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A novel predictor for the use of concurrent chemotherapy in early-stage cervical cancer with intermediate-risk factors

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ABSTRACT

Objective: For early-stage cervical cancer patients experiencing radical surgery, postoperative radiotherapy was recommended for patients with a combination of intermediate-risk factors. However, there was no consensus on whether to administer concurrent chemotherapy. The aim of the study was to confirm the clinical value of the controlling nutritional status (CONUT) score in guiding the use of concurrent chemotherapy during postoperative radiotherapy.

Methods: A total of 969 patients with FIGO stage IB-IIA cervical cancer were retrospectively analyzed. Kaplan-Meier survival analysis was performed to compare disease-free survival (DFS) and cancer-specific survival (CSS) rates between different group. A Cox proportional hazards regression test was used to conduct multivariate analyses.

Results: For the patients in the high CONUT group (≥3), the addition of concurrent chemotherapy had better 5-year DFS (91.2 % vs. 72.8 %, P = 0.005) and CSS (93.8 % vs. 77.4 %, P = 0.013) than those without it. Meanwhile, the patients with concurrent chemotherapy had less rate of locoregional recurrence (8.5 % vs 16.7 %, P = 0.034) and distant metastases (11.7 % vs 30.4 %, P = 0.015). The multivariate analysis showed that concurrent chemotherapy was detected to be a factor significantly associated with DFS (P = 0.011), local control (P = 0.041), distant metastasis (P = 0.005) and CSS (P = 0.023). For the patients in low CONUT group (<3), there was no difference in prognosis between patients.

Conclusion: Pretreatment CONUT score may be a predictive factor for the use of concurrent chemotherapy in early-stage cervical cancer with intermediate-risk factors during postoperative radiotherapy, and it can be helpful to determine the adjuvant treatment scheme.

1. Introduction

Currently, early-stage cervical cancer is often cured by either radiotherapy or radical hysterectomy (type III) and pelvic lymph node dissection, with a 5-year overall survival rate of 80–90 % (Landoni et al., 1997; Hopkins and Morley, 1991). For patients who undergo surgical treatment, adjuvant therapy is given according to risk factors for recurrence. Postoperative concurrent chemoradiotherapy (CCRT) is the standard adjuvant therapy for cervical cancer patients with high-risk factors such as lymph node metastasis, parametrial involvement and positive surgical margins (Peters et al., 2000). For patients whose clinicopathologic findings present with a combination of intermediate-risk factors such as large size, deep stromal invasion, and lymphovascular involvement, postoperative pelvic radiotherapy (RT) is suggested (Rotman et al., 2006), although the use of concurrent chemotherapy is still controversial (Kim et al., 2020; Li et al., 2019). A biomarker that can

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Table 1
The basic clinicopathologic characteristics according to adjuvant treatment.

Factors	RT(n = 454)	CCRT(n = 515)	P value (p < 0.05)
Age (year)Median	60 (24–76)	59 (28–77)	0.544
FIGO stageIBIIA	296 (65.2) 158 (34.8)	325 (63.1) 190 (36.9)	0.615
HistologySquamous cell carcinomaAdenocarcinomaAdenosquamous cell carcinoma	348 (76.7)75 (16.5)31 (6.8)	361 (70.1) 125 (24.3)29 (5.6)	0.499
Hemoglobin≥ 110 g/L< 110 g/L	408 (89.9)46 (10.1)	477 (92.6)38 (7.3)	0.755
BMI (Kg/m2)≥18.5< 18.5	224 (49.3) 230 (50.7)	325 (63.2) 190 (36.8)	0.041
Histological gradeG1G2G3	33(7.2) 345 (76.1)76 (16.7)	60(11.7) 359 (69.7)96 (18.6)	0.245
Tumor size≥ 4 cm< 4 cm	316 (69.7) 138 (30.3)	367 (71.3) 148 (28.7)	0.538
DSI≥ 1/2< 1/2	382 (84.2)72 (15.8)	416 (80.8)99 (19.2)	0.773
LVSI PositiveNegative	210 (46.3) 244 (53.7)	269 (52.2) 246 (47.8)	0.665
Risk factorsLTS + DSI LTS + LVSI DSI + LVSI LTS + LVSI + DSI	130 (29.4) 30 (6.8)247 (55.9)35 (7.9)	107 (21.2)11 (2.2)246 (48.9) 139 (27.6)	0.020
HDR brachytherapyYesNo	15(3.3) 439 (96.7)	26(5)489 (95)	0.717

Abbreviation: Values are presented as median (interquartile range) or number (%). FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index; DSI, deep stromal invasion; LVSI, lymph-vascular space invasion; LTS, large tumor size; HDR, High-dose rate.

further classify the risk of patients who have a combination of intermediate-risk factors and guide physicians in their use of concurrent chemotherapy.

Nutritional status and cancer-related inflammation not only affect the occurrence, promotion, invasion and metastasis of tumors but also affect the clinical outcomes of various malignant tumors (McMillan, 2009; Dolan et al., 2017; Dolan et al., 2017). Some nutritional scoring systems, such as the prognostic nutritional index (PNI) (Kang et al., 2017), nutritional risk index (NRI) (Yim et al., 2016), patient-generated subjective global assessment (Correira Pereira et al., 2014), and body mass index (BMI) (Campbell et al., 2012), have been devised to assess nutritional risk and treatment efficacy and predict prognosis in cancer patients. As biomarkers of inflammation have attracted extensive attention, a large number of inflammatory biomarkers, such as platelet count (Zheng et al., 2017), the systemic immune-inflammation index (SII) (Wang et al., 2017), the neutrophil-to-lymphocyte ratio (NLR) (Asano et al., 2016), the lymphocyte-to-monocyte ratio (LMR) (Song et al., 2016), and the platelet-to-lymphocyte ratio (PLR) (Min et al., 2017), have been found to predict the prognosis of multiple malignant tumors. Controlling nutritional status (CONUT), a newly proposed scoring system, is composed of the serum albumin concentration, total blood cholesterol level, and total peripheral lymphocyte count and reflects the nutritional and immune status of cancer patients (Ignacio de Ulíbarri et al., 2005). The pretreatment CONUT score has been reported to predict the prognosis of various malignancies (Liang et al., 2017) and the response to treatment (Daitoku et al., 2018). However, no previous studies have evaluated the relationship between CONUT and clinical outcomes of early-stage cervical cancer patients with intermediate-risk factors.

Therefore, we conducted a retrospective study to confirm the clinical value of the pretreatment COUNT score in guiding the use of concurrent chemotherapy and predicting survival outcomes in patients with early-stage cervical cancers with intermediate-risk factors.

2. Methods

2.1. Patients

The medical records of 1012 consecutive patients with 2009 International Federation of Gynecology and Obstetrics (FIGO) stages IB-IIA cervical cancer were retrospectively examined at our institutions from 2009 to 2018. The inclusion criteria of the study were as follows: histologically confirmed FIGO stage IB-IIA cervical cancer; received radical hysterectomy and pelvic lymph node dissection and/or para-aortic lymph node sampling; pathologically confirmed at least two of the following three intermediate-risk prognostic factors: deep stromal invasion (defined as an invasion into > half the thickness of the cervical stroma), lymphovascular space invasion, or tumor size ≥4 cm; treated with postoperative RT or CCRT; and the patient's liver and renal function were normal. Patients who underwent preoperative RT or neoadjuvant chemotherapy or experienced postoperative complications were excluded from our study. Finally, 969 patients who met the inclusion criteria were included in our retrospective study (**Supplemental fig. 1**).

We obtained all patient data from their medical records, including a history and physical examination; contrast-enhanced thoracic computed tomography (CT); contrast-enhanced abdominal and pelvic magnetic resonance imaging (MRI) or positron emission tomography-CT (PET-CT); and complete blood count. The study was approved by the Institutional Ethics Committee. All medical information was anonymous, and the Institutional Review Board waived informed consent was waived due to the retrospective nature of this study.

2.2. Treatment

Whether concurrent chemotherapy should be added to postoperative radiotherapy for early cervical cancer with intermediate risk factors was determined by the physician's preference. All patients received postoperative intensity-modulated radiotherapy (IMRT) 4–6 weeks after surgery. The IMRT technique included conventional fixed-field IMRT or helical tomotherapy (HT). The clinical target volume (CTV) included regional lymph node regions (obturator, internal, external and common iliac nodal regions), presacral area, and the upper vagina. The prescribed dose of 45–50.4 Gy in 25–28 fractions was given to the planned target volume (PTV) with external irradiation. High-dose rate (HDR) intracavitary brachytherapy was indicated for the patients if the tumor was adjacent (<5 mm) to the surgical margin of the vagina with a prescription dose of 20 Gy/4 fractions. In the study, 41 patients were treated with intracavitary brachytherapy. The concurrent chemotherapy regimen was paclitaxel 135 mg/m^2 and cisplatin 70 mg/m^2 every 3 weeks for 2 cycles (180 patients), paclitaxel 135 mg/m^2 and carboplatin AUC 5 every 3 weeks for 2 cycles (77 patients), weekly 40 mg/m^2 cisplatin for 6 cycles (129 patients) or cisplatin 75 mg/m^2 every 3 weeks for 2 or 3 cycles (129 patients).

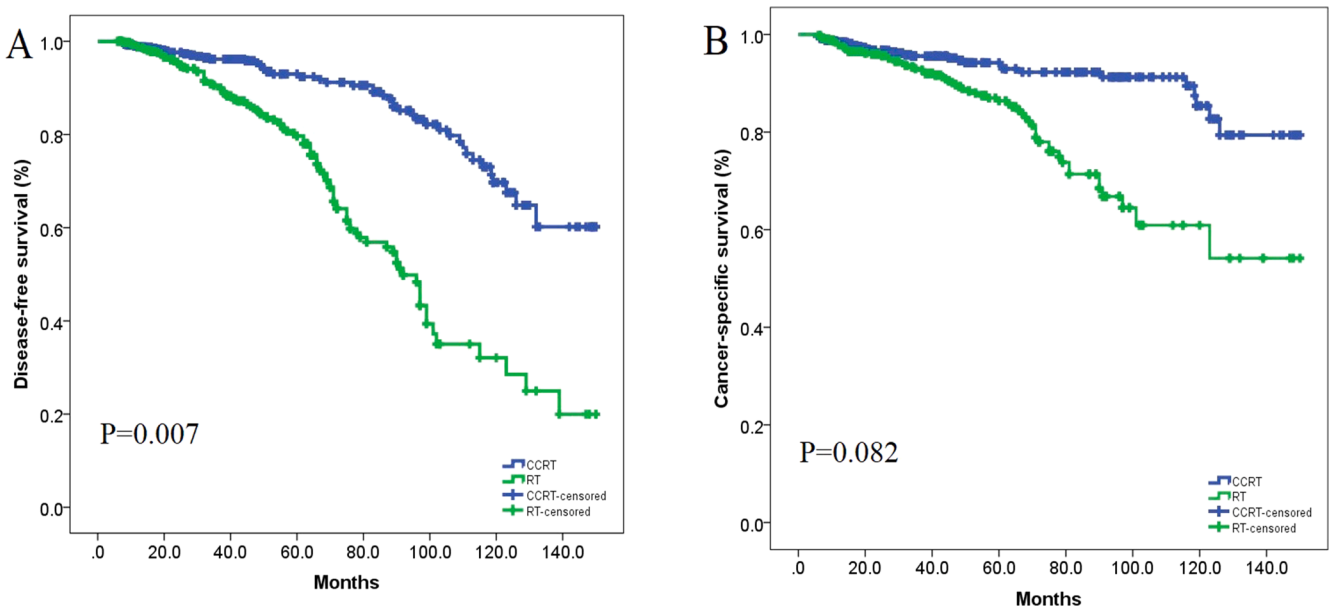

Fig. 1. A and B Disease-free survival (90.4 % vs. 75.6 %) and cancer-specific survival (94.3 % vs. 85.4 %) based on adjuvant treatment for all enrolled patients.

2.3. Definition of CONUT score

The CONUT score was calculated using data for each patient's serum albumin level, total cholesterol level, and total lymphocyte counts at the time of admission prior to radical surgery (Ignacio de Ulíbarri et al., 2005). The specific details of the CONUT score are as follows: First, albumin levels ≥ 3.5, 3.0–3.49, 2.5–2.99, and < 2.5 g/dL were scored as 0, 2, 4, and 6 points, respectively; Second, total cholesterol levels ≥ 180, 140–179, 100–139, and < 100 mg/dL were scored as 0, 1, 2, and 3 points, respectively; Third, total lymphocyte counts ≥ 1600, 1200–1599, 800–1199, and < 800/mm3 were scored as 0, 1, 2, and 3 points, respectively. The CONUT score was defined by adding the scores of all three biological parameters together. The optimal cutoff CONUT value suggested by our previous studies was 3 (Zhang et al., 2021). The patients were divided into 2 groups: the low CONUT group (score < 3) and the high CONUT group (score ≥ 3).

2.4. Follow-up and statistical analysis

The first follow-up examination was conducted 1 month after the initial treatment. Subsequent follow-up examinations were conducted every 3 months in the first 2 years, every 6 months from the third to fifth years and annually after 5 years. The conventional follow-up evaluation included gynecological examinations, blood count, abdomen and pelvic enhanced MRIs, and chest enhanced CT. If a patient showed signs of recurrence, PET/CT and biopsy were performed. All patients were followed up until June 2022 or their death.

The statistical analyses of the data were conducted with SPSS software, version 19.0 (IBM Corporation, Armonk, NY, USA). Local recurrence was defined as recurrence within the irradiated field, and distant recurrence was defined as recurrence outside the irradiated field. We analyzed the categorical variables with the chi-square test or Fisher's exact test, and the continuous variables were analyzed with the Mann-Whitney *U* test. A Cox proportional hazards regression test was used to conduct multivariate analyses of disease-free survival (DFS), local control (LC), distant metastasis (DM) and cancer-specific survival (CSS). Cancer-specific survival (CSS) was defined from the date of surgery until death from cervical cancer or the last follow-up. A level of $P < 0.05$ was considered to be significant. The DFS and CSS rates were determined by the Kaplan-Meier method.

3. Results

3.1. Patient characteristics

Among the 969 eligible patients for the study, 515 patients received postoperative CCRT, whereas another 454 patents underwent only postoperative RT. The basic clinical features of the patients were shown in Table 1. The median follow-up was 51.6 months (range: 6.5–150 months). A total of 490 (50.6 %) patients with a score < 3 were included in the low CONUT group, and 479 (49.4 %) patients with a score ≥ 3 were included in the high CONUT group. There were no significant differences in FIGO stage, hemoglobin level, histology, differentiation, pretreatment tumor size, LVSI, DSI or HDR brachytherapy between the two groups. Patients who received CCRT tended to have a higher BMI and multiple intermediate risk factors than those who received RT alone ($P = 0.041$ and 0.020, respectively).

The patients receiving concurrent chemotherapy had a better DFS ($P = 0.007$) (Fig. 1A). The 5-year DFS rates for the two groups were 90.4 % and 75.6 %, respectively. The 5-year CSS rates for patients with and without concurrent chemotherapy were 94.3 % and 85.4 %, respectively, a difference that was not statistically significant ($P = 0.082$) (Fig. 1B). In the total sample, 98 patients (10.1 %) had died at the end of the follow-up period. A total of 161 patients (16.6 %) had tumor recurrence, including 25 patients (2.6 %) with local relapse (in-field failure), 102 patients (10.5 %) with distant metastases (out-field failure), and 34 patients (3.5 %) with concurrent local relapse and distant metastases. The most common sites of distant metastasis were the paraaortic node (42 patients), supraclavicular lymph node (19 patients), and lung (18 patients).

3.2. Effect of CONUT score and statistical analysis

In the group with low CONUT scores, 248 patients (51 %) received postoperative RT, and 242 patients (49 %) experienced postoperative CCRT. There was no difference in the 5-year CSS (94.5 % vs. 90.7 %, $P = 0.536$) and DFS (90.6 % vs. 83.1 %, $P = 0.209$) between patients who did and patients who did not receive concurrent chemotherapy (Fig. 2 A and B, Table 2). The type of tumor recurrence was also not significantly different between the two groups (Table 3).

Of the 479 patients with high CONUT scores, 206 patients (43 %) received postoperative RT alone, and 273 patients (57 %) received

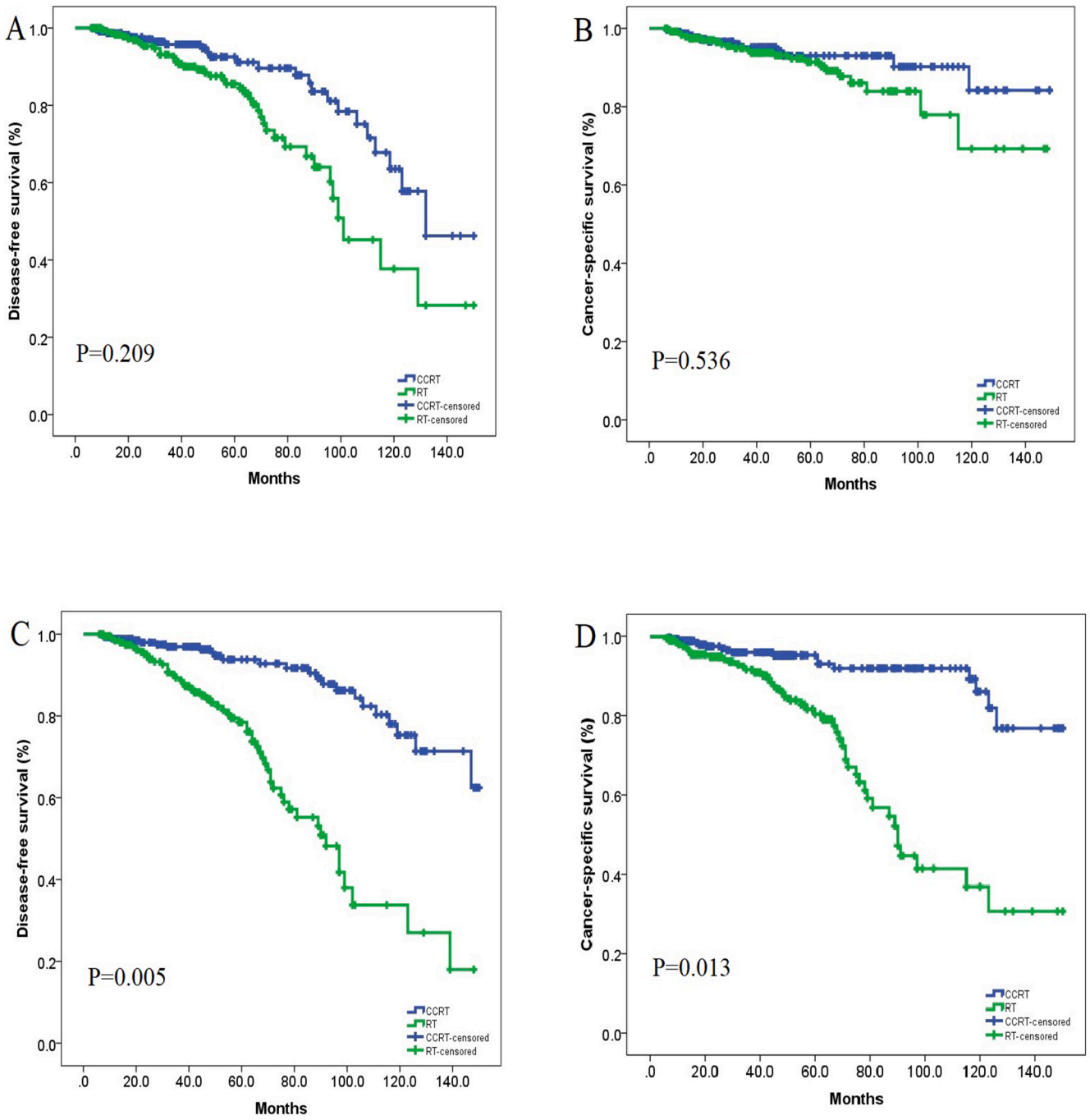

Fig. 2. A and B Disease-free survival (90.6 % vs. 83.1 %) and cancer-specific survival (94.5 % vs. 90.7 %) for the patients with low CONUT scores. C and D Disease-free survival (91.2 % vs. 72.8 %) and cancer-specific survival (93.8 % vs. 77.4 %) for the patients with high CONUT scores.

Table 2
Survival of patients with different CONUT scores.

Group	Low CONUT group (score < 3)			High CONUT group (score ≥ 3)		
	RT (248)	CCRT (242)	P-value	RT (206)	CCRT (273)	P-value
5-year DFS	83.1 %	90.6 %	0.209	72.8 %	91.2 %	0.005
5-year CSS	90.7 %	94.5 %	0.536	77.4 %	93.8 %	0.013

P < 0.05; CONUT, controlling nutritional status; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; DFS, disease-free survival; CSS, cancer-specific survival.

Table 3
Recurrence according to different CONUT scores.

Group	Low CONUT group (score < 3)			High CONUT group (score ≥ 3)		
	RT (248)	CCRT (242)	P-value	RT (206)	CCRT (273)	P-value
5-year LRF	7.5 %	5.4 %	0.741	16.7 %	8.5 %	0.034
5-year DM	16.2 %	13.5 %	0.625	30.4 %	11.7 %	0.015

P < 0.05; CONUT, controlling nutritional status; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; LRF, locoregional failure; DM, distant metastasis.

Table 4
Multivariate analysis of factors influencing LC, DM, DFS and CSS for patients with high CONUT score.

Factors	LCHR(95 %CI)	P	DM HR(95 %CI)	P	DFSHR(95 %CI)	P	CSSHR(95 %CI)	P
StageIBIIA	Ref. 2,127 (1.589–2.848)	0.217	Ref. 2.189 (1.641–2.921)	0.189	Ref. 2.285 (1.717–3.037)	0.394	Ref. 1.943 (1.453–2.957)	0.113
Tumor size < 4 cm≥ 4 cm	Ref. 1.425 (1.038–1.955)	0.025	Ref. 0.878 (0.651–1.187)	0.397	Ref. 1,295 (0.961–1.774)	0.101	Ref. 1.434 (1.188–2.902)	0.234
DSI< 1/2≥ 1/2	Ref. 1.142 (0.780–1.689)	0.751	Ref. 1.181 (0.823–1.721)	0.608	Ref. 1.377 (0.899–1.813)	0.118	Ref. 1.414 (0.762–2.282)	0.228
LVSI NegativePositive	Ref. 1,275 (0.817–1.978)	0.293	Ref. 2.928 (0.948–2.379)	0.071	Ref. 1.221 (0.945–1.568)	0.431	Ref. 1.312 (0.889–1.678)	0.301
Number of risk factors2 3	Ref. 0.883 (0.624–1.254)	0.475	Ref. 1.433 (1.029–1.996)	0.033	Ref. 1.977 (0.633–2.291)	0.241	Ref. 1.144 (0.862–1.519)	0.354
Concurrent chemotherapyNoYes	Ref. 0.722 (0.524–0.992)	0.041	Ref. 1.816 (1.332–2.478)	0.005	Ref. 1.707 (1.244–2.365)	0.011	Ref. 1.657 (1.198–2.292)	0.023

P < 0.05; HR, hazard ratio; CI, confidence interval; DSI, deep stromal invasion; LVSI, lymph-vascular space invasion; DFS, disease-free survival; LC, local control; DM, distant metastasis; CSS, cancer-specific survival.

CCRT. In the high CONUT score group, patients who received concurrent chemotherapy had a better 5-year CSS rate (93.8 % vs. 77.4 %, P = 0.013) and DFS (91.2 % vs. 72.8 %, P = 0.005) than those who did not receive concurrent chemotherapy (Fig. 2C and D, Table 2). The study showed that the addition of concurrent chemotherapy significantly reduced the chances of locoregional recurrence (8.5 % vs. 16.7 %, P = 0.034) and distant metastases (11.7 % vs. 30.4 %, P = 0.015) (Table 3). We also performed a multivariate analysis of the data for patients with high CONUT scores (Table 4). The results revealed that a large tumor size (≥4 cm) indicated worse LC (P = 0.025, 95 % CI: 1.038–1.955). Patients with three intermediate-risk factors were more likely to suffer from distant metastasis (P = 0.033, 95 % CI: 1.029–1.996). The decision about whether a patient did or did not receive concurrent chemotherapy was determined to be the unique factor that was significantly associated with LC (P = 0.041, 95 % CI: 0.524–0.992), DM (P = 0.005, 95 % CI: 1.332–2.478), DFS (P = 0.011, 95 % CI: 1.244–2.365) and CSS (P = 0.023, 95 % CI: 1.198–2.292), thus indicating that patients receiving concurrent chemotherapy could significantly improve their oncologic outcome compared with RT alone.

4. Discussion

For early-stage cervical cancer with intermediate-risk factors, there was no consensus on whether concurrent chemotherapy should be added to postoperative radiotherapy and the significance of CCRT on clinical outcome. Several studies have demonstrated that postoperative CCRT improves survival compared with radiotherapy alone for the intermediate-risk cervical cancer (Ryu et al., 2011; Song et al., 2012; Okazawa et al., 2013; Sun et al., 2018). However, other studies have reported contradictory results (Kim et al., 2020; Matsuo et al., 2017). Our present study showed that for early-stage cervical cancer patients with intermediate-risk factors, those who received postoperative CCRT achieved a better DFS than those who received RT alone, but there was no significant difference in CSS. When performing subgroup analysis based on the level of pretreatment CONUT score, our study revealed that concurrent chemotherapy was clinically significant only for patients with a high CONUT score, improving both DFS (CCRT vs. RT, 91.2 % vs. 72.8 %, P = 0.005) and CSS (CCRT vs. RT, 93.8 % vs. 77.4 %, P = 0.013). Concurrent chemotherapy did not improve survival outcomes in patients with low CONUT scores. Furthermore, according to the multivariate analysis, our study demonstrated that concurrent chemotherapy was an independent prognostic factor for LC (P = 0.041), DM (P = 0.005), DFS (P = 0.011) and CSS (P = 0.023) in patients with high pretreatment CONUT scores. Our study is the first to reveal that the clinical value of the pretreatment CONUT score in early-stage cervical cancer with intermediate-risk factors lies in its ability to predict the efficacy of concurrent chemotherapy.

In the study of Liang et al., an elevated preoperative CONUT score was a strong predictor of poor survival in solid tumors and has been used to predict tumor recurrence after treatment (Liang et al., 2017). The CONUT score is a prognostic factor for the survival of multiple tumors (Liang et al., 2017; Daitoku et al., 2018; Miyata et al., 2018; Harimoto et al., 2018), which is mainly determined by its three parameters. It not only reflects the nutritional and immune status, but also reflects the progression of tumors. Serum albumin levels, as a reliable marker of systemic immunity and inflammation (McMillan et al., 2001), were reportedly associated with tumor necrosis and the survival of cancer patients (Ayhan et al., 2017). While total lymphocyte counts reflect immunological status, lymphopenia in advanced cancer patients generates a microenvironment suitable for cancer cell proliferation and metastasis, resulting in a poor prognosis (Ray-Coquard et al., 2009). Finally, the total cholesterol concentration has been reported to correlate with tumor progression, as cholesterol metabolism enhances the antitumor immune response of CD8(+) T cells (Yang et al., 2016). These results suggest that the CONUT score which was directly calculated from clinical data could act as a marker in objectively predicting clinical outcomes.

As shown in previous studies, for cervical cancer patients with intermediate-risk factors, although the use of adjuvant RT reduces the recurrence rate (Rotman et al., 2006; van den Akker et al., 2020), a large number of patients suffer from extrapelvic recurrence (Kim et al., 2020; Li et al., 2019). However, the main goal of postoperative adjuvant therapy is not only to control local recurrence, but also to reduce distant metastasis. The addition of postoperative adjuvant chemotherapy can effectively control distant metastasis in early-stage cervical cancer patients with intermediate-risk factors (Lee et al., 2008). In the current study, for patients with high CONUT scores, the addition of concurrent chemotherapy significantly improved the local control and distant metastasis compared with RT alone. In patients with a low CONUT score, CCRT seemed to contribute little in improving the oncologic outcome. We found that the pretreatment CONUT score might be able to be used to guide the concurrent chemotherapy in postoperative RT. According to our multivariate analysis, large tumor size was an independent predictor of local recurrence, and more intermediate-risk factors were an independent predictor of distant metastasis. These results are the same as those of previous studies (Sun et al., 2018; Ayhan et al., 2004).

Our study had a few limitations. This was a retrospective study, and it was not feasible to completely exclude the potential for selection bias. The high treatment expenses or seeking traditional Chinese medicine treatment after surgery were the main reasons for patients drop out. Second, there is no consensus on the use of concurrent chemotherapy, and decisions about postoperative adjuvant treatment vary according to the preferences of physicians. Third, we did not perform an analysis of toxicity associated with postoperative adjuvant therapy because of incomplete data. Fourth, we knew that the nutritional status of the patient and comorbidities can affect inflammatory and nutritional parameters. However, because some patients received treatment in the

outpatient department, doctors did not always record the patient's relevant medication history and comorbidities on time. Consequently, we were unable to collect all the relevant data. Our study did not analyze the relationship between a systemic infection or comorbidities and mortality. To address these limitations, we are conducting a multicenter prospective randomized controlled trial to validate our findings. However, in order to confirm the effectiveness of CCRT in the cervical cancer with intermediate-risk factors, the prospective study GOG 263 (NCT01101451) will provide us with clear results in the near future.

In conclusion, the pretreatment CONUT score may be a predictive factor for the use of concurrent chemotherapy in early-stage cervical cancer patients with intermediate-risk factors during postoperative RT. Patients with high CONUT scores were able to benefit from postoperative CCRT. Our study findings suggest that a patient's pretreatment CONUT score can be helpful physicians make decisions about the postoperative adjuvant treatment protocol they prescribe.

Authors contributions

CLF: study conception and design, data analysis, interpretation of data, writing-original draft and writing-review & editing.. **CW**: study conception and design, clinical data collection, data analysis, writing-original draft and writing-review & editing.. **QHQ**: clinical data collection, data analysis. **YZY**: clinical data collection, data analysis. **CDM**: data analysis, interpretation of data. **LM**: clinical data collection, data analysis. **GYZ**: study conception and design, data analysis, interpretation of data, revision of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary materials

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2023.101228.

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