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碩士論文

子宮頸癌 IB2 治療方式探討-
以中部某醫學中心為個案醫院

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Treatments for stage IB2 of cervical cancer – A study at medical center in central area of Taiwan

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摘要

子宮頸癌是全世界女性罹患率第三高的癌症。根據估計在 2008 年子宮頸癌有 530,000 個新發生的病例(約佔所有女性診斷癌症的近十分之一(9%))。根據 FIGO 年度報告，IB1 和 IB2 的五年存活率從 90%大幅下降到 75%。IB2 的治療方式比其他期別更有爭議：包括同步化學及放射治療、直接子宮頸癌根除性手術及後腹腔淋巴腺切除術，以及同步化學及放射治療後再加子宮切除，每種方法都有其優缺點。

在 IB2 子宮頸癌的治療，術前輔助化療後再行根除性子宮切除術較單純手術提高存活率。強度調控放射治療(IMRT)和同期化療，跟傳統同步化療合併放射線治療比較起來有類似的療效，同時於急性和晚期毒性也較低。

既然，對於子宮頸癌 IB2 的患者，這兩種治療策略都有其優點，究竟哪一種方式更好，或直接手術、直接放射線治療，需要以臨床試驗來確定。然而，在已發表之醫學文獻中，這方面之比較較少。因此，我們希望藉由本回溯性的研究，來針對子宮頸癌 IB2 之治療方式進行探討。

關鍵字詞：子宮頸癌期別 IB2、放射治療、強度調控放射治療、術前輔助性化學治療、子宮頸根除性手術

Treatments for stage IB2 of cervical cancer – A study at medical center in central area of Taiwan

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ABSTRACT

Cervical cancer is the third leading cause of female cancer worldwide. It is estimated to be responsible for 530,000 new cases of cancer in 2008 (nearly one in ten (9%) of all cancers diagnosed in women). From the FIGO annual repot the average 5 year survival rate drop dramatically from 90% to 75% for stage IB1 and IB2, respectively. The treatment policy for stage IB2 is more controversial than other stages and including concomitant chemoradiation, primary radical hysterectomy with retroperitoneal lymph dissection, and concomitant chemoradiation followed by hysterectomy. Each method has their benefits and shortcomings.

In treatment stage IB2 cervical cancer, neoadjuvant chemotherapy followed by radical hysterectomy will improve survival compare to operation alone. Intensity modulated radiotherapy (IMRT) and concomitant chemotherapy was found to have good efficacy at the same time favorable acute and late toxicities.

Now that these two treatment strategies both offer benefits to stage IB2 cervical cancer patients, which one should be the first choice, including: radical hysterectomy, neoadjuvant chemotherapy followed by radical hysterectomy, radiotherapy, or concomitant chemoradiation therapy should be determined by clinical trials.

However, from Pubmed search, there were only few studies involving the comparison of these four methods of treatment. Therefore , we hope that through this retrospective study to explore ways for the treatment of cervical cancer IB2.

Keywords：cervical cancer，Radiation Therapy，Intensity Modulation Radiation Therapy，neoadjuvant chemotherapy，radical hysterectomy，stage IB2

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Yours in Hsien-Ai Lin

Department of Industrial Engineering and Management Information Tunghai University

Master Program for Health Administration

June 2015

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Chapter 1 Introduction

1.1 Background

Cervical cancer is the third leading cause of female cancer worldwide. [21] It is estimated to be responsible for 530,000 new cases of cancer in 2008 (nearly one in ten (9%) of all cancers diagnosed in women). [21]

From the experience in US, the death rate from cervical cancer has declined dramatically since 1955 (74% from 1955 to 1992) largely from the increased use of the Pap smear. This means that cervical cancer is a preventable disease. [52] However, According to the statistical data from American Cancer society, between 60% and 80% of American women who are newly diagnosed with cervical cancer have not had a Pap smear within the last five years. Thus, less frequent Pap smear becomes the most significant risk factor for cervical cancer.

The condition is quite similar in Taiwan. From the report of Health Promotion Administration, Ministry of Health and Welfare, 45% of women more than 30 years of age didn't receive Pap smear in previous three years. [27] These women were at higher risk for cervical cancer.

General speaking, the prognosis of cervical cancer is relatively good (average five years survival rate near 70%). [49] From the FIGO annual repot 2006, stage IB2 (tumor confined in cervix, greater diameter larger than 4 cm) cervical cancer accounts for 8% of all cervical cancer. However, the average 5 year survival rate drop dramatically from 90% to 75% for stage IB1 and IB2, respectively. Thus, the treatment of bulky cervical tumor should be different from earlier stage IB1 cervical cancer.

1.2 Research motivation

The treatment policy for stage IB2 is more controversial than other stages. According to National Comprehensive Cancer Network (NCCN) guideline 2013, the treatment option for stage IB2 cervical cancer includes concomitant chemoradiation, primary radical hysterectomy with retroperitoneal lymph dissection, and concomitant chemoradiation followed by hysterectomy.[5] The benefit of primary surgery is to provide accurate evaluation of the extent of tumor spreading, and to preserve ovarian and vaginal function. However, some patient may require postoperative irradiation or chemoradiation, thus the gastrointestinal and urinary tract complication may be much more increased. The benefit of primary chemoradiation is curative for some patients after the treatment. The shortcoming is late complication specific to irradiation and higher failure rate due to bulky tumor, which requiring post-irradiation surgery.

Neoadjuvant chemotherapy followed by surgery was adopted for decades of years in certain area around the world. Cochrane review 2012 indentified six studies which included more than one thousand cases found that this neoadjuvant chemotherapy significantly improves both progression-free survival (HR=0.75, p=0.008) and overall survival (HR=0.77, p=0.02).[6-11] The rationale of neoadjuvant chemotherapy including significant decreased in adverse pathological findings, lymph metastasis, and parametrial infiltration. Also, there exists a trend toward less distal recurrence (OR=0.75, P=0.07) and increased rate of resection (OR=1.55, P=0.11). Therefore, neoadjuvant chemotherapy followed by radical hysterectomy is widely adopted in certain hospitals.

1.3 Objective

Now that these two treatment strategies both offer benefits to stage IB2 cervical cancer patients, which one should be the first choice, including: radical hysterectomy, neoadjuvant chemotherapy followed by radical hysterectomy, radiotherapy, or concomitant chemoradiation therapy should be determined by clinical trials. However, from Pubmed search, there were only few studies involving the comparison of these four methods of treatment. Therefore , we hope that through this retrospective study to explore ways for the treatment of cervical cancer IB2.

1.4 Papers Architecture

Research framework of this study is shown in Figure 1-1 .

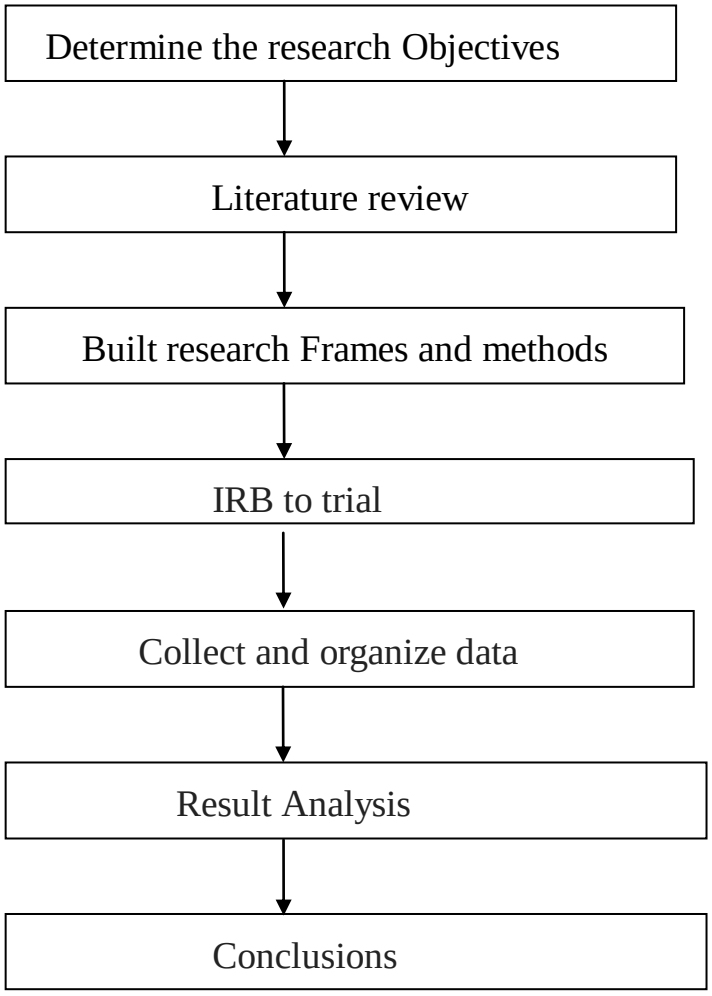

Figure 1.1 The study process research

Chapter 2 Literature review

The cervix is the lower third of the uterus. It is roughly cylindrical in shape, projects through the upper, anterior vaginal wall and communicates with the vagina through an orifice called the external os. Cancer of the cervix may originate on the vaginal surface or in the canal. Cervical cancer is one of the most common cancers diagnosed in women worldwide [43]

2.1 Stage of cervical cancer

The size of cervical tumor has been regarded as an indication of disease recurrent for cervical cancers [5, 14, 15, 20, 22, 24, 22, 44, 45]. It has prompted the American Joint Committee on Cancer and the International Federation of Gynecology and Obstetrics define stages of cervical cancer as invasive cancer. Usually, Stage of cervical cancer is based on clinical evaluation. Accordingly, careful clinical examination should be implemented in all cases. Stages of cancer of the uterine cervix are predicated by the tumor's character to confine itself to the cervix, and then spread in a progressive and predictable manner through regional lymphatics. Staging of carcinoma of the cervix uteri is shown as table 2.1

Table 2.1 Carcinoma of the cervix uteri: FIGO nomenclature (Montreal, 1994)

Stage 0	Carcinoma *in situ*, cervical intraepithelial neoplasia Grade III.
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).

	Ia	Invasive carcinoma which can be diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are allotted to Stage Ib carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0mm and a horizontal extension of not >7.0 mm. Depth of invasion should not be >5.0mm taken from the base of the epithelium of the original tissue – superficial or glandular. The involvement of vascular spaces – venous or lymphatic – should not change the stage allotment. Ia1 Measured stromal invasion of not >3.0mm in depth and extension of not >7.0 mm. Ia2 Measured stromal invasion of >3.0mm and not >5.0mm with an extension of not >7.0 mm
	Ib	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than Stage Ia. Ib1 Clinically visible lesions not >4.0 cm. Ib2 Clinically visible lesions >4.0 cm.
Stage II		Cervical carcinoma invades beyond uterus, but not to the pelvic wall or to the lower third of vagina. IIa No obvious parametrial involvement. IIb Obvious parametrial involvement
Stage III		The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to other cause. IIIa Tumor involves lower third of the vagina, with no extension to the pelvic wall. IIIb Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
Stage IV		The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV. IVa Spread of the growth to adjacent organs. IVb Spread to distant organs.

2.2 Therapy

In spite of the treatment whether by surgery or irradiation, In patients with large stage IB cervical cancers their local control and survival are poorer than those who with smaller stage I cancers [16, 17, 18, 19, 28, 46]. There are controversies over the most suitable treatment of patients with large size of tumor at stage IB2 cervical carcinomas since the late 1960s [16, 17] Histopathologic features which are capable of predicting the risk of recurrence and death have been evaluated within the capabilities of current surgical technologies [6, 18, 19, 23, 24, 28, 46]. It has been mentioned that the 5-year survival for stage IB drops from 80-90% to 50-70% as soon as one or more risk factors is found, in spite of what the modern treatment is. In fact, combination or multimodality therapy have been introduced to patients with high-risk lesions and try to make some improvement [1, 7, 37, 47, 53].

Historically, many series have addressed the issue of multimodality treatment of stage IB2 or bulky cervical cancer. It was reported that in patients with bulky stage I and II tumors had survival improved if additional fascial hysterectomy was executed. Meanwhile, to evaluate post-radiation hysterectomy in a randomized cervical cancers trail, the rate of local recurrent decreased only and not improving in survival [31] Subsequently, others have reported that pelvic radiotherapy after radical hysterectomy is well tolerated with minimal treatment related complications [1, 7, 37].

Another multimodality therapy for women with bulky tumors limited to the cervix is radiation with radio-sensitizing chemotherapy. Several studies on phase II had been conducted and suggested that in patients with high risk factors could have potential benefit when adjuvant chemo-radiation is used. It was the combination of cisplatin-based chemotherapy and fluorouracil (5-FU) which demonstrated activity in patients with advanced or metastatic cervical cancers [31-33]. Both cisplatin and 5-FU are radiation sensitizers and their concurrent use seems to be synergistic [30]. Furthermore, it seemed that the combination of cisplatin (with or without 5-FU) and pelvic irradiation improve local control and overall survival in patients with advanced disease in phase II trials [2, 3, 10, 25, 28].

According to a patterns of care study performed by the American College of Surgeons, surgery is increasingly being used in the United States as the

primary mode of treatment. However, there are great controversies among physicians on the dichotomization between (1) primary surgery followed by dichotomy postoperative therapy based on surgical risk factors and (2) primary radiation and chemotherapy in the treatment of stage IB2 cervical cancer However, there are great controversies among physicians on the dichotomization

Most data have suggested similar cure rates between these two diverse approaches [16, 25], in spite of some suggestion of additional surgery of excision of metastatic lymph nodes does offer the advantage of surgical staging, higher (essentially 100%) local complete response rate, as well as increased cure rates. However, the standard approach to stage IB2 cervical cancer has apparently become combination radiation and chemotherapy since the cure rates of this approach are not clearly lower than when treatment planning involves radical hysterectomy.

Currently, study was designed to reveal if the addition of CT to standard pelvic RT could improve survival and overall survival in patients with high risk for recurrent after primary radical hysterectomy. Many questions remain unanswered in this issue. Specifically, how often will postoperative radiation or radiation and chemotherapy be needed if the primary radical hysterectomy approach is chosen? Uncertainty still exists as to what complications might be if radiation with or without chemotherapy were to be routinely implemented after radical hysterectomy.

Both radial hysterectomy with pelvic lymphadenectomy and radical radiation therapy (RT) are used as primary therapy for early-stage carcinoma of the cervix. Recently, Gynecologic Oncology Group (GOG) have published two researches reports on investigating the indications for postoperative radiation and chemotherapy [47, 53]. They suggest that in patients with large and deeply invasive tumors with capillary lymphatic space invasion, to whom adjuvant pelvic radiation should be implemented and chemotherapy should be added to the radiation if nodal metastases, parametrial extension or positive surgical margins are present. After radical hysterectomy, adjuvant RT has commonly been used to prevent patients at high risk from recurrence. By a retrospective comparisons, patients who with positive pelvic lymph nodes and had treated with postoperative RT have generally shown a decrease in the local recurrence

rate but no improvement in long-term survival. [47, 51].

Obviously, survival is the very deciding factor, at last, in choosing primary chemotherapy and radiation over surgery followed by adjuvant therapy. GOG had begun such a prospective trial comparing with therapies. In patients who suffer from lymph node and parametrium involvement or surgical margins with large or deeply invasive lesions recurrent much more frequent [1, 6-7, 16, 19, 23-24, 28, 31, 53] The treatment of cervical cancer has changed over time. Patients with ‘‘bulky’’ stage IB2 cervical cancers treated with radical hysterectomy is the preferred method of therapy currently. However, since there were complicating issues reported, to retrospectively review the feasibility, results and treatment related morbidity among patients and to estimate the need for adjuvant therapy after radical hysterectomy based on recently published data are carrying on [4].

Treatment for cervical cancer is relatively well defined for most stages; however, for stage IB2, there are no clear guidelines as to the best single treatment approach. Either primary surgery or radiotherapy (RT) is considered to be feasible. The merits of primary surgery include pathologic assessment of the merits of disease and preservation of ovarian and vaginal function. However, adjuvant treatment is more often required with primary surgery than with primary RT, which also carries a greater risk of delayed toxicity. [2] Treatment definitions are given in Table 2.2

Table 2.2 Carcinoma of the cervix uteri: Definitions of treatments

Treatment	Definition
None	No treatment.
Surgery alone	Surgery as first therapy and no other therapy(ies) within 90 days from the date of surgery. Subsequently, patients can be given any further treatment.
Radiotherapy alone	External radiotherapy and/or intracavitary irradiation as first therapy(ies)

Treatment	Definition
	and no other therapy(ies)within 90 days from the end of eletherapy/brachytherapy. Subsequently, patients can be given any further treatment.
Radio-surgery	External radiotherapy/ intracavitary irradiation as first therapy and then surgery within 90 days from the end of teletherapy/brachytherapy. Subsequently, patients can be given any further treatment. (Chemotherapy can be associated within 120 days from the date of surgery.)
Neoadjuvant chemotherapy + surgery	Chemotherapy as first therapy and then surgery within 42 days from the end of chemotherapy. Subsequently, patients can be given any further treatment.
Surgery + adjuvant radiotherapy	Surgery as first therapy and then radiotherapy within 90 days from the date of surgery. Subsequently, patients can be given any further treatment. (Chemotherapy can be associated within 120 days from the date of surgery.)
Surgery + adjuvant chemotherapy	Surgery as first therapy and then chemotherapy within 90 days from the date of surgery or of the end of radiotherapy
Chemo-radiotherapy	Radiotherapy with chemotherapy (either neoadjuvant, concomitant or sequential) administered together or at least within 90 days from the end of either therapy.
Chemotherapy alone	Chemotherapy as first therapy and no other therapy(ies) within 90 days from the end of

Treatment	Definition
	chemotherapy. Subsequently, patients can be given any further treatment.

2.3 Intensity-modulated radiotherapy (IMRT)

There is a refined and more precise radiotherapy called Intensity-modulated radiation therapy (IMRT). It uses computer-controlled linear accelerators to deliver precise radiation doses to a fatal tumor or specific areas within the tumor. IMRT allows for the radiation dose apply more precisely to the three-dimensional (3-D) shape of the tumor by modulating the intensity of the radiation beam. In addition, IMRT allows higher radiation doses to be focused to regions within the tumor while minimizing the dose to surrounding normal structures. At present, patient's 3-D computed tomography (CT) or magnetic resonance (MRI) images can be implemented well and find a suitable treatment. Meanwhile, does is computerized to determine the intensity pattern that will best conform to the tumor shape At present, patient's 3-D computed tomography (CT) or magnetic resonance (MRI) images can be implemented well and find a suitable treatment. Meanwhile, does is computerized to determine the intensity pattern that will best conform to the tumor shape.

There is fewer side effects compared with conventional radiotherapy techniques since the ratio of normal tissue dose to tumor dose is reduced to a minimum with the IMRT approach, in addition higher and more effective radiation doses can safely be delivered to tumors. Furthermore, IMRT has the potential to reduce treatment toxicity, even when doses are not increased. Because of its complexity, IMRT does require longer daily treatment times, additional planning and safety checks before the patient can start the treatment than conventional radiotherapy.

Today, IMRT has been used most extensively to treat cancers of the prostate head and neck and central nervous system. In some situations IMRT has also been used in treating breast, thyroid, lung, as well as in gastrointestinal, gynecologic malignancies and certain types of sarcomas, even pediatric malignancies. Radiation therapy, including IMRT, stops cancer cells from dividing and growing, thus slowing or stopping tumor growth. In many cases,

radiation therapy is capable of killing all of the cancer cells, thus shrinking or eliminating tumors. [30]

Recently, the use of IMRT has increased significantly. [11] Its usage increased from 32% to 73% over the years 2002 to 2004. The significant dosimetric benefits were found to be translated into less toxicities, especially gastrointestinal and bone marrow. [54] In reviewing the cases with advanced cervical cancer treated with IMRT and in conjunction with chemotherapy from 2004 to 2008 and found good efficacy at the same time favorable acute and late toxicities. [12] IFGO prescribed ‘‘bulky’’ stage IB cervical cancer and defined as tumors greater than 4 cm in diameter. [10] The sub-classification of stage IB cervical cancer recognizes that bulkier cervix-confined tumors may require different treatment approaches. To reduce normal tissue toxicity in cervix cancer with or without treatment intensification IMRT is being increasingly explored as a means [3, 9, 26, 39, 48, 57]. Reductions in acute and late toxicities with the use of IMRT have been reported in conjunction with low rates of conjunction failures [9, 26, 55]. Accurate target definition is important to ensure the target is not under-treated and to limit the dose to surrounding normal tissues.

In spite of published guidelines on clinical target volume (CTV) have defined a number of tumor sites including the postoperative gynecological and prostatectomy setting IMRT for the radical treatment of cervix cancer remain variable [9, 26, 40-41, 48, 56-57]. As a matter of fact, cervix cancer patients reveal more substantial than in prostate cancer on the amount of organ motion, tumor regression, and deformation [8, 13, 29, 34-36, 42]. It implies great caution when IMRT is used in this site than for prostate cancer as to these complex intrapelvic organ dynamics. In order for IMRT to be delivered safely, adequate planning tumor volume (PTV) margins are necessary to account for CTV motion.

Chapter 3 Research Design and Methods

3.1 Research and data collection architecture

The present study was conducted to explore the architecture as shown in Figure 3-1.

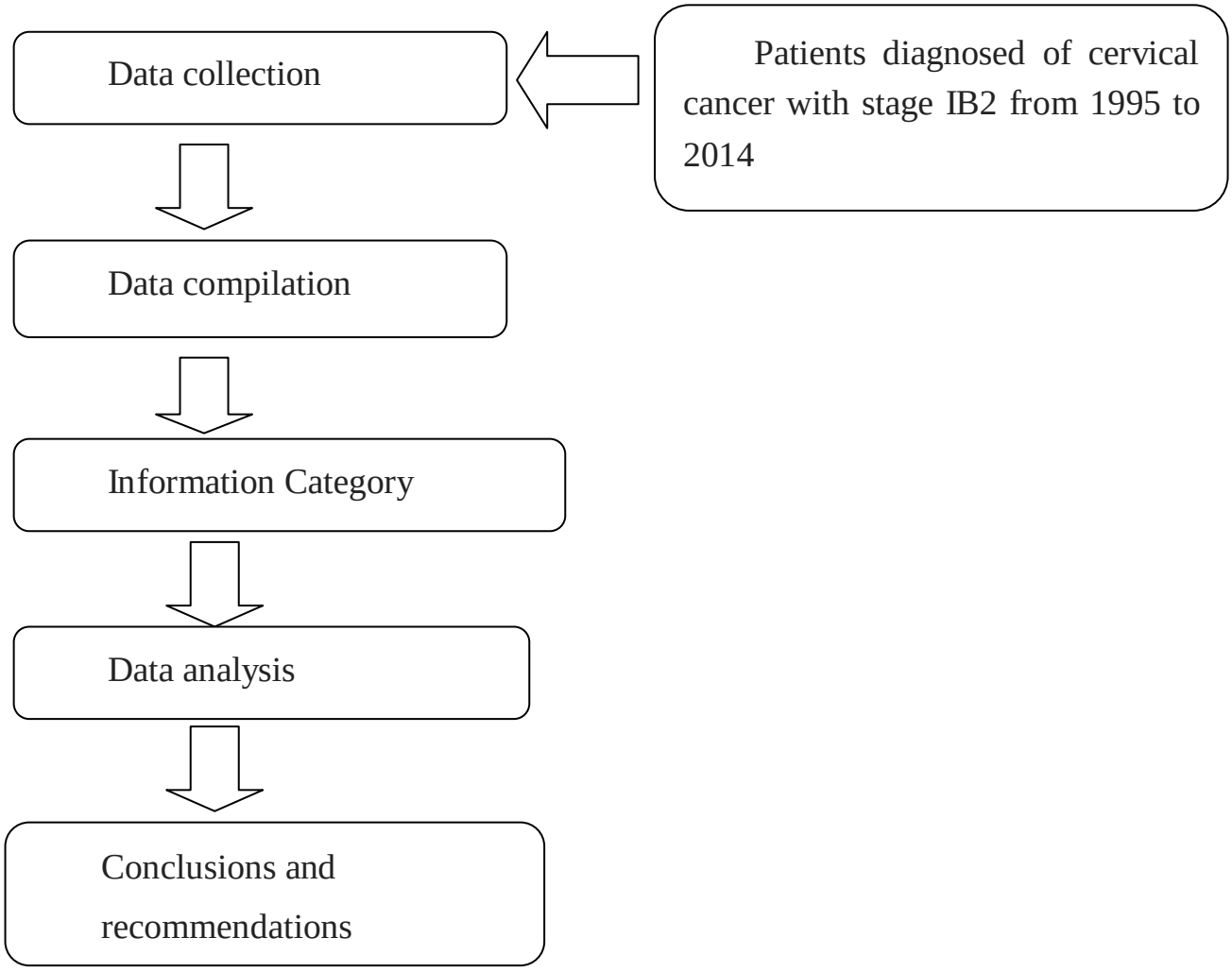

Figure 3.1 Study Chart

3.2 Research methods and steps

IRB approval will be obtained from TCVGH Institutional review board (IRB) for conducting the trial.

1. Cases enrollment:

All the patients diagnosed with cervical cancer FIGO stage IB2 will be enrolled into data analysis. The list of cases will be obtained from Cancer registration, Clinical Research Informatics and Development Center.

2. Criteria of inclusion:

(1). Pathological diagnosis of cervical cancer should be made in TCVGHT or other institute that had been recorded clearly in the medical chart.

(2). FIGO staging IB2 by pelvic examination, or sonography.

(3). Diagnosis equals or later than year 1995

(4). Histological type:

squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma

3. Criteria of exclusion:

(1).Clear cell carcinoma, serous carcinoma, neuroendorine carcinoma of cervix.

(2). Diagnosis before year 1994.

(3). Uncertainty for primary endometrial cancer or cervical cancer.

(4). Age younger than 20 y/o.

(5). At pregnancy.

(6). Coexisting or history of other malignancy then uterine cervix.

(7). Immunocompromised.

4. Statistical Analyses:

The progression free survival and overall survival will be calculated with Descriptive statistical analysis and Fisher's exact test and Yates's correction for continuity .

3.3 Statistical Analyses:

The progression free survival and overall survival will be calculated with Descriptive statistical analysis and Fisher's exact test and Yates's correction for continuity .

1. Descriptive statistical analysis

Descriptive manner and explain aggregated sample data structure , the use of frequency distribution , averages and other data distribution to describe the situation in order to understand its structural properties . This approach focuses on data compilation , describe and explain the need to organize a jumble and drive meaningful data analysis and information classification can not be understood , mainly based on statistical variables manner , statistical analysis of samples relevant information , and narrative analysis and inference. The subject of time sheets to collect collate , classify , simplify and graphed as a value stream map , to describe and summarize data relationships between features and disguise.

2. Fisher's exact test

Fisher's exact test is a statistical significance test used in the analysis of contingency tables. Although in practice it is employed when sample sizes are small, it is valid for all sample sizes. It is one of a class of exact tests, so called because the significance of the deviation from a null hypothesis (e.g., P-value) can be calculated exactly, rather than relying on an approximation that becomes exact in the limit as the sample size grows to infinity, as with many statistical tests.

3. Purpose and scope

The test is useful for categorical data that result from classifying objects in two different ways; it is used to examine the significance of the association (contingency) between the two kinds of classification. So in Fisher's original example, one criterion of classification could be whether milk or tea was put in the cup first; the other could be whether Dr Bristol thinks that the milk or tea was put in first. We want to know whether these two classifications are associated Most uses of the Fisher test involve, a 2 × 2 contingency table. The p-value from the test is computed as if the margins of the table are fixed, and will therefore provide guesses with the correct number in each category. As pointed out by Fisher, this leads under a null hypothesis of independence to a

hypergeometric distribution of the numbers in the cells of the table.

With large samples, a chi-squared test can be used in this situation. However, the significance value it provides is only an approximation, because the sampling distribution of the test statistic that is calculated is only approximately equal to the theoretical chi-squared distribution. The approximation is inadequate when sample sizes are small, or the data are very unequally distributed among the cells of the table, resulting in the cell counts predicted on the null hypothesis (the "expected values") being low. The usual rule of thumb for deciding whether the chi-squared approximation is good enough is that the chi-squared test is not suitable when the expected values in any of the cells of a contingency table are below 5, or below 10 when there is only one degree of freedom (this rule is now known to be overly conservative). In fact, for small, sparse, or unbalanced data, the exact and asymptotic *p*-values can be quite different and may lead to opposite conclusions concerning the hypothesis of interest. In contrast the Fisher test is, as its name states, exact as long as the experimental procedure keeps the row and column totals fixed, and it can therefore be used regardless of the sample characteristics. It becomes difficult to calculate with large samples or well-balanced tables, but fortunately these are exactly the conditions where the chi-squared test is appropriate.

For hand calculations, the test is only feasible in the case of a 2 × 2 contingency table. However the principle of the test can be extended to the general case of an $m \times n$ table, and some statistical packages provide a calculation (sometimes using a Monte Carlo method to obtain an approximation) for the more general case.

4. Controversies

Despite the fact that Fisher's test gives exact p-values, some authors have argued that it is conservative, i.e. that its actual rejection rate is below the nominal significance level. The apparent contradiction stems from the combination of a discrete statistic with fixed significance levels. To be more precise, consider the following proposal for a significance test at the 5%-level: reject the null hypothesis for each table to which Fisher's test assigns a p-value equal to or smaller than 5%. Because the set of all tables is discrete, there may not be a table for which equality is achieved. If α_e is the largest p-value smaller than 5% which can actually occur for some table, then the proposed test

effectively tests at the α_e-level. For small sample sizes, α_e might be significantly lower than 5%.While this effect occurs for any discrete statistic (not just in contingency tables, or for Fisher's test), it has been argued that the problem is compounded by the fact that Fisher's test conditions on the marginals. To avoid the problem, many authors discourage the use of fixed significance levels when dealing with discrete problems.

5. Yates's correction for continuity

In statistics,Yates' correction for continuity(or Yates' chi-squared test) is used in certain situations when testing for independence in a contingency table. In some cases, Yates' correction may adjust too far, and so its current use is limited.

6. Correction for approximation error

Using the chi-squared distribution to interpret Pearson's chi-squared statistic requires one to assume that the discrete probability of observed binomial frequenciesin the table can be approximated by the continuous chi-squared distribution. This assumption is not quite correct, and introduces some error.

To reduce the error in approximation, Frank Yates, an English statistician, suggested a correction for continuity that adjusts the formula for Pearson's chi-squared test by subtracting 0.5 from the difference between each observed value and its expected value in a 2 × 2 contingency table. This reduces the chi-squared value obtained and thus increases its p-value.

The effect of Yates' correction is to prevent overestimation of statistical significance for small data. This formula is chiefly used when at least one cell of the table has an expected count smaller than 5. Unfortunately, Yates' correction may tend to overcorrect. This can result in an overly conservative result that fails to reject the null hypothesis when it should (a type II error). So it is suggested that Yates' correction is unnecessary even with quite low sample sizes.

Chapter 4 Results and analysis

At the duration from January 1995 to December 2014，we enrolled women of all ages who had stages IB squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix according to the staging system of the International Federation of Gynecology and Obstetrics (Table 1) or one of these cancers with a tumor diameter of at least 5 cm or biopsy-proved metastasis to pelvic lymph nodes. Women were excluded from the study if they met any of the following criteria: disease outside the pelvic area or spread to para-aortic lymph nodes; a prior cancer other than cutaneous basal-cell carcinoma; medical contraindications to chemotherapy; a rare histologic subtype; and prior hysterectomy or transperitoneal staging procedure for cervical cancer, pelvic radiotherapy, or systemic chemotherapy.

A medical history taking and clinical examination were required before enrollment. The initial evaluation also included chest radiography, cystoscopy, proctoscopy, a complete blood count, and measurement of liver and renal function. The renal-collecting system of each patient was assessed by intravenous pyelography or contrast computed tomography. Para-aortic lymph nodes were evaluated by bipedal lymphangiography or retroperitoneal surgical exploration.

The surveillance committees of the Institutional review board(IRB) approved this trial. Patients were required to understand the trial and provide written informed consent.

1.Recurrence of histological patterns

There are 4 out of 24 patients who are Categorized as histological patterns of squamous cell carcinoma (SCC) recurrence after treatment .Yates's corrected Chi-square method was used with a p-value of .2636.In addition ,Fisher exact one tailed was implemented with a p-value of .1322.These p-value revealed that there was no significant difference between non-recurrence patients with histological patterns of SCC and adenocarcinoma, as shown in Table 4.1.

Table 4.1 2 x 2 Table (IB2) Recurrence of histological patterns

	Column 1	**Column 2**	**Row Totals**
SCC	20	4	24
Percent of total	50.000%	10.000%	60.000%
adenocarinorma	10	6	16
Percent of total	25.000%	15.000%	40.000%
Column totals	30	10	40
Percent of total	75.000%	25.000%	
Chi-square (df=1)	2.22	p= .1360	
V-square (df=1)	2.17	p= .1410	
Yates corrected Chi-square	1.25	p= .2636	
Phi-square	.05556		
Fisher exact p, one-tailed		p= .1322	
two-tailed		p= .1592	
McNemar Chi-square (A/D)	6.50	p= .0108	
Chi-square (B/C)	1.79	p= .1815	

2.**Histological pattern on survival**

To be categorized as histological patterns of SCC, There are 22 out of 24 patients survived after treatment. Meanwhile, those patients who cure categorized as adenocarcinoma.12 out of 16 patients survived after treatment.

Either Yates's corrected Chi-square or Fisher exact p,one-tailed test revealed non-significant difference between these two histological patters with p values .3201 and .1603, respectively, as shown in Table 4.2.

Table 4.2 2 x 2 Table (IB2) Histological pattern on survival

	Column 1	**Column 2**	**Row Totals**
SCC	22	2	24
Percent of total	55.000%	5.000%	60.000%
adenocarcinoma	12	4	16
Percent of total	30.000%	10.000%	40.000%
Column totals	34	6	40
Percent of total	85.000%	15.000%	
Chi-square (df=1)	2.09	p= .1481	
V-square (df=1)	2.04	p= .1533	
Yates corrected Chi-square	.99	p= .3201	
Phi-square	.05229		
Fisher exact p, one-tailed		p= .1603	
two-tailed		p= .1953	
McNemar Chi-square (A/D)	11.12	p= .0009	
Chi-square (B/C)	5.79	p= .0162	

3.**Recurrence of treatment methods**

There are two major treatment methods to be implemented in the study, NACT+RH. and CCRT. There are 23 patients who took the treatment of NACT+RH Six out of twenty patients recurrence after treatment of NACT+RH

Meanwhile, Four out of twelve patients recurrence after treatment of CCRT. Yates's corrected Chi-square test and Fisher exact p, one –tailed test were applied with p values of .7670 and .6199,respectively,Either Yates' corrected Chi-square test or Fisher exact p one-tailed reveal significant difference between the rate of non-rucurrence of treatments NACT+RH and CCRT, as shown in Table 4.3.

Table 4.3 2 x 2 Table (IB2) Recurrence of treatment methods

	Column 1	**Column 2**	**Row Totals**
NACT+RH	17	6	23
Percent of total	43.590%	15.385%	58.974%
CCRT	12	4	16
Percent of total	30.769%	10.256%	41.026%
Column totals	29	10	39
Percent of total	74.359%	25.641%	
Chi-square (df=1)	.01	p= .9390	
V-square (df=1)	.01	p= .9398	
Yates corrected Chi-square	.09	p= .7670	
Phi-square	.00015		
Fisher exact p, one-tailed		p= .6199	
two-tailed		p=1.0000	
McNemar Chi-square (A/D)	6.86	p= .0088	
Chi-square (B/C)	1.39	p= .2386	

4.**Survival of treatment methods**

There are 21 of 23 patients survive after treatment of NACT+RH. Meanwhile, there are 14 out of 16 patients survive after treatment of CCRT. Yates' corrected Chi-square test and Fisher exact p one-tailed test were implemented to tell whether there is a significant difference between the rate or survival of treatment NACT+RH and CCRT. P values of these two testing methods are .8797(Yates') and .5478(Fisher), respectively, and showed non-significant difference. as shown in Table 4.4

Table 4.4 2 x 2 Table (IB2) Survival of treatment methods

	Column 1	**Column 2**	**Row Totals**
NACT+RH	21	2	23
Percent of total	53.846%	5.128%	58.974%
CCRT	14	2	16
Percent of total	35.897%	5.128%	41.026%
Column totals	35	4	39
Percent of total	89.744%	10.256%	
Chi-square (df=1)	.15	p= .7001	
V-square (df=1)	.14	p= .7038	
Yates corrected Chi-square	.02	p= .8797	
Phi-square	.00380		
Fisher exact p, one-tailed		p= .5478	
two-tailed		p=1.0000	
McNemar Chi-square (A/D)	14.09	p= .0002	
Chi-square (B/C)	7.56	p= .0060	

The study sampled from Taichung Veterans General Hospital, the patient Republic between 1995 January to 2014 in December diagnosed with cervical cancer IB2, the information collected for all patients. The study was drawn first study collected data flow diagram, through data analysis, to assist the medical team members a clear understanding of the scope and objectives of this study, in the treatment of IB2 cervical cancer, preoperative chemotherapy before making the eradication of hysterectomy improve survival compared with surgery alone.

Intensity modulated radiation therapy (IMRT) and concurrent chemotherapy , concurrent chemotherapy with conventional radiation therapy compared merger have similar efficacy , while in acute and late toxicity is low.

Since , IB2 cervical cancer patients , both of therapeutic strategies has its advantages , which way actually better , or direct operation , direct radiation therapy , clinical trials need to be determined . However, it has been published in the medical literature, and compares this facet of the few. Therefore, we hope that through this retrospective study, for the treatment of patients with cervical cancer IB2 -depth discussion.

Chapter 5 Discussion and Conclusions

Cervical cancer is one of the most common cancers diagnosed in women worldwide. Concurrent chemoradiotherapy (CCRT) is the mainstay treatment for locally advanced cervical cancer. The purpose of this study was to investigate the treatment outcomes and toxicity of definitive intensity-modulated radiotherapy (IMRT) with concurrent chemotherapy for patients with locally advanced carcinoma of the cervix in a single institution.

5.1 Discussion

This case study received a total of 47 cases , including histological patterns were 24 cases of SCC , Adenocarcinoma were 16 cases , these two histologic patterns for a total of 40 cases , compared with a comparative sense , so this two histologic type Compare incorporate state ; histologic patterns other minorities such as Papillary SCC (2 cases), Endometrioid carcinoma (1 case), Adenosquamous cell carcinoma (3 patients), Carcinoma (1 case) , because the number of cases less than normal, can not be compared , so this study can only compare to the more meaningful comparison of the histological patterns in disease recurrence and survival aspects of the treatment.

In addition , for the choice of treatment of diseases , adopted by NACT + RH treatment of 23 cases of treatment were adopted CCRT of 16 cases, more than two treatments accounted for 39 cases ; other forms of treatment , such as : CCRT + BSO (1 case), CCRT + EBRT + RH (1 case), CCRT + EBRT (1 case), NACT + CCRT + RH (1 case), RT (1 case) „ RH (there 3 cases) , less than normal because of the number of cases , can not be compared , and reinforce comparative research only on the more meaningful comparison of treatment in disease recurrence and survival aspects of the treatment.

5.2 Conclusions

Patients with locally advanced cervical cancer treated with definitive IMRT and concurrent cisplatin-based chemotherapy achieved good outcomes, and this combined treatment was well tolerated with favorable acute and late toxicity.

The study received a total of 47 cases , different histological patterns and treatment , the disease situation and compare the recurrence of the situation whether for survival , net histological patterns were less common (in this study, the number of cases recorded in only 1 ~ two cases of persons) , only 40 seats

of patients with stage IB2 cervical cancer were analyzed. Through use Yates corrected Chi-square and Fisher exact p, one-tailed statistical method of comparative analysis , The results showed that the histological patterns of adenocarcinoma and SCC who are not statistically different feelings of recurrence and survival situations ; estimate the number of samples that can be analyzed may be the less , it can not compare.

In conclusion, radical hysterectomy and lymphadenectomy followed by tailored adjuvant therapy remains a reasonable alternative to primary chemoradiation for patients with stage IB2 cervical cancer. Patients in our series with low- and intermediate-risk factors had satisfactory results with surgery alone, and complication rates were similar to prior studies. Prognosis is expected to improve further with the addition of adjuvant chemoradiation for patients with intermediate- or high-risk factors. A prospective randomized trial planned by the GOG will clarify the role of primary radical surgery in patients with stage IB2 disease.

5.3 Limit

In order to alter the unpleasantness of time-consuming and cumbersome for gynecological exams and enhance women to take Pap smear, government propagandizes “six minutes protect life” in 1995. The slogan is to emphasize that a female citizen spends a few minutes only to take regular smear test annually and she can benefit from early detection and treatment. At present, people know what the slogan means and the number of women who take Pap smear have increased every year. The effectiveness of prevention of cervical cancer has keep up with western countries by the joint efforts of government and private sectors over years.

According to the statistics from Department of Health, the mortality rate of cervical cancer had been dropped 60% at the duration from 1995 to 2011. Cervical cancer has dropped from the fourth place to the tenth on the listing of the top ten causes of death. It is worth to know much about “six minutes protect life” to make female citizens pay more attentions to their own health.

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