original article

Five-year outcome of concurrent radiotherapy and chemotherapy in Saudi women with locally advanced cervical cancer: single-institution experience

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BACKGROUND AND OBJECTIVES: We aimed to evaluate long-term treatment outcomes and toxicity profile of combined radiotherapy and chemotherapy in Saudi women with locally advanced cervical cancer.

DESIGN AND SETTINGS: Retrospective study in a tertiary care cancer center in Riyadh, Saudi Arabia.

METHODS AND MATERIALS: The medical records of patients with histopathologically proven, locally advanced cervical cancer were analyzed. These patients received three-dimensional conformal radiotherapy with concurrent chemotherapy followed by high dose rate brachytherapy in our center between July 2007 and April 2012. The data regarding the safety profile, response rates, occurrence of locoregional or distant failure, disease-free survival, and overall survival rates were recorded.

RESULTS: The median follow-up period was 60 months (range, 8-66) for 74 patients. The median age of study population was 52.3 years (32-78), and the stage IIB was the predominant stage (49 patients [66.2%]). A total of 45 patients (60.9%) had radiologic-positive pelvic ± para-aortic lymphadenopathy. The 5-year locoregional and distant control rates were 84.3% and 78.5%, respectively. The 5-year disease-free and overall survival rates were 75.7% and 64.5%, respectively. Stage, nodal status, and hemoglobin levels were found to be important prognostic factors for locoregional and distant control. Acute grade 3 hematological and nonhematological toxicities were seen in 4 (5.4%) and 4 (5.4%) patients. Late toxicities were mild, and only 1 (1.4%) patient presented with subacute intestinal obstruction.

CONCLUSION: Concurrent chemoradiation in Saudi women with locally advanced cervical cancer showed better locoregional and distant control and survival rates with minimal toxicity.

Cervical cancer ranks as the 11th most frequent cancer among women in Saudi Arabia, and the 8th most frequent cancer among women in the age group of 15 to -44 years, and every year 152 new cases are diagnosed, of whom 55 (36.1%) die from the disease.[1] Because of inadequate cytological screening program and poor acceptance by women population, the majority of women are diagnosed at locally advanced stages—International Federation of Gynecologists and Obstetrics (FIGO) stage IIB-IVA—for which surgery is inadequate due to parametrial invasion.[2] The standard treatment for locally advanced cervical cancer is prescribed as combined chemotherapy and pelvic irradiation, based on the results of 5 Western and North American randomized trials showing survival benefit by 10% to 15% and local and distant recurrence reduction rates by 30% to 40%.[3-5] However, disease-free survival (DFS) and overall survival (OS) benefit of combined chemotherapy and pelvic irradiation in Saudi women with locally advanced cervical cancer is not well known. El-Senoussi, et al have reported 5-year DFS and OS rates of 68.3% and 57.9%, respectively, in 164 Saudi women with FIGO stage I and II cervical cancer.[6] However, this study incorporated conventional EBRT

followed by low dose rate brachytherapy techniques. However, over the last decade the advent of novel radiation therapy techniques (three-imensional conformal radiation therapy [3DCRT] and intensity modulated radiation therapy [IMRT]) have shown improvements in locoregional control and minimal toxicity.

We aimed to evaluate the efficacy, toxicity, and treatment outcomes of 3DCRT pelvic irradiation with chemotherapy followed by high dose rate brachytherapy in Saudi women with locally advanced cervical cancer and also to evaluate the prognostic factors affecting locoregional and distant control.

METHODS AND MATERIALS

Eligibility

After getting approval from institutional Review Committee, the medical records of patients with locally advanced cervical cancers were looked for demographic, symptomatology, tumor characteristics, radiologic imaging, pathologic examination, radiation therapy techniques, concurrent chemotherapy regimen, acute and chronic side effects, and response rates. Patients with locally advanced cervical cancer between July 2007 and May 2012 were studied when they met the following eligibility criteria:

(1) histologically proven squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma of cervix uteri; (2) clinical and radiologic FIGO stage IIB-IVA with no other evidence for distant metastasis outside the pelvis; (3) Eastern Co-operative Oncology Group performance status 0 to 2; and (4) patients who received radical concurrent chemoradiation. Patients with a previous history of hysterectomy, retroperitoneal surgery, abdominal or pelvic radiotherapy, prior chemotherapy, and pregnancy were excluded.

Treatment Protocol

External beam irradiation

All patients were scanned for simulation on a CT simulator from epigastrium to mid thighs, and 3DCRT planning was performed. After data acquisition, the gross tumor volume (GTV; clinical target volume [CTV-1] (GTV+uterus+1 cm margins+common, internal, and external iliac lymph nodes±para-aortic nodes), planning target volume (PTV-1; CTV-1 + 0.5 to 1 cm margins), CTV-2 (parametrium + 1 cm margin with 4 cm midline shielding), PTV-2 (CTV+ 0.5 cm margins), and organs at risks (kidneys, small bowel, bladder, rectum, and femoral heads) were delineated. Four equally spaced, coplanar 3DCRT field plans for pelvis and anteroposterior and posteroanterior field for para-aortic regions were generated. The prescribed radiation doses were 45 to 50.4 Gy/25 to 28 fractions to PTV-1 and 54 to 59.4Gy/30 to 33 fractions to PTV-2, 5 days per week, and up to 7% variation was considered acceptable. During planning, the mean dose to the rectum was constrained to <50 Gy, and the total doses to the small bowel, kidneys and bladder were constrained to <45 Gy, <20 Gy, <60 Gy, respectively (**Figures 1 and 2**).

Concurrent chemotherapy

All patients received weekly cisplatin 40 mg/m^2 before the administration of radiotherapy for 6 doses. During concurrent chemoradiation (CCRT), the doses modifications were done on weekly basis. If the WBC count was below 2000/mm^3 or the platelet count was below 50 000/mm^3, all chemotherapy for that week was omitted. If the white blood cell count was below 1000/mm^3 or the platelet count was below 25 000/mm^3, CCRT was withheld until the white blood cell count and the platelet count recovered to 1000/mm^3 or greater and 25 000/mm^3 or greater, respectively. If the serum creatinine level was above 1.8 mg/dL, the cisplatin was withheld. Patients were deemed unsuitable for further chemotherapy if the delay to resume treatment was longer than 2 weeks.

High dose rate brachytherapy

Fletcher-Suit tandem and ovoids afterloading applicators were used for high dose rate (HDR)-brachytherapy with iridium-192 sources once a week under conscious sedation after 45 Gy of external beam irradiation therapy (EBRT). A dose of 7 Gy per fraction using 4-6 insertions to point A with a total dose of 21 Gy was delivered, based on the dose limit derived from the treatment plan for the rectum and bladder. The dose constraints were 75 Gy and 80 Gy for the rectum and bladder, respectively (**Figure 2**).

Toxicity scoring

The National Cancer Institute Common Toxicity Criteria version 2.0 were used to score acute radiation and chemotherapy toxicity (<90 days from the start of radiation therapy). During CCRT, weekly weight, performance status, pelvic examination findings, hematologic, and blood chemistry determinations were also recorded.

The Radiation Therapy Oncology Group Late Radiation Morbidity Scoring Criteria were used to score radiation toxicity persisting beyond 90 days from the completion of radiotherapy. After completion of the

CCRT, patients were seen every 3 months for the first 2 years, and every 6 months thereafter at radiation oncology and gynecology oncology clinics. The response evaluation consisted of a physical and pelvic examination; a Pap smear; hematology, hepatic, renal function tests; computed tomography (CT) chest and abdomen; and pelvic magnetic resonance imaging (MRI) every 6 months for the first 2 years.

Statistical analysis

The primary endpoints were toxicity, locoregional and systemic control, and DFS and OS rates. DFS was defined as the duration between the completion of CCRT and the date of documented disease recurrence, death resulting from the cancer, and/or last follow-up visit (censored). OS was defined as the duration between the completion of CCRT and the date of patient death or last follow-up visit (censored). The probabilities of local, para-aortic, and distant control, and DFS and OS rates were determined with the Kaplan-Meier method. The comparisons for various endpoints were performed using the log-rank test. The Student unpaired *t* test was used to determine the significance of the difference between the 2 groups. A *P* value of .05 was considered statistically significant. Cox regression model was used to evaluate the effect of the potential prognostic factors on locoregiona controll, distant control, and DFS. Bonferroni correction was applied to overcome multiplicity problem. Statistical analyses were performed using the computer program SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA).

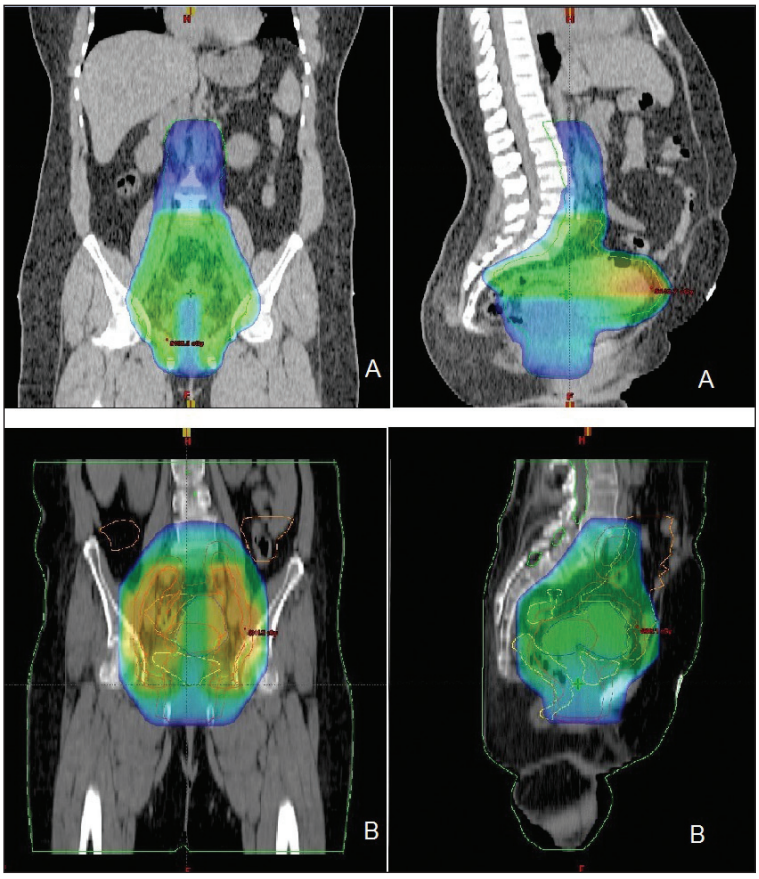

Figure 1. Initial phase radiotherapy (A) extended field and (B) pelvic field three-dimensional conformal radiation therapy (3DCRT) plans showing 45 Gy to PTV-1 in coronal and sagittal views.

RESULTS

Characteristics of the patients and treatment compliance and toxicity profile

Common presenting symptoms were vaginal bleeding in 45 patients (60.8%), followed by vaginal discharge in 16 patients (21.6%), and low backache in 13 patients (17.6%). The median duration of symptoms was 9 months (3-15). The median age of cohort was 52.3 years (32-78). FIGO stage IIB was the predominant stage in 49 patients (66.2%) followed by IIIA in 12 patients (16.2%). Twenty-nine patients (39.1%) had negative pelvic nodal at the time of CCRT. The common site of gross pelvic lymph nodes were as follows: iliac in 21 patients (28.4%), common iliac in 16 patients (21.6%), and gross para-aortic in 8 patients (10.8%). Thirty-six patients (48.7%) were treated with pelvic irradiation, and pelvic and para-aortic irradiation was used in 38 patients (51.3%) (**Table 1**).

The median follow-up time was 5 years (range, 3-5.5 years). Among all 74 patients who received CCRT, the treatment protocol completion rate was 90 % (95% confidence interval [CI], 85-100). The weekly concurrent cycles of cisplatin in both treatment groups were completed in all 74 (100%) patients with no interruption. The median duration of radiation therapy in both groups was 55.5 days (48-58).

The overall grade 3 or 4 acute hematological and nonhematological toxicities were seen in 8 patients (10.8%). Grade 3 or 4 acute gastrointestinal toxicity was seen in 4 patients (5.4%) (**Table 2**).

During the follow-up time of 5 years in the EF-CCRT group, 1 patient (1.4%) experienced sub-acute intestinal obstruction. No patient in either group underwent surgery for the radiation-induced damage or died because of the treatment-related side effects.

Response rates, locoregional and distant control, and survival rates

At the time of the last follow-up, 13 patients (17.6%)

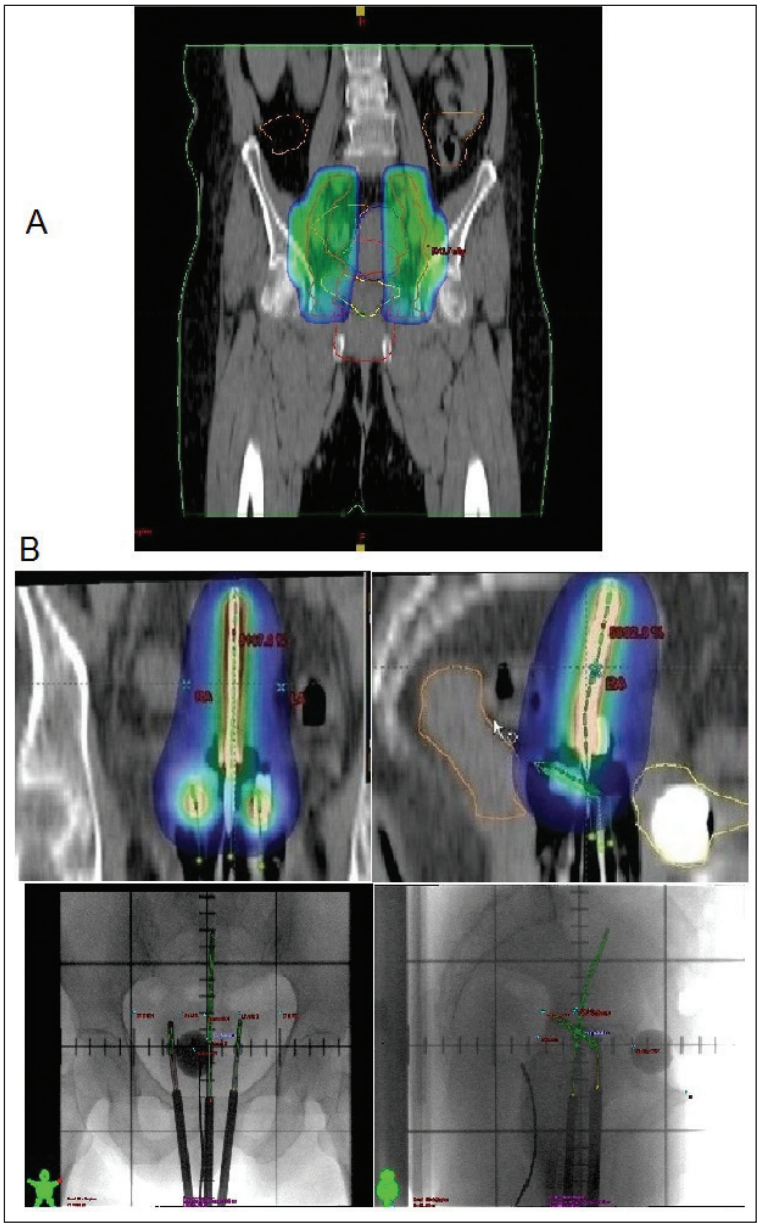

Figure 2. (A) Parametrial boost of 9 Gy with midline shielding followed by high dose rate brachytherapy 21 Gy in 3 sessions.

Table 1. Patient characteristics.

Variables	CCRT (n=74)
Age	52.3 y (32-78)
Comorbidities	
Hypertension	
Yes	33 (44.6%)
No	41 (55.4%)
Diabetes	
Yes	30 (40.6%)
No	44 (59.4%)
Histopathology	
Squamous cell carcinoma	67 (90.5%)
Adenocarcinoma	5 (6.7%)
Adenosquamous cell carcinoma	2 (2.7%)
FIGO staging	
IIB	49 (66.2%)
IIIA	12 (16.2%)
IIIB	7 (9.5%)
IVA	6 (8.1%)
Radiological primary tumor size	
<5 cm	27 (36.5%)
>5 cm	47 (63.5%)
MRI-based nodal involvement	
Negative	29 (39.1%)
Iliac	21 (28.4%)
Common Iliac	16 (21.6%)
Para-aortic	8 (10.8%)
Pretreatment hemoglobin	
>10 gm/dL	69 (93.3%)
<10 gm/dL	5 (6.7%)
Treatment	
EBRT:	
Whole pelvis	45 Gy (42-50.4)
Para-aortic	45 Gy (45-50.4)
Parametrial boost	9 Gy (0-9)
HDR-BT:	
Dose/Fraction	7 Gy/fraction
Total dose/fraction	21 Gy/3
Point A BED	86.4 Gy (80.5-102.7)
ICRU 38 rectal point BED	85 Gy (80.5-100)
ICRU 38 bladder point BED	86 Gy (80.5-102)
Concurrent weekly cisplatin cycle:	
Dose/wk	30 mg/m^2
Mean cycles	5 (4-7)

FIGO: International Federation of Gynecologists and Obstetrics, CCRT: concurrent chemoradiation, MRI: magnetic resonance imaging, EBRT: external beam radiation therapy, BED: biologic effective dose, ICRU: international commission of radiation units, HDR-BT: high dose rate brachytherapy.

had locoregional recurrences (**Figure 3A**). Among those, 6 patients (46.1%) had pelvic recurrences, 5 patients (38.5%) had para-aortic recurrences, and 2 patients (15.4%) had isolated vaginal recurrences that were treated with surgery. Eight patients (72.7%) with pelvic/para-aortic nodal recurrences were treated with salvage chemotherapy and 2 patients (18.1%) received additional para-aortic irradiation. Salvage chemotherapy was generally poorly tolerated.

Distant failures were seen in 9 patients (12.1%). The common sites of distant failure were as follows: lungs in 4 patients (44.6%), mediastinal in 3 patients (33.3%), supraclavicular nodes in 1 patient (11.1%), and bone in 1 patient (11.1%) (**Figure 3B**). The median time to initial locoregional and distant failure was 20 months (range 19–24 months). Combined distant and locoregional failures were observed in 4 patients (18.2%). All

Table 2. Acute and late toxicity profile.

Toxicity	CCRT (n=74)	
Acute:	G3	G4
Hematologic		
Neutropenia	4 (5.4%)	0
Thrombocytopenia	0	0
Anemia	0	0
Nonhematologic		
Nausea/Vomiting	4 (5.4%)	0
Diarrhea	0	0
Cystitis	0	0
Deranged renal functions	0	0
Deranged liver functions	0	0
Late:		
Chronic cystitis		0
Intestinal obstruction	1 (1.35%)	
Proctitis		0
Neuropathy/Plexopathy		
Hearing loss		0
Renal	2 (2.7%)	

CCRT: Concurrent chemoradiation, G: grade.

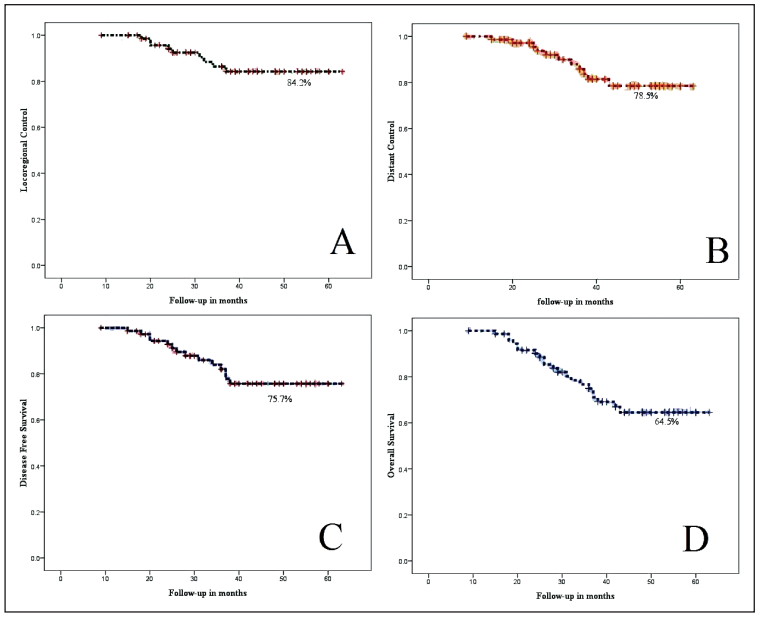

Figure 3. Five-year (A) locoregional control, (B) distant control, (C) disease-free survival, and (D) overall survival rates in concurrent chemoradiation.

Table 3. Cox regression model analysis of variables on locoregional, distant control, and disease-free survival rates.

Overall Survival *P* value HR (95% CI)	Disease-Free Survival *P* value HR (95% CI)	Distant Metastasis Control *P* value HR (95% CI)	Locoregional Control *P* value HR (95% CI)	Variable
0.80 0.80 (0.77-0.98)	0.70 0.50 (0.10-2.41)	0.60 1.10 (0.89-2.00)	0.80 1.80 (0.79-2.10)	Age (<50 y vs > 50 y)
0.04 2.20 (1.60-4.11)	1.0 1.80 (0.79-2.10)	0.90 1.80 (0.79-2.10)	0.90 0.88 (0.67-0.97)	Comorbids (Yes vs No)
0.01 2.56 (1.70-6.50)	0.01 3.95 (1.91-10.35)	0.02 4.65 (1.81-9.65)	0.001 7.21 (3.22-16.30)	FIGO stage (<IIB vs >IIB)
0.03 3.0 (2.40-7.25)	0.01 4.01 (2.21-11.59)	0.03 3.66 (1.75-9.36)	0.001 6.34 (4.52-11.34)	N stage (N0 vs N1)
0.50 1.10 (0.89-2.00)	0.40 0.78 (0.23-2.38)	0.50 1.10 (0.89-2.00)	0.05 1.10 (0.96-1.20)	Hemoglobin level (<10 gm/dL vs >10 gm/dL)
0.40 1.21 (1.10-2.10)	0.70 1.21 (1.10-2.10)	0.60 1.10 (0.89-2.00)	0.40 1.21 (1.10-2.10)	Cell type (squamous vs nonsquamous)
0.50 1.10 (0.98-1.20)	0.60 1.10 (0.89-2.00)	0.90 0.88 (0.67-0.97)	0.03 3.21 (2.45-7.85)	Treatment duration (<54 vs >54 d)

FIGO: International Federation of Gynecologists and Obstetrics, OR: odds ratio, CI: confidence intervals, N: nodal status.

distant failures were treated with salvage chemotherapy and radiotherapy for bone and supraclavicular nodes. At the time of analysis, 51 patients were found without disease with overall DFS of 75.7%. Forty-seven patients were alive at the time of analysis with OS of 64.5% (**Figure 3C and D**).

Cox regression model analysis showed that nodal status, FIGO stage, and CCRT duration were important prognostic factors for locoregional and distant control (**Figure 4 and Table 3**).

DISCUSSION

Pelvic irradiation with concurrent chemotherapy is considered the standard treatment by many North

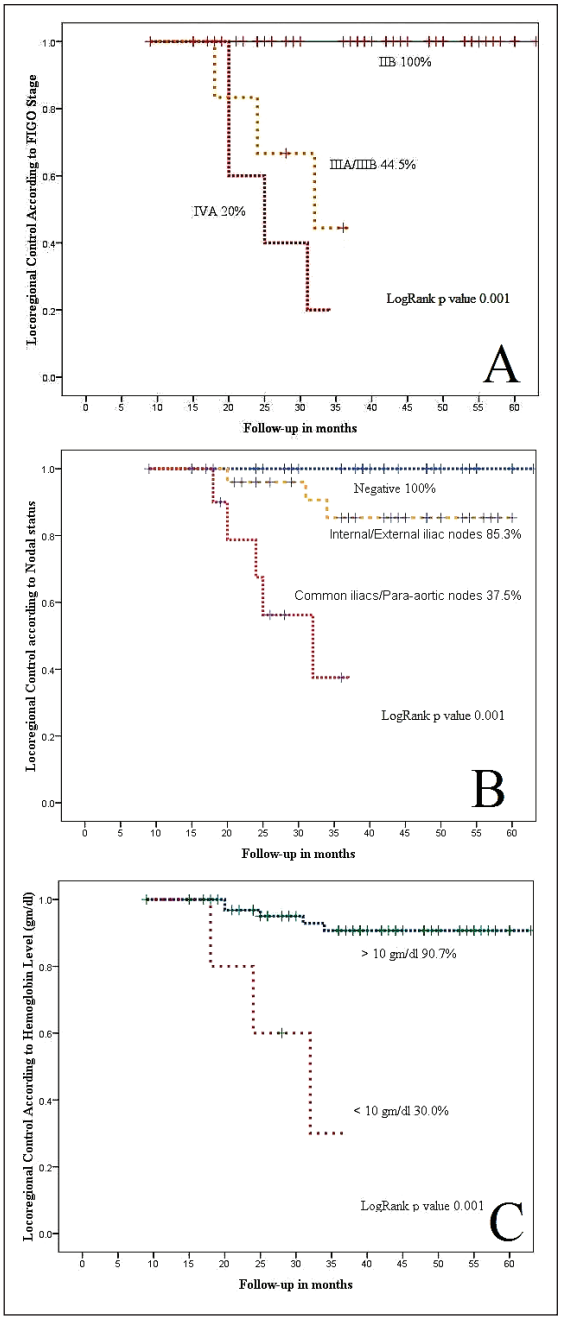

Figure 4. Five-year locoregional control according to (A) FIGO stage, (B) nodal status, and (C) pretreatment hemoglobin levels.

American and European teams for the treatment of locally advanced cervical cancer, which has resulted in survival gain of 10% to 20%.[7] The 10-year results of a Radiation Therapy Oncology Group (RTOG-97-20) trial, which compared pelvic irradiation with para-aortic and pelvic irradiation, have shown an improvement in the survival gain of 11% in the prophylactic para-aortic and pelvic irradiation group, but no difference in locoregional control.[8,9] A subsequent another RTOG trial (RTOG 90-01) compared prophylactic extended-field radiotherapy versus pelvic irradiation with chemotherapy in locally advanced cervical cancer patients. This showed 5-year OS rates for patients treated with pelvic irradiation and concurrent chemotherapy, which was significantly greater than for patients treated with the extended-field radiation alone (67% vs41% at 8 years), and pelvic irradiation with concurrent chemotherapy resulted in a 51% reduction in the risk of recurrence and a 52% reduction in the risk of death.[10]

To the best of our knowledge, our single institutional study is the first one to report the 5-year treatment outcomes of 3DCRT and HDR brachytherapy–based concurrent chemoradiation in FIGO IIB-IVA locally advanced cervical cancer in Saudi Arabia. The 5-year locoregional control, distant control, and DFS and OS rates in our study were 84.3%, 78.5%, 75.7%, and 64.5%, respectively, which are similar or better in some outcomes than the previously reported trials.[11,12] The course of treatment was well tolerated in our patients, and hematological and nonhematological toxicities were minimal and better than those reported in other trials of using CCRT. The possible explanation for lower toxicity profile and better outcomes in our study is as follows: (a) majority of our patients had FIGO Stage IIB, pelvic nodes negative, (b) surgical staging for para-aortic lymph nodes was not carried out as reported in other trials that enhances the gastrointestinal toxicity, instead, (c) optional FDG/PET was performed, (d) moderate doses of weekly cisplatin, and (e) use of better radiation techniques (3DCRT and HDR brachytherapy). We used radiologic (CT/MRI) staging along with FIGO staging, as the tumor size and lymph node involvement are also important prognostic factors that influence the locoregional control and survival as seen in our study and mentioned by other related studies.[13,14] The reason for the relatively lower OS rate is that the majority of our cohort was hypertensive (44.6%) and diabetic (59.4%), which have been known as important prognostic factors for OS in cervical cancer.[15]

Further, our results have shown that in addition to the FIGO stage, nodal status and treatment duration are also significant prognostic factors for locoregional control; however prognostic factors for distant control and DFS in our study were FIGO stage and nodal status. Pretreatment hemoglobin <10 gm/dL has been considered an important prognostic factor for OS,[16] but we could not see its impact on locoregional controland OS in our patients. The total duration of con-

comitant chemoradiation has been suggested to be restricted within 56 days to increase locoregional control and OS;[17] however, the majority (90%) of our patients finished treatment within 55 days, which reflects the better locoregional control and DFS in our patients.

The strengths of our study were as follwos: reasonable sample size of Saudi women with locally advanced cervical cancer, use of modern radiation therapy techniques (3DCRT and HDR brachytherapy), and longer follow-up period. The limitations of our study were as follows: retrospective data and the majority of cohort was with comorbidities and gross pelvic lymphadenopathy, which warrants the need of diabetic and hypertension awareness campaigns along with routine cytological screening in Saudi Arabia.

In conclusion, the combined chemotherapy and radiation therapy in Saudi women with locally advanced cervical cancer results into better locoregional control, distant control, and DFS, which is consistent with international data. However, in future, trials incorporating IMRT in locally advanced cervical shall be done to see additional benefit of combined chemoradiation.

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