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Review

Impact of body mass index on treatment outcome of neoadjuvant chemoradiotherapy in locally advanced rectal cancer

Y. Sun [1], Z. Xu [1], H. Lin, X. Lu, Y. Huang, S. Huang, X. Wang, P. Chi*

Department of Colorectal Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian, PR China

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Abstract

Aim: To determine the effect of obesity, measured by body mass index (BMI), on tumor response and surgical outcome in patients with locally advanced rectal cancer (LARC) undergoing neoadjuvant chemoradiotherapy (nCRT) and radical surgery.
Method: LARC patients undergoing nCRT and radical surgery from 2008 to 2014 were included and divided into three groups: non-obese (BMI $<$ 25.0 kg/m^2), obese I (BMI 25.0–29.9 kg/m^2), and obese II (BMI $\geq$ 30.0 kg/m^2). Tumor response, surgical and oncological outcome were compared between groups. Multivariate analyses were performed to identify risk factors for local recurrence.
Results: A total of 522 LARC patients were analyzed (407 non-obese, 93 obese I, 22 obese II). Post-operative complications did not differ between groups. Increased BMI was associated with poorer T downstaging and Rectal Cancer Regression Grade (P = 0.116, P = 0.036). With a mean follow-up of 57 months, the 5-year overall survival and distant metastasis rates did not differ between groups (P = 0.861, P = 0.116). The 5-year local recurrence rate in obese II patients was 14.6%, higher than that in non-obese and obese I groups (P = 0.015). Cox regression analysis demonstrated that BMI $\geq$30 kg/m^2 (HR = 6.187, P = 0.010) was significantly associated with increased risk for local recurrence.
Conclusion: Obesity was associated with poorer T downstaging and Rectal Cancer Regression Grade, and thus poor local control in LARC following nCRT in Asian patients. More effective treatment strategies to improve treatment outcome for obese patients with LARC are warranted.

Keywords: Rectal cancer; Chemoradiotherapy; Body mass index; Obesity; Outcome

Introduction

Obesity is a world-wide health concern associated with numerous chronic morbidities [1]. Body mass index (BMI), the basic assessment of obesity, has been shown to be a risk factor for occurrence and progression of colorectal cancer [2–4]. Among rectal cancer patients, obesity may present a technical challenge in surgical resection, and the effect of obesity on surgical outcome of rectal cancer remains controversial [5–9]. Nevertheless, the increasing prevalence of obesity highlights the need for physicians to provide personalized care for these obese patients [10].

In the modern era of multimodality treatment in rectal cancer, neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) has become the standard of care for patients with locally advanced rectal cancer (LARC) [11]. Patient characteristics such as obese body habitus and internal distribution of adipose tissue has the potential to affect radiation dosing and/or delivery, and thus may lead to significant differences in treatment

* Corresponding author. Department of Colorectal Surgery, Fujian Medical University Union Hospital, 29 Xinquan Road, Fuzhou, 350001, Fujian, PR China.
E-mail address: chipan363@163.com (P. Chi).
[1] Contributed equally to this study.

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response and survival outcomes [12–14]. It has been reported that obesity was associated with lower rates of sphincter preservation and local control in patients with LARC treated with post-operative chemoradiotherapy [8]. Additionally, higher BMI has been shown to be a risk factor for recurrence following adjuvant chemotherapy for colon cancer patients [15]. However, few studies have focused on the effect of obesity, as measured by BMI, on treatment and oncological outcomes in LARC following nCRT.

This study was aimed to evaluate the impact of obesity, as measured by BMI, on tumor response, surgical and oncological outcomes in LARC patients following nCRT. Factors associated with local recurrence were also evaluated.

Patients and methods

Patient population

A total of 522 LARC patients who underwent nCRT and radical resection between 2008 and 2014 were identified from our prospectively maintained database. The inclusion criteria were as follows: (1) cT3–4 or cN+ (by endorectal ultrasound, or magnetic resonance imaging), (2) tumors were within 12 cm from the anal verge, and (3) histologically proven adenocarcinoma. The exclusion criteria were: (1) concurrent with previous or concurrent malignancies; (2) patients who underwent emergent surgery, palliative resection, or local excision. This study was approved by the institutional review board of our hospital.

Treatment and follow-up

The preoperative long-course radiotherapy protocol consisted of 50.4 Gy delivered in fractions of 1.8 Gy with 5 fractions per week for 5 consecutive weeks followed by a boost of 5.4 Gy. Preoperative chemotherapy was initiated on the first day of radiotherapy and included two different regimens: 5FU plus oxaliplatin (FOLFOX) and capecitabine plus oxaliplatin (CapeOX).

Operation was performed 6–8 weeks after the completion of the radiation. Surgical techniques, such as TME and inferior mesenteric artery (IMA) high ligation, were standardized at our institution. TME was performed for mid and low rectal cancers, and partial TME with a distal margin of 5 cm was performed for high rectal cancers. The IMA lymph nodes were dissected to the IMA just below the bifurcation of the left colic artery to preserve the hypogastric nerve, irrespective of the operative findings with regard to the status of lymph node involvement. Pelvic autonomic nerves were identified and preserved. Air leak test was used to identify mechanically insufficient anastomosis. Diverting loop ileostomy was planned before surgery based on the general health of the patient, the distance of the anastomosis from the anal verge, and the use of nCRT. About 3–4 weeks after surgery, patients received adjuvant chemotherapy (FOLFOX or CapeOX) for 6 months.

Follow-up was performed every 3 months for the first 3 years, then every 6 months for the next 2 years, and annually thereafter. At each visit, a physical examination, serum carcinoembryonic antigen (CEA), chest X-ray or Computed Tomography (CT) scans, and abdominopelvic Magnetic Resonance Imaging (MRI) or CT scans were performed. A colonoscopy was conducted annually post-operatively.

Definitions

BMI was collected from the medical records at the visit before the start of nCRT. Obesity was defined as a BMI $\geq$25 kg/m^2 according to the Asian BMI classification by the Asia Cohort Consortium of the World Health Organization [16], BMI cutoff points were used to categorize patients into three groups: non-obese (BMI <25.0 kg/m^2), obese I (BMI 25.0–29.9 kg/m^2), and obese II (BMI >30.0 kg/m^2) [17]. Post-operative morbidity was defined as any complication occurring within 30 days after surgery, and was graded according to the Clavien–Dindo classification [18]. Perioperative mortality was defined as any death either within 30 days after surgery or during the hospitalization period. Tumor regression was graded according to the Rectal Cancer Regression Grade (RCRG) method [19]; that is, RCRG 1, sterilization or only microscopic foci of adenocarcinoma remaining, with marked fibrosis; RCRG 2, marked fibrosis but macroscopic disease present; RCRG 3, little or no fibrosis, with abundant macroscopic disease.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS INC., Chicago). Categorical variables were presented in frequencies and percentages, and were assessed using Chi-square or Fisher's exact test. Continuous variables were reported in means and standard deviation between BMI groups, and assessed via the analysis of variance test. Survival outcomes were assessed using the Kaplan–Meier method and log-rank test. A Cox proportional hazards model was performed to identify risk factors for local recurrence. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

The clinicopathological characteristics of the 522 LARC patients were presented in Table 1. Of the 522 patients, 407 (78.0%), 93 (17.8%), and 22 (4.2%) patients were classified into the non-obese, obese I, and obese II groups, respectively. The median BMI in the non-obese, obese I, and obese II groups was 21.4, 26.3, and 31.2 kg/m^2,