Clinical significance of the cachexia index in patients with small-cell lung cancer

Se-Il Go
Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine

Mi Jung Park
Gyeongsang National University Hospital, Gyeongsang National University College of Medicine

Gyeong-Won Lee (brightree24@gmail.com)
Gyeongsang National University Hospital, Gyeongsang National University College of Medicine

Research Article

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Abstract

Background: Cancer cachexia worsens the treatment outcomes of patients with small-cell lung cancer (SCLC). However, no reliable biomarker of cancer cachexia is yet known.

Methods: We retrospectively evaluated SCLC patients who received induction chemotherapy or concurrent chemoradiotherapy. The cachexia index (CXI) was calculated as the skeletal muscle index × serum albumin level (g/dL)/the neutrophil-to-lymphocyte ratio. Male and female cutoffs were defined based on a time-dependent receiver operating characteristic curve, and all patients divided into low- and high-CXI groups.

Results: Of 302 patients, 94 and 208 had low and high CXI values, respectively. Only one patient (1.1%) in the low-CXI group achieved a complete response (CR), whereas 35 of 208 patients (16.8%) in the high-CXI group achieved CRs ($p < 0.001$). More low-CXI patients (compared to the high-CXI patients) required early discontinuation of treatment because of treatment-related toxicity (20.2% vs. 6.3%, $p < 0.001$) and experienced treatment-related mortality (8.5% vs. 2.9%, $p = 0.031$). The median progression-free survival (PFS) and overall survival (OS) were significantly poorer in the low-CXI group than in the high-CXI group (5.8 vs. 6.9 months and 8.3 vs. 15.6 months, respectively, both $p < 0.001$). These differences did not vary according to cancer stage. On multivariate analysis, a low-CXI status was an independent poor prognostic factor for both PFS and OS.

Conclusion: A low CXI was associated with treatment intolerance, a poor treatment response rate, and a poor prognosis of SCLC.

Background

Small-cell lung cancer (SCLC) is a highly aggressive disease characterized by rapid tumor growth, early widespread dissemination, and a high probability of relapse [1, 2]. Although the response duration is short, etoposide or irinotecan plus platinum-based chemotherapy with or without concurrent radiotherapy is associated with a high response rate and prolongs survival [3-5]. The addition of immunotherapy to chemotherapy further improved the treatment outcomes of patients with extensive-stage disease (ED) [6, 7]. However, elderly patients or those of poor performance status (PS) experience more treatment-related toxicity and tend to be unable to undergo optimal treatment [8-10]. As the prognosis of SCLC patients who fail to complete treatment is extremely poor, those who cannot tolerate induction chemotherapy should be identified and treated with intensive supportive care.

Cancer cachexia (an ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support [11]) is associated with more treatment-related toxicity, a reduced quality of life, and poor prognosis [12-14]. In SCLC patients, weight loss is associated with a poor treatment response, decreased quality of life, and short survival [15-17]. Several biomarkers of cachexia such as sarcopenia, a cachexia score, and nutritional indices have been suggested to be prognostic in SCLC patients [18-22]. The cachexia index (CXI) is a novel measure of cachexia in patients with advanced non-small-cell lung

cancer and non-Hodgkin's lymphoma [23, 24]. The CXI considers the skeletal muscle index (SMI), serum albumin level, and neutrophil-to-lymphocyte ratio (NLR), and may thus comprehensively reflect cachectic status. Currently, any role for the CXI in SCLC remains unclear. Therefore, we investigated whether the CXI reflected the prognosis and treatment outcomes of SCLC patients.

Methods

Patients

From July 2006 to June 2020, all consecutive SCLC patients receiving etoposide or irinotecan plus platinum combination chemotherapy as first-line treatment (with or without radiotherapy) in a single institution were retrospectively reviewed. Patients with another type of cancer and/or a serious active infection were excluded. Those who were not available for serum albumin levels and complete blood counts measured within 7 days before the first cycle of chemotherapy, and patients for whom baseline chest computed tomography (CT) scans were unavailable, were excluded. The study was approved by the Institutional Review Board of Gyeongsang National University Hospital.

Assessments

Clinical, laboratory, and radiological data were extracted from electronic medical records. The CXI was calculated as the SMI × serum albumin level (g/dL)/the NLR [23]. We used the pectoralis major and minor muscles to measure the SMI based on a previously described method [19]. Briefly, the cross-sectional areas of the bilateral pectoralis muscles were separately calculated using CT histograms. The average area was normalized to height (m^2); the SMI thus had the unit cm^2/m^2. Underweight was defined as a body mass index (BMI) < 18.5 kg/m^2 (the Asian criterion). The response to anticancer therapy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 [25]. Therapy-related adverse events were assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events ver. 4.0. Treatment-related mortality (TRM) was defined as death from any cause other than cancer progression before 30 days after the last cycle of first-line chemotherapy. Early discontinuation of treatment was noted when first-line chemotherapy ceased because of treatment-related toxicity, regardless of the response to treatment.

Statistical analysis

The CXI cutoff was determined by maximizing the Youden index (the sum of sensitivity and specificity) for predicting 1-year overall survival (OS) using a time-dependent receiver operating characteristic (ROC) curve [26]. The cutoff differed by sex because muscle mass varies by sex. By reference to the cutoffs, patients were divided into low- and high-CXI groups. Correlations between dichotomous and continuous or categorical variables were explored using the Mann-Whitney U-test and the chi-squared test as appropriate. OS was defined as the time from the first day of treatment to death or the last follow-up. Progression-free survival (PFS) was calculated as the time from the first day of treatment to progression, death, or the last follow-up. The Kaplan-Meier method and the log-rank test were used to estimate survival

data. A Cox's regression model was employed for multivariate analysis. All variables with *p*-values < 0.10 on univariate analyses were included in the multivariate regression model. A two-sided *p*-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using R ver. 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) and STATA ver. 16.1 (College Station, TX, USA).

Results

Patient characteristics

The mean (± standard deviation) and median (range) CXI values were, respectively, 9.35 (± 6.18) and 7.65 (0.47 – 34.15) for males and 7.76 (± 6.32) and 5.90 (1.18 – 30.57) for females. The area under the curve (AUC) (calculated using time-dependent ROC data) was 0.651 for males and 0.602 for females (**Supplementary Fig. 1**). The CXI cutoffs were 5.23 (sensitivity 41.4% and specificity 85.9%) for males and 6.79 (sensitivity 72.6% and specificity 58.4%) for females. In total, 208 and 94 patients were assigned to the high- and low-CXI groups, respectively.

Patient baseline characteristics are presented in **Table 1**. The median age was 68 years (range 40 – 86 years). Most patients were male (88.4%) and of Eastern Cooperative Oncology Group (ECOG) PS 0 – 1 (78.5%). The low-CXI group had a higher proportion of patients with a poor PS (ECOG PS 2 – 3, 37.2% vs. 14.4%, $p < 0.001$), more advanced-stage disease (ED, 73.4% vs. 53.4%, $p = 0.001$), and received prophylactic cranial irradiation less frequently (25.5% vs. 49.0%, $p < 0.001$), compared to the high-CXI group. As expected, the BMI was lower in the low-CXI group than in the high-CXI group (median 21.3 vs. 23.2 kg/m^2, $p < 0.001$).

Treatment response

Of 302 patients, 285 were available for the assessment of treatment response (**Table 2**). The objective response rates [ORRs; complete response (CR) + partial response (PR)] were 71.3% and 89.4% in the low- and high-CXI groups, respectively ($p < 0.001$). Only one (1.1%) patient in the low-CXI group achieved a CR, compared to 35 of 208 (16.8%) patients in the high-CXI group ($p < 0.001$). All 36 patients who achieved CRs completed their planned treatments. When 60 patients who discontinued treatment early (because of toxicity or patient decision) or for whom treatment response was not assessed were excluded from the analysis, the ORR remained lower in the low-CXI group compared to the high-CXI group (78.3% vs. 91.2%, $p = 0.008$).

Treatment-related toxicity

Adverse treatment-related events are listed in **Table 3**. Neutropenia of grade ≥ 3 was more frequently observed in the high-CXI group than in the low-CXI group ($p = 0.033$). However, low-CXI patients received fewer cycles of chemotherapy (median 5 vs. 6 cycles, $p < 0.001$) and more frequently discontinued treatment early because of treatment-related toxicity (20.2% vs. 6.3%, $p < 0.001$) compared to high-CXI

patients. TRM occurred in 8 of 94 (8.5%) patients in the low-CXI group but in only six (2.9%) patients in the high-CXI group (p = 0.031).

Survival

The median follow-up duration was 41 months. PFS was significantly shorter in the low-CXI group than in the high-CXI group (median 5.8 vs. 6.9 months, p < 0.001; **Fig. 1A**). OS was also shorter in the former group (median 8.3 vs. 15.6 months, p < 0.001; **Fig. 1B**). Similar findings were obtained following subgroup analyses by stage. In limited-stage disease (LD) patients, those with a low CXI had a shorter PFS (median 6.8 vs. 13.3 months, p < 0.001; **Fig. 2A**) and OS (median 8.3 vs. 23.9 months, p < 0.001; **Fig. 2B**) compared to those with a high CXI. In ED patients, those with a low CXI also had a shorter PFS (median 5.1 vs. 6.2 months, p = 0.014; **Fig. 2C**) and OS (median 8.1 vs. 12.9 months, p < 0.001; **Fig. 2D**) compared to those with a high CXI. On multivariate analysis, an ECOG PS of 2 – 3, ED, and a low CXI were independent poor prognostic factors for PFS [low CXI, hazard ratio (HR) 1.472, 95% confidence interval (CI) 1.107 – 1.958, p = 0.008] and OS (low CXI, HR 1.644, 95% CI 1.225 – 2.207, p = 0.001) (**Table 4**).

Discussion

This is the first study to report that a low CXI is closely related to poor clinical outcomes in SCLC patients. The CR rate differed greatly between the low- and high-CXI groups (1.1% vs. 16.8%). Although certain baseline characteristics such as the ECOG PS and disease stage, which are important prognostic factors, were not balanced between the two groups, PFS and OS were much poorer in the low-CXI group even after adjusting for those factors. Although any role for the CXI has not yet been examined in SCLC patients, each CXI factor has been suggested to be prognostic in several studies. The survival of sarcopenic SCLC patients was poorer than that of non-sarcopenic patients [18]. When models that included both sarcopenia and levels of inflammatory markers were used, the clinical significance of sarcopenia was emphasized [19, 27]. Hypoalbuminemia and other indices reflecting low serum albumin levels were associated with reduced survival, increased treatment-related toxicity, and a low treatment response rate [21, 22, 28-30]. A high NLR was related to poor PS, a high probability of recurrence, and reduced survival [31-33]. The results of the present study and previous studies thus suggest that the CXI is significantly prognostic in SCLC patients.

Cancer cachexia must be carefully assessed. Percentage weight loss alone is of limited utility in the era of obesity [34, 35]. Sarcopenia has been used to diagnose and stage cancer cachexia [11]. Cross-sectional CT optimally assesses muscle mass [11]. Inflammatory cytokines produced by tumor cells [tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8] contribute to muscle wasting by inducing oxidative stress in skeletal muscles and activating muscle degradation pathways [36-38]. TNF-α inhibited albumin expression in a murine model of cachexia even before the onset of weight loss [39]. Ideal biomarkers of cancer cachexia must therefore reflect these various processes. Several studies have explored the clinical utilities of composite biomarkers or scoring systems for cachexia in SCLC patients [20-22, 30]. However, unlike the CXI, the biomarkers did not consider either sarcopenia or systemic

inflammation. Although the CXI is more complex than other biomarkers, the factors can be measured non-invasively via routine baseline imaging and laboratory tests. The CXI may serve as an ideal biomarker of cachexia in SCLC patients.

The low-CXI group very frequently discontinued treatment early because of treatment-related toxicity (20.2%) and experienced TRM (8.5%). A recent study reported that malnourished patients exhibited increased rates of toxicity of grade ≥3 and were more likely to be hospitalized in phase I and II oncology clinical trials [40]. Several studies found that sarcopenia is a significant predictor of dose-limiting toxicity in patients with various malignancies [41-44]. Chemotherapy doses are generally based on body surface area. Therefore, among patients of the same height and weight, sarcopenic patients receive relatively higher doses than do non-sarcopenic patients because drug metabolism occurs predominantly in lean body tissue [35]. Given that no patient who did not complete planned treatment achieved a CR, the treatment intolerance observed in the low-CXI group may be associated with a poor response to chemotherapy.

Our work had several limitations. First, the data were retrospectively collected and thus associated with a risk of selection bias. We also lacked detailed toxicity profiles. Second, the method used to measure the SMI and CXI cutoffs differed from those of previous studies, rendering comparisons difficult. Chest CT performed during SCLC diagnostic work-up does not routinely include the L3 level. However, SMIs calculated using muscles at other vertebral levels, or the pectoralis muscle, correlated strongly with the L3-SMI [45-47]. Previous studies used the median to determine the CXI cutoff [23, 24]. The time-dependent ROC analysis employed in the present study is efficient to measure the performance of a biomarker at certain time point in survival data compared with other methods although the censoring is still problematic [26]. Third, the utility of the CXI in females remains unclear because of the small sample size. A large prospective study is needed.

In conclusion, we found that cachectic patients with low CXIs more frequently discontinued treatment early, experienced TRM, and exhibited poor prognosis in SCLC. Intensive supportive care and dose adjustment may improve the treatment outcomes of cachectic patients receiving chemotherapy or chemoradiotherapy. We anticipate that the CXI will become accepted as the ideal biomarker of cancer cachexia.

Abbreviations

AUC: Area under the curve; BMI: Body mass index; CI: Confidence interval; CR: Complete response; CT: Computed tomography; CXI: Cachexia index; ECOG PS: Eastern Cooperative Oncology Group performance status; ED: Extensive-stage disease; HR: Hazard ratio; IL: Interleukin; LD: Limited-stage disease; NLR: Neutrophil-to-lymphocyte ratio; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors; ROC: Receiver operating characteristic; SCLC: Small-cell lung cancer; SMI: Skeletal muscle index; TNF: Tumor necrosis factor; TRM: Treatment-related mortality

Declarations

Acknowledgement

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Authors' contributions

Study conceptualization and design: SG and GL

Data collection: SG and MJP

Data analysis and interpretation: SG, MJP, and GL

Overall supervision: GL

Manuscript writing: SG and MJP

All authors have read, revised, and approved the manuscript.

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Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Gyeongsang National University Hospital and conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Patient baseline characteristics

Characteristic	High-CXI group ($n = 208$)	Low-CXI group ($n = 94$)	p
Age			0.653
< 70 years	123 (59.1%)	53 (56.4%)	
≥ 70 years	585 (40.9%)	41 (43.6%)	
Median, years (range)	67.5 (40 – 85)	69 (43 – 86)	0.378
Sex			< 0.001
Male	193 (92.8%)	74 (78.7%)	
Female	15 (7.2%)	20 (21.3%)	
ECOG PS			< 0.001
0 – 1	178 (85.6%)	59 (62.8%)	
2 – 3	30 (14.4%)	35 (37.2%)	
Smoking status			0.118
Never-smoker	7 (3.4%)	7 (7.5%)	
Current/former smoker	201 (96.6%)	87 (92.6%)	
Stage			0.001
LD	97 (46.6%)	25 (26.6%)	
ED	111 (53.4%)	69 (73.4%)	
Regimen			0.026
Etoposide and platinum	201 (96.6%)	85 (90.4%)	
Irinotecan and cisplatin	7 (3.4%)	9 (9.6%)	
Prophylactic cranial irradiation			< 0.001
Yes	102 (49.0%)	24 (25.5%)	
No	106 (51.0%)	70 (74.5%)	
Lactate dehydrogenase status ($n = 232$)			0.063
Normal	68 (43.9%)	24 (31.2%)	
Elevated	87 (56.1%)	53 (68.8%)	
Median BMI (range), kg/m^2	23.2 (16.6 – 30.6)	21.3 (14.9 – 33.6)	< 0.001

CXI cachexia index, *ECOG PS* Eastern Cooperative Oncology Group performance status, *LD* limited-stage disease, *ED* extensive-stage disease, *BMI* body mass index

Table 2 Treatment responses

Treatment response	High-CXI group ($n = 208$)	Low-CXI group ($n = 94$)	p
Complete response (CR)	35 (16.8%)	1 (1.1%)	< 0.001
Partial response (PR)	151 (72.6%)	66 (70.2%)	
Stable disease or progressive disease	17 (8.2%)	15 (16.0%)	
Not available	5 (2.4%)	12 (12.8%)	
Objective response rate (CR + PR)	186 (89.4%)	67 (71.3%)	< 0.001

CXI cachexia index

Table 3 Treatment-related toxicity and treatment compliance

Adverse event	High-CXI group ($n = 208$)	Low-CXI group ($n = 94$)	p
Hematological toxicity ≥ grade 3			
Anemia	39 (18.8%)	21 (22.3%)	0.469
Neutropenia	190 (91.4%)	78 (83.0%)	0.033
Thrombocytopenia	47 (22.6%)	28 (29.8%)	0.181
Median treatment cycles (range)	6 (1 – 9)	5 (1 – 10)	< 0.001
Early discontinuation of treatment	13 (6.3%)	19 (20.2%)	< 0.001
Treatment-related mortality	6 (2.9%)	8 (8.5%)	0.031

CXI cachexia index

Table 4 Cox's regression analysis for PFS and OS

Factor	PFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age												
< 70 years	Ref.						Ref.					
≥ 70 years	1.017	0.796 – 1.300	0.890				1.159	0.890 – 1.509	0.273			
Sex												
Male	Ref.						Ref.					
Female	0.783	0.535 – 1.146	0.208				0.722	0.473 – 1.102	0.131			
ECOG PS												
0 – 1	Ref.			Ref.			Ref.			Ref.		
2 – 3	1.915	1.434 – 2.558	< 0.001	1.546	1.134 – 2.109	0.006	2.754	2.035 – 3.725	< 0.001	2.273	1.649 – 3.133	< 0.001
Smoking												
Never-smoker	Ref.						Ref.					
Current/former smoker	1.233	0.674 – 2.257	0.497				1.479	0.759 – 2.883	0.251			
Stage												
LD	Ref.			Ref.			Ref.			Ref.		
ED	2.973	2.555 – 3.919	< 0.001	2.738	2.068 – 3.624	< 0.001	2.262	1.700 – 3.012	< 0.001	2.036	1.521 – 2.735	< 0.001
Regimen												
Etoposide and platinum	Ref.						Ref.					
Irinotecan and cisplatin	1.488	0.896 – 2.472	0.124				1.325	0.784 – 2.237	0.293			
BMI												
Other (≥ 18.5 kg/m^2)	Ref.			Ref.			Ref.					
Underweight (< 18.5 kg/m^2)	1.420	0.965 – 2.089	0.075	1.225	0.830 – 1.808	0.307	1.251	0.831 – 1.883	0.284			
CXI												
High	Ref.			Ref.			Ref.			Ref.		
Low	2.054	1.580 – 2.671	< 0.001	1.472	1.107 – 1.958	0.008	2.366	1.800 – 3.109	< 0.001	1.644	1.225 – 2.207	0.001

PFS progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *LD* limited-stage disease, *ED* extensive-stage disease, *BMI* body mass index, *CXI* cachexia index

Figures

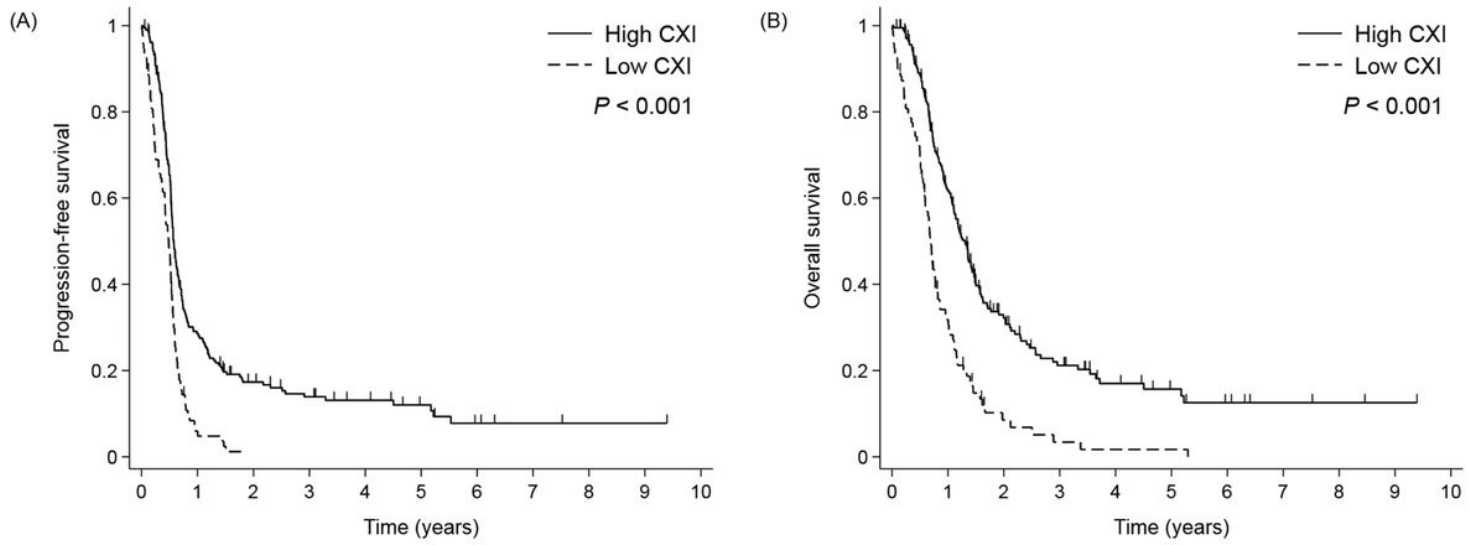

Figure 1

Kaplan-Meier curves for (A) progression-free survival and (B) overall survival according to the cachexia index (CXI)

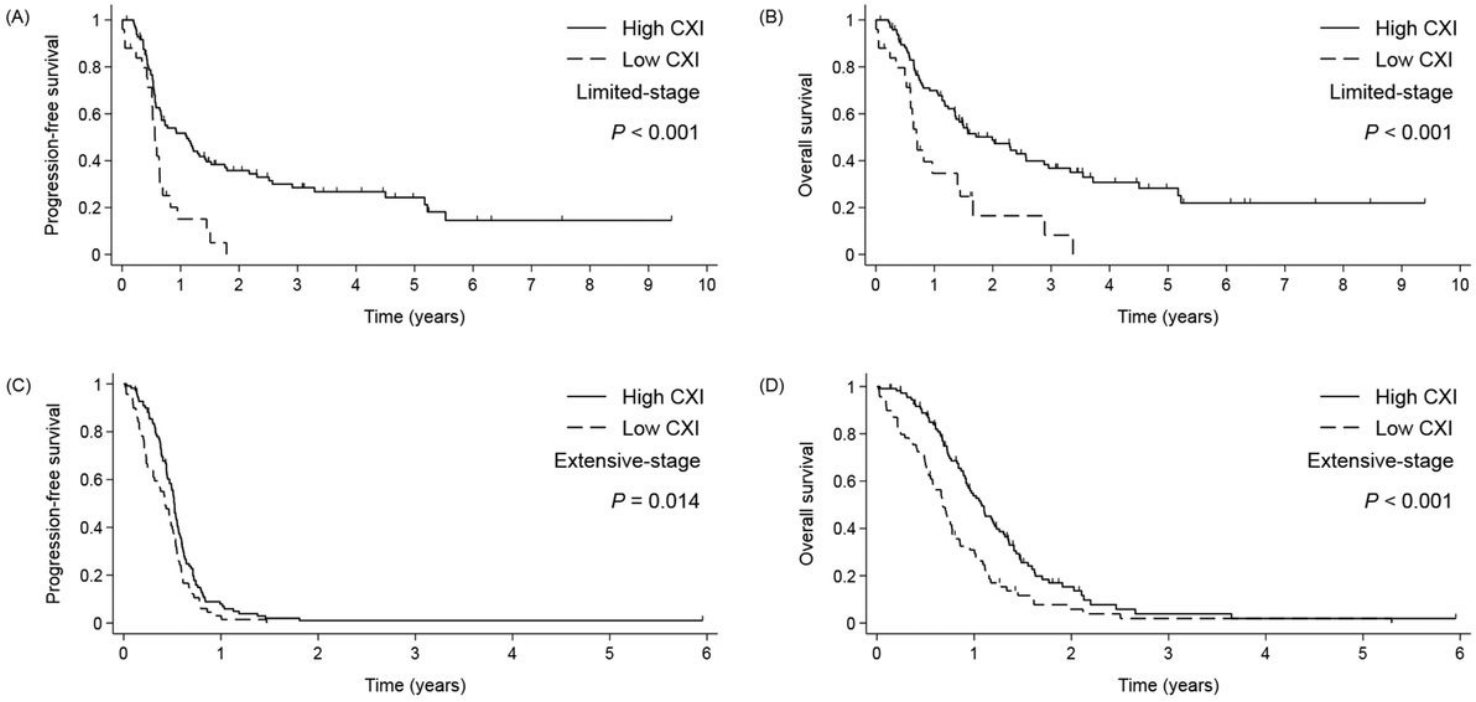

Figure 2

Kaplan-Meier curves for (A, C) progression-free survival and (B, D) overall survival according to the cachexia index (CXI) and disease stage

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.tif