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Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer

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ABSTRACT

Objectives: Low skeletal muscle mass (SMM) or sarcopenia is emerging as an adverse prognostic factor for chemotherapy dose-limiting toxicity (CLDT) and survival in cancer patients. Our aim was to determine the impact of low SMM on CDLT in patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC) treated with primary radiochemotherapy (RCT).

Patients and methods: Consecutive patients diagnosed with LA-HNSCC and treated with primary RCT between 2007 and 2011 in our center were included. Clinical variables were retrospectively retrieved and SMM was measured at the level of the third cervical vertebra using pre-treatment head and neck CT-scans. After determining a cut-off value for low SMM, multivariate analysis was performed to identify prognostic factors for CDLT.

Results: Of 112 patients included, 30.4% experienced CDLT. The optimal cut-off value for low SMM as a predictor of CDLT was $\leq$43.2 cm^2/m^2. Using this cut-off, 54.5% patients had low SMM. Patients with low SMM experienced CDLT more frequently than patients with normal SMM (44.3% vs. 13.7%, $p < 0.001$) and received a higher dose of chemotherapy/kg lean body mass (estimated from SMM, $p = 0.044$). At multivariate analysis, low SMM was independently inversely associated with CDLT (OR 0.93, 95%CI: 0.88–0.98). Patients experiencing CDLT had a lower overall survival than patients who did not (mean 36.6 vs. 54.2 months, $p = 0.038$).

Conclusion: Low SMM is an independent risk factor for CDLT in LA-HNSCC patients treated with primary RCT. Pre-therapeutic estimation of SMM using routine CT-scans of the head and neck region may identify patients at risk of CDLT.

Introduction

In recent years, sarcopenia has emerged as a negative prognostic factor in geriatric and cancer patients. Sarcopenia is a generalized and progressive loss of skeletal muscle mass (SMM) and muscle function, and is associated with unfavorable conditions such as functional impairment, physical disabilities and early death in geriatric patients [1,2]. In cancer patients, loss of SMM is associated with various negative clinical outcomes [3]. Sarcopenia has been linked to a higher risk of developing postoperative complications, worse outcome after surgery, longer hospital stay [4–7] and decreased disease-free and overall survival [8–13]. Studies also show sarcopenia to be a significant predictor of

Abbreviations: SMM, skeletal muscle mass; CDLT, chemotherapy dose-limiting toxicity; HNSCC, head and neck squamous cell carcinoma; LA-HNSCC, locally advanced head and neck squamous cell carcinoma; RCT, radiochemotherapy; C3, third cervical vertebra; L3, third lumbar vertebra; CSA, cross-sectional area; HU, Hounsfield Units; OS, overall survival; LBM, lean body mass.

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chemotherapy dose-limiting toxicity (CDLT) in patients with a variety of malignancies, including lung cancer, renal cell cancer, colorectal cancer and breast cancer [14–20].

The relationship between sarcopenia and CDLT in patients with head and neck cancer squamous cell carcinoma (HNSCC) has not been evaluated. Although malnutrition, one of the risk factors for developing sarcopenia, is highly common in HNSCC patients. At diagnosis, up to 46–49% of patients with HNSCC present with signs of malnutrition, such as weight loss and vitamin deficiencies [21,22]. Locally advanced HNSCC (LA-HNSCC) is frequently treated with radiotherapy combined with concurrent platinum based chemotherapy (radiochemotherapy, RCT) [23]. The addition of cisplatin-based chemotherapy to radiotherapy alone has been proven to significantly increase survival, but may also cause severe side effects (e.g. bone marrow depression or nephrotoxicity). Up to 30 percent of HNSCC patients experience CDLT [24], which may lead to treatment delay, dose reduction and/or failure to complete the full treatment. It has been suggested that sarcopenic patients have a higher risk of chemotherapy related toxicity with platinum-based chemotherapy because platinum is mainly distributed in the fat-free compartments (e.g. kidneys, liver, pancreas and muscle tissue) [25]. Because SMM is the largest contributor to the fat-free mass, it is interesting to investigate the possible association between SMM and CDLT in HNSCC patients. A better understanding of this relationship could be relevant in creating feasible treatment plans and developing personalized treatment schedules.

Computed Tomography (CT) is an accurate method to determine body composition and SMM [26–28]. Most studies investigating sarcopenia measure SMM using a single CT-slide at the level of the third lumbar vertebra (L3), which has been shown to provide an accurate estimation of the total body muscle mass when correlated with whole body MRI [26]. However, not all centers routinely perform diagnostic CT-scans of the abdominal area in LA-HNSCC patients. Our research group recently investigated the correlation between SMM at level L3 and at the level of the third cervical vertebra (C3) and found a strong correlation [29]. This novel method allows for accurate assessment of SMM in LA-HNSCC patients using routinely performed head and neck CT scans.

Definitions and specific SMM cut-offs for sarcopenia vary between studies. Different outcome measures, such as survival and chemotherapy toxicity, have been used to determine an optimal cut-off value for low SMM or sarcopenia. The primary purpose of this study is to investigate the predictive value of low SMM on CDLT in LA-HNSCC patients treated with primary RCT. The secondary purpose is to determine whether low SMM is related to overall survival. We hypothesize that low SMM increases the risk of CDLT and decreases overall survival.

Patients and methods

Ethical approval

The design of this study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht (approval ID 14-544/C).

Patients and study design

We retrospectively identified all consecutive patients treated with RCT for LA-HNSCC at the University Medical Center of Utrecht, The Netherlands, between January 2007 and December 2011. Patients were included for analysis if they were diagnosed with stage III or IV HNSCC (according to the AJCC staging manual) and were treated with primary RCT with platinum-based chemotherapy. Patients were excluded if they were treated with adjuvant RCT. Subsequently, relevant clinical information such as weight, stature, smoking history, use of alcohol, loss of weight, ECOG performance status, TNM-staging, treatment plan, chemotherapy toxicity data, and survival data was extracted from patient medical records.

Therapy

The chemotherapy regimen consisted of three cycles of intravenous platinum based chemotherapy on days 1, 22 and 43 of treatment. Chemotherapy dose was 100 mg/m^2 for cisplatin or 400 mg/m^2 for carboplatin. Chemotherapy dose was standardized for Body Surface Area (BSA). Radiation was administered once daily, 5 fractions a week, with a total dose of 70 Gray in 35 fractions.

Chemotherapy dose-limiting toxicity

We defined CDLT as any toxicity resulting in a chemotherapy dose-reduction of $\geq$50% (e.g. due to neutropenia or nephrotoxicity), a postponement of treatment of $\geq$4 days (e.g. in the case of bone marrow suppression) or a definite termination of chemotherapy after the first or second cycle of therapy. In the case of significant ototoxicity after the first or second cycle of chemotherapy, cisplatin was switched to carboplatin. As long as the patient completed three cycles of chemotherapy (without a significant dose reduction), a therapy switch from cisplatin to carboplatin was not regarded as CDLT.

Survival

Overall survival (OS) was defined as the time between the date of the first tumor-positive biopsy and death or last recorded date of follow-up. If the patient was lost to follow-up, we contacted the patient's general practitioner.

Body composition measurements

Weight and height were recorded by a nurse on the first day of RCT and were used to calculate Body Mass Index (BMI): [weight (kg)/height (m^2)], and the BSA according to the Mosteller formula: [BSA (m^2) = ([height (cm) $*$ weight (kg)]/3600)$^{1/2}$].

CT image analysis

As part of radiotherapy planning, pre-treatment head and neck CT-imaging in radiation mould was performed in all patients. SMM was determined for each patient according to the method previously described by Swartz et al. [29]. In brief, a single axial CT-slide at level C3 was selected using a standard procedure: the first slide to completely show the entire vertebral arc when scrolling through the C3 vertebra from caudal to cephalic direction was selected. Skeletal muscle tissue was identified using Hounsfield unit (HU) ranges settings from −29 to +150 HU, to avoid overestimation of skeletal muscle area [29,30]. The outer contours of the sternocleidomastoid and paravertebral muscles were traced manually (Fig. 1) using the Volumetool v.1.6.5 Research Software Package, designed in our center as an image evaluation, registration and delineation system for radiotherapy [31]. The cross-sectional muscle area (CSA) at the level of C3 was calculated as the sum of the delineated areas of the paravertebral muscles and both sternocleidomastoid muscles within HU ranges of −29 to +150 in cm^2. All CT slides were analyzed by a single researcher (A.W.W.). Subsequently, skeletal muscle CSA at level L3 was estimated using the prediction rule as described by Swartz et al. (Eq. (1)) [29].