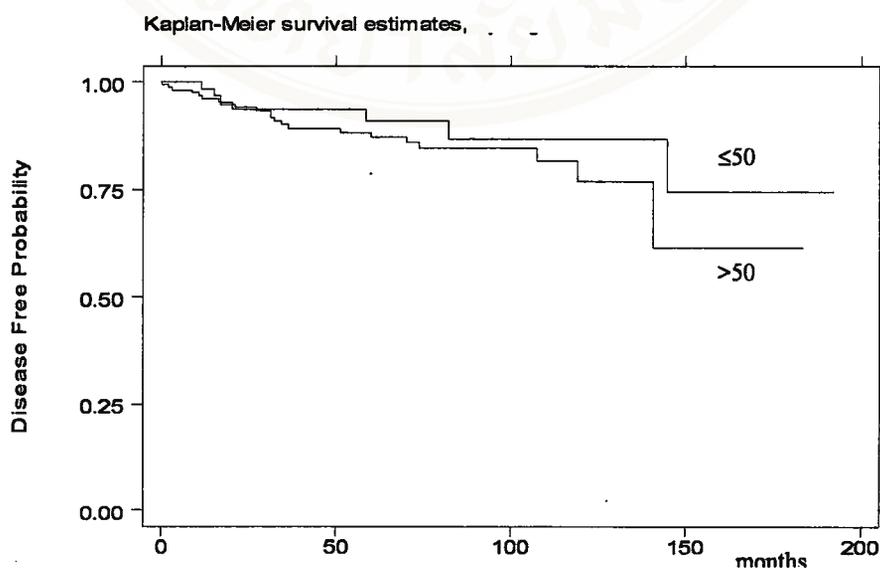
Kaplan-Meier survival estimates,

Figure 4-17   Comparison of relapse-free survival curves of patients with tumor size ≤3 cm and >3 cm

Figure 4-18 shows comparison of relapse-free survival curves of patients with free and not free surgical margin. The Log-rank test for equality of survivor function showed no significant difference.
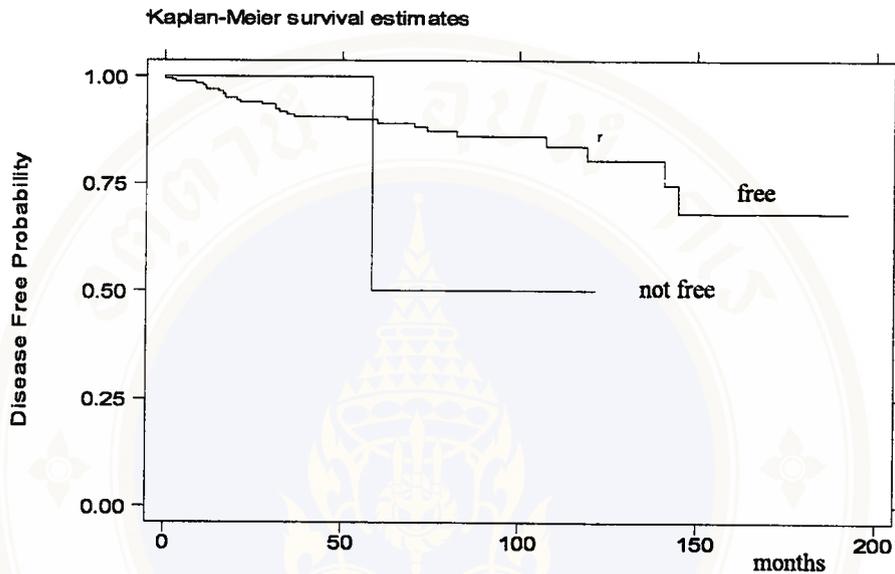
Figure 4-18   Comparison of relapse-free survival curves of patients with free and not free surgical margin

Figure 4-19 shows comparison of relapse-free survival curves of patients with no and present of pelvic nodes metastasis. The Log-rank test for equality of survivor function showed significant difference.

Kaplan-Meier survival estimates,
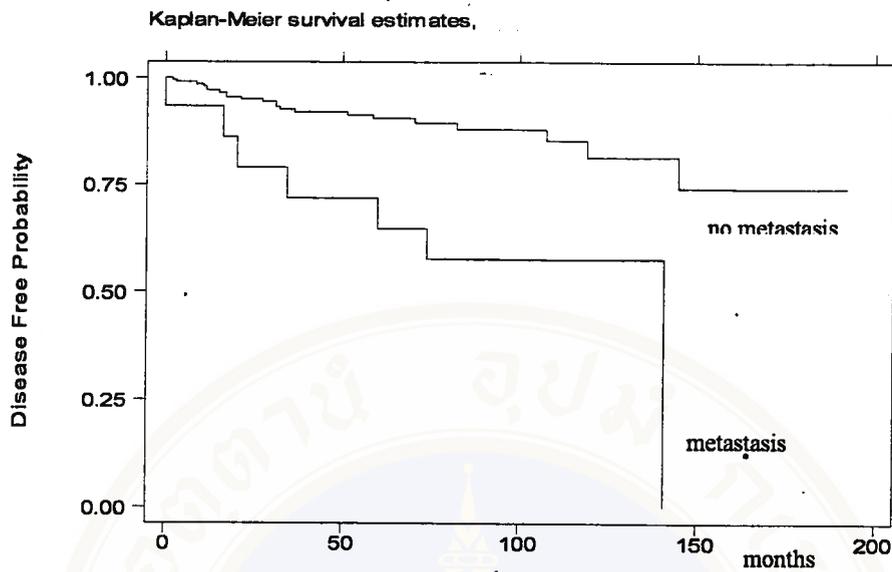
Figure 4-19   Comparison of relapse-free survival curves of patients with no and present of pelvic nodes metastasis

Figure 4-20 shows comparison of relapse-free survival curves of patients with no and present of parametrial involvement. The Log-rank test for equality of survivor function showed no significant difference.

Kaplan-Meier survival estimates
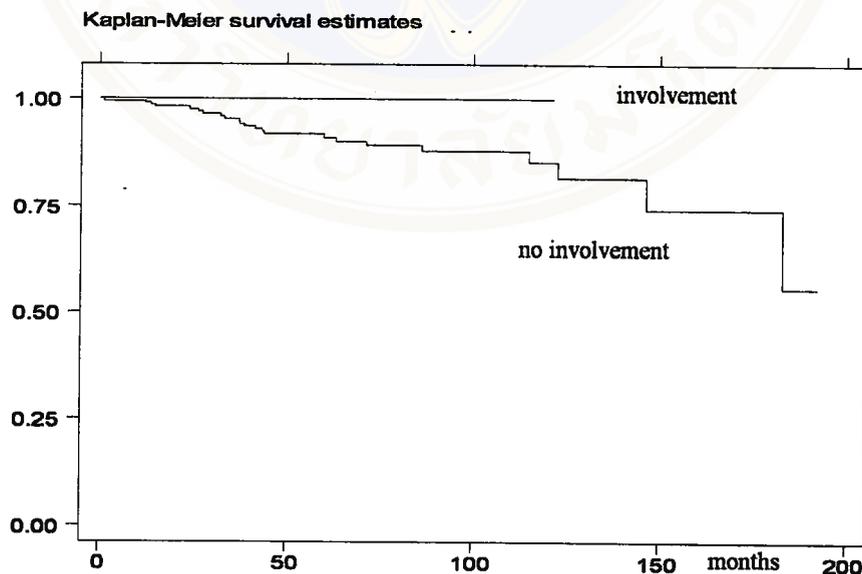
Figure 4-20   Comparison of relapse-free survival curves of patients with no and present of parametrial involvement

Figure 4-21 shows comparison of relapse-free survival curves of patients with and without blood transfusion. The Log-rank test for equality of survivor function showed no significant difference.
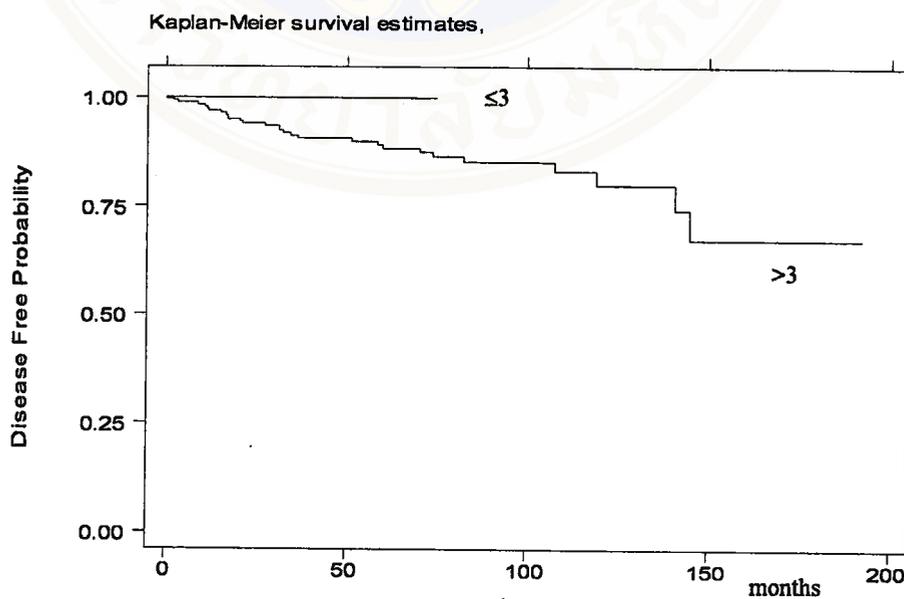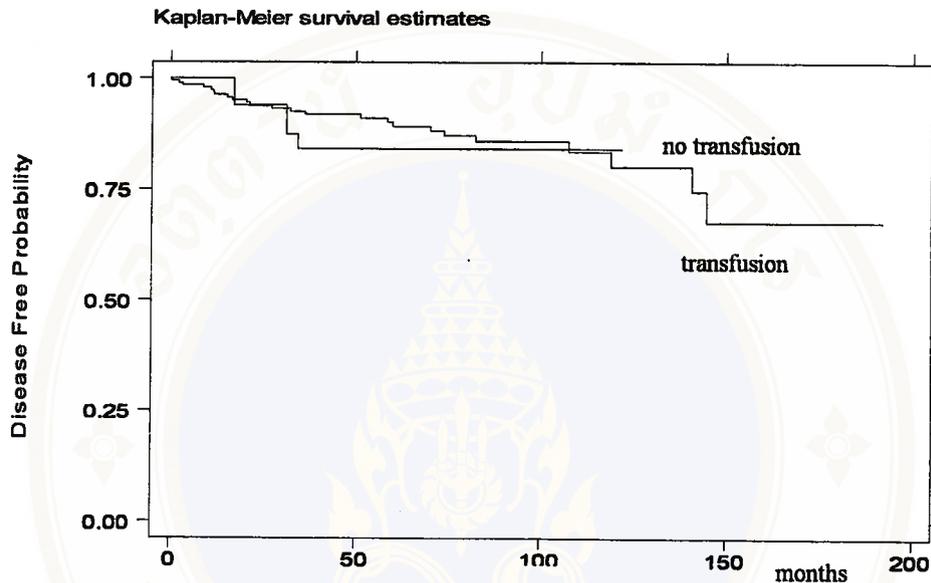

Figure 4-21   Comparison of relapse-free survival curves of patients with and without blood transfusion

Figure 4-22 shows comparison of relapse-free survival curves of patients with estimated blood loss ≤1,000 and >1,000 ml. The Log-rank test for equality of survivor function showed no significant difference.
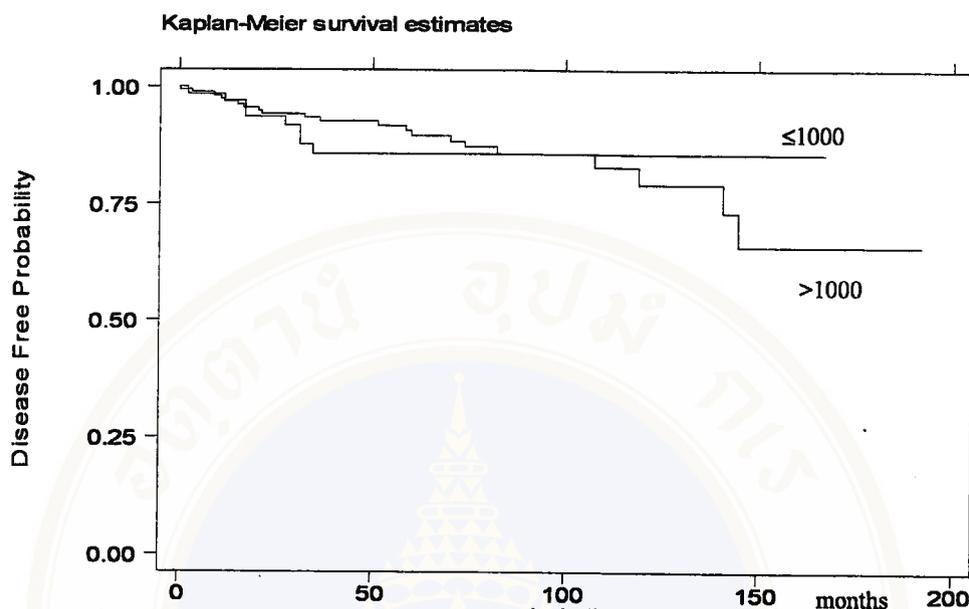
Figure 4-22   Comparison of relapse-free survival curves of patients with estimated blood loss ≤1,000 and >1,000 ml

In univariate analysis, the hazard ratio of the prognostic factors were found statistical significant for pelvic nodes metastasis, as shown in Table 4-10.

Table 4-10   Hazard ratio and 95 per cent confidence interval of the prognostic factors, univariate analysis, relapse-free survival

Prognostic factors	Hazard ratio (HR)	95% CI	P-value
Age	1.22	0.50-3.00	0.66
Weight	1.55	0.65-3.69	0.318
Cell type	1.11	0.58-2.11	0.752
Grade	1.26	0.74-1.99	0.333
Tumor size	1.24×10^{-14}	0	1.000
Surgical margins	3.08	0.41-22.89	1.099
Pelvic nodes metastasis	4.18	1.76-9.91	0.001
Parametrial involvement	4.55×10^{-15}	0	1.000
Blood transfusion	0.76	0.28-2.02	0.578
Estimated blood loss	0.88	0.38-1.99	0.751

The hazard ratio of main interested prognostic factors, which was pelvic nodes involvement, was 4.18 (95% CI, 1.76 to 9.91). After adjusted for each of prognostic factors, the adjusted hazard ratios for pelvic nodes metastasis were minimally changed and did not show confounding effect (i.e. confounding index <1.15) from other prognostic factors, as shown in Table 4-11.

Table 4-11   Hazard ratios (HR) of pelvic nodes metastasis (PNM) adjusted for another one prognostic factor and confounding index

Adjusted factors	Adjusted HR of PNM	Confounding Index
Age	4.15	1.00
Weight	3.95	1.06
Cell type	4.17	1.00
Grade	4.10	1.02
Tumor size	4.14	1.01
Surgical margins	4.08	1.02
Parametrial involvement	4.64	1.11
Blood transfusion	4.20	1.00
Estimated blood loss	4.58	1.10

Because all of the studied prognostic factors are clinical significant, they were all calculated in Cox multivariate analysis. The pelvic nodes metastasis was highly significant (P = 0.001, hazard ratio, HR = 4.73, 95% confidence interval 4.84 to 12.11) and also surgical margins was significant (P = 0.008, HR = 19.59, 95% confidence interval 2.15 to 178.6), while other factors were not significant, as shown in Table 4-12.

Table 4-12   Hazard ratios (HR) of prognostic factor, Cox proportional hazards model

Prognostic factors	HR (95% CI)	P-value
Age	1.04 (0.41-2.59)	0.938
Weight	1.35 (0.51-3.56)	0.548
Cell type	1.23 (0.63-2.40)	0.546
Grade	1.28 (0.79-2.06)	0.314
Tumor size	3.13×10^{-15} (0)	1.000
Surgical margins	19.59 (2.15-178.6)	0.008 *
Pelvic nodes metastasis	4.73 (1.84-12.11)	0.001 *
Parametrial involvement	2.58×10^{-17} (0)	1.000
Blood transfusion	0.91 (0.32-2.57)	0.858
Estimated blood loss	0.68 (0.27-1.71)	0.416

* = Statistically significant

For the tests of the assumption of the Cox proportional hazards model, the Table 4-13 showed both covariate-specific and global tests. There were no evidence that the proportional hazards assumption had been violated.

Table 4-13   Tests for proportional hazards assumption in details and global tests

	Rho	χ^2	Prob $> \chi^2$
Age	-0.02037	0.01	0.9134
Weight	0.01652	0.01	0.9223
Tumor size	0.20159	0.00	1.0000
Cell type	-0.07887	0.26	0.6105
Grade	-0.25990	2.36	0.1243
Surgical margin	0.14449	0.59	0.4421
Parametrial involvement	-0.18569	0.00	1.0000
PNM	0.01299	0.01	0.9414
Blood transfusion	-0.18004	0.72	0.3975
Estimated blood loss	0.14709	0.47	0.4928
Global test	**4.40**	**10**	**0.9277**

CHAPTER V

DISCUSSION

1. Study results

This study was undertaken to evaluate prognostic factors in stage IB cervical cancer treated with radical hysterectomy and to evaluate the survival outcomes. There were 273 patients evaluated. The mean age was 40.9 years which quite almost similar to the previous report from this hospital in 1988 (39.4 years). This may be the effect of selection criteria for surgery in stage IB cervical cancer and natural history of cervical cancer which occurs early and usually in young women.

The mean body weight was 53.0 kg, range from 32 to 76 kg, which was the around average body weight of Thai women. No patients were found to be markedly obese because most of the obese cases were treated with radiotherapy according to the belief of expected difficulty in surgery. The body mass index (BMI), more accurate measurement for obesity, was not used due to no data of patients' height were available in the records. The average clinical tumor size was not large (mean of 2 cm in diameter) due to the selected criteria for surgery. The larger tumor size, the more pelvic lymph nodes metastasis was found (13). Finding of lymph nodes metastasis results in postoperative adjunctive irradiation treatment.

Estimated blood loss during operation was more than other gynecologic surgery (average 1,339 ml) with wide range (700 to 8,000 ml). In this study, the tumor size was not related to blood transfusion and blood loss during operations.

Postoperative radiotherapy was found in 17 case (6.23 per cent) and correlated to pelvic lymph node metastastatic rate (5.5 per cent). The microscopic extension of tumor cells into the parametria was rarely found, this result may be associated with the accuracy of clinical staging before surgery. The baseline characteristics of the two groups of patients, died or survived for overall survival and recurrent or not recurrent for relapse-free survival, were not statistically different (Table 4-2, Table 4-8), except the pelvic nodes metastasis. These metastasis were found more common in the worse survival outcomes.

In univariate analysis, only pelvic nodes metastasis was found to be associated with difference 5-year survival rates, both overall survival and relapse-free survival (Table 4-3, Table 4-9). To evaluate whether other factors might add further prognostic information, the pelvic nodes metastasis whereas other variable were treated as stratification variables. The results of adjusted hazard ratio for pelvic lymph nodes metastasis were not significantly changed, so the others factors did not show confounding effect, both in overall and relapse-free analysis.

Similar findings were obtained using Cox multivariate analysis. Surgical margins factor was added significantly in the model, but the wide ranges of 95 per cent confidence intervals (1.94-179.4 of overall survival, 2.15-178.6 of relapse-free survival) showed the low precision (Table 4-6, Table 4-12).

The pelvic lymph node metastasis was the only prognostic factor in this study, using multivariate analysis. The HR of 6.42 and 4.73 from overall and relapse-free survival outcomes was highly significant. This results agreed with previous reports (48, 49, 68, 69, 71). The prognostic factors for treatment failure, identified in this study, can be used as selection criteria for clinical trials to test the effects of other adjuvant treatments, such as chemotherapy. Patients with a single lower pelvic lymph node metastasis have a relatively good prognosis and may not need adjuvant treatment beyond radiation therapy. These prognostic factors should be considered in patient counseling and treatment planning. Based on these factors, a more aggressive treatment to improve survival in these subsets of high-risk patients might be justified. New therapeutic regimens and modalities aimed to overcome treatment failure should be investigated.

2. Possible sources of bias and limitations of the study

1. Selection bias

1.1 Referral bias

Because Ramathibodi Hospital is the referral center from the rural hospitals, the patients who were referred to this hospital may be different from other referral centers in according to age, health performance status, economical status, and others which may limit the external validity of the result of the study.

1.2 Selection for surgical treatment

The patients with large lesions were usually treated with radiotherapy, so few patients with large lesion were assigned for surgery. The association of the tumor lesion size and survival may be under estimated.

1.3 Loss to follow up

The assumption that the probability of death for the patients who remain through the study is the same as of those loss to follow up. The exact probabilities are not known. The test for comparing base-line characteristics between these two groups may increase the likelihood that the result of the study will be accurately estimated.

2. Information bias

2.1 Loss records

The missing informations can assumingly occur randomly. The imputation can be done by substitution the mean value of the complete observations for the unknown values.

3. Confounding variables

Though many new prognostic variables have been reported as described in the early pages, the measurement of these variables can not be done in this hospital. These factors which cannot be evaluate in this study, may have confounding effect on survival, such as human papilloma virus, etc.

CHAPTER VI

CONCLUSION

This study was undertaken to evaluate survival outcomes and prognostic factors of stage IB cervical cancer patients treated with radical hysterectomy and pelvic lymphadenectomy from January 1969 to December 1995, at Ramathibodi Hospital, Faculty of Medicine, Mahidol University. There were 273 patients evaluated. The mean age was 40.9 years which was quite almost similar to the previous reports. The mean body weight was 53 kg. The clinical tumor size was not large (mean of 2 cm in diameter) due to the selection criteria for surgery. The low pelvic node metastatic rate was found (5.5 per cent), together with low incidence of parametrial metastasis and tumor involvement at surgical margins (3.7 and 0.7 per cent respectively). These low incidence rate may lead to the results of being non-significant prognostic factor in multivariate analysis.

The base-line characteristics between the two groups of patients, died or alive and recurrent or not recurrent, were not statistically different, except the pelvic node metastasis.

The recurrent and dead rates were found 10.6 and 8.4 per cent. The reported 5-year survival and 5-year relapse-free survival rates of 89.2 and 87.5 per cent were similar to previous reviews.

In univariate analysis, only pelvic nodes metastasis was found to be associated with difference 5-year survival rates, both overall and relapse-free survivals. Other studied prognostic factors did not show confounding effect, both in overall and relapse-free survival.

The results of Cox multivariate analysis showed pelvic lymph node metastasis was remained independent prognostic factor for both survival outcomes. Surgical margins factor was also found to be a prognostic factor, with low precision.

These two prognostic factors should be considered in patient counseling and treatment planning. New adjuvant treatment regimens and modalities should be investigated to overcome treatment failure.

Limitation of the study

The selection bias espectially selection criteria for surgery, resulting in low incidence rate of some prognostic factors, may associated with being non-significant prognostic factors in multivariate analysis. The application of results of this study to other institute should be considered carefully.

Recommendation

The further study using larger sample size and larger follow up period should be investigated to minimize bias and confounders. The prospective data collection of new prognostic variables will enhance the validity of the study.

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APPENDIX

APPENDIX I

FIGO* STAGING FOR CARCINOMA OF THE CERVIX UTERI (1995)

STAGE	DESCRIPTION
Stage 0	Carcinoma in situ, intraepithelial carcinoma.
Stage I	The carcinoma is strictly confined to the cervix.
Stage IA	Invasive cancer identified only microscopically. All gross lesions even with superficial invasion are Stage IB cancers. Invasion is limited to measured stromal invasion with maximum depth of 5 mm and no wider than 7 mm.**
Stage IA1	Measured invasion of stromal no greater than 3 mm in depth and no wider than 7 mm.
Stage IA2	Measured invasion of stromal greater than 3 mm and no greater than 5 mm in depth, and no wider than 7 mm.
Stage IB	Clinical lesions confined to the cervix or pre-clinical lesions greater than Stage IA.
Stage IB1	Clinical lesion no greater than 4 cm in size.
Stage IB2	Clinical lesion greater than 4 cm in size.
Stage II	The carcinoma extends beyond the cervix but has not extended to the pelvic wall. The carcinoma involves the vagina but not as far as the lower third.
Stage IIA	No obvious parametrial involvement.
Stage IIB	Obvious parametrial involvement.
Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with a hydronephrosis or nonfunctioning kidney are included unless they are known to be due to other causes.
Stage IIIA	No extension to the pelvic wall.
Stage IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucous of the bladder or rectum. A bulbous edema as such does not permit a case to be allotted to stage IV.
Stage IVA	Spread of the growth to adjacent organs.
Stage IVB	Spread to distant organs.
*	FIGO, International Federation of Gynecology and Obstetrics.
**	The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.

APPENDIX II

DATA RECORD FORM

Data record form

Number _____

HN _____

Date of birth _____

Tumor size

Cell type

Surgical margin   ( ) free   ( ) not

Parametrial involvement ( ) yes   ( ) no

Pelvic lymph node metastases ( ) yes   ( ) no

Grade

Blood transfusion   ( ) yes   ( ) no

Blood transfusion _____ units

Date of diagnosis _____

Date of surgery _____

Date of complete RT _____

Coding

Number _____

HN _____

Age _____ years

    Age group

    $0 = \leq 35$, $1 = > 35$

Tumor size _____ cm

    $0 = \leq 4$ cm, $1 = > 4$ cm

Cell type: 1 = SCC

            2 = adeno CA

            3 = others

Surgical margin:

    0 = free, 1 = not free

Parametrial involvement:

    0 = no, 1 = positive

Pelvic lymph nodes metastases

    0 = no, 1 = yes

Grade:

1 = well differentiated

2 = moderately differentiated

3 = poorly differentiated

Blood transfusion:

    0 = no, 1 = yes

Transfusion _____ units

APPENDIX II (Cont'd)

Date of disease-recurrence diagnosed _____

	Recurrence-free survival ___ months
Date of last follow up.	Follow up time _____ months
Status at last FU	Status:

     ( ) lost to follow up   0 = loss to follow up

     ( ) dead from disease   1 = dead from disease

     ( ) dead from other causes   2 = dead from other causes

     ( ) alive with disease   3 = alive with disease

     ( ) alive without disease   4 = alive without disease

Recurrence   ( ) yes   ( ) no   Recurrence: 0 = no, 1 = yes

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