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Results of Adjuvant Radiotherapy based on Sedlis Criteria in Early Stage Cervical Cancer

Erken Evre Serviks Kanserinde Sedlis Kriterleri Gözönünde Bulundurularak Uygulanan Adjuvant Radyoterapi Sonuçları

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Abstract

Aim: Investigation of the efficacy of adjuvant radiotherapy (RT) in cervical cancer stage I-IIA according to the International Federation of Gynecology and Obstetrics (FIGO, 2018) in terms of risk factors and oncologic outcomes.

Material and Method: The study included 113 patients with FIGO stage I-IIA. Patients who received adjuvant external pelvic RT and/or intracavitary brachytherapy (ICBT) after surgery retrospectively analyzed for demographic data, histology, grade, tumor size, stage, lymphovascular stromal invasion (LVSI), stromal invasion depth (SID), type of lymphadenectomy, number of dissected pelvic / paraaortic lymph nodes, surgical margin, adjuvant therapies, local relapse, distant failure, overall survival (OS), and progression-free survival (DFS).

Results: After a median follow-up of 160 months, local recurrence was observed in 3 patients, distant metastasis in 6 patients and all-cause death in 15 patients. It was observed that only SID had a statistically significant effect on overall survival among the Sedlis criteria (p=0.04). The ten-year DFS and OS rates were 95% and 94%, respectively .

Conclusions: Promising oncological results were obtained in early stage cervical cancer with adjuvant RT based on Sedlis criteria.

Keywords: Radiotherapy, sedlis criteria, cervix cancer

Öz

Amaç: FIGO (the International Federation of Gynecology and Obstetrics, 2018) Evre I-IIA serviks kanserinde adjuvan radyoterapinin risk faktörleri ve onkolojik sonuçlar açısından etkinliğinin araştırılmasıdır.

Gereç ve Yöntem: FIGO evre I-IIA olan 113 hasta çalışmaya dahil edilmiştir. Cerrahi sonrası adjuvan eksternal pelvik RT ve / ve ya intrakaviter brakiterapi (ICBT) uygulanan hastalar demografik veriler, histoloji, grade, tümör boyutu, evre, LVSI, stromal invazyon derinliği (SID), lenfadenektomi tipi, diseke edilen pelvik/paraaortik lenf nodu sayısı, cerrahi sınır durumu, uygulanan adjuvant tedaviler, lokal relaps, uzak hastalık, genel sağkalım (OS), and hastalıksız sağkalım (DFS) açısından retrospektif olarak incelenmiştir.

Bulgular: Medyan 160 aylık takip sonunda 3 hastada lokal nüks, 6 hastada uzak metastaz, 15 hastada tüm nedenlere bağlı ölüm gözlenmiştir. Sedlis kriterleri içerisinde sadece SID 'ın OS üzerinde istatistiksel anlamlı olarak etkili olduğu gözlenmiştir. (p=0.04). On yıllık DFS ve OS oranı sırasıyla 95% ve 94% olarak bulunmuştur.

Sonuç: Erken evre serviks kanserinde Sedlis kriterlerine dayalı adjuvan RT ile yüz güldürücü onkolojik sonuçlar elde edilmiştir.

Anahtar Kelimeler: Radyoterapi, sedlis kriterleri, serviks kanseri

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INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide and the leading cause of cancer-related deaths.[1] According to the 2018 revised the International Federation of Gynecology and Obstetrics (FIGO) staging system, Stage I-IIA, which is limited to the cervix and uterus, is defined as early stage disease and accounts for approximately 50-75% of all cervical cancer patients.[2]

The indication for postoperative radiotherapy in early stage cervical cancer is determined by the stage of the disease and the risk factors associated with recurrence. High risk factors include positive surgical margin, lymph node metastasis, presence of parametrial invasion; while medium risk factors include tumor size, presence of lymphovascular stromal invasion (LVSI), cervical stromal invasion defined as Sedlis criteria.[3-7]

Studies are still ongoing on which adjuvant treatment or treatment combinations should be applied in the presence of different risk factors in early stage cervical cancer. Answers to questions such as in which patients chemotherapy (CT) should be combined with RT, in which subgroup vaginal brachytherapy alone may be sufficient, in which groups vaginal brachytherapy may contribute to external pelvic RT are still being sought.[8]

Sedlis criteria were developed to predict recurrence based on data from patients with SCC histology. However, research is ongoing on different biomarkers and nomograms, including other histologies and other factors, which may help in the selection of adjuvant therapy for early stage disease.[9-12]

Therefore, in this study, we aimed to share adjuvant treatments and oncologic outcomes in patients with early stage cervical cancer without lymph node metastasis according to the current FIGO (2018) staging system.

MATERIAL AND METHOD

Study Population

Among the patients who admitted to our center with the diagnosis of cervix cancer between 2000 and 2020, patients with stage I-IIA were evaluated retrospectively. The study included 113 patients who underwent adjuvant external pelvic RT and/or intracavitary brachytherapy (ICBT) after surgery. Patients with lymph node metastases or parametrial invasion were excluded from the study.

All patients were evaluated for demographic data, histology, grade, tumor size, stage, LVSI, stromal invasion depth (SID), type of lymphadenectomy, number of dissected pelvic / paraaortic lymph nodes, surgical margin, adjuvant therapies, local relapse, distant failure, overall survival, and progression-free survival. Patients were staged according to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO 2018).[13] The study was carried out with the permission of Istanbul Prof. Dr. Cemil Tascioglu City Hospital. Ethics Committee (Date: 23.01.2023, Decision No: E-48670771-514.99-20792411)

Statistical Analysis

The data for continuous variables were expressed as the median (range), and categorical variables were reported as number and percentage. Data distribution was assessed by the Kolmogorov–Smirnov test. In consideration of the sample size, the non-normal distribution of variables was assumed, and nonparametric tests were used for between-group comparisons. So, the Mann–Whitney U test for continuous variables, and the Chi-square test for categorical variables were used. Kaplan-Meier curves were generated for OS and DFS, and significance was assessed using the log-rank test. Statistical analyses were performed using SPSS 25 software (SPSS Inc., Chicago, IL, USA). A probability value of $p<0.05$ was considered significant.

RESULTS

Patient Characteristics

The median age of the patients was 49 (range, 30-72). Median follow-up was 160 (range, 6-275) months. 82% of patients had squamous cell histology. The baseline characteristics of the patients are presented in **Table 1**. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO). The median tumor size was 3.5 cm (range: 0.5-9.5) and patients with a tumor size of 4 cm or more were 36.3%.

Table 1: Patient and tumor characteristics

	Patients (n:113,%)
Age	Median; 49 (range 30-72)
<40 yr	20 (17.7%)
40-59 yr	76 (67.3%)
≥60 yr	17 (15%)
Histology	93 (82%)
Squamous cell	15 (13.3%)
Adenocarcinoma Adenosquamous	4 (3.7%)
Clear cell	1 (1%)
Tumor grade	
G1	35 (31%)
G2	55 (48.7%)
G3	23 (20.3%)
Tumor Size	
<4 cm	72 (63.7%)
≥4 cm	41 (36.3%)
FIGO Stage	
I (A/B)	94 (83.2%)
IIA	19 (16.8%)
LVSI	
Negative	59 (52.2%)
Positive	54 (47.8%)
Stromal Invasion Depth	
Superficial	29 (25.7%)
Medium	41 (36.3%)
Deep	43 (38%)
Surgical margin	
Negative	103 (91.2%)
Positive	10 (8.8%)

The rate of patients who did not undergo LND was also 36.3%. Surgical margins were positive in 10% of the patients. Cisplatin based concomitant chemoradiotherapy were given of% 40 and all patients underwent postoperative pelvic external RT and/or ICBT. The median dose of external RT administered was 46 Gy (45-50.4 Gy) and median ICBT dose was (15-30 Gy). Adjuvan treatment details are presented in **Table 2**.

Table 2: Treatment Details

	Patients (n:113,%)
Lymphadenectomy	
Only pelvic	49 (43.4%)
Pelvic + paraaortic / Paraaortic sampling	23 (20.4%)
None	41 (36.3%)
Number of LNs removed (median, range)	
Number of pelvic LNs removed	Median; 12 (range 1-49)
Number of paraoartic LNs removed	Median; 6 (range 1-25)
Chemotherapy	
No	73 (64.6%)
Yes	40 (35.4%)
Radiotherapy	
Whole pelvic RT	28 (24.8%)
Whole pelvic RT + Brachytherapy	74 (65.5%)
Only Brachytherapy	11 (9.7%)

Oncological Results

After a median follow-up of 160 months, local recurrence was observed in 3 patients, distant metastasis in 6 patients and all-cause death in 15 patients. The effects of age groups (<40 yr, 40-59 yr, ≥60 yr), pretreatment hemoglobin level, tumor size above/under 4 cm, SID, number or type of pelvic dissected LNs, stage, surgical margin status and presence of LVSI on OS were analyzed. Among these parameters, only SID had a statistically significant effect on OS. (p=0.04). The ten-year DFS and OS rates were 95% and 94%, respectively (**Figure 1-2**).

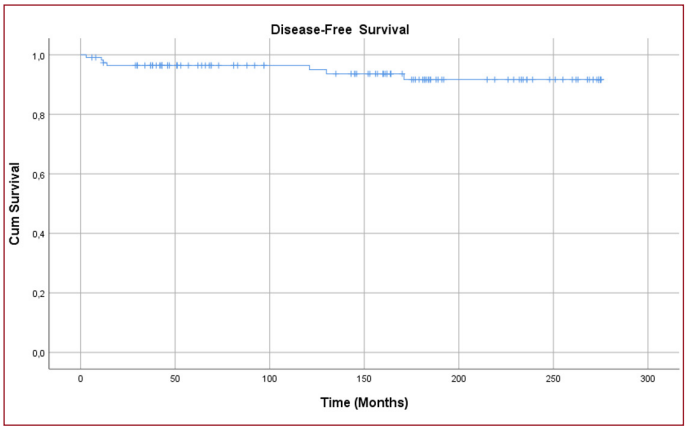

Figure 1. Kaplan-Meier plots of disease free survival.

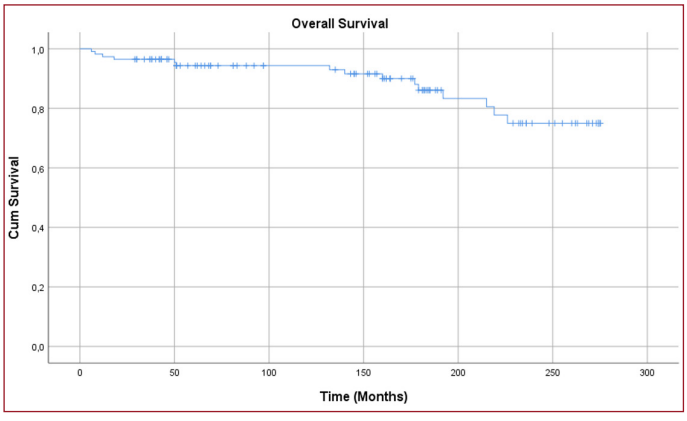

Figure 2. Kaplan-Meier plots of overall survival.

DISCUSSION

A significant number of studies examining the role of adjuvant therapy in early stage cervical cancer were conducted according to the FIGO 2009 staging criteria and included lymph node positive patients.[14-16] The patients in our study were staged according to the current FIGO staging system, which was revised in 2018 and included pelvic/paraaortic lymph node involvement in the staging. Therefore, it does not include lymph node positive patients. However, there was no effect of whether pelvic/ paraaortic dissection was performed or the number of lymph nodes dissected. The reason for this was thought to be that 90.5% of the patients in the study underwent pelvic +/- ICBT. When analyzed according to Sedlis criteria, no effect of tumor size >4 cm or presence of LVSI on OS was shown in our study. The only effective factor on OS was found to be SID.

Rotman et al. investigated the role of postoperative RT in a Phase 3 randomized trial involving 277 patients with stage 1B. They found that postoperative external RT reduced the risk of recurrence, progression or death in patients with two or more risk factors such as LVSI (+), stromal invasion deeper than 1/3 and tumor diameter greater than 4 cm (p=0.007 and p=0.009 respectively).[17]

Gan et al. retrospectively evaluated 221 patients who underwent hysterectomy for early stage cervical cancer. They observed a statistically significant increase in 3-year local recurrence-free survival (LRFS) in patients who received adjuvant RT compared to surgery alone.[18]

Solis et al. analyzed the data of 28 patients who underwent adjuvant small pelvic field radiotherapy without brachytherapy or chemotherapy for intermediate risk. They reported OS, DFS and LRFS as 100%, 82% and 86% respectively at a median follow-up of 41 months. They also stated that small pelvic area RT is a tolerable and safe treatment with any grade 3-4 GIS/GUS toxicity.[19] In our study, no difference was observed between patients who received pelvic RT only, ICBT only or external pelvic RT and ICBT together.

Fabrini et al. analyzed the role of postoperative RT in 51 patients with clinical FIGO stage 1B cervical cancer. It was observed that 56% of patients received concomitant CT and 64% received brachytherapy. At a median follow-up of 58 months, the 5-year DFS and OS rates were 74.9% and 82.0%, respectively.[20]

GUO et al. compared the results of adjuvant RT and adjuvant chemoradiotherapy (CRT) treatment in early stage cervical cancer through a meta-analysis. In the evaluation of 3601 patients, it was observed that similar results were recorded in terms of RT vs CRT in the presence of a single risk factor, but better recurrence-free survival results were obtained in the CRT arm in the presence of multiple risk factors.[21] In our study, 18% of the patients had non-SCC histology and 10% of the patients were surgical margin positive patients with high risk factors. ICBT with external pelvic RT was performed in 65% of patients and concurrent CT in 40% of patients. We did not observe any effect of CT on disease-free survival or OS.

In a Phase 3 randomized trial, Huang et al. examined the effect of sequential or concurrent CT administration on DFS compared to RT alone in early-stage cervical cancer. 1048 patients were randomized into 3 arms: RT alone, sequential CT-RT and concurrent CRT as adjuvant treatment after surgery. No difference was observed between the concurrent CT arm and the RT alone arm. However, they observed a decrease in the risk of death and an increase in the 3 year DFS and distant DFS rate in the sequential CT-RT arm compared to the other arms.[22]

Nie et al. retrospectively analyzed 596 patients with FIGO (2018) Stage I-IIA according to whether they received adjuvant therapy. With a median follow-up of 62 months patients were evaluated according to adjuvant CT alone, RT alone, concurrent CRT and observation arms. They claimed 5-year PFS (progression-free survival) rates of 93.9%, 93.4%, 91.6%, 74.6% and 5-year OS rates of 93.9%, 93.4%, 92.4%, and 76% respectively. They observed that OS and PFS rates were better in patients who received adjuvant therapy than in those who did not, and PFS and OS rates were lower in the RT alone arm than in the CT alone arm and in the CRT arm ($P<0.05$). They also reported no difference between patients with a single or multiple risk factors.[23]

Xiao-Li Yu et al. compared the two groups that received and did not receive brachytherapy with external pelvic RT in adjuvant treatment in two hundred and twenty-five patients with early-stage operated cervical cancer. It was observed that the 5-year local regional recurrence-free survival rates were statistically significantly higher in the brachytherapy group. It was also emphasized in the study that the indication for brachytherapy treatment with pelvic RT could be determined by considering more factors.[24]

CONCLUSION

Adjuvant external pelvic RT+/- ICBT in early-stage cervical cancer has shown very good ten year OS and DFS results. Large-scale randomized trials are needed for modeled adjuvant treatment selection according to subgroups.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Prof. Dr. Cemil Tascioglu City Hospital. Ethics Committee (Date: 23.01.2023, Decision No: E-48670771-514.99-20792411)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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