Definitive Treatment for Locally Advanced Cervical Cancer: A Retrospective Analysis from A Singe Institution

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ABSTRACT

The primary aim of this study was to evaluate the long-term treatment outcomes of definitive chemoradiotherapy (CRT) of locally advanced cervical cancer and beside this to identify prognostic factors and related toxicities. Between February 2001 and September 2013, 327 patients were retrospectively evaluated. The median age was 56 years (range, 24-82 years). Ninety-five percent of patients had ≥Stage IIB disease. External pelvic radiotherapy (RT) (45-50.4 Gy) and concomitant chemotherapy followed by 28 Gy in 4 fractions high dose rate brachytherapy was administered. Boost doses of 10-15 Gy were administered to <2 cm lymph nodes (LNs) or distal parametrial involved sites. The median follow-up time was 68 months (range, 45-90 months). Two-, 5- and 10-year cancer specific survival (CSS) rates were 80%, 68%, and 65%; disease-free survival (DFS) rates were 73%, 66%, and 64%; local recurrence-free survival (LRFS) rates were 94%, 92%, and 91%; loco-regional recurrence-free survival (LRRFS) were 92%, 89%, and 86%; distant metastases-free survival (DMFS) were 81%, 76%, 75%, respectively. In multivariate analysis, age, clinical stage and LN metastasis at diagnosis were independent prognostic factors for both CSS and DFS. Third month response to treatment was the most important prognostic factor for all end points in univariate and multivariate analysis. With the aggressive radiotherapeutic approach, it seems that distant metastases rather than locoregional recurrence determines the survival rates. Consolidation chemotherapy may be a good option after definitive CRT which needs to be supported with future phase III studies.

Keywords: Locally advanced, Cervix cancer, Chemoradiotherapy, Treatment response, Prognosis

ÖZET

Lokal İleri Serviks Kanserinde Definitif Tedavi: Tek Bir Enstitüden Retrospektif Bir Analiz

Çalışmamızın primer amacı, lokal ileri evre serviks kanserlerinde definitif kemoradyoterapi (KRT) ile tedavinin uzun dönem sonuçlarının değerlendirilmesi ve bunun yanında ilişkili prognostik faktörlerin ve toksisite sonuçlarının tanımlanmasıdır. Şubat 2001 ve Eylül 2013 tarihleri arasında, 327 hasta dosyası retrospektif olarak incelenmiştir. Ortanca yaş 56 yıldır (aralık, 24-82 yıl). Hastaların %95'i ≥evre IIB hastalığa sahiptir. Eksternal pelvik radyoterapi (RT) (45-50.4 Gy) ile eş zamanlı kemoterapiyi takiben 4 fraksiyonda 28 Gy yüksek doz hızlı brakiterapi uygulanmıştır. Distal parametriyal tutulum olan bölgeye ya da <2 cm lenf nodlarına (LN) 10-15 Gy ek doz verilmiştir. Ortanca izlem süresi 68 aydır (aralık, 45-90 ay). Sırasıyla 2-, 5- ve 10-yıllık kanser spesifik sağkalım (CSS) oranları %80, %68 ve %65; hastalıksız sağkalım oranları (DFS) %73, %66 ve %64; lokal rekürrenssiz sağkalım (LRFS) oranları %94, %92 ve %91; lokal-bölgesel rekürrenssiz sağkalım oranları (LRRFS) %92, %89 ve %86; uzak metastazsız sağkalım oranları (DMFS) %81, %76 ve %75'tir. Çok değişkenli analizde; yaş, klinik evre ve tanıda LN metastazı varlığı, CSS ve DFS için bağımsız prognostik faktör olarak bulunmuştur. Tek ve çok değişkenli analizde, 3. aydaki tedavi yanıtı tüm sonlanım noktaları için anlamlı prognostik faktör olarak saptanmıştır. Agresif RT yaklaşımına karşın, sağkalım oranlarını lokal-bölgesel rekürrensten çok uzak metastazların belirlediği görülmektedir. Definitif KRT sonrası konsolidasyon kemoterapisi, faz III çalışmalarla desteklenmesi gereken iyi bir seçenek olabilir.

Anahtar Kelimeler: Lokal ileri evre, Serviks kanseri, Kemoradyoterapi, Tedavi yanıtı, Prognoz

INTRODUCTION

Cervical cancer is the third most common malignancy after breast and colorectal cancers and the fourth leading cause of cancer death in women worldwide.[1] In the year 2008 cervix cancer was ranked 10th among the most frequent tumors in females in the United States with a rate of 9/100.000.[2]

While surgery and radiotherapy (RT) produce similar outcomes in early stages, concurrent chemoradiotherapy (CRT) is the standart of care in locally advanced disease.[3-8] In the International Federation of Gynecology and Obstetrics (FIGO) 26th Annual Report, it was shown that stage of the disease and lymph node (LN) involvement were the most important prognostic factors.[9] In the early studies, the most important predictors for recurrence and survival were expressed as the presence of positive para-aortic (PA) LNs in patients with locally advanced disease treated with definitive RT.[10-11] In patients with pelvic confined disease on the other hand, most important prognostic factors were the pelvic nodal involvement and tumor size. Other clinical prognostic parameters were indicated as clinical stage, age, and performance status.[10] Low hemoglobin (Hb) levels on the other hand were also shown to be associated with decreased 3-year survival.[12]

The main problem in locally advanced disease was local or regional recurrence or resistance of the disease. Pelvic recurrence forms two thirds of the recurrent disease after treatment. Hematogenous metastasis on the other hand is very rare at diagnosis and the most common sites of metastasis were the lung, followed by bone, the peritoneal cavity and supraclavicular nodes.[13-14]

The primary aim of this retrospective study was to investigate treatment results of cervical cancer patients who were treated with curative intent at a single institution. All patients were treated with concomitant chemotherapy and external beam RT (EBRT) followed by high dose rate (HDR) intracavitary brachytherapy (BRT). Secondary aims were to determine the prognostic factors and treatment related toxicities.

PATIENTS AND METHODS

Patients

A total of 327 patients with FIGO stage IB-IVA cervical cancer treated with primary concurrent CRT between February 2001 and September 2013 were retrospectively evaluated. All cancers were histologically confirmed. None of the patients had received prior radiotherapy. Patients with evidence of enlarged paraaortic LNs, known distant metastatic disease at initial presentation, or referred for recurrent disease were excluded. All patients had gynecological examination under general anesthesia and they were clinically staged according to the FIGO staging criteria. Pelvic magnetic resonance imaging (MRI) and thoracic and abdominal computed tomography (CT) or positron emission tomography (PET)/CT after the year 2008 were the routine imaging techniques performed for all patients in order to detect or rule out distant metastases. All patients had adequate bone marrow, renal and liver function. This retrospective study was approved by the institutional ethics committee and was conducted in compliance with principles of Helsinki declaration.

Treatment

All patients received EBRT to a total dose of 45-50.4 Gy in 1.8-2.0 Gy daily fractions delivered with pelvic box technique using 6-18 MV X-rays. When there was pelvic side wall involvement or LNs highly suspicious of containing metastatic disease detected by imaging techniques but <2 cm in the maximum diameter, 10-15 Gy boost doses were administered in addition. According to our institute's policy, LN dissection (LND) prior to EBRT was routine practice in patients with LNs more than 2 cm in diameter. Concomitant chemotherapy was basically in the form of 40 mg/m^2 cisplatinum on weekly basis during EBRT. HDR BRT with 7 Gy per fraction prescribed to either point A or high risk clinical target volume (HRCTV) to a total dose of 28 Gy was applied to all patients.

EBRT was given two dimensionally (2D) in 236 (72%) patients. In this 2D-RT technique, upper border was at L4-L5 level, lower border was below the obturator foramen and lateral borders as 2 cm to lateral margin of the bony pelvis. In left and

right fields the posterior border was defined as the line between sacral 2 and 3 vertebras and the anterior border was the line just in front of the symphisis pubis. Ninety-one (28%) patients received three dimensional (3D) RT and target volumes including all cervical and entire uterus, bilateral parametrium and proximal vagina as primary clinical target volume (CTV) and internal iliac, external iliac and presacral lymphatics as lymphatic CTV were contoured based on the Radiation Therapy Oncology Group (RTOG) contouring atlas.[15]

Image based 3D treatment planning of BRT was available in our department since May 2012 and only 13% of our patients included in this study were treated with this technique. In 2D-BRT, all patients were evaluated with gynecological examination in the 3rd week of EBRT to determine whether there was adequate tumour regression and when it was so the first HDR BRT procedure was applied at the beginning of 4th week and followed by the rest 3 fractions once a week during the remaining and following EBRT. The dose was prescribed to point A defined by the Manchester system.[16] In 3D-BRT patients were evaluated both with gynecological examination and pelvic MRI at the end of EBRT and BRT was administered every other day as 28 Gy in 4 fractions. In this technique HRCTV, intermediate risk CTV (IRCTV) and critical organs like rectum, bladder and the sigmoid were outlined as proposed by the "Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology " (GEC-ESTRO) on CT scans.[17-18] The prescribed dose was 7 Gy to HRCTV and the optimisation was made to obtain 90% of the HRCTV (D90) should receive at least 100% of the prescribed dose and 100% volume of IRCTV should receive at least 50% of the dose. With this dose delivery combined with EBRT, it is assumed that the HRCTV receives 85-90 Gy and IRCTV at least 60 Gy EQD2 (equivalent dose in 2 Gy fractions) when α/β of cervical cancer taken as 10. Dose optimization was also made for 2 cc of bladder volume received ≤7 Gy, 2 cc of rectum and sigmoid volume as ≤5 Gy.

Follow up

Patients were assessed weekly for acute toxicity during CRT. After the completion of CRT to assess treatment response, detailed gynecological examination at 1 month and pelvic MRI and/or PET/CT in addition to Pap smear at 3 months were performed in all patients. Response assessment was done according to the Response Evaluation Criteria in Solid Tumors (RECIST)) criteria.[19] A complete response (CR) was defined as the complete disappearance of all target lesions and the absence of new lesions. A partial response (PR) was defined as at least a 30% reduction in the sum of the longest dimensions of the target lesions. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest dimensions of the target lesions or the development of new lesions. Stable disease (SD) defined as neither sufficient shrinkage (compared to baseline) to qualify for CR or PR nor sufficient increase (taking as reference the smallest sum of diameters at baseline or while on study, whichever is smallest) to qualify for progressive disease (PD).

When there was a complete tumor response, gynecological examination, annual smear test and imaging studies when necessary were done every 3 months for the first 2 years, every 6 months until fifth years and annualy thereafter. During follow up, patients were evaluated for local, regional or distant recurrence, and treatment related toxicities. Acute and late toxicity was scored using European Organisation for Research and Treatment of Cancer (EORTC)/RTOG scoring system.[20]

Statistical Analysis

Statistical analysis was performed using PASW Statistics for Windows v.18.0 (SPSS, Inc., Chicago, IL). All survival analyses were done using by the Kaplan-Meier method and a value of $p \leq 0.05$ was considered statistically significant. Log-rank test was used to determine following prognostic factors: age (≤56 years vs. >56 years), Hb level before RT (<11 g/dL vs. ≥11 g/dL), histological subtype (squamous cell carcinoma-SCC vs. other), LN metastasis at diagnosis (yes vs. no), stage (<IIB vs. ≥IIB), LND status (yes vs. no), hydronephrosis (yes vs. no), and 3rd month response status (complete vs. other). Multivariate analysis was performed using the Cox Regression analysis. Overall survival (OS) was defined as the time from end of the treat-

ment until death from any cause. Time to relapse or death from any cause, which ever comes first was taken for disease-free survival (DFS). Time to develop local, regional or distant recurrence was taken for local recurrence-free survival (LRFS), locoregional recurrence-free survival (LRRFS) and distant metastases-free survival (DMFS). We also calculated cause-specific survival (CSS) which was defined as time to relapse or death from cancer including complications of the treatment, which ever comes first.

RESULTS

Patient and Tumor Characteristics

Clinicopathological characteristics of 327 patients included in this study are shown in Table 1. Median age of the patients was 56 years (range, 24-82 years) and more than 90% were over 40 years. Three hundred and nine patients (95%) had stage ≥IIB disease. The majority of patients (90%) were with squamous cell carcinoma (SCC). Median maximum tumor size at the time of diagnosis was 5 cm (range, 1-11 cm) and median maximum LN size was 2.4 cm (range, 0.8-7 cm). One hundred and one patients (31%) were considered as having clinical LN metastasis and LN positivity was detected by MRI in 67 (66%), MRI and PET/CT in 27 (27%), and PET/CT in 2 (0.2%) cases. Two hundred and fifty-one (77%) patients were having Hb level >11 g/dl at the beginning of RT. All patients were given transfusions in order to increase serum Hb level >11 g/dl when necessary before and/or during treatment.

Table 1. Patient and tumor characteristics

Characteristics	n	%
Age (years)		
≤56	186	57
>56	141	43
Tumor Histology		
Squamous cell carcinoma	295	90
Adenocarcinoma	24	7
Clear cell carcinoma	3	1
Others	5	2
Grade		
I (well differantiated)	38	12
II (moderate differantiated)	53	16
III (poor differantiated)	64	20
Unknown	172	52
Tumor Size (cm)		
≤4	68	21
>4	252	77
Unknown	7	2
Parametrial Involvement		
Positive	293	89
Negative	33	10
Unknown	1	1
Lymph Node Involvement		
Positive	101	31
Negative	226	69
FIGO Stage (2009)		
IB2	8	2
IIA2	10	3
IIB	182	56
IIIA	16	5
IIIB	88	27
IVA	23	7
Hb Level		
≤11	76	23
>11	251	77

Abbreviatons: FIGO= International Federation of Gynecology and Obstetrics, Hb= Hemoglobin

Treatment Parameters

Treatment details are shown in Table 2. One hundred and thirty (40%) patients underwent LND, mostly administered extraperitonealy (82%). Eighteen patients (5%) were treated with neoadjuvant chemotherapy with different protocols and 12 out of these patients were referred for RT with PR and 4 with SD after neoadjuvant chemotherapy.

The median total EBRT dose was 50.4 Gy (range, 45-50.4 Gy) and 39 (12%) patients were given 10-15 Gy boost dose due to stage IIIB disease and/or LN involvement. HDR BRT dose was mostly 28 Gy in 4 fractions (93%). Only in 23 patients, BRT fraction doses were reduced to 6-6.5 Gy in order to keep rectum and bladder doses in tolerance limits.

Concomitant weekly cisplatin chemotherapy was given to 288 of 296 patients (91%) during EBRT while remaining 8 patients received carboplatin and other different schemes due to medical contraindications to cisplatin. One hundred and eighty-one patients (55%) received at least 4 cycles of concomitant chemotherapy while 34% of patients received less than 4 cycles due to the toxicity issues.

Table 2. Treatment characteristics

Characteristics	n	(%)
Lymph Node Dissection		
Yes	130	40
No	197	60
External Radiotherapy		
Conventional (2D)	236	72
3DCRT	91	28
Brachytherapy		
2D-BRT	285	87
3D-BRT	42	13
Concomitant Chemo		
Yes	296	91
No	31	9
Concomitant Chemo Cycle		
<4	111	34
≥4	181	55
Unknown	35	11
Neoadjuvant Chemo		
Yes	18	5
No	309	95

Abbreviatons: 2D= Two Dimensional, 3DCRT= Three dimensional conformal radiotherapy, 2D-BRT= Two dimensional brachytherapy, 3D-BRT= Three dimensional brachytherapy, Chemo= Chemotherapy

Response to treatment

Eighty percent of patients at the 3rd month after RT showed CR whereas 13% of patients showed PR, 1% of patients showed SD and 3% of patients showed PD 3% of patients had no 3rd month response evaluation. The median follow-up time was 68 months (range, 45-90 months). One hundred and forty-six (45%) patients were considered as alive with no evidence of disease at the last follow-up, while 8 (3%) alive with evidence of disease, 93 (28%) death with disease and 80 (25%) death with other causes than cancer or treatment complication.

Survival outcomes and prognostic factors

The 2-, 5- and 10-year CSS rates were 80%, 68%, and 65%; DFS rates were 73%, 66%, and 64%; LRFS rates were 94%, 92%, and 91%; LRRFS were 92%, 89%, and 86%; DMFS were 81%, 76%, 75%, OS rates were 68%, 52% and 42%, respectively.

In univariate analysis; LN metastasis at diagnosis, low Hb levels before RT and incomplete treatment response at 3rd month were found as poor prognostic factors for OS. Clinical stage, LN metastasis at diagnosis, hydronephrosis, 3rd month response to treatment were significant prognostic factors for CSS, DMFS and DFS; whereas LND status was another prognostic factor for CSS. Histological subtype and 3rd month response to treatment were significant prognostic factors for LRFS and 3rd month response to treatment and LN metastasis at diagnosis were significant prognostic factor for LRRFS (Table 3). In multivariate analysis, age, clinical stage and LN metastasis at diagnosis were independent prognostic factors for CSS and DFS, and 3rd month response to treatment was significant for all five endpoints (Table 4) (Figure 1).

Patterns of Failure

In our study, local and locoregional failure rates were found to be 6.6% and 8.3%, respectively. Distant failure rates were 18.3%. Distant failure sites were seen as mostly lung (n= 15), bone (n= 8) or multiple organ metastasis (n= 7).

Acute toxicity

During treatment 144 patients (44%) developed acute grade 1-3 gastrointestinal system (GIS) toxicity, 105 patients (32%) developed acute grade 1-3 genitourinary system (GUS) toxicity and 25 patients (8%) developed acute grade 1-3 hematologic toxicity. Acute GIS toxicity was observed as diarrhea, nausea and vomiting and proctitis in 13%, 12%, and 19% of patients, respectively. Acute GUS toxicity was observed as dysuria in 26%, urine emergency in 1% and vaginitis in 5% of patients; and acute hematologic toxicity was observed as neutropenia in 4%, anemia in 2% and neutropenia combined with anemia in 2% of patients.

Late Toxicity

In 20 (6%) of patients, late grade 2-4 GUS toxicity was observed and late grade 2-5 GIS toxicity was observed in 27 (8%) of patients. Late GUS toxicity

Table 3. Univariate analysis of prognostic factors for cancer-spesific survival, disease-free survival, local recurrence-free survival, locoregional recurrence-free survival, distant metastases-free survival and overall survival

Survival	Factor	2 years (%)	5 years (%)	10 years (%)	p
CSS	Hydronephrosis				
	Yes	66	48	47	0.003
	No	82	72	68	
	Lymph node metastasis				
	Yes	73	56	50	0.01
	No	82	72	70	
	Stage				
	<IIB	78	77	76	<0.0001
	≥IIB	80	68	65	
	LND				
	Yes	88	72	70	0.038
	No	75	65	61	
	3rd month response				
	Complete	83	72	69	<0.0001
	Other	60	46	42	
DFS	Hydronephrosis				
	Yes	62	51	51	0.009
	No	76	68	67	
	Lymph node metastasis				
	Yes	62	51	47	0.001
	No	79	71	70	
	Stage				
	<IIB	77	76	76	<0.0001
	≥IIB	74	65	64	
	3rd month response				
	Complete	77	69	67	0.001
	Other	55	44	43	
LRFS	Histology				
	SCC	95	93	93	0.018
	Others	82	81	81	
	3rd month response				
	Complete	95	93	93	0.012
	Other	86	82	82	
LRRFS	3rd month response				
	Complete	95	92	89	<0.0001
	Other	78	71	71	
OS	Lymph node metastasis				
	Yes	61	42	30	0.008
	No	71	57	47	
	Hb level				
	<11	54	37	29	0.002
	≥11	72	58	46	
	3rd month response				
	Complete	71	54	43	0.001
	Other	55	41	38	
DMFS	Hydronephrosis				
	Yes	72	60	60	0.023
	No	82	79	78	
	Lymph node metastasis				
	Yes	70	65	61	0.001
	No	85	81	81	
	Stage				
	<IIB	78	77	77	0.001
	≥IIB	81	76	75	
	3rd month response				
	Complete	84	79	78	0.001
	Other	64	57	57	

Abbreviations: CSS= Cancer-spesific survival, DFS= Disease-free survival, LRFS= Local recurrence-free survival, LRRFS= Locoregional recurrence-free survival, OS= Overall survival, LND= Lymph node dissection, SCC= Squamous cell cancer

Table 4. Multivariate analysis of prognostic factors for cancer-spesific survival, disease-free survival, local recurrence-free survival, locoregional recurrence-free survival and distant metastases-free survival.

Survival	Factor	Hazard Ratio	95% CI	p
CSS	Age (y)			
	≤56	1	1.043- 2.475	0.032
	>56	1.6		
	Lymph node metastasis			
	Yes	1	0.374- 0.926	0.022
	No	0.588		
	Stage			
	<IIB	1	1.071- 2.042	0.017
	≥IIB	1.479		
	3rd month response			
	Complete	1	0.984- 2.032	0.029
	Other	1.41		
DFS	Age (y)			
	≤56	1	1.057-2.478	0.027
	>56	1.618		
	Lymph node metastasis			
	Yes	1	0.313- 0.755	0.001
	No	0.487		
	Stage			
	<IIB	1	1.055-2.013	0.022
	≥IIB	1.457		
	3rd month response			
	Complete	1	1.133 -2.870	0.013
	Other	1.804		
LRFS	3rd month response			
	Complete	1	4.767- 50.519	<0.0001
	Other	15.519		
LRRFS	3rd month response			
	Complete	1	3.041- 17.551	<0.0001
	Other	7.306		
DMFS	Lymph node metastasis			
	Yes	1	0.298-0.827	0.007
	No	0.496		
	3rd month response			
	Complete	1	1.203 -3.554	0.009
	Other	2.068		

Abbreviations: CI= Confidence interval, CSS= Cancer-spesific survival, DFS= Disease-free survival, LRFS= Local recurrence-free survival, LRRFS= Locoregional recurrence-free survival, DMFS= Distant metastases-free survival

was observed as dysuria in 8 patients, hematuria in 3 patients, vesicovaginal fistula in 4 patients and urinary incontinence in 5 patients. Late GIS toxicity was observed as rectal bleeding in 21 (6%) patients, rectovaginal fistula in 4 (1%) patients, intestinal obstruction in 1 (0.3%) patient, and intestinal perforation in 1 (0.3%) patient. The patient who developed bowel perforation died due to this complication.

DISCUSSION

Concomittant CRT is the standart approach in locally advanced cervical carcinoma.[21,22] With concurrent CRT, 10% increase at OS and 13% increase at progression free survival (PFS) have been shown with a risk of increasing grade 3-4 toxicity at the same time.[21] In a recent metaanalysis of randomized trials, Datta et al. demonstrated that concomittant chemotherapy improved the CR rates by a factor of 10.2%, locoregional control rates by 8.4% and OS rates by 7.5%.[23] In the phase III

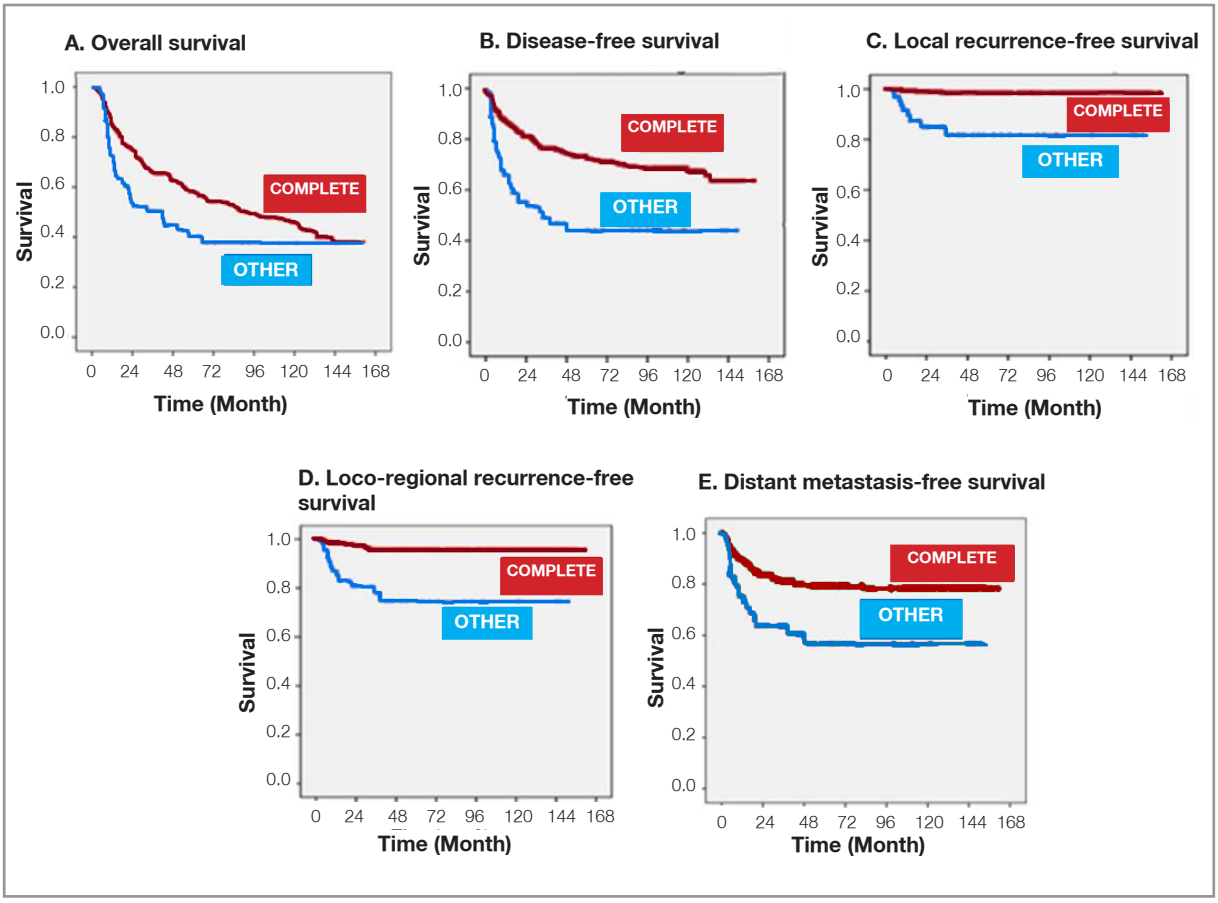

Figure 1. Kaplan-Meier curves of overall survival **(A)**, disease-free survival **(B)**, local recurrence-free survival **(C)**, locoreginal recurrence-free survival **(D)** and distant metastases-free survival **(E)** according to 3rd month treatment response

Gynecologic Oncology Group (GOG) 120 study, the 2-, 5-, and 10-year PFS rates in patients with stage IIB-IVA disease who received concurrent cisplatin-based CRT were 63%, 58% and 46%, respectively.[24] In our study, the corresponding DFS rates for 2-, 5-, and 10-years were found as 73%, 66% and 64% which seems to be quite higher than GOG 120 study. However a more recent study by Dueraz-Gonzalez et al., the 2- and 5-year PFS rates in patients with stage IIB-IVA disease were reported as 70% and 60%, respectively, which is very similar to our study.[25]

In our study, local and locoregional failure rates were found to be 6.6% and 8.3%, respectively. These figures were reported to be around 18% in RTOG 90-01 and 21-22% in GOG 120 studies.[8,24] The median EBRT dose in our study was 50.4 Gy and patients with more than 2 cm LNs were referred for LND. Patients with having either stage IIIB disease and/or involved LNs were also treated with additional 10-15 Gy EBRT dose. The total EQD2 dose in our study was ≥85 Gy which is higher than the EQD2 doses of RTOG and GOG trials in which the total EQD2 doses were around 85 Gy and 81 Gy, respectively. We think that high doses to both HRCTV and distal parametrium and LNs containing metastasis in addition to LND in patients with bulky LN metastasis led us to achieve these high locoregional control rates.

The most significant prognostic factor in our study for all oncological end points was the presence of complete clinical disappearance of tumor at the 3rd month follow up visit. Cancer mortality rate was increased up to 40% in patients without CR at three months. There was an increase of 1.8 times in any recurrence risk, 15 times in local progression risk, 7.3 times in locoregional progression risk and 2 times in distant metastasis risk when there

was no CR after concurrent CRT. In a similar study by Grisby et al, 5-year CSS was reported to be around 80% in patients with functional CR detected with PET/CT and it was 32% when there was no functional CR.[26] Similar results were shown in other studies.[27,28] However in a recent retrospective study by Kim et al., around 60% of patients with less than 2 cm residual disease after CRT showed spontaneous regression without any salvage treatment.[29] Close surveillance can be performed in a subgroup of patients with minor residual disease after CRT but prospective trials are needed to determine which patients can be left without salvage surgery. Until that time it is possible to say that post-treatment clinical and functional response rate is the most important prognostic factor in locally advanced cervical cancer.

The age was another prognostic factor in multivariate analysis determining the CSS and DFS in our study besides the other well known prognostic factors as LN metastasis, stage of the disease and low Hb level. The prognostic efficacy of age in locally advanced cervical cancer is controversial. According to some reports, age is not a prognostic factor in cervical cancer.[30] Other reports on the other hand demonstrated worse survival in women younger than 35-40 years of age.[31] In a study by Mittchell et al. on the other hand tumor recurrence and death from cancer were more common in the elderly patients.[32] The median age in our study was 56 years and we found that patients older than 56 years showed 1.6 times higher risk of disease recurrence and 1.6 times higher risk of cancer death when compared to the younger counterparts. When we looked at our data we found that there were no significant differences in terms of prognostic or treatment related factors between the 2 age groups, only patients younger than 56 years had significantly higher LN metastasis. Though having less lymphatic metastasis, patients older than 56 years showed worse prognosis and we do not know the reason.

Another prognostic factor for LRFS was histopathological subtype other than SCC. In our study SCC histology was found as good prognostic factor for LRFS. The median LRFS in patients with SCC was 41.5 months and it was 26 months in patients other than SCC histology. In a study by Rose et al., adeno- and adenosquamous carcinomas of the cervix were associated with worse OS when treated with RT alone but with similar PFS and OS compared to SCCs of the cervix when treated with cisplatin-based CRT.[33] However in another study by Yokoi et al., patients with adeno- and adenosquamous cancer of the cervix exhibited significantly shorter OS and PFS than the patients with SCC of the cervix.[34] There was only LRFS disadvantage of histology other than SCC in our study without any detrimental effect on the other oncological outcomes.

The majority of our patients were having either stage IIB or IIIB disease. Eighty percent of our patients experienced CR 3 months after concurrent CRT. With a median follow up of 68 months, the LRRFS was 89% at 5 years. However the corresponding DMFS rate was 76%. In a retrospective study by Jelavic TB et al., patients treated with concurrent CRT and a consolidation with four cycles of the same drug combination as an adjuvant, showed 86.4% DMFS after a median follow-up of 96 months.[35] In another study by GOG, Southwest Oncology Group (SWOG) and RTOG, Peters et al. showed highly significant PFS and OS rates with adddition of concomitant and consolidation chemotherapy in patients with high risk features after radical hysterectomy.[21]

The weakest part of our study is its retrospective nature. We cannot exclude potencial sources of biases in this aspect. Moreover, the treatment strategies are heterogenous regarding the use of neoadjuvant chemotherapy, concurrent chemotherapy scheme and RT technique etc. However the majority of our patients were treated with standart approach as having concomittant weekly basis CRT with standard external and BRT doses. In addition all patients were followed up obeying strict procedures as thorough gynecological examination, MRI and/or PET/CT imaging at certain times after treatment.

In conclusion, though retrospective, our study confirms that the response to treatment is the major prognostic factor in locally advanced cervical cancer and the majority of patients show CR after concurrent CRT. The LRRFS in these patients seems quite satisfactory however distant metastases deteriorate the oncologic outcomes. Consolidation

chemotherapy may be an option to reduce the rate of distant metastases in high risk patients. Hovewer well designed phase III studies are needed in this regard.

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