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ORIGINAL RESEARCH

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Clinical implications of overweight regarding response and survival in locally advanced cervical cancers treated with curative chemoradiation: a retrospective and multi-institutional research

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Abstract

A multi-institutional investigation was conducted to investigate the impacts of overweight on the outcomes of locally advanced cervical cancers (LACC) treated by curative chemoradiation. Based on their body mass index (BMI), the patients were classified into an overweight (BMI, 25–29.9) or normal (BMI, 18.5–24.9) group. Parametric statistics were used to balance their baseline and treatment-related characteristics. The primary outcome was tumor response, and secondary outcomes were overall survival (OS) and disease-free survival (DFS). Univariate and multivariate logistic regressions were performed to test the contribution of overweight as a risk factor. Of the 707 patients enrolled, 228 were assigned to the overweight group and 479 to the normal group. The findings showed that the objective response rate (ORR) and disease control rate (DCR) of the overweight group was notably decreased as compared to normal group (50.0% *vs.* 58.5%, $p = 0.03$; 67.1% *vs.* 76.2%, $p = 0.01$, respectively). The median DFS of the overweight and normal groups were 34.0 and 35.0 months, respectively, with an hazard rate (HR) of 1.09 (95% confidence interval (CI): 0.87–1.36, $p = 0.42$). Moreover, the median OS of the overweight and normal groups were 49.0 and 52.0 months, respectively, with an HR of 1.22 (95% CI: 0.97–1.53, $p = 0.06$). Univariate analysis revealed that overweight was independently associated with poor ORR (odds ratio (OR): 0.710, 95% CI: 0.517–0.975; $p = 0.035$) and DCR (OR: 0.629, 95% CI: 0.444–0.891; $p = 0.009$), which was confirmed in multivariate logistic regression (OR: 0.564, 95% CI: 0.402–0.793, $p = 0.001$; OR: 0.513, 95% CI: 0.354–0.742, $p = 0.001$, respectively). To be summarized, overweight is characterized as an independent factor of poor response for curative chemoradiation, underscoring the importance of stratifying patients based on BMI during the LACC treatment process.

Keywords

Overweight; Cervical cancer; Chemoradiation; Response; Survival

1. Introduction

Cervical cancers are responsible for approximately 500,000 new cervical cancer cases and 300,000 related deaths annually [1] and therefore remain a considerable and desirable subject. Locally advanced cervical cancers (LACC), treated with platinum-based chemoradiation, are partly lost on the way to durable response or superior survival. There are a vast majority of researches focusing on identifying innovative predictors of treatment or survival to improve the management of cervical cancers. Currently used predictive biomarkers such as tumor mutation burden, programmed cell death-1 and microsatellite instability are usually heterogeneous and insufficiently validated. In this regard, noninvasive or demographic characteristics, *i.e.*, the body mass index (BMI), are being assessed for their crucial role in predicting response or prognosis.

Over the past two decades, overweight along with BMI, body fat or obesity has been emerging as an increasing concern thoroughly known worldwide. A significant association between elevated BMI and the increasing incidence of various tumors is widely confirmed. System metabolic alternations and excess adiposity occurring in individual cohorts were also depicted to be independently associated with the initiation and progression of breast, colorectal and lung cancer [2–4]. Until now, several retrospective studies have explored the clinical relevance of BMI exporting on outcomes of gynecological malignant tumors [5, 6], while studies on the interaction between BMI and cervical cancers have been lacking. Leslie H Clark *et al.* [7] observed an association between both extremes of BMI and poor survival in cervical cancers. In contrast, Hopkins *et al.* [8] reported no discrepancy in obesity-related survival in

advanced squamous cervical cancers. Another cohort study also attracted attention to weight-loss-related toxicity during radiotherapy in LACC [9]. However, in regard to underweight, existing literature on the outcomes of cervical cancers has been consistent with each other. For instance, Lee *et al.* [10] reported that a BMI <18.5 kg/m^2 was associated with higher risks of late gastrointestinal toxicity in patients with LACC treated with intensity modulated radiation therapy, which was similarly described in the study of Leslie H Clark's *et al.* [7].

To sum up, the main limitations of current literature are the limited relevant studies and contradicting results regarding overweight, single-institutional designs, and under-discovered treatment response. Here, we hypothesize that an elevated BMI (overweight) may be associated with unfavorable outcomes, especially with treatment response, excluding extremes such as obesity or underweight due to the finite sample size or confirmed conclusion. Thus, in this present study, we analyze the relationship between overweight and cervical cancer treatment response and prognosis using a sizeable multi-institutional database.

2. Methods

2.1 Subject and definition

Cases were recruited retrospectively from 01 July 2013, to 01 July 2016, at the department of obstetrics and gynecology of Nanjing Second Hospital, Nanjing Drum Tower Hospital and Nanjing First Hospital. Eventually, 228 cases were allocated into an overweight group and 479 cases into a normal weight group. The patients provided written informed consent prior to project launching. This study was conducted in accordance with the Helsinki Declaration. Social-demographic and clinical-pathologic data were retrieved and recorded from the Electronic Medical Records at the respective hospitals. Obesity cases were excluded to reduce the loss of statistical power. Patients' cancer staging was based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) system. Tumor size was measured by Magnetic Resonance Imaging, combined with Computed Tomography Scan and cervical conization or physical examination. Pelvic lymph nodes involved the parametrical nodes, obturator nodes and iliac nodes. Local recurrence was confined to the pelvic tissue, pelvic lymph nodes or vaginal wall, whereas distant recurrence was located outside the pelvis. BMI, calculated as weight in kilograms divided by height in meters squared, was determined at the initial stage of the enrollment and classified as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2).

2.2 Eligibility criteria and ineligibility criteria

The study eligibility criteria were: (i) confirmed histological diagnosis of cervical cancer; (ii) classified as the 2009 FIGO Stage IIB–IIIB or Stage IB–IIA with pelvic lymph nodes metastasis or tumor size ≥5cm; (iii) Receiving curative chemoradiation; (iv) BMI within 18.5–24.9 or 25–29.9; (v) medical records free from incomplete information for study analysis. Study exclusion criteria were: (i) previous treatments; (ii) presence of recurrence or distant metastasis; (iii) dysfunction of major organs (heart, lung, liver, kidney and bone marrow); (iv) presence of serious concurrent disease (uncontrolled diabetes mellitus, malignant hypertension and cardiovascular disease); (v) contraindications to chemotherapy (infection, intestinal ileus, hematological disorder or other evaluated by attending physicians); (vi) active bleeding, surgery operation or invasive procedure within 3 months with cervical biopsy excluded; (vii) more than 3-week delay during the chemotherapy cycles or 1-week delay during the radiotherapy intervals.

2.3 Outcomes and evaluations

The primary endpoint was tumor response, including objective response rate (ORR) and disease control rate (DCR). Response to clinical treatment was measured using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1: Complete response (CR) was defined as clinically absolute disappearance of the tumor lesion; partial response (PR) as at least 30% reduction in maximum tumor diameter; stable disease (SD) as tumor diameter-sized reduction insufficiently to be defined as CR or PR, and; progressive disease (PD) as above 20% growth in tumor diameter. The secondary endpoints were disease-free survival (DFS) and overall survival (OS). DFS was preoperatively defined from the initial visit to the date of relapse (local, distant or both) or cancer-related death. The data were censored if deaths were not cancer-related or toxicity-related. OS was defined from the initial visit to the date of death regardless of the cause or toxicity following the Common Terminology Criteria for Adverse Events version 2.0.

2.4 Clinical treatments

External radiotherapy was performed using the Varian Truebeam Linear Accelerator (TrueBeam®, VARIAN Inc., Palo Alto, CA, USA) to irradiate the gross lesion, uterine body, uterosacral ligaments, sufficient vaginal margin (at least 3 cm from the gross disease) and pelvic lymph node drainage area (parauterine, presacral nodes, obturator foramen and iliac vascular area) in 25 fractions of 2.0 Gy, 5 times a week, from Monday to Friday. The total targeted dose was 45–55 Gy [11]. It was common to deliver external radiation therapy using conventional three-dimensional or intensity modulated radiation therapy during the course of the standard external radiotherapy. The brachytherapy protocol was initiated one week after external radiotherapy by dilating the uterine cervix at an appropriate angle and size for the intrauterine tandem insertion. The corresponding dose and treatment were based on point A in accordance with the prescription. The organ at risk was contoured on a computer tomography scan to determine its volumetric dose. Three fractions of brachytherapy were discretely delivered in a week, each delivering 7 Gy, depending on the Nucletron microSelection Classic brachytherapy device (Nucletron Corporation, Veenendaal, Netherlands). The paclitaxel platinum (TP) cycle was composed of paclitaxel (Aosaikang Pharmaceutical Co., Ltd, Nanjing, China, batch number: H20064299) 135 mg/m^2, D1, and cisplatin (Qilu Pharmaceutical Co., Ltd, Jinan, China, batch number: H37021358) 50–60 mg/m^2, D2. Each TP cycle lasted for 21–

28 days, depending on the adverse events [12]. The therapeutic schedule was discontinued at the onset of unacceptable adverse events or hard tolerability. Thereafter, the patients were followed-up at 3-month intervals for 2 years and 6-month intervals for following 3–5 years subsequently.

2.5 Statistical analysis

Continuous variables were displayed as mean ± standard deviation, ranging in age, hemoglobin, paclitaxel plus cisplatin cycles, and dose of radiotherapy; categorical variables were expressed as counts or percentages involving smoking, comorbidities, lymph node status, histology, FIGO stage, chemotherapy dose reduction and chemoradiation delay. Student's *t*-test was carried out to estimate the continuous variables; Pearson's χ^2-test or Fisher's exact test was conducted to assess categorical variables appropriately; cumulative OS or DFS was generated by Kaplan-Meier curve and estimated by log-rank test; the effect of covariates on ORR or DCR was modeled by logistic regression with odds ratios adjusted by tumor size, lymph node status and FIGO stage in multivariable model. Two-sided *p*-value of <0.05 was set significantly different. SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was performed for statistical analysis, and GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA) was implemented to display figures.

3. Results

The data of 707 patients treated at the affiliated institutions from 01 July 2013, to 01 July 2016, were retrospectively retrieved. Of them, 228 were assigned to the overweight group and 479 cases to the normal group (Fig. 1). The patients' baseline characteristics are listed in Table 1. Most patients were middle-aged (39.4 ± 6.8 *vs.* 40.4 ± 8.9, $p = 0.10$) and had mild anemia (10.5 ± 3.2 *vs.* 10.8 ± 3.5, $p = 0.27$). Approximately 30% of the patients (31.5% in the overweight group and 34.0% in the normal group) were comorbidity-related, involving hypertension or diabetes under control, hyperlipidemia, cardiovascular disease in stable stage and inflammatory status. Over 90% of the cases were of squamous histology, ranging from stage IIA to IIIA. Treatment-related characteristics are listed in Table 2. Half of the patients had dose reduction with paclitaxel (62.7% in the overweight group and 63.3% in the normal group, $p = 0.44$) and cisplatin (56.1% in the overweight group and 58.7% in the normal group, $p = 0.60$). Less than 50% of patients had chemotherapy delayed by ≥7 days, while over 50% had radiotherapy delayed by ≥3 days.

The number of patients with CR, PR, SD, PD, indeterminate status were 27 (11.8%), 87 (38.1%), 39 (17.1%), 47 (20.6%), 28 (12.4%) in the overweight group and 68(14.2%), 212 (44.3%), 85(17.9%), 73 (15.2%), 41 (8.4%) in the normal group, respectively (Table 3). The ORR (CR + PR) and DCR (CR + PR + SD) of the overweight group was significantly decreased compared to the normal group (50.0% *vs.* 58.5%, $p = 0.03$; 67.1% *vs.* 76.2%, $p = 0.01$, respectively). The median follow-up period was 36.8 months (range, 4–65). The median DFS was 34.0 and 35.0 months in the overweight and the normal group, respectively, with an HR of 1.09 (95% CI: 0.87–1.36, $p = 0.42$) (Fig. 2). Moreover, the median OS was 49.0 and 52.0 months in the overweight and the normal group, respectively, with an HR of 1.22 (95% CI: 0.97–1.53, $p = 0.06$) (Fig. 3).

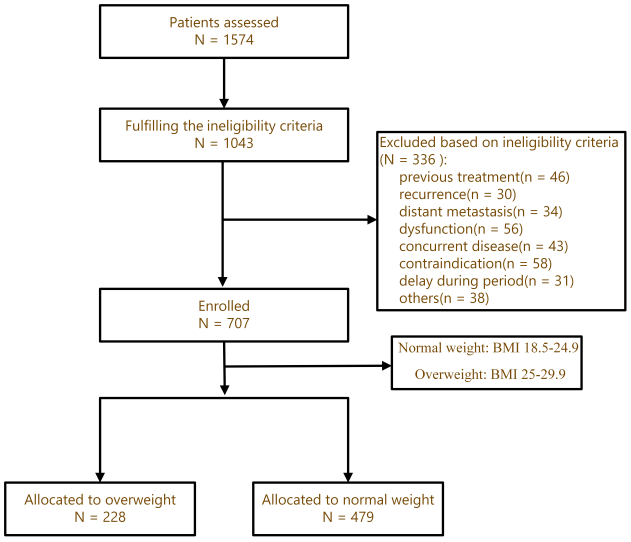

FIGURE 1. Schematic process of bioinformatics analysis. BMI: body mass index.

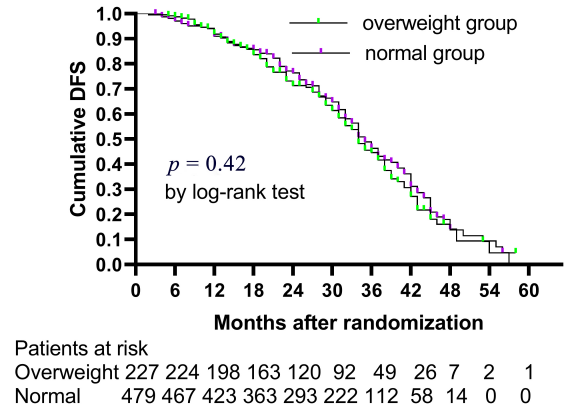

FIGURE 2. Kaplan-Meier for cumulative DFS. Abbreviation: DFS, disease-free survival.

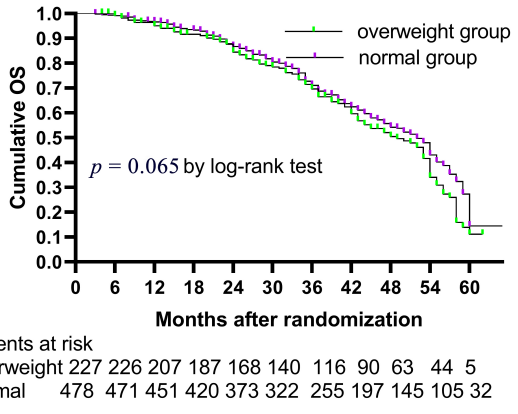

FIGURE 3. Kaplan-Meier for cumulative OS. Abbreviation: OS, overall survival.

TABLE 1. Patients' baseline characteristics.

	Overweight (n = 228)	Normal weight (n = 479)	*p*-value
Age (years)	39.4 ± 6.8	40.4 ± 8.9	0.10
Hemoglobin (g/dL)	10.5 ± 3.2	10.8 ± 3.5	0.27
Smoking	19 (8.3%)	36 (7.5%)	0.70
Comorbidities	72 (31.5%)	163 (34.0%)	0.51
Radiologic pelvic lymph node status			
Positive	79 (34.6%)	149 (31.1%)	0.34
Negative	149 (65.4%)	330 (68.9%)	
Histology			
Squamous	201 (88.2%)	437 (91.2%)	
Adenocarcinoma	20 (8.8%)	25 (5.2%)	0.30
Adensquamous	5 (2.2%)	10 (2.1%)	
Unspecified	2 (0.8%)	7 (0.5%)	
FIGO stage (2009)			
IB	21 (9.2%)	59 (12.3%)	
IIA	52 (22.8%)	107 (22.3%)	
IIB	78 (34.2%)	163 (34.0%)	0.80
IIIA	45 (19.7%)	89 (18.6%)	
IIIB	32 (14.1%)	61 (12.8%)	

Data presented as n (%) or mean ± standard deviation.
Abbreviation: FIGO, International Federation of Obstetrics and Gynecology.

TABLE 2. Treatment-related characteristics.

	Overweight (n = 228)	Normal weight (n = 479)	*p*-value
Paclitaxel plus cisplatin cycles	4.9 ± 1.6	5.1 ± 1.9	0.14
Paclitaxel dose reduction			
Yes	143 (62.7%)	303 (63.3%)	
No	58 (25.4%)	133 (27.8%)	0.44
N/A	27 (11.9%)	43 (8.9%)	
Cisplatin dose reduction			
Yes	128 (56.1%)	281 (58.7%)	
No	69 (30.2%)	145 (30.3%)	0.60
N/A	31 (13.7%)	53 (11.0%)	
Radiotherapy delay by ≥3 days			
Yes	83 (36.4%)	143 (29.9%)	
No	115 (50.4%)	248 (51.8%)	0.09
N/A	30 (13.2%)	88 (18.3%)	
Total dose of external radiotherapy (Gy)	47.1 ± 8.5	48.3 ± 10.9	0.11
Total dose of brachytherapy (Gy)	27.6 ± 9.6	28.7 ± 9.5	0.15
Radiotherapy delay by ≥3 days			
Yes	128 (56.1%)	298 (62.2%)	
No	59 (25.9%)	108 (22.5%)	0.30
N/A	41 (18.0%)	73 (15.3%)	

Data presented as n (%) or mean ± standard deviation.
Abbreviation: N/A, not applicable.

TABLE 3. Tumor response.

	Overweight (n = 228)	Normal weight (n = 479)	*p*-value
Complete response	27 (11.8%)	68 (14.2%)	
Partial response	87 (38.1%)	212 (44.3%)	
Stable disease	39 (17.1%)	85 (17.9%)	
Progressive disease	47 (20.6%)	73 (15.2%)	
Indeterminate	28 (12.4%)	41 (8.4%)	
Objective response rate	114 (50.0%)	280 (58.5%)	0.03
Disease control rate	153 (67.1%)	365 (76.2%)	0.01

Data presented as n (%).

TABLE 4. Effect of overweight on ORR and DCR.

	Univariate OR (95% CI)	Univariate *p* value	Multivariate OR (95% CI)	Multivariate *p* value
ORR				
Normal group	-	-	-	-
Overweight group	0.710 (0.517–0.975)	0.035	0.564 (0.402–0.793)	0.001
DCR				
Normal group	-	-	-	-
Overweight group	0.629 (0.444–0.891)	0.009	0.513 (0.354–0.742)	0.001

Abbreviation: ORR, objective response rate; DCR, disease control rate; CI, confidence interval; OR, odds ratio.

Univariate and multivariate logistic regression were performed to assess the effects of overweight on tumor response (Table 4). Univariate analysis results showed a significant association of overweight with ORR (OR: 0.710, 95% CI: 0.517–0.975; $p = 0.035$) and DCR (OR: 0.629, 95% CI: 0.444–0.891; $p = 0.009$). Afterwards, the point and interval estimates of ORR and DCR were confirmed by multivariate logistic regression (OR: 0.564, 95% CI: 0.402–0.793, $p = 0.001$; OR: 0.513, 95% CI: 0.354–0.742, $p = 0.001$, respectively).

4. Discussion

Considering that most cervical cancer patients have lost their chance of curative surgery or are unresponsive to some therapies, novel indicators are of great need for improving the management and outcomes of LACC patients. To explore the implication of overweight/obesity on the outcomes of LACC, we performed this retrospective multi-institutional research, which had a statistical power >0.8 with approximately 700 cases. Logistic regression was performed to elucidate the contribution of overweight as a risk factor. Apart from survival, we also explored the chemoradiotherapy response rate, including ORR and DCR, which are, to our knowledge, less frequently analyzed. In addition, this multi-institutional study also balanced patients' heterogeneity regarding demographic and radiotherapy- and chemotherapy-related parameters.

Our results, report herein, indicated an association of overweight with a decrease in tumor response in LACC patients treated with curative chemoradiation, adding more evidence on BMI as a potential risk factor in regard to treatment outcomes. Furthermore, this result also suggests that overweight could result in poor response but not survival based on logistic regression analysis using forward selection steps. Increasing BMI, calculated at the beginning of chemoradiotherapy, could decrease response to curative treatment, then resulting in decreased adherence in primary diagnosed LACC.

After a median follow-up of 36.8 (range, 4–65) months, the observed median DFS and OS of this study were 35 months and 52 months, respectively, lower than in previous reports [12–14]. We hypothesized that this could be possibly attributed to disparities in race or standard of care treatment. No discrepancies in survival irrespective of OS or DFS was observed between patients with BMI 18.5–24.9 versus BMI 25.0–29.9, which was consistent with the study of Michael Frumovitz, who reported that I stage B1–IVA overweight and obese cervical cancer patients did not present with an increased risk of death via a database including related cases treated from 1980 to 2007 [15]. We speculated that overweight, as a body-fat indicator at the beginning of chemoradiation, could hardly continue to affect survival during dynamic weight change even it works. Therefore, future studies should also focus on weight loss or gain during treatment. In contrast, Nora T Kizer reported an increased 5-year OS in obese patients (BMI >25.0) compared to underweight patients (BMI <18.5) from a cohort of 404 LACC cases [16]. Based on the hypothesis of similar statistical strength among studies, we attributed this inconsistency to the chemoradiation-dose change or time delay, which was not well-balanced in Nora T Kizer's study.

As for response rate, the ORR (CR + PR) and DCR (CR + PR + SD) of overweight individuals were significantly lower compared with normal-weight cases (50.0% *vs.* 58.5%, $p = 0.03$; 67.1% *vs.* 76.2%, $p = 0.01$, respectively). The results indicated that an elevated level of body fat could be a negative factor for chemoradiation-specific responses. This study's findings might also be attributed to the overweight-induced inflammation, characterized by insulin, C-reactive protein and interleukin 6 [17–20], as this could serve as the trigger for cell proliferation and inhibition of apoptosis. Insulin can elicit insulin-like growth factor 1 or PI3K/AKT/mTOR pathway, whereas C-reactive protein and interleukin 6 act as an activation of nuclear factor-κB [21, 22], both contributing to the disability of enhanced proliferation and apoptosis. Based on such effects, the following question arises: could metabolic abnormality sufficiently define the definitive setting? After a literature review on cervical cancer survival, we noted that potential body-fat-induced co-morbidities, potentially ignored in most studies, could likely account for such observations. For instance, the response could be affected by micro-thrombosis, a decrease in drug-toxicity metabolism or mild cardiovascular events. In addition, other researchers reported notable nonadherence to cervical screening or follow-up in body-fat patients [23, 24], which may lead to decreased response rates. Lastly, there is still a possibility that increasing BMI could be a clinical relevance of biological pathology due to advanced cancer or other comorbidities. The specific pathology could thereby weaken major organ functions or stimulate myelosuppression, leading to the discontinuation or decreased sensitivity to chemoradiotherapy. To further underline this issue, a cohort study is warranted to be conducted where BMI is dynamically calculated as the follow-up is ongoing. In regard to the prognostic factors investigated in this present study, potential clinical bias was well-balanced by parametric test (Table 1 and Table 2). However, confounding factors, including tumor size and lymph node metastasis, could aggravate the decrease in statistical power, resulting in a less convincing conclusion. Hence, univariate and multivariate logistic regression based on forward steps was performed, validating the independent risk factor of overweight when adjusted by tumor size, lymph node status and FIGO stage.

We noted there is no apparent difference in histopathology, dose of radiotherapy and chemotherapy between groups, which could possibly bias the conclusion caused by those non-statistical differences. Indeed, Table 2 showed that the paclitaxel and cisplatin dose reduction and radiotherapy delay were apparently lower in overweight group, which may alleviate the bias caused by the reduced doses of chemoradiotherapy or specific adenocarcinoma.

There are some limitations in this present study. First, this is a retrospective cohort study and other extremes such as obesity are not included. Second, overweight/BMI might not be enabled to characterize body fat distribution and may hardly differentiate muscle mass change from sarcopenia. Third, the change in pretreatment or treatment-period weight, which could bias clinical endpoints including poor response or adherence, is lack of analysis. Despite this, the association between overweight and poor response is still strengthened based on the strict balance of baseline parameters, treatment-related characteristics, and also the point or interval estimates with logistic regression administrated.

5. Conclusions

In conclusion, overweight is found to be associated with poor chemoradiotherapy response but not survival, indicating BMI as a risk predictor for LACC management. The effects of other factors, such as diet or exercise intervention on treatment response should also be explored using prospective settings.

AUTHOR CONTRIBUTIONS

AWX—Manuscript writing, data collection, data analysis; TM—Data collection; KHW—Protocol development; SLZ—Data analysis, data collection; MMY—Protocol development, revision of manuscript, support of funding.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research was granted by the Institutional Ethics Committee of Nanjing Second Hospital, Nanjing Drum Tower Hospital, and Nanjing First Hospital (identifier: 2021-LY-kt075).

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For whom it shines, for whom it shadows, I was, am, and would always try picking up myself lost in your world.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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