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Comparison of four different treatment modalities in Stage IIA cervical cancer: single center experience of 22 years

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Summary

Objectives: To evaluate the efficacy and the survival rate depending on different treatment modalities in FIGO Stage IIA cervical cancer. *Materials and Methods:* The authors identified 59 FIGO Stage IIa patients from 844 cervical cancer patients who were treated between January, 1992 and February, 2014. Medical records were retrospectively reviewed and patients were classified according to four different treatment modalities and compared regarding complications, recurrence, and overall survival rates. *Results:* Fifty-nine (6.99%) of the 844 cervix cancer patients were at FIGO Stage IIA. Fourteen patients received primary radiotherapy (RT), 27 patients primary chemoradiotherapy (CRT), ten patients had radical hysterectomy followed by adjuvant RT, and eight patients had radical hysterectomy followed by adjuvant CRT. Five-year overall survival rates among the primary RT , primary CRT, adjuvant RT after radical hysterectomy (RH), and adjuvant CRT after RH groups were found to be 55.6%, 72.7%, 62.5%, and 71.4% ($p = 0.802$), respectively and five-year disease free survival rates of these groups were found to be 71.4%, 88.9% , 80% , and 87.5% ($p = 0.537$), respectively. *Conclusion:* No statistically significant difference was identified regarding the efficacy and the rate of survival among four different treatment modalities in Stage IIa cervical cancer patients.

Key words: Cervical cancer; Treatment modalities; Radiotherapy; Radical hysterectomy.

Introduction

With 528,000 new cases every year, cervical cancer is the fourth most common cancer affecting women worldwide, after breast, colorectal, and lung cancers [1]. Management of the cervical cancer depends on the International Federation of Gynecology and Obstetrics (FIGO) Staging. For Stage IB1 and IIA2 cancers which invade upper vagina and cervix and which are smaller than 4 cm without any lymph node metastasis, radical hysterectomy (RH) procedure is performed. For patients who have a local invasion (two-thirds lower part of vagina, parametrium or metastasis of bladder) or a bulky tumor ≥ 4 cm or lymph node metastasis (IB2, IIA2-IVA), the treatment option is chemoradiotherapy (CRT). However, the treatment algorithm for the Stage IIa cervical cancer patients (defined as cancer involvement of the upper two-thirds of the vagina, without parametrial invasion) is uncertain [1]. In the literature, treatment of these cases consists of primary RH, primary radiotherapy (RT), and combined CRT.

The aim of this study is to research the effects of four different treatment options (primary RH adjuvant radiotherapy, primary RH adjuvant CRT, primary RT, and primary CRT) on survival and the recurrence status of FIGO Stage IIA cervical cancer cases over a 22-year period in a third level gynecologic oncology center.

Materials and Methods

The records of 59 patients who were diagnosed as Stage IIA cervical cancer and treated between January, 1992 and February, 2014 in Tepecik Teaching and Research Hospital Gynecologic Oncology Clinic, were retrospectively evaluated. The study was approved by the ethics committee of the present institution. All the diagnoses of the patients were confirmed by histopathologically and they had FIGO clinical Stage IIA cervical cancer. Clinical staging was performed by the examination under general anesthesia. At initial diagnosis, blood count levels were measured and patients were evaluated by imaging modalities. Recurrence, metastasis, disease free survival (DFS, overall survival (OS), type and dose of chemotherapy, dose of RT were analyzed. Patients were followed up for 16 months to 180 months. Criteria for quitting the follow-up were death or on the patient's request. Women completed follow-up evaluations every three months for the first two years, every six months for the next three years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. Patient groups who had received primary RT, primary CRT, adjuvant RT after radical hysterectomy (RH +adjuvant RT) and adjuvant CRT after RH + adjuvant CRT were analyzed for the recurrence and survival.

Among 27 patients who were treated by primary CRT, 24 patients received 40-50 mg/m^2 weekly cisplatin regimen and three received two AUC weekly carboplatin regimen. The number of chemotherapy cycles were between three to six. Internal RT dose ranged from 5 to 9.25 Gy and external RT doses ranged from 45 to 64.8 Gy. RH was carried out on 18 patients. Pelvic and paraaortic lymph node dissection was added to the procedure in 12 patients and only pelvic lymph node dissection was added in six

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Table 1. — *Demographic data and the clinical characteristics of the patients in the study group.*

	Primary RT	Primary CRT	RH+ adjuvant RT	RH+ adjuvant CRT	Total
Number of patients	14	27	10	8	59
Age (years)	58.2 ± 10.8	51.3 ± 9.6	44.8 ± 13.5	51.3 ± 13.8	51.8 ± 11.7
Mean tumor size (cm)	3.7 ± 1.4	4.5 ± 2.7	4.6 ± 2.8	2.5 ± 2.0	4.2 ± 2.3
Hemoglobin (g/dL)	12.2 ± 1.3	12 ± 1.4	12.3 ± 2.0	11.9 ± 0.8	12.2 ± 1.4
Histology					
SCC (%)	78.6	88.9	70	75	81.4
Adenocarcinoma (%)	21.4	7.4	20	12.5	13.6
Adenosquamous carcinoma (%)	-	3.7	10	12.5	5.1

RT: radiotherapy; CRT: chemoradiotherapy; RH: radical hysterectomy; SCC: squamous cell cancer.

patients. Eight patients who had adjuvant CRT, received 50 mg/m^2 weekly cisplatin regimen. The remaining ten patients only received adjuvant RT. Survival data were analyzed in February 2014.

Survival analysis was based on the Kaplan-Meier method and the results were compared using a log-rank test. DFS was defined as of the date of the primary surgery to detection of recurrence or the latest observation. OS was defined as of the date of the primary surgery to death or the latest observation. The χ^2 test and Student's *t*-test for unpaired data were used for statistical analysis. Cox regression analysis was used to determine the factors affecting survival, presented as hazard ratios (HR). All statistical analyses were performed using Med-Calc software (ver. 11.5). A $p < 0.05$ was considered to indicate statistical significance.

Results

Fifty-nine (6.99%) of the 844 cervix cancer patients were FIGO Stage IIA in retrospective analysis of the data. Demographic data and the clinical characteristics of the cases are shown in Table 1.

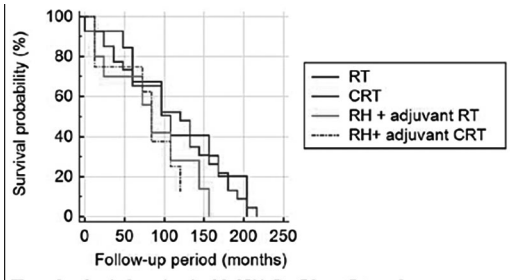
Mean PFS for RT, CRT, RH + adjuvant RT, and RH + adjuvant CRT were 92.5 ± 65.4, 100.0 ± 64.7, 69.6 ± 52.7, and 76.5 ± 43.4 months, respectively ($p = 0.522$). Mean OS for RT, CRT, RH + adjuvant RT, and RH + adjuvant CRT were 95.1 ± 61.9, 101.3 ± 63.5, 69.6 ± 52.7, and 76.5 ± 43.4 months, respectively ($p = 0.452$).

During the follow-up, metastasis was detected in six patients (10.2%); metastasis rates were reported as 1.7% in lungs, 1.7% in supraclavicular lymph node, 1.7% in vertebrae, 1.7% in vagina, and 3.4% in both lungs and liver. In 50% of the primary RT group, in 33.3% of the primary CRT group, and in 16.7% of the RH plus adjuvant RT group, metastasis was observed. In the patients who developed isolated lung metastasis or both lung and liver metastasis, six cycles five AUC carboplatin and + 175 mg/m^2 paclitaxel were administered in three weekly doses. In vertebral metastasis, three cycles cisplatin and iphosphamide were given (50 mg/m^2 of cisplatin + 5,000 mg/m^2 of iphosphamide were given in three weekly doses). In vaginal metastasis patients received five AUC of carboplatin in three weekly doses. RT was added to the treatment of the patients who had vertebral and supraclavicular lymph node metastasis. Three patients developed uremia. Two of the uremia patients were in the primary CRT group and the other patient was in the RH plus adjuvant RT group. In the primary RT given group, one patient developed rectovaginal fistula (3.7%) and one patient had vesicovaginal fistula (3.7%). Leucopenia was seen in one of chemotherapy receiving patients. Although, five patients had histopathologically confirmed pelvic lymph node metastasis, none of the patients had para-aortic lymph node metastasis. To the patients who had pelvic lymph node metastasis, RT was given. Lymphovascular space invasion (LVSI) was detected in six patients and these patients received RT. The patients who developed distant metastases, did not have any LVSI or pelvic lymph node metastases.

Five-year OS rates among the RT, CRT, RH + adjuvant RT, and RH + adjuvant CRT groups were found as 55.6%,72.7%, 62.5%, and 71.4% ($p = 0.802$), respectively; and five-year DFS rates of these groups were found as 71.4%, 88.9%, 80%, and 87.5% ($p = 0.537$), respectively. There were no statistically significant differences among four different treatment modalities used in the management of Stage IIA cervical cancer with regards to survival rates. Survival curves are shown in Figures 1 and 2.

Discussion

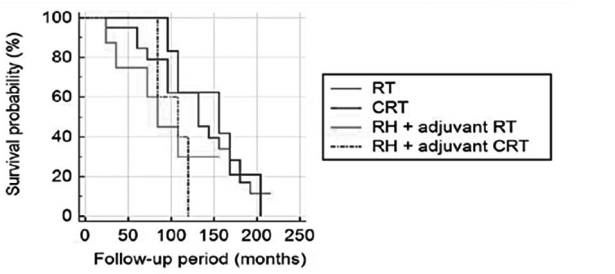
In this retrospective study, 59 patients who were diagnosed as Stage IIA cervical cancer, were evaluated and four different treatment modalities were compared. Among these treatment options, there were no statistically significant difference in terms of DFS and OS. Although cervical cancer has a certain treatment algorithm, there is no consensus about the treatment of the patients who have Stage IIA cervical cancer. The treatment options for Stage IIA tumors consisted of CRT, primary RT, adjuvant RT after RH, and adjuvant CRT after RH. The tumor size (> 4 cm tumor = bulky cervical cancer) is an important criterion to decide performing a RH. In the presence of a bulky cervical cancer, most of the gynecologic oncologists usually avoid per-



Hazard ratios (column/row) with 95% Confidence Interval

Group	RT	CRT	RH + adjuvant CRT	RH + adjuvant CRT
RT	-	1,3026 0,5618 to 2,1642	1,8136 0,6612 to 4,9744	1,9619 0,6606 to 5,8269
CRT	0,9070 0,4621 to 1,7801	-	1,6449 0,6544 to 4,1346	1,7794 0,6492 to 4,8768
RH+ adjuvant RT	0,5514 0,2010 to 1,5123	0,6080 0,2419 to 1,5282	-	1,0818 0,3078 to 3,8019
RH + adjuvant CRT	0,5097 0,1716 to 1,5138	0,5620 0,2051 to 1,5401	0,9244 0,2630 to 3,2488	

Figure 1. — Kaplan-Meier curve of the disease-free survival between four different treatment modalities in Stage IIA cervical cancer. RT: primary radiotherapy, CRT: primary chemoradiotherapy, RH +adjuvant RT: adjuvant radiotherapy after radical hysterectomy, RH + adjuvant CRT: adjuvant chemoradiotherapy after radical hysterectomy.



Hazard ratios (column/row) with 95% Confidence Interval

Group	RT	CRT	RH + adjuvant CRT	RH + adjuvant CRT
RT	-	1,1237 0,4583 to 2,7555	1,9024 0,5110 to 7,0834	2,3171 0,5683 to 9,4472
CRT	0,8899 0,3629 to 2,1821	-	1,6930 0,5316 to 5,3918	2,0620 0,5846 to 7,2728
RH+ adjuvant RT	0,5256 0,1412 to 1,9571	0,5907 0,1855 to 1,8812	-	1,2180 0,2496 to 5,9433
RH + adjuvant CRT	0,4316 0,1059 to 1,7596	0,4850 0,1375 to 1,7105	0,8210 0,1683 to 4,0064	-

Figure 2. — Kaplan-Meier curve of the overall survival between four different treatment modalities in Stage IIA cervical cancer. RT: primary radiotherapy, CRT: primary chemoradiotherapy, RH +adjuvant RT: adjuvant radiotherapy after radical hysterectomy, RH + adjuvant CRT: adjuvant chemoradiotherapy after radical hysterectomy.

forming surgery. Several features are taken into consideration to choose the treatment modality such as age, fertility desire, accompanying diseases, tumor size, invasion depth, LVSI, lymph node metastasis, and the histopathological type of the tumor. In the literature, studies had not shown differences between efficacy and survival rates of different treatment options. However, complications of treatments, morbidity, and effects on the life quality should be taken into consideration.

Among the patients with Stage IIA cervical cancer without a bulky tumor, the five-year OS rates of the RT and RT after surgery groups were determined as 75% and 83%, respectively; for patients who had bulky tumor in Stage IIA cervical cancer these rates were reported as 69% and 60% [2]. In the treatment of Stage IIA1 cervical cancer patients compared to the Stage IIA2 patients, primary RT (47.2% *vs.* 64.7%, $p < 0.001$) and adjuvant radiotherapy (60.5% *vs.* 77.5%, $p = 0.006$) were used more frequently [3]. Among the Stage IIA cervical cancer treatment options, patients who had ≤ 2 cm tumor size, grade 2-3 tumor, non-squamous cell tumor, and age ≤ 65 are found appropriate for the RH [3]. The ratio of adjuvant RT after RH was found as 86% in patients who had > 6 cm tumors and 48% in patients who had < 2 cm tumors [3]. The five-year OS rates were reported in Stage IIA1 and IIA2 cervical cancer in 65.8% and 59.5%, respectively [3]. The survival did not significantly differ between Stage IIA cervical cancer patients who were treated by RH or primary RT [3]. In a study, five-year DFS rates in Stage IIA1 and IIA2 cervical cancers were reported to be 84.6% and 88.7%, respectively ($p = 0.67$), and OS rates were found as 83.4% and 90%, respectively [4]. After RH and pelvic lymph node dissection, adjuvant RT was given in 72.4% of the Stage IIA1 and 84.4% of the Stage IIA2 patients [4].

In the present study, five-year OS rates among the primary RT, primary CRT, adjuvant RT after RH, and adjuvant CRT after RH groups were found to be 55.6%,72.7%, 62.5%, and 71.4%, respectively, and five-year DFS rates of these groups were found to be 71.4%, 88.9%, 80%, and 87.5%, respectively. The study demonstrated that the difference between treatment groups was not statistically significant.

Early-term complication rates in patients with local advanced stage cervical cancer who had RH after CRT were reported as 45% vascular, 31% urinary, and 9% gastrointestinal system originated and late-term complications were found as 6% vascular, 64% urinary, and 22% gastrointestinal system originated [5]. In the present study, one of the patients (3.7%) who had received primary CRT, had rectovaginal fistula and the other (3.7%) developed vesicovaginal fistula. Leucopenia was seen in one of chemotherapy-receiving patients.

Potential limitations of this study include its retrospective nature, small sample, and differences in the number of patients among groups. Furthermore, life quality and sexual functions could not be evaluated. Moreover, patients were not divided according to tumor size (≤4 cm and > 4 cm) because of the small sample size. Despite these limitations, the similarity of demographic characteristics in the study population, availability of good follow-up data, and performance of treatments in a single institution by the same team probably increased the validity of results and

mitigated weaknesses.

In conclusion, no statistically significant difference was identified regarding the efficacy and survival among four different treatment modalities in Stage IIA cervical cancer patients. The treatment option should be individualised and an algorithm study should be performed to use in the treatment of local advanced stage cervical cancer. Future multicenter prospective studies are necessary to find the most benefical treatment option for this stage of cervical cancer.

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