Meta Analysis of Cervical Treatment Stage 1B and 2A between Chemotherapy First, or Surgery First, or Surgery Followed by Radiotherapy.

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Abstract: Background: Cervical cancer is the most common gynecologic malignancy in female population of developing countries. However, the treatment of early-stage cervical cancer (IB and IIA) includes radical hysterectomy following by either chemotherapy or radiation therapy remains controversial. **Aims:** The purpose of this study was to evaluate the adverse effects and survival outcome of cervical cancer stage 1B and 2A treatment with 1) chemotherapy first 2) or surgery first, or 3) Surgery followed by radiotherapy. **Methods:** A systematic review of literature and published studies between 1974-2012 in cervical treatment stage 1B and 2A was performed, and a meta-analysis and the summary information from eligible studies was used to estimate and calculate Odd ratio (OR) and 95% confidence interval (CI). **Results:** After reviewing the published articles, we chose 10 studies, which were eligible for meta-analysis and fit the criteria. The average sample size was 190 patients. Meta analysis proved that for cervical cancer stage 1B and 2A the best option of treatment is radical hysterectomy with lymph nodes removal followed by radiotherapy. The Meta analysis found that of the 10 studies, 5 studies have statistically significant treatment effect. The significant odd ratios (OR) at the 5% level ($P<0.05$) of having a favourable outcome among the studies using radiotherapy after radical hysterectomy were 0.097 (95% CI, 0.055 – 0.1771) 1.71 (95% CI, 1.254 – 0.2.347), and 0.097 (95% CI, 0.055 – 0.1771). The narrow width of CI for these studies indicated the more precise estimates for their results. On the other hand, the significant odds ratio (OR) at the 5% level ($P<0.05$) of having a favourable outcome among the studies using chemotherapy plus radiotherapy after radical hysterectomy were 3.973 (95% CI, 1.934 – 8.16), and 3.973 (95% CI, 1.934 – 8.16) However, the width of CI for these studies may indicate the less precise estimates for their results. Conclusions: The best option of treatment cervical cancer stage 1B and 2A was radical hysterectomy with lymph nodes removal followed by radiotherapy. Based on our result, we recommend that postoperative radiation be considered in the management of patients with stage 1B-2A cervical carcinomas found to have regional lymph node metastases; however, alternate forms of therapy deserve consideration when the tumor extends to both the parametrium and pelvic lymph nodes.

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1. Introduction.

Meta-analysis is defined as the statistical analysis of a collection of analytical results for the purpose of integrating the findings. Such analyses are becoming increasingly popular in medical research where information on efficacy of a treatment is available from a number of clinical studies with similar treatment protocols. If these studies are considered separately each study either too small or too limited in scope to come to unequivocable or generalized conclusions about the effect of treatment. Combining the findings across such studies represent an attractive alternative to strengthen the evidence about the treatment efficacy (Der Simonian and Laird, 1986; Der Simonian & Laird, 1983; Laird & Der Simonian, 1982).

Cervical cancer is the second most common cancer among women worldwide and the main cancer affecting women in Sub-Sahara and Africa, Central America and South – Central Asia. A significant decline in incidence and mortality have been seen in North America, parts of Europe, Australia and New Zealand where screening programmes have been implemented for some time (Jemal et al., 2002). The purpose of this study was to evaluate the adverse effects and survival outcome of cervical cancer stage 1B and 2A treatment with (1) chemotherapy first (2) or surgery first (3) or surgery followed by radiotherapy.

2. Materials and Methods.

A literature search was carried out for comparing treatments of cervical cancer stage 1B and 2A between (1)- chemotherapy first (2)- or surgery first or (3)- surgery followed by radiotherapy. The published literature between 1974-2012 was identified through a

search of the following computerized database: Pub Med, the Lancet, Elsevier Gynecological Oncology, Elsevier EJSO, Gynecological Radiology, Med Line, Cross Ref Med Line, Gynecological Oncology group publications and Cancer literature.

Study inclusion criteria.

Through the steps of screening the title, reading the abstract and the entire article, ten trials were identified. Studies were eligible for inclusion, if they fulfilled all of the following selection criteria:

- Studies that evaluate the effectiveness of cervical cancer stage 1B and 2A treatment with chemotherapy, surgery or, surgery followed by radiotherapy.
- Studies with 2 or 5-year survival rate
- Full-length of study articles

Data Collection and Analysis:

All eligible studies were retrieved and evaluated. The name of the first author and the year of publication of the article were used for identification purposes and for treatment allocation, tumour response, survival, cause of death and acute and late toxicity. Baseline data on age, histology, international federation of gynecology and obstetrics stage, tumour grade, and performance status and lymph node involvement were also sought. The outcomes of interest were adverse effects and the overall survival (OS), complications and recurrence. The resulting citation abstracts were reviewed for potential eligibility and the full article texts were obtained for further evaluation for the determination of eligibility. After reviewing the research several studies were excluded because of the absence of full-length articles (Cheung et al., 2011; Soisson et al., 1990; Barter et al., 1989; Fabrini et al., 2009). Finally 10 studies were eligible for meta-analysis and fit the criteria (Table1).

Random effects of Meta analysis with a mixed treatment comparison analysis were performed using the MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium). Effect sizes (odd ratios) were stated along with a 95 % confidence interval (CI) range, and presented in both quantitative format and graphical representation (forest plots). Forest plots graph depict each trial as a horizontal diamond shape in the middle representing the effect size, and the end points representing both ends of the CI. These diamond shapes were presented on a graph with a central line representing the zero mark. The left side of the graph (< zero) represents the side favoring treatment, while the right side (> zero) represents the side of not favoring the treatment.

3. Results:

After reviewing the researches, trials and published articles, we chose fourteen studies. Of the 14, we used 10 of the studies, which were eligible for meta-analysis and fit the criteria. The average sample size was 190 patients (from 45 to 611 patients). The outcomes of interest were adverse effects and the overall survival (OS), complications and recurrence. The follow-up time was from two months to two hundred and forty nine months. The studies were published between 1974-2012 and included nine retrospective studies (Kim et al., 2008; Schorge et al., 1997; Takeshima eat al., 2006; Siriwaranya et al., 2003;Sittidilokratna et al., 2010; Monk et al.,1998; Suprasert et al., 2005; Cheng et al., 2004; Gadducci et al., 2010), and one randomized study (Landoni etal.,1997). Of ten included trials, three trials were conducted in Thailand (Siriwaranya et al., 2003; Sittidilokratna et al., 2010; Suprasert et al., 2005), two in Italy (Landoni etal.,1997; Gadducci et al., 2010) and the United States of America (Schorge et al., 1997; Monk et al.,1998), one in China (Cheng et al., 2004) and Korea (Kim et al., 2008).

Seven studies reported the adverse effects of the different treatment of this study including symptomatic lymphocyst, lymphedema, radiation hemorrhagic cystitis, gastro-intestinal toxicity, vomiting, nausea, bowel obstruction or cystitis and proctitis, gallstone and pelvic abscess (Landoni etal.,1997; Kim et al., 2008; Schorge et al., 1997; Takeshima eat al.,2006; Siriwaranya et al.,2000; Monk et al.,1994; Suprasert et al., 2005). Complication rate differs due to the treatment applied: surgery plus chemotherapy or surgery plus radiotherapy. Also leukopenia or neutropenia were included in the study together with lymphaedema. Presence of (+) lymph nodes and (-) lymph nodes are also recorded in seven trials. Studies showed the data of the overall survival calculated by the Kaplan-Meier Method to calculate Hazard ratio (HR) and 95% confidence interval (CI). Eight studies reported the 5-year overall survival (OS) (Landoni etal.,1997; Kim et al., 2008; Schorge et al., 1997; Takeshima eat al., 2006; Siriwaranya et al., 2003; Monk et al.,1994;; Cheng et al., 2004; Gadducci et al., 2010), one study reported 2-year overall survival (OS) (Suprasert et al., 2005), and one study reported 3 and 5-year survival (Sittidilokratna et al., 2010). The 5-year disease - free survival rate were different from one trial to another due to the changes in treatment procedures (Table2). 10 studies reported follow up events as shown in Table (3) & figure (1). The shortest median follow up reported was that of Suprasert et al. (2005) 19 months, while the longest reported in the study was that of Schorgeet et al. (1997) 84 months. The follow up shown in the study gave an idea about the presence of complication and recurrence or without recurrence. The number of patients alive was despite problems from surgery or combined therapy. The follow up of

treated patients also showed if patients died from other diseases or due to recurrence.

Results of 10 trials indicated that patients developed recurrence were between 3.3% and 42% and this was also changed in the surgery group than in radiotherapy treatment and chemotherapy. After statistical analysis used in Meta analysis, the collection of analytic results for the purpose of integrating the findings, and combining all the results, facts and figures, Meta analysis proved that for cervical cancer stage 1B and 2A the best option of treatment after reviewing the complications, recurrence and overall survival rate for 5 years is radical hysterectomy with lymph nodes removal followed by radiotherapy. The Meta analysis found that of the ten studies, five studies have statistically significant treatment effects. The significant odd ratios (OR) at the 5% level ($P<0.05$) of having a favourable outcome among the studies using radiotherapy after radical hysterectomy were 0.097 (95% CI, 0.055 – 0.1771) (Monk et al., 1994), 1.71 (95% CI, 1.254 – 0.2.347) (Landoni et al., 1997), and 0.097 (95% CI, 0.055 – 0.1771) (Sittidilokratna et al., 2010). The narrow width of CI for these studies indicated the more precise estimates for their results. On the other hand, the significant odds ratio (OR) at the 5% level ($P<0.05$) of having a favourable outcome among the studies using chemotherapy plus radiotherapy after radical hysterectomy were 3.973 (95% CI, 1.934 – 8.16) (Kim et al., 2008), and 3.973 (95% CI, 1.934 – 8.16) (Siriwaranya et al., 2003). However, the width of CI for these studies may indicate the less precise estimates for their results.

Discussion:

Our findings are based on the literature and researches from authentic trials in different parts of the world. These trials were done on thousands of women with proper follow-ups worldwide. After reading all the published researches from 1974- 2012, we very carefully selected 14 studies and published trials that included large samples. Our Meta analysis was based on 10 of the 14 research studies because they fit the criteria and showed very clear results that surgery followed by radiotherapy improved overall free survival rate among the cervical cancer patients.

Thus, we used Meta-analysis to evaluate the adverse effects and survival outcome of cervical cancer stage 1B and 2A treatment with (1) chemotherapy first (2) or surgery first or (3) surgery followed by radiotherapy to determine the best option for cervical cancer treatment.Within the ten research studies we were able to look closely at different types of cervical cancer stage 1B and 2A treatment: chemotherapy first, or surgery first, or surgery followed by radiotherapy. In our Meta analysis most of the studies showed higher rates of lymph node removal. These results meet the data of previous trials (Fregnane et al., 2006;Giardi and Hass 1993; Arango et al., 2000). The comprehensive pelvic lymphadenectomy should obtain at least twenty lymph nodes to ensure the real condition of the pelvic tumor spread (Lentz et al., 2004; Shingleton & Orr 1995; Winter 1996; Kjorsad et al., 1984). Surgery allows the status of the lymph nodes to be assessed accurately. Hysterectomy with pelvic node dissection in early stages of cervical cancer has been associated with 7-14 % of incidence of swelling one or both lower limbs. It is a possible complication of cervical cancer and may be caused by the treatment or the disease. Many trials of the Meta analysis, such as the studies of Barter et al. 1989 and Supraset et al. 2005, reported lymphedema as a complication. These studies showed the reported incidence vary between 3.6 – 49 % (Abu_Rustum et al., 2003; Ryan et al., 2003). The problem with these studies is that they are not generally comparable due to differences in patient's groups, treatment techniques and the lack of standardized rules. Patients experience with lower limb lymphedema experienced deterioration in their quality of life including changes in sensation, appearance, pain (franks et al., 2006; Ryan et al., 2003), and distress (Bergmark et al., 2006). Another treatment included in the meta-analysis was pelvic radiation. Pelvic radiation was given to positive pelvic lymph nodes and positive or close surgical margins and it was reported that it reduces the risk of relapse (Berk and Hacker, 2000). However, studies show that pelvic radiation reduces the risk of pelvic recurrence, it does not improve the survival rate. These findings are not surprising because patients with close surgical margins are mainly at risk for pelvic recurrence whereas patients with positive pelvic lymph nodes are mainly at risk for para aortic and systemic recurrence. Supplementing pelvic radiation with radiotherapy did improve survival for high-risk patients. However, during radiation treatment of cervical cancer the pelvic organs receive significant radiation dose that results in both acute and late toxicity. Late changes occur at least three months post radiotherapy. Late radiation complications are due to small vessel injury with endothelial damage, inflammation, fibrosis, ischemia and necrosis. Symptoms of late radiation affect the bladder, which can include urinary frequency, urgency, dysuria, hematuria, ulceration and the potential for proliferation and fistula formation (Parkin et al., 1987; Parkin et al., 1988). However, primary surgery may offer a more efficient treatment, according to a Borduka_Bevers et al. (2000) study in 1993 where patients with FIGO 1B disease were reviewed after their primary surgery or primary radiotherapy. 13 % of radiotherapy patients developed

recurrent disease whereas 9 % of surgical patients developed recurrence. All asymptomatic recurrences occurred in the first 16 months of the follow up. Cervical cytology did not detect a single asymptomatic recurrence. The results showed 37 out of 1993 patients developed recurrent disease in central pelvis, 21 patients had recurrence in either lungs or pelvic sidewall and 22 patients had the recurrence in the lymph nodes. The median survival from the recurrence was 11 months for symptomatic disease and 42 months for asymptomatic. Another radiotherapy study (Hong et al., 2004) reviewed 1292 women of all FIGO stages after radiotherapy and it showed 29 % had either local or distant recurrence and around 10 % of them had 25 year survival rate. Conversely, in a surgical therapy study, 291 patients were followed up for 5 years after the surgery for cervical cancer and the results showed 18.2 % developed recurrent disease (Lim et al., 2004). The median time period for recurrence was 17.6 months. Recurrent disease was only detected in 7 out of 53 patients in routine follow up and 2 were asymptomatic. A systemic review and Meta analysis of individual patients and data from 18 randomized trials was conducted to assess the effect of chemo radiotherapy on all outcomes. The current research pre specified analyses to investigate whether the effect of chemo radiotherapy differed by trial or patient characteristics (Vale et al., 2008). They found that overall survival data that were supplied for 15 trials including 3452 women, and among those 1138 deaths have been recorded. On the basis of 14 trials that compared chemo radiotherapy versus the same radiotherapy, they added 19 % relative reduction in the risk of deaths with chemo radiotherapy compared with regular radiotherapy and translated to an absolute survival benefit of 6% at 5 years (from 60 % to 66 %). The survival curves for these 14 trials and for the two trials in which chemotherapy was used followed a similar pattern, although the separation of the curves is greater with adjuvant chemotherapy. In the 14 trials, the 5 year overall survival rate reported higher than the reported trials of one of the other two and the chemotherapy treatment revealed a high benefit ratio. A study conducted by Hu et al., (2012) about the use of the drug Cisplatin weekly versus triweekly with radiotherapy in the treatment of cervical cancer to evaluate the adverse effect and survival outcome of weekly and triweekly Cisplatin with radiotherapy in treatment of cervical cancer. The analysis established that weekly dose has a lower risk of causing haematologic toxicity within the patient than a triweekly dose with concurrent radiotherapy in the treatment of cervical cancer. However there was no difference in the progression-free survival and overall survival between weekly Cisplatin and triweekly Cisplatin. In addition, weekly Cisplatin combined with concurrent radiation does not improve survival. Triweekly Cisplatin treatment has longer intervals and it is therefore more convenient. Berck and Hacker (2000), showed in the efficacy of further pelvic radiation in their study of 977 women. Preliminary randomized results compared patients who received adjuvant whole pelvic radiation at a dose of 50.4 GY with patients who received no further treatment after radical hysterectomy for patients with high risk with lymph node negative stage 1B cervical cancer. The addition of radiation significantly reduced the risk of recurrence with a recurrence free rate of 88 % for radiation and 79 % for no further treatment for 2 years. Severe (GOG grade ¾) gastrointestinal or urological toxicity occurred in 5.8 % of cases. The result corroborated with results in Soisson et al. (1990) with a recurrence rate of 84 % after radiotherapy. In addition, Berck and Hacker (2000) study added that GOG published the results of 732 patients with stage 1B cervical carcinoma treated by radical hysterectomy and bilateral pelvic lymphadectomy. Out of 732 patients, 645 patients had no gross disease beyond the cervix / uterus and negative para-aortic nodes. 100 patients had micro metastases in pelvic nodes but their survival was not significantly different from patients with negative lymph nodes. A relative risk was calculated for each prognostic variable and an overall estimate of risk determined by multiplying the appropriate relative risk for the three independent variables (clinical tumor size, lymph vascular space invasion, depth of tumor invasion). Delgado el at., (1990) Showed that the disease free survival curves were constructed for several (RR) groups. The result estimated and revealed that the likelihood of recurrence for a patient with a GOG score greater than 120 is 40 % at 3 years. Moreover, this study recommended that consideration should be given to the adjuvant chemotherapy in addition to radiotherapy to treat cervical cancer stage 1B and 2A. Radical hysterectomy and radiotherapy in addition to lymphadenectomy produce favorable results with low morbidity in high-risk patients. Surgery plus radiotherapy increase the survival rate and decrease the pelvic recurrence and metastasis. After careful review of the literature between 1974- 2012, fourteen studies were chosen and ten among those were selected for Meta analysis because they fulfilled the strict criteria for evaluating the efficacy of cervical treatment stage 1B and 2A between chemotherapy first or surgery first or surgery followed by radiotherapy.

Table (1) The 10 eligible studies for meta-analysis.

Studies	Accurate period	Age (years)	Stage	No. of patients	CT dose	CT schedule		RT dose (Gy)	RT duration
						No. of cycles	Freq / week		
Landoni,1997	1986 - 1991	30 - 70	1B - 2A	343	–	–	–	47	3-5 w
Cheng, 2004	1992 - 1997	Median 49	1B - 2A	66	CP&5FU[1]	2-3	3	35-45	–
Kim, 2008	1997 - 2005	Median 50	1B - 2A	110	Different[2]	2-3	3-4	4500-5100(cGy)	–
Schorge, 1997	1974 - 1992	Median 46	1B - 2A	171	–	–	–	4500 (CGY)	4.5-55w
Takeshima, 2006	1993 - 2002	Interm. 49 High risk 43	1B - 2A	65	Different[3]	3−5	4	–	–
Siriwaranya, 2003	1998 - 2003	45	1A2 - 2A	156	75CP[4]	4	3	40-50	5 fractions/w
Sittidilokratna, 2010	2003 - 2006	42	1B1 - 2A	611	40 CP	6	1	Not mention	1w
Monk, 1994	1977- 1987	35	1B - 2A	95	–	–	–	5040- 5500 (CGY)	180 fractions/5−6 w
Suprasert, 2005	2001 - 2003	42.5 - 46.5	1B - 2A	242	40 CP	6	1	40-50	5 fractions/w
Gadducci, 2010	1995 - 2009	47	1B - 2A	45	CP &others	Different	Different	_	–

1Cisplatin and fluorouracil (5FU) chemotherapy.
2five-fluorouracil + cisplatin (11 patients), 5-fluoro- uracil + carboplatin + interferon gamma (2 patients), epirubicin + cisplatin (one patient), paclitaxel + carboplatin (one patient).
3 It consisted of bleomycin (5 mg in 500 mL saline infused intravenously [IV] continuously for 7 consecutive days), vincristine (0.7 mg/m2 as an IV bolus on day 7), mitomycin (7 mg/m2 as an IV bolus on day 7), and cisplatin (10 mg/m2 dissolved in 500 mL saline and infused over 4 h on days 1 through 7).
4 Cisplatin (cancer drug).

Table (2) The Meta Analysis Studies, Treatments and Survival Rate.

Studies	Treatments	5 year survival rate
Landoni, 1997	Compared radiotherapy with radical hysterectomy	Surgery pts. 83% Radiotherapy pts. 74%
Kim, 2008	Compared chemo radiation with radiation	Chemo radiation (CRT) pts. 89% Radiotherapy (RT) pts. 67%
Schorge, 1997	Adjuvant pelvic radiotherapy following radical hysterectomy	**5 year overall survival (OS)** 89 % Radical Hysterectomy (RH) pts. 90 % Radical hysterectomy (RH)+ Radiotherapy (RT) 85 %
Takeshima, 2006	Adjuvant therapy followed by chemotherapy	**5 year OS 93.39 %** High risk tumour 85.7 % Squamous cell carcinoma 100 % Adenosquamous cell carcinoma 71.4 %
Siriwaranya, 2003	Pelvic lymphadenectomy and radical hysterectomy follow by RT, CT, or non	**5 year OS 80 %** Early stage cervical cancer (surgery + high risk) 50 -75 %
Sittidilokratna, 2010	Post-operative adjuvant pelvic radiation therapy	**3 year OS 67.6%** **5 year OS** Pts. with tumour smaller than 2.0 cm 100 % **5 year OS** Pts. with tumour larger than 2.0 cm 16.9 %.
Monk, 1993	Radical hysterectomy (RH) followed by radiotherapy (RT)	**5 year OS for entire study population** 67% Deep cervical stromal invasion 73% Node-positive group, 78% with no parametrium extension Node-positive group, 39% with parametrium extension 39%
Suprasert, 2005	Radical hysterectomy & pelvic lymphadenectomy (RHPL)	**2 year disease free survival** Abandoned RH group = 58.5% RHPL group = 58.5 %
Cheng, 2004	Radical surgery followed with RT, CT, RT+CT	53.5% adjuvant RT, 12.6% not adjuvant therapy, 49.2% adjuvant CT, 56.1% adjuvant RT+ CT 56.1 % 40.7 % pelvic lymph nodes metastases, 56.5% one +node
Gadducci, 2010	CT followed by RH with pelvic lymphadenectomy	5 year overall free survival rate is related with the FIGO stage

Table (3) The Meta Analysis Studies, Follow up, Survival Rate and Recurrence.

Studies	Median Follow up/months	5 year survival rate	Recurrence
Landoni, 1997	87 Range (57- 120)	Surgery pts. 83% Radiotherapy pts. 74%	Over all recurrence 25.5% Surgery pts. 25 % Radiotherapy pts. 26 %
Kim, 2008	48 Range (1-92)	Chemo radiation (CRT) pts. 89% Radiotherapy (RT) pts. 67%	Chemo radiation (4 pts.) Radiotherapy (8pts.)
Schorge, 1997	84 Range (7-249)	**5 year overall survival (OS)** 89 % Radical Hysterectomy (RH) pts. 90 % Radical hysterectomy (RH)+ Radiotherapy (RT) 85 %	RH 17% RH + RT 11%
Takeshima, 2006	75 Range (39–132)	**5 year OS 93.39 %** High risk tumour 85.7 %, Squamous cell carcinoma 100 % Adenosquamous cell carcinoma 71.4 %	Intermediate risk group 3.3 % High risk group 8.6 %
Siriwaranya, 2003	26	**5 year OS 80 %** Early stage cervical cancer (surgery + high risk) 50 - 75 %	Tumour recurrence 7.7 %
Sittidilokratna, 2010	26.5	**3 year OS 67.6%** **5 year OS** Pts. with tumour smaller than 2.0 cm 100 % **5 year OS** Pts. with tumour larger than 2.0 cm 16.9 %.	Recurrence 6.20% (38pts.) RH + RT 42 %, RH + Cisplatin CRT 42 %
Monk, 1993	51 Range (3-144)	**5 year OS for entire study population** 67% Deep cervical stromal invasion 73% Node-positive group, 78% with no parametrium extension Node-positive group, 39% with parametrium extension 39%	Pelvic recurrences alone 13% Recurred outside of the radiation 15%
[1]Suprasert, 2005	19 Range (6-94)	**2 year disease free survival** Abandoned RH group = 58.5%	Pelvis 8.7% Abandoned RH group 26.1%
Cheng, 2004	32 Range (2-108)	53.5% adjuvant RT, 12.6% not adjuvant therapy, 49.2% adjuvant CT 56.1% adjuvant RT+ CT 56.1 % 40.7 % pelvic lymph nodes metastases, 56.5% one +node	Pelvic recurrence =42.1 % Distant metastases=31.6 %
Gadducci, 2010	53 Range (4-167)	5 year overall free survival rate is related with the FIGO stage	Recurrence 28.90% Died of tumour = 23.9 %

Table (4): Odd ratios with 95%CI for the Meta analysis studies.

Study	Treatment	Odd	95% CI		Sign.
			L	U	
(1) Landoni, 2001	Compared radiotherapy with radical hysterectomy	1.71	1.245	2.347	✔
(3) Kim, 2008	Compared the treatment outcome of chemo radiation with that of radiation	3.973	1.934	8.16	✔
(4) Schorge, 1997	Compared chemo radiation with radiation	1.588	1	2.522	-
(5) Takeshima, 2006	Surgery and CT	1.929	0.609	6.105	-
(6) Siriwaranya, 2003	Adjuvant pelvic radiotherapy following radical hysterectomy.	3.5	1.702	7.197	✔
(7)Sittidilokratna, 2010	Surgery and CT	2.327	1.637	3.306	✔
(9) Monk, 1993	Surgery& radiotherapy	0.097	0.055	0.171	✔
(10) Suprasert, 2005	Adjuvant therapy followed by chemotherapy	0.843	0.638	1.113	-
(11) Cheng, 2004	Surgery (radical hysterectomy & pelvic lymphadenectomy)	9.847	0.151	188.373	-
(12) Gadducci, 2010	Surgery & CT or irradiation	1.294	0.573	2.921	-
Test for heterogeneity Q = 123.3906, DF = 9, P < 0.0001					

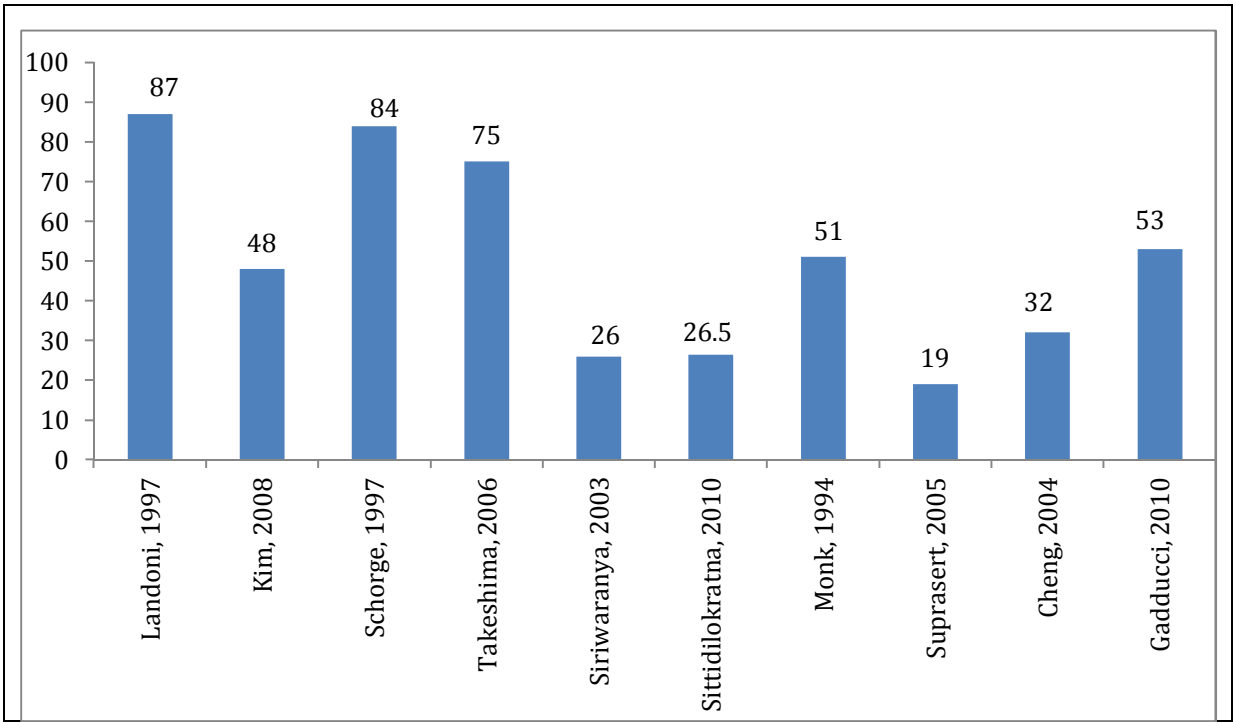

Fig (1): Indicating follow up time of the 10 studies.

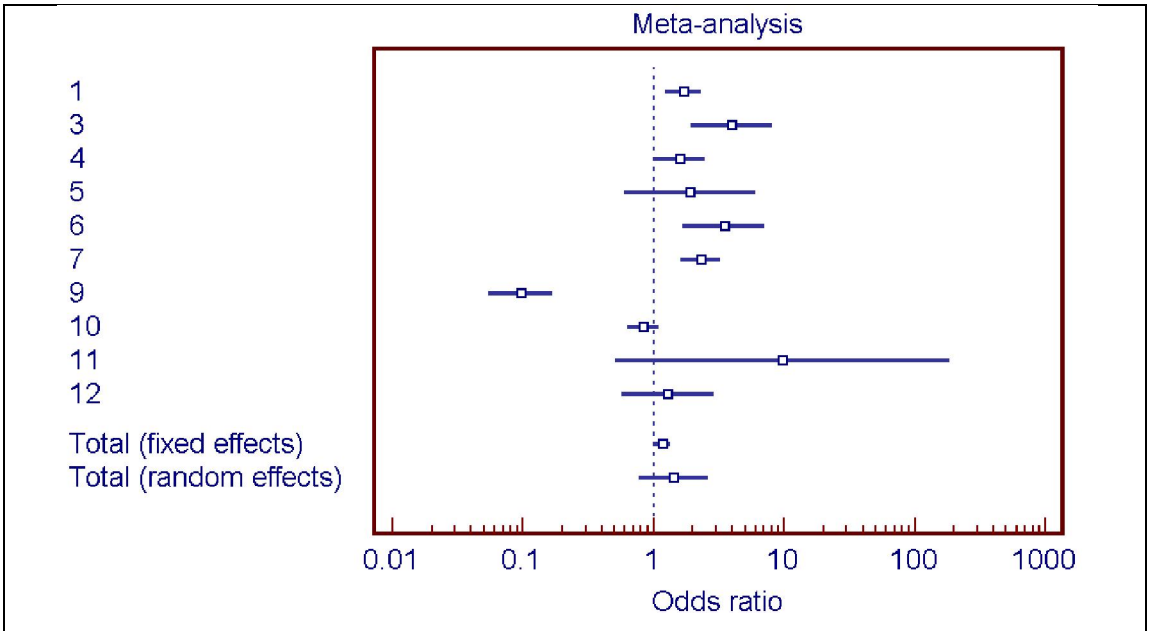

Figure (2): The forest plot of the log of odd ratio shows the results of the different studies, with 95% CI, and the overall effect with 95% CI.
Studies including: (1) Landoni, 1997, (3) Kim, 2008; (4) Schorge,1997, (5) Takeshima , 2006; (6) Siriwaranya,2003, (7) Sittidilokratna, 2010, (9) Monk,1998; (10) Suprasert, 2005, (11) Cheng, 2004, (12) Gadducci, 2010.

After statistical analysis used in Meta analysis, the collection of analytic results for the purpose of integrating the findings and combining all the results, facts and figures, Meta analysis proved that for cervical cancer stage 1B and 2A the best option of treatment after reviewing the complications, recurrence and overall survival rate for 5 years is radical hysterectomy with lymph nodes removal followed by radiotherapy.

Conclusion

After statistical analysis used in Meta analysis, we indicated that the best option of treatment cervical

cancer stage 1B and 2A after reviewing the complications, recurrence and overall survival rate for 5 years is radical hysterectomy with lymph nodes removal followed by radiotherapy. While, radical hysterectomy and radiotherapy plus lymphadectomy produce favorable results with low morbidity. In addition, surgery plus radiotherapy increase the survival rate and decrease the pelvic recurrence. Based on our result, we recommend that postoperative radiation be considered in the management of patients with stage 1B-2A cervical carcinomas found to have regional lymph node metastases; however, alternate forms of therapy deserve consideration when the tumor extends to both the parametrium and pelvic lymph nodes.

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References

1. Abu-Rustum NR, Gemignani ML, Moore K, Sonoda Y, Venkatraman E, Brown C, Poynor E, Chi DS, Barakat RR. Total laparoscopy radical hysterectomy with pelvic lymphadenectomy using the argon learn coagulation. Gynecol Onco. 2003;9: 402 – 9.
2. Arango HA, Hoffman MS, Roberts WS, DeCesare SL, Fiorica JV, Drake J. Accuracy of lymph node palpation to determine need for lymphadenectomy in gynecologic malignancies. Obstet gynecol. 2000; 15:553 – 61.
3. Barter JF, Soong SJ, Shingleton HM, Hatch KD, Orr JW Jr. Complications of combined radical hysterectomy postoperative radiation therapy in women with early stage cervical cancer. Gynecologic oncology.1989;32, 292 – 6.
4. Berek, J and Hacker, N. Practical gynecologic oncology. Lippincott Williams and Wilkins, New York, 2000.
5. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. lymphedema and bladder emptying difficulties after radical hysterectomy for early cervical cancer and among population controls. Int. Gynecol cancer. 2006;16(3):1130-9.
6. Bodurka-Bevers D, Morris M, Eifel PJ, Levenback C, Bevers MW, Lucas KR, Wharton JT. Post therapy surveillance of women with cervical cancer: an outcome analysis. Gynecol Oncol. 2000;78(2):187-93.
7. Cheung TH, Lo KW, Yim SF, Yau SH, Yu MM, Yeung WK. Debulking metastatic pelvic nodes before radiotherapy in cervical cancer patients: a long term follow up results. Int. J Clin. Oncol. 2011;16(5); 546 – 52.
8. Cheng X, Cai S, Li Z, Tang M, Xue M, Zang R. The prognosis of women with stage IB – IIB node positive cervical carcinoma after radical surgery. World J for surgical Oncology. 2004.
9. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol. 1990; 38:352 – 57.
10. Dersimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
11. Dersimonian R, and Laird N.Evaluating the effect of coaching on SAT scores: a metaanalysis. Harvard Ed Rev.1983;53:1 – 15.
12. Fabrini MG, Gadducci A, Perrone F, Cosio S, Laliscia C, Pasqualetti F, Grespi S, Cionini L. Clinical outcome of tailored adjuvant postoperative chemoradistherapy in IB Figo stage cervical cancer. Int. anticancer research. Anticancer Res. 2009;29(10):4205-10.
13. Franks PJ, Moffatt CJ, Doherty DC, Williams AF, Jeffs E, Mortimer PS. Assessment of health related quality of life in patients with lymphedema of the lower lymb. Wound repairregen.2006;14(2):110 – 8.
14. Fregnani JH, Latorre MR, Novik PR, Lopes A, Soares FA. Assessment of pelvic mode micronstestatic disease in stage IB – IIA of carcinoma of the uterine cervix. Int J Gynceol cancer. 2006;16(3)1188 – 94.
15. Gadducci A, Teti G, Barsotti C, Tana R, Fanucchi A, Orlandini C, Fabrini MG, Genazzani AR. Clinicopathological variables predictive of clinical outcome in patiens with figo stage B2 – IIB cervical cancer treated with cisplatin – based Neoadjuvant chemotherapy followed radical hysterectomy. Anticancer Res. 2010;30(1):201-8.
16. Girardi F, Haas J. The importance of the histologic processing of pelvic lymph nodes in the treatment of cervical cancer. Int J Gynecol Cancer. 1993;3(1):12-17.
17. Hong JH, Tsai CS, Lai CH, Chang TC, Wang CC, Chou HH, Lee SP, Hsueh S. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. Int. J. Radiat Oncol Biol. Phys.2004; 60:149 – 57.
18. Hu, Y., Cai, Z., Sw, X. Concurrent weekly cisplatin versus its weekly cisplatin with radiotherapy in the treatment & cervical cancer.

A Meta-analysis result. Asian Pacific J & Cancer Prevention. 2012;13: 4301 – 4.
19. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics. CA Cancer J Clin. 2002;52(1):23-47.
20. Kim K, Kang SB, Chung HH, Kim JW, Park NH, Song YS. Comparison of chemoradiation with radiation as postoperative adjuvant therapy in cervical cancer patients with intermediate risk factors. Eur J Surg Oncol.2008; 1-5.
21. Kjorstad K, Kolbenstvedt A, Stricker T. Value of a complete lymphadenectomy in the radical treatment of cancer of the cervix. Cancer. 1984;54: 2215 – 9.
22. Land N and Dersimorian R. Issues in combining evidence from several comparative trials of clinical therapy. In: proceeding of the X1 international Biometric conference.1982; 91 –7.
23. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, Favini G, Ferri L, Mangioni C.. Randomised study of radical surgery versus radiotherapy for stage Ib-lla cervical cancer. Lancet.1997; 350(9077): 535-40.
24. Lentz SE, Muderspach LI, Felix JC, Ye W, Groshen S, Amezcua CA. Identification micrometastases in histologically negative nodes of early-stage cervical cancer patients. Obstet Gynecol.2004; 103, 1204 – 10.
25. Lim K, Howells, Absurd, Evans A. The role of clinical follows up in early stage cervical cancer in South Wales. Biog.2004; 111:1444 – 8,
26. Monk BJ, Cha DS, Walker JL, Burger RA, Ramsinghani NS, Manetta A, DiSaia PJ, Berman ML. Extent of disease as an indication for pelvic radiation following radical hysterectomy and bilateral pelvic node dissection in the treatment of stage IB – IIA cervical carcinoma. Gynecologic oncology. 1994;54:4 – 9.
27. Parkin D, Davis J, Symonds R. Long term bladder symptomatology following radiotherapy for cervical carcinoma. Radio Onco.1987;l 9:195 – 99.
28. Ryan, M, Stainton, M, Slaytor, E, et al: Aetiology and preference of lower limb lymphodectomy following treatment for gynaecological cancer. Aus NZJ Obstet Gynaecol. 2003; 43:148 – 51.
29. Schorge J, Kelly M, Keolliker D. Stage IB – IIA cervical cancer with negative lymph nodes, the role of adjuvant radiotherapy after radical hysterectomy. Gynecologic oncology.1997; 66:31 – 35.
30. Shingleton, However, Orr, J. Primary surgical treatment of invasive cancer. Philadelphia, Lippincott.1995;123 – 54.
31. Siriwaranya T, Suprasert P, Siriaunkgul S, Khunamornpong S, Srisomboon J, Charoenkwan K, Siriaree S, Phongnarisorn C, Cheewakriangkrai C, Lorvidhaya V. Outcome of high-risk stage IA2 – IIA cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy. Thai J. Obstetrics and Gynecology. 2003;15:93 – 99.
32. Sittidilokratna K, Cheewakriangkrai C, Siriaurnkgul S. Recurrence pattern after radical hysterectomy in stage IB – IIA cervical. Asian pacific journal of cancer prevention.2010; 2(4): 99 – 502.
33. Soisson AP, Soper JT, Clarke-Pearson DL, Berchuck A, Montana G, Creasman WT. Adjuvant radiotherapy following radical hysterectomy for patients with stage IB, IIA cervical cancer. Gynecol Oncol.1990; 37: 390 – 5.
34. Suprasert P, Srisomboon J, Charoenkwan K, Siriaungul S, Khunamornpong S, Siriaree S, Phongnarisorn C, Lorvidhaya V. Outcomes of abandoned radical hysterectomy in patients with stages IB – IIA cervical cancer found to have positive nodes during the operation. Int. J gynecol cancer.2005;15(3), 498 – 502.
35. Takeshima N, Umayatara K, Fujiwara K. Treatment results of adjuvant chemotherapy after radical hysterectomy for intermediate and high risk stage IB – IIA cervical cancer. Gynecology oncology.2006; 103, 618 – 22.
36. Vale C, Tierne J, and Stweart L. Reducing uncertainties about the effect of chemoradiotherapy for cervical cancers A systematic review and Metaanalysis of individual patient data from 18 randomized trials. J of clinical Oncology.2008; 26, 5802 – 12.
37. Van de Putte G, Lie AK, Vach W, Baekelandt M, Kristensen GB. Risk grouping in stage IB squamous cell cervical carcinoma. Gynecol Oncol. 2005; 99(1): 106-12.
38. Winter R. Radical abdominal hysterectomy. Societa Editrice Universos Rome,.1996;19 – 26.

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