OUTCOME OF EXTERNAL RADIOTHERAPY PLUS LOW-DOSE-RATE BRACHYTHERAPY FOR CERVICAL CANCER TREATMENT

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ABSTRACT

***Objectives**: Evaluate the outcome of external radiotherapy plus low-dose-rate brachytherapy for cervical cancer treatment by reccurrence, metastasis, survivals and comlications.*

***Materials and methods**: Randomized prospective study from 96patients of cervical cancer treated by radicaltherapy (Telecobalt + LDR Brachytherapy using Césium) at Hue Central Hospital's Oncology Center, from 2005 to 2012.*

***Results**:*

- Common recurrence rate was 13.5%; local recurrence rate was 38.5% and extensive invasion was 61.5%; meantime of recurrence was 13.0 ± 11.9 months (1.5 - 36.0 months); recurrence before 2 year was 76.9%. recurrence after 2 year was 23.1%.

- Common metastasis rate was 16.7%; mean time of metastatis was 10.7 ± 7.5months; metastasis before 2 year was 93.7%. metastasis after 2 year was 6.3%; lung metastasis was 25.0%. bone 25.0%. supraclavicular lymph node 18.8%. paraaortic lymph node 12.5%. liver 6.3%.

-Mean Overall survival (OS) was 6.3 ± 0.3 year. Mean following-up period was 4.1 year (0.3 - 7.6 year). 5 year OS was 75.9%; 5 year OS of stage IIA was 85.7%. stage IIB was 80.2%. stage IIIA was 77.8% and stage IIIB was 65.5% (p = 0.357).

-Mean Disease-Free survival (DFS) was 5.7 ± 0.3 year: 1 year DFS was 81.3%; 2 year was 76.0%. 3 year was 73.7%. 5 year was 72.4%.

- Inter-radiotherapy complications: Five (4.8%) patients experienced hemorrhage shattered vagina. managed by suture for stop bleeding then carry on brachytherapy. Skin redness was 80.2%. radiative field skin burn was 63.5%. skin ulcer was 19.8%. intestinal inflammation was 63.5%.

- Post-radiotherapy complications: hemorrhage bladder inflammation was 1.0%. with the time of occurrence was 22 months. Hemorrhage protitis was 5.2%. with mean time of occurrence was 23.8 ± 3.9 month (18.0 - 28.0 month). Sacrococcyx ulcer was 1.0%. time of occurrence was 10.0 month.

***Conclusions**: External radiotherapy plus low-dose-rate brachytherapy in treatment of cervical cancer improves outcomes of reccurrence, metastasis, complications, Overall survival and disease free survival. Radioactive source of brachytherapy - Cesium – has a long half life, therefore it is suitable for hospitals which are less number of cervical cancer patients.*

***Key words:** radiotherapy, cervical cancer.*

I. INTRODUCTION

Cervical cancer is one of the most common cancers worldwide. It ranks 4thin women and 7th in both genders, the incidence in 2012 was 528.000 cases, 266.000 deaths, 85% of them were in developing countries. In South East Asia region, age standard rate (ASR) in 2012 was 175/1000.000 and deaths was 94/100.000 [9]. According to cancer registration in Vietnam published in 2010, cervical cancer was the 4th common ranked after breast, colorectal and bron-

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chial cancer respectively, ASR was 13,6/100.000 [2]. In Thua Thien Hue province,according to data of cancer registration during 2001 – 2004, cervical cancer ranked 3rd, after breast and gastric cancer, and ASR was 4.8/100.000 [4]

Treatments for Cervical Cancer are majorily radiotherapy, surgery and chemoradiotherapy in combination, and radiotherapy is the main and basic treatment modality, it is described as "the spinal cord" of therapies. Since 2005, Hue central hospital's Center of Oncology started applying low-dose-rate brachythepay in cervical cancer treatment. In order to evaluate the outcomes after treatment and longterm follow up duration, we carried out this study due to two objectives:

1/ Evaluating the outcome of external radiotherapy plus low-dose-rate brachytherapy in cervical cancer treatment by reccurence, metastasis and survivals.

2/ Evaluating the outcome of external radiotherapy plus low-dose-rate brachytherapy in cervical cancer treatment by complications during and after treatment.

II. MATERIALS AND METHODS

Patient eligibility:

96 patients of cervical cancer treatedby external radiotherapy plus low-dose-rate brachytherapy since 2005 to 2012, mean time of following up was 4.1 years (0.3 - 7.6years), Hue central hospital's Center of Oncology.

Include criteria:

+ Pathology was Squamous cell carcinoma and Adenocarcinoma

+ Without concurrent chemoradiation; no surgegry before or after radiation.

+ After whole pelvic external beam of 50Gy, cervical tumor size was under 4cm and patients' condition allows brachytherapy.

+ Performance status (PS) score was 0 to 2 [11].

Exclude criteria:

+ Patients disagreed to brachytherapy; unsufficient radiotherapy

+ Pregnant women.

+ Patients had another type of cancer.

Methods

Uncontrolled randomisez prospective study

Materials

+Clinical staging by FIGO 1995.

+External radiotherapy using Chisobalt 60-Cobansource of Czech.

+Brachytherapy with Fletcher applicator, Césiumsource (figure 1).

+ Dose volume histogram calculating according to Plato Software of Radiation Department - Hospital of SAINT LUC university - Belgium. (figure 2).

Figure 1: Fletcher applicator and Césium source

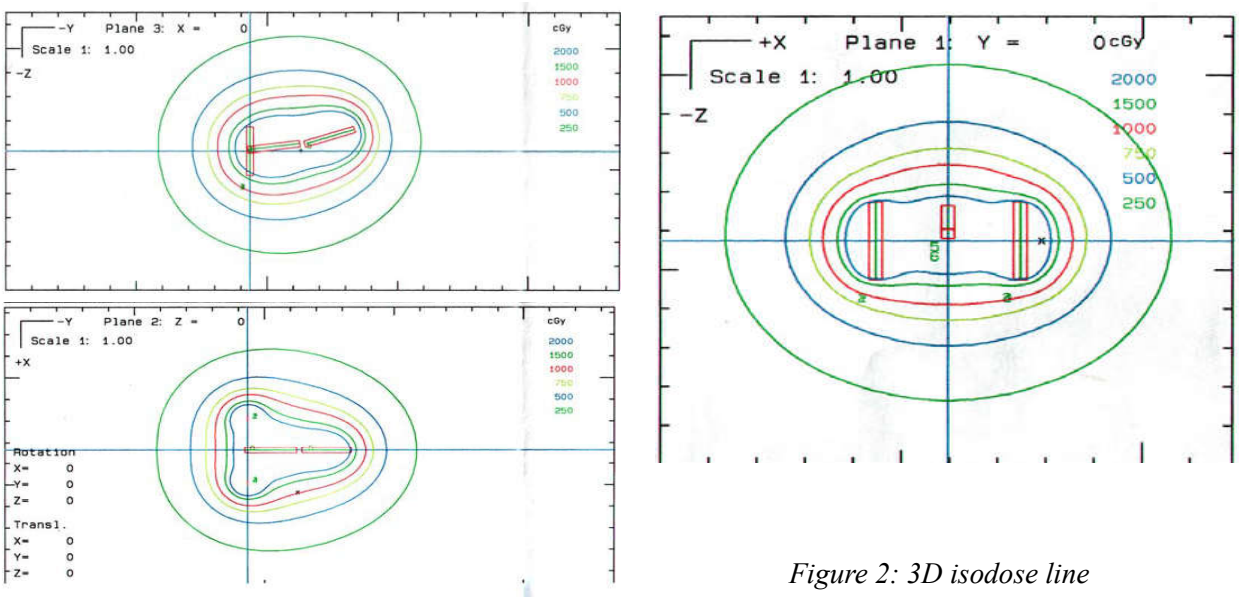


Figure 2: 3D isodose line

+ RT Regimen: External RT for the whole pelvic of 50 Gy, followed by LDR Brachy therapy of 28-30 Gy/3-4 insertions at point A.

Data Analysis

Data were analised by SPSS 19.0, qualitative variables were described by percentage rate; survivalrate were estimatedusing Kaplan–Meier method,comparation of survival rate by Log rank audit.

III. RESULTS

1. Some general characteristics

Table 1: Some general characteristics

Characteristics		n	%
Age	< 40	4	4.2
	40 - 49	24	25.0
	50 - 59	35	36.5
	60 - 69	25	26.0
	≥ 70	8	8.3
Pathology	SCC	83	86.5
	Adenocarcinoma	13	13.5
Clinical stage	IIA	11	11.5
	IIB	40	41.7
	IIIA	18	18.8
	IIIB	27	28,1

Mean age was 55.2 ± 10.2; common age was 40 - 69 (87.5%). Squamous cell carcinoma was 86.5%, adenocarcinoma was 13.5%. Clinical stage IIA was 11.5%, IIB, IIIA, IIIB were 41.7%, 18.8%, and 28.1% respectively.

3.2. Recurrence

Table 2: Recurrence status

Recurrence status		**n**	**%**
Recurrence	Yes	13	13.5
	No	83	86.5
Sites ofRecurrence	Local	5	38.5
	Local +extensive	8	61.5
Time of Recurrence	<12 months	8	61.5
	12-24 months	2	15.4
	≥24 months	3	23.1

General recurrence rate was 13.5%; local recurrence was 38.5% and wide extension was 61.5%; average recurrence time was 13.0 ± 11.9 month (1,5 - 36.0 month); recurrence before 2 years was 76.9%, after 2 years was 23.1%.

3.3. Metastasis

Table 3: Metastasis status

Metastasis status*		**n**	**%**
Metastasis	Yes	16	16.7
	No	80	83.3
Metastasis sites	Liver	1	6.3
	Bone	4	25.0
	Supraclavicular node	3	18.7
	Para-aortic node	2	12.5
	Lung	4	25.0
	Others	2	12.5
Metastasis time	< 12 months	11	68.7
	12 - 24 months	4	25.0
	≥ 24 months	1	6.3

* There were 3 patients had both recurrence and metastasis

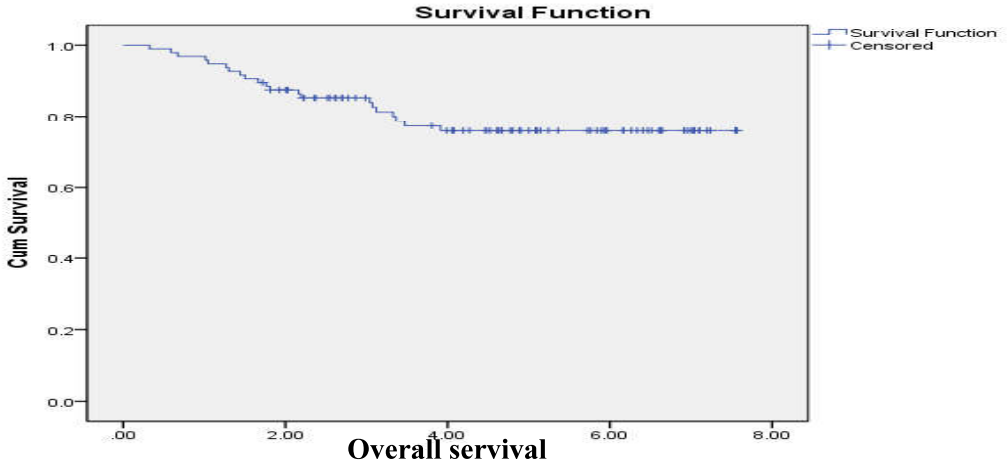
General metastasis rate was 16.7%; mean time of metastasis was 10.7 ± 7.5 month; metastasis before 2 years was 93.7%, lung metastasis was 25.0%, bone, supraclavicular lymph node and para-aortic lymph node and liver metastasis were 25.0%, 18.8%, 12.5%, and 6.3% respectively.

3.4. Survival

3.4.1. Overall survival

Table 4: Overall survival by Kapplan - Meier

Survival (years)	1	2	3	5	7
Accumulative deaths	3	12	14	21	21
Accumlative survival rate by Kaplan - Meier (%)	96,9	87,5	85,3	75,9	75,9
Mean survival time ± standard deviation(year)	6,3 ± 0,3				



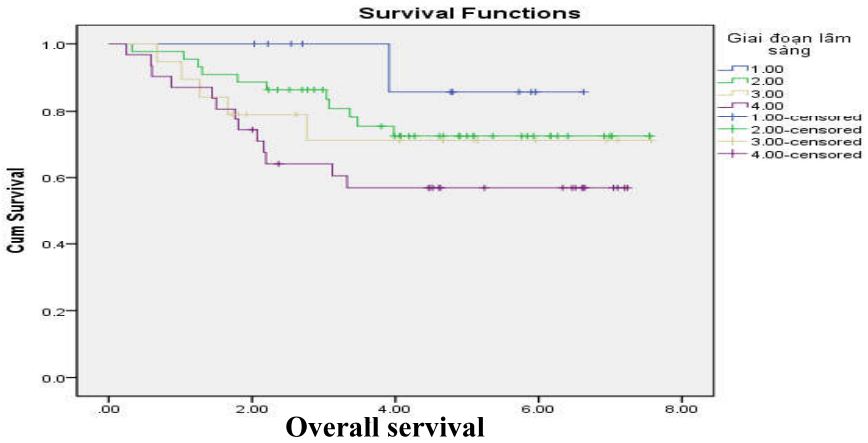
Graph 1: Overall survival

Overall survival (OS) was 6.3 ± 0.3year. Mean follow up time was 4.1year (range: 0.3 - 7.6year). Overall survival rate after 1 year was 96.9%, 2 year, 3 year, 5 year and 7 year were 87.5%, 85.3%, 75.9%, and 75.9%, respectively.

3.4.2. Years overall survival by clinical stages

Table 5: 5 years overall survival by clinical stages

Stages	IIa	IIb	IIIa	IIIb
No. of patients	11	40	18	27
Accumulative deaths	1	7	4	9
Accumulative death rate by Kaplan - Meier (%)	90.9	80.2	77.8	65.5
Average overall survival ± SD (year)	6.2 ± 0.4	6.5 ± 0.4	6.1 ± 0.6	5.4 ± 0.5
Log Rank audit: **χ2= 3,235,** free level = 3, p = 0,357				



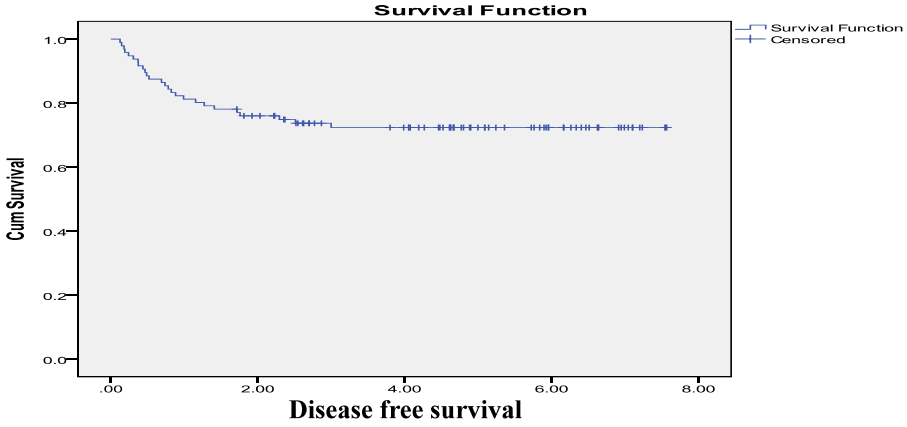
Graph 2: 5 year overall survival by clinical stages

Overall survival rate after 1, 3, 5, 7 year of stage IIA were 100,0%, 100,0%, 85,7%, 85,7%, respectively; of stage IIB were: 97,5%, 92,5%, 80,2%, 80,2%, respectively; of stage IIIA were : 94,4%, 77,8%, 77,8%, 77,8% respectively and stage IIIB were 96,3%, 73,7%, 65,5%, and 65,5% respectively (p = 0,357).

3.4.3. Disease free survival (DFS)

Table 6: Disesse free survival by Kapplan - Meier

Survival (year)	1	2	3	5	7
No of accumulative recurrence-metastasis	18	23	25	26	26
Accumulative survival rate by Kaplan - Meier (%)	81.3	76.0	73.7	72.4	72.4
Average DFS ± SD (year)	5.7 ± 0.3				



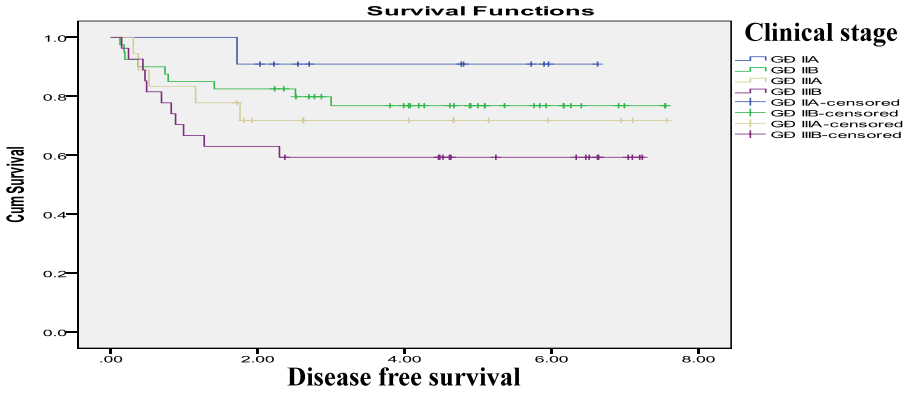
Graph 3: Disease free survival

Average DFS was 5,7 ± 0,3year. DFS rate after 1, 2, 3, 5 and 7 year were 81.3%, 76.0%, 73.7%, 72.4% and 72.4% respectively.

3.4.4. year disease free survival by clinical stages

Table 7: 5 year DFS by clinical stages

Stages	IIa	IIb	IIIa	IIIb
No. of patients	11	40	18	27
No. of accumulative recurrence-metastasis	1	9	5	11
Accumulative survival rate by Kaplan - Meier (%)	90.9	76.8	71.8	59.3
Average DFS ± SD (year)	6.2 ± 0.4	6.1 ± 0.4	5.7 ± 0.7	4.6 ± 0.6
Log Rank audit: $\chi 2$= 4,748, free level = 3, p = 0,191				



Graph 4: 5 year DFS by clinical stages

1. 3. 5 year DFS rate of stage IIA were 90.9%. 90.9%. 90.9%; of stage IIB were: 85.0%. 79.8%. 76.8%. of stage IIIA were: 83.3%. 71.8%. 71.8%. of stage IIIB were : 66.7%. 59.8%. 59.8%. respectively (p = 0.191).

5. Complications

5.1. Inter-radiation complication

Table 8: inter-radiation complications

Symptoms	Skin rash		Skin burn		Skin ulcer		Intestinal inflammation	
	n	%	n	%	n	%	n	%
Yes	77	80.2	61	63.5	19	19.8	61	63.5
No	19	19.8	35	36.5	77	80.2	35	36.5
Total*	96	100.0	96	100.0	96	100.0	96	100.0

* There was no patient had bladder inflammation or haemorrhageprotitis. There was 5 (5,2%) patients had haemorrhage vaginal rupture, managed by sututre for stopping bleeding and carry on brachytherapy .

Skin rash was 80,2%, skin burn at radiation field was 63,5%, skin ulcer was 19,8%, intestinal inflammation was 63,5%.

5.2. Post radiation complications

Table 9: Post radiation complications

Complications*		**n**	**%**	Mean time of complications' occurrence ± SD (month) (range)
Haemorrhage bladder inflammation	Yes	1	1.0	22.0
	No	95	99.0	
Protitis	Yes	2	2.1	14.0 ± 11.3 (6.0 - 22.0)
	No	94	97.9	
Haemorrhageprotitis	Yes	5	5.2	23.8 ± 3.7 (18.0 - 28.0)
	No	91	94.8	
Fibrosis at radiation field	Yes	1	1.0	18.0
	No	95	99.0	
Cocco-Sacrum ulcer	Yes	1	1.0	10.0
	No	95	99.0	

* There were not any patientsexperiencing intestinal, bladder inflammation, no bladder-vagina fistule and rectum-vagina fistule after radiotherapy.

Post-radiation haemorrhage bladder inflammation was 1,0%, time of post-radiation haemorrhage bladder inflammationoccurrence was 22 month.

Post-radiation protitis was 2,1%, mean time of post-radiation protitis occurrence was 14,0 ± 11,3 month (6,0 - 22,0 month).

Post-radiation protitis was 5,2%, mean time of post-radiation haemorrhageprotitis occurrence was 23,8 ± 3,7month (18,0 - 28,0 month).

Radiation field fibrosis was 1,0%, time of fibrosis occurrence was 18 month.

Cocco-sacrum ulcer was 1,0%, time of ulcer occurrence was 10,0 month.

V. DISCUSSION

Radiotherapy is the main method for treating cervical cancer including external radiotherapy and brachytherapy. External radiotherapy with high dose can affect on adjacent urinary and digestive organs. Besides, high-dose delivery can build up at skin and tissues under the skin. To make good the disadvantages of external radiotherapy, since 2005, we have applied low-dose-ratebrachytherapyalone or combined with the external radiotherapy. The combination of low-dose brachytherapy and external radiotherapy has got many considerable values till now. Thus, the aim of our study is to clearify the role of combination between the low-dose brachytherapy and external radiotherapy in cervical cancer treatment.

Recurrence

Treatment failure is the local recurrence. Results of many researches had been reported about the rate of local recurrence. In Kim JC Park's study, this rate is 23,9%, 39,53%. In a follow-up study nearly 17 years of Nguyen Thanh Ai on 258 patients treated by external radiotherapy with Chisobalt machine, the local recurrence rate was 39.53% [1]. In a study of Ngoc Linh Tran Dang in 2000 when applying the combination of Telecobalt external radiotherapy and high dose brachytherapy in 325 patients with cervical cancer, the rate of local recurrence was 26.7%. Besides, there was 10.9% of 109 patient has recurrence after 3 years treated with external radiotherapy and low-dose brachytherapy. In our study, the rate is 13.5%. This result is lower than some merely (alone/ purely) external radiotherapy studies and equivalent to other studies of combination with brachytherapy.

Metastasis

In a study of Carlos A.Perez in 1986, 970 patients, after receiving external radiotherapy alone had distant metastasis, 13% of those were at stage IB, 22% was at IIA and IIB, and 32% was at stage III. In another 17 years follow-up study of Thanh Ai Nguyen, the common rate of metastasis in 258 patients treated by external radiation therapy with Chisobalt was 15.5%. Morever, the rate of distant metastasis after 5 years was 46.7% in Ngoc Linh Dang Tran's study on 325 patients receiving the combined treatment by Telecobalt external radiotherapy and high- dose brachytherapy in 2000. The rate of metastasis in our study is 16.7%, lower than another studies due to the difference of the number of patients and clinical staging.

Overall survival – Disease-Free survival

In Nguyen Thanh Ai's follow-up study for 17 years in 258 patients treated with external radiotherapy by Chisobalt machine, mean overall survival (OS) was 6.2 ± 0.4 years, 5 years OS was 40.7%, 10 years OS was 23.6% and 15 years OS was 18.2% [1]. In another study of Tharavichitkul E that combined external radiotherapy with high-dosed brachytherapysince 2008 to 2011 with the same remedy, 3 years OS rate was 93.6% and disease-free survival rate was 85.1%. According to Ferringo R 's study in 190 patients first treated by Telecobaltradiation therapy, then followed by once or twice low-dose brachytherapy with. Césium since 1989 to 1995, OS and disease-free survival rate after 70 months of patients in stage I, II and III was 83%, 82% and 49%; 83%, 78%, and 46%, respectively. Kim JC Park (1995) reported the OS rate and disease-free survival were 81.9% and 70.4% [12].

In our study, 7 years OS was 78.1% (75/96), time of mean OS was 6.3 ± 0.3 years. 1 year, 3year, 5 year and 7 year OS rate of stage IIA was 100.0%, 100.0%, 85.7%, 85.7%, of stage IIB was 97.5%, 92.5%, 80.2%, 80.2%; of stage IIIA was 94.4%, 77.8%, 77.8%, 77.8% and of stage IIIB was 96.3%, 73.7%, 65.5%, 65.5% (p = 0.357). 7 years Disease-free survival was 72.9% (70/96), mean DFS was 5,7 ± 0,3 years. 1year, 3 year, 5 year DFS of stage IIA was 90.9%, 90.9%, 90.9%; of stage IIB was 85.0%, 79.8%, 76.8%, of stage IIIA was 83.3%,

71.8%, 71.8%, of stage IIIB was 66.7%, 59.8%, 59.8% (p = 0,191). This was a good result because it has proven the overall survival and disease-free survival ofbrachytherapy were higher than external radiotherapy alone.

Inter and post radiation complication

The radiation therapy on the whole pelvic region with 50Gy helps delivery enough dose into the lymph node system in pelvic region, after that with increasing dosage localized at the cervix by low-dose brachytherapy from 28 to 30Gy and 3-4 fractions can cause a variety of complications, especially with Telecobalt radiation resource. Many complications happening in radiation progress need followed up and managed carefully, such as on skin, mucosa of gut and vagina. Radiation therapy on the abdominal/pelvic area may cause diarrhea, abdominal cramping, increased frequency of bowel movements, frequent urination; leaking of urine. There are increased risks of vagina inflammation due to the development of opportunity bacteria causing itchy, fluid excretion… as well as risk of bladder and rectum bleeding can happen and accelerate the hemorrhoid underlying [5], [7], [10].

Post-radiation complications include haemorrage, fibrinosis and ischemic of tissue. Radiation at overall pelvic area causes chronic bladder inflammation with symptoms of fibrosis, urinary tract irritation, bleeding. Besides, radiation can cause vagina atrophy, making sexual contact painful, rectal and sigmoid inflammation causing pain and high risk of haemorrhage, a minor of vagina-bladder or vagina-rectum fistula due to increasing dosage at cervical. Post- radiation complication areusually severe and hard to manage whichconsiderably affect patients' life quality and health [5], [14].

In a study of Tharavichitkul E with combination of external radiotherapy and high-dose brachytherapy on treating cervical cancer since 2008 to 2011 with the same therapy, it was reported that the rate of post-radiation complications at grade 3-4 of rectum and bladder was 2.1% and 2,1%, without reported complication of fibrosis at radiated area. The rate of complications at rectum, small intestine and urinary system after 5 years radiation was 16.1%, 4.6% and 7.6% in follow –up study of Ferrigno R [8]. In the same therapy with purely external radiotherapy of Maduroa, complications often occurred in first 2 years after radiation and this rate was 10%, the complication of urinary system was above 10% and increased up to time after treatment.

In our study, the complications in radiation included: skin ulcer was 19.8%, colitis was 63.5%, without complication on bladder or rectum. Post-radiation complications involved: heamorrage bladder inflammation was 1.0%, heamorrageprotitis was 5.2%, fibrinosis at radiated region was 1%, cocco-sacrum ulcer was 1%. Thus, our result was equivalent to studies of brachytherapy and lower significantly than purely external radiotherapy studies.

VI. CONCLUSION

Randomized prospective study on 96 patients with cervical cancer treated by external radiation therapy combined to low-dose-rate brachytherapy at Hue Central Hospital's Center of Oncology from 2005 to 2012 showed the results:

- Mean age was 55.2 ± 10.2, commonly in group 40-69 (87.5%), histopathology mainly was squamouse cell carcinoma (86.5%), clinical stage IIB was 41.7%.

- Common recurrence rate was 13.5%; mean recurrence time was 13.0 ± 11.9 months (1.5 - 36.0 month); recurrence before 2 year was mainly (76.9%)

- Common metastasis rate was 16,7%; mean metastatis time was 10.7 ± 7.5month; metastasis before 2 year was 93.7; mainly lung and bone metastasis

- Mean Overall survival (OS) was 6.3 ± 0.3 year. 1 year, 3 year, 5 year OS was 96.9%, 85.3%, 75.9%;

5 year OS of stage IIA was 85.7%,5 year of stage IIB was 80.2%, 5 year of stage IIIA was 77.8% and 5 year of stage IIIB was 6.5%.

- Mean Disease-Free survival (DFS) was 5.7 ± 0.3 year: 1 year DFS was 81.3%; 3 year was 73.7%, 5 year was 72.4%. 5 year DFS of stage IIA was 90.9%, of stage IIB was 76.8%, of stage IIIA was 71.8%, of stage IIIB was 59.3%.

- Inter-radiotherapy complications: Skin inflammation was 80.2%, radiative field skin burn was 63,5%, skin ulcer was 19,8%, intestinal inflammation was 63,5%, without patients with bladder inflammation or haemorrhageprotitis.

- Post-radiotherapy complications: no patients had bowel and bladder inflammation, bladder-vagina fistula or rectum-vagina fistula after radiation. Other complications were:haemorrhage bladder inflammation, region fibrosis related to radiation and Sacrococcyx ulcer were low (1,0%). Haemorrhage rectum inflammation was 5,2%.

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