Prognostic factors treated with chemo-radiotherapy for locally advanced cervical cancer in older age ≥ 50

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***Abstract*—Objective:** The outcome of aging in cervical cancer is controversial. We conducted a retrospective analysis to investigate the characteristics and prognosis of elderly patients undergoing advanced cervical cancer treatment. **Methods:** Medical records of 66 patients over 50 years old treated with chemo-radiotherapy from January 2012 to January 2017 were collected. Patients had stage IB-IVB cervical cancer and were treated with daily concurrent chemo-radiotherapy (CCRT). The daily CCRT comprised pelvic external beam radiotherapy (1,8 Gy/d-25-28 fraction) with weekly cisplatin (40mg/m^2) and high dose rate brachytherapy. Prognosis, patient characteristics, and treatment results were evaluated.
Results: The median age was 62 years (range, 50-81 years). The median follow-up duration was 47 months (17-89 months). The 5 year overall survival (OS), loco-regional free survival (LRFS), distant metastasis free-survival (DMFS) was 84,9%,80,2% and 68,2%, respectively. The median; tumor size was 51 mm (range 31-130*)*, external radiotherapy dose was 45Gy (45-50,4Gy).The histology of tumor was 87,9 % squamous cell cancer and 12,1 % adenocarcinoma,38 (57,6%) patients had pelvic lymph node in pelvic MRI before treatment. The most common stage was IIB and III. Residual tumors were detected in 27 (40,9%) patients after pelvic CCRT. Six patients (9,1%) with visible residual disease were found six months after CCRT with positron emulsion tomography (PET). In univariate analysis, detection of residual disease at 6 months and external radiotherapy after CCRT had a negative effect on OS,LRFS and DMFS. Tumor size greater than 4cm had a worse prognosis in OSS (p=0,05), pelvic lymph node positivity before treatment had a negative effect on LRFS (p=0,01) and DMFS (p=0,03).
Conclusion: CCRT had a good prognosis in elderly locally advanced cervical cancer. The presence of residual disease after treatment is the most important prognostic factor for survival, these patients needs more medical treatment after CCRT.

Keywords—Cervical cancer, chemo-radiotherapy, elderly cervical cancer, residual disease.

I. INTRODUCTION

Cervical cancer is the second most common malignancy among gynecological cancers (1). The standard treatment of locally advanced cervical cancer depends on stage of disease is concurrent chemo-radiotherapy (CCRT). As the age of the human population increases, the proportion of cervical cancer elderly women increases. Previous studies have shown that elderly women with cervical cancer receive less aggressive therapy (2).Age, as an independent prognostic factor for cervical cancer, is unclear and controversial topic in the literature. There is some evidence to suggest that old age can be an independent factor for poor prognosis (3,4), but other studies have not found this relationship (5,6).

Since the outcome of cervical cancer related to age is controversial. The aim of this study was to evaluate the patterns of treatment outcome in elderly women with cervical cancer patients,we conducted a retrospective analysis in patients treated in our institution in order to investigate the prognosis, patient characteristics, treatment of older patients with locally advanced cervical cancer.

II-MATERIAL-METHODS

a- Patients

From January 2012 to January 2017, 66 patients 50 years or older were newly diagnosed as having locally advanced cervical cancer and treated with concurrent chemo-radiotherapy at SBU, Dr Lutfi Kırdar Training and Research Hospital Radiation Oncology Department. Data were collected retrospectively from the records of 66 consecutive patients and all patients had provided written informed consent for treatment.
The patients included in this study presented with International Federation of Gynecology and Obstetrics (FIGO) stages IB2–IVB, good performance status, no uncontrolled concomitant disease, no connective tissue disease, and no prior irradiation.

b- Radiation Therapy

External beam radiation therapy was delivered in a conventional fraction (1,8Gy/fraction, five fractions/week) using a 18 MV photon beam from a linear accelerator. A total dose of 45-50,4 Gy was administered to the entire pelvis. This was followed by high dose rate (HDR) intracavitary brachytherapy at a

dose of 6 Gy in five fractions which was delivered by a remote afterloding system.

c- Chemotherapy

Cisplatin was the chemotherapy agent administered. Cisplatin was given in a dose of 40 mg/m2/week concurrently with radiotherapy. Patients were seen weekly by a physician for a physical examination and a complete blood count test. Chemotherapy was stopped if creatinine clearance was ,<30 mL/minute, and interrupted if patients had grade 3 gastrointestinal toxicity, the total white blood cell count was ≤4,000/mm3, or platelets were ≤100,000/mm3.

d- Statistical analysis

The primary endpoint was overall survival and the secondary endpoints were loco-regional free survival (LRFS), and distant metastasis free-survival (DMFS) . Data were stored and analyzed using SPSS version 17.0 software (IBM, Armonk, NY, USA). The OS, LRFS, and DMFS endpoints were estimated using the Kaplan-Meier method, and the differences were compared using logrank tests in univariate analysis. Multivariate analysis using the Cox proportional hazards model was performed to identify independent predictors among the prognostic factors.

III-RESULTS

a- Patient characteristics

In a total, 66 patients were included from January 2012 to January 2017. The median age of the patients was 66 (range,50-81) and 58 patients had squamous cell carcinoma, 8 had adenocarcinoma. The median tumor size was 5 cm.(range, 3-13cm).Thirty-nine patients were diagnosed in FIGO stage IIB and 18 was FIGO stage III. Pelvic lymp-node metastasis was found in 38 patients on magnetic resonance (MR) or positron emulsion tomography (PET). All patients received concurrent chemotherapy with pelvic radiotherapy and all patients completed that treatment. Twenty- seven (40,9%) patients had residual tumor after external chemo-radiotherapy on pelvic MR. Six months after treatment, residual tumor was still detected in PET-CT in six patients (9,1%). Patient characteristics are outlined in Table 1.

b –Survival

With a median follow-up time of 47 months (range,17-89 months), during the follow-up interval 11 (16,7%) died of tumor-related disease. Tumor recurrence was observed in 11 (16,7%) patients and metastasis occurred in 19 (28,8%) patients. The 5 year overall survival (OS), loco-regional free survival (LRFS), distant metastasis free-survival (DMFS) was 84,9%,80,2% and 68,2%, respectively.

Potential prognostic factors for OS, LRFS and DMFS were analyzed. In univariate analysis, detection of residual disease both after external radiotherapy and after 6 months had a negative effect on OS, LRFS and DMFS. Tumor size greater than 4cm had a worse prognosis in OSS (p=0,05), pelvic lymph node positivity before treatment had a negative effect on LRFS (p=0,01) and DMFS (p=0,03). In multivariate analysis, among the prognostic factors for OS and LRFS, only residual disease 6 months after CCRT (95% confidence interval, 0.04–0.90; hazard ratio, 0.26, p = 0.03) was statistically significant.

III-DICUSSION

Concurrent chemo-radiotherapy (CCRT) and ıntracavitary brachytherapy is the standard of care for women with locally advanced cervical cancer. Several studies have reported that CCRT has equivalent effectiveness of age(7,8,9). Ikushima et al. (10) reviewed 727 women with locally advanced cervical cancer, there was no 5 or 10 year difference in overall or disease specific survival for older 65 age. In the literature, some authors reported that older women tolerate CCRT well (10, 11, 12); however others have reported higher toxicity in older women(13,14). Grant also showed that 10 (32%) did not complete treatment and 4 (13%) died of treatment related complications (14). The problem appeared to be related to performance status and not age.

Although large population-based studies have also demonstrated that survival for cervical cancer is inversely correlated with stage, survival among older women regardless of stage has been reported to be worse than women in their 40s and 50s (15,16). However, in our study, CCRT over 50 years of age was very well tolerated and OS, LRFS and DMFS results were almost the same compared to younger ages. This is in accordance with Lindegaard et al, that reported that age was not only significant factor for survival, patients' performance status, stage and co-morbidities was the most important factors for survival in elderly patients (17).

This study showed that the presence of residual tumor 6 months after CCRT was the most significant prognostic factor for survival and found poor survival outcomes compared with those without residual tumor. Hequet et (18) al. and Touboul et al.(19) also reported that patients with pathologic residual disease larger than 10 mm had poorer disease- free survival and OS. The involved lymph node was associated with LRFS and DMFS in univariate analysis but not with OS. Similar results, as reported by Song et al. described that large lymph nodes showed lower survival rates (20).

The definition of 'elderly'(i.e., over 55-60 or 65 years old) is differs in many studies. Older patients are more exposed to adverse events, such as renal failure, vomiting, proctitis, cystitis, or denutrition, reflecting frailty. However, other retrospective studies claimed that CCRT is well tolerated (21,22, 23). In our study performance status fit locally advanced patients

treated as young patients and the median age of our study was 66. This showed us that age was not independent prognostic factor for survival, the other risk factors were more important such as; stage, response to treatment, lymph-node status and tumor size.

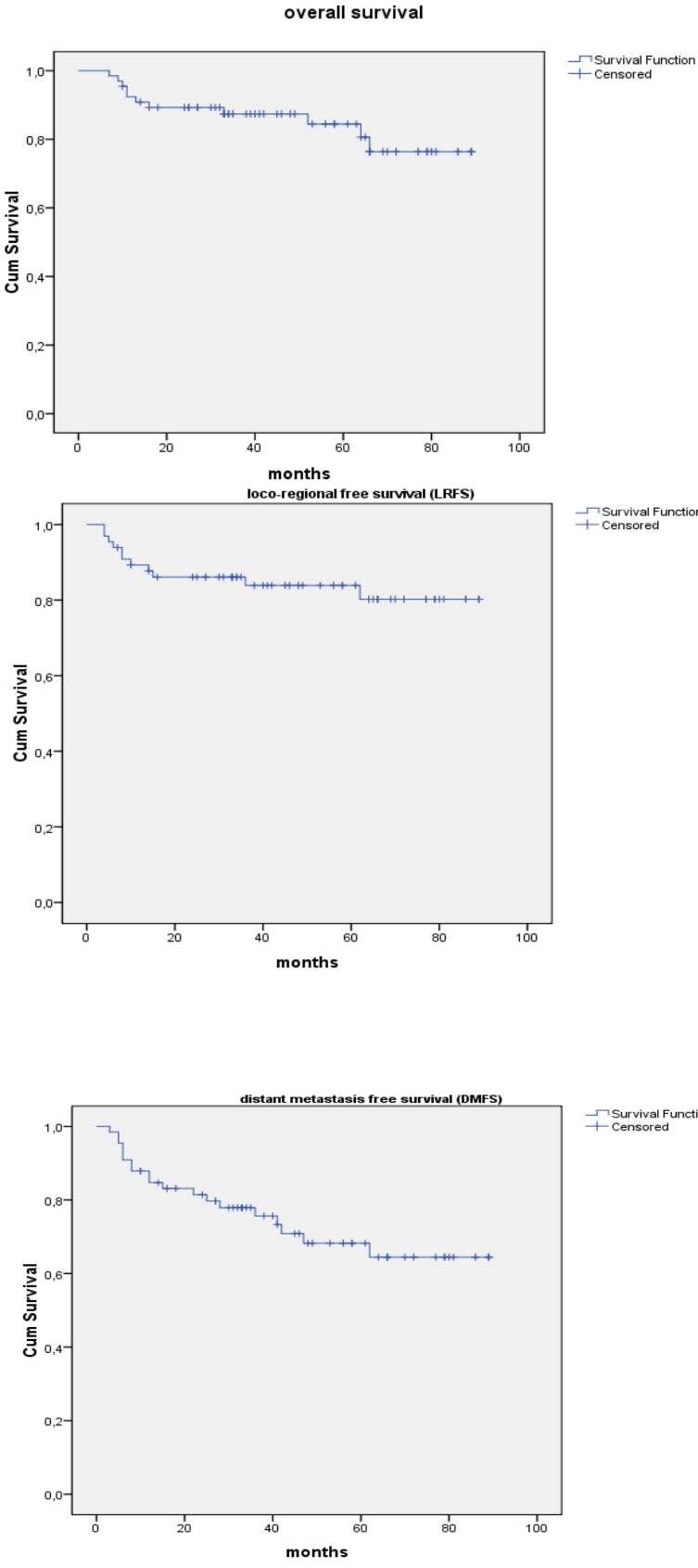
The major limitation of this study is the retrospective nature of the clinical data. There is no clear age limit for old age in the literature. The second limitation of our study is the older age limit. In our study, the median age was 66 and the age cut off limit was ≥ 50. Our study demonstrate that CCRT had a good prognosis in elderly locally advanced cervical cancer. The presence of residual disease after treatment is the most important prognostic factor for survival, these patients needs more medical treatment after CCRT.

Table 1: Patient and tumor characteristics.

	N %
Age (years) Median (range)	62(50-81)
Performance status 0 1 2	60(91%) 6(9%) -
FIGO stage IB2 IIB IIIA IIIB IVA	4(6%) 39(59%) 8(12%) 10(15%) 5 (8%)
Extent of lymph node involvement Yes No	38(58%) 28(42%)
Primary tm size Median(range)	50mm(30-130mm)
Prescribed EBRT* dose (Gy)** Median (range)	45(45-50.4Gy)
Brachtherapy dose (Gy) Median(range)	30(27.5-30Gy)
Residual disease ***After CCRT*** Yes No ***6 months after*** Yes No	 27(41%) 39(59%) 6(9%) 60(91%)

EBRT*:external beam radiotherapy
Gy**:Gray

Graphic 1: Overall survival, Loco-regional free survival, Distant metastasis free survival



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