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Health-related quality of life in locally advanced cervical cancer patients treated with neoadjuvant therapy followed by radical surgery: A single-institutional retrospective study from a prospective database

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HIGHLIGHTS

- Physical/role functioning improved 6 months after concurrent chemoradiation (CCRT)/radiation (RT) + radical surgery (RS).
- Tumor-related symptoms of fatigue and insomnia decreased 6 months after treatment.
- Treatment-related symptoms of lymphedema and menopausal symptoms increased after treatment.
- Sexuality was not impaired significantly except for a worsened sexual worry in the RT + RS group.
- Generally RT + RS seems superior to CCRT+RS with greater improvement in functioning and less toxicity.

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ABSTRACT

Objective. To evaluate the health-related quality of life (HRQOL) in locally advanced cervical cancer (LACC) patients treated with neoadjuvant concurrent chemoradiation (CCRT) or radiation (RT) alone followed by radical surgery (RS).

Methods. In a single-center retrospective study from a prospective database, 275 FIGO Stage IB2-IIIB patients who underwent CCRT/RT + RS were included. HRQOL was prospectively assessed by EORTC QLQ-C30 and EORTC QLQ-CX24 prior to any treatment (baseline) and 6 months after surgery, respectively.

Results. A statistically significant and clinically relevant improvement in physical functioning ($P < 0.001$) and role functioning ($P = 0.002$, $P = 0.031$) was observed in patients receiving either CCRT+RS or RT + RS at follow-up. In addition, quality of life (QoL), physical functioning, and social functioning were better in the RT + RS group than the CCRT+RS group after treatment ($P = 0.028$, $P = 0.010$, $P = 0.014$). Symptom scores of fatigue decreased in both groups over time ($P < 0.001$, $P = 0.004$) while insomnia decreased only in the RT + RS group ($P = 0.042$). Worsened menopausal symptoms were documented in both groups at follow-up ($P = 0.001$, $P = 0.047$), while lymphedema was deteriorated only in patients receiving CCRT + RS ($P < 0.001$). Sexuality scores did not differ between groups or over time with the exception of sexual worry, which was deteriorated in patients receiving RT + RS ($P = 0.042$).

Conclusions. QLQ-C30 functioning and tumor-related symptoms scores improved while lymphedema and menopausal symptoms worsened 6 months after neoadjuvant CCRT or RT alone followed by RS in LACC patients. Patients treated with RT + RS had a generally better HRQOL compared with those receiving CCRT+RS, though further validation with prospective randomized clinical trials is warranted.

1. Introduction

Cervical cancer is the fourth most common cancer and fourth leading cause of cancer death in women worldwide, which accounts for 569,847 new cases and 311,365 deaths annually [1]. In China, there are 98,900 newly diagnosed cervical cancer cases and 30, 500 associated deaths

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annually [2]. Moreover, China has shown an increasing trend of morbidity compared to the decreasing trend in transitioned countries, which may be related to insufficient cervical cancer screening, increasing incidence of human papillomavirus (HPV) infection, and relative shortage of HPV vaccines in China [2].

Concurrent chemoradiation has been widely used as the standard of care for locally advanced cervical cancer (LACC) patients since the 1999 National Cancer Institute alert [3]; however, the absolute survival benefits were not very satisfying with this strategy [4]. In light of this, new treatment modalities compromising neoadjuvant chemotherapy, radiation (RT), or concurrent chemoradiation (CCRT) followed by radical surgery (RS) have been investigated over the last two decades which yielded promising survival outcomes [5–13].

It is not surprising that many studies evaluating new therapeutic protocols for cancer patients mainly considered survival outcomes as primary response measures. However, the choice of therapeutic strategy should also involve careful consideration of its effects on health-related quality of life (HRQOL). Especially for cervical cancer patients, the improved survival with early detection and developed therapy entails a prolonged time with sequelae of treatment [14,15]. Indeed, a common criticism against multimodal therapeutic regimens is a higher rate and severity of toxicity [16–18], which is also associated with a negative impact on HRQOL including impaired daily life activities and emotional distress in cervical cancer patients [15,19–21].

Because of the paucity of studies on HRQOL in LACC patients who received neoadjuvant therapy followed by RS, we have conducted a single-institutional retrospective study from a prospective database to assess the changes of HRQOL over time, compare HRQOL characteristics associated with different treatment modalities (CCRT + RS vs. RT + RS), and analyze potential influencing factors for HRQOL in such patients.

2. Methods

2.1. Patient population – LACC patients receiving neoadjuvant CCRT/RT + RS

Patients admitted with cervical cancer at the Department of Obstetrics and Gynecology of Xijing Hospital (Xi'an, People's Republic of China) between September 2013 and Jun 2018 were included in our study if they were aged ≥18 years-old, had histological proven LACC (FIGO stage IB2-IIIB), were planned to receive neoadjuvant therapy followed by RS, and if they or their legally authorized representative gave informed consent. We excluded patients with para-aortic lymph node metastasis according to magnetic resonance (MR) or computed tomography (CT) imaging (pelvic lymph node metastasis shown on MR or CT imaging was not an exclusion criteria), previous diagnosis of other malignancies or abdominal radiotherapy/surgery, significant psychological or mental illness who were unable to cooperate, and presence of a confounding condition (e.g., pregnancy) or disease that could potentially impact HRQOL (e.g., myocardial infarction, severe infection, severe liver and renal malfunction, autoimmune diseases).

2.2. Treatment – neoadjuvant CCRT + RS vs. RT + RS

LACC Patients were treated with neoadjuvant CCRT or RT followed by RS as previously reported [7,9,22]. Briefly, whole pelvic three-dimensional conformal or intensity-modulated radiation therapy was delivered with a total planned dose of 40–50 Gy in 20–25 fractions. Concurrent chemotherapy consisted of either cisplatin every 3 weeks (75 mg/m^2) or weekly (40 mg/m^2) for 3–6 cycles. Chemotherapy was withheld under the following conditions: white blood cell count <2.0 × 10^9/L, absolute neutrophil count <1.0 × 10^9/L, platelet count <50 × 10^9/L, or grade 3–4 radiation toxicities. Decision on the choice of treatment modalities was made based on patient preference after detailed consultation with the radiation oncologists and gynecologists. After 3–4 weeks from completion of CCRT or RT alone, objective response was evaluated by pelvic MR or CT imaging and transvaginal ultrasound. Eligible patients consulted by at least 2 gynecologists underwent RS with type B radical hysterectomy and pelvic lymphadenectomy via laparotomy, laparoscopy, or robotic surgeries.

2.3. Assessment and data collection

A database was established to prospectively collect associated information and schedule follow-up appointments. Demographic and clinical variables including age, educational level, occupational status, marital status, menopausal status at diagnosis, FIGO stages, histologic subtypes, lymph node involvement, lymph vascular space invasion (LVSI), and comorbidities (diabetes, hypertension, hypercholesterolemia, etc.) were recorded.

The standard Chinese version of the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30, version3.0) and Cervical Cancer Module (CX24) were applied to prospectively assesse HRQOL prior to any treatment (baseline) and 6 months after surgery, respectively. The EORTC QLQ-C30 is a basic tool universally used for all types of cancer patients, which contains five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global health/QoL scale, six single items assessing symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), and the perceived financial burden [23,24]; while the EORTC QLQ-CX24 is a specific tool designed for cervical cancer patients, which consists of three scales (symptom experience, body image, and sexual/vaginal functioning), and six single items addressing disease-specific and treatment-related symptoms (lymphedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity, and sexual enjoyment) [25,26]. The raw scores for each domain and single item were transformed linearly to give a value between 0 and 100 as previously described [27]. For EORTC QLQ-C30, higher scores correspond to better levels of functioning for functional scales and global health status/QoL scale, but more severe symptoms for symptom-oriented scales. For QLQ-CX24, higher scores correspond to more severe symptoms and worse functioning except for sexual activity and sexual enjoyment (i.e. higher scores denote higher active and higher enjoyment). A difference in HRQOL scores of at least 10 points (on a 0–100 scale) was considered as clinically relevant [28].

Informed consent was obtained from each patient in this study before any treatment. Review and analysis of patient information were approved by the Ethical Committee of Xijing Hospital. The protocol adheres to the principles set forth in the US Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects, revised June 23, 2005, and the World Medical Association Declaration of Helsinki.

2.4. Statistical analysis

To test whether variables differed across groups, the chi-square test or Fisher exact test was used according to the testing condition. Comparisons between continuous data were done using ANOVA or Mann-Whitney *U* test according to the testing condition. Multinomial logistic regression was used to identify possible predictors of the HRQOL scores. Statistical significance was defined as $p < 0.05$. All of the tests were 2-sided. Statistical analysis was performed using SPSS software (version 16.0, SPSS, Inc.).

3. Results

3.1. Patient characteristics

A total of 371 patients were screened for eligibility, of whom 76 were excluded (not meeting inclusion criteria, n = 71; declined to participate, n = 5). Of the remaining 295 patients, 4 were ineligible for RS

after neoadjuvant therapy, 2 refused to consent for surgery, 3 had disease recurrence within 6 months, 11 were lost to follow-up, and thus were excluded from data analysis. Our results are therefore based on 275 patients and an as-treated analysis was performed. The mean age of patients at the time of enrollment was 46.6 ± 9.2 years (range 26–69 years). About 71.6% of the patients (n = 197) received CCRT followed by RS whereas 28.4% were treated with RT alone followed by RS. Sociodemographic and clinical features were not significantly different between the two groups according to treatment modalities (Table 1). Scores of EORTC QLQ-C30 and CX24 at baseline vs. at 6-month follow-up after RS are summarized in Tables 2 and 3 based on treatment modalities.

3.2. EORTC QLQ-C30 QoL and functioning scales

Baseline scores of QoL and functioning scales were not significantly different between the CCRT+RS group and the RT + RS group with the exception of social functioning, which was significantly better in the RT + RS group (79.5 ± 27.2 vs. 65.9 ± 29.7, P = 0.032, Table 2).

Table 1
Patient characteristics at enrollment.

Parameter	Total	CCRT+RS group	RT + RS group	p Value
		No. of patients (%)		
No. of patients	275	197 (71.6)	78 (28.4)	
Age (years)				0.380
≤45	133 (48.4)	92 (46.7)	41 (52.6)	
>45	142 (51.6)	105 (53.3)	37 (47.4)	
Menopause (at diagnosis)				0.106
No	189 (68.7)	141 (71.6)	48 (61.5)	
Yes	86 (31.3)	56 (28.4)	30 (38.5)	
BMI				0.468
<18.5	6 (2.2)	3 (1.5)	3 (3.8)	
18.5–23.9	219 (79.6)	157 (79.7)	62 (79.5)	
>24	50 (18.2)	37 (18.8)	13 (16.7)	
Education				0.113
No education/Primary school	137 (49.8)	94 (47.7)	43 (55.1)	
Secondary school/high school	85 (30.9)	68 (34.5)	17 (21.8)	
College/more than college	53 (19.3)	35 (17.8)	18 (23.1)	
Occupation				0.864
Employed	85 (30.9)	60 (30.5)	25 (32.1)	
Homemaker	114 (41.5)	84 (42.6)	30 (38.5)	
Unemployed	67 (24.4)	46 (23.4)	21 (26.9)	
Retired	9 (3.3)	7 (3.6)	2 (2.6)	
Marital status				0.736
Unmarried (Single/divorced)	29 (10.5)	20 (10.2)	9 (11.5)	
Married	246 (89.5)	177 (89.8)	69 (88.5)	
Concomitant diseases				
CHD/Hypertension	32 (11.6)	22 (11.2)	10 (12.8)	0.700
Diabetes	42 (15.3)	29 (14.7)	13 (16.7)	0.686
Smoker	8 (2.9)	6 (3.0)	2 (2.6)	>0.999
Liver/Gall bladder	25 (9.1)	18 (9.1)	7 (9.0)	0.966
Lung	13 (4.7)	8 (4.1)	5 (6.4)	0.528
Miscellaneous	9 (3.3)	5 (2.5)	4 (5.1)	0.278
FIGO stage				0.226
IB2	84 (30.5)	54 (27.4)	30 (38.5)	
IIA	117 (42.5)	83 (42.1)	34 (43.6)	
IIB	63 (22.9)	51 (25.9)	12 (15.4)	
IIIA	4 (1.5)	3 (1.5)	1 (1.3)	
IIIB	7 (2.5)	6 (3.0)	1 (1.3)	
Pelvic Lymph node involvement				0.160
Negative	208 (75.6)	144 (73.1)	64 (82.1)	
Positive	67 (24.4)	53 (26.9)	14 (17.9)	
LVSI				0.115
Negative	185 (67.3)	127 (64.5)	58 (74.4)	
Positive	90 (32.7)	70 (35.5)	20 (25.6)	
Histologic subtype				0.363
Squamous	252 (91.6)	179 (90.9)	73 (93.6)	
Adeno	18 (6.5)	13 (6.6)	5 (6.4)	
Other	5 (1.8)	5 (2.5)	0	

CCRT = concurrent chemoradiation, CHD = chronic heart disease, LVSI = lymph vascular space invasion, QOL = quality of life, RS = radical surgery, RT = radiation.

Table 2
Descriptive statistics of EORTC QLQ-C30 in LACC patients according to treatment modality.

Variable	Treatment modality	Baseline (Mean ± SD)	At 6-month follow-up (Mean ± SD)	p Value
Functioning scale[a]				
Global health status/QOL	CCRT+RS	61.0 ± 30.1	60.8 ± 27.4	0.929
	RT + RS	72.3 ± 18.7	73.4 ± 22.0	0.899
	p Value	0.057	0.028[c]	
Physical functioning	CCRT+RS	75.9 ± 22.0	86.2 ± 17.1	<0.001[c]
	RT + RS	82.1 ± 15.3	94.8 ± 6.9	<0.001[c]
	p Value	0.178	0.010	
Role functioning	CCRT+RS	79.5 ± 26.9	89.9 ± 21.4	0.002[c]
	RT + RS	82.7 ± 26.0	93.2 ± 10.0	0.031[c]
	p Value	0.581	0.176	
Emotional functioning	CCRT+RS	74.3 ± 24.3	75.9 ± 22.8	0.747
	RT + RS	81.7 ± 22.6	81.5 ± 18.9	0.945
	p Value	0.152	0.218	
Cognitive functioning	CCRT+RS	76.1 ± 22.3	82.9 ± 19.8	0.005
	RT + RS	79.5 ± 27.2	85.1 ± 21.4	0.161
	p Value	0.494	0.592	
Social functioning	CCRT+RS	65.9 ± 29.7	69.6 ± 32.1	0.215
	RT + RS	79.5 ± 27.2	85.1 ± 19.4	0.254
	p Value	0.032[c]	0.014[c]	
Symptoms scales/items[b]				
Fatigue	CCRT+RS	34.5 ± 23.1	24.2 ± 20.7	<0.001[c]
	RT + RS	30.8 ± 22.7	17.9 ± 14.0	0.004[c]
	p Value	0.449	0.071	
Nausea/vomiting	CCRT+RS	12.0 ± 22.0	6.8 ± 16.9	0.052
	RT + RS	4.5 ± 14.6	1.2 ± 6.3	0.147
	p Value	0.099	0.088	
Pain	CCRT+RS	22.5 ± 24.7	16.6 ± 22.5	0.028
	RT + RS	17.3 ± 22.8	9.5 ± 15.3	0.109
	p Value	0.322	0.114	
Dyspnea	CCRT+RS	19.8 ± 25.4	13.1 ± 19.8	0.012
	RT + RS	12.8 ± 19.0	11.9 ± 16.3	0.766
	p Value	0.183	0.767	
Insomnia	CCRT+RS	27.5 ± 30.5	22.6 ± 28.7	0.129
	RT + RS	38.5 ± 34.9	22.6 ± 24.1	0.042[c]
	p Value	0.104	0.994	
Appetite loss	CCRT+RS	18.1 ± 27.8	12.2 ± 23.9	0.036
	RT + RS	9.0 ± 22.2	7.1 ± 13.9	0.329
	p Value	0.119	0.275	
Constipation	CCRT+RS	19.4 ± 28.7	21.4 ± 29.5	0.470
	RT + RS	14.3 ± 19.1	16.7 ± 25.4	0.496
	p Value	0.365	0.449	
Diarrhea	CCRT+RS	8.4 ± 16.8	14.5 ± 24.1	0.047
	RT + RS	6.0 ± 15.9	10.3 ± 20.6	0.057
	p Value	0.468	0.403	
Financial difficulties	CCRT+RS	47.3 ± 38.0	50.6 ± 37.5	0.123
	RT + RS	39.3 ± 37.5	44.8 ± 43.1	0.480
	p Value	0.307	0.486	

CCRT = concurrent chemoradiation, QOL = quality of life, RS = radical surgery, RT = radiation.
[a] Scores range from 0 to 100 with higher scores indicating higher level of functioning.
[b] Scores range from 0 to 100 with higher scores indicating greater burden of symptoms.
[c] Clinical relevance ≥10 points differences.

An improved trend was observed in QoL and all functioning scales at 6-month follow-up after treatment compared with baseline, while statistically significant and clinically relevant differences were only witnessed in physical functioning (mean score difference of 10.3 for CCRT + RS, P < 0.001; and 12.7 for RT + RS, P < 0.001) and role functioning (mean score difference of 10.4 for CCRT + RS, P = 0.002; and 10.5 for RT + RS, P = 0.031) in both groups, respectively. Cognitive functioning was statistically improved in the CCRT+RS group (P = 0.005), however this improvement was not clinically relevant (Table 2).

Social functioning remained significantly better in the RT + RS group after treatment (85.1 ± 19.4 vs. 69.6 ± 32.1, P = 0.014). Additionally, QoL and physical functioning were also better in the RT + RS group than the CCRT+RS group at 6-month follow-up (73.4 ± 22.0 vs. 60.8 ± 27.4, P = 0.028; 94.8 ± 6.9 vs. 86.2 ± 17.1, P = 0.010).

Table 3
Descriptive statistics of EORTC QLQ-CX24 in LACC patients according to treatment modality.

Variable	Treatment modality	Baseline (Mean ± SD)	At 6-month follow-up (Mean ± SD)	p Value
Symptoms scales/items[a]				
Symptom experience	CCRT+RS	16.7 ± 11.4	18.0 ± 15.8	0.679
	RT + RS	16.8 ± 10.6	15.3 ± 11.7	0.620
	p Value	0.966	0.389	
Lymphedema	CCRT+RS	12.8 ± 26.1	34.5 ± 34.7	<0.001[d]
	RT + RS	13.3 ± 25.5	27.4 ± 34.0	0.088
	p Value	0.931	0.331	
Peripheral neuropathy	CCRT+RS	16.3 ± 24.0	23.2 ± 25.4	0.002
	RT + RS	14.7 ± 19.4	17.9 ± 21.2	0.540
	p Value	0.749	0.307	
Menopausal symptoms	CCRT+RS	17.8 ± 24.4	28.2 ± 28.5	0.001[d]
	RT + RS	17.3 ± 30.6	30.9 ± 31.9	0.047[d]
	p Value	0.936	0.563	
Sexual worry	CCRT+RS	23.7 ± 31.2	23.8 ± 30.8	0.849
	RT + RS	21.3 ± 34.5	33.3 ± 37.0	0.042[d]
	p Value	0.732	0.165	
Functioning scale[b]				
Body image	CCRT+RS	30.8 ± 29.8	24.4 ± 24.7	0.011
	RT + RS	21.0 ± 24.5	19.5 ± 23.2	0.528
	p Value	0.114	0.353	
Sexual activity	CCRT+RS	8.4 ± 19.3	8.1 ± 21.6	0.783
	RT + RS	10.7 ± 23.0	2.5 ± 8.9	0.211
	p Value	0.562	0.164	
Sexual enjoyment[c]	CCRT+RS	36.7 ± 34.0	34.6 ± 28.5	0.504
	RT + RS	33.3 ± 47.1	33.3 ± 36.5	>0.999
	p Value	0.899	0.928	
Sexual/vaginal functioning[c]	CCRT+RS	28.4 ± 20.6	28.7 ± 32.2	0.952
	RT + RS	33.9 ± 22.8	25.0 ± 11.8	0.208
	p Value	0.676	0.874	

CCRT = concurrent chemoradiation, QOL = quality of life, RS = radical surgery, RT = radiation.
[a] Scores range from 0 to 100 with higher scores indicating greater burden of symptoms.
[b] Scores range from 0 to 100 with higher scores indicating lower level of functioning except for sexual activity and sexual enjoyment.
[c] Data obtained from sexually active patients.
[d] Clinical relevance ≥10 points differences.

3.3. EORTC QLQ-C30 and CX24 symptom scales

Neither symptom scores at baseline nor scores at 6-month follow-up differed between the CCRT+RS group and the RT + RS group (Tables 2 and 3).

A general trend of decreased burden of symptoms was documented in EORTC QLQ-C30 assessments 6 months after treatment, which was clinically relevant concerning fatigue in both groups (mean score decrease of 10.3 for CCRT+RS, $P < 0.001$; and 12.9 for RT + RS, $P = 0.004$, Table 2). Insomnia decreased significantly only in the RT + RS group from 38.5 ± 34.9 to 22.6 ± 24.1 ($P = 0.042$); while pain, dyspnea, and appetite loss decreased only in the CCRT+RS group with statistically but not clinically significant differences (Table 2). On the other hand, a bunch of symptoms including constipation, diarrhea, and financial difficulties deteriorated after treatment compared to baseline in both groups. A statistically significant but not clinically relevant deterioration was observed with regard to diarrhea in the CCRT+RS group, while diarrhea in the RT + RS group and the other symptoms were not impaired to a statistically significant degree (Table 2).

On contrary, a general trend of increased symptoms was shown in cervical cancer specific EORTC QLQ-CX24 assessments over time. Menopausal symptoms were statistically and clinically worsened in both groups, from 17.8 ± 24.4 to 28.2 ± 28.5 ($P = 0.001$) in the CCRT+RS group, and from 17.3 ± 30.6 to 30.9 ± 31.9 ($P = 0.047$) in the RT + RS group, respectively. For the CCRT+RS group, a clinically relevant deterioration of lymphedema was observed (mean score difference of 21.7, $P < 0.001$) whereas the worsening of peripheral neuropathy was only statistically significant without clinical relevance (mean score difference of 6.9, $P = 0.002$) (Table 3).

Body image was also improved in both groups at 6-months follow-up after treatment, though the improvement was only statistically significant in the CCRT+RS group ($P = 0.011$) and not clinically relevant in either group (Table 3).

3.4. EORTC QLQ-CX24 sexuality

Scores of sexuality modules were not different between the two groups neither prior to nor 6 months after treatment. Sexual activity, sexual enjoyment, and sexual functioning all showed a generally stable pattern over time (Table 3). Nevertheless, sexual worry was statistically and clinically deteriorated after treatment in the RT + RS group (mean score difference of 12.0, $P = 0.042$).

3.5. Predictors for HRQOL in LACC patients

For EORTC QLQ-C30 functioning scales, univariate analysis showed significant association between a better QoL and the following two parameters: negative LVSI ($P = 0.022$), and treatment modality of RT + RS ($P = 0.028$). Treatment with RT + RS was also correlated with better social functioning ($P = 0.014$) and physical functioning ($P = 0.010$) (Supplemental Table 1). Multivariate logistic regression including variables with $P < 0.100$ in the univariate analysis showed that none of the variables had a significant correlation with any of the QoL and functioning scores (data not shown).

For QLQ-C30 symptoms scales, older age (>45) and occupational status without employment were found to correlate with worse financial difficulties in univariate analysis ($P = 0.020$ and 0.003, respectively) (Supplemental Table 2). Multivariate analysis confirmed that age (β coefficient, 0.899; OR, 2.456; 95% CI, 1.178–5.121; $P = 0.017$) and occupational status (β coefficient, 1.285; OR, 3.616; 95% CI, 1.456–8.979; $P = 0.006$) were independent predictors for financial difficulties.

For EORTC QLQ-CX24 symptom scales, age and FIGO stage showed significant associations with lymphedema in univariate analysis ($P = 0.019$ and 0.048, respectively) while lymph node involvement had a significant association with peripheral neuropathy ($P = 0.004$) (Supplemental Table 3). In multivariate analysis, only age (β coefficient, 0.864; OR, 2.372; 95% CI, 1.100–5.113; $P = 0.028$) was found to influence lymphedema significantly, while lymph node involvement (β coefficient, 1.684; OR, 5.385; 95% CI, 1.614–17.962; $P = 0.006$) remained the sole independent predictor for peripheral neuropathy.

For QLQ-CX-24 sexuality modules, age influenced sexual activity negatively in univariate analysis ($P = 0.044$). Nevertheless, age and menopause at diagnosis were related to better scores of sexual worry ($P < 0.001$ and $=0.006$, respectively) (Supplemental Table 3). None the variables was retained as independent factors affecting sexuality scores in multivariate analysis.

4. Discussion

With the development of new treatment strategies for cervical cancers patients including neoajuvant therapy followed by RS, the prolonged survival has called into attention the impact of toxicity on patients' HRQOL associated with multimodal therapeutic regimens [15,19]. Few literatures existed concerning HRQOL characteristics in cervical cancer patients triaged to preoperative neoajuvant chemotherapy, RT, or CCRT to date [19,29]. To our best knowledge, this is the first study from a prospective and longitudinal database to compare HRQOL in LACC patients treated with CCRT followed by RS and RT alone followed by RS.

4.1. Change of HRQOL over time

Though the QoL score displayed a stable pattern at 6-month follow-up compared to baselines, several QLQ-C30 functioning scales improved considerably with clinical relevance, including physical functioning and

role functioning in both treatment groups as well as cognitive functioning (with mild relevance of 6.4% difference) in the CCRT + RS group. Though previous studies have shown an early and profound deterioration of QoL and some functioning scales during and immediately after active treatment, most of them returned to baseline 3 months later and continued to improve as time prolonged, which in comparison with our results at 6-months follow-up were generally in common [21,30,31]. Moreover, the considerable rise in physical and role functioning (as well as a mildly better "body image" in CX24 scales) in our series implied a definitive enhancement of patient-perceived HRQOL 6 months after neoadjuvant therapy.

Meanwhile, results at 6-months follow-up indicated alleviation of symptom burden involving decreased fatigue in both groups, decreased insomnia in the RT + RS group, as well as decreased pain, dyspnea, and appetite loss in the CCRT+RS group. These results were in line with previous studies showing similar pattern of decreased tumor-related symptoms over time [20,21,32].

On the other hand, some treatment-related symptoms did develop or deteriorate dramatically over time as revealed in both QLQ-C30 and CX24 scales. Diarrhea and menopausal symptoms worsened because of the early toxicity of RT, which were also indicated in previous studies to remain persistently impaired for a prolonged time [19,21].

Not surprisingly, lymphedema was found to be another disabling symptom, given the characteristics of the current cohort of patients who underwent RS with pelvic lymphadenectomy in combination with RT, both of which were major risk factors for lymphedema [19,33]. This finding resembles other series that lymphedema exert a substantial negative impact on patients' HRQOL and daily life activities after treatment [19,34]. In order to minimize the adverse effects of lymphedema in LACC patients, efforts have been made to identify patients who may benefit from individualized pelvic lymphadenectomy based on assessment of imaging- and histological-diagnosed lymph node involvement [22,35]. Besides, for patients who cannot be spared from lymphadenectomy, pre-planned supportive strategies including patient and family counseling, clinical monitoring, medical management, and additional social support may be helpful.

Sexuality is acknowledged as a crucial and specific component of HRQOL in cervical cancer patients. In contrast to some studies reporting significant sexual dysfunctions in terms of decreased sexual activity and enjoyment due to anatomic involvement of cancer and side effects of treatments, [20,32,36,37] sexual functioning in our series did not impair significantly over time except for sexual worry, which was substantially worsened in patients receiving RT + RS. Treatment modalities involving intensity-modulated RT, attempts of surgical preservation of pelvic autonomous nerves, and lack of brachytherapy might have accounted for the less significant sexual dysfunctions [19]. In addition, the extent of deterioration in menopausal symptoms was larger in patients receiving RT + RS than those receiving CCRT + RS (mean score change of 13.6 vs. 10.4), which was paralleled by significantly increased sexual worry in the former group. In view of this, menopausal symptoms merit proper interventions such as hormone replacement therapy.

4.2. HRQOL characteristics between different treatment modalities

Almost all functioning and symptoms scores of QLQ-C30 and CX24 were similar at baseline in our patients treated with CCRT+RS vs. RT + RS. The only exception was social functioning which was better in the RT + RS group at baseline and remained better in the same group at follow-up. Notably, the RT + RS group also demonstrated a greater improvement in QoL and physical functioning compared with the CCRT+RS group at 6-months follow-up after treatment. It is conceivable as CCRT is associated with more toxicities than RT alone, [17,18] which was also supported by the findings of a more dramatic worsening of lymphedema only in patients treated with CCRT+RS at 6-month follow-up compared to baseline. However, no additional differences were indicated between the two groups with regard to functioning, symptom and sexuality scales at 6-month follow-up after treatment.

Our previous studies have shown the superiority of CCRT + RS to RT + RS in terms of complete response rates and survival outcomes [7]. The HRQOL data represented here may further help clinician and patients in selecting the preferable treatment regimens considering their existed burdens and expectations.

4.3. Clinico-pathological predictors for HRQOL

Though several clinico-pathological parameters including treatment modalities showed associations with QLQ-C30 scores in univariate analysis, only age and occupational status were retained as independent predictors for financial difficulties in multivariate analysis. The absence of significant correlation between clinico-pathological variables and functioning scales as well as general QoL was consistent with previous studies, which also reflected the patients' ability to recover form HRQOL disruption associated with cervical cancer and treatment [19,21]. However, the impact of socio-demographic and environmental factors over patients' perception of HRQOL should not be overlooked. For instance the economic burden posed to cervical cancer survivors which is related to not only medical expenses, but also work interruption, loss of employment and family income, [38] has been shown to be a significant factor influencing patients' HRQOL in both previous studies [20,36,37] and ours, especially in developing countries. This also underlined the importance of interventions compromising social and family support, psychological intervention, and physical rehabilitation to improve the HRQOL.

For QLQ-CX24 symptom scores, age was the sole predictor for lymphedema while lymph node involvement was the sole predictor for peripheral neuropathy. The true reason behind these associations remains to be explored, however, it is plausible as overall HRQOL commonly declined with increasing age [37,39]. On the other hand, the neurotoxicity of RT and chemotherapy, which are usually more aggressively delivered to patients with positive lymph node involvement, has to be taken into account as a contributing factor to peripheral neuropathy [15,18].

For QLQ-CX24 sexuality, no predicative variable was retained as significant in multivariate analysis. However, it is noteworthy that age was found to be the most negative factor influencing sexual activity and the most positive factor influencing sexual worry, which is well aligned with findings of Bjelic-Radisic et al. [15]

4.4. Strength and limitations

The strength of the current study is the relatively large sample size and homogenously cohort in terms of RT plans, surgical procedures, and chemotherapy regimens, as well as the prospective evaluation of HRQOL using validated instruments. One major limitation of the current study is the lack of assessments at multiple time intervals to reflect a more detailed pattern of fluctuations for HRQOL with regard to acute phase during and immediately after active treatment as well as long-term outcomes. However, the follow-up assessment chosen at 6 months after treatment is representative and remarkable for cervical cancer patients because it is the key point in the course of psychological adaptation to cope with difficult treatment regimens and to take over the responsibilities as mother, wife, and etc. [20,40] On the other hand, the use of pre-treatment "baseline" may also be misleading in comparing the effects of interventions on HRQOL, as HRQOL is particularly low just before an intervention due to the anxiety related to the upcoming intervention. Therefore the improved scores at 6-months follow-up should be interpreted with caution. Furthermore, the lack of a reference HRQOL in patients receiving primary surgery evaluated at the same time points limits the interpretation of the data in comparing the change of HRQOL associated with neoadjuvant therapy versus that of primary surgery. Another limitation is the risk of inadequate power

to evaluate differences between the groups (CCRT+RS vs. RT + RS) due to lack of dedicated sample size calculation for outcomes measured in this study. Nevertheless, the risk of an underpowered sample size was to some extent counter-balanced by a post-hoc power analysis for global health/QoL scale, which yielded a post-hoc power of 97.8%. In addition, our single-institutional experience limits the generalizability of the findings. Lastly, the current study is an observational study and different therapeutic regimens were not allocated randomly. Therefore the findings need to be validated in future prospective randomized clinical trials.

5. Conclusions

Improved general QoL and functioning, reduced tumor-related symptoms, but worsened treatment-related symptoms including lymphedema and menopausal symptoms were observed 6 months after neoadjuvant therapy with CCRT or RT alone followed by RS in LACC patients. Patients treated with RT + RS had a generally better HRQOL 6 months post-treatment than those receiving CCRT + RS in terms of greater improvement in functioning and less toxicity. The findings of the current study may serve as a reference to evaluate the efficacy and safety of new treatment strategies including neoadjuvant chemotherapy and/or radiation in terms of secondary outcomes as well as a stepping stone to promote further research into the evaluation and intervention of patient-perceived HRQOL.

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Author contributions

Conception and design: B Liu, L Wei, S Liu. Acquisition of data: B Liu, L Li, M Wang, L Wei, J Li, W Zou, Y Lv, H Zhang, S Liu. Analysis and interpretation of data: B Liu, L Wei, S Liu. Drafting the article: B Liu, S Liu. Critically revising the article: B Liu, L Li, M Wang, L Wei, J Li, W Zou, Y Lv, H Zhang, S Liu. Reviewed submitted version of manuscript: all. Approved the final version of the manuscript: all. Statistical analysis: B Liu, S Liu. Administrative/technical/material support: L Wei, H Zhang, S Liu. Study supervision: S Liu.

Declaration of Competing Interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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