Concurrent Chemoradiotherapy for Locally Advanced Cervical Cancer: Outcome Analysis – RMS Experience

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ABSTRACT

Objective: This study aimed to evaluate clinical outcomes concerning treatment response, treatment toxicity, local control, and survival rates among patients with locally advanced cervical cancer (LACC) who underwent concurrent chemoradiotherapy (CCRT).

Methods: A retrospective analysis was conducted on 63 LACC patients who underwent CCRT with cisplatin (40 mg/m^2) and external-beam radiotherapy (EBRT), followed by brachytherapy (BT), between January 2013 and May 2018. Overall survival (OS), distant metastasis-free survival (DMFS), and locoregional failure-free survival (LRFFS) were estimated using the Kaplan-Meier method, taking into account age and lymph node (LN) involvement. The Fisher exact test was employed to compare treatment responses (RECIST criteria) between groups with positive and negative LN involvement. Treatment-related toxicities were graded according to the RTOG and CTCAE criteria.

Results: The mean age at diagnosis was 52.1 years, and the mean patient follow-up period was 52 months. The five-year rates for OS, DMFS, and LRFFS were 87.3%, 84.1%, and 88.9%, respectively. Complete response (CR) was observed in 50.8% of LACC patients. Treatment response significantly differed between the two groups (positive vs. negative LN involvement) ($p = 0.05$). Patients with negative LN involvement exhibited higher CR than those with positive LN involvement. Grade 3-4 early hematological, gastrointestinal, and genitourinary toxicities occurred in 6.3% of patients, while grade 3–4 late gastrointestinal and genitourinary toxicities were reported in 20.6%. Treatment failure was noted in 17.5% of patients.

Conclusion: Our study demonstrated high OS, DMFS, and LRFFS rates among LACC patients treated with CCRT. Genitourinary toxicities emerged as the most prevalent adverse effects in these patients.

Keywords: Locally advanced cervical cancer, concurrent chemoradiotherapy, treatment toxicity, survival rate.

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Introduction

With an estimated 604,000 new cases and 342,000 deaths in 2020, cervical cancer is the fourth most prevalent cancer among women globally. Around 90% of these new cases and fatalities occurred within low- and middle-income countries (1).

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Across all instances of cervical cancer, the estimated median rate of locally advanced cervical cancer (LACC) reached 37.0% (with a range of 5.6–97.5% and an interquartile range of 25.8–52.1%); these estimates exhibited the lowest values in North America and the highest in Asia (2). The incidence rate of cervical cancer in Jordan was 2.3 cases per 100,000 women in 2019 (3).

Cervical cancer is histologically categorized into three types: squamous cell carcinoma (SCC), adenocarcinoma (AC), and adenosquamous carcinoma (AC/ASC). Among these, SCC accounts for the highest prevalence at 75%, while adenocarcinoma (AC) constitutes 20–25%, and AC/ASC represents a smaller portion (4,5).

In the case of patients diagnosed with LACC, concurrent chemoradiotherapy (CCRT) stands acknowledged as the gold standard of care (6), boasting a 5-year overall survival (OS) rate spanning from 65% to 70% (6, 9). However, within the realm of CCRT-treated cervical cancer patients, treatment failure manifests in 30% to 50% of cases (7). Although CCRT yields the potential to enhance progression-free survival and curtail both local and distant recurrence rates (10), these advantages are juxtaposed with the burden of acute and delayed toxicity (10,11).

Numerous prognostic factors have garnered recognition, encompassing various domains, including patient-related factors like age (6,12), performance status (6), and comorbidities (13); disease-related factors such as stage (6,12), tumor size (6,12), lymph node (LN) metastasis (6,14,15,16), histological type, and differentiation (6,12,17); and treatment-related factors including overall treatment time (18), incomplete response to radiotherapy (16), and radiotherapy dose (17).

This study assessed the clinical outcomes concerning treatment response, toxicity, local control, and survival rates among LACC patients subjected to CCRT.

Methods

Patients and clinical data

This retrospective chart evaluation of patients with LACC who were scheduled to receive definitive concurrent chemoradiotherapy (CCRT) at Royal Medical Services between January 2013 and May 2018. Women aged 18 or older with a confirmed diagnosis of LACC (stages IB2-IVA) through biopsy were eligible to participate in the study . Women who underwent surgical intervention before CCRT and patients with insufficient clinical data were excluded.

Pretreatment evaluation encompassed the following clinical data: patient age, age at diagnosis, stage of cervical cancer, grade, tumor volume, LN involvement and location, histologic type, and radiological findings. Treatment evaluation included the total radiation therapy time, radiation dosage, type of chemotherapy treatment, number of chemotherapy cycles, and treatment-related toxicity.

The International Federation of Gynecology and Obstetrics (FIGO) staging system (19) was employed to categorize patients with cervical cancer. The histologic types were classified as SCC, adenocarcinoma (AC), or a combination of AC and AC/ASC. Tumor staging necessitated a contrast-enhanced CT scan or magnetic resonance imaging of the pelvis, with additional imaging conducted to identify distant metastases as indicated.

Concurrent chemoradiotherapy treatment

All patients underwent a comprehensive treatment regimen involving concurrent radiotherapy and chemotherapy. The radiotherapy regimen comprised 3D-conformal external-beam radiotherapy (EBRT) and brachytherapy (BT), administering a cumulative dose of 80–85 Gy to point A. The chemotherapy protocol included administering cisplatin at 40 mg/m^2 once per week for four to six cycles. Dosages and

fractions of both EBRT and BT were meticulously examined and documented for each individual. The total radiation therapy time was calculated from the commencement of radiation therapy until its culmination.

Treatment toxicity

Treatment toxicity was assessed in accordance with the Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) (20). Chemotherapy-related toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, issued in November 2017 (21). In instances of grade 3 or 4 acute hematologic toxicity, the administration of concurrent chemotherapy was delayed.

Treatment response

Regarding tumor response assessment, the responses were categorized as follows: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), utilizing the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (22). The evaluation of treatment response took place three months following the initiation of concurrent chemoradiotherapy (CCRT) (23).

Survival rate

In terms of survival analysis, the overall survival (OS) duration is calculated from the initial date of CCRT to either the date of death or the latest follow-up. Locoregional failure-free survival (LRFFS) is determined from the initiation of radiotherapy until the occurrence of any locoregional failure (LRF) within the radiation field or until the most recent follow-up date when the patient was still alive and without failure within the radiation field. Distant metastasis-free survival (DMFS) is gauged from the commencement of initial radiotherapy until the manifestation of any evidence of distant metastasis (DM) beyond the radiation field or until the latest follow-up date during which the patient was confirmed alive and without failure outside the radiation field.

Data analysis

The statistical analysis of the data was conducted utilizing the SPSS for Windows version 25 software package (SPSS Inc., Chicago, IL, USA). Clinical data were presented as means and standard deviations for continuous variables, while frequencies and proportions were used for categorical variables. The Fisher exact test assessed differences in treatment response between groups, specifically those with positive and negative lymph node (LN) involvement.

For the analysis of OS, locoregional failure-free survival (LRFFS), and DMFS, the Kaplan-Meier method was applied, categorized by age groups ($\leq$ 50 years vs. > 50 years) and LN involvement (positive vs. negative). The log-rank test was employed to ascertain differences in survival outcomes between these groups. The threshold for statistical significance was set at a P value of ≤ 0.05.

Results

Patients' characteristics and clinical data

A total of 63 patients diagnosed with LACC were included in the study. Their mean age at the time of diagnosis was 52.1 years, ranging from 32 to 80 years. The majority of them were non-smokers. SCC constituted the most prevalent type of LACC (87.3%), followed by the adenocarcinoma (AC) type (11.1%) and the mixed AC/ASC type (1.6%).

According to the FIGO classification system, over 75% of the patients had stage IIB (34.9%) or stage IIIC1 (41.3%). Positive LN involvement was observed in 36 patients (57%). Among those patients, 41.3%

exhibited involvement limited to pelvic LNs, while 15.8% displayed involvement of both pelvic and para-aortic LNs. Most patients (88.9%) had tumor sizes exceeding 40 mm. The average follow-up duration for the patients was 52 months (Table I).

Table I. Characteristics and clinical data of LACC patients (n = 63).

Characteristics	Subgroup	Frequency	Percent
Age, years	≤ 50	21	33.3
	> 50	42	66.7
Smoking status	No	51	81.0
	Yes	12	19.0
Histology	SCC	55	87.3
	AC	7	11.1
	AC/ASC	1	1.6
FIGO stage	IB2	1	1.6
	IIA1	2	3.2
	IIA2	2	3.2
	IIB	22	34.9
	IIIC1	26	41.3
	IIIC2	9	14.2
	IVA	1	1.6
Lymph node status	Negative	27	42.9
	PLN only	26	41.3
	PLN and PALN	10	15.8
Tumor size, mm	≤ 40 mm	7	11.1
	> 40mm	56	88.9

LACC: Locally advanced cervical cancer; SCC: squamous cell carcinoma; AC: adenocarcinoma; ASC: adenosquamous carcinoma; FIGO: International Federation of Gynecology and Obstetrics; PLN: pelvic lymph node; PALN: para-aortic lymph node.

Treatment characteristics

The average treatment duration was 11.07 weeks, ranging from 8 to 15 weeks. The mean external-beam radiation therapy (EBRT) and brachytherapy (BT) doses administered were 49.84 Gy and 22.15 Gy, respectively. One patient was unable to undergo BT due to financial constraints. Patients were administered intravenous infusions of 40 mg/m^2 of cisplatin once weekly as part of chemotherapy, spanning 4 to 6 cycles (mean = 5.17 cycles) (Table II).

Table II. Description of treatment characteristics.

Characteristics	N	Mean	SD	Min	Max
Treatment Duration, weeks	63	11.07	1.75	8.00	15
EBRT dose	63	49.84	2.66	45.00	59.4

BT dose	62	22.15	5.25	12.00	30
Number of chemotherapy cycle	63	5.17	0.42	4	6

EBRT: external-beam radiotherapy; BT: brachytherapy; SD: standard deviation; Min: minimum; Max: maximum

Treatment response

Among the 63 patients who underwent concurrent chemoradiotherapy (CCRT), 32 patients (50.8%) achieved CR, 27 patients (42.9%) achieved PR, 3 patients (4.7%) exhibited SD, and only one patient (1.6%) experienced PD. A notable disparity in treatment response emerged concerning LN status ($p = 0.05$). Most patients with negative LN involvement achieved CR (66.6%), whereas those with positive LN involvement mostly attained PR (52.7%). Notably, one patient with positive lymph node involvement experienced PD, whereas none of the patients lacking lymph node involvement developed PD (Table III).

Table III. Descriptions of treatment response based on lymph node status.

Treatment response	Negative lymph node N (%)	Positive lymph node N (%)	P
PR	8 (29.6)	19 (52.8)	0.05
CR	18 (66.7)	14(38.9)	
SD	1 (3.7)	2 (5.5)	
PD	0 (0)	1 (2.8)	

PR: partial response; CR: complete response; SD: stable disease; PD: progressive disease

Treatment toxicity

Early treatment-related toxicities emerged during or within two months of concurrent chemoradiotherapy (CCRT). Hematological toxicities of grades 1–2 were recorded in 12 patients, characterized by varying degrees of anemia, thrombocytopenia, and/or neutropenia. Two patients encountered grade 3–4 treatment-related toxicity, involving one case of severe anemia (hemoglobin < 6 g/dL) and another instance of thrombocytopenia (platelets $< 30 \times 10^9$/L). These individuals necessitated hospitalization for blood and platelet transfusions. Gastrointestinal toxicities of grades 1–2 were noted in 11 patients, encompassing symptoms such as diarrhea and vomiting. One patient necessitated hospitalization due to acute diarrhea and received parenteral support.

Among the patients, 18 experienced genitourinary toxicities of grades 1–2, presenting symptoms including urinary incontinence, dysuria, urgency, urinary tract infections, and vaginal spasms. A single patient encountered grade 3 urinary toxicity marked by ureterohydronephrosis, requiring hospital admission. Notably, there were no instances of treatment-related fatalities.

Regarding late-onset toxicity, the prevailing concern was genitourinary-related adverse effects affecting 32 patients. Among this group, 28 patients reported experiencing vaginal stenosis and vaginal dryness. Notably, seven of these patients exhibited severity reaching grades III and IV, necessitating surgical interventions. Furthermore, two patients developed grade III and IV cystitis.

Six patients experienced grade III and IV proctitis, indicating a notable severity level. Moreover, one patient diagnosed with stage IVA SCC type of LACC underwent a treatment regimen involving 50.4 Gy/28 fractions of EBRT followed by 25 Gy/5 fractions of brachytherapy (BT). Alarmingly, this patient developed

a rectovaginal fistula eight months following cervical cancer treatment, necessitating surgical intervention (Table IV).

Table IV. Treatment toxicity experienced by patients treated with CCRT (n = 63), according to the Common Terminology Criteria for Adverse Events (CTCAE) and Radiation Therapy Oncology Group (RTOG).

		Toxicity grade			
Toxicity	**Total**	**1**	**2**	**3**	**4**
Early					
Hematological toxicity	14	8	4	1	1
Gastrointestinal toxicity	12	6	5	1	0
Genitourinary toxicity	19	9	9	1	0
Total	45	23	18	3	1
Late					
Gastrointestinal toxicity	7	2	1	3	1
Genitourinary toxicity	32	5	18	6	3
Total	39	7	19	9	4

Types of treatment failure

Treatment failure manifested in 11 (17.5%) patients, with recurrence patterns as follows: 4.8% experienced local recurrence exclusively, 7.9% encountered both local and distant metastases, and 4.8% faced distant metastases exclusively. Among the 11 patients with treatment failure, nine pursued salvage treatment strategies encompassing surgery, chemotherapy, or radiotherapy, while two chose not to undergo salvage therapy. Notably, metastases predominantly affected the lungs, followed by the bone and the brain. Additionally, one patient presented with lung and bone metastases (Table V).

Table V. Descriptions of treatment failure in the study sample (n= 11).

Characteristics		**No of patients (%)**
Type of recurrence	Local only	3 (4.8)
	Local and distant metastasis	5 (7.9)
	Distant metastasis only	3 (4.8)
Site of Distance metastasis		
	Lung	4 (6.3)
	Bone	2 (3.2)
	Brain	2 (3.2)
	Colon	1 (1.6)

Kaplan-Meier survival analysis

The estimated 5-year OS rate, stratified by age, stood at 87.3%. This projection was derived from an estimated mean survival time of 52.14 months, with a median survival of 55 months. In the subgroup of patients aged less than 50 years, the OS rate was notably higher, reaching 90.5%. This subgroup displayed an estimated mean survival period of 55.75 months, with a median survival of 56 months. Conversely, among patients aged over 50 years, the OS rate was slightly lower at 85.7%, corresponding to an estimated mean survival duration of 48.1 months and a median survival of 54 months. Statistical analysis using the

log-rank test revealed a significant disparity between these age-based groups regarding OS (p = 0.021). The study noted cancer-related deaths in three patients and one patient who succumbed to non-cancer-related causes (Figure 1).

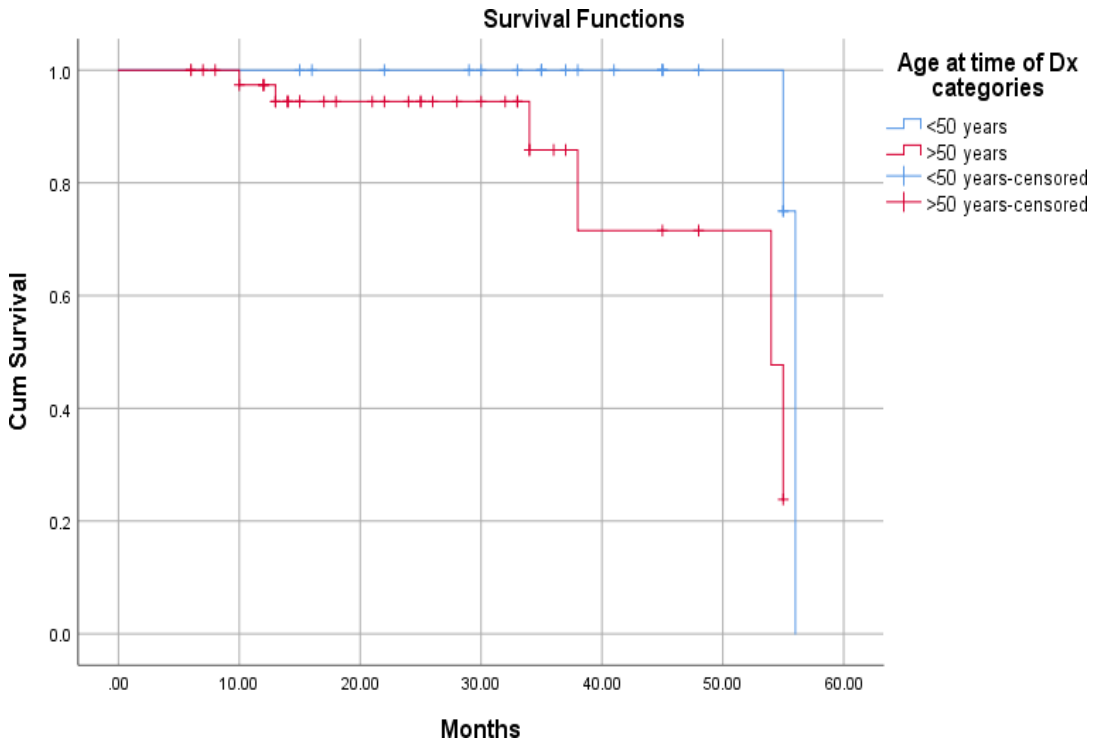

Figure 1. Overall survival based on age groups.

The projected OS rate for patients lacking LN involvement (negative) stood at 96%, with an estimated mean survival period of 55 months. In contrast, patients with positive LN involvement exhibited an OS rate of 81.6%, alongside an estimated mean survival duration of 50 months. Notably, the computation of median survival time was rendered infeasible because the probability of survival for patients without LN involvement exceeded 50% at the longest observation point. Noteworthy statistical divergence was observed between the two groups based on LN involvement, as indicated by the log-rank test (p = 0.032) (Figure 2).

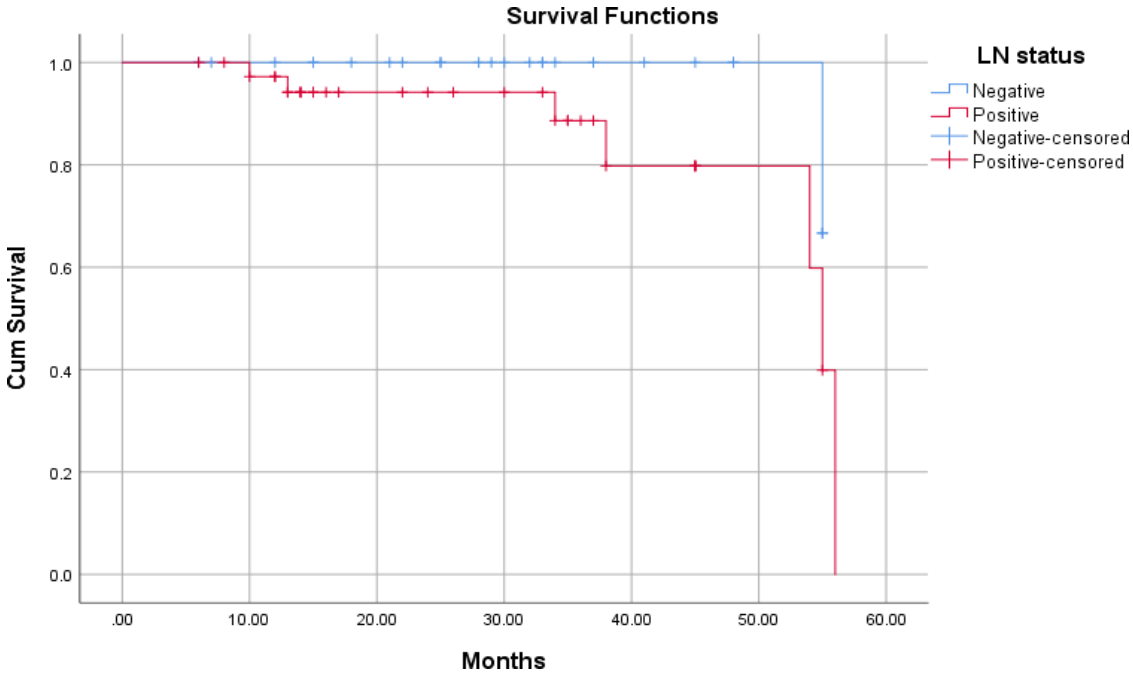

Figure 2. Overall survival based on lymph node status.

The estimated 5-year DMFS rate, categorized by age, reached 84.1%. This projection was derived from an estimated mean DMFS duration of 48.29 months. Within the subset of patients under 50 years, the DMFS rate stood at 85.7%, accompanied by an estimated mean DMFS period of 50.63 months. Similarly, patients aged over 50 years exhibited a DMFS rate of 83.3%, associated with an estimated mean DMFS duration of 45.91 months. Notably, no statistically significant differences were observed between these age-based groups concerning DMFS, as determined by the log-rank test ($p = 0.385$). It is important to note that the computation of median survival time was precluded, as the probability of survival for both groups exceeded 50% at the longest follow-up point (Figure 3).

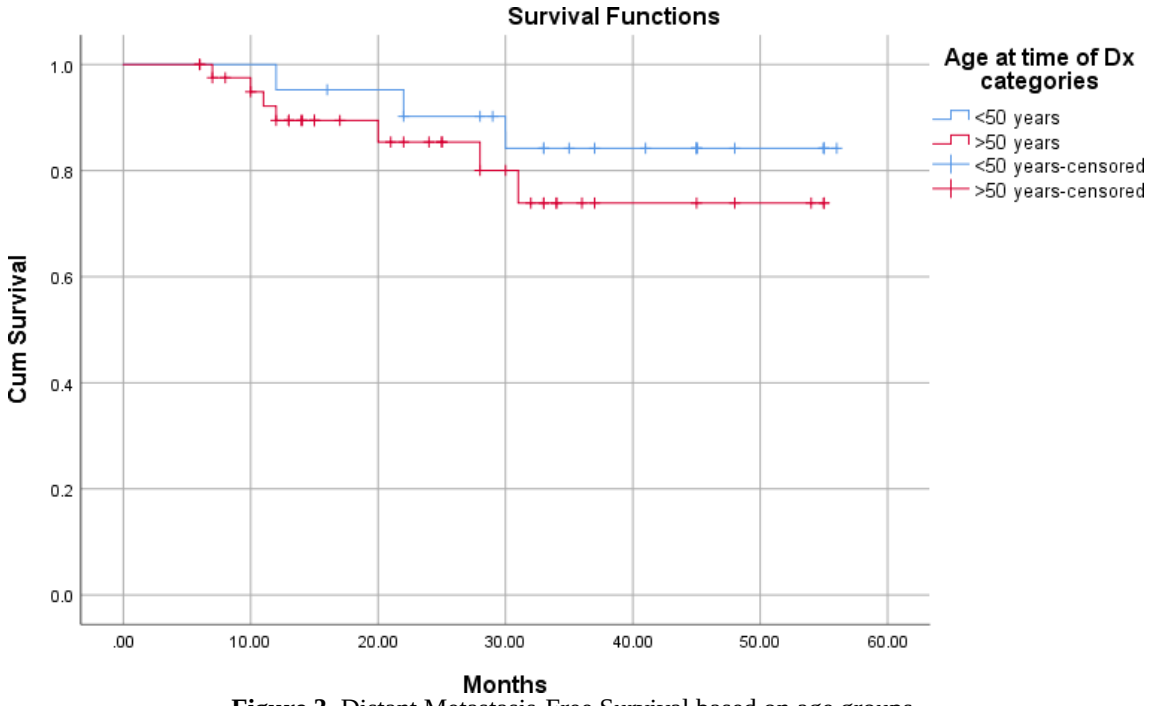

Figure 3. Distant Metastasis-Free Survival based on age groups.

The projected 5-year DMFS rate for patients without LN involvement was 88%, associated with an estimated mean DMFS period of 49.21 months. Conversely, for patients with LN involvement, the DMFS rate was 81.6%, linked to an estimated mean DMFS duration of 46.54 months. Notably, the log-rank test identified a statistically significant disparity between the two groups predicated on LN involvement (p = 0.015). The computation of median survival time was precluded because the probability of survival for both groups exceeded 50% at the longest follow-up juncture (Figure 4).

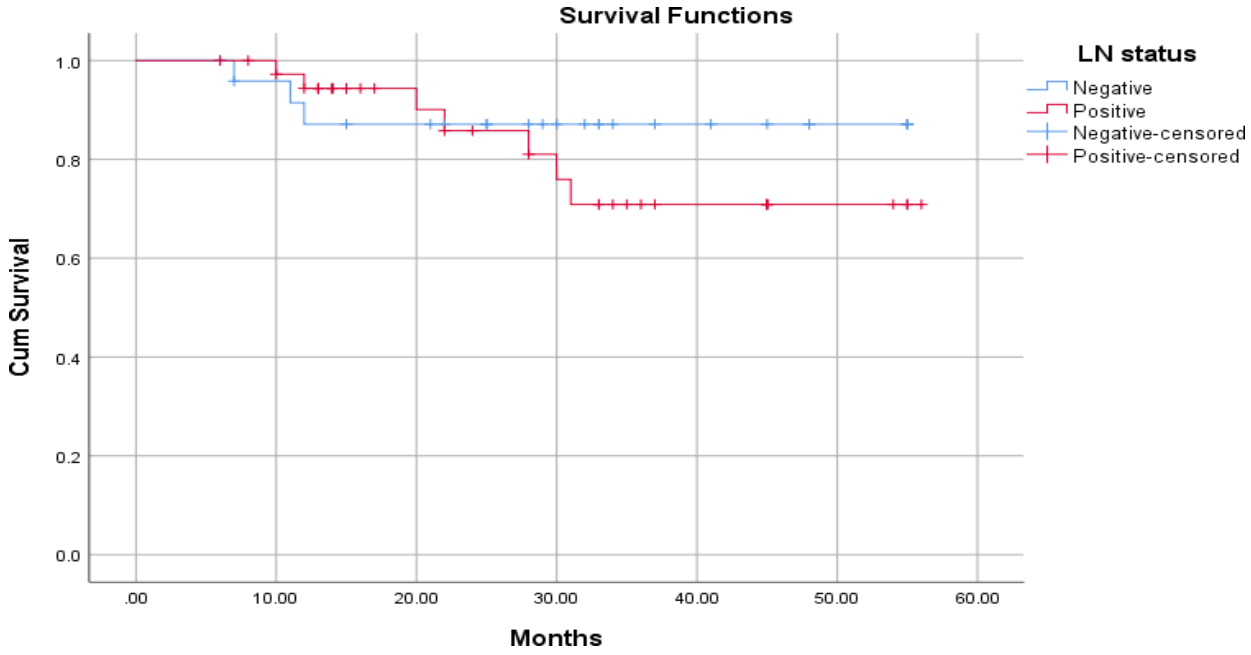

Figure 4. Distant Metastasis-Free Survival based on lymph node status.

The estimated 5-year locoregional failure-free survival (LRFFS) rate, stratified by age, reached 88.9%. This projection was derived from an estimated mean LRFFS duration of 45.06 months. Within the subgroup of patients aged less than 50 years, the LRFFS rate was notably higher at 90.1%, with an estimated mean LRFFS period of 47.68 months. In contrast, among patients over 50 years, the LRFFS rate was 88.1%, associated with an estimated mean LRFFS duration of 41.09 months. However, statistical analysis using the log-rank test did not reveal significant differences between these age-based groups regarding LRFFS (p = 0.154). Importantly, the computation of median LRFFS time was unfeasible since both groups' survival probability exceeded 50% at the longest follow-up interval (Figure 5).

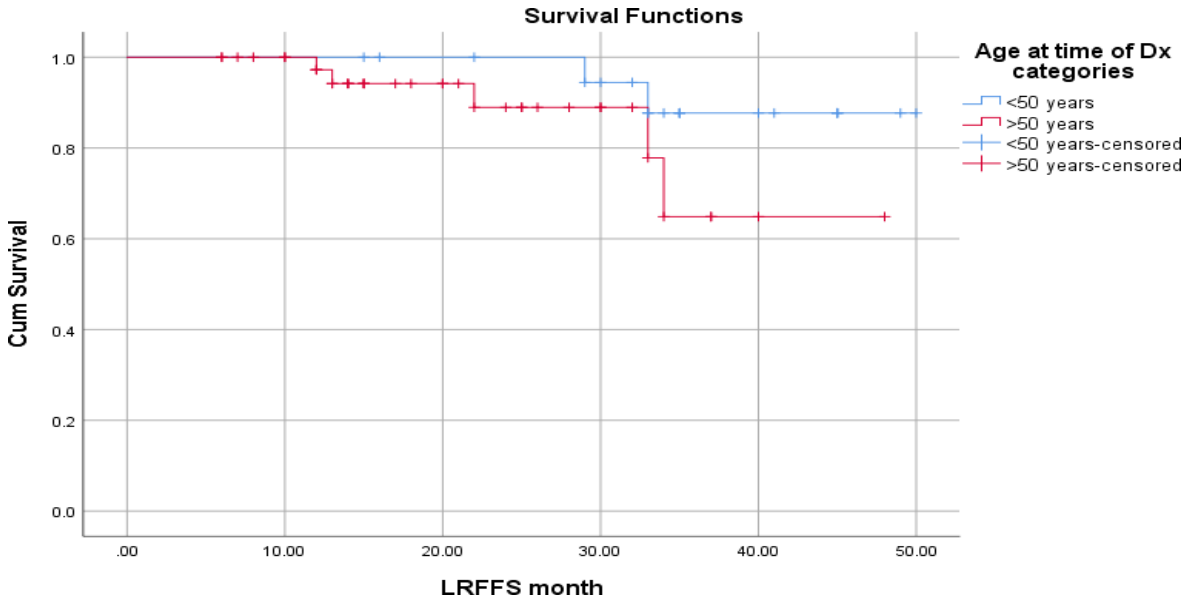

Figure 5. Locoregional failure-free survival based on age groups.

The projected 5-year locoregional failure-free survival (LRFFS) rate for patients lacking LN involvement stood at 96%, correlated with an estimated mean LRFFS period of 48 months. In contrast, patients with LN involvement exhibited an LRFFS rate of 84.2%, corresponding to an estimated mean LRFFS duration of 41.91 months. Notably, the log-rank test demonstrated a statistically significant divergence between the two groups based on LN involvement (p = 0.039). It's worth noting that the computation of median LRFFS time was not feasible, given that the probability of survival for both groups surpassed 50% at the longest follow-up interval (Figure 6).

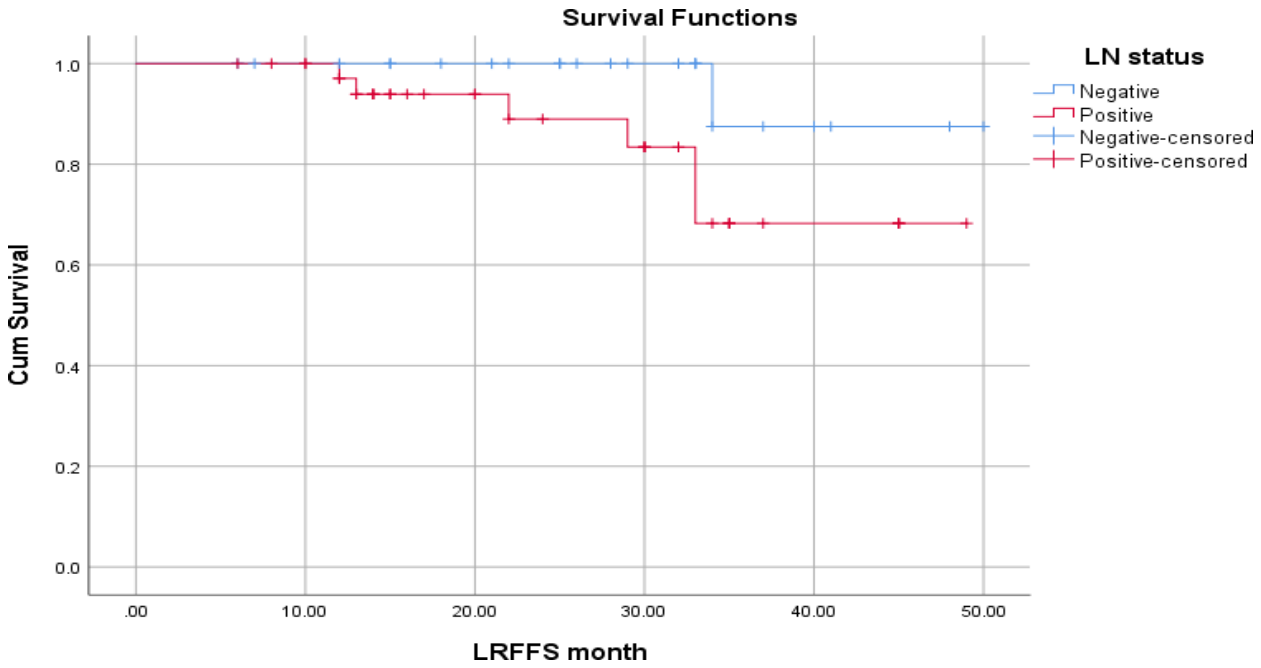

Figure 6. Locoregional failure-free survival based on lymph node status.

Discussion

Women in Jordan face a significant risk of developing cervical cancer, particularly due to the absence of a national healthcare policy regarding vaccination against Human Papilloma Virus (HPV) subtypes 6, 11, 16, and 18 (24, 25). A recent screening study in Jordan revealed a relatively high prevalence (73.2%) of HPV infection among the female population (26). Cervical cancer ranks the 11th most common form of cancer among women in Jordan and holds the 10th spot among cancers affecting individuals aged 15 to 44 (24).

In LACC cases, concurrent chemoradiotherapy (CCRT) stands as the established standard treatment, followed by brachytherapy. Comprehensive systematic reviews and meta-analyses have consistently demonstrated the superior efficacy of CCRT compared to radiotherapy (RT) alone in managing LACC (27, 28). Recommendations highlight the importance of completing the entire treatment regimen within an 8-week to minimize the risk of treatment failure (29). Notably, 50% to 61% of patients experienced treatment failure within the initial two years (30).

Throughout this study, the durations of CCRT varied between 8 to 15 weeks. Within our sampled population, a reported 17.5% encountered treatment failure. This aligns with findings from Tovanabutra et al., where patients diagnosed with LACC at FIGO stages IIB–IVA, lacking pelvic and para-aortic LN (PALN) enlargement, and treated with weekly cisplatin, exhibited a comparable treatment failure rate of 17.1% (31).

In our study, we conducted a retrospective analysis to evaluate the clinical outcomes of 63 LACC patients (FIGO staging IB2–IVA) who underwent CCRT followed by BT. The current study's findings revealed that 32 patients (50.8%) achieved a complete treatment response after three months of CCRT. Notably, a significant disparity in treatment response was observed between patients with positive and negative LN involvement. These results align with the findings reported by Yoo et al. (32). Prior investigations have established LN metastasis as a prognostic factor influencing treatment response and survival rate (6, 14 - 16). Additionally, it is worth noting that the choice of chemotherapy and the total radiotherapy dose can impact treatment response.

A retrospective study involving the use of a combination of low-dose gemcitabine (60 mg/m^2) and cisplatin (35 mg/m^2) in the treatment of 30 LACC patients (ranging from stage IIB to stage IVA) demonstrated that the total radiotherapy dose administered at point A fell between 85 and 90 Gy. This regimen yielded a

commendable CR rate of 73%, highlighting the efficacy of gemcitabine and cisplatin in conjunction with radiotherapy. However, it is important to acknowledge the noteworthy incidence of toxicity associated with this approach. Hematologic toxicity was particularly prominent, leading to hospitalization in 16.7% of patients and treatment interruptions in 26.7% (33).

In our analysis, patients received cisplatin treatment, while the total radiotherapy dose delivered to point A ranged from 80 to 85 Gy. Importantly, grade 3 to 4 early treatment toxicity necessitated treatment delays and constituted a mere 6.3% in our study. Conversely, grade 3 to 4 late treatment toxicity accounted for 20.6%, with many patients reporting vaginal stenosis and dryness complaints.

Among our study sample, the most prevalent sites of metastasis were the lung and bone. While a couple of studies by Rose et al. (1999) and Whitney et al. (1999) specifically focused on lung metastases (34, 35), the majority of published trials did not provide comprehensive details regarding the specific locations of distant metastases (36-38).

Regarding OS, disease-free survival (DMFS), and local recurrence-free survival (LRFFS), the survival rates were notably high at 87.3%, 84.1%, and 88.9%, respectively. These rates demonstrated even greater prominence in patients under the age of 50 and those without LN involvement. Yin et al. (2018) conducted a comparative analysis of treatment outcomes in LACC based on histopathological type. Their findings revealed remarkable OS, DMFS, and LRFFS rates of 90%, 78.8%, and 96.6%, specifically for the LACC SCC type, surpassing the rates observed in other histological groups (39). Notably, the SCC type constituted the predominant histological type in our study, accounting for 87.3% of cases.

A recent retrospective examination of 192 treatment-naive LACC patients (stage IIB–IVA) who underwent concurrent platinum-based chemotherapy and radiotherapy at Xiangya Hospital between January 2014 and June 2017 corroborated our findings, reporting a comparable OS rate of 89.1% (15). Notably, our study yielded a higher OS rate compared to previous trial outcomes (34-36, 38), where the 5-year OS ranged from 60% to 70%. The cumulative survival of LACC patients subjected to CCRT has notably improved over time. However, the determinants contributing to this marked improvement remain subjects requiring further investigation.

Limitation

Several limitations were evident within our study. Firstly, the relatively modest number of enrolled LACC patients could potentially curtail statistical robustness and introduce selection bias. Thus, the validation of these survival outcomes and their influencing factors would benefit from expansive multicenter prospective investigations. Secondly, the study omitted incorporating additional potential contributors to survival rates, notably comorbidities, autoimmune disorders, and hereditary conditions. Thirdly, it's noteworthy that the SCC subtype of LACC is predominantly featured in our study, underscoring the imperative to further explore diverse histological subtypes.

Notwithstanding these limitations, this study is a pioneering endeavor within Jordan, representing the first to appraise the clinical outcomes of LACC patients subjected to CCRT. Earlier research predominantly comprised descriptive studies on cervical cancer prevalence (Sharkas et al., 2017) and cervical cancer screening (Muhaidat et al., 2022; Fram et al., 2023). These investigations underscore the imperative of instituting a comprehensive cervical screening program in Jordan.

Conclusion

Our study showcased notably elevated 5-year OS, disease-free survival (DMFS), and LRFFS rates. Patients under 50 and those lacking LN involvement exhibited superior survival rates when juxtaposed with their counterparts aged 50 and above or with positive LN involvement. Remarkably, half of the patients achieved a complete treatment response. Genitourinary toxicity emerged as the principal manifestation of early and late treatment-related adverse effects. Notably, treatment failure was documented in 17.5% of patients, with the lung and bone emerging as the most prevalent sites of metastasis.

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