A COMPARISON OF SURVIVAL RATE IN CERVICAL CANCER PATIENTS TREATED BY STANDARD CONCURRENT RADIATION THERAPY WITH CISPLATIN BASED VERSUS STANDARD CONCURRENT RADIATION WITH CARBOPLATIN BASED

NUCHAPONG NOUMTONG

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OF THE REQUIREMENTS FOR
THE FEGREE OF MASTER OF SCIENCE (BIOSTATISTICS)
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A COMPARISON OF SURVIVAL RATE IN CERVICAL CANCER PATIENTS TREATED BY STANDARD CONCURRENT RADIATION THERAPY WITH CISPLATIN BASED VERSUS STANDARD CONCURRENT RADIATION WITH CARBOPLATIN BASED

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ABSTRACT

The primary objective of this research was compar the survival rate of cervical cancer patients treated by standard concurrent radiation therapy with cisplatin with the survival rate of patients treated by standard concurrent radiation with carboplatin. This was a retrospective cohort study using secondary data collected from medical records. The research included all the patients who had received treatment between January 1, 2002 and August 31, 2004; the cut-off point of follow up for survival times was September 12, 2006. There were 266 patients 80 (30.08%)in the cisplatin group and 186 (69.92%)carboplatin group . The follow-up time ranged from 1.48-55.21 months (median 31.66 months). The 75^{th} percentiles survival of overall group, cisplatin group and carboplatin group were 29.05, 25.18 and 30.39 months, respectively. There was no difference (*p-value* = 0.82, Log rank test) in the survival rate of the cisplatin and carboplatin groups. By Cox proportional hazard model, only response after treatment at 3^{rd} months had considerably difference (*p-value*<0.001).

The secondary objective was to compare the acute and late complications between the two treatment groups. There were four complications of statistical significance which carboplatin was reference based *i.e.* leukocytes (OR=3.87,*p-value*=0.007), creatinine (OR=2.55,*p-value*=0.05), nausea (OR=13.31,*p-value*=0.008) and vomit (OR=13.31,*p-value*=0.008). The last objective was to compare the late complications between the cisplatin group and the carboplatin group. The only complication which was statistically was mucous membrane (OR=1.15,*p-value*=0.026), which cisplatin was reference based.

KEY WORDS: SURVIVAL RATE/ ACUTE COMPLICATIONS/ LATE COMPLICATIONS/ CISPLATIN/ CARBOPLATIN

161 pp.

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การเปรียบเทียบอัตราการรอดชีพในผู้ป่วยมะเร็งปากมดลูกที่ได้รับการรักษาด้วยการฉายแสงและใส่แร่ควบคู่กับยาเคมีบำบัดกลุ่มซิสพลาติน เปรียบเทียบกับ กลุ่มผู้ป่วยที่ได้รับการฉายแสงและใส่แร่ควบคู่กับยาเคมีบำบัดกลุ่มคาร์โบพลาติน (A COMPARISON OF SURVIVAL RATE IN CERVICAL CANCER PATIENTS TREATED BY STANDARD CONCURRENT RADIATION THERAPY WITH CISPLATIN BASED VERSUS STANDARD CONCURRENT RADIATION WITH CARBOPLATIN BASED)

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บทคัดย่อ

การศึกษาครั้งนี้มีจุดประสงค์เพื่อศึกษาเปรียบเทียบอัตราการรอดชีพของผู้ป่วยมะเร็งปากมดลูกที่ได้รับการรักษาด้วยการฉายแสงและใส่แร่ตามมาตรฐานควบคู่กับยาเคมีบำบัดกลุ่มซีสพลาติน เปรียบเทียบกับการรักษาด้วยการฉายแสงและใส่แร่ตามมาตรฐานควบคู่กับยาเคมีบำบัดกลุ่มคาร์โบพลาติน ซึ่งข้อมูลที่นำมาวิเคราะห์นั้นเป็นข้อมูลทุติยภูมิจากข้อมูลประวัติการรักษา ข้อมูลผู้ป่วยที่ใช้ในการวิเคราะห์อยู่ในช่วงวันที่ 1 มกราคม 2545 ถึงวันที่ 31 สิงหาคม 2547 และติดตามดูสถานภาพการมีชีวิตจนถึงวันที่ 12 กันยายน 2549 ในการวิเคราะห์อัตราการรอดชีพ มีผู้ป่วย 266 คน แบ่งเป็นกลุ่มซีสพลาติน 80 (30.08%) คน ช่วงระยะเวลาการเฝ้าติดตามอยู่ระหว่าง 1.48-55.21 เดือน (ค่ามัธยฐาน เท่ากับ 31.66) อัตราการรอดชีพที่เปอร์เซ็นไทล์ 75 ของกลุ่มตัวอย่างทั้งหมดเท่ากับ 29.05 เดือน ของกลุ่มซิสพลาตินเท่ากับ 25.18 เดือน และ ของกลุ่มคาร์โบพลาตินเท่ากับ 30.39 เดือน เมื่อพิจารณาด้วยสถิติ Log rank ไม่พบความแตกต่างกันของอัตราการรอดชีพของยาทั้ง 2 กลุ่ม (*p-value*=0.82) และเมื่อพิจารณาด้วย Cox proportional hazard พบว่ามีเพียงตัวแปรผลการรักษาที่ 3 เดือนเท่านั้นที่มีความแตกต่างทางสถิติ (*p-value*<0.001)

วัตถุประสงค์รองในการศึกษาเปรียบเทียบความแตกต่างระหว่างยา 2 กลุ่มได้แก่อาการ leukocytes โดยกลุ่มซิสพลาตินมีโอกาสเสี่ยงต่อการเกิดมากกว่ากลุ่มคาร์โบพลาติน 3.87 เท่า (*p-value*=0.007) อาการ creatinine ในกลุ่มซิสพลาตินเสี่ยงสูงกว่าคาร์โบพลาติน 2.55 เท่า (*p-value*=0.05) อาการคลื่นไส้ และอาเจียน มีค่าเท่ากันคือกลุ่มซิสพลาตินมีความเสี่ยงในการเกิดสูงกว่ากลุ่มคาร์โบพลาติน 13.31 เท่า (*p-value*=0.008) ส่วนอาการแทรกซ้อนระยะยาว มีเพียงอาการเดียวที่มีความแตกต่างทางสถิติระหว่างยา 2 ชนิด คือ อาการเยื่อบุช่องคลอดตีบตัน โดยกลุ่มคาร์โบพลาตินมีโอกาสเกิดอาการเยื่อบุช่องคลอดตีบตันมากกว่ากลุ่มซิสพลาติน 1.15 เท่า (*p-value=0.026*)

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CHAPTER I
INTRODUCTION

1.1 Rationale and Justification

The overall incidence of invasively cervical carcinoma has declined steadily since the mid-1940s. Worldwide, cervical cancer kills more women annually than childbirth, and it is estimated that it could affect as many as 750,000 women by 2020 and as many as 1 million new cases by 2050. (Chichareon ,2004:204-222) Currently, about 230,000 women die annually of cervical cancer and nearly 80 percent of these cases occur in underdeveloped and poverty-stricken countries (Yahoo, 2005). Of the predominant gynecologic cancers, cancer of the uterine cervix is the least common, with only 10,370 new cases anticipated in the United States in the year 2005. Nevertheless, approximately 3,710 women die of the uterine cervix annually in the United States (Benedet, *et al*. 1998: 5-38). The cervical cancer was still the most common cancer among Thai women in 1995-1997 with the age-standardized incidence rate (ASR) 19.5 per 100,000 (Chichareon ,2004:204-222) The risk of cervical cancer increases gradually as a woman gets older. In Thailand, at Siriraj hospital, most cervical cancer occurs in women between the ages of 35 and 55 (Siriraj Cancer Center, 2001). It rarely occurs in women younger than 20. Slightly over 20% of women with cervical cancer are diagnosed when they are over 65. It is important for older women to continue having regular Pap tests at least until age 70, and possibly longer (American Cancer Society,2005).

Detection of cervical cancer at an early stage, when the disease is less severe, provides a greater chance of longer survival time. The most important predictor of treatment outcome of cervical cancer patients is disease severity at the time of the treatment. Treatment of cervical cancer involves surgery and radiotherapy with or without chemotherapy. Surgery, in the form of a hysterectomy (more or less extensive, to include surrounding tissues, according to spread of disease and local

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practices) is carried out for early stage disease. However mostly cases of cervical cancer in underdeveloped countries was found as advanced stage of disease. It is supplemented by radiotherapy usually a combination of brachytherapy(local irradiation of tissue with a radio active source in the vagina and uterus) plus external beam irradiation of tissues further from the cervix itself. The success of treatment in prolonging life is measured as survival, the proportion (or percentage) of new cases surviving for different periods of time after diagnosis. The 5-year survival rates for women with cervical cancer who have surgery and radiation treatment are approximately (Stephen Grund, 2005):

80-85% for tumors limited to the cervix and uterus.

60-80% when the upper part of the vagina is involved.

30-50% for tumors beyond the cervix and upper vagina, but still in the pelvis.

14% when the cancer has invaded the bladder or rectum or has spread beyond the pelvis.

Until 1999, there was an announcement of the National Cancer Institute's (NCI) five different studies - showing that women in the studies were benefited by the use of radiation therapy with concomitant platinum-based chemotherapy .(Whitney, 1999:1339-1348; Morris, 1999:1137-1143; Rose, 1999:1144-1153; Perter, 2000:1606-1613; Keys, 1999:1606-1613). The studies found that the proportion of survival after three years of follow-up was higher in groups receiving chemotherapy (cisplatin and 5-fulorouracil or cisplatin alone) plus radiation than those receiving only radiation therapy(National Institute of Health,2005). Since then, Thailand has begun to use cisplatin as a standard treatment in 2002. Anyway, disadvantage of cisplatin is the risk of renal toxicity. Before cisplatin infusion, the patients will receive intravenous fluid of more than 1000- 2000 ml. to protect the kidneys. Hence, the patients that receive cisplatin have to be admitted as in-patients at the hospital. That could be a problem for a hospital where admission beds are not always available. Therefore, this study was conducted to evaluate the efficacy and safety of carboplatin, which is a platinum compound chemotherapy drug that acts like an alkylating agent, same as cisplatin, but has less kidney side effects compared to cisplatin and doesn't require hydration before treatment (American Cancer Society,2005).

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1.2 Research Objectives

1.2.1 To compare survival rate with 95% CI in patients treated by cisplatin group versus carboplatin group.

1.2.2 To compare acute complications between two treatments(cisplatin group and carboplatin group) .

1.2.3 To compare late complications between two treatments (cisplatin group and carboplatin group).

1.3 Hypotheses

1.3.1 Survival rate of cisplatin group differ from carboplatin bgroup.

1.3.2 Acute complications of cisplatin group differ from carboplatin group.

1.3.3 Late complications of cisplatin group differ from carboplatin group.

1.4 Operational Definitions

Cervical cancer patients: patients who were diagnosed as cervical cancer patients by diagnostic criteria by FIGO staging and receive their first treatment between January 1, 2002- August 31, 2004 and follow-up until September 12, 2006.

1.4.1 Survival time In survival or time-to-event, which is count for day from the starting point for each patient, that is the first date of treatment to the end point of interest. The end point may be death or survival at the end of the study by follow-up until September 12, 2006.

1.4.2 Censored Survival data may be censored for any of following three reasons.

1.3.2.1. The patients who are lost to follow-up.

1.3.2.2. Patients who do not experience the event before the study end.

1.4.3 Event Patients who died from cause of treatment or other causes.

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1.4.4 Lost to follow-up Patients who withdraws from the study or lose contact for any reason before experiencing the event

1.4.5 Age Age of patients when first diagnosed (in years).

1.4.6 Pathological type(Benda & Zaino, 2005) histological cell types were coded according to the official pathological reports from pap smears.

1.4.7 Staging the FIGO (International Federation of Gynecology and Obstertrics) staging system was used to classify patients.[Shepherd,1996: 405-406, Chapter II]

1.4.8 Acute Complications Patients will take a physical exam, talking history and the blood examined to investigate kidney and bone marrow function during radio-chemotherapy. Creatinine is common procedure used to evaluate renal function. The normal value is 0.8 to 2.0 mg/dl. Creatinine level are divide for 4 grades see in Appendix B as well as bone marrow function.

1.4.9 Late Complications The symptoms of gastrointestinal (GI tract) such as diarrhea, nausea, vomiting. Adverse effects occurring as a result of period of time after 3 months of treatment. Diarrhea are divide for 4 grades of symptoms[Appendix C].

1.4.10 Vital status: means last status of patient at the end of the study by follow-up until December 31, 2005. Patients will be categorized into 2 groups of patient: death or survive

1.4.11. Response after treatment at 3rd months : The status at third months after complete of radiation. Separated for three groups as complete response(CR) which disappearance of all signs of cancer in response to treatment., partial response(PR) mean a decrease in the size of a tumor, or in the extent of cancer in the body and progress disease(PD) mean cancer that is growing, spreading.

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1.4.10.1 Cisplatin group Patients who receive concurrent radiation and cisplatin group chemotherapy regimen for treatment of cervical cancer in Siriraj hospital. The patients have received complete radiation treatment (external and brachytherapy). Cisplatin group regimen chemotherapy could be cisplatin alone weekly or Cisplatin – 5 FU 4 wks regimen [Siriraj radiation practice guideline for cervical cancer, Appendix A].

1.4.10.2 Carboplatin group Patients who receive concurrent radiation and Carboplatin group chemotherapy regimen for treatment of cervical cancer in Siriraj hospital. The patients have received complete radiation treatment (external and brachytherapy). Carboplatin group regimen chemotherapy could be Carboplatin (AUC2) weekly or Carboplatin – 5 FU 4 wks regimen [Appendix A].

1.5 The Scope of Study

This study enrolled patients treated between January 1, 2002 to August 31, 2004 and observed the vital status until to September 12,2006.

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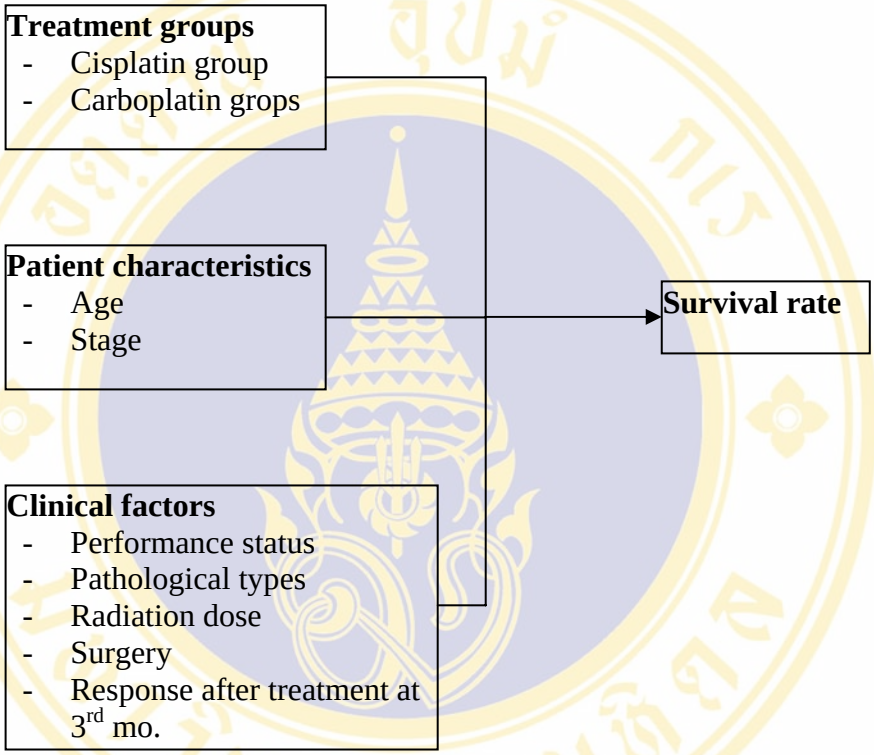

Fig. 1 Conceptual Framework for Survival Rate

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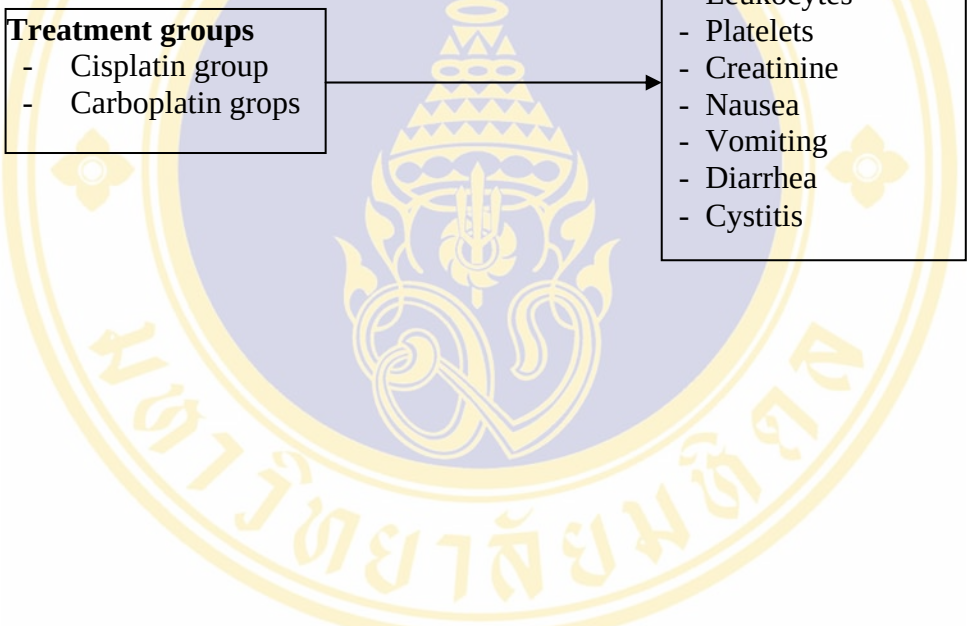

Fig. 2 Conceptual Framework for Acute Complications

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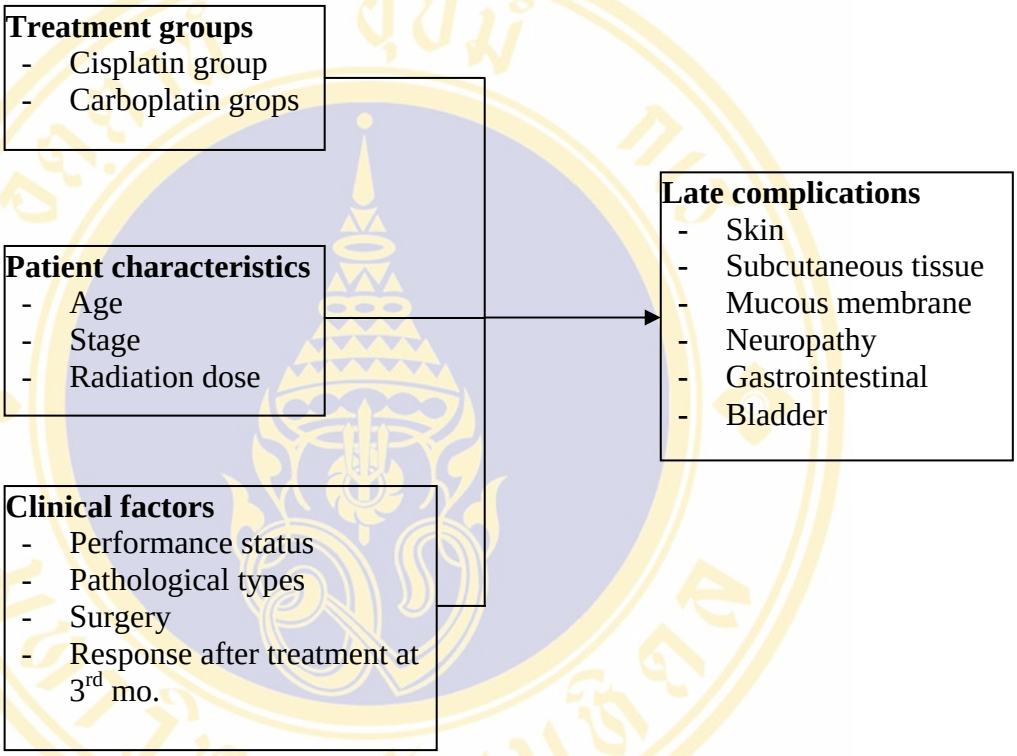

Fig. 3 Conceptual Framework for Late Complications

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CHAPTER II

LITERATURE REVIEW

Reviewing of the literature is divided in four parts as follows:

2.1 Cervical Cancer

2.2 Review of Treatments

2.3 Factors Relate to Survival Rate

2.4 Factors Relate to Acute and Late Complications

2.1 Cervical Cancer

Cervical cancer is malignancy of the cervix. Worldwide, it is the second most common cancer of women. It may be noted with vaginal bleeding but symptoms may be absent until the cancer is in advanced stages. It is the most frequent cause of death among female gynecologic diseases (Benedet, 1998: 5-34; Yahoo news, 2005; Health Square, 2004; American Cancer Society, 2004).

2.1.1 Pathology

There are 2 main types of cervical cancers: squamous cell carcinoma and adenocarcinoma. Cervical cancers and cervical precancers are classified by how they look under a microscope. About 80% to 90% of cervical cancers are squamous cell carcinomas, which are composed of cells that resemble the flat, thin cells called squamous cells that cover the surface of the endocervix. Squamous cell carcinomas most often begin where the ectocervix joins the endocervix. The remaining 10% to 20% of cervical cancers are adenocarcinomas. Adenocarcinomas are becoming more common in women born in the last 20 to 30 years. Cervical adenocarcinoma develops

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from the mucus-producing gland cells of the endocervix. Less common cervical cancers have features of both squamous cell carcinomas and adenocarcinomas. These are called adenosquamous carcinomas or mixed carcinomas (Canadian Cancer Encyclopedia, 2005).

2.1.2 Clinical Presentation

Cervical cancer may not cause any signs or symptoms in its early stages. Early detect to cervical cancer are often picked up during routine Pap tests. In early stage disease the patients may complain of abnormal bleeding, spotting or bloodstained discharge from the vagina between periods, unusually long or heavy periods, bleeding after sexual intercourse, pain during sexual intercourse, watery discharge from the vagina, increased amount of discharge from the vagina, bleeding from the vagina after menopause. Late signs and symptoms occur as the cancer grows larger or spreads to other parts of the body, including other organs. That their symptoms such as pain in the pelvic area or lower back that may go down the leg(s), foul-smelling discharge from the vagina(Canadian Cancer Encyclopedia, 2005).

2.1.3 Carcinoma of the Cervix Uteri: 1995 Modification of FIGO Staging

Stages are defined by the Federation International of Gynecology Obstetrics (FIGO) system Different staging or classification systems are used for different cancer sites and types (Shepherd, 1996: 405-406).

FIGO STAGING:

Stage I is carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded.

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 a maximum depth of 5 mm and no wider than 7 mm.

IA1: Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm diameter.

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IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.

IB: Clinical lesions confined to the cervix or preclinical lesions greater than stage IA.

IB1: Clinical lesions no greater than 4 cm in size.

IB2: Clinical lesions greater than 4 cm in size.

Stage II is carcinoma that extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.

IIA: No obvious parametrial involvement. Involvement of up to the upper two thirds of the vagina.

IIB: Obvious parametrial involvement, but not onto the pelvic sidewall.

Stage III

Stage III is carcinoma that has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumor and the pelvic sidewall. The tumor involves the lower third of the vagina. All cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to other causes.

IIIA: No extension onto the pelvic sidewall but involvement of the lower third of the vagina.

IIIB: Extension onto the pelvic sidewall or hydronephrosis or nonfunctioning kidney.

Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.

IVA: Spread of the tumor onto adjacent pelvic organs.

IVB: Spread to distant organs.

2.2 Review of Treatments

2.2.1 Treatment of Cervical Cancer

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Treatments of cervical cancer most often involves radiation and chemotherapy. Chemotherapy is becoming standard in treatment as well.

2.2.2 Radiation

2.2.2.1 External Radiation

External beam radiation therapy (EBRT) for cervical cancer is administered on an outpatient basis, 5 days a week for several weeks. EBRT begins with a planning session, or simulation, where marks are placed on the body and measurements are taken in order to line up the radiation beam in the correct position for each treatment. External beam radiation therapy for cervical cancer is administered on an outpatient basis for approximately 4 to 6 weeks. So radiation therapy, rays are directed at the tumor from outside the body. Most centers administer radiation in single doses of 180 to 200 centigray (cGy) each weekday.

A combination of external beam radiation therapy and implant radiation is used to increase the dose of radiation administered to the cancer. Implant or internal radiation is further described in the section below. When these two methods are combined, the external beam radiation therapy is given for 4-6 weeks, and the final "boost" of radiation to the cervix is given with the implant radiation. (CancerConsultants:2005)

2.2.2.2 Intracavitary Radiation

2.2.2.2.1 Low-Dose-Rate (LDR)-Implant radiation(Cesium-137), sometimes referred to as brachytherapy, refers to treatment where radioactive material is placed directly into the cervix. Placing the radiation in this manner allows a high radiation dose to be delivered directly to the cancer, while reducing radiation to surrounding normal organs, such as the rectum and bladder. A small device is placed into the cervix and vagina. This device is later "loaded" with the radiation capsules while the patient is in a lead-shielded hospital room. The radioactive material is left in

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place for 1-2 days. This procedure may be performed once or twice during the course of treatment. (CancerConsultants:2005)

2.2.2.2.2 High-Dose Rate (HDR)- Brachytherapy is an innovative form of internal radiotherapy (radiation treatments), also called interstitial irradiation. HDR Brachytherapy may greatly reduce both your recovery time and damage to healthy tissue. It is typically combined with external beam radiation, and can often be done on an outpatient basis. Brachytherapy is a quicker, more effective way to give radiation treatments. Brachytherapy places the radiation inside your tumor, tightly focused within the site of the cancer. This technique ensures the maximum radiation dose is given where you need it most, while allowing little radiation to reach the healthy surrounding tissue. In many cases, Brachytherapy is an effective alternative to surgical removal of a tumor and the affected organ.(Cancer treatment centers of America,2005)

2.2.3 Chemotherapy:

For years, chemotherapy was considered an ineffective treatment modality for women with invasive cervical cancer. Its use was limited to treating women with advanced metastasis disease. In 1999, five landmark papers reported significant improvements in the survival rates of women with locally advanced cervical cancer with the concurrent administration of cisplatin-based chemotherapy and radiation therapy. Because of these findings, the National Cancer Institute issued a recommendation that cisplatin-based chemotherapy be added to the treatment of women receiving radiation therapy for cervical cancer(American Cancer Society, 2005).

2.2.3.1 Cisplatin (Platinol)

Cisplatin is a platinum compound chemotherapy drug that acts like an alkylating agent.

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2.2.3.1.1 Process to Given

Cisplatin is given by an injection into the vein over at least 1 hour. Sometimes you will be given other medicines that will help flush the medicine out quickly through the kidneys. You will also get a saline solution by vein and medicine to prevent or stop nausea or vomiting. Before and after the medicine you should drink 2 to 3 quarts of fluid a day (an 8 oz. glass of water or fluid every hour while awake) to protect your kidneys. Your doctor will check your kidney function before giving the medicine. Your dose depends upon the type of cancer being treated, your size, and how well your kidneys are working. (American Caner Society, 2005)

2.2.3.1.2 Reviews of Chemotherapy

At 1999, there was an announcement from the National Cancer Institute(NCI) to thousands of physicians stating that strong consideration should be given to adding chemotherapy to radiotherapy in treatment of invasive cervical cancer. That finding was consistent remarkable from five trials. So they are likely to change the universal standard of care for cervical cancer.

Rose, P.G., *et al*. The randomized trial of radiotherapy in combination with three concurrent chemotherapy regimens- cisplatin alone; cisplatin,fluorouracil, and hydroxyurea; and hydroxyurea alone, in patients locally advanced cervical cancer with primary untreated of cervical cancer stage IIB-IVA, without involvement of para-aortic lymphnodes. Conclusions, the regimens of radiotherapy and chemotherapy that contain cisplain improve the rates of survival and progression-free survival among women with locally advanced cervical cancer(Rose, et al.,1999:1144-1153).

Key, H.M., *et al*. Show that the two groups of randomized control trial, received radiotherapy alone or combination with cisplatin weekly, then followed in all patients by adjuvant hysterectomy. So conclusions, weekly of cisplatin with radiotherapy followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers(Key, et al., 1999: 1154-1161**)**.

Peter, W., *et al*. that randomized control trial stage IA_2, IB and IIA of cervical cancer. So patients divided in two groups and received radiotherapy alone and radiotherapy with concurrent cisplatin weekly. The results significantly improves

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progression-free and overall survival for high-risk in group of cisplatin combined with radiation with the project overall survival rate at 4 years is 71% with radiation and 81% with radiation andcisplatin (Perter, et al., 2000: 1606-1613).

Morris, M., *et al*. That randomized control trial stage IIB-IVA or IB,IIA(with tumor involvement to pelvic lymphnode). Then patients divided in two group ,that received radiation to the pelvic and para-aortic lymph nodes or 45 Gy of radiation to the pelvic alone plus two cycles of fluorouracil and cisplatin. Patients were then to received one or two applications of low-dose-rate of intracatitary radiation, with a third cycle chemotherapy in combined-therapy group.The results significantly improved survival in treatment of fluorouracil and cisplatin with radiotherapy (Morris, et al., 1999:1137-1143).

Whitney, C.W. *et al*. The study demonstrates that for patients with locally advanced carcinoma of the cervix, the combination of fluorouracil and cisplatin with radiotherapy , that results show better progression-free-survival and overall survival in group of hydroxyurea alone at 5 year survival 54% and 44% , respectively(Whitney, et al., 1999:1339-1348).

Table 1 Conclusions of Review Journal Concurrent Cisplatin and Radiation Therapy for Cervical Cancer

Reference	FIGO Stages	No. of patients	Chemo Regimen	Overall Survival
(Rose, et al., 1999)	IIB-IVA	177	Cisplatin/5-FU	67%
		191	(Hydroxyurea)	57%
(Morris, et al.,1999)	IB2-IVA	195	Cisplatin/5-FU	75%
		193	None	63%
(Peters, et al.,2000)	IA2-IIA, select	127	Cisplatin/5-FU	81%
		116	None	71%
(Key, et al., 1999)	IB2	183	Weekly Cisplatin	83%
		186	None	74%
(Whitney, et al.,1999)	IIB-IVA	177	Cisplatin/5-FU	54%
		191	Hydroxyurea	44%

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2.2.3.2 Carboplatin (Paraplatin)

Carboplatin is a platinum chemotherapy drug that belongs to a general group of drugs known as alkylating agents. It is used to treat ovarian, lungs, and other cancers.

2.2.3.2.1 Process to Given:

Carboplatin is given as an injection in the vein over 15 to 60 minutes. You will probably get an antinausea drug before receiving this medicine. The dose depends upon your size but may be lowered or not given if your blood counts are low. It can also be given as an infusion into a vein over 24 hours or directly into the peritoneal cavity in advanced ovarian cancer. (American Cancer Society, 2005)

2.2.3.2.2 Reviews of Chemotherapy

The most common agent used in chemoradiation programs is cisplatin. Carboplatin, a related platinum agent with lower nephrotoxicity and emetogenicity, has demonstrated equivalent cytotoxicity in many other solid tumors(Rao, et al., 2005:168-172).

Rao, G.G., *et al.* The study demonstrates that for patients with locally advanced stage IB_2-IVA , cervical cancer treated with radiotherapy with concurrent weekly paclitaxel and carboplatin was followed by two intracavitary radiation, estimated 2 years progression-free survival and overall survival are 80% and 86%(Rao,G.G., *et al*., 2005:168-172).

Dubay, A.R., *et al.* A retrospective study was performed to identify patients treated with carboplatin and concurrent radiation therapy for locally advanced cervical cancer with minimum follow-up period of 24 months. Twenty-one patients with cervical carcinoma stage IB_2-IVA treated with carboplatin chemotherapy were identified. The median carboplatin AUC was 3.9 (range 3.0-5.0). Six patients developed recurrent disease (five local and one distant) with a pelvic control rate of 76% and an overall survival of 71%(Dubay,A.R., *et al.,* 2004: 121-124).

Muderspach, I. L., *et al*. A pilot study before a prospective study was designed to evaluate carboplatin as a radiosensitizer in advanced cervical cancer. Standard

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radiotherapy techniques were used to treat patients with stage IIA-IIIB cervical cancer. Intravenous carboplatin was administered twice weekly concurrent with external beam radiation. Of 22 evaluable patients, there were 19 complete responders of whom 15 remain alive: 11 patients were alive and disease free at last visit for a median duration of 15 months follow-up(range, 4-43 months) and 4 patients remain alive with disease for a median duration of 17 months (range, 3-55 months) (Muderspach,I.L., *et al*., 1997).

Nagao, S., *et al* .This is a pilot study for a future trial to assess the efficacy and safety of combination chemotherapy with docetaxel and carboplatin in advanced or recurrent uterine cervix cancer. The patients eligible for this study had histologically confirmed, advanced (stage IB_2-IV) 17 patients were enrolled. The overall response rate was 76% (2 CR, 11 PR, and 4 SD) (Nagao, S.,*et al*., 2005: 805-809).

Tinker, V. A., *et al*. All patients treated with the carboplatin-paclitaxel chemotherapy protocol for gynecologic malignancies at British Columbia Cancer Agency, that have a diagnosis of either recurrent or stage IVB. The chemotherapy regimen consisted of intravenous carboplatin and paclitaxel. Both drug schedule for up to 6-9 cycles. There was 1 20% PR and a 20% CR rate (10/25). The median overall survival was 21 months(Tinker,V.A., *et al*., 2005: 54-58).

Table 2 Conclusions of Review Journal Concurrent Carboplatin and Radiation Therapy for Cervical Cancer

Reference	FIGO Stages	No. of patients	Chemo Regimen	Overall Survival
(Rao, *et al*., 2005)	IIB-IVA	15	Weekly Paclitaxel and Carboplatin	86%
(Dubay,*et al*.,2004)	IIB-IVA	21	Every 3 wks(6 courses) Carboplatin	71%
(Muderspach , *et al*.,1997)	IIA-IIIB	22	Twice weekly Carboplatin	-

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Table 2 Conclusions of Review Journal Concurrent Carboplatin and Radiation Therapy for Cervical Cancer (Cont.)

Reference	FIGO Stages	No. of patients	Chemo Regimen	Overall Survival
(Nagao, *et al*., 2005)	IB_2-IV	17	Docetaxel and followed by carboplatin (1-6 courses)	76%
(Tinker, *et al*., 2005)	IA-IVB	25	Carboplatin-Paclitaxel (6-9 courses)	Median 21 months

2.3 Factors Relate to Survival Rate.

2.3.1 Age

(Hong, et al., 2005:492-499) Studied 1031 patients with stage IB-IVA squamous cell carcinoma of cervix treated with full-course RT but without any chemotherapy were included for analysis. The 5-years local relapse-free survival rate was 86% for patients $\geq$ 45 years and had a grater significant rate than the other subgroups.

(Saibishkumar, P. E.,et al., 2006:142-146) The retrospective study included 556 patients of cancer cervix stage IIIB treated between 1996 and 2001 with EBRT (46Gy/23fx/4.5 weeks) followed by intracavitary radiotherapy(ICRT). Concluded that patients with age more than 50 years had more no gross residual tumor response (77%) than patients with age less than 50 years (63.8%).

2.3.2 Stage

(Hong, J.H.,*et al*., 2005:492-499) Studied 1031 patients with stage IB-IVA squamous cell carcinoma of cervix treated with full-course RT but without any chemotherapy were included for analysis. For stage IB-IIA nonbulky, Stage IB-IIA bulky, IIB, III, and IVA disease have local failue rate 4%, 13%, 15%, 22% and 35%, respectively.

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(Chen, S.W.,*et al*., 2003: 69-76) Studied 257 patients with stage IB-IVA who underwent external radiotherapy combined with between two and four courses of HDR intracavitary brachytherapy and a minimum of 3 years of follow-up (median 57 months), were analyzed. The 5-year cause-specific survival for all stages was 83 and 65% for these same overall treatment time groups (OTTs) (*p-value* = 0.004). This trend was also evident for stage IB/IIA (97% and 79%, *p-value* = 0.01), but not for stage IIB (75% and 72%; *p-value* = 0.79) and stage III (65% and 49%; *p-value* = 0.2). The 5-year pelvic control rate was 93 and 83% for the two OTTs (*p-value* = 0.002). Furthermore, a similar trend was evident comparing OTTs <63 and $\geq$63 days for stage IB/IIA(100% and 87%; *p-value*=0.02), but not for stage IIB (93% and 87%;*p-value*=0.83) and stage III(83% and 72%;*p-value*=0.21).

2.3.3 Pathological

Squamous cell carcinoma accounts for 80 to 85% of all cervical cancers; adenocarcinomas account for most of the rest.

(Rotman, M.,*et al.*,2006:1-8)To investigate, in a phase III randomized trial, whether postoperative external-beam irradiation to the standard field improves the recurrence-free interval and overall survival in women with stage IB. The planed pelvic dose was from 46 Gy in 23 fractions to 50.4 Gy in 28 fractions.The result with RT are showed 8.8% of patients(3 of 34) with adenosquamous or adenocarcinoma tumors recurred vs. 44.0%(11 of 25) in observation. Fewer recurrences were seen with RT in patients adenocarcinoma or adenosquamous histologies relative to other (HR for RT by histology interaction = 0.23, 90% CI= 0.07 to 0.74, *p*= 0.019).

2.3.4 Radiation Dose

Radiation therapy is a standard treatment for invasive cervical cancer. It employs high-energy rays aimed at the body from an outside machine(external beam radiation) and radioactive materials placed inside the body against the cervix (intracavitary radiation).

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(Devita, T. V., *et al*., 2001) Bulky endocervical tumors and so-called barrel shaped cervix have higher incidences of central recurrence, pelvic and periaortic lymph node metastasis, and distant dissemination. Because of the inability of the intracavitary sources to encompass all of the tumor in a high-dose volume, larger doses of external irradiation to the whole pelvis or extrafascial hysterectomy, or both, have been advocated to improve therapeutic results. Durrance and co-workers and Nelson and colleagues recommended and extrafascial conservative hysterectomy 6 weeks after completion of high-dose preoperative irradiation(20 Gy to the whole pelvis, additional 30 Gy to the parametria with midline shielding, and one intracavitary insertion for 5500 mgh, delivering about 50 Gy to point A) (total dose to point A,70 Gy). Higher doses for irradiation alone yield equivalent pelvic tumor control and survival.

(Devita, T. V., *et al*., 2001) In 965 patients with invasive carcinoma of the cervix, identified FIGO stage as the most significant prognostic factor, followed by dose of radiation to point A and overall time of radiation therapy. When the analysis was limited to patients treated with doses of 75 Gy or more, radiation dose was no longer a significant factor. The 10-year survival rate was 62% in 743 patients receiving doses of 85 Gy or higher to point A, compared with 53% for 222 patients receiving lower doses. Patients with higher hemoglobin levels who did not receive transfusions had a 10-year survival rate of 60% (595 patients), compared with 42% in 353 patients who were given transfusion for lower hemoglobin levels. Patients with squamnous cell carcinoma had a 61% disease-free survival rate at 5 years, compared with 55% for those with adenocarcinoma or adenosquamous carcinoma.

2.3.5 Surgical Histology

In the early stages of cervical cancer, surgery is often the preferred primary treatment approach. Hysterectomy. A hysterectomy attempts to eliminate the cancerous tissue by removing the uterus. There are several variations of this operation, depending on the location of the tumor.

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(Houvenaeghel ,G.,*et al.*, 2006: 338-343) To report the long-term survival of 35 patients who underwent surgery after concomitant chemoradiation for locally advanced cervical cancers from 1988 to 1992. Surgery had been only palliative in 6 cases (17.1%). A pelvic control has been achieved in 31 patients (88.6%). Pelvic recurrence occurred after a median interval of 7 months. Distant metastases occurred in 10 patients (28.6%), after a median interval of 20 months. So far, 16 patients have died (45.7%). The 10-year DFS is 56.7% in the whole series. Only the type of surgery significantly affected the OS. Only the para-aortic lymphatic status significantly affected the DFS.

2.3.6 Performance Status

(Chung , Y. L., *et al.*, 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the characteristics of the patient, the majority of the patients had Karnofsky performance status scores of 90 or 100 percent.

2.4 Factors Relate to Acute and Late Complications

2.4.1 Acute Complications

Chemotherapy affects all fast-growing cells, including healthy ones, so some side effects are inevitable. Fast-growing cells include those that form blood, hair, and the lining of the digestive tract. The Chemotherapy that affects these cells can cause temporary lowered resistance to infection, irregular menstruation, hair loss, and nausea or vomiting. There are a number of treatments are available to help reduce the effects of some of these side effects.

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2.4.1.1 Hemoglobin

(Tinker, A. V.,*et al*., 2005: 54-58) Patients with advanced or recurrent carcinoma of the cervix treated with carboplatin–paclitaxel from April 2000 were included in the study. Starting doses of carboplatin–paclitaxel were: AUC 5–6 and 155–175 mg/m2, respectively, repeated every 28 days. Reported the result of common toxicity of anemia grade 1 or 2 ,68%; grade 3 or 4 anemia, 32%.

(Chung , Y. L., *et al.,* 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of common toxicity of anemia grade 1,8(16%); grade 2,5(8%); grade 3,1(2%) and didn't have patients in grade 4 and 5.

2.4.1.2Leukocytes (Total White Blood Cells)

There are various types of cells in the blood. The lowering of the white blood cells that fight infections is known as Neutropenia. It is the most important complication of chemotherapy. It is almost always due to impairment of bone marrow to produce cells and normally occurs a few days to a few weeks after chemotherapy. It is most severe in patients who receive aggressive treatments.

(Tinker, A. V.,*et al*., 2005: 54-58) Patients with advanced or recurrent carcinoma of the cervix treated with carboplatin–paclitaxel from April 2000 were included in the study. Starting doses of carboplatin–paclitaxel were: AUC 5–6 and 155–175 mg/m2, respectively, repeated every 28 days. Reported the result of common toxicity of neutropenia grade 3 or 4, 32%; and grade 1 and 2, 32%.

(Chung , Y. L., *et al.,* 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation,

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HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of common toxicity of neutropenia grade 1, 19(39%); grade 2, 13(21%); grade 3, 1(2%) and didn't have patients in grade 4 and 5.

(Toita, T., et al., 2005:665-670) A retrospective study ;52 consecutive patients with FIGO stage IB-IVA . The patients treated with concurrent chemoradiotherapy (cisplatin) using high-dose-rate intracavitary brachytherapy. Reported the result of acute toxicity(NCI-CTC Version 2.0) of leukocytes grade2, 7(17.5%); grade3, 29(72.5%); grade4, 4(10%).

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of common toxicity of neutropenia grade1,2,3,4 and 5 were 1(3.3%); 1(3.3%); 5(16.6%); 1(3.3%) and 0, respectively.

2.4.1.3 Platelets

Thrombocytopenia refers to lowering of the platelets, the blood cells that prevent us from bleeding. The medical term for a platelet is Thrombocyte. Various medical conditions such as drugs (Chemotherapy drugs among them) and Radiation therapy as well as immune disorders can cause Thrombocytopenia. A serious reduction in the number of these cells can result in bleeding.

(Tinker, A. V.,*et al*., 2005: 54-58) Patients with advanced or recurrent carcinoma of the cervix treated with carboplatin–paclitaxel from April 2000 were included in the study. Starting doses of carboplatin–paclitaxel were: AUC 5–6 and 155–175 mg/m2,

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respectively, repeated every 28 days. Reported the result of common toxicity of thrombocytopenia grade 1, 4(16%) and grade 3, 3(12%).

(Chung , Y. L., *et al.,* 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of common toxicity of thrombocytopenia grade1, 8(16%); grade2, 5(8%); grade3, 1(2%) and didn't have patients in grade 4 and 5.

(Toita, T., et al., 2005:665-670) A retrospective study ;52 consecutive patients with FIGO stage IB-IVA . The patients treated with concurrent chemoradiotherapy (cisplatin) using high-dose-rate intracavitary brachytherapy. Reported the result of acute toxicity(NCI-CTC Version 2.0) of platelets grade0, 14(35%); grade1, 9(22.5%); grade2, 7(17.5%); grade3, 7(17.5%); grade4, 3(7.5%).

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of common toxicity of platelets grade 1,2,3,4 and 5 were 5(16.6%); 3(10%); 1(3.3%); 0 and 0, respectively

2.4.1.4 Creatinine

(Toita, T., et al., 2005:665-670) A retrospective study ;52 consecutive patients with FIGO stage IB-IVA . The patients treated with concurrent chemoradiotherapy (cisplatin) using high-dose-rate intracavitary brachytherapy. Reported the result of

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acute toxicity(NCI-CTC Version 2.0) of creatinine grade0, 36(90%); grade1, 4(10%).

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of common toxicity of creatinine grade 1,2,3 and 4 were 2(6.6%); 1(3.3%); 0 and 0, respectively.

2.4.1.5 Nausea

Nausea and vomiting were the most uncomfortable side effects of chemotherapy. The real reason that cancer drugs cause nausea and vomiting is still under investigation. However, it seems true that drugs can stimulate and irritate certain key areas in the brain and cause nausea and vomiting.

(Tinker, A. V.,*et al*., 2005: 54-58) Patients with advanced or recurrent carcinoma of the cervix treated with carboplatin–paclitaxel from April 2000 were included in the study. Starting doses of carboplatin–paclitaxel were: AUC 5–6 and 155–175 mg/m2, respectively, repeated every 28 days. Reported the result of common toxicity of nausea grade 1 , 5(20%) and grade 2, 2(8%).

(Chung , Y. L., *et al.,* 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of common toxicity of nausea grade1, 9(14%); grade2, 19(30%); grade3, 1(2%) and didn’t have patients in grade 4 and 5.

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(Toita, T., et al., 2005:665-670) A retrospective study ;52 consecutive patients with FIGO stage IB-IVA . The patients treated with concurrent chemoradiotherapy (cisplatin) using high-dose-rate intracavitary brachytherapy. Reported the result of acute toxicity(NCI-CTC Version 2.0) of nausea grade0, 2(5%); grade1, 9(22.5%); grade2, 18(45%); grade3, 11(27.5%).

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of common toxicity of nausea grade 1,2,3,4 and 5 were 2(6.6%); 13(43.3%); 7(23.3%); 3(10%) and 0, respectively.

2.4.1.6 Vomiting

(Tinker, A. V.,*et al*., 2005: 54-58) Patients with advanced or recurrent carcinoma of the cervix treated with carboplatin–paclitaxel from April 2000 were included in the study. Starting doses of carboplatin–paclitaxel were: AUC 5–6 and 155–175 mg/m2, respectively, repeated every 28 days. Reported the result of common toxicity of vomiting grade1 only 1 patient (4%).

(Chung , Y. L., *et al.,* 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of common toxicity of vomiting grade1, 9(14%); grade2, 19(30%); grade3, 1(2%) and didn’t have patients in grade 4 and 5.

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(Toita, T., et al., 2005:665-670) A retrospective study ;52 consecutive patients with FIGO stage IB-IVA . The patients treated with concurrent chemoradiotherapy (cisplatin) using high-dose-rate intracavitary brachytherapy. Reported the result of acute toxicity(NCI-CTC Version 2.0) of vomiting grade0, 2(5%); grade1, 9(22.5%); grade2, 18(45%); grade3, 11(27.5%).

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of common toxicity of vomiting grade 1,2,3,4 and 5 were 2(6.6%); 13(43.3%); 7(23.3%); 3(10%) and 0, respectively.

2.4.1.7 Diarrhea

(Chung , Y. L., *et al.*, 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of common toxicity of diarrhea grade1, 13(21%); grade2, 35(56%) and didn’t have patients in grade 3, 4 and 5.

(Toita, T., et al., 2005:665-670) A retrospective study ;52 consecutive patients with FIGO stage IB-IVA . The patients treated with concurrent chemoradiotherapy (cisplatin)using high-dose-rate intracavitary brachytherapy. Reported the result of acute toxicity(NCI-CTC Version 2.0) of diarrhea grade0, 6(15%); grade1, 11(27.5%); grade2, 17(42.5%); grade3, 5(12.5%); grade4, 1(2.5%).

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(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of common toxicity of diarrhea grade 1,2,3,4 and 5 were 2(6.6%); 6(20%); 7(23.3%); 4(13.3%) and 0, respectively.

2.4.1.8 Cystitis

(Chung , Y. L., *et al.,* 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of common toxicity of cystitis grade1, 11(17%); grade2, 3(5%) and didn't have patients in grade 3, 4 and 5.

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of common toxicity of cystitis grade 1,2,3,4 and 5 were 3(10%); 1(3.3%); 0; 0 and 0, respectively.

2.4.2 Late Complications

Long-Term Complications include proctitis (inflammation of the rectum) and cystitis (inflammation of the bladder). Side effects of radiation therapy include

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fatigue, redness or dryness in the treated area, diarrhea, frequent or uncomfortable urination, and vaginal dryness, itching, or burning.

2.4.2.1 Skin

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of late toxicity of skin grade1,2,3,4 and 5 were 0; 0; 1(3.4%); 0 and 0, respectively.

2.4.2.2 Subcutaneous Tissue

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of late toxicity of subcutaneour tissue grade1,2,3,4 and 5 were 0; 1(3.4%); 0; 0 and 0, respectively.

2.4.2.3 Mucous Membrane

(Toita, T., *et al.*, 2003: 1344-1353) Eighty-eight patients were enrolled to this study with no previously treated uterine cervical squamous cell carcinoma with FIGO stage IB-IVA. The patients were treated with external radiotherapy and high-dose-rate intracavitary brachytherapy. Reported the result of late toxicity of mucous membrane grade 1,2,3,4 equal 0 in each groups.

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph

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nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of late toxicity of mucous membrane grade1,2,3,4 and 5 were 4(13.7%); 1(3.4%); 1(3.4%); 0 and 0, respectively.

2.4.2.4 Spinal Cord

(Chung , Y. L., *et al.*, 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of late toxicities of sacral plexopathy grade3, 1(2%) and didn't have patients in grade 1,2,4 and 5.

2.4.2.5 Small/Large Intestine

(Chung , Y. L., *et al.*, 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of late toxicities of colitis grade1, 3(5%); grade2, 8(13%); grade3, 4(6%) and didn't have patients in grade 4 and 5. The result of proctitis grade1, 3(5%); grade2, 8(13%); grade4, 2(3%) and didn't have patients in grade 3 and 5.

(Toita, T., et al., 2005:665-670) A retrospective study ;52 consecutive patients with FIGO stage IB-IVA . The patients treated with concurrent chemoradiotherapy

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(cisplatin) using high-dose-rate intracavitary brachytherapy. Reported the result of late toxicity of enterocolitis grade1, 3(7.5%); grade2, 1(2.5%); grade3, 1(2.5%). The result of proctitis grade1, 3(7.5%); grade2, 1(2.5%) and didn't have patients in grade 3 and 4.

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of late toxicity of small bowel grade 1,2,3,4 and 5 were 1(3.4%); 0; 0; 1(3.4%) and 0 , respectively. Large bowel grade1,2,3,4 and 5 were 3(10.3%); 2(6.8%); 0; 3(10.3%) and 0, respectively.

2.4.2.6 Bladder

(Chung , Y. L., *et al.*, 2005: 126-135) A prospective study, with the Institutional Board Committee approval in 1998, was conducted to investigate the toxicity and efficacy of concurrent treatments of extended-field chemoirradiation, HDR intracavity brachytherapy, and adjuvant chemotherapy on patients with locally advanced cervical cancer. Between 1998 and 2003, 63 women with both clinical FIGO and MRI/CT-based TNM stages IIB–IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study. Reported the result of late toxicity of grade1, 2(3%); grade2, 9(14%); grade4, 1(2%) and didn't have patients in grade 3 and 5.

(Toita, T., et al., 2005:665-670) A retrospective study ;52 consecutive patients with FIGO stage IB-IVA . The patients treated with concurrent chemoradiotherapy (cisplatin) using high-dose-rate intracavitary brachytherapy. Reported the result of late toxicity of cystitis grade1,2,3 and 4 equal 0 patient.

(Grigsby, W. P., et al., 2001:982-987) This study was designed to administer twice-daily radiation doses of 1.2 Gy to the pelvis and lumbar para-aortic lymph nodes (simultaneously) at 4–6-h intervals, 5 days/week. The total external radiation

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doses were 24–48 Gy to the whole pelvis. The patients receive 1 or 2 intracavitary implants were performed to deliver a minimum total dose of 85 Gy to point A. Cisplatin (75 mg/m2) and 5-fluorouracil (1,000 mg/m2/24 h × 4 consecutive days) were given for two or three cycles. The reported of late toxicity of bladder grade 1,2,3,4 and 5 were 2(6.8%); 0; 0; 0 and 0, respectively.

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CHAPTER III

METHODOLOGY

3.1 Study Design

This study was retrospective cohort study. There were used data from medical record from Siriraj hospital. The recruitment period was during January 1, 2002 to August 31, 2004 based on inclusion and exclusion criterions. The last follow-up visit was cut-point on September 12, 2006.

Inclusion Criterions

- The patients who had received chemo drugs as cisplatin group or carboplatin group.
- The patients who had first diagnostic as cervical cancer at stage IB2-IVA.
- The patients who had not received treatment before.
- No evidence cancer or metastasis.

Exclusion Criterions

- The patients who had history of metastases to the other organs.
- Loss contact between radiation therapy (external and internal radiations).

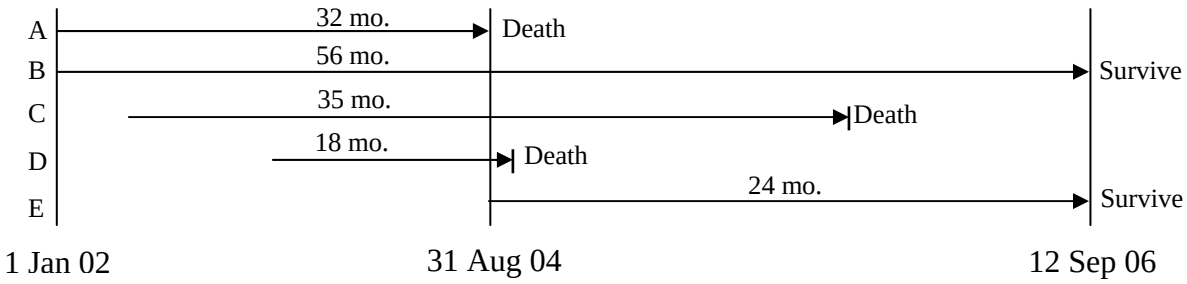

Fig. 4 Example of Survival Data

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Case A: Patient who has total of survival time of 32 months. She had started treatment on 1 January 2002 and died on 31 August 2004.

Case B: Patient who has total of survival time of 56 months. She had started treatment on 1 January 2002 and survives until study ended.

Case C: Patient who has total of survival time of 35 months. She had started treatment on 1 April 2002 and died on 31 March 2005.

Case D: Patient who has total of survival time of 18 months. She had started treatment on 1 May 2003 and died on 31 October 2004.

Case E: Patient who has total of survival time of 24 months. She had started treatment on 31 August 2004 and survives until study ended.

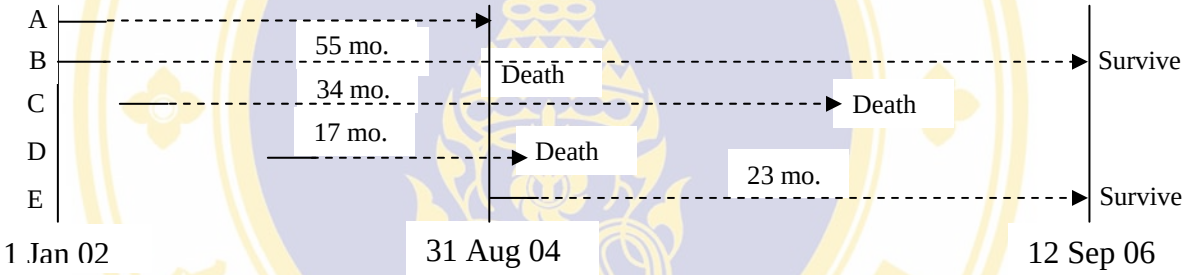

Fig. 5 Example of Complications Data

The border line defines 1 month of treatment time of each person and a dash line refers to follow-up time. Each of person had 8 follow-up times. One is acute complication, observed at the first month when finishing the treatment. The others are late complication, follow-up for every 3 months.

3.1.1 Cisplatin Group (Standard Treatment)

Patients who receive concurrent radiation and Cisplatin-based chemotherapy regimen for treatment of cervical cancer in Siriraj hospital. The patients have received complete radiation treatment (external and brachytherapy). Cisplatin-based regimen chemotherapy could be cisplatin alone weekly or Cisplatin – 5 FU 4 wks regimen. (Siriraj radiation practice guideline for cervical cancer, Appendix A)

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3.1.2 Carboplatin Group (New Treatment)

Patients who receive concurrent radiation and Carboplatin-based chemotherapy regimen for treatment of cervical cancer in Siriraj hospital. The patients have received complete radiation treatment (external and brachytherapy). Carboplatin-based regimen chemotherapy could be Carboplatin (AUC2) weekly or Carboplatin – 5 FU 4 wks regimen. (Appendix A)

3.2 Sample Size (Southworth, H.,2002)

To determine the sample size requirement for a study, we calculate the number of subjects needed for there to be certain chance of declaring θ to be significantly different from zero when the true, but unknown, log-hazard ratio is θ_R. Here, θ_R is the *reference value* of θ. It will be a reflection of the magnitude of the treatment difference that it is important to detect, using the test of significance. In this study to compare a new treatment with a standard there is likely to be a minimum worthwhile important and a maximum envisaged improvement. The actual choice of θ_R will then lie between these two values.

The required number of deaths in a survival study, d, can be obtained from the equation

$$d = \frac{4(z_{\alpha/2} + z_{\beta})^2}{\theta_R^2} \qquad (1)$$

Where $z_{\alpha/2}$ and z_{β} are the upper $100(\alpha^{th})$ and $100(\beta^{th})$ percentiles of the standard normal distribution. It is convenient to write $c(\alpha,\beta) = (z_{\alpha/2} + z_{\beta})^2$ in equation (1), giving

$$d = 4c(\alpha,\beta)/\theta_R^2 \qquad (2)$$

The derivation of the result in equation (2) assumes that the same number of individuals is to be assigned to each treatment group. If this is not the case, a modification has to be made. In particular, if the proportions of individuals to be

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allocated to Group I and II are π_1 and π_2 respectively, the required total number of deaths becomes

$$d = \frac{c(\alpha, \beta)}{\pi_1 \pi_2 \theta_R^2}$$

The survival rate in two years for the new treatment group is 0.86 (Rao, et al., 2005) and it yields 0.68 (Rose, et al., 1999)for the standard treatment group. This information can be used to calculate a value for θ_R. To do this, we use the result that if the hazard functions are assumed to be proportional, the survivor function for an individual on the new treatment at time *t* is

$$S_N(t) = [S_S(t)]^{\psi} \quad (3)$$

where $S_S(t)$ is the survivor function for an individual on the standard treatment at *t* and ψ is the hazard ratio. Therefore,

$$\psi = \frac{\log S_N(t)}{\log S_S(t)}$$

and so the value of ψ corresponding to an increase in *S(t)* from 0.68 to 0.86 is

$$\psi = \frac{log(0.86)}{log(0.68)} = 0.3911$$

To calculate the number of deaths that would be required in a study to compare the two treatments, we will take $\alpha = 0.05$ and $1 - \beta = 0.8$. With theses values of α and β, the value of the function $c(0.05, 0.2) = 7.85$ and taking $\theta_R = log(0.3911) = -0.4077$, the number of deaths required to have a 80% chance of detecting a hazard ratio of 0.3911 to be significant at the 90% level is then given by

$$d = \frac{4 \times 7.85}{0.4077^2} = 188.91$$

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Allowing for possible underestimation, this can be rounded up to 190 deaths in total. This means that approximately 95 deaths would need to be observed in each treatment group.

3.3 Data Collection

The steps of collecting data was following:

1 The Proposal will be submitted to the ethic committee of the Faculty of Medicine Siriraj Hospital.

2 The researcher searched for all hospital numbers of cervical cancer who had received treatment between 1 January 2002 to 31 August 2004 at the Department of Radiotherapy, Siriraj Hospital. From the original, about a list of 400 patients. So we selected all of those subjects from medical record.

3.3.1 Preparing Data

The variables in this study were classified into two groups.

3.3.1.1 **Dependent Variables:** survival time in months and last status (death or survive) , grading of acute complications(Hemoglobin, Leukocytes, Platelets, Creatinine, Nausea, Vomiting, Diarrhea and Cystitis) and grading of late complications(Bladder, Gastrointestinal, Mucous Membrane, Skin, Neuropathy and Subcutaneous Tissue).

3.3.1.2 **Independent Variables:**age,staging,pathological types,Kanofsky Performance Status, Radiation Dose, Surgery and Response after treatment at 3 months.

The total of independent variables had seven. Five of them were category variables, consist of Pathological Types, Stage, Radiation Dose, Surgery and Response after treatment.

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Table 3 Coding for the Category Variables

Variable	Category variables	Dummy variables (D)		
	Independent variables	**D1**	**D2**	**D3**
X1	**Pathological types**			
	Squamous cell carcinoma	0	0	
	Adenocarcinoma	1	0	
	Others	0	1	
X2	**Stage**			
	Stage I	0	0	0
	Stage II	1	0	0
	Stage III	0	1	0
	Stage IV	0	0	1
X3	**Radiation dose**			
	Standard dose(45-60 Gy+Brachy)	0	0	
	Less than standard dose	1	0	
	More than standard dose	0	1	
X4	**Surgery**			
	Yes	0		
	No	1		
X5	**Response after treatment at 3rd mo.**			
	Complete response (CR)	0	0	
	Partial response (PR)	1	0	
	Progress disease (PD)	0	1	

3.4 Statistical Analysis

3.4.1 Survival Analysis

1. Using descriptive(frequency and percent) to describe independent variables such as stage, pathological types, radiation dose, surgery and result. And

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median use to describe continuous variables such as age and Kanofsky Performance Status(KPS).

2. Kaplan-Meier method was used to interpret survival rate that was adjusted by each independent variables; such as age, stage, pathological types, radiation dose, KPS, surgery and result.

3. Cox's Proportional Hazard Model was used to determine prognostic factors of death of cervical cancer. Model selection was performed using the *Wald* chi-squared test.

3.4.2 Acute Complications

1. Using frequency and percent to describe independent variables such as stage, pathological types, radiation dose, surgery and result. And, median use to describe continuous variables such as age and Kanofsky Performance Status(KPS).

2. Chi-square test and Fisher's exact test used to analyze the differentiate of acute complications between cisplatin based and carboplatin based; such as Hemoglobin, Leukocytes, Platelets, Creatinine, Nausea, Vomiting, Diarrhea and Cystitis.

3. Binary Logistic Regression used to analyze the differentiate of acute complication between cisplatin based and carboplatin based; such as Hemoglobin, Leukocytes, Platelets, Creatinine, Nausea, Vomiting, Diarrhea and Cystitis.

4. Compared the resulted of Chi-square test or Fisher's exact test and Binary Logistic Regression; such as *p-value*, 95% CI of OR and Odds ratio.

3.4.3 Late Complications

1. Using frequency and percent to describe independent variables such as stage, pathological types, radiation dose, surgery and result. And, median and range used to describe continuous variables such as age and Kanofsky Performance Status(KPS)

2. Generalized Estimating Equations used to analyse each late complications. Model fitting were considered by *p-value* and *Wald* Chi-Squared.

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CHAPTER IV
RESULTS

The total number of patients was 266, that were available for the analysis of survival. 244 patients the number in analysis of acute complications, because 22 patients were excluded due to lost of contact during treatments. 198 patients were available for analysis the late complications. The reasons to exclude were patients who had lost contact between treatments or had follow-up less than 4 times.

The contents of result were separated into 3 parts as following.

4.1 Result of Survival Analysis

4.2 Result of Acute Complications

4.3 Result of Late Complications

4.1 Result of Survival Analysis

There were 266 patients , 186 (69.92%) in Carboplatin group and 80 (30.08%) in Cisplatin group. For the survival rate study of two treatment groups, the results were divide into 3 parts, in following.

4.1.1 Characteristics of the sample

4.1.2 Descriptive of survival rate and survival function by Kaplan-Meier and survival rate

4.1.3 Model fitting by Cox proportional hazard

4.1.1 Characteristics of the Sample

The covariate variables were age, stage pathological types, kanofsky performance status(KPS), radiation dose , sugery and response after treatment. In age group, 45-59 year old group has much more than the others with 42(53.16%) and 81(43.78%) in

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cisplatin and carboplatin arms respectively. Almost all of the pathological types were squamouscell carcinoma 200(75.1%), 59(73.8%) and 141(75.8%) by total, cisplatin and carboplatin; respectively.

The homogeneity of treatment groups with respect to patients' characteristics, were analyzed the seven variables to describe the difference of two treatment groups. There were two variables that showed statistically significant associations with two treatment groups. Theses variables were the age groups (*P-value* = 0.003) and radiation dose (*P-value* = 0.005) and we concluded that the others variables were not different between the two treatment groups shown in Table 4.

Table 4 Patients Characteristic (Separate by Treatment Groups, n=266)

Variables	Cisplatin No. (%)	Carboplatin No. (%)	Total (%)	*P*-value Of χ^2
Age				**0.003***
< 45	31(39.24)	56(30.27)	87(32.95)	
45-59	42(53.16)	81(43.78)	123(46.60)	
≥ 60	6(7.60)	48(25.95)	54(20.45)	
Total	**79(100.0)**	**185(100.0)**	**264(100.0)**	
Stage				**0.511**
IB	5(6.25)	14(7.53)	19(7.14)	
IIA	0(0.0)	10(5.38)	10(3.76)	
IIB	34(42.5)	81(43.55)	115(43.23)	
IIIA	0	2(1.07)	2(0.75)	
IIIB	41(51.25)	79(42.47)	120(45.12)	
Total	**80**	**186**	**266**	
Pathological Types				**0.840**
Squamouscell carcinoma	59(73.75)	141(75.81)	200(75.19)	
Adenocarcinoma	18(22.5)	42(22.58)	60(22.56)	
Others	3(3.75)	3(1.61)	6(2.25)	
Total	**80**	**186**	**266**	

* = Significant with *p-value* ≤ 0.05

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Table 4 Patients Characteristic (Separate by Treatment Groups, n=266) (Cont.)

Variables	Cisplatin No. (%)	Carboplatin No. (%)	Total (%)	*P*-value Of χ^2
Kanofsky Performance Status				**0.299**
≤ 80 %	17(21.25)	28(15.14)	45(16.98)	
>80 %	63(78.75)	157(84.86)	220(83.02)	
Total	**80**	**185**	**265**	
Radiation Dose [Appendix A]				**0.005***
Standard radiation dose	50(62.50)	154(82.79)	204(76.69)	
Less than standard dose	4(5.00)	9(4.85)	13(4.89)	
More than standard dose	20(25.00)	20(10.75)	40(15.04)	
Data Missing	6(7.5)	3(1.61)	9(3.38)	
Total	**80**	**186**	**266**	
Surgery				**0.308**
Yes (Pre or Post Treatment)	3(3.75)	15(8.06)	18(6.77)	
No	77(96.25)	171(91.94)	248(93.23)	
Total	**80**	**186**	**266**	
Response after treatment				**0.526**
CR	67(84.81)	145(78.80)	212(80.61)	
PR	10(12.66)	33(17.93)	43(16.35)	
PD	2(2.53)	6(3.24)	8(3.04)	
Total	**79**	**184**	**263**	

* = Significant with *p-value* ≤ 0.05

4.1.2 Descriptive of survival rate and survival function by Kaplan-Meier and survival rate

4.1.2.1 Life Table

Life table of cisplatin group and carboplatin group are shown in Table 5 and Table 6. Table 5 (cisplatin grop) shown the intervals of 12-14, 24-26, 36-38 months had the proportion of alive 0.8000, 0.7500 and 0.7250, respectively. And Table 6 (carboplatin group) shown the intervals of 12-14, 24-26, 36-38 months had the proportion of alive

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0.8875, 0.7742 and 0.7097, respectively. For cisplatin, the proportion of alive after 29 months was constant at 0.7250. But carboplatin was constant after 38 months at 0.7097. The result shown after 36 months,the proportion of alive of cisplatin had higher than carboplatin.

Table 5 Life table of Cisplatin Group

Days since Entry *t*	Number of patients Alive *m*[*t*]	Number of deaths Since entry *d*[*t*]	Proportion alive $\hat{S}[t] = m[t]/n$	Proportion dead $\hat{D}[t] = d[t]/n$
0	80	0	1.0000	0.0000
1-2	79	1	0.9875	0.0125
3-5	79	1	0.9875	0.0125
6-8	78	2	0.9750	0.0250
9-11	74	6	0.9250	0.0750
12-14	71	9	0.8875	0.1125
15-17	66	14	0.8250	0.1750
18-20	64	16	0.8000	0.2000
21-23	61	19	0.7625	0.2375
24-26	60	20	0.7500	0.2500
27-29	59	21	0.7375	0.2625
30-32	58	22	0.7250	0.2750
33-35	58	22	0.7250	0.2750
36-38	58	22	0.7250	0.2750
39-41	58	22	0.7250	0.2750
42-44	58	22	0.7250	0.2750
45-47	58	22	0.7250	0.2750
48-50	58	22	0.7250	0.2750
≥51	58	22	0.7250	0.2750

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Table 6 Life table of Carboplatin Group

Days since Entry *t*	Number of patients Alive *m*[*t*]	Number of deaths Since entry *d*[*t*]	Proportion alive $\hat{S}[t] = m[t]/n$	Proportion dead $\hat{D}[t] = d[t]/n$
0	80	0	1.0000	0.0000
1-2	79	1	0.9875	0.0125
3-5	79	1	0.9875	0.0125
6-8	78	2	0.9750	0.0250
9-11	74	6	0.9250	0.0750
12-14	71	9	0.8875	0.1125
15-17	66	14	0.8250	0.1750
18-20	64	16	0.8000	0.2000
21-23	61	19	0.7625	0.2375
24-26	60	20	0.7500	0.2500
27-29	59	21	0.7375	0.2625
30-32	58	22	0.7250	0.2750
33-35	58	22	0.7250	0.2750
36-38	58	22	0.7250	0.2750
39-41	58	22	0.7250	0.2750
42-44	58	22	0.7250	0.2750
45-47	58	22	0.7250	0.2750
48-50	58	22	0.7250	0.2750
≥51	58	22	0.7250	0.2750

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4.1.2.2 Test The Assumption for Survival Analysis

One of the main assumptions of the Cox proportional hazard model is proportionality. We will check proportionality by including time-dependent covariates in the model. Time dependent covariates are interactions of the predictors and time. In this analysis we choose to use the interactions with log(**time**). The time-dependent covariate is no significant this indicates no violation of the proportionality assumption for specific predictor.

4.1.2.3 Survival Function by Kaplan-Meier

For the part of Kaplan- Meier, we shows for only significantly variables from chi-square test(Table 4; *i.e.* age and radiation dose) and describe for overall survival(OS) and disease-specific survival(DSS).

4.1.2.4 Overall Function

In this study, at the end of observation (cut-point on September 12, 2006), the number of patients that died can not reach 50%, so we can't identify median survival. But at 75th percentiles survival of overall group, ciplatin group and carboplatin group were 29.05, 25.18 and 30.39months, respectively.

In the cisplatin group, 58 of 80 patients were alive. The carboplatin group, 131 from 186 patients were alive. Fig. 4 shows the overall survival rate. The difference between cisplatin and carboplatin was not significant (*P-value* = 0.82, by log rank test).

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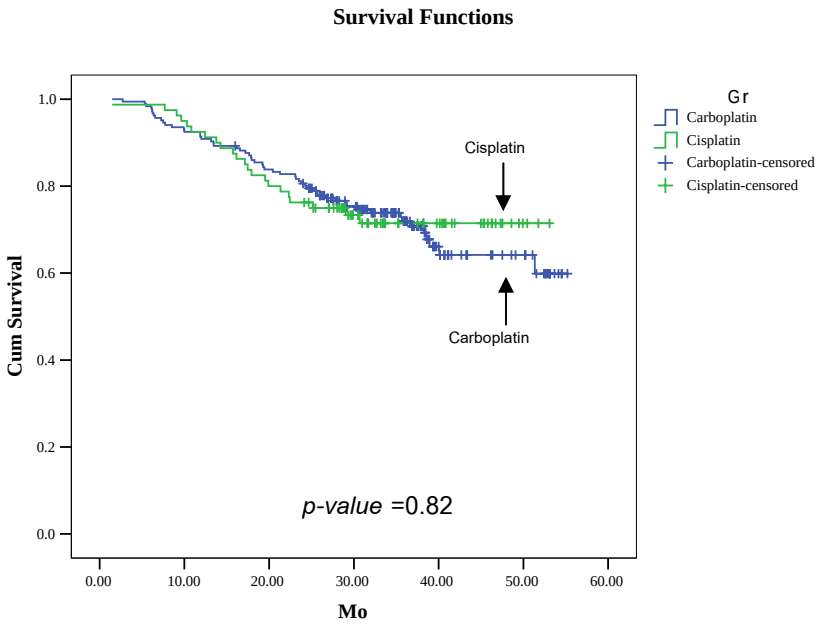

Figure 6. Overall survival function

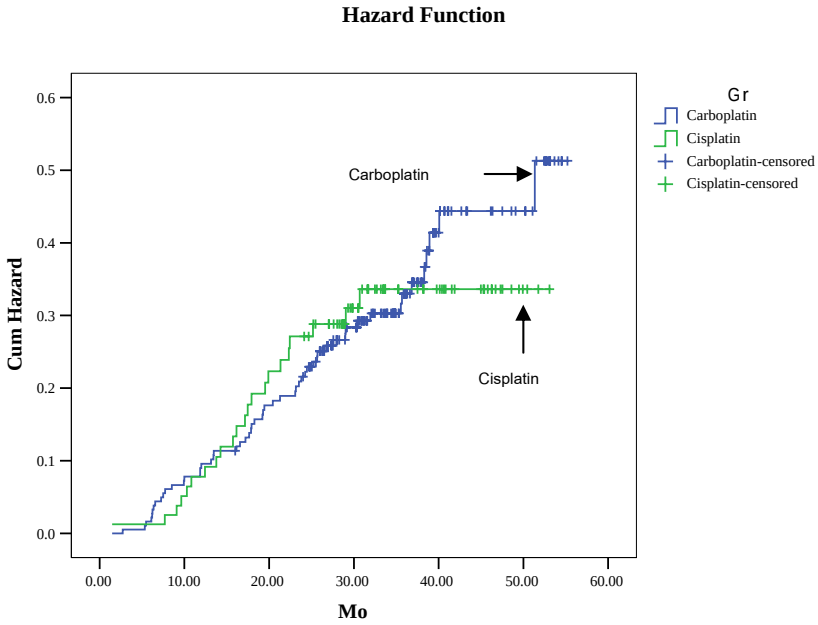

Figure 7. Overall hazard function

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4.1.2.5 Disease – Specific Survival(DSS) of Cervical Cancer by Treatment Groups

Fig.6 shows graphs of disease-specific survival by treatment groups. Table 8 shows the number of disease-specific survival in cisplatin groups was dead of disease(DOD) = 16(72.73%), other=4(18.18%), unknown=2(9.09%). Carboplatin groups was DOD =40(72.73%), other= 9(16.37%) and unknown = 6(10.90%). The difference between cisplatin and carboplatin was not significant (*P-value* = 0.838).

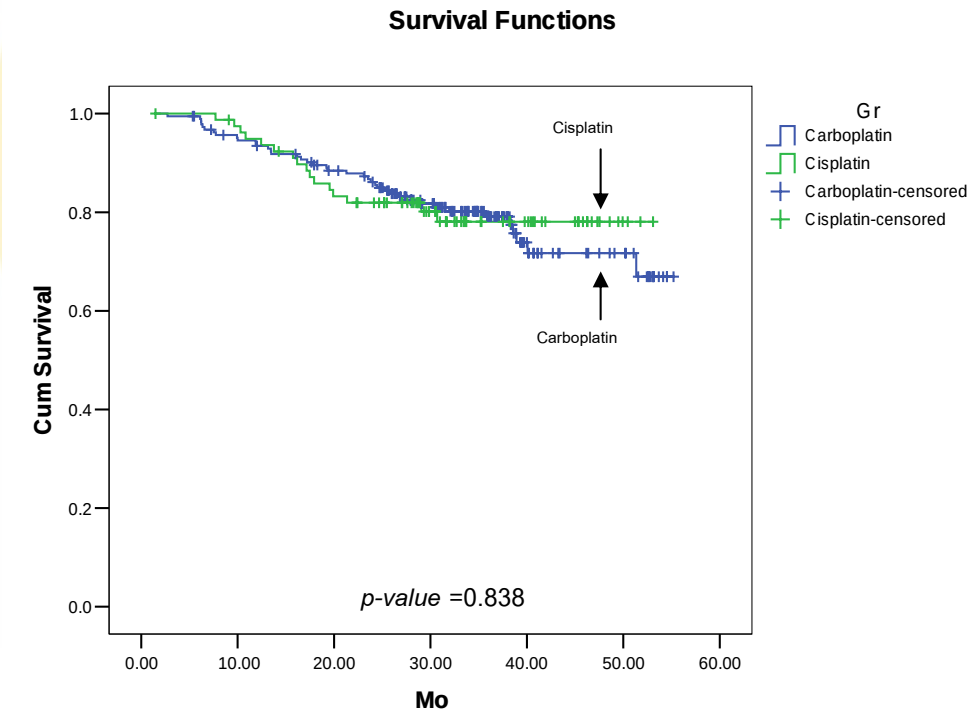

Fig.8 Kaplan-Meier Survival and Hazard Functions of DSS of Cervical Cancer by Treatment Groups

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Table 7 Count number of cause of death by treatment group

Time	Cisplatin			Carboplatin		
	DOD	Others	Unknown	DOD	Others	Unknown
< 3 mo.	-	-	-	1	-	-
3-5 mo.	-	-	-	-	2	-
6-11 mo.	4	1	-	11	1	1
12-17 mo.	7	1	-	7	2	1
18-23 mo.	3	1	1	6	2	2
24-29 mo.	1	1	-	7	1	1
30-35 mo.	1	-	-	3	-	1
36-41 mo.	-	-	-	4	1	-
42-47 mo.	-	-	-	-	-	-
> 48 mo.	-	-	1	1	-	-

4.1.2.6 Survival Function Adjusted by Age

The survival function stratifications by age are shown as Fig.9-Fig.11 The Kaplan-Meier survival functions were separated for 3 stratums: age less than 45 years , age between 45-59 years and age more than or equal 60 years. *P-value* for pooled over stratums was 0.829. So, that was no statistically significant when we adjusted by age agoup. Fig.9 shows age less than 45 years(Log rank test, *p-value* =0.701); the survival rate of cisplatin and carboplatin group at 12 mo.= 0.9143 and 0.8793, 24 mo. =0.7714 and 0.7759, 36 mo. = 0.7005 and 0.6536 , 48 mo. = 0.7005 and 0.5716, respectively. Fig.10 shows the age between 45-59 years(Log rank test, *p-value* =0.570); the survival rate of cisplatin and carboplatin at 12 mo.= 0.9091 and 0.9213, 24 mo. 0.7500= and 0.8021, 36 mo. 0.7167 = and 0.7390 , 48 mo. 0 .7167 = 0.6880, respectively. The Fig. 11 shows age more than or equal 60 years(Log rank test, *p-value* =0.117); the survival rate of cisplatin and carboplatin at 12 mo. 0.8333 = and 0.9167, 24 mo. = 0.6667 and 0.8333, 36 mo. = 0.4444 and 0.8098 , 48 mo. = none(cisplatin) and 0.7499(carboplatin), respectively

Table 8-Table 10 shows the cumulative(Cum.) survival rate(SR) and standard error of cum. SR at steps of 1 month, 3 months, 6 months, 1 year, 2 years, 3 years and 4 years.

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4.1.2.6.1 Age Less than 45 Years

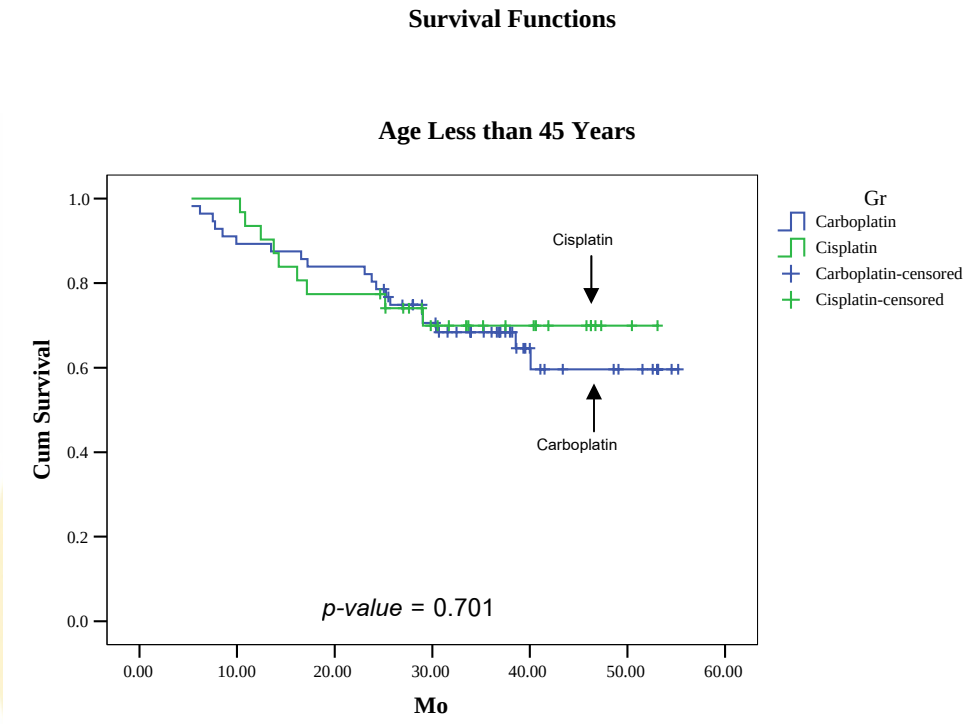

Fig.9 Survival Function of Age Below 45 Years

Table 8 Survival Rate(SR) of Age Less Than 45 Years

Time	Cisplatin		Carboplatin	
	Cum. Survival Rate(SR)	SE of Cum. (SR)	Cum. Survival Rate(SR)	SE of Cum. (SR)
1 mo.	1.0000	0.0000	1.0000	0.0000
3 mo.	1.0000	0.0000	1.0000	0.0000
6 mo.	1.0000	0.0000	0.9655	0.0240
1 yr.	0.9143	0.0473	0.8793	0.0428
2 yr.	0.7714	0.0710	0.7759	0.0548
3 yr.	0.7005	0.0806	0.6536	0.0655
4 yr.	0.7005	0.0806	0.5716	0.0793

***P-value* of Log Rank statistic = 0.701**

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4.1.2.6.2 Age Between 45-59 Years

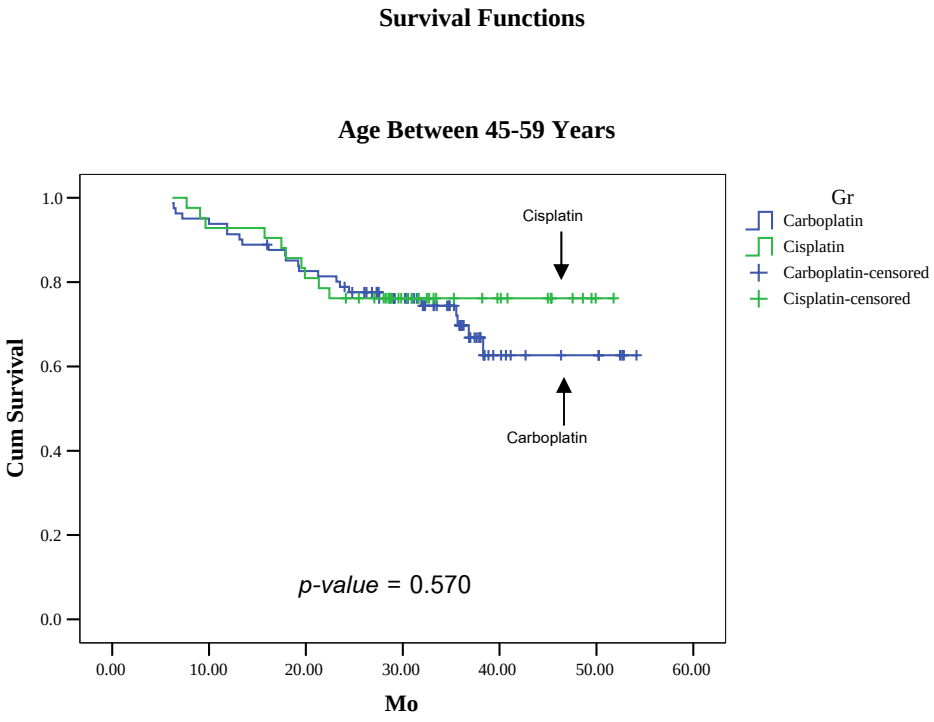

Fig.10 Survival Function of Age Between 45-59 Years

Table 9 Survival Rate(SR) of Age Between 45-59 Years

Time	Cisplatin		Carboplatin	
	Cum. Survival Rate(SR)	SE of Cum. (SR)	Cum. Survival Rate(SR)	SE of Cum. (SR)
1 mo.	0.9773	0.0225	1.0000	0.0000
3 mo.	0.9773	0.0225	0 .9921	0.0078
6 mo.	0.9773	0.0225	0.9528	0.0188
1 yr.	0.9091	0.0433	0.9213	0.0239
2 yr.	0.7500	0.0653	0.8021	0.0355
3 yr.	0.7167	0.0704	0.7390	0.0433
4 yr.	0 .7167	0.0704	0.6880	0.0533

***P-value* of Log Rank statistic = 0.570**

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4.1.2.6.3 Age More Than or Equal 60 Years

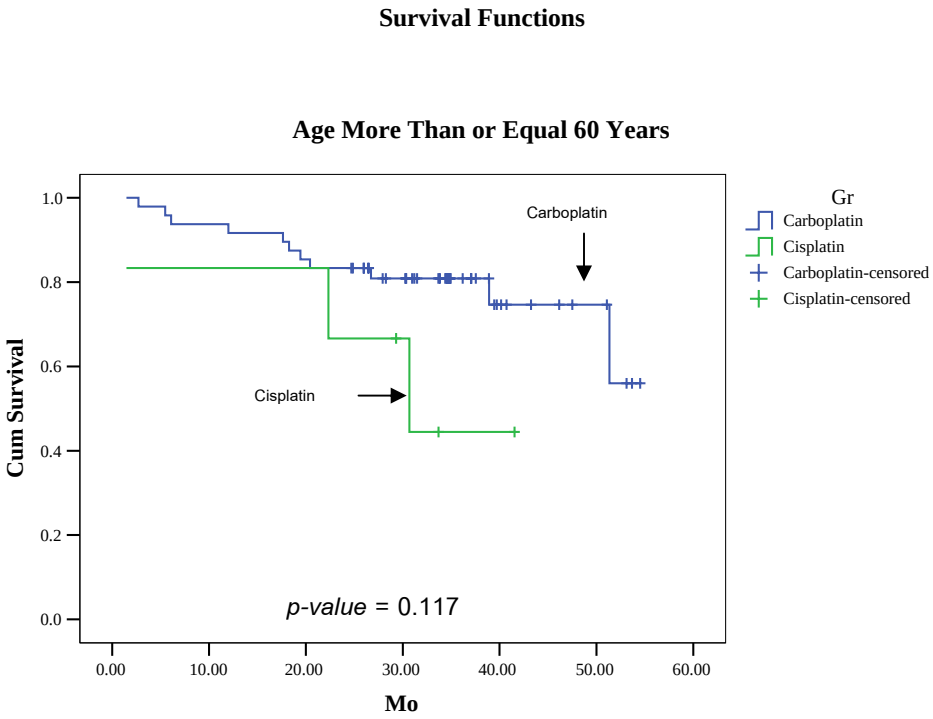

Fig.11 Survival Function of Age Upper or Equal 60 Years

Table 10 Survival Rate(SR) of Age Upper or Equal 60 Years

Time	Cisplatin		Carboplatin	
	Cum. Survival Rate(SR)	SE of Cum. (SR)	Cum. Survival Rate(SR)	SE of Cum. (SR)
1 mo.	0.8333	0.1521	1.0000	0.0000
3 mo.	0.8333	0.1521	0.9792	0.0206
6 mo.	0.8333	0.1521	0.9375	0.0349
1 yr.	0.8333	0.1521	0.9167	0.0398
2 yr.	0.6667	0.1924	0.8333	0.0537
3 yr.	0.4444	0.2222	0.8098	0.0571
4 yr.	-	-	0.7499	0.0783

***P-value* of Log Rank statistic = 0.117**

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4.1.2.7 Survival Function Adjusted by Radiation Dose

The survival function stratifications by Radiation Dose are shown as Fig.12-Fig.14 The Kaplan-Meier survival functions were separated for 3 stratums: standarad radiation dose, More than standard dose and Less than standard dose. *P-value* for pooled over stratums was 0.831. So, that was not statistically significant when adjusted by radiation dose. Fig.12 shows standarad radiation dose(Log rank test, *p-value* = 0.892); the survival rate of cispltin and carboplatin at 12 mo. =0.9200 and 0.9091, 24 mo. = 0.7600 and 0.7914, 36 mo. = 0.7383 and 0.6988 , 48 mo. = 0.7383 and 0.6799, respectively. Fig.13 shows More than the standard dose(Log rank test, *p-value* = 0.786); the survival rate of cisplatin and carboplatin at 12 mo.= 0.8500 and 0.9000, 24 mo. = 0.6500 and 0.8000, 36 mo. = 0.6500 and 0.6933 , 48 mo. = none(cisplatin) and 0.5547(carboplatin), respectively. The Fig.14 shows Less than the standard dose(Log rank test, *p-value* = 0.420); the survival rate of cisplatin and carboplatin at 12 mo.= 1.0000 and 0.8889, 24 mo. = 1.0000 and 0.8889, 36 mo. = 0.5000 and 0.8889 and none at 48 mo., respectively.

Table 11-Table 13 show the cumulative(Cum.) survival rate(SR) and standard error of cum. SR at steps of 1 month, 3 months, 6 months, 1 year, 2 years, 3 years and 4 years.

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4.1.2.7.1 Standard Radiation Dose

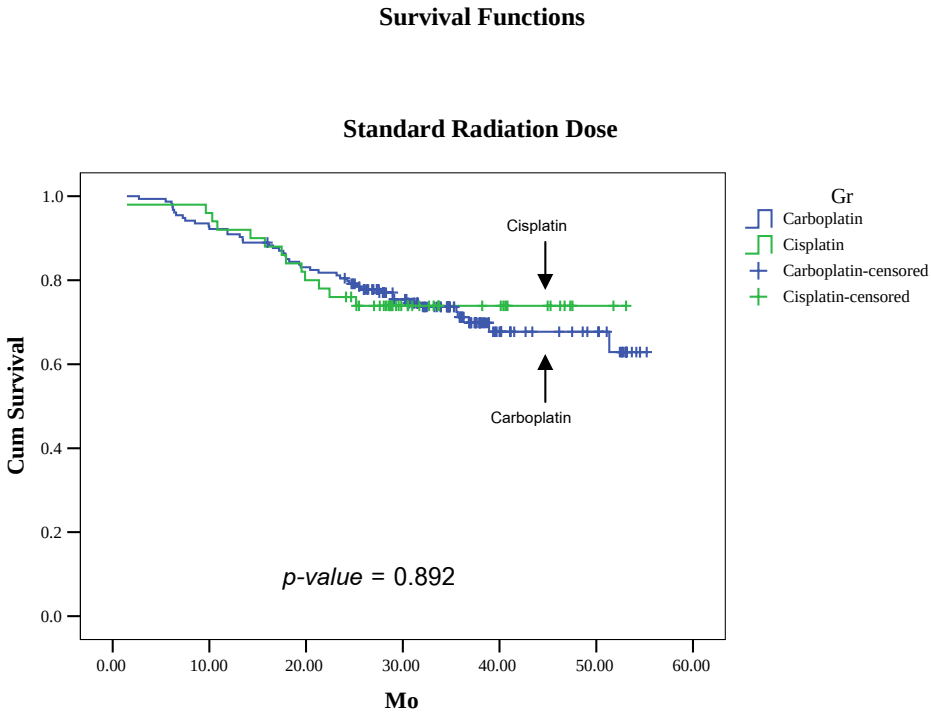

Fig.12 Survival Function of Standard Radiation Dose

Table 11 Survival Rate(SR) of Standard Radiation Dose

Time	Cisplatin		Carboplatin	
	Cum. Survival Rate(SR)	SE of Cum. (SR)	Cum. Survival Rate(SR)	SE of Cum. (SR)
1 mo.	0.9800	0.0198	1.0000	0.0000
3 mo.	0.9800	0.0198	0.9935	0.0065
6 mo.	0.9800	0.0198	0.9545	0.0168
1 yr.	0.9200	0.0384	0.9091	0.0232
2 yr.	0.7600	0.0604	0.7914	0.0328
3 yr.	0.7383	0.0625	0.6988	0.0407
4 yr.	0.7383	0.0625	0.6799	0.0438

***P-value* of Log Rank statistic = 0.892**

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4.1.2.7.2 More Than Standard Radiation Dose

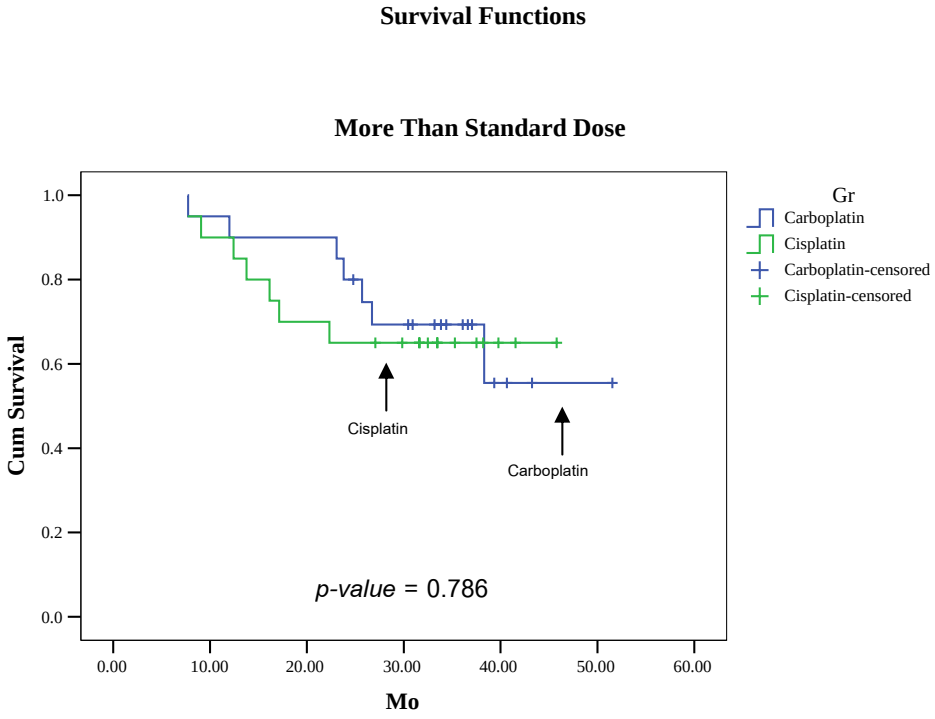

Fig.13 Survival Function Upper Standard Radiation Dose

Table 12 Survival Rate(SR) of More Than Standard Radiation Dose

Time	Cisplatin		Carboplatin	
	Cum. Survival Rate(SR)	SE of Cum. (SR)	Cum. Survival Rate(SR)	SE of Cum. (SR)
1 mo.	1.0000	0.0000	1.0000	0.0000
3 mo.	1.0000	0.0000	1.0000	0.0000
6 mo.	1.0000	0.0000	1.0000	0.0000
1 yr.	0.8500	0.0798	0.9000	0.0671
2 yr.	0.6500	0.1067	0.8000	0.0894
3 yr.	0.6500	0.1067	0.6933	0.1046
4 yr.	-	-	0.5547	0.1496

***P-value* of Log Rank statistic = 0.786**

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4.1.2.7.3 Less Than Standard Radiation Dose

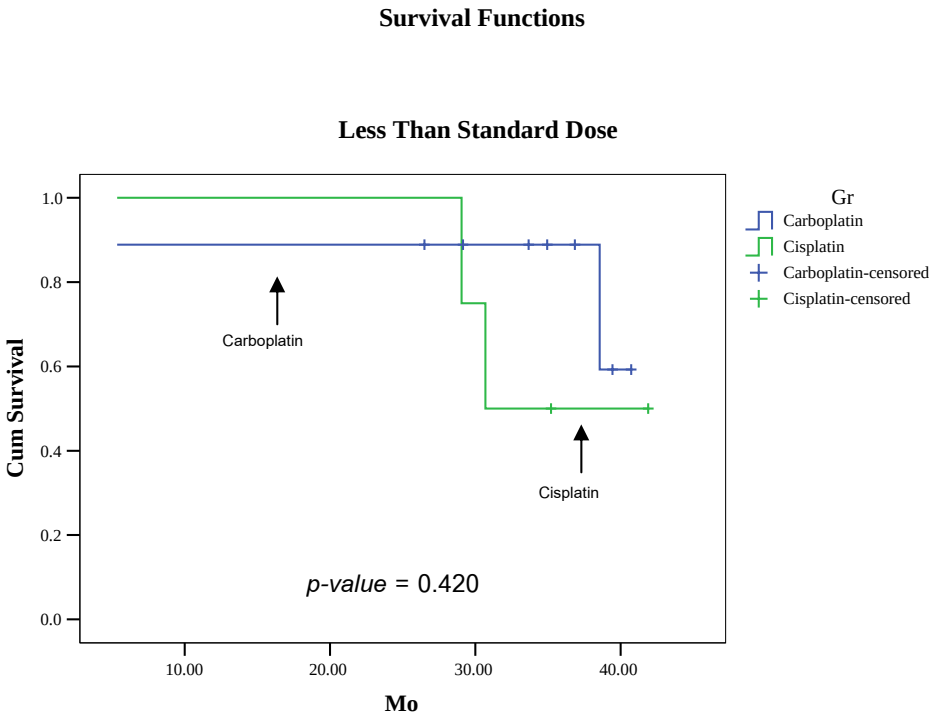

Fig.14 Survival Function of Less Than Standard Radiation Dose

Table 13 Survival Rate(SR) of Less Than Standard Radiation Dose

Time	Cisplatin		Carboplatin	
	Cum. Survival Rate(SR)	SE of Cum. (SR)	Cum. Survival Rate(SR)	SE of Cum. (SR)
1 mo.	1.0000	0.0000	1.0000	0.0000
3 mo.	1.0000	0.0000	1.0000	0.0000
6 mo.	1.0000	0.0000	0.8889	0.1048
1 yr.	1.0000	0.0000	0.8889	0.1048
2 yr.	1.0000	0.0000	0.8889	0.1048
3 yr.	0.5000	0.2500	0.8889	0.1048
4 yr.	-	-	-	-

***P-value* of Log Rank statistic = 0.420**

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4.1.3 Model Fitting by Cox Proportional Hazard Analysis

The independent variables have 8 variables, classified by six qualitative variables such as stage, pathological, radiation dose, surgery, treatment groups and response after treatment. And two quantitative were age and Kanofsky Performance Status(KPS). In the methods of the model selection, the researcher used to compare between ENTER and BACKWARD. The final model of those methods didn't different, So we will show only the method of ENTER at final step(Fifthth step). For Firstst step – Forthth step, those showed step by step for removed each variables in Appendix F(Part B).

The final step ,the result shown in Table 14,the independent variables for this pattern was age, stage, group and response after treatment. The -2 log likelihood was 767.845. When we considered each independent variable,only one variable was significant (response after treatment). Therefore, we described the relative risk for each independent variable such age, stage, group of treatments and response after treatment.

For age, when the age increase for 1 year, that means the patients had lower risk of death by 0.99 times (95% CI, 0.967 to 1.1013) and *p-value* equal 0.374. The stage, the relative risk for stage II equals 0.919. That means, the patients with stage II had lower risk of death by 0.919 times relative to those with stage I (95% CI, 0.316 to 2.673) and *p-value* equal 0.876. For stage III, the coefficient equals 0.660. So, the patients with stage III had a higher risk of death by 1.935 times relative to those with stage I(95% CI, 0.667 to 5.612) and *p-value* equal 0.224.For a group of treatments, the relative risk of carboplatin group equals 1.196. That means, the patients with carboplatin group had a higher risk by 1.196 times relative to those with cisplatin group (95% CI,0.705 to 2.208) and *p-value* equal 0.507. And the response after treatment, the relative risk for partial response(PR) equal 2.026. That means, the patients with PR had higher risk by 2.026 times relative to those with complete response(CR) (95% CI, 1.179 to 3.500) and *p-value* equal 0.011. And for progress disease (PD), the relative risk equal 15.185 times relative to those with CR (95% CI, 6.907 to 33.383) and *p-value* lower than 0.001.

The cox proportional hazard model in the final step was the following:

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5th STEP

$$\ln\left(\frac{h_{it}}{h_{0t}}\right) = -0.010\boldsymbol{Age} - 0.085\boldsymbol{StageII} + 0.660\boldsymbol{StageIII} + 0.179\boldsymbol{Carboplatin} + 0.706\boldsymbol{PR} + 2.720\boldsymbol{PD}$$

Table 14 Cox Proportional Hazard Function for 5th Step

Variables	$\hat{\beta}$	RR	95 % CI of RR		*P*-value
			Lower	Upper	
Age	-0.010	0.990	0.967	1.013	0.374
Stage					
Stage I	-	1			
Stage II	-0.085	0.919	0.316	2.673	0.876
Stage III	0.660	1.935	0.667	5.612	0.224
Group					
Cisplatin	-	1			
Carboplatin	0.179	1.196	0.705	2.028	0.507
Response after treatment at 3rd mo.					
Complete Response(CR)	-	1			
Partial Response(PR)	0.706	2.026	1.173	3.500	0.011*
Progress Disease(PD)	2.720	15.185	6.907	33.383	< 0.001*

***** = Significant (*P*-value $\leq$ 0.05)

4.2. Result of Acute Complications

The part of acute complications, have eight variables such as hemoglobin, leukocytes, platelets, creatinine, nausea, vomiting, diarrhea and cystitis. The result was discussed in 2 ways, the first was explained by Odds Ratio for each complication which was significant. It is divided by the result from Fisher's exact test(Table16) and the result form binary logistic regression(Table 17). And the last way was compared by the result of Fisher's exact test and binary logistic regression (Table 18) in the term of Odds ratio(OR), 95%CI of OR and *p-value*.

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Table 15 The Frequency for Acute Complications by Cisplatin Group and Carboplatin Group.

Complications	Grade	Group	
		Cisplatin	Carboplatin
Hemoglobin	0	59(84.28%)	146(83.91%)
	1	7(10.00%)	20(11.49%)
	2	3(4.29%)	7(4.03%)
	3	1(1.43%)	1(0.57%)
	4-5	-	-
Leukocytes	0	47(67.14%)	137(78.73%)
	1	12(17.14%)	29(16.67%)
	2	8(11.43%)	6(3.45%)
	3	3(4.29%)	2(1.15%)
	4-5	-	-
Platelets	0	70(100.00%)	172(98.86%)
	1	-	-
	2	-	1(0.57%)
	3	-	-
	4	-	1(0.57%)
	5	-	-
Creatinine	0	58(82.86%)	123(70.69%)
	1	8(11.43%)	7(4.03%)
	2	4(5.71%)	3(1.72%)
	3-5	-	-
	Data Missing	-	41(23.56%)
Nausea	0	54(77.14%)	167(95.98%)
	1	11(15.72%)	6(3.44%)
	2	5(7.14%)	1(0.58%)
	3-5	-	-
Vomit	0	55(78.57%)	168(96.55%)
	1	10(14.29%)	5(2.88%)
	2	5(7.14%)	1(0.57%)
	3-5	-	-
Diarrhea	0	55(78.57%)	142(81.61%)
	1	13(18.57%)	24(13.79%)
	2	2(2.86%)	8(4.60%)
	3-5	-	-
Cystitis	0	60(85.71%)	159(91.38%)
	1	8(11.43%)	8(4.60%)
	2	2(2.86%)	3(1.72%)
	3	-	4(2.30%)
	4-5	-	-

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4.2.1.1 Acute Complications and Treatment Groups by Fisher's Exact Test

The Fisher's exact test was used to analyse acute complications as in Table 16. From eight acute complications, those showed four which were statistically significant, such as leukocytes, creatinine, nausea and vomiting. The complications weren't significant, such as hemoglobin, diarrhea and cystitis. For platelets, this variable couldn't compare the severity by treatment groups because it did not have patients in the group of cisplatin which had complication more than grade 1.

The first significant complication was Leukocytes (OR=3.87), that means the patients with cisplatin group had a higher risk to have leukocytes grade≥2 by 3.87 times relative to those with carboplatin group(*p-value*=0.007 and 95%CI, 1.484 to 10.083). Creatinine had OR equal 2.55, that means the patients with cisplatin group had a higher risk to have creatinine grade≥1 by 2.55 times relative to those with carboplatin group (*p-value* = 0.005 and 95%CI, 1.039 to 6.231). Nausea had OR equal 13.31, that means the patients with cisplatin group had a higher risk to have nausea grade≥2 by 13.31 times relative to those with carboplatin group (*p-value* = 0.008 and 95%CI, 1.526 to 116.07). And Vomiting had OR equal 13.31, that means the patients with cisplatin group had a higher risk to have vomiting grade≥2 by 13.31 times relative to those with carboplatin (*p-value* = 0.008 and 95%CI,1.526 to 116.07).

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Table 16 Comparison of Patients' Acute Complications and Treatment Groups by Fisher's Exact Test

Variables (No.)	Treatment groups		OR	95 % CI of OR		*P*-value Of χ^2
	Cisplatin(%)	Carboplatin(%)[R]		Lower	Upper	
Total No. of patients (244)	70	174	-	-	-	-
Hemoglobin (244)						
Grade ≤ 1	66 (94.28)	166 (95.40)	1.26	0.366	4.318	**0.747** [F]
Grade ≥ 2	4 (5.72)	8 (4.60)				
Leukocytes(244)						
Grade ≤ 1	59 (84.29)	166 (95.40)	3.87	1.484	10.083	**0.007***
Grade ≥ 2	11 (15.71)	8 (4.60)				
Platelets (244)						
Grade 0	70 (100.00)	172 (98.85)	-	-	-	**1.000**
Grade ≥ 1	0	2 (1.15)				
Creatinine (203)						
Grade 0	58 (82.86)	123 (70.69)	2.55	1.039	6.231	**0.05***
Grade ≥ 1	12 (17.14)	10 (5.75)				
Data Missing	0	41 (23.56)				
Nausea (244)						
Grade ≤ 1	65 (92.86)	173 (99.43)	13.31	1.526	116.07	**0.008*** [F]
Grade ≥ 2	5 (7.14)	1 (0.57)				
Vomiting (244)						
Grade ≤ 1	66 (94.29)	166 (95.40)	13.31	1.526	116.07	**0.008*** [F]
Grade ≥ 2	4 (5.71)	8 (4.60)				
Diarrhea (244)				0.126	2.948	
Grade ≤ 1	68 (97.14)	166 (95.40)	0.61			**0.729** [F]
Grade ≥ 2	2 (2.86)	8 (4.60)				
Cystitis (244)				0.752	4.148	
Grade ≤ 0	60 (85.71)	159 (91.38)	1.77			**0.242**
Grade ≥ 1	10 (14.29)	15 (8.62)				

F = Fisher's exact test, **R =** Reference group

* = Significant with *p-value* ≤ 0.05

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4.2.1.2 Compared of Patients' Acute Complications and Treatment Groups by Binary Logistic Regression

Table 17 showed the acute complications which statistic significant (*p-value* < 0.005) had 4 complications (i.e. Leukocytes, Creatinine, Nausea and Vomiting). So, the complications which had not statistic significant were Hemoglobin, Diarrhea and Cystitis. Platelets couldn't analysed because in the cisplatin group didn't have patients who had cystitis complications more than grade 0.

Leukocytes had OR equal 3.87, that means the patients with cisplatin group had a higher risk to have leukocytes grade≥2 by 3.87 times relative to those with carboplatin group (*p-value* = 0.006 and 95%CI, 1.484 to 10.083). Creatinine had OR equal 2.55, that mean the patients with cisplatin group had a higher risk to have creatinine grade≥1 by 2.55 times relative to those with carboplatin group (*p-value* = 0.041 and 95%CI, 1.039 to 6.231). Nausea had OR equal 13.3, that means the patients with cisplatin group had a higher risk to have nausea grade≥2 by 13.3 times relative to those with carboplatin group (*p-value* = 0.019 and 95%CI, 1.526 to 116.08). Vomiting had OR equal 13.31, that means the patients with cisplatin group had a higher risk to have vomiting grade≥2 by 13.31 times relative to those with carboplatin group(*p-value* = 0.019 and 95%CI, 1.526 to 116.08).

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Table 17 Acute Complications and Treatment Groups by Binary Logistic Regression.

Variables (No.)	Treatment grups		OR	95 % CI of OR		*P*-value
	Cisplatin(%)	Carboplatin(%)[R]		Lower	Upper	
Total No. of patients (244)	70	174	-	-	-	-
Hemoglobin (244)						
Grade ≤ 1	66 (94.28)	166 (95.40)	1.26	0 .366	4.318	**0.716**
Grade ≥ 2	4 (5.72)	8 (4.60)	1			
Leukocytes(244)						
Grade ≤ 1	59 (84.29)	166 (95.40)	3.87	1.484	10.083	**0.006***
Grade ≥ 2	11 (15.71)	8 (4.60)	1			
Platelets (244)						
Grade 0	70 (100.00)	172 (98.85)	-	-	-	**1.000**
Grade ≥ 1	0	2 (1.15)				
Creatinine (203)						
Grade 0	58 (82.86)	123 (70.69)	2.55	1.039	6.231	**0.041***
Grade ≥ 1	12 (17.14)	10 (5.75)	1			
Data Missing	0	41 (23.56)				
Nausea (244)						
Grade ≤ 1	65 (92.86)	173 (99.43)	13.31	1.526	116.08	**0.019***
Grade ≥ 2	5 (7.14)	1 (0.57)	1			
Vomiting (244)						
Grade ≤ 1	65 (92.86)	173 (99.43)	13.31	1.526	116.08	**0.019***
Grade ≥ 2	5 (7.14)	1 (0.57)	1			
Diarrhea (244)						**0.539**
Grade ≤ 1	68 (97.14)	166 (95.40)	0.61	0.126	2.948	
Grade ≥ 2	2 (2.86)	8 (4.60)	1			
Cystitis (244)						**0.191**
Grade ≤ 0	60 (85.71)	159 (91.38)	1.77	0.752	4.148	
Grade ≥ 1	10 (14.29)	15 (8.62)	1			

R = Reference group

* = Significant with $\alpha < 0.05$

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Table 18. was the summary of OR , 95% CI of OR and *P-value* of 2 , which was separated by Fisher's exact test and Binary logistic regression. The value of them sees no difference between two methods.

Table 18 Summary of OR , 95% CI and *P-value* Compared for Fisher's Exact Test (FET) and Binary Logistic Regression(BLR) and Classified by Acute Complications.

Variable	Method	OR	95 % CI		*P*-value
			Lower	Upper	
Hemoglobin	FET	1.26	0.366	4.318	**0.747**
	BLR	1.26	0.366	4.318	**0.716**
Leukocytes	FET	3.87	1.484	10.083	**0.007**
	BLR	3.87	1.484	10.083	**0.006**
Creatinine	FET	2.55	1.039	6.231	**0.05**
	BLR	2.55	1.039	6.231	**0.041**
Nausea	FET	13.31	1.526	116.070	**0.008**
	BLR	13.31	1.526	116.080	**0.019**
Vomit	FET	13.31	1.526	116.070	**0.008**
	BLR	13.31	1.526	116.080	**0.019**
Diarrhea	FET	0.61	0.126	2.948	**0.729**
	BLR	0.61	0.126	2.948	**0.539**
Cystitis	FET	1.77	0.752	4.148	**0.242**
	BLR	1.77	0.752	4.148	**0.191**

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4.3 Result of Late Complications

In the part of late complications, the dependent variables had six such as bladder, gastrointestinal, mucous membrane, skin, neuropathy and subcutaneous tissue. The Generalized estimating equations(GEE) used for selected for each model's complications. In the part for analysis of late complications, the sample size of this part was 198 patients, separated by two treatment groups; cisplatin and carboplatin. The the numbers for each group were 56 and 142, respectively. That mean, the patients were lost for the overall group, cisplatin group and carboplatin group; 68(25.56%) , 24(30%) and 44(21.51%), respectively. The independent variables had nine variables, in those 4 variables were general characteristics, time ,age, stage and radiation dose. The others independent variables, such as Kanofsky Performance Status(KPS), Pathological types, surgery, response after treatment, and treatment groups. The time variable defined as months of follow-up. And the groups variable were separated by cisplatin group and carboplatin group, the cisplatin group was the based line group. Then when we chose the best model by method ENTER.

4.3.1 Bladder Complication

This symptom was defined by 0 to 5 scoring [Appendix C]. Table 19 shows only final step(4^{th} step), for details of 1^{st} – 3^{rd} were showed at Appendix G. The independent variables consisted of time(months), treatment groups, age, stage, pathological types and radiation dose. Three variables having statistically significance. *i.e.* time, pathological types and radiation dose. For treatment groups having no statistically significant difference (*p-value* = 0.141).The generalized estimating equation model for predicting bladder complications was:

$$\hat{y} = -0.0380 + 0.0049\boldsymbol{Time} + 0.0529\boldsymbol{Carboplatin} + 0.0011\boldsymbol{Age} - 0.0035\boldsymbol{StageII} - 0.0089\boldsymbol{StageIII} - 0.0792\boldsymbol{Adenocarcinoma} - 0.0116\boldsymbol{Others} - 0.0584\boldsymbol{Less(RT)} + 0.0182\boldsymbol{More(RT)}$$

Which, y = 0-5 (bladder grade)

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For final model, the *Wald* χ^2 was equal 25.90.

Table 19 The Final Model for Bladder Complications

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0049	1.00	0.021*	1.0007	1.0091
Group					
Cisplatin	-	1.00			
Carboplatin	0.0529	1.05	0.141	0.9826	1.1312
Age	0.0011	1.00	0.352	0.9987	1.0035
Stage					
Stage I	-	1.00			
Stage II	-0.0035	0.99	0.914	0.9335	1.0635
Stage III	-0.0089	0.99	0.796	0.9259	1.0608
Pathological Types					
Squamouscell carcinoma	-	1.00			
Adenocarcinoma	-0.0792	0.92	< 0.001*	0.8885	0.9604
Others	-0.0116	0.98	0.854	0.8726	1.1195
Radiation Dose					
Standard RT	-	1.00			
Less than RT	-0.0584	0.94	0.045*	0.8907	0.9987
More than RT	0.0182	1.01	0.654	0.9405	1.1026
Constant	-0.0380				

***** = Significant (*P*-value $\leq$ 0.05)

Then we present a variety of correlation structures that are commonly considered when performing a correlated analysis. Table 20. compared for 3 correlation structures as follow: Exchangeable, Independent and AR1 autoregressive. The assumption behind the use of the exchangeable correlation structure is that any two responses within a cluster have the same correlation (ρ). The assumption behind the use of the independent correlation structure is that responses are uncorrelated within a cluster. Finally, the AR1

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assumption is that the correlation between any two responses from the same subject equals a baseline correlation (ρ) raised to a power equal to the absolute difference between the times of the responses. Table 21. shows the *p-value* is not different within each of correlation structure. But the *p-value* of AR1 was small less than the others.

Table 20 Comparing With-in Group Correlation Structure of Bladder Complication

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
4th model	**Exchangeable**				
	Time	1.00	1.0007	1.0091	0.021
	Carboplatin	1.05	0.9826	1.1312	0.141
	Age	1.00	0.9987	1.0035	0.352
	StageII	0.99	0.9335	1.0635	0.914
	StageIII	0.99	0.9259	1.0608	0.796
	Adenocarcinoma	0.92	0.8885	0.9604	< 0.001
	Others	0.98	0.8726	1.1195	0.854
	Less than RT	0.94	0.8907	0.9987	0.045
	More than RT	1.01	0.9405	1.1026	0.654
	***Wald* chi-square=25.90**				
	Independent				
	Time	1.01	1.0008	1.0093	0.019
	Carboplatin	1.05	0.9816	1.1324	0.147
	Age	1.00	0.9988	1.0038	0.302
	StageII	0.99	0.9306	1.0620	0.862
	StageIII	0.99	0.9234	1.0612	0.776
	Adenocarcinoma	0.92	0.8882	0.9612	< 0.001
	Others	1.00	0.8770	1.1302	0.946
	Less than RT	0.94	0.8842	0.9972	0.041
	More than RT	1.02	0.9382	1.1005	0.693
	***Wald* chi-square= 25.25**				

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Table 20 Comparing With-in Group Correlation Structure of Bladder Complication (Cont.)

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
	Autoregressive(1)				
	Time	1.00	1.0005	1.0090	0.027
	Carboplatin	1.05	0.9796	1.1308	0.162
	Age	1.00	0.9989	1.0037	0.278
	StageII	0.99	0.9275	1.0631	0.841
4th model	StageIII	0.99	0.9193	1.0622	0.748
	Adenocarcinoma	0.92	0.8848	0.9592	<0.001
	Others	0.99	0.8715	1.1138	0.812
	Less than RT	0.94	0.8836	0.9934	0.029
	More than RT	1.02	0.9445	1.1115	0.558
	***Wald* chi-square= 25.26**				

4.3.3 Gastrointestinal Complication

This symptom was defined by 0 to 5 scoring [Appendix C]. Table 21 shows only the final model (5th step), details of 1st -4th were showed at Appendix G. The independent variables consisted of time, groups, age, stage and radiation dose. Five variables were entered into this model, four having statistically significance. *i.e.* time, age, stage and radiation dose. For treatment groups having no statistically significant difference (*p-value* = 0.063). The generalized estimating equation model for predicting gastrointestinal complications was:

$$\hat{y} = -0.2446 + 0.0058\boldsymbol{Time} - 0.0555\boldsymbol{Carboplatin} + 0.0047\boldsymbol{Age} + 0.0533\boldsymbol{StageII} + 0.0868\boldsymbol{StageIII} - 0.0071\boldsymbol{Less(RT)} - 0.0629\boldsymbol{More(RT)}$$

Which, y = 0-5 (gastrointestinal grade)

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For final model, the $Wald\ \chi^2$ equal 21.52. Table 22 shows a comparison of within group correlation structure of gastrointestinal complication and the *p-value* with no difference within each of correlation structure.

Table 21 The Final Model for Gastrointestinal Complication

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0058	1.01	0.004*	1.0019	1.0099
Group					
Cisplatin	-	1.00			
Carboplatin	-0.0555	0.95	0.063	0.8922	1.0029
Age	0.0047	1.00	0.051*	0.9999	1.0096
Stage					
StageI	-	1.00			
StageII	0.0533	1.05	0.027*	1.0059	1.1060
StageIII	0.0868	1.09	0.035*	1.0060	1.1824
Radiation Dose					
Standard RT	-	1.00			
Less than RT	-0.0071	0.99	0.941	0.8205	1.2012
More than RT	-0.0629	0.94	0.024*	0.8892	0.9916
Constant	-0.2446				

***** = Significant (*P*-value $\leq$ 0.05)

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Table 22 Comparing With-in Group Correlation Structure of Gastrointestinal

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
5th model	**Exchangeable**				
	Time	1.01	1.0019	1.0099	0.004
	Carboplatin	0.95	0.8922	1.0029	0.063
	Age	1.00	0.9999	1.0096	0.051
	StageII	1.05	1.0059	1.1060	0.027
	StageIII	1.09	1.0060	1.1824	0.035
	Less than RT	0.99	0.8205	1.2012	0.941
	More than RT	0.94	0.8892	0.9916	0.024
	***Wald* chi-square= 21.52**				
	Independent				
	Time	1.01	1.0018	1.0097	0.004
	Carboplatin	0.94	0.8883	0.9986	0.045
	Age	1.00	0.9996	1.0097	0.068
	StageII	1.06	1.0069	1.1112	0.025
	StageIII	1.09	1.001	1.1881	0.045
	Less than RT	0.98	0.8186	1.1810	0.857
	More than RT	0.94	0.8862	0.9924	0.026
	***Wald* chi-square= 20.49**				
	Autoregressive(1)				
	Time	1.01	1.0021	1.0095	0.002
	Carboplatin	0.95	0.8916	1.0039	0.067
	Age	1.00	0.9996	1.0093	0.071
	StageII	1.06	1.0072	1.1099	0.024
	StageIII	1.09	1.0060	1.1799	0.035
	Less than RT	0.99	0.8171	1.2033	0.932
	More than RT	0.94	0.8905	0.9945	0.031
	***Wald* chi-square= 21.47**				

4.3.4 Mucous Membrane Complication

This symptom was defined by 0 to 5 scoring [Appendix C]. Table 23 shows only the final model (5^{th} step), details of $1^{st} - 4^{th}$ were shown in Appendix G. The independent variables consisted of time, groups, age, stage and radiation dose. Five variables were entered into this model, with three having statistical significance. *i.e.* time, group and age. For treatment groups having statistically significant difference (*p-value* = 0.026).

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The generalized estimating equation model for predicting mucous membrane complications was:

$$\hat{y} = -0.1984 + 0.0063\boldsymbol{Time} + 0.1373\boldsymbol{Carboplatin} + 0.0068\boldsymbol{Age} - 0.0300\boldsymbol{StageI} + 0.0989\boldsymbol{Stage(2)} - 0.0450\boldsymbol{Less(RT)} - 0.0083\boldsymbol{More(RT)}$$

Which, y = 0-5 (gastrointestinal grade)

For final model, the *Wald* χ^2 equal 20.51. Table 24 shows a comparison of within group correlation structure of mucous membrane complication and the *p-value* that no difference within each of correlation structure.

Table 23 The Final Model for Mucous Membrane

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0063	1.01	0.030*	1.0006	1.0121
Group					
Cisplatin	-	1.00			
Carboplatin	0.1373	1.15	0.026*	1.0168	1.2943
Age	0.0068	1.01	0.023*	1.0009	1.0128
Stage					
StageI	-	1.00			
StageII	-0.0300	0.97	0.686	0.8390	1.1223
StageIII	0.0989	1.10	0.217	0.9433	1.2921
Radiation Dose					
Standard RT	-	1.00			
Less than RT	-0.0450	0.96	0.744	0.7298	1.2522
More than RT	-0.0083	0.99	0.910	0.8577	1.1466
Constant	-0.1984				

***** = Significant (*P*-value $\leq$ 0.05)

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Table 24 Comparing With-in Group Correlation Structure of Mucous Membrane

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
	Exchangeable				
	Time	1.01	1.0006	1.0121	0.030
	Carboplatin	1.15	1.0168	1.2943	0.026
	Age	1.01	1.0009	1.0128	0.023
	StageII	0.97	0.8390	1.1223	0.686
	StageIII	1.10	0.9433	1.2921	0.217
	Less than RT	0.96	0.7298	1.2522	0.744
	More than RT	0.99	0.8577	1.1466	0.910
	***Wald* chi-square= 20.51**				
	Independent				
	Time	1.01	1.0006	1.0127	0.031
	Carboplatin	1.15	1.0216	1.2997	0.021
	Age	1.01	1.0003	1.0131	0.038
5th model	StageII	0.97	0.8317	1.1258	0.670
	StageIII	1.11	0.9446	1.3081	0.202
	Less than RT	0.96	0.7189	1.2760	0.768
	More than RT	0.99	0.8524	1.1480	0.887
	***Wald* chi-square= 20.71**				
	Autoregressive(1)				
	Time	1.01	1.0005	1.0118	0.033
	Carboplatin	1.15	1.0217	1.2925	0.020
	Age	1.01	1.0002	1.0126	0.040
	StageII	0.97	0.8349	1.1203	0.657
	StageIII	1.10	0.9377	1.2863	0.245
	Less than RT	0.94	0.7272	1.2032	0.603
	More than RT	0.97	0.8457	1.1168	0.688
	***Wald* chi-square= 18.69**				

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4.3.4 Skin Complication

This symptom was defined by 0 to 5 scoring [Appendix C]. Table 25 shows only the final model(4^{th} step), details of 1^{st} -3^{rd} were shown in Appendix G. The independent variables consisted of time, groups, age, stage, radiation dose and response after treatment. Six variables were entered into this model, and two having statistical significance. *i.e.* time and response after treatment. For treatment groups having no statistically significant difference (*p-value* = 0.068). The generalized estimating equation model for predicting skin complications was:

$$\hat{y} = 0.0168 - 0.0027\boldsymbol{Time} + 0.0416\boldsymbol{Carboplatin} + 0.0010\boldsymbol{Age} - 0.0113\boldsymbol{StageII} - 0.0096\boldsymbol{StageIII} - 0.0151\boldsymbol{Less(RT)} - 0.0023\boldsymbol{More(RT)} - 0.0602\boldsymbol{PR} - 0.0150\boldsymbol{PD}$$

Which, y = 0-5 (skin complication)

For the final model, the *Wald* χ^2 equal 14.42. Table 26 shows a comparison of with-in group correlation structure of skin complication and the *p-value* that was no difference within each of correlation structure.

Table 25 The Final Model for Skin Complication

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	-0.0027	1.00	0.034*	0.9946	0.9997
Group					
Cisplatin	-	1.00			
Carboplatin	0.0416	1.04	0.068	0.9969	1.0902
Age	0.0010	1.00	0.065	0.9999	1.0021
Stage					
StageI	-	1.00			
StageII	-0.0113	0.99	0.658	0.9404	1.0395
StageIII	-0.0096	0.99	0.707	0.9420	1.0413

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Table 25 The Final Model for Skin Complication (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Radiation dose					
Standard RT	-	1.00			
Less than RT	-0.0151	0.98	0.447	0.9472	1.0241
More than RT	-0.0023	1.00	0.911	0.9583	1.0386
Response after treatment					
CR	-	1.00			
PR	-0.0602	0.94	0.004*	0.9042	0.9804
PD	-0.0150	0.99	0.287	0.9582	1.0127
Constant	0.0168				

***** = Significant (*P*-value < 0.05)

Table 26 Comparing With-in Group Correlation Structure of Skin Complication

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
	Exchangeable				
	Time	1.00	0.9946	0.9997	0.034
	Carboplatin	1.04	0.9969	1.0902	0.068
	Age	1.00	0.9999	1.0021	0.065
	StageII	0.99	0.9404	1.0395	0.658
4th model	StageIII	0.99	0.9420	1.0413	0.707
	Less than RT	0.98	0.9472	1.0241	0.447
	More than RT	1.00	0.9583	1.0386	0.911
	PR	0.94	0.9042	0.9804	0.004
	PD	0.99	0.9582	1.0127	0.287
	***Wald* chi-square= 14.42**				

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Table 26 Comparing With-in Group Correlation Structure of Skin Complication (Cont.)

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
4^{th} model	**Independent**				
	Time	1.00	0.9945	0.9998	0.035
	Carboplatin	1.04	0.9972	1.0902	0.066
	Age	1.00	0.9999	1.0021	0.069
	StageII	1.00	0.9417	1.0386	0.659
	StageIII	0.99	0.9436	1.0412	0.727
	Less than RT	0.98	0.9473	1.0230	0.426
	More than RT	1.00	0.9603	1.0405	0.986
	PR	0.94	0.9031	0.9806	0.004
	PD	0.98	0.9590	1.0088	0.201
	***Wald* chi-square= 14.82**				
	Autoregressive(1)				
	Time	1.00	0.9944	0.9995	0.023
	Carboplatin	1.04	0.9954	1.0897	0.078
	Age	1.00	0.9999	1.0022	0.065
	StageII	0.99	0.9349	1.0408	0.619
	StageIII	0.99	0.9370	1.0426	0.669
	Less than RT	0.99	0.9432	1.0308	0.536
	More than RT	1.00	0.9589	1.0431	0.995
	PR	0.94	0.9009	0.9789	0.003
	PD	0.98	0.9563	1.0142	0.309
	***Wald* chi-square= 15.28**				

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4.3.5 Neuropathy Complication

This symptom was defined by 0 to 5 scoring [Appendix C]. Table 27 shows only the final model(4^{th} step), details of 1^{st} – 3^{rd} were shown in Appendix G. The indendent variables consisted of time, groups, age, stage and pathological types and radiation dose. Six variables were entered into this model, only one variable having statistical significance. *i.e.* pathological types. For treatment groups having no statistical significant difference (*p-value* = 0.332). The generalized estimating equation model for predicting neuropathy complications was:

$$\hat{y} = 0.0078 - 0.0004\boldsymbol{Time} + 0.0066\boldsymbol{Carboplatin} - 0.0001\boldsymbol{Age} + 0.0012\boldsymbol{StageII} + 0.0137\boldsymbol{StageIII} - 0.0064\boldsymbol{Adenocarcinoma} - 0.0121\boldsymbol{Others} + 0.0097\boldsymbol{Less(RT)} + 0.0097\boldsymbol{More(RT)}$$

which, y = 0-5 (neuropathy complication)

For the final model, the $Wald\ \chi^2$ equal 8.15. Table 28 shows a comparison of with-in group correlation structure of neuropathy complication and the *p-value* that no difference within each of correlation structure.

Table 27 Final Model for Neuropathy Complication

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	-0.0004	1.00	0.135	0.9990	1.0001
Group					
Cisplatin	-	1.00			
Carboplatin	0.0066	1.01	0.332	0.9932	1.0202
Age	-0.0001	1.00	0.755	0.9995	1.0003
Stage					
StageI	-	1.00			
StageII	0.0012	1.00	0.668	0.9954	1.0071
StageIII	0.0137	1.01	0.071	0.9988	1.0291

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Table 27 Final Model for Neuropathy Complication (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Pathological Types					
Squamouscell carcinoma	-	1.00			
Adenocarcinoma	-0.0064	0.99	0.020*	0.9881	0.9989
Others	-0.0121	0.99	0.070	0.9750	1.0009
Radiation Dose					
Standard RT	-	1.00			
Less than RT	0.0097	1.01	0.488	0.9823	1.0379
More than RT	0.0084	1.01	0.311	0.9921	1.0250
Constant	0.0078				

***** = Significant (*P*-value < 0.05)

Table 28 Comparing With-in Group Correlation Structure of Neuropathy Complication

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
	Exchangeable				
	Time	1.00	0 .9990	1.0001	0.135
	Carboplatin	1.01	0 .9932	1.0202	0.332
	Age	1.00	0 .9995	1.0003	0.755
	StageII	1.00	0 .9954	1.0071	0.668
4th model	StageIII	1.01	0 .9988	1.0291	0.071
	Adenocarcinoma	0.99	0 .9881	0.9989	0.020
	Others	0.99	0 .9750	1.0009	0.070
	Less than RT	1.01	0 .9823	1.0379	0.488
	More than RT	1.01	0 .9921	1.0250	0.311
	***Wald* chi-square= 8.15**				

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Table 28 Comparing With-in Group Correlation Structure of Neuropathy Complication (Cont.)

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
4th model	**Independent**				
	Time	1.00	0.9990	1.0001	0.135
	Carboplatin	1.01	0.9931	1.0199	0.346
	Age	1.00	0.9995	1.0003	0.750
	StageII	1.00	0.9955	1.0071	0.655
	StageIII	1.01	0.9987	1.0293	0.072
	Adenocarcinoma	0.99	0.9879	0.9989	0.020
	Others	0.99	0.9751	1.0009	0.068
	Less than RT	1.01	0.9823	1.0374	0.496
	More than RT	1.01	0.9921	1.0251	0.312
	***Wald* chi-square= 8.13**				
	Autoregressive(1)				
	Time	1.00	0.9990	1.0001	0.136
	Carboplatin	1.01	0.9930	1.0199	0.348
	Age	1.00	0.9995	1.0003	0.747
	StageII	1.00	0.9955	1.0071	0.659
	StageIII	1.01	0.9987	1.0295	0.072
	Adenocarcinoma	0.99	0.9879	0.9989	0.020
	Others	0.99	0.9751	1.0009	0.068
	Less than RT	1.01	0.9822	1.0376	0.497
	More than RT	1.01	0.9920	1.0250	0.314
	***Wald* chi-square= 8.13**				

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4.3.6 Subcutaneous Tissue Complication

This symptom was defined by 0 to 5 scoring [Appendix C]. Table 29 shows only the final model(4^{th} step), details of 1^{st} – 3^{rd} were shown in Appendix G. The independent variables consisted of time, groups, age, stage, pathological types and radiation dose. Six variables were entered into this model, and two having statistical significance. *i.e.* pathological types and radiation dose. For treatment groups having no statistical significant difference (*p-value* = 0.275). The generalized estimating equation model for predicting subcutaneous tissue complications was:

$$\hat{y} = -0.0737 + 0.0018\boldsymbol{Time} + 0.0365\boldsymbol{Carboplatin} + 0.0015\boldsymbol{Age} + 0.0125\boldsymbol{StageII} + 0.0680\boldsymbol{StageIII} - 0.0314\boldsymbol{Adenocarcinoma} - 0.0672\boldsymbol{Others} - 0.0775\boldsymbol{Less(RT)} - 0.0352\boldsymbol{More(RT)}$$

Which, y = 0-5 (subcutaneous tissue)

For the final model, the *Wald* χ^2 equal 12.96. Table 30 shows a comparison of with-in group correlation structure of subcutaneous tissue complication and the *p-value* that no difference within each of correlation structure.

Table 29 Final Model for Subcutaneous Tissue Complication

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0018	1.00	0.158	0.9992	1.0043
Group					
Cisplatin	-	1.00			
Carboplatin	0.0365	1.04	0.275	0.9712	1.1077
Age	0.0015	1.00	0.453	0.9975	1.0054
Stage					
StageI	-	1.00			
StageII	0.0125	1.01	0.485	0.9775	1.0490
StageIII	0.0680	1.07	0.072	0.9939	1.1527

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Table 29 Final Model for Subcutaneous Tissue Complication (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Pathological Types					
Squamouscell carcinoma	-	1.00			
Adenocarcinoma	-0.0314	0.97	0.049*	0.9392	0.9998
Others	-0.0672	0.93	0.019*	0.8839	0.9888
Radiation Dose(RT)					
Standard RT	-	1.00			
Less than RT	-0.0775	0.92	0.019*	0.8673	0.9872
More than RT	-0.0352	0.97	0.183	0.9165	1.0168
Constant	-0.0737				

***** = Significant (*P*-value $\leq$ 0.05)

Table 30 Comparing With-in Group Correlation Structure of Subcutaneous Tissue Complication

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
	Exchangeable				
	Time	1.00	0.9992	1.0043	0.158
	Carboplatin	1.04	0.9712	1.1077	0.275
	Age	1.00	0.9975	1.0054	0.453
	StageII	1.01	0.9775	1.0490	0.485
4th model	StageIII	1.07	0.9939	1.1527	0.072
	Adenocarcinoma	0.97	0.9392	0.9998	0.049
	Others	0.93	0.8839	0.9888	0.019
	Less than RT	0.92	0.8673	0.9872	0.019
	More than RT	0.97	0.9165	1.0168	0.183
	***Wald* chi-square=12.96**				

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Table 30 Comparing With-in Group Correlation Structure of Subcutaneous Tissue Complication (Cont.)

Variable	Method	OR	95 % CI of OR		*P*-value
			Lower	Upper	
4th model	**Independent**				
	Time	1.00	0.068	0.9998	1.0050
	Carboplatin	1.04	0.283	0.9703	1.1085
	Age	1.00	0.365	0.9976	1.0063
	StageII	1.01	0.581	0.9733	1.0493
	StageIII	1.07	0.082	0.9917	1.1486
	Adenocarcinoma	0.97	0.062	0.9374	1.0016
	Others	0.94	0.040	0.8805	0.9971
	Less than RT	0.92	0.020	0.8503	0.9862
	More than RT	0.96	0.130	0.9085	1.0123
	***Wald* chi-square= 12.23**				
	Autoregressive(1)				
	Time	1.00	0.068	0.9998	1.0046
	Carboplatin	1.04	0.258	0.9724	1.1099
	Age	1.00	0.399	0.9979	1.0050
	StageII	1.01	0.674	0.9761	1.0380
	StageIII	1.07	0.056	0.9983	1.1379
	Adenocarcinoma	0.98	0.152	0.9513	1.0077
	Others	0.94	0.052	0.8899	1.0006
	Less than RT	0.93	0.020	0.8733	0.9885
	More than RT	0.96	0.136	0.9144	1.0122
	***Wald* chi-square= 10.92**				

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CHAPTER V
DISCUSSION

This chapter is concerned with the discussion for this study. The details can be described in four parts,

5.1 Material and methods

5.2 Discussion of results from survival analysis

5.3 Discussion of results from acute complications

5.4 Discussion of results from late complications

5.1 Material and Methods

This study was a retrospective cohort. There were used medical record from Siriraj hospital. There were 266 patients with cisplatin group 80(30.08%) and 186(69.92%). According to the limitation of sample size of cisplatin group.In this study, the researcher recruited all of the patients who had received treatment between January 1, 2002 to August 31, 2004 based on treatment criterions. And the follow-up time used cut point on September 12, 2006, the median follow-up time was 31.66 months. The sample size estimate was about 95 deaths for each treatment group [Chapter III], but in cisplatin group had patients who died 22(27.50%) and carboplatin group died 55(29.57%). Then that couldn’t calculate the median survival.

5.2 Discussion of Results from Survival Analysis

Two hundred and sixty-six patients were evaluated in the part of survival analysis. The median age was 49 years,which is similar to the previous study of(Houvenaeghel,

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G., *et al.*;2005)and (King, M.,*et al.*;2006)Most of the samples were in age group of 45-59 years 123(46.60%), similar to (Houvenaeghel,G., *et al.*;2005). For FIGO stage I had 19(7.14%) patients,stage II had 125(46.99%)patients and according to stageIII had 122 (45.86%)patients.This statistics were different to Tumor Registry(Siriraj Cancer Center; 2004).The pathological types divided into three groups.They consisted of squamouscell carcinoma 200(75.19%), adenocarcinoma 60(22.56%) and others 6(6.25%) which are similar to (Tinker.V.A., *et,al.*;2005).

In this study, the overall survival by Kaplan-Mier estimating functions showed *p-value* = 0.82, therefore we focused for each time of two treatment groups. In the beginning, those seem not to be different between two treatment groups. But after 40 months, they began to separated. Then the survival rate at 36,48 months of cisplatin group were 0.71 ,0.71 and carboplatin group were 0.71, 0.64. But King, M., *et al.*(2006) showed the different survival result of cisplatin group at 36 months by 0.87, that study had 79 patients ,those had patients in early stage (FIGO IIA or less)38% and 62% had locally advance tumors. The disease-specific survival (DSS) in Cisplatin groups consist to dead of disease(DOD) 16(72.73%), other 4(18.18%) and unknown 2(9.09%). So, Carboplatin groups had dead of disease(DOD) 40(78.43%), other 9(17.65%) and unknown 2(3.92%).

5.3 Discussion of Results from Acute Complications

The acute complications were defined as those occurring during or within 90 days of completing radiotherapy. The complications data contained two weakness for comparing the two groups.Firstly,there was no frequency in some grades(grade 4 and 5),secondly, the frequency in grade 0 was very big. This study showed the descriptive frequency for Hemoglobin grade 0, 1-2 and 3-5 by cisplatin and carboplatin group as 59(84.29%):146(83.91%) ,10(14.28%):27(15.52%) and 1(1.43%):1(0.57%), respectively. Leukocytes grade 0, 1-2, 3-5 by cisplatin and carboplatin as 47(67.14%):137(78.73%), 20(28.57%):35(20.12%) and 3(4.29%):2(1.15%), respectively. Platelets grade 0, 1-2, 3-5 by cisplatin and carboplatin as 70(100.00%):172(98.86%), 0: 1(0.57%) and 0: 1(0.57%),

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respectively. Creatinine grade 0, 1 - 2 and 3 -5 by cisplatin and carboplatin as 58(82.86%):123(92.48%), 12(17.14%):10(7.52%) and 0:0, respectively. Nausea grade 0, 1-2 and 3-5 by cisplatin and carboplatin as 54(77.14%):167(95.98%), 16(22.86%) :7(4.02%) and 0:0, respectively. Vomiting grade 0, 1 - 2 and 3 - 5 55(78.57%) :168(96.55%), 15 (21.43%):6(3.45%) and 0:0, respectively. Diarrhea grade 0, 1-2 and 3-5 by cisplatin and carboplatin as 55(78.57%):142(81.61%), 15(21.43%):32(18.39%) and 0:0, respectively. Cystitis grade 0 , 1 - 2 and 3 – 5 by cisplatin and carboplatin as 60(85.71%):159(91.38%), 10(14.29%):11(6.32%) and 0: 4(2.30%), respectively. For half, acute complications had statistical significant which *p-value* less than 0.05. Those were Leukocytes, Creatinine, Nuasea and Vomiting, the p-value according to 0.007, 0.05, 0.008 and 0.008, there were used Fisher's exact test and Binary Logistic Regression, the results from two methods were similar .By the way , there are a lack of researches which

aim to compare between cisplatin group and carboplatin group by Odd ratio. Therefore, we will discuss the Odd ratio for significant variables. The Odds ratio of Leukocytes which reference by carboplatin group was 3.87 ;the patients with cisplatin group have higher risk to had leukocytes grade≥2 by 1.26 times relative to those with carboplatin group(*p-value*=0.007 and 95%CI, 1.484 to 10.083). The Creatinine shows odds ratio as 2.55, the cisplatin group have higher risk to had creatinine grade ≥ 1 by 2.55 times (*p-value* = 0.005 and 95% CI, 1.039 to 6.231). The Nausea shows Odds ratio as 13.31, the cisplatin groups have higher risk to had nausea grade ≥ 2 by 13.31 times (*p-value* = 0.008 and 95%CI, 1.526 to 116.07). Vomiting shows Odds ratio as 13.31, the cisplatin groups have higher risk to had vomiting grade≥2by13.31times(*p-value*=0.008 and 95%CI, 1.526 to 116.07) (Tinker.V.A, *et.al.*, 2005) reported for anemia toxicity grade 1,2, 3 and 4 for 24%, 44%, 28% and 4%, respectively.(Ikushima. H., *et. al.*, 2006) reported for severed white blood cells toxicity grade3 and 4: 76.19% and 4.76%, respectively.

5.4 Discussion of Results from Late Complications

The late complications were defined as those occurring more than 90 days. The follow-up for patients had range 4 to 8 times, and each period were 3 months. The late

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complication had six variables as Bladder, Gastrointestinal, Mucous Membrane, Skin, Neuropathy and Subcutaneous Tissue.Those complications were categories of grade 0 to 5,which defined as 0 for no complications and each higher grade for more severe complications[Appendix C]. The model for bladder complication after adjusted other covariates such as time,pathological types and radiation dose;the result showed cisplatin and carboplatin had no difference to occurring bladder complication (*p-value*=0.141). Gastrointestinal had a model after adjusting covariates such as time, age, stage and radiation dose, the result showed cisplatin and carboplatin groups had no difference to occurrance by *p-value*=0.063. Mucous membrane had a model after adjusting covariates such as time, age, stage and radiation dose , the result showed cisplatin and carboplatin group had difference to occurring mucous membrane by *p-value*= 0.026. Skin had a model after adjusting covariates such as time, age, stage, radiation dose and response after treatment, the result showed cisplatin and carboplatin group had no difference to occurred skin by *p-value*=0.068. Neuropathy had a model after adjusting covariates such as time,age,stage,pathological types and radiation dose. The result showed cisplatin and carboplatin group had no difference to occurred neuropathy by *p-value*=0.332. And subcutaneous tissue had a model after adjusting covariates such as time, age, stage, pathological types and radiation dose, the result showed cisplatin and carboplatin group had no difference to occurred subcutaneous tissue by *p-value*= 0.275. (Grigsby. W.P.,*et.al.*,2001) reported frequency of late complication. Bladder reported for grade 1 (6.89%) and lack of the others grade. Gastrointestinal reported for grade1, 2 and 4 as 14.28%, 9.52% and 14.28%, respectively. Mucous membrane reported for grade 1, 2 and 3 as 19.05%, 4.76% and 4.76%, respectively. Skin reported for grade 3 as 4.76%. Subcutaneous tissue reported for grade 2 as 4.76%. (Chung.L.Y.,*et.at.*,2005) reported for neuropathy grade 3 as 2%.

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CHAPTER VI
CONCLUSION

Our of the purposes of this research is to test the difference of survival rate between cisplatin group and carboplatin group. This was an analytically retrospective cohort study. The data collection used was secondary data from medical records. The recruitment period started from January 1, 2002 to August 31, 2004 and the cut-point of follow up for survival times was on September 12, 2006. Two hundred and sixty-four cervical cancer patients separated by cisplatin group 79(29.92%) and carboplatin group 185(70.08%). After analysis by survival statistics, the results reveal that survival rates of cisplatin group and carboplatin group had no difference tested by Log rank with *p-value* = 0.82. When we fitted the model by Cox Proportional Hazard, the final model concluded the patients' risk such as age, stage and response after treatment(3^{rd} months), from those, the response after treatment(3^{rd} months) was statistically significant with *p-value*<0.005. The response after treatment(3^{rd} months) had 3 categories *i.e.* Complete Response(CR), Partial Response(PR) and Progress Disease(PD), the relative risks(RR) showed that PR was a higher risk of death than CR by 2.03 times and PD was a higher risk of death than CR by 15.19 times.

The next purpose was to compare the acute and late complications between two treatment groups. The acute complications were defined as symptoms occurring during or within 90 days of completing radiotherapy. From eight complications (hemoglobin, leukocytes, platelets, creatinine, nausea, vomiting, diarrhea and cystitis). The complications between cisplatin and carboplatin having no statistically significant difference were hemoglobin, diarrhea and cystitis. There were four complications with statistical significance *i.e.* leukocytes (*p-value* =0.007), creatinine (*p-value* = 0.05), nausea (*p-value* = 0.008) and vomiting (*p-valu e*= 0.008), those were tested by Fisher's Exact Test and Binary Logistic Regression. With 3.87 OR of Leukocytes , Cisplatin group had higher risk to have leukocytes grade$\geq$2 by 3.87 times relative to those with Carboplatin group(95%CI, 1.484 to 10.083). with 2.55 OR of Creatinine , Cisplatin group

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had higher risk to have creatinine grade≥1 by 2.55 times relative to those with Carboplatin group (95%CI, 1.039 to 6.231). With 13.31 OR of nausea, Cisplatin group had a higher risk to having nausea grade≥2 by 13.31 times relative to those with Carboplatin group (*p-value* = 0.008 and 95%CI, 1.526 to 116.07). With 13.31 OR of vomiting , Cisplatin group had a higher risk to have vomiting grade≥2 by 13.31 times relative to those with Carboplatin (95%CI,1.526 to 116.07). For descriptive statistics of severe complications(grade ≥ 3) separated by cisplatin group and carboplatin group, the hemoglobin complication had cisplatin = 1(1.43%) and carboplatin = 1(0.57%). Leukocytes complication had cisplatin = 3(4.29%) and carboplatin = 2(1.15%). Platelets complication had no number in cisplatin group, for carboplatin had 1(0.57%). For creatinine, nausea, vomit and diarrhea had no number of severities in both of treatment. And cystitis had no number in cisplatin group, for carboplatin group had 4(2.30%).

The last objective was to compare the late complications between Cisplatin group and Carboplatin group. The late complications were defined as occurring more than 90 days, *i.e.* bladder, gastrointestinal, mucous membrane, skin, neuropathy and subcutaneous tissue. The generalized estimating equations(GEEs) was used for analysis. The independent variables included time(Wks), age, stage, treatment groups(cisplatin and carboplatin),KPS, Surgery and response after treatment(3 months) and radiation dose. The complications between cisplatin group and carboplatin group having no statistically significant difference were bladder, gastrointestinal, skin, neuropathy and subcutaneous tissue, those had *p-value* more than 0.05. The only one complication which was statistically significant between cisplatin group and carboplatin group was mucous membrane. The last model for mucous membrane consisted of time, group, age, stage and radiation dose. Two of those were significant, time(*p-value*=0.03) and group(*p-value*= 0.026). With 1.15 OR of treatment groups(group), Carboplatin group had a higher risk to having mucous membrane complication by 1.15 times relative to those with cisplatin (95%CI,1.0168 to 1.2943)

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Recommendations

1. The sample sizes calculation for survival statistics was not possible for this study (Sample size; CHAPTER III), which required death for 95 patients for each treatment groups. By the limitation for the number of death, the patients dying in cisplatin group equal 22(27.5%) and 55(29.57%) in carboplatin group. The total time to recruitment was about 32 months. So, if this study wanted to reach the goal of the sample size, we would have observed about 83 months. That is really difficult to do because Thailand began to use Cisplatin as standard treatment in 2002. And, those patients who received Cisplatin was a small group because the disadvantage of Cisplatin is risk of renal toxicity.

2. The disadvantage of cisplatin is a higher risk of renal toxicity than carboplatin and the doctor often uses cisplatin for younger patients more than elder patients. This population has often arbitrary dose modification of chemotherapy owing to fear of excessive side-effects. This study was undertaken to evaluate Cisplatinum in patients of younger age. Eighty patients were evaluated in Cisplatin group, 31(39.24%) for age below 45 years,42(53.16%) for age 45-59 years and 6(7.60%) for age elder than 60 years. For Carboplatin group, 56(30.27%) for age below 45 years, 81(43.78) for age 45-59 years and 48(25.95) for age elder than 60 years.

3. The final model by Cox proportional hazard shows interesting result. By stage II having lower risk of death by 0.919 times relative to those with stage I (Table 14). This, because of most of stage I was stage IB2. Then, the prognosis factor was worse than other level of stage I.

Recommendation for Further Studies

1. The survival rate from Kaplan-Meier tested by Log rank, showed no difference between Cisplatin and Carboplatin *p-value* = 0.82 [Fig. 6-7]. But for a long time more than 40 months, each curve of treatment groups seem to separated. Furthermore, observation for a longer period of time could help to make better decisions.

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APPENDIX

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APPENDIX A

Practice guideline to treat by Radiation

Instrument of external radiation : Linear Accelerator 6, 10 MV.

Cobalt-60.

Instrument of internal radiation : Low Dose Rate (LDR) Cesium-137 Remote-control after-loading

Applied Fletcher-Suit tandem and 2 ovoids.

Definition:

TDF (Time-Dose-Fractionation): There is the number that received from estimate the relative between total dose from radiation and dose per fraction. It is used to compared the total dose radiation for patient.

Point A : There is fixed at 2 cm. above the cervical os to tandem and 2 sides from triangle to tandem 2 cm.

Point B: There is fixed at 3 cm. for one side from point A.

Point A Dose: The position to treat by radiation

Bladder Dose: Estimated dose of radiation from insertion at lower point of posterior wall in urinary bladder.

Rectal Dose: Estimated dose of radiation from insertion point of internal radiation at rectal Probe between simulation. The calculation is mostly near point of ovoids and used to consider with dose from rectal probe before treatment.

Stage IA1

Treatment: Intracavitary Radiation (ICRT) 2 times.

Duration: 1-2 week after first treatment.

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Dose: TDF at point A = 54/fraction/F x 2 times

Stage IA2

Treatment :

1. External Radiation (ERT)+ Intracavitary Radiation (ICRT) 2 times.

Duration: 1-2 week after first treatment.

ERT: Dose – 4000 cGy. 180-200 cGy/F , 5 F/ wk

Field – Whole Pelvis with central shielding (CS)

ICRT: Dose – TDF point A = 54/F x 2 times

2. External Radiation (ERT) + Intracavitary Radiation (ICRT) x 1 time

Duration: Dose – 4000 cGy., 180-200 cGy/F, 5 F/wk.

Field – Whole Pelvis (WP) 3000 cGy.

Whole Pelvis with central shielding (CS) 1000 cGy.

ICRT – TDF point A = 54

Stage IB1

Treatment : External Radiation (ERT) + Intracavitary Radiation (ICRT) x 1 time

Duration : There must not longer 10-14 days after start central shielding.

ERT: Dose – 5000 cGy., 180-200 cGy/F, 5F/wk.

Field – Whole Pelvis with central shielding (CS) 3000 cGy.

ICRT: Dose – TDF point A = 82.

Stage IB2, IIA

Treatment : External Radiation (ERT) + Intracavitary Radiation (ICRT) x 1 time.

Duration : There must not longer 10-14 days after start central shielding

ERT: Dose – 5000 cGy., 180-200 cGy./F, 5F/wk.

Field – Whole Pelvis (WP) 3000 cGy.

Whole Pelvis with central shielding (CS) 2000 cGy.

ICRT: Dose – TDF point A = 82

Stage IIB

Treatment : External Radiation (ERT) + Intracavitary Radiation (ICRT) x 1 time

Duration : There must not longer 10-14 days after start central shielding.

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ERT: Dose – 5000 cGy., 180-200 cGy./F, 5F/wk.
Field – Whole Pelvis (WP) 3600 cGy.
Whole Pelvis with central shielding (CS) 1400 cGy.
ICRT: Dose – TDF point A = 82

Stage IIIA

Treatment : External Radiation (ERT) + Intracavitary Radiation (ICRT) x 1 time

Duration : There must not longer 10-14 days after start central shielding.

ERT: Dose – 5000 cGy., 180-200 cGy./F, 5F/wk.
Field – Whole Pelvis + bilateral groin AP(BG) } 3600 cGy.
Whole Pelvis PA
Whole Pelvis + bilateral groin with central shielding (CS) 1400 cGy.
Inguinal boost 1000 cGy. In case of anterior field
ICRT: Dose – TDF point A = 82

Stage IIIB

Treatment

1. External Radiation (ERT) + Intracavitary Radiation (ICRT) x 1 time
   Duration : There must not longer 10-14 days after start central shielding.
   ERT: Dose – 5600-6000 cGy., 180-200 cGy./F, 5F/wk.
   Field – Whole Pelvis (WP) 3600 cGy.
   Whole Pelvis with central shielding (CS) 1400 cGy.
   Parametrium boost 600-1000 cGy.
   ICRT: Dose – TDF point A = 82
2. 2. External Radiation (ERT) + Intracavitary Radiation (ICRT) x 2 time
   Duration : There must not longer 10-14 days after start central shielding.
   The second intracavitary radiation must not longer 1-2 week.
   ERT: Dose – 5600-6000 cGy., 180-200 cGy./F, 5F/wk.
   Field – Whole Pelvis (WP) 3000 cGy.
   Whole Pelvis with central shielding (CS) 2000 cGy.
   Parametrium boost 600-1000 cGy.

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ICRT: Dose – TDF point A = 54/F x 2 times

Stage IVA

Treatment : External Radiation (ERT) + Intracavitary Radiation (ICRT) x 1 time

Duration : There must not longer 10-14 days after start central shielding.

ERT: Dose – 5000 -6000 cGy., 180-200 cGy./F, 5F/wk.

Field – Whole Pelvis (WP) 4000-5000 cGy.

±Whole Pelvis with central shielding (CS) 1000 cGy.

±Paramertium boost 600-1000 cGy.

ICRT: Dose – TDF point A = 82

Conclusion of Guide line treatment

Stage	ERT dose (cGy)			ICRT			Total point A dose (cGy)	Total point B dose (cGy)
	Whole Pelvis (WP)	Whole pelvis with central shielding	Parametrial boost (PMT)	No. of insertions	TDF	ERT equivalent dose* (cGy)		
IA1	-	-	-	2	54+54	6400	6400	1800
IA2	-	4000	-	2	54+54	6400	6400	5800
	3000	1000	-	1	54	3200	6200	4900
IB1	2000	3000	-	1	82	5000	7000	6400
IB2,IIA	3000	2000	-	1	82	5000	8000	6400
IIB	3600	1400	-	1	82	5000	8600	6400
IIIA	3600	1400	-	1	82	5000	8600	6400
IIIB	3600	1400	600-1000	1	82	5000	8600	7400
	3000	2000	600-1000	2	54+54	6400	9400	7800
IVA	4000-5000	± 1000	±600-1000	1	82	5000	9000	7400

*** Mark:**

- In case of paraaortic LN positive increase field of paraaortic area with External Radiation (ERT)

Dose – 6000 cGy., 180 cGy./F, 5F/wk.

Field – Paraaortic field (PF) 4500 cGy.

Boost small field 1500 cGy.

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- The calculation of intracavitary radiation are compared with external radiation by table of TDF
- The estimate dose from point B is come from average of total dose at point B about 28% of point A from intracavitary radiation, hence , this estimated was just average.

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APPENDIX B

Common Terminology Criteria for Adverse Event v3.0 (CTCAE)

Publish Date: June 10, 2003

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a board classification of Aes based on anatomy and/or pathophysiology. Within each CATEGORY, Aes are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEe are listed alphabetically within **CATEGORIES.**

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Short AE Name

The 'Short Name' column is new and it used to simplify documentation of AE names on CASE Report Forms.Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CRCAE document. It lists sign/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grades refers to the severity of the AE. The CTCAE v3.0 displays Grades1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade1 Mild AE

Grade2 Moderate AE

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Grade3	Severe AE
Grade4	Life-threatening or disabling AE
Grade5	Death related to AE

A Semi-colon indicates ‘or’ within the description of the grade.

An ‘Em dash’ (-) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer that five options for Grade selection.

Grade5

Grade5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: ‘Death not associated with CTCAE term - *Select*’ with 4 AE options : Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to used in the situation where a death
    1. cannot to reported using a CTCAE v3.0 term associated with Grade5, or
    2. cannot be reported within a CTCAE CATEGORY as ‘Other (Specify)’

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BLOOD						
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemoglobin	Hemoglobin	<LLN-10.0 g/dL <LLN- 6.2 mmol/L <LLN- 100g/L	<10.0-8.0 g/dL <6.2-4.9 mmol/L <100-80g/L	<8.0-6.5g/dL <4.9-4.0 mmol/L <80-65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Leukocytes (total WBC)	Leukocytes	<LLN-3000/mm^3 <LLN-3.0×10^9/L	<3000-2000/mm^3 <3.0-2.0×10^9/L	<2000-1000/mm^3 <$2.0\text{-}1.0\times10^9$/L	<1000/mm^3 <1.0×10^9/L	Death
Platelets	Platelets	<LLN-75,000/mm^3 <LLN-75.0×10^9/L	<75,000-50,000/mm^3 <$75.0\text{-}50.0\times10^9$/L	<50,000-25,000/mm^3 <$50.0\text{-}25.0\times10^9$/L	<25,000/mm^3 <25.0×10^9/L	Death
METABOLIC/LABORATORY						
Creatinine	Creatinine	>ULN-1.5×ULN	>1.5-3.0×ULN	>3.0-6.0×ULN	>6.0×ULN	Death
GASTROINTESTINAL						
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IVF indicated<24 hrs	Inadequate oral caloric or fluid intake; IVF, tube feedings, or TPN indicated ≥ 24 hrs	Life-threatening consequences	Death
Vomiting	Vomiting	1 episode in 24 hrs.	2-5 episodes in 24 hrs; IVF indicated <24 hrs.	≥6 episodes in 24 hrs; IVF, or TPN indicated ≥ 24 hrs.	Life-threatening consequences	Death

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GASTROINTESTINAL						
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Diarrhea	Diarrhea	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stool/day over baselines;IVF indicated<24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stool/day over baseline;incontinence; IVF≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences(e.g., hemodynamic collapse)	Death
RENAL/GENITOURINARY						
Cystitis	Cystitis	Asymptotic	Frequency with dysuria; macroscopic hematurea	Transfusion; IV pain medication; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death

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APPENDIX C

LATE RTOG(Radiation Therapy Oncology Group)

MORBIDITY SCORING CRITERIA

Toxicity	1	2	3	4	5
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy, moderate telangiectasia; total hair loss	Marker atrophy; gross telangiectasia	Ulceration	Death directly related to radiation late effects
Subcutaneous Tissue	Slight induration (fibrosis) and loss of subcutaneous	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis	Death directly related to radiation late effects
Mucous Membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness, severe telangiectasia	Ulceration	Death directly related to radiation late effects

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Toxicity	1	2	3	4	5
Neuropathy	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level	Mono, para, or quadriplegia	Death directly related to radiation late effects
Small/Large Intestine	Mild diarrhea; mild cramping; bowel movements 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 times daily; excessive rectal mucous or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis; perforation; fistula	Death directly related to radiation late effects
Bladder	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency, generalized telangiestasia; intermittent macroscopic hematuria	Severe frequency and dysuria; severe generalized telangiectasia (often with petechiae); frequency hematuria; reduction in bladder capacity (<150 cc)	Necrosis; contracted bladder (capacity < 100 cc), severe hemorrhagic cystitis	Death directly related to radiation late effects

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APPENDIX D

Reviews of Survival Methods:

Survival analysis is the phase used to describe the analysis of data that correspond to the time from a well-defined *time origin* until the occurrence of some particular *event* or *end-point* to define the survival time. A distinctive feature of survival data is that the event of interest (death, developing diseases) may not be observed for every subject. Although we would like to know the exact survival time for every subject. So, the survival time of an individual is said to be *censored* when the end-point of interest has not been observed for that individual. This may happen for example if the subject moves to a different country after being enrolled in the study or chooses to withdraw from the study.

Person	Survival time	Failed (1); censored (0)
A	5	1
B	12	0
C	3.5	0
D	8	0
E	6	0
F	3.5	1

Fig. 15 Example of survival time data.(Kleinbaum, et al.,1995:7)

In Fig.15 presented a table of survival time data for six persons. For each person, we have given the corresponding survival time up to the event's occurring or up to censorship. We have indicated in the last column whether this time was censored or not

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(with 1 denoting failed and 0 denoting censored). This table is a simplified illustration of the type of data to be analyzed in a survival analysis

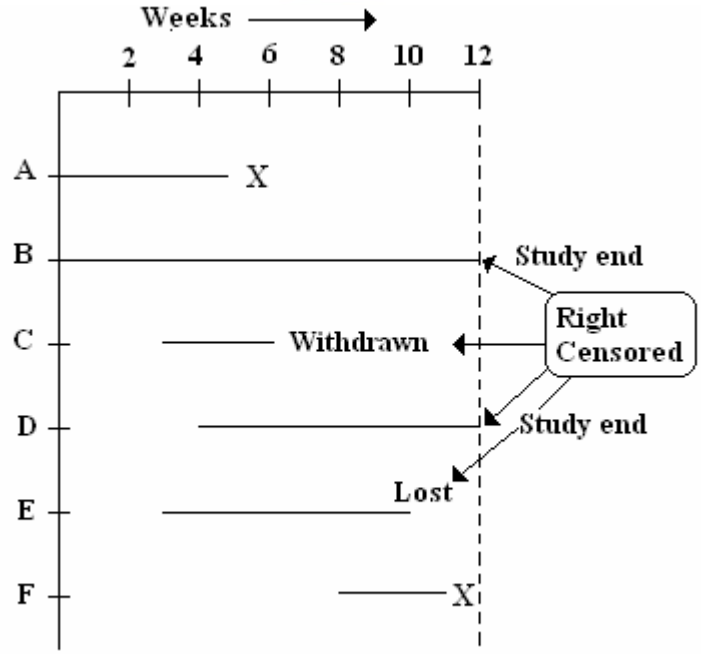

Fig.16 Example of each of person. (Kleinbaum, et al.,1995:7)

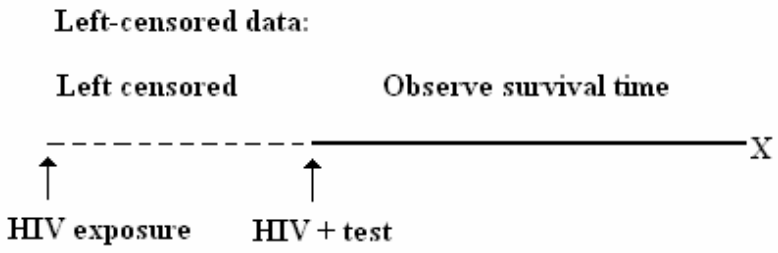

Fig. 17 Left- censored data (Kleinbaum, et al.,1995:7) .

In Fig. 16 presented by graph of example data in Figured 1.In each of the four persons censored, we generally refer to this kind of data as **right-censored.** For these data, the

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complete survival time interval, which we don't really know, has been cut off (i.e., censored) at the right side. Although data can also be **left-censored**, most survival data is right-censored. In the reminder of this text, we will consider right-censored data only.

In summarizing survival data, there are two functions of central interest, namely the *survival function* and *hazard function.*

Note also that when d=0, the survival time T cannot be observed. For this reason we will also use the term "*follow-up time*" to indicate the actual length of time each subject is observed. This will be denoted by t_f (where "*f*" stands for *f*ollow-up) with t_f=T when d=1. We will also refer to the *"exit date"*, the date when the follow-up ends, $t_x = t_e + t_f$ (where *"x"* stands for *e*xit and *"e"* stands for *e*ntry).

The Survival Function (Mann, V.,2005)

First, survival function is a useful way to summarize the survival data. The actual survival time , t , of an individual can be regarded as the value of a variable T, which can take any non-negative value. The different values that T can take have a *probability distribution*, and we call T the random variable associated with the survival time. Now suppose that the random variable T has a probability distribution with underlying *probability density function f(t).* The *distribution function* of T is then given by

$$F(t) = P(T < t) = \int_0^t f(u)du, \qquad (4)$$

and represents the probability that the survival time is less than some value t.

The *survival function*, *S(t)*, is defined to be the probability that the survival time is greater than or equal to t, and so

$$S(t) = P(T > t) = 1 - F(t) \qquad (5)$$

Suppose first that we have a single sample of survival times, where non of the observation are censored. The survival function *S(t)*, defined in equation (5), is the probability that an individual survives for a time greater than or equal to t. This function can be estimated by the *empirical survival function*, given by

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$$\tilde{S}(t) = \frac{Number\ of\ individuals\ with\ survival\ times \geq t}{Number\ of\ individuals\ in\ the\ data\ set} \quad (6)$$

The Hazard Function (Mann, V.,2005)

An alternative way to describe survival data is to use the hazard function. The hazard function denoted by *h(t)* gives the instantaneous potential per unit time for the event to occure, give that the individuals has survived up to time *t*. The hazard function focuses on failing (the event occurring) in contrast to the survival function that focuses on not failing.

There earlier defined the survival function as:

$$S(t) = P(T > t) \quad (7)$$

This is just *1-F(t)* where *F(t)* is familiar cumulative density function $P(T \leq t)$.

Hence the *Probability density function* is

$$f(t) = F'(t) = \lim_{\delta t \to 0} \frac{P(t \leq T \leq t + \delta t)}{\delta t} \quad (8)$$

For survival data the probability that an event of interest occurs in a tiny of time, [*t*, $t+\delta t$], is proportional to *f(t)*.

It is often more convenient and natural to talk about the proportional that someone who has survived up to *t* will suffer the event in the next little time interval. This is a probability conditional on survival to time *t*. That can think of it as an instantaneous risk. It is known as the *hazard* or *rate function*.

The hazard function is formally defined as, for small δt (strictly: in the limit as $\delta t \to 0$):

$$h(t) = \frac{P(T < t + \delta t | T \geq t)}{\delta t} \quad (9)$$

To obtain a more formal definition of the hazard function, consider the probability that the random associated with an individual's survival time, *T*, lies between *t* and $t+\delta t$, conditional on *T* being grater than or equal to *t*. The hazard function *h(t)* is then limiting value of this probability divided by the time interval δt , *as* δt tends to zero, so that:

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$$h(t) = \lim_{\delta t \to 0} \left\{ \frac{P(t \le T < t + \delta t | T \ge t)}{\delta t} \right\} \quad (10)$$

In practice, when there are no censored observation, the hazard function is estimated as the proportion of patients dying in an interval per unit time, given that they have survived to be beginning of the interval:

$$\tilde{h}(t) = \frac{Number\ of\ patients\ dying\ per\ unit\ time\ in\ the\ interval}{Number\ of\ patients\ surviving\ at\ t} \quad (11)$$

Actuaries usually use the average hazard rate of the interval in which the number of patients dying per unit time in the interval is divided by the average number of survivors at the midpoint of the interval:

$$\tilde{h}(t) = \frac{Number\ of\ patients\ dying\ per\ unit\ time\ in\ the\ interval}{(Number\ of\ patients\ surviving\ at\ t) - \frac{1}{2}(Number\ of\ death\ in\ the\ interval\ width)}$$

Relationship Between Density, Hazard and Survival Functions (Mann, V.,2005)

It is useful to relate all these concepts to each other.

Since, by definition, $f(t) = F'(t)$ and $F(t) = 1 - S(t)$, then

$$f(t) = -S'(t) \quad (12)$$

Further, from the definitions of $h(t)$ and of conditional probability, we have

$$h(t) = \frac{P(T < t + \delta t | T \ge t)}{\delta t} = \frac{P(t \le T < t + \delta t)}{P(T \ge t)\delta t} \quad (13)$$

and comparing this with the definition of $f(t)$:

$$h(t) = f(t)/S(t)$$

So,
$$h(t) = -S'(t)/S(t) = -\frac{d}{dt}\log S(t) \quad (14)$$

As the cumulative hazard $H(t)$ measures how much hazard a subject has experienced by time t. Thus integrating equation (11) we have

$$H(t) = \int_0^t h(u)du = -\log S(t)$$

and
$$S(t) = exp[-H(t)] \quad (15)$$

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Equation (15) shows that the probability of surviving past time *t* depends only on the cumulative amount of hazard experienced by time *t*.

We now consider the general data layout for a survival analysis. We will provide two types of data layouts, one giving the form appropriate for computer use and the other giving the form that helps us understand how a survival analysis works.

Group1 (Treatment)n=21	Group2 (Treatment)n=21
6, 6, 6, 7, 10, 13, 16, 22, 23 6+, 9+, 10+,11+, 17+, 19+, 20+, 25+, 32+, 32+, 34+, 35+	1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

	#failed	#censored	Total
Group1	9	12	21
Group2	21	0	21

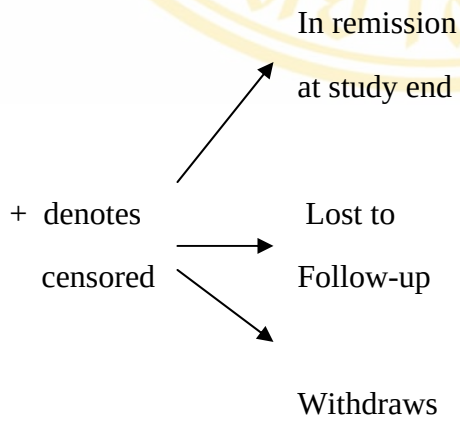

Fig. 18 Basic Data Layout for Computer.(Kleinbaum, et al.,1995:18)

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As presented in Fig. 18, the data are not yet in tabular form for the computer, as we will see shortly. A person is censored if the observe remains in remission until the end of the study, is lost to follow-up, or withdraws before the end of the study. The censored data here are denoted by a plus sign next to survival time.

	Indiv. #	*t* (week)	δ (failed or censored)	X (Group)		Indiv. #	*t* (week)	δ (failed or censored)	X (Group)
	1	6	1	1		22	1	1	0
	2	6	1	1		23	1	1	0
	3	6	1	1		24	2	1	0
	4	7	1	1		25	2	1	0
	5	10	1	1		26	3	1	0
	6	13	1	1		27	4	1	0
GROUP	7	16	1	1	**GROUP**	28	4	1	0
1	8	22	1	1	**2**	29	5	1	0
	9	23	1	1		30	5	1	0
	10	6	0	1		31	8	1	0
	11	9	0	1		32	8	1	0
	12	10	0	1		33	8	1	0
	13	11	0	1		34	8	1	0
	14	17	0	1		35	11	1	0
	15	19	0	1		36	11	1	0
	16	20	0	1		37	12	1	0
	17	25	0	1		38	12	1	0
	18	32	0	1		39	15	1	0
	19	32	0	1		40	17	1	0
	20	34	0	1		41	22	1	0
	21	35	0	1		42	23	1	0

Fig. 19 Data input for computer.(Kleinbaum, et al.,1995:18)

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We now put this data in tabular form for the computer, as shown. The list starts with the 21 persons in group1 (listed 1-21) and follow 21 persons in group 2 (listed 22-42). Our *n* for the composite group is 42.

Basic Data Layout For Understanding Analysis.(Kleinbaum, et al.,1995:20)

First, to get ordered failure times from survival times, we must first remove from the list of unordered survival times all those times that are censored; we are thus working only with those times at which people failed. We then order the remaining failure times from smallest to largest, and count ties only once. The value *k* gives the number of the distinct times at which subjects failed

Ordered failure $(t_{(j)})$	**# of failures** (m_j)	**#censored in** $(t_{(j)}, t_{(j+1)})$	**Risks set** $R(t_{(j)})$
$t_{(0)}= 0$	$m_0=0$	q_0	$R(t_{(0)})$
$t_{(1)}$	m_1	q_1	$R(t_{(1)})$
•	•	•	•
•	•	•	•
$t_{(k)}$	m_k	q_k	$R(t_{(k)})$

Fig. 20 Remission Data for Analysis

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Group1

(n=21, 9 failures, k=7)

$t_{(j)}$	mj	q_i	$R(t_{(j)})$
$t_{(0)}$=0	0	0	21 persons survive≥0 weks
$t_{(1)}$=6	3	1	21 persons survive≥6 wks
$t_{(2)}$=7	1	1	17 persons survive≥ 7 wks
$t_{(3)}$=10	1	2	15 persons survive≥ 10 wks
$t_{(4)}$=13	1	0	12 persons survive≥ 13 wks
$t_{(5)}$=16	1	3	11 persons survive≥ 16 wks
$t_{(6)}$=22	1	0	7 persons survive≥ 22 wks
$t_{(7)}$=23	1	5	6 persons survive≥ 23 wks
Totals	**9**	**12**	

Group2

(n=21, 21 failures, k=12)

$t_{(j)}$	mj	q_i	$R(t_{(j)})$
$t_{(0)}$=0	0	0	21 persons survive≥0 wks
$t_{(1)}$=1	2	0	21 persons survive≥1 wks
$t_{(2)}$=2	2	0	19 persons survive≥2 wks
$t_{(3)}$=3	1	0	17 persons survive≥ 3 wks
$t_{(4)}$=4	2	0	16 persons survive≥4 wks
$t_{(5)}$=5	2	0	14 persons survive≥5 wks
$t_{(6)}$=8	4	0	12 persons survive≥8 wks
$t_{(7)}$=11	2	0	8 persons survive≥11 wks
$t_{(8)}$=12	2	0	6 persons survive≥12 wks
$t_{(9)}$=15	1	0	4 persons survive≥15 wks
$t_{(10)}$=17	1	0	3 persons survive≥17 wks
$t_{(11)}$=22	1	0	2 persons survive≥ 22 wks
$t_{(12)}$=23	1	0	1 persons survive≥ 23 wks
Totals	**21**	**0**	

Fig. 20 Remission Data for Analysis (Cont.)

For example, there are nine failures , k=7 distinct survival times in group1, including 3 persons each at 6 wks and 1 person each at 7, 10,13,16, 22 and 23 wks. Turning to group2, there are 21 failures , *k*=12 distinct survival times. These times are listed in the first column for group2.

Kaplan-Meier: non-parametric Methods (Mann, V.,2005)

We now make the assumption that the deaths of the individuals in the sample occur independently of one another. Then, the estimated the survival function at any time in the *k*'th constructed time interval from $t_{(k)}$ to $t_{(k+1)}$, k=1,2,…,r, where $t_{(r+1)}$ is defined to be ∞, will be the estimated probability of surviving beyond $t_{(k)}$. This is actually the probability of surviving through the interval from $t_{(k)}$ to $t_{(k+1)}$, and all preceding intervals. This is Kaplan-Meier estimate of the survival function, which is given by

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$$\hat{S}(t) = \prod_{j=1}^{k}\left(\frac{n_j - d_j}{n_j}\right) = \prod_{j=1}^{k}(1 - p_j) \qquad (16)$$

For $t_{(k)} \leq t < t_{(k+1)}$, k=1,2,….,r with $\hat{S}(t) = 1$ for $t<t_{(1)}$ and where $t_{(r+1)}$ is taken to be ∞. Strictly speaking, if the largest observation is a censored survival time, t^*, say, $\hat{S}(t)$ is undefined for $t>t^*$. On the other hand, if the largest observed survival time, $t_{(r)}$, is an uncensored observation, $n_r=d_r$, and so $\hat{S}(t)=0$ for $t \geq t_{(r)}$. A plot of Kaplan-Meier estimate of the survival function is a step function, in which, in which the estimated survival probability are constant between adjacent death times and decrease at each death time.

Note that if there are no censored survival times in the data set, n_j-d_j=n_{j+1}, j=1,2,…,k, in equation (16), and on expanding the product we get

$$\hat{S}(t) = \frac{n_2}{n_1} \times \frac{n_3}{n_2} \times \ldots \times \frac{n_{k+1}}{n_k} \qquad (17)$$

This reduces to n_{k+1}/n_1 ,for k=1,2,…,r-1, with $\hat{S}(t)=1$ for $t<t_{(1)}$ and $\hat{S}(t)=0$ for $t<t_{(r)}$. Now, n_1 is the number of individuals at risk just before the first death time, which the number of individuals in the sample, and n_{k+1} is the number of individuals with survival times greater than or equal to $t_{(k+1)}$. Consequently, in the absence of censoring, $\hat{S}(t)$ is simply the empirical survival function defined in equation (6).

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Table 31 Kaplan-Meier Estimate(*product-limit estimate*) of the Survival Function

Time interval t_j	At risk n_j	#failed d_j	#censored l_j	Prob(Death) p_j	Prob(Surv.) $(1-p_j)$	Cumulative survival $\hat{S}(t)$
23	13	1	0	1/13	12/13	12/13
47	12	1	0	1/12	11/12	12/13*11/12
69	11	1	0	1/11	10/11	11/13*10/11
70	10	0	1	0	10/10	10/13*1
71	9	0	1			
100	8	0	1			
101	7	0	1			
148	6	1	0	1/6	5/6	10/13*5/6
181	5	1	0	1/5	4/5	10/13*5/6*4/5
198	4	0	1			
208	3	0	1			
212	2	0	1			
224	1	0	1			

$$\hat{S}(t) = \prod_{j=1}^{k}(1-p_j) = \hat{S}(181) = \frac{10}{13}\times\frac{5}{6}\times\frac{4}{5} = 0.5128$$

To derive the standard error of the Kaplan-Meier estimator by assuming that the (1-p_j) terms are independent. Taking logs,

$$\log \hat{S}_k = \sum_{j=1}^{j=k} \log(1-p_j)$$

$$\text{var}[\log \hat{S}_k] = \sum_{j=1}^{j=k} \text{var}[\log(1-p_j)]$$

To work out var[log(1-p_j)] we use the “variance transformation formular”:

$$\text{var}[f(X)] \approx \{f'(E[X])\}^2 \text{ var } X$$

With X= p_j and $f(p_j)$ = log (1- p_j). This gives

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$$\text{var}[\log(1-p_j)] \approx \frac{\text{var}(p_j)}{(1-p_j)^2}$$

The right hand side can be estimated by putting $\text{var}(p_j)=p_j(1-p_j)/n_j$ and $p_j=d_j/n_j$,giving

$$\text{var}[\log(1-p_j)] \approx \frac{d_j}{n_j(n_j-d_j)}$$

So putting it all together we get

$$var[\log \hat{S}_k] \approx \sum_{j=1}^{j=k} \frac{d_j}{n_j(n_j-d_j)} \quad (18)$$

Finally we again use the variance transformation formula in the form $\text{var}[\log X] \approx \text{var}(X)/X^2$ to get $\text{var}(X) \approx \text{var}[\log X] \times X^2$ from which the **Greenwood's formula** follow:

$$\text{var}(\hat{S}_k) \approx \hat{S}_k^2 \sum_{k=1}^{j=k} \frac{d_j}{n_j(n_j-d_j)} \quad (19)$$

Since 95% confidence intervals based on the Greenwood's formula may lead to values outside (0,1), a better approach is to carry out the calculations first for logg(-log S_k) (because this goes from $-\infty$ to ∞ as S_k goes from o to 1). So using the variance transformation formula yet again, we get

$$\text{var}[\log(-\log S_k)] \approx \frac{\text{var}[-\log S_k]}{(\log S_k)^2} \approx \frac{1}{(\log S_k)^2} \sum_{j=1}^{j=k} \frac{d_j}{n_j(n_j-d_j)}$$

The 95% confidence intervals are estimated for each time point where an event occurs and should not really be connected to each other. A proper measure of reliability of the entire survival curve is a simultaneous confidence band covering the whole set of estimated probabilities. This would be wider than the one implied by the joining of the 95% confidence intervals.

Mantel-Haenszel(Log-Rank Test): non-parametric Methods (Mann, V.,2005)

Unlike the method just considered, the Mantel-Haenszel(MH) test, often called in the context of survival analysis *log-rank test*, compared the whole survival

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distributions in the two groups. Formally, with H_0 and H_A indicating the null and alternative hypotheses, it tests:

$$\begin{cases} H_0 : S_1(t) = S_2(t) \\ H_A : S_1(t) = [S_2(t)]^{\theta} \end{cases} \quad (20)$$

If $\theta > 1$ then $S_1(t) < S_2(t)$ for every t, i.e. the first group experiences overall a better survival than the second group. Alternatively, if $\theta < 1$ then $S_1(t) > S_2(t)$ for every t.

Considering the relationship between the hazard functions, instead of the survival function, the hypotheses in equation (20) may be re-written as:

$$\begin{cases} H_0 : h_1(t) = h_2(t) \\ H_A : h_1(t) = \theta\ [h_2(t)] \end{cases} \quad (21)$$

Hence, the Mantel-Haenszel test is used when the hazard in one group is greater than the hazard in the other group at all times. Actually θ could vary over time. The MH test most powerful when θ(t) does not change over time. When this occurs, the hazards are said to be *"proportional"*

Formally, at the *j*th failure time,

Group	**Death**	**Surviving**	**At risk**
	at t_j	Beyond t_j	t_j
1	d_{1j}	$n_{1j} - d_{1j}$	n_{1j}
2	d_{2j}	$n_{2j} - d_{2j}$	n_{2j}
Total	d_j	$n_j - d_j$	n_j

And under the null hypothesis that the groups are equivalent, e_{1j}=expected deaths in group 1 = $d_j * n_{1j}/n_j$.

The MH test compares the total observed deaths in group 1,

$$O_1 = \sum_j d_{1j}$$

With the total expected deaths in group 1,

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$$E_1 = \sum_j e_{1j}$$

To compute the test we need the variance v_{1j} of d_{1j}. We look at the distribution of d_{1j} conditional on the margins n_{1j},n_{2j},d_j :

$$v_{1j} = \frac{n_{1j} n_{2j} d_j (n_j - d_j)}{n_j^2 (n_j - 1)}$$

So the variance of O_1 is (as the death times are independent)

$$V = \sum_j v_{1j}$$

and so under the null hypothesis of no difference between the groups,

$$\frac{(O_1 - E_1)^2}{V} \sim X_1^2$$

Cox Model(Proportional Hazards Model): Regression Methods (Mann, V.,2005)

There are situations where the underlying hazard function is changing with time, but in the groups when want to compare, the ratio of the hazards remains constant.

$$h_i(t) = h_0(t)\theta_i \qquad (22)$$

Where $h_0(t)$ is called the **baseline hazard** e.g.it is the hazard for a subject with $\theta_i = 1$. We want to relate θ_i to explanatory variables x_i. Since the hazard ratio cannot be negative, it is convenient to use exponential link:

$$\theta_i = \exp(\beta\ x_i)$$

This then can be extended to include more than one explanatory variables just as for any generalized linear model, and they can be continuous variables or factors:

$$\theta_i = \exp(\sum_{k=1}^{K} \beta_k x_{ki})$$

Giving the general form of proportional hazards or Cox model:

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$$h_i(t) = h_0(t)\exp(\sum_{k=1}^{K}\beta_k x_{ki}) \quad (23)$$

Since $h_0(t)$ is not specified, we cannot use an ordinary likelihood to estimate the β parameters. Instead Cox formulated a so-called *partial* likelihood which is based only on the θ_i part of model (22).

To obtain this likelihood we order the observations which end with a failure according to either failure time (Fig. 21). We then look at each of these failures (indicated by an $\times$) in turn, and list all the subjects who were still at risk at the time of the failure. This group of subjects, together with the individual who failed, is the *risk set* for the failure.

Note that the risk set of each failure includes the failure and all subjects whose observation lines cross the appropriate vertical.

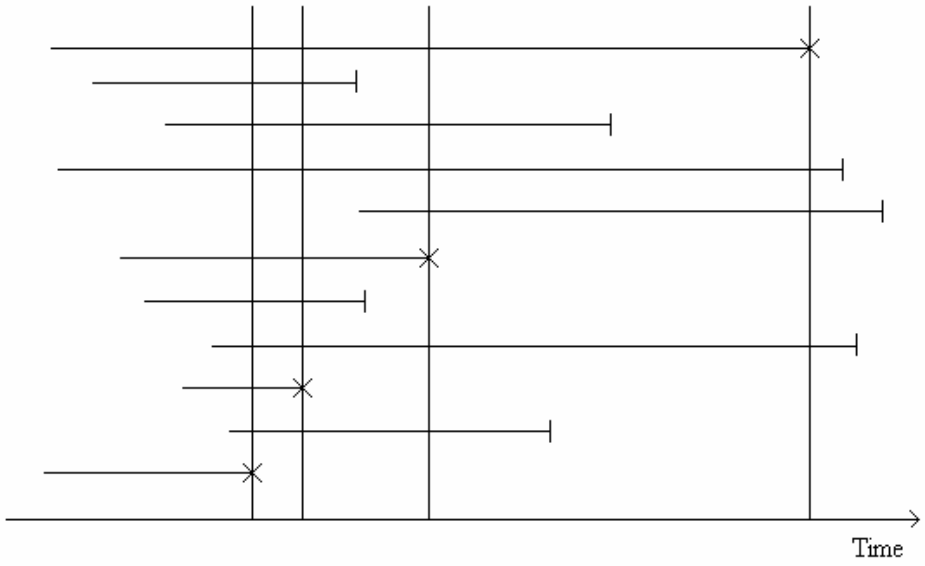

Fig. 21 Composition of Risk Sets

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It is useful to write $t_{(j)}$ = time of the *j* th event.

$R_{(j)}$ = set of subjects at risk at *j* th event

$x_{(j)}$ = value of *x* for subject who fails at *j* th event

$h_{(j)}(t)$ = hazard at *t* for subject who fails at *j* th event

The probability that an individual with covariate *x* fails in a small interval *(t, t+dt)*, given his survival up to time *t*, is *h(t)dt*. Thus the probability that it is the individual with covariate $x_{(j)}$ the one who fails, conditional on the fact that one subject failed at $t_{(j)}$, is:

$$= \frac{h_j(t)dt}{\sum_{i \in R_{(j)}} h_i(t)dt}$$

$$= \frac{\exp(\beta x_j)}{\sum_{i \in R_{(j)}} \exp(\beta x_i)} \qquad (24)$$

Because *dt* and the baseline hazard cancel out.

Multiplying these conditional probabilities over all the event times, we find the likelihood:

$$L(\beta) = \prod \frac{\exp(\beta x_{(j)})}{\sum_{i \in R(j)} \exp(\beta_{xi})} \qquad (25)$$

$L(\beta)$ is called a partial likelihood because it only uses part of the information, but it behaves just like an ordinary likelihood. So to estimate β we (numerically)maximize equation (25)

The Weibull Model: Regression Methods (Mann, V.,2005)

An extension of the exponential model is the Weibull model defined as:

$$h_i(t) = \lambda(x_i)\gamma\ t^{\gamma-1} \qquad (26)$$

Where γ and $\lambda(x_i)$ are both > 0. Further the latter is specified as function of explanatory variables as $\log\ \lambda(x_i) = \log \lambda_0 + \beta x_i$

When γ <1 the hazard decreases with time, when γ >1 the hazard increases with time.

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APPENDIX E

Review of Generalized Estimating Equations

(Kleinbaum G. D., *et al.*,2002:332) Generalized linear models (GLMs) are a standard method used to fit regression models for univariate data that are presumed to follow an exponential family distribution. Frequently researchers are interested in analyzing data that arise from a longitudinal, repeated measures or closeted design, and there exists correlation between observations on a given subject. If the outcomes are an approximately multivariate normal, then there are well established methods of analysis that have been widely implemented in general purpose statistical packages. But if the outcomes are binary or conts, general likelihood based approaches are less tractable. For clused binary outcomes, several approaches have been suggested(e.g., Fitzmaurice and Laird 1993), but these have not been incorporated into general purpose statistical computing packages.

Generalized estimating equations (GEEs) were developed to extend the GLM to accommodate correlated data, and are widely used by researchers in a number of fields. In this article we will review GLMs and GEE methodology, and though an example, compare the GEE implementations of several general purpose statistical package.

Generalized Linear Models

For many statistical models, including logistic regression, the predictor variables (i.e., independent variables) are considered fixed and the outcome, or response (i.e., dependent variable), is considered random. In this framework, the model for *Y* consists of a fixed component $\left[f(X_1, X_2, \ldots, X_p) \right]$ and random component $(\in)$. A function (*f*) for the fixed predictors and a distribution for the random error $(\in)$ are specified.

General form of many statistical models:

$$Y = f(X_1, X_2, \ldots, X_p) + \in$$

Where: *Y* is the random

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$X_1, X_2, \ldots, X_p$ are fixed

$\in$ is random

Logistic regression belongs to a class of models called generalized linear models (GLM). Other models that belong to the class of GLM include linear and Poisson regression. For correlated analyses, the GLM framework can be extended to a class of models called generalized estimating equations (GEE) models. Before discussing correlated analyses using GEE, we shall describe GLM.

GLM are a natural generalization of the classical linear model [Kleinbaum, G. D., & Klein, M. (2002)]. In classical linear regression, the outcome is a continuous variable, which is often assumed to follow a normal distribution. The mean response is modeled as linear with respect to the regression parameters.

In standard logistic regression, the outcome is a dichotomous variable. Dichotomous outcomes are often assumed to follow a binomial distribution, with an expected value (or mean μ) equal to a probability $\left[\text{e.g.}, \mathrm{P}(\mathrm{Y}=1)\right]$. It is this probability that is modeled in logistic regression.

Logistic regression outcome

Outcome

-dichotomous

-binomial distribution: $\mathrm{E}(\mathrm{Y}) = \mu = \mathrm{P}(\mathrm{Y}=1)$

Logistic regression used to model

$$\mathrm{P}\left(\mathrm{Y} \middle| \mathrm{X}_1, \mathrm{X}_2, \mathrm{K}\ , \mathrm{X}_\mathrm{p}\right)$$

The binomial distribution belongs to a larger class of distributions called the exponential family. Other distributions belonging to the exponential family are the normal, Poisson, exponential, and gamma distributions. These distributions can be written in a similar form and share important properties.

Let μ represent the mean response $\mathrm{E}(\mathrm{Y})$, and $\mathrm{g}(\mu)$ represent a function of mean response. A generalized linear model with *p* independent variables can be

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expressed as $g(\mu)$ equal β_0 plus the summation of the *p* independent variables times their beta coefficients.

Generalized Linear Model

$$g(\mu) = \beta_0 + \sum_{h=1}^{p} \beta_h X_h$$

Where: μ is the mean response $E(Y)$

$g(\mu)$ is function of the mean

There are three components that comprise GLM: (1) a random component, (2) a systematic components are described as follows:

1. The random component is that the outcome (Y) is required to follow a distribution from the exponential family. This criterion is met for logistic regression (unconditional) since the response variable follows a binomial distribution, which is a member of the exponential family.
2. The systematic component requires that the *X*'s be combined in the model as a linear function $\left(\beta_0 + \sum \beta_h X_h\right)$ of the parameters. This potion of the model is not random. This criterion is met for a logistic model, since the model from contains a linear component in its denominator.

   Logistic model:

$$P(X) = \frac{1}{1 + \exp\left[-\left(\beta_0 + \sum \beta_h X_h\right)\right]}$$

3. The **link function** refers to that function of the mean response, $g(\mu)$, that is modeled linearly with respect to the regression parameters. This function serves to "link" the mean of the random response and the fixed linear set of parameters.

   For logistic regression, the **log odds** (or **logit**) of the outcome is modeled as linear in the regression parameters. Thus, the link function for logistic regression is the logit function.

   Logistic regression(logit link)

$$g(\mu) = \log\left[\frac{\mu}{1-\mu}\right] = \log it(\mu)$$

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Alternately, one can express GLM in terms of the inverse of the link function $\left(g^{-1}\right)$, which is the mean μ. In other words, $g^{-1}\left(g\left(\mu\right)\right)=\mu$. This **inverse** function is modeled in terms of the predictors (**X**) and their coefficient $\left(\beta\right)$(i.e., $g^{-1}\left(X,\beta\right)$). For logistic regression, the inverse of the logit link function is the familiar logistic model of the probability of an event, as shown on the left. Notice that this modeling of the mean (i.e., the inverse of the link function) in not a linear model. It is the *function* of the mean (i.e., the link function) that is modeled a linear in GLM.

Alternate formulation

Inverse of link function= g^{-1} satisfies

$$g^{-1}\left(g\left(\mu\right)\right)=\mu$$

Inverse of ligit function in terms of $\left(X,\beta\right)$

$$g^{-1}\left(X,\beta\right)=\mu=\frac{1}{1+\exp\left[-\left(\alpha+\sum_{h=1}^{p}\beta_h X_h\right)\right]}$$

Where

$$g\left(\mu\right)=\text{logit}\,P\left(D=1\middle|X\right)=\beta_0+\sum_{h=1}^{p}\beta_h X_h$$

GLM uses maximum likelihood methods to estimate model parameters. This requires knowledge of the likelihood function (*L*), which, in turn, requires that the distribution of the response variable be specified.

If the responses are independent, the likelihood can be expressed as the product of each observation's contribution (L_i) to the likelihood. However, if the responses are not independent, then the likelihood can become complicated, or intractable.

For nonindependent outcomes whose joint distribution is multivariate (MV) normal, the likelihood is relatively straightforward, since the multivariate normal distribution is completely specified by the means, variances, and all of the pairwise covariances of the random outcomes. This is typically not case for other

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multivariate distributions in which the outcomes are not independent. For these circumstances, quasi-likelihood theory offers an alternative approach to model development.

Quisi-likelihood methods have many of the same desirable statistical properties that maximum likelihood methods have, but the full likelihood does not need to be specified. Rather, the relationship between the mean and variance of each response is specified. Just as the maximum likelihood theory lays the foundation for GLM, the quasi-likelihood theory lays the foundation for GEE models.

GEE Models

GEE represent a class of models that are often utilized for data in which the responses are correlated (Liang and Zeger,1986). GEE models can be used to account for the correlation of continuous or categorical outcomes. As in GLM, a function of the mean $g(\mu)$, called the **link function**, is modeled as linear in the regression parameters.

GEE:class of models for correlated data

Link function *g* modeled as

$$g(\mu) = \beta_0 + \sum_{h=1}^{p} \beta_h X_h$$

For a dichotomous outcome, the logit link is commonly used. For this cases, $g(\mu)$ equals logit (P), where P is the probability that Y=1. If there are *p* independent variables, this can be expressed as: logit $P(Y=1|X)$ equals β_0 plus the summation of the *p* independent variables times their beta coefficients.

$$g(\mu) = \text{logit}\, P(Y=1|X) = \beta_0 + \sum_{h=1}^{p} \beta_h X_h$$

The logistic model for correlated data looks identical to the standard logistic model. The difference is in the underlying assumptions of the model, including the presence of correlation, and the way in which the parameters are estimated.

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GEE is a generalization of quisi-likelihood estimation, so the joint distribution of the data need not be specified. For clustered data, the user specifies a “working” correlation structure for describing how the responses within clusters are related to each other. Between clusters, there is an assumption of independence.

For GEE models the likelihood ratio test cannot be used since a likelihood is never formulated. However, the *Wald* test can also be used for GEE models since parameter estimates for GEE models are asymptotically nomal [Kleinbaum, G. D., & Klein, M.:2002].

(Twisk J.W.R., *et.al.*,2003: 60-68) considered the longitudinal relationship between a continuous outcome variable Y and one or more predictor variables X can be described by equation

$$Y_{it} = \beta_0 + \sum_{j=1}^{J} \beta_{1j} X_{itj} + \varepsilon_{it} \tag{27}$$

where Y_{it} are observations for subject i at time t, β_0 is the intercept, X_{ijt} is the independent variable j for subject i at time t, β_{1j} is the regression coefficient for independent variable j, J is the number of independent variables, and ε_{it} is the error for subject i at time t. The subscripts t indicate that the outcome variable Y is repeatedly measured on the same subject, and that the predictor variable X can be repeatedly measured on the same subject. In model (27), the coefficients of interest are β_{1j}, because these regression coefficients show the magnitude of the relationship between the longitudinal development of the outcome variable (Y_{it}) and the development of the predictor variables (X_{ijt}). In addition of a time indicator t as equation

$$Y_{it} = \beta_0 + \sum_{j=1}^{J} \beta_{1j} X_{itj} + \beta_2 t + \varepsilon_{it} \tag{28}$$

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where Y_{it} are observations for subject i at time t, β_0 is the intercept, X_{ijt} is the independent variable j for subject i at time t, β_{1j} is the regression coefficient for independent variable j, J is the number of independent variables, t is time, β_2 is the regression coefficient for time, and ε_{it} is the error for subject i at time t.

From equation (28) can be expanded to a general form, in which a correlation for both time-dependent covariates (Z_{ikt}) and time-independent covariates (G_{im}) is modeled as equation

$$Y_{it} = \beta_0 + \sum_{j=1}^{J} \beta_{1j} X_{itj} + \beta_2 t + \sum_{k=1}^{K} \beta_{3k} Z_{ikt} + \sum_{m=1}^{M} \beta_{4m} G_{im} + \varepsilon_{it} \qquad (29)$$

where Y_{it} are observations for subject i at time t, β_0 is the intercept, X_{ijt} is the independent variable j for subject i at time t, β_{1j} is the regression coefficient for independent variable j, J is the number of independent variables, t is time, β_2 is the regression coefficient for time, Z_{ikt} is the time-dependent covariate k for subject i at time t, β_{3k} is the regression coefficient for time-dependent covariate k, K is the number of time-dependent covariates, G_{im} is the time-independent covariate m for subject i, β_{4m} is the regression coefficient for time-independent covariate m, M is the number of time-independent covariates, and ε_{it} is the error for subject i at time t. GEE is an iterative procedure, using quasi-likelihood to estimate the regression coefficients. Because the repeated observations within one subject are not independent of each other, a correlation must be made for these within-subject correlations. With GEE, assuming a priori a certain working correlation structure for the repeated measurements of the outcome variable Y carries out this correlation. The within-subject correlation structure is treated as a nuisance variable, i.e. a covariate. So, in principle, the way in which GEE

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analysis corrects for the dependency of observations within one subject is the way that has been shown in equation

$$Y_{it} = \beta_0 + \sum_{j=1}^{J} \beta_{1j} X_{itj} + \beta_2 t + \sum_{k=1}^{K} \beta_{3k} Z_{ikt} + \sum_{m=1}^{M} \beta_{4m} G_{im} + C_{it} + \varepsilon_{it} \quad (30)$$

where Y_{it} are observations for subject i at time t, β_0 is the intercept, X_{ijt} is the independent variable j for subject i at time t, β_{1j} is the regression coefficient for independent variable j, J is the number of independent variables, t is time, β_2 is the regression coefficient for time, Z_{ikt} is the time-dependent covariate k for subject i at time t, β_{3k} is the regression coefficient for time-dependent covariate k, K is the number of time-dependent covariates, G_{im} is the time-independent covariate m for subject i, β_{4m} is the regression coefficient for time-independent covariate m, M is the number of time-independent covariates, C_{it} is the working correlation structure, and ε_{it} is the error for subject i at time t.

Table 32 Sample Data:Infant Care Study (Kleinbaum G. D.**,** *et al*.,2002:332)

IDNO	MO	OUTCOME	BIRTHWGT	GENDER	DIARRHEA
00282	1	0	2000	Male	0
00282	2	0	2000	Male	0
00282	3	1	2000	Male	1
.	.	.	.	.	.
00282	8	0	2000	Male	1
00282	9	0	2000	Male	0

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Table 32 Sample Data:Infant Care Study (Cont.)

IDNO	MO	OUTCOME	BIRTHWGT	GENDER	DIARRHEA
00283	1	0	2950	Female	0
00283	2	0	2950	Female	0
00283	3	1	2950	Female	0
.	.	.	.	.	.
00283	8	0	2950	Female	0
00283	9	0	2950	Female	0
00287	1	1	3250	Male	1
00287	2	1	3250	Male	1
00287	3	0	3250	Male	0
.	.	.	.	.	.
00287	8	0	3250	Male	0
00287	9	0	3250	Male	0

IDNO: identification number

MO: observation month(provides order to subject-specific measurements)

OUTCOME: dichotomous *z*-score(value can change month to month)

Independent variables:

1. Time-dependent variable: can vary month to month within a cluster

   DIARRHEA: dichotomous variable for presence of symptoms

2. Time-independent variable: do not vary month to month within a cluster

   BIRTHWGT

   GENDER

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APPNDIX F
COX PROPORTIONAL HAZARD MODEL

1st STEP

$$\ln\left(\frac{h_{it}}{h_{0t}}\right) = -0.10\textbf{\textit{Age}} + 0.0001\textbf{\textit{KPS}} - 0.134\textbf{\textit{StageII}} + 0.568\textbf{\textit{StageIII}} - 0.052\textbf{\textit{Adenocarcinoma}} - 12.104\textbf{\textit{Others}} - 0.556\textbf{\textit{Less(RT)}} + 0.498\textbf{\textit{More(RT)}} + 0.53\textbf{\textit{Sur(No)}} + 0.11\textbf{\textit{Carboplatin}} + 0.782\textbf{\textit{PR}} + 2.837\textbf{\textit{PD}}$$

Table 33 Cox proportional hazard function for pattern1

Variables	$\hat{\beta}$	RR	95 % CI of RR		*P*-value
			Lower	Upper	
Age	-0.10	0.99	0.966	1.015	0.431
KPS	0.0001	1.0001	0.960	1.042	0.994
Stage					0.046*
Stage I	0	1			
Stage II	-0.134	0.875	0.283	2.704	0.816
Stage III	0.568	1.766	0.559	5.574	0.332
Pathological Types					0.987
Squamouscell carcinoma	0	1			
Adenocarcinoma	-0.052	0.949	0.497	1.811	0.874
Others	-12.104	0.0001	0.000	3.102	0.971
Radiation Dose(RT)					0.165
Standard radiation dose	0	1			
Less than standard dose	-0.556	0.573	0.170	1.937	0.371
More than standard dose	0.498	1.645	0.881	3.071	0.118

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Table 33 Cox proportional hazard function for pattern1 (Cont.)

Variables	$\hat{\beta}$	RR	95 % CI of RR		*P*-value
			Lower	Upper	
Surgery(Sur)					0.377
Yes	0	1			
No	0.530	1.699	0.524	5.504	
Group					0.703
Cisplatin	0	1			
Carboplatin	0.110	1.117	0.634	1.967	
Response after treatment					< 0.001*
Complete Response(CR)	0	1			
Partial Response(PR)	0.782	2.186	1.201	3.977	0.01*
Progress Disease(PD)	2.837	17.056	7.168	40.583	< 0.001*

-2 log likelihood = 742.616

2nd STEP

$$\ln\left(\frac{h_{it}}{h_{0t}}\right) = -0.01\textbf{\textit{Age}} + 0.002\textbf{\textit{KPS}} - 0.117\textbf{\textit{StageII}} + 0.597\textbf{\textit{StageIII}} - 0.538\textbf{\textit{Less(RT)}} + 0.491\textbf{\textit{More(RT)}} + 0.587\textbf{\textit{Sur(No)}} + 0.149\textbf{\textit{Carboplatin}} + 0.804\textbf{\textit{PR}} + 2.867\textbf{\textit{PD}}$$

Table 34 Cox proportional hazard function for pattern2

Variables	$\hat{\beta}$	RR	95 % CI of RR		*P*-value
			Lower	Upper	
Age	-0.01	0.99	0.966	1.015	0.436
KPS	0.002	1.002	0.961	1.045	0.911

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Table 34 Cox proportional hazard function for pattern2 (Cont.)

Variables	$\hat{\beta}$	RR	95 % CI of RR		*P*-value
			Lower	Upper	
Stage					0.036*
Stage I	0	1			
Stage II	-0.117	0.89	0.292	2.712	0.837
Stage III	0.597	1.816	0.588	5.612	0.3
Radiation Dose(RT)					0.177
Standard radiation dose	0	1			
Less than standard dose	-0.538	0.584	0.173	1.971	0.386
More than standard dose	0.491	1.634	0.874	3.052	0.124
Surgery(Sur)					0.312
Yes	0	1			
No	0.587	1.798	0.577	5.602	
Group					0.605
Cisplatin	0	1			
Carboplatin	0.149	1.161	0.660	2.043	
Response after treatment					< 0.001*
Complete Response(CR)	0	1			
Partial Response(PR)	0.804	2.235	1.231	4.059	0.008*
Progress Disease(PD)	2.867	17.578	7.474	41.344	< 0.001*

-2 log likelihood = 742.616

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3rd STEP

$$\ln\left(\frac{h_{it}}{h_{0t}}\right) = -0.01\textbf{\textit{Age}} - 0.115\textbf{\textit{StageII}} + 0.6\textbf{\textit{StageIII}} - 0.545\textbf{\textit{Less(RT)}} + 0.489\ \textbf{\textit{More(RT)}}$$
$$+ 0.592\textbf{\textit{Sur(No)}} + 0.148\textbf{\textit{Carboplatin}} + 0.801\textbf{\textit{PR}} + 2.869\textbf{\textit{PD}}$$

Table 35 Cox proportional hazard function for pattern3

Variables	$\hat{\beta}$	RR	95 % CI of RR		*P*-value
			Lower	Upper	
Age	-0.01	0.99	0.966	1.014	0.406
Stage					0.035*
Stage I	0	1			
Stage II	-0.115	0.891	0.292	2.718	0.84
Stage III	0.6	1.822	0.590	5.626	0.297
Radiation Dose(RT)					0.176
Standard radiation dose	0	1			
Less than standard dose	-0.545	0.58	0.173	1.949	0.378
More than standard dose	0.489	1.631	0.873	3.048	0.125
Surgery(Sur)					0.306
Yes	0	1			
No	0.592	1.808	0.582	5.611	
Group					0.608
Cisplatin	0	1			
Carboplatin	0.148	1.159	0.659	2.039	
Response after treatment					< 0.001*
Complete Response(CR)	0	1			
Partial Response(PR)	0.801	2.228	1.230	4.037	0.008*
Progress Disease(PD)	2.869	17.62	7.498	41.406	< 0.001*

-2 log likelihood = 742.616

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4th STEP

$$\ln\left(\frac{h_{it}}{h_{0t}}\right) = -0.012\boldsymbol{Age} - 0.222\boldsymbol{StageII} + 0.474\boldsymbol{StageIII} + 0.593\boldsymbol{Sur(No)} + 0.222\boldsymbol{Carboplatin} + 0.696\boldsymbol{PR} + 2.873\boldsymbol{PD}$$

Table 36 Cox proportional hazard function for pattern4

Variables	$\hat{\beta}$	RR	95 % CI of RR		*P*-value
			Lower	Upper	
Age	-0.012	0.988	0.965	1.011	0.303
Stage					0.036*
Stage I	1	1			
Stage II	-0.222	0.801	0.270	2.379	0.690
Stage III	0.474	1.607	0.532	4.854	0.400
Surgery(Sur)					
Yes	1	1			
No	0.593	1.810	0.591	5.544	0.299
Group					
Cisplatin	1	1			
Carboplatin	0.222	1.249	0.732	2.131	0.415
Response after treatment					< 0.001*
Complete Response(CR)	1	1			
Partial Response(PR)	0.696	2.006	1.159	3.469	0.013*
Progress Disease(PD)	2.873	17.699	7.637	41.016	< 0.001*

-2 log likelihood = 767.845

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APPNDIX G

LATE COMPLICATIONS MODELS

BLADDER COMPLICATIONS

Table 37 Bladder Complication for Pattern1

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0 .0048	1.00	0.022	1.0006	1.0091
Group					
Cisplatin	0	1.00			
Carboplatin	0.0616	1.06	0.103	0.9876	1.1453
Age	0.0013	1.00	0.308	0.9987	1.0039
Kps	-0.0006	1.00	0.659	0.9964	1.0022
Stage					
Stage I	0	1.00			
Stage II	0.0121	1.01	0.727	0.9456	1.0833
Stage III	0.0075	1.00	0.832	0.9398	1.080
Pathological Types					
Squamouscell carcinoma	0	1.00			
Adenocarcinoma	-0.0867	0.91	< 0.001	0.8801	0.9552
Others	-0.0251	0.97	0.699	0.8583	1.1078
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0642	0.93	0.043	0.8810	0.9981
More than RT	0.0168	1.02	0.672	0.9406	1.0994

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Table 37 Bladder Complication for Pattern1 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Surgery					
Yes	0	1.00			
No	-0.0509	0.95	0.103	0.8937	1.0103
Response after treatment					
CR	0	1.00			
PR	-0.0944	0.91	0.034	0.8339	0.9927
PD	0.0160	1.02	0.720	0.9310	1.1090
Constant	0.0408				
Wald χ^2 **= 29.01**					

Table 38 Bladder Complication for Pattern 2

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0048	1.00	0.022	1.0006	1.0090
Group					
Cisplatin	0	1.00			
Carboplatin	0.0608	1.06	0.103	0.9878	1.1433
Age	0 .0012	1.00	0.324	0.9987	1.0038
Stage					
Stage I	0	1.00			
Stage II	0.0144	1.01	0.676	0.9481	1.0856
Stage III	0.0087	1.01	0.805	0.9414	1.0808

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Table 38 Bladder Complication for Pattern 2 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Pathological Types					
Squamouscell carcinoma	0	1.00			
Adenocarcinoma	-0.0864	0 .91	< 0.001	0.8806	0.9552
Others	-0.0246	0.97	0.702	0.8599	1.1069
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0599	0.94	0.065	0.8837	1.0037
More than RT	0.0174	1.02	0.663	0.9407	1.1007
Surgery					
Yes	0	1.00			
No	-0.0516	0.95	0.099	0.8932	1.0096
Response after treatment					
CR	0	1.00			
PR	-0.0948	0.91	0.031	0.8344	0.9913
PD	0.0154	1.02	0.728	0.9306	1.1083
Constant	-0.0152				

Wald χ^2 **= 29.13**

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Table 39 Bladder Complication for Pattern 3

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0048	1.00	0.021	1.0007	1.0090
Group					
Cisplatin	0	1.00			
Carboplatin	0.0556	1.06	0.126	0.9845	1.1351
Age	0.0012	1.00	0.356	0.9986	1.0038
Stage					
Stage I	0	1.00			
Stage II	-0.0033	1.00	0.920	0.9327	1.0649
Stage III	-0.0089	1.00	0.797	0.9253	1.0614
Pathological Types					
Squamouscell carcinoma	0	1.00			
Adenocarcinoma	-0.0786	0.92	< 0.001	0.8890	0.9611
Others	-0.0115	0.99	0.858	0.8708	1.1220
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0615	0.94	0.053	0.8834	1.0008
More than RT	0.0195	1.02	0.628	0.9420	1.1038
Response after treatment					
CR	0	1.00			
PR	-0.0785	0.92	0.127	0.8357	1.0226
PD	0.0148	1.01	0.739	0.9299	1.1077
Constant	-0.0439				

Wald χ^2 **= 25.02**

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GASTROINTESTINAL COMPLICATIONS

Table 40 Gastrointestinal Complication for Pattern1

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0061	1.01	0.002	1.0022	1.0101
Group					
Cisplatin	0	1.00			
Carboplatin	-0.0555	0.94	0.038	0.8976	0.9968
Age	0.0045	1.00	0.068	0.9996	1.0095
Kps	-0.0003	1.00	0.798	0.9967	1.0025
Stage					
Stage I	0	1.00			
Stage II	0.0636	1.06	0.114	0.9849	1.1530
Stage III	0.0894	1.09	0.152	0.9675	1.2359
Pathological Types					
Squamouscell carcinoma	0	1.00			
Adenocarcinoma	-0.0366	0.96	0.299	0.8995	1.0330
Others	-0.0122	0.98	0.853	0.8678	1.1244
Radiation Dose					
Standard RT	0	1.00			
Less than RT	0.0004	1.00	0.997	0.8247	1.2135
More than RT	-0.0653	0.94	0.026	0.8843	0.9923
Surgery					
Yes	0	1.00			
No	-0.0479	0.95	0.592	0.7997	1.1359

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Table 40 Gastrointestinal Complication for Pattern1 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Result after treatment					
CR	0	1.00			1.8098
PR	0.1839	1.20	0.378	0.7982	1.0857
PD	-0.0085	0.99	0.854	0.9054	
Constant	-0.1607				
Wald χ^2 **= 22.01**					

Table 41 Gastrointestinal Complication for Pattern2

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0061	1.01	0.002	1.0021	1.0101
Group					
Cisplatin	0	1.00			
Carboplatin	-0.0479	0.95	0.120	0.8972	1.0125
Age	0.0047	1.00	0.061	0.9997	1.0096
Kps	-0.0003	1.00	0.809	0.9967	1.0025
Stage					
Stage I	0	1.00			
Stage II	0.0715	1.07	0.057	0.9979	1.1561
Stage III	0.0990	1.10	0.090	0.9845	1.2382
Pathological Types					
Squamouscell carcinoma	0	1.00			
Adenocarcinoma	-0.0366	0.96	0.292	0.9006	1.0319
Others	-0.0197	0.98	0.762	0.8627	1.1142

Table 41 Gastrointestinal Complication for Pattern2 (Cont.)

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Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0027	1.00	0.978	0.8230	1.2084
More than RT	-0.0643	0.94	0.028	0.8854	0.9930
Surgery					
Yes	0	1.00			
No	-0.0655	0.94	0.435	0.7946	1.1038
Constant	-0.1598				

Wald χ^2 **= 22.21**

Table 42 Gastrointestinal Complication for Pattern 3

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0061	1.01	0.002	1.0022	1.0101
Group					
Cisplatin	0	1.00			
Carboplatin	-0.0502	0.95	0.102	0.8954	1.0100
Age	0.0047	1.00	0.058	0.9998	1.0097
Kps	-0.0003	1.00	0.815	0.9968	1.0024
Stage					
Stage I	0	1.00			
Stage II	0.0708	1.07	0.042	1.0026	1.1490
Stage III	0.1038	1.11	0.055	0.9979	1.2334

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Table 42 Gastrointestinal Complication for Pattern 3 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0052	0.99	0.957	0.8193	1.2076
More than RT	-0.0643	0.94	0.024	0.8867	0.9915
Surgery					
Yes	0	1.00			
No	-0.0489	0.95	0.569	0.8045	1.1270
Constant	-0.1894				

Wald χ^2 **= 21.37**

Table 43 Gastrointestinal Complication for Pattern 4

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0058	1.01	0.004	1.0019	1.0098
Group					
Cisplatin	0	1.00			
Carboplatin	-0.0515	0.95	0.093	0.8942	1.0086
Age	0.0049	1.00	0.050	1.0000	1.0098
Stage					
Stage I	0	1.00			
Stage II	0.0709	1.07	0.049	1.0003	1.1521
Stage III	0.1053	1.11	0.053	0.9984	1.2364

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Table 43 Gastrointestinal Complication for Pattern 4 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0056	0.99	0.953	0.8220	1.2026
More than RT	-0.0652	0.94	0.022	0.8858	0.9906
Surgery					
Yes	0	1.00			
No	-0.0494	0.95	0.567	0.8035	1.1274
Constant	-0.2212				

Wald χ^2 **= 21.69**

Table 44 Gastrointestinal Complication for Pattern 5

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0058	1.01	0.004	1.0019	1.0099
Group					
Cisplatin	0	1.00			
Carboplatin	-0.0555	0.95	0.063	0.8922	1.0029
Age	0.0047	1.00	0.051	0.9999	1.0096
Stage					
Stage I	0	1.00			
Stage II	0.0533	1.05	0.027	1.0059	1.1060
Stage III	0.0868	1.09	0.035	1.0060	1.1824

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Table 44 Gastrointestinal Complication for Pattern 5 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0071	0.99	0.941	0.8205	1.2012
More than RT	-0.0629	0.94	0.024	0.8892	0.9916
Constant	-0.2446				

Wald χ^2 **=21.52**

MUCOUS MEMBRANE

Table 45 Mucous Membrane Complication for Pattern1

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.00643	1.01	0.028	1.0006	1.0122
Group					
Cisplatin	0	1.00			
Carboplatin	0.1259	1.13	0.044	1.0035	1.2818
Age	0.0070	1.01	0.027	1.0008	1.0134
Kps	0.0021	1.00	0.439	0.9967	1.0075
Stage					
Stage I	0	1.00			
Stage II	-0.0396	0.96	0.624	0.8204	1.1259
Stage III	0.0777	1.08	0.380	0.9086	1.2855

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Table 45 Mucous Membrane Complication for Pattern1 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Pathological Types					
Squamouscell carcinoma	0	1.00			
Adenocarcinoma	-0.0340	0.96	0.589	0.8543	1.0935
Others	-0.0131	0.99	0.897	0.8087	1.2043
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0379	0.96	0.777	0.7405	1.2517
More than RT	-0.0069	0.99	0.925	0.8586	1.1485
Surgery					
Yes	0	1.00			
No	0.0145	1.01	0.845	0.8772	1.1735
Response after treatment					
CR	0	1.00			
PR	0.2557	1.29	0.209	0.8668	1.9238
PD	0.0432	1.04	0.659	0.8616	1.2652
Constant	-0.3964				

Wald χ^2 **= 27.54**

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Table 46 Mucous Membrane Complication for Pattern2

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0064	1.01	0.028	1.0007	1.0122
Group					
Cisplatin	0	1.00			
Carboplatin	0.1240	1.13	0.041	1.0052	1.2749
Age	0.0071	1.01	0.025	1.0008	1.0134
Kps	0.0021	1.00	0.438	0.9967	1.0075
Stage					
Stage I	0	1.00			
Stage II	-0.0397	0.96	0.626	0.8189	1.1276
Stage III	0.0828	1.09	0.347	0.9139	1.2913
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0400	0.96	0.765	0.7383	1.2500
More than RT	-0.0072	0.99	0.923	0.8578	1.1489
Surgery					
Yes	0	1.00			
No	0.0293	1.03	0.694	0.8895	1.1921
Response after treatment					
CR	0	1.00			
PR	0.2546	1.29	0.211	0.8652	1.9233
PD	0.0405	1.04	0.678	0.8602	1.2606
Constant	-0.4229				

Wald χ^2 **= 26.34**

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Table 47 Mucous Membrane Complication for Pattern 3

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0064	1.01	0.028	1.0007	1.0122
Group					
Cisplatin	0	1.00			
Carboplatin	0.1267	1.14	0.036	1.0084	1.2776
Age	0.0072	1.01	0.024	1.0009	1.0135
Kps	0.0021	1.00	0.436	0.9967	1.0076
Stage					
Stage I	0	1.00			
Stage II	-0.0292	0.97	0.701	0.8366	1.1274
Stage III	0.0940	1.10	0.249	0.9361	1.2892
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0392	0.96	0.770	0.7392	1.2506
More than RT	-0.0085	0.99	0.908	0.8571	1.1469
Response after treatment					
CR	0	1.00			
PR	0.2449	1.28	0.221	0.8628	1.8916
PD	0.0408	1.04	0.674	0.8609	1.2603
Constant	-0.4111				

Wald χ^2 **= 26.31**

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Table 48 Mucous Membrane Complication for Pattern 4

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0063	1.01	0.029	1.0006	1.0121
Group					
Cisplatin	0	1.00			
Carboplatin	0.1331	1.14	0.031	1.0125	1.2888
Age	0.0070	1.01	0.022	1.0010	1.0131
Kps	0.0022	1.00	0.415	0.9968	1.0077
Stage					
Stage I	0	1.00			
Stage II	-0.0248	0.98	0.743	0.8403	1.1321
Stage III	0.1042	1.11	0.200	0.9463	1.3016
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0371	0.96	0.788	0.7348	1.2632
More than RT	-0.0087	0.99	0.905	0.8578	1.1454
Constant	-0.4109				

Wald χ^2 **= 25.10**

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SKIN COMPLICATIONS

Table 49 Skin Complication for Pattern1

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	-0.0027	1.00	0.034	0.9946	0.9997
Group					
Cisplatin	0	1.00			
Carboplatin	0.0391	1.04	0.092	0.9936	1.0885
Age	0.0010	1.00	0.060	0.9999	1.0022
Kps	0.0009	1.00	0.244	0.9993	1.0024
Stage					
Stage I	0	1.00			
Stage II	-0.0107	1.00	0.709	0.9351	1.0466
Stage III	-0.0070	0.99	0.805	0.9390	1.0499
Pathological Types					
Squamous cell carcinoma	0	1.00			
Adenocarcinoma	0.0144	1.01	0.482	0.9744	1.0562
Others	-0.0062	0.99	0.844	0.9335	1.0578
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0123	1.00	0.519	0.9513	1.0254
More than RT	-0.0022	1.00	0.916	0.9577	1.0395
Surgery					
Yes	0	1.00			
No	0.0123	1.01	0.622	0.9638	1.0635

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Table 49 Skin Complication for Pattern1 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Response after treatment					
CR	0	1.00			
PR	-0.0605	0.94	0.007	0.9006	0.9836
PD	-0.0179	0.98	0.225	0.9541	1.0110
Constant	-0.0800				
Wald χ^2 **= 15.49**					

Table 50 Skin Complication for Pattern2

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	-0.0027	1.00	0.033	0.9946	0.9997
Group					
Cisplatin	0	1.00			
Carboplatin	0.0392	1.04	0.090	0.9938	1.0883
Age	0.0010	1.00	0.062	0.9999	1.0022
Kps	0.0009	1.00	0.239	0.9993	1.0024
Stage					
Stage I	0	1.00			
Stage II	-0.0115	0.99	0.688	0.9342	1.0459
Stage III	-0.0102	0.99	0.728	0.9341	1.0487
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0112	0.99	0.546	0.9532	1.0256
More than RT	-0.0020	1.00	0.922	0.9577	1.0398

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Table 50 Skin Complication for Pattern2 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Surgery					
Yes	0	1.00			
No	0.0071	1.01	0.717	0.9687	1.0472
Response after treatment					
CR	0	1.00			
PR	-0.0591	0.94	0.010	0.9012	0.9858
PD	-0.0165	0.98	0.243	0.9566	1.0112
Constant	-0.0699				

Wald χ^2 **= 15.07**

Table 51 Skin Complication for Pattern3

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	-0.0028	1.00	0.033	0.9946	0.9997
Group					
Cisplatin	0	1.00			
Carboplatin	0.0399	1.04	0.077	0.9956	1.0877
Age	0.0010	1.00	0.057	0.9999	1.0022
Kps	0.0009	1.00	0.239	0.9993	1.0024
Stage					
Stage I	0	1.00			
Stage II	-0.0089	0.99	0.728	0.9422	1.0424
Stage III	-0.0074	0.99	0.770	0.9439	1.0436

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Table 51 Skin Complication for Pattern3 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0110	1.00	0.554	0.9534	1.0259
More than RT	-0.0023	1.00	0.910	0.9580	1.0389
Response after treatment					
CR	0	1.00			
PR	-0.0614	0.94	0.003	0.9033	0.9788
PD	-0.0164	0.98	0.245	0.9566	1.0113
Constant	-0.0670				
Wald χ^2 **= 15.31**					

NEUROPATHY COMPLICATIONS

Table 52 Neuropathy Complication for Pattern1

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	-0.0004	1.00	0.126	0.9989	1.0001
Group					
Cisplatin	0	1.00			
Carboplatin	0.0072	1.01	0.324	0.9928	1.0210
Age	-0.0001	1.00	0.755	0.9995	1.0003
Kps	0.0001	1.00	0.847	0.9996	1.0004

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Table 52 Neuropathy Complication for Pattern1 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Stage					
Stage I	0	1.00			
Stage II	0.0027	1.00	0.342	0.9971	1.0083
Stage III	0.0157	1.01	0.048	1.0000	1.0317
Pathological Types					
Squamous cell carcinoma	0	1.00			
Adenocarcinoma	-0.0066	0.99	0.022	0.9877	0.9990
Others	-0.0137	0.99	0.047	0.9731	0.9998
Radiation Dose					
Standard RT	0	1.00			
Less than RT	0.0100	1.01	0.461	0.9834	1.0374
More than RT	0.0082	1.01	0.336	0.9914	1.0252
Surgery					
Yes	0	1.00			
No	-0.0031	1.00	0.402	0.9896	1.0041
Response after treatment					
CR	0	1.00			
PR	-0.0169	0.98	0.076	0.9648	1.0017
PD	-0.0028	1.00	0.710	0.9822	1.0122
Constant	0.0064				

Wald χ^2 **= 8.25**

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Table 53 Neuropathy Complication for Pattern 2

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	-0.0004	1.00	0.128	0.9989	1.0001
Group					
Cisplatin	0	1.00			
Carboplatin	0.0073	1.01	0.306	0.9933	1.0216
Age	-0.0001	1.00	0.728	0.9995	1.0003
Stage					
Stage I	0	1.00			
Stage II	0.0026	1.00	0.371	0.9968	1.0084
Stage III	0.0155	1.02	0.043	1.0005	1.0310
Pathological Types					
Squamous cell carcinoma	0	1.00			
Adenocarcinoma	-0.0066	0.99	0.021	0.9877	0.9990
Others	-0.0137	0.99	0.047	0.9730	0.9998
Radiation Dose					
Standard RT	0	1.00			
Less than RT	0.0099	1.01	0.471	0.9829	1.0378
More than RT	0.0082	1.01	0.331	0.9916	1.0253
Surgery					
Yes	1.0000	1.00			
No	-0.0030	1.00	0.414	0.9896	1.0043
Response after treatment					
CR	0	1.00			
PR	-0.0168	0.98	0.079	0.9649	1.0019
PD	-0.0027	1.00	0.722	0.9823	1.0124
Constant	0.0102				

Wald χ^2 = **8.24**

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Table 54 Neuropathy Complication for Pattern 3

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	-0.0004	1.00	0.129	0.9990	1.0001
Group					
Cisplatin	0	1.00			
Carboplatin	0.0070	1.01	0.309	0.9934	1.0208
Age	-0.0001	1.00	0.711	0.9995	1.0003
Stage					
Stage I	0	1.00			
Stage II	0.0015	1.00	0.600	0.9957	1.0074
Stage III	0.0145	1.01	0.070	0.9988	1.0306
Pathological Types					
Squamous cell carcinoma	0	1.00			
Adenocarcinoma	-0.0061	0.99	0.024	0.9886	0.9991
Others	-0.0128	0.99	0.064	0.9739	1.0007
Radiation Dose					
Standard RT	0	1.00			
Less than RT	0.0098	1.01	0.475	0.9829	1.0376
More than RT	0.0084	1.01	0.326	0.9916	1.0255
Constant	0.0084				

Wald χ^2 **= 8.18**

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SUBCUTANEOUS TISSUES COMPLICATIONS

Table 55 Subcutaneous Tissue Complication for Pattern1

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0018	1.00	0.152	0.9993	1.0044
Group					
Cisplatin	0	1.00			
Carboplatin	0.0300	1.03	0.328	0.9703	1.0943
Age	0.0016	1.00	0.456	0.9973	1.0058
Kps	-0.0014	1.00	0.422	0.9949	1.0021
Stage					
Stage I	0	1.00			
Stage II	-0.0032	1.00	0.895	0.9498	1.0459
Stage III	0.0494	1.05	0.221	0.9706	1.1372
Pathological Types					
Squamous cell carcinoma	0	1.00			
Adenocarcinoma	-0.0341	0.97	0.030	0.9370	0.9967
Others	-0.0558	0.95	0.071	0.8901	1.0047
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0866	0.92	0.028	0.8489	0.9904
More than RT	-0.0357	0.96	0.191	0.9146	1.0179
Surgery					
Yes	0	1.00			
No	0.0208	1.02	0.433	0.9691	1.0758

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Table 55 Subcutaneous Tissue Complication for Pattern1 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Response after treatment					
CR	0	1.00			
PR	0.2110	1.23	0.284	0.8395	1.8166
PD	0.0254	1.02	0.638	0.9224	1.1407
Constant	0.0432				
Wald χ^2 **= 14.89**					

Table 56 Subcutaneous Tissue Complication for Pattern 2

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0018	1.00	0.159	0.9992	1.0043
Group					
Cisplatin	0	1.00			
Carboplatin	0.0380	1.039	0.269	0.9710	1.1111
Age	0.0015	1.00	0.435	0.9976	1.0055
Kps	-0.0013	1.00	0.445	0.9950	1.0021
Stage					
Stage I	0	1.00			
Stage II	0.0077	1.01	0.714	0.9669	1.0502
Stage III	0.0654	1.07	0.077	0.9928	1.1480
Pathological Types					
Squamous cell carcinoma	0	1.00			
Adenocarcinoma	-0.0319	0.97	0.043	0.9391	0.9989
Others	-0.0684	0.93	0.023	0.8804	0.9904

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Table 56 Subcutaneous Tissue Complication for Pattern 2 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0859	0.92	0.022	0.8527	0.9875
More than RT	-0.0365	0.96	0.181	0.9139	1.0170
Surgery					
Yes	0	1.00			
No	0.0017	1.00	0.934	0.9617	1.0433
Constant	0.0487				
Wald χ^2 **= 14.47**					

Table 57 Subcutaneous Tissue Complication for Pattern 3

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Time	0.0018	1.00	0.159	0.9992	1.0043
Group					
Cisplatin	0	1.00			
Carboplatin	0.0381	1.04	0.254	0.9729	1.1093
Age	0.0015	1.00	0.432	0.9976	1.0054
Kps	-0.0013	1.00	0.445	0.9950	1.0021
Stage					
Stage I	0	1.00			
Stage II	0.0083	1.01	0.697	0.9670	1.0513
Stage III	0.0660	1.07	0.084	0.9912	1.1512

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Table 57 Subcutaneous Tissue Complication for Pattern 3 (Cont.)

Variable	$\hat{\beta}$	OR	*P-value*	95 % CI of OR	
				Lower	Upper
Pathological Types					
Squamous cell carcinoma	0	1.00			
Adenocarcinoma	-0.0321	0.97	0.043	0.9386	0.9989
Others	-0.0688	0.93	0.021	0.8804	0.9896
Radiation Dose					
Standard RT	0	1.00			
Less than RT	-0.0858	0.92	0.022	0.8527	0.9876
More than RT	-0.0366	0.96	0.177	0.9141	1.0167
Constant	0.0495				

Wald χ^2 **= 14.43**

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BIOGRAPHY

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INSTITUTIONS ATTEND	Mahidol University, 1998-2002: Bachelor of Nurse(Siriraj Hospital)
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