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Original article

Muscle wasting and survival following pre-operative chemoradiotherapy for locally advanced rectal carcinoma

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SUMMARY

Background & aims: Neoadjuvant chemoradiotherapy (NACRT) has increased local control in locally advanced rectal cancer. Reduced skeletal muscle mass (sarcopenia), or ongoing muscle wasting, is associated with decreased survival in cancer. This study aims to assess the change in body composition during NACRT and its impact on outcome using computed tomography (CT) imaging in locally advanced rectal cancer (LARC) patients.

Methods: LARC patients treated with NACRT were selected from a prospectively maintained database and retrospectively analyzed. One-hundred twenty-two patients who received treatment between 2004 and 2012 with available diagnostic CT imaging obtained before and after NACRT were identified. Cross-sectional areas for skeletal muscle was determined, and subsequently normalized for patient height. Differences between skeletal muscle areas before and after NACRT were computed, and their influence on overall and disease-free survival was assessed.

Results: A wide distribution in change of body composition was observed. Loss of skeletal muscle mass during chemoradiotherapy was independently associated with disease-free survival (HR0.971; 95% CI: 0.946–0.996; p = 0.025) and distant metastasis-free survival (HR0.942; 95% CI: 0.898–0.988; p = 0.013). No relation was observed with overall survival in the current cohort.

Conclusions: Loss of skeletal muscle mass during NACRT in rectal cancer patients is an independent prognostic factor for disease-free survival and distant metastasis-free survival following curative intent resection.

1. Introduction

Colorectal cancer is the third most common malignancy among male and second most common malignancy among female patients worldwide [1]. It is a leading cause of cancer death in more developed countries. Rectal cancer accounts for up to 30% of all colorectal malignancies. For patients with locally advanced rectal cancer, neoadjuvant chemoradiotherapy (NACRT) combined with total mesorectal excision (TME) is considered best available treatment [2,3].

Recently, sarcopenia (muscle wasting) has been described as a potent prognostic marker in gastrointestinal and hepatopancreatobiliary malignancies [4–15]. Sarcopenic patients, i.e. patients with a lesser quantity of muscle mass, have an increased risk for early death. Age, cancer cachexia and oncological treatment may contribute to this state of low muscle mass [16–18]. Interestingly, NARCT itself has been reported to reduce skeletal muscle mass in esophagogastric cancer patients [16]. Another study confirmed these findings, and furthermore showed that greater loss of muscle mass during neoadjuvant treatment is associated with an increased risk of postoperative mortality [19]. Likewise, in non-resectable colorectal cancer patients, skeletal muscle loss after systemic chemotherapy is an independent, negative prognostic factor [20]. Interventions to stop or even reverse progressive muscle wasting in patients undergoing potentially curative anti-cancer therapy are currently being investigated and would, if found, provide new strategies in the management of cancer patients.

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To this moment, the impact of NACRT on body composition in patients with locally advanced rectal cancer (LARC) has not yet been described. Therefore, in the current study we aim to (1) investigate whether NACRT induces a change in body composition in LARC patients, (2) assess the impact of change in body composition during NACRT on outcome (i.e. short-term outcome, overall survival, disease-free survival, and development of distant metastases).

2. Methods

2.1. Patients

All histologically confirmed, LARC patients who underwent NACRT and TME in the Erasmus MC Cancer Institute, a tertiary referral center in the Netherlands for locally advanced and stage IV colorectal cancer, between August 2004 and December 2012 289 patients were enrolled in a prospectively maintained database and retrospectively analyzed. The study protocol was approved by medical ethical committee of the Erasmus MC, University Medical Center, Rotterdam, The Netherlands (MEC-2017-239). LARC was defined as T3 or T4 rectal tumors (i.e. tumors located $\leq$15 cm of the anal verge as determined by MRI and colonoscopy) with clinical suspicion of narrow or involved circumferential resection margins (CRM) with or without potentially malignant lymph nodes, or rectal tumors with potentially malignant lymph nodes outside the TME plane, as previously described [21]. Collected data included details on patient age, gender, body-mass index (BMI), comorbidities, cancer stage, carcinoembryonic antigen (CEA), surgical and chemoradiotherapeutic treatment, clinical response rate, recurrence and survival. From the initial 289 patients, 122 patients received abdominal computed tomography (CT) imaging before standardized preoperative chemoradiotherapy (preCRT), and a restaging CT scan (postCRT) to identify any possible previously non-detectable distant metastases, according to local protocol [22]. Only patients with adequate preCRT and postCRT scans were considered eligible for inclusion in the current study.

2.2. Preoperative chemoradiotherapy and surgical resection

All patients received preoperative chemoradiation therapy as a long course (50 Gy) delivered in 25 fractions in accordance to the Dutch guidelines, i.e. chemoradiotherapy for rectal cancer classified as LARC. Capecitabine (825 mg/m^2) was administered orally twice a day during radiotherapy days, and radiotherapy was administered via a three-field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy [23].

TME was performed after completing chemoradiation, if considered eligible for resection. A midline laparotomy was carried out in all patients. A primary anastomosis was performed whenever possible. A diverting ileostomy was created at the discretion of the treating physician. In T4 tumors involving the sphincter apparatus after NACRT, an abdominoperineal resection was performed. In T4 tumors involving adjacent structures after NACRT (e.g. prostate, uterus, bladder) these were resected simultaneously. Intraoperative radiotherapy was applied if the circumferential resection margin (CRM, $\leq$2 mm) was considered to be at risk [24].

2.3. Postoperative follow-up

Patients follow up was done on an outpatient basis by periodic six months CT imaging or abdominal ultrasonography during the first two postoperative years, followed by yearly imaging for the remainder of the follow-up. Serum CEA determination was done at intervals of three to six months during the first three years of follow-up, and subsequently every six months during the final years of follow-up. Patients were followed up for at least 5 years in case of no recurrence. None of the patients were treated with adjuvant chemotherapy according to the Dutch guidelines. The national civil registry was consulted for definitive survival data.

2.4. Assessment of body composition

Body composition was measured on standard diagnostic CT scans with FatSeg version 4.0 (Erasmus MC – BIGR, Rotterdam, Netherlands). Cross-sectional areas (cm^2) of skeletal muscle mass were measured at the level of the third lumbar vertebrae as previously described [15].

2.5. Statistical analysis

Continuous data are presented as mean ± SD or median (IQR) as appropriate. Categorical data are presented as number counts and percentages. The Student's *t*-test was used for assessment of differences between groups for continuous variables. The χ^2 or Fisher's exact test was used for assessment of differences between groups for categorical variables where appropriate. Skeletal muscle mass was normalized for patient height (skeletal muscle index [SMI]). Paired *t*-test was used for the between group comparisons of continuous variables for SMI on preCRT and postCRT scans. Relative change in cross-sectional areas (Δ CSA = postCRT/preCRT) were computed for SMI. Gender specific tertiles were determined for Δ SMI. Overall and disease-free survival rates were calculated using the non-parametric Kaplan–Meier method and subsequently compared with the log rank test. Univariate and multi-variable Cox regression analyses were performed to investigate the association between Δ SMI and survival. Hazard Ratios (HR) with 95% confidence intervals (95% CI) were computed. Furthermore, age, gender, diabetes, BMI, tumor location, CEA, surgical procedure, intraoperative radiotherapy, pathologic T-, N- and M-stage, circumferential resection margin, and pathologic complete response were included in the univariate Cox regression analysis. These variables were checked for interaction and confounding. They were subsequently included in the multivariable model if a p-value < 0.05 was found in univariate analysis.

All statistical analyses were performed using SPSS version 21.0 (SPSS, Chicago, Illinois, USA). A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics and body composition

One hundred and twenty-two patients, with a median follow-up of 41 months (IQR 26–62) were eligible for inclusion (Table 1). During the follow-up period, 50 (41.0%) patients developed recurrent or metastatic disease, and 35 patients (28.7%) died. Forty (32.8%) patients had metastatic disease at onset of NACRT. Twenty-nine (23.8%) patients were treated by liver first approach [25,26]. Eleven patients underwent synchronous resection. In the studied population, median length of hospital stay was 8 (IQR: 7–11) days.

Abdominal CT-imaging was obtained at median 48 (IQR: 35–65) days prior to onset of NACRT. Restaging scans were obtained at a 28 (IQR: 21.5–39.5) days after completion of NACRT. Following NACRT,

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