Purpose: A standard treatment for squamous cell cancer of the head and neck with unknown primary (HNCUP) is external beam radiation therapy to the mucosal sites and bilateral neck, combined with chemotherapy and/or surgery. Initial reports demonstrated that radiation treatment using the current standard of IMRT (intensity modulated radiation therapy) offered excellent local-regional control, but was associated with increased levels of swallowing toxicity (e.g., Sher et al, Int. J. Rad Onc. Biol, Phys, 80:1405, 2011). We examined the effect of changes in the dose prescribed to the mucosa on subsequent development of strictures.

Patients and Materials: We performed a retrospective analysis of patients with HNCUP treated at the Dana Farber Cancer Institute from 8/04 through 7/13 with radiation therapy to the mucosal sites and bilateral necks. Patients were grouped by the dose prescribed to the mucosal structures, which ranged from 56 to 64 Gy. Local-regional and distant control, as well as the development of strictures, determined by video swallows, were assessed.

Results: A total of 58 patients were identified with a median follow up of 40 months [range: 0-104 months]. Fifty-one patients had >N2 nodal disease and 56/58 patients were treated with concurrent systemic therapy, including 13 who received induction chemotherapy. Median dose to gross nodal disease was 70 Gy. Three patients received 63-64 Gy to the mucosal surfaces, 21 received 60 Gy and 34 received 56 Gy. The crude rates of recurrence for the entire cohort were: local-regional 6.9% and distant metastases 3.4%, with a 2 year overall survival of 93.5%. There were no significant differences between recurrences for the 3 different dose groups. However there was a statistically significant difference with respect to the development of strictures based on dose: 63-64 Gy-2 of 3 patients developed a stricture; for 60 Gy 9/21 (42.9%) and for 56 Gy 4/34 (11.8%; p<0.008, c/w 60 Gy group). In addition, the median duration of having a PEG in place (192 vs 123 days) was decreased for those patients treated to 56, as compared with 60 Gy.

Conclusions: In this single institution study, IMRT based chemoradiotherapy achieved excellent local-regional control and survival. The current IMRT approach, using 56 Gy to the mucosal surfaces, demonstrated significant improvements in swallowing toxicity.
Objective: Prolonged radiation treatment time (RTT) with or without concurrent chemotherapy is associated with worse tumor control. We sought to identify factors that predict for treatment prolongation in VA patients undergoing concurrent chemoradiation and also to determine clinical implications of these factors, particularly those related to treatment toxicity.

Methods/Materials: During July 2000 to October 2013, 81 consecutive patients (median age 62 years [range 27 - 80 years], gender=all males) with stage III-IVB oropharyngeal squamous cell carcinoma treated with definitive radiotherapy with concurrent chemotherapy (cisplatin-based [n=64] or cetuximab [n=17]) at the Veterans Affairs Greater Los Angeles Healthcare System were retrospectively reviewed. Patients were treated with intensity modulated (n=75) and 3D-conformal radiotherapy (n=6). Primary sites were base of tongue (n=36), tonsil (n=41), soft palate (n=2) and oropharyngeal wall (n=2). Fifteen patients (18.5%) also received induction chemotherapy. Multivariate regression analysis was employed to identify factors associated with prolonged RTT and the effects of prolonged RTT and other variables on local control (LC) and overall survival (OS).

Results: Overall, 29 patients (35.8%) had RTT prolonged by >=10 days from the expected completion time. RTT prolongation was attributed to acute toxicity from chemotherapy (n=8, 27.6%), radiotherapy (n=7, 24.1%), or both (n=7, 24.1%), or to reasons unrelated to side effects (n=7, 24.1%). There was no significant difference in RTT for patients treated with concurrent cisplatin versus cetuximab, or in patients treated with or without induction chemotherapy. Patients who received both induction chemotherapy and concurrent high-dose cisplatin (n=9, 11.1%) had significantly shorter RTT compared to the rest of the cohort (mean 53.4 days vs 58.1 days, p=0.019). Similarly, on multivariate analysis, use of both induction chemotherapy and high-dose cisplatin predicted for shorter RTT (p=0.049). With a median follow up of 22.1 months (0.9 - 154 months), univariate analysis demonstrated that the 1/3 year LC and OS rates were 83.4%/76.3% and 83.5%/63.6% for patients without prolonged RTT vs. 61.8%/61.8% and 82.8%/73.8% for those with prolonged RTT (p=0.05). On multivariate analysis, advanced nodal stage and prolonged RTT were significant predictors for decreased LC (p=0.003 and p=0.037, respectively); whereas lower nodal stage and use of induction chemotherapy were significant predictors for improved OS (p=0.023 and p=0.002, respectively).

Conclusions: Prolonged RTT was a significant predictor of worse locoregional control in this cohort of stage III-IVB oropharyngeal cancer patients. In our VA population, prolonged RTT was due to radiation and chemotherapy side effects more often than patient social or economic factors. Use of more aggressive chemotherapy regimens including induction chemotherapy followed by concurrent high-dose cisplatin did not result in prolonged RTT.
A HIGH BMI AT THE START OF RADIATION THERAPY IS ASSOCIATED WITH BETTER SURVIVAL IN PATIENTS WITH OROPHARYNGEAL CANCER

Sandra Ottosson, PhD, Karin Söderström, MD, Elisabeth Kjellén, PhD, MD, Per Nilsson, PhD, Björn Zackrisson, PhD, MD, Göran Laurell, PhD, MD; Umeå University, Uppsala University, Lund University

Introduction

Previous research on the relation between nutritional factors and survival in patients with head and neck cancer (HNC) is inconclusive. The strongest relation can be found between body mass index (BMI) and survival and a BMI > 25 have in patients with HNC been correlated with a better survival. Patients with HNC are known to lose weight during and after radiation therapy (RT) due to tumor burden and treatment related factors. It is believed that loss of fat free mass rather than the weight loss per se is responsible for the negative physical function seen in patients with weight loss. It can therefore be hypothesized that the amount of adipose tissue may have important clinical implications in patients with HNC with expected weight loss during RT.

The aim was to investigate the relation between BMI at the start of RT and five-year overall survival in a cohort of patients with oropharyngeal cancer.

Methods

The data has its origin from the ARTSCAN (Accelerated Radiotherapy of Squamous cell Carcinoma of the head and Neck) trial, a randomized prospective multicenter trial conducted at twelve treatment centers in Sweden between the years of 1998 - 2006. In total, 203 patients with oropharyngeal cancer were studied. Time to death was calculated from the start of RT up to five years in surviving patients. BMI at the start of RT was grouped according to: underweight <20 kg/m2 (<22 kg/m2 if >=70 years of age), normal weight 20 - 25 kg/m2 (22 - 27 kg/m2 if >=70 years of age), and overweight/obesity >25 kg/m2 (>27 kg/m2 if >=70 years of age) and analyzed together with different patient (age and sex), tumor (clinical stage) and treatment related factors (RT schedule and surgery) using a Cox regression analysis.

Results

In the study cohort, 52.2% of the patients were treated with conventional fractionation (2Gy/day, total 68Gy), 47.8% with accelerated fractionation (2Gy + 1.1Gy per fraction, total 68Gy) and 52.2% received surgery post RT (neck dissection). The majority of patients (89.2%) had clinical stage III or IV disease. At the start of RT, 8.4% of the patients were underweight, 33.0% normal weight and 58.6% were overweight or obese. Patients with underweight or normal weight had lower survival rates (58.8% and 56.7%, respectively) than patients with overweight or obesity (83.2%). In the adjusted Cox regression, the Hazard Ratios and 95% CI were 3.78 (1.46-9.75) (p = 0.006) and 2.57 (1.43-4.62) (p = 0.002) in patients with underweight and normal weight, respectively.

Conclusion

Patients with overweight or obesity at the start of RT had a better five-year overall survival compared to patients with normal weight or underweight. Hence, the protective effect of the adipose tissue on fat free mass might in patients with anticipated weight loss during treatment support the notion that patients with a low BMI should be encouraged to gain weight before the start of RT.
** background: ** DAHANCA, The Danish Head and Neck Cancer Group has since 1977 coordinated and organized a national population based treatment of HNSCC in Denmark. In addition has a national database with more than 30,000 HNSCC patients been established. The treatment has been based on national guidelines originated in a large number (> 30) of clinical trials. These trials are typically large unbiased population based controlled clinical studies including all eligible patients with the country, (and represents some of the World’s largest randomized trials in HNSCC - see www.dahanca.dk).

** methods: ** The most pivotal of the studies have focused on improving the efficacy of radiotherapy in advanced HNSCC on a biological basis, by exploring in successive and additive order the role of hypoxic modification with nimorazole, accelerated fractionation with 6 fx per week, chemo-radiotherapy with weekly cisplatin and EGRr inhibition by Zalutumumab. The current study is an analysis of these trials, (DAHANCA 5,6,7,10,18,19) conducted in the years 1985 to 2011. Although the radiotherapy technique may have changed over time is the definition of the tumor target comparable among the studies. All patients were treated with RT only without any additional (nodal) surgery. The primary endpoint for all studies was 5-years loco-regional tumor control after radiotherapy.

** results: ** A total of 1983 comparative patients (i.e. found in all trials) with advanced stage 3-4 larynx or pharynx HNSCC are included in the analysis which showed an increase in 5-year LR rate from 27% after normo-fractionated RT alone to 83% after treatment with accelerated fx, nimorazole and weekly cisplatin. Addition of EGFr-inhibitor did not add further improve the loco-regional control probability.

During the years has the number of HPVpositive oropharyngeal tumors been increasing, and HPV/p16 status was obtained pro- or retrospectively from most tumors. A multivariate analysis corrected for HPV positivity in oropharyngeal tumors (HR: 0.47 [0.37-0.60, 95% cfl.]), large T-size (HR: 1.58 [1.33-1.87]) and N-positivity (HR: 1.99 [1.63-2.44]) showed independent benefit of hypoxic modification (HR: 0.64 [0.52-0.80]); accelerated fractionation (HR: 0.63 [0.53-0.77]); chemo-radiotherapy (HR: 0.46 [0.35-0.59]); but with no benefit of EGFr-inhibition (p = 0.17). Similar effects were found when using death from cancer as endpoint. HPV positivity in non-oropharyngeal tumors showed no influence on outcome (p=0.91). All gained benefits have been included in current national guidelines (www.dahanca.dk).

** conclusion: ** By an more than 3 times increase of the long-term curability of HNSCC, has this national population based series of prospective clinical trials conducted over more than 25 years show the importance of collaborative clinical research, when the results consequently is implemented into guidelines and routine practice.
A RANDOMIZED PHASE III TRIAL OF ACCELERATED VERSUS CONVENTIONAL FRACTIONATION RADIOThERAPY FOR GLOTTIC CANCER OF T1-2N0M0 (JCOG 0701): COMPARISON OF ACUTE TOXICITY AND TREATMENT COMPLIANCE

Takeshi Kodaira, PhD, MD, Naoto Shikama, PhD, MD, Yoshikazu Kagami, PhD, MD, Satoshi Ishikura, PhD, MD, Masahiro Hiraoka, PhD, MD, Kenichi Nakamura, MD, Junki Mizusawa, MSc, Yoshihiro Saito, MD, PhD, Yasuo Matsumoto, MD, PhD, Kinji Nishiyama, MD, PhD, Jun Itami, MD, PhD, Yoshinori Ito, MD, Tetsuo Akimoto, MD, PhD, Kensei Nakata, MD, PhD, Masahiko Oguchi, MD, PhD, Yasumasa Nishimura, MD, PhD, Keiichi Nakagawa, MD, PhD, Yasushi Nagata, MD, PhD, Tetsuo Nishimura, MD, PhD, Takashi Uno, MD, PhD, Masaaki Kataoka, MD, PhD, Atsunori Yorozu, MD, PhD; Japan Clinical Oncology Group

Purpose: JCOG0701 is a randomized controlled trial to demonstrate the non-inferiority of the efficacy of accelerated fractionation with 2.4 Gy/fraction (Ax group) to that of standard fractionation with 2 Gy/fraction (SF group) for glottic cancer (UMIN-CTR: UMIN000010298). Here we report the acute radiation toxicities and treatment compliances in each arm.

Materials and methods: Eligibility criteria included glottic cancer of T1N0M0 or T2N0M0 without impaired vocal cord mobility, pathologically proven squamous cell carcinoma, aged 20-80, PS of 0-1, no previous radiotherapy to the head and neck region, no active double cancers, and sufficient organ function. Patients were treated with 66 Gy within 45 days for T1, 70 Gy within 47 days for T2 in SF group, while 60 Gy within 33 days for T1, 64.8 Gy within 37 days for T2 were given in Ax group. Both groups received radiotherapy five times a week. The primary endpoint was 3-year progression-free survival. The secondary endpoints included proportion of treatment completion and adverse events. The planned sample size was 360 patients and the primary analysis is planned in 2016. Acute radiation toxicities were evaluated according to CTCAE v3.0.

Results: From September 2007 to January 2013, 370 patients from 32 institutions were enrolled with 184 patients randomized to SF group and 186 patients to Ax group. All randomized patients included 356 males/14 females, and 341/29 patients with PS 0/1. Among SF group, 138/46 patients had T1/T2 disease, while 140/42 had T1/T2 in Ax group. Median age was 68 (range, 39-80) for SF group, and 67 (range, 35-79) for Ax group. One hundred seventy-five patients (95.1%) from SF group and 183 patients (98.4%) from Ax group completed planned radiation therapy within the planned schedule period. By October 2013, a minimum of 90 days follow-up was achieved in 360 patients (177, SF group; 183, Ax group) and acute radiation toxicities were evaluated for these patients. Eight ineligible patients (4, SF group; 4, Ax group) were included in this safety analysis. Three untreated patients (2, SF group; 1, Ax group) and one patient having received standard fractionation in Ax group were excluded from this analysis.

No patient developed any grade 4 toxicity in both groups. Grade 3 acute radiation toxicities (until 90 days after start of radiation therapy) in SF/Ax group were as follows: skin, 10.2%/3.8%; mucosa-larynx (symptomatic), 4.0%/5.5%; mucosa-larynx (functional), 1.1%/0.5%; dysphagia, 0%/0%; pain, 0%/0%; laryngeal edema, 0%/0%; and voice change, 1.1%/2.2%. Counting multiple toxicities together in SF/Ax group, grade 3 mucosa-larynx (symptomatic or functional) was observed in 5.1%/6.0%, grade 3 of any type of mucositis in 5.1%/6.0%, and grade 3 of any acute toxicity in 12.4%/10.9%. Conclusion: Accelerated radiation group revealed to have similarly good compliance compared to SF group without significantly increasing acute toxicity.
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CAN WE REDUCE TO DOSE TO THE ELECTIVE NODAL SITES FOR HEAD AND NECK CANCER? RESULTS OF A MULTICENTRE RANDOMIZED CLINICAL TRIAL.

Sandra Nuyts, MD, PhD, Daan Nevens, MD, Maarten Lambrecht, MD, Duprez Frédéric, MD, PhD, Jean-François Daisne, MD, PhD, Danielle Van den Weyngaert, MD, Nele Platteaux, MD, Yasmyne Geussens, MD, Mia Voordecker, MD, Indira Madani, MD, PhD, Wilfried De Neve, MD, PhD; University Hospitals Leuven - University Hospitals Gent- University Hospital Brussel-Clinique et Maternité Sainte-Elisabeth, Namur, Ziekenhuis Network Antwerp

Introduction

Radiotherapy with curative intent for head and neck cancer results in a significant amount of side effects. A multi-center randomized clinical trial was initiated to investigate whether a reduction of the dose to the elective nodal sites delivered by IMRT would result in a reduction of late side effects without compromising tumour control.

Material & Methods

Two hundred patients were randomly assigned to either the standard arm: elective nodal volumes (PTV elect) irradiated up to a dose of 50 Gy in 2 Gy fractions or the experimental arm: a dose of 40 Gy in 2 Gy fractions was prescribed to the PTV elect. The dose to the swallowing apparatus was kept as low as reasonably possible without compromising coverage of the therapeutic PTV (PTV ther) in both arms.

Late toxicity was scored at 6, 12, 18 and 24 months using the RTOG scoring system and analysed using a proportional odds model. Outcome was measured using a Kaplan-Meier product limit estimate and compared using a log-rank test.

Results

Dosimetrically, no significant difference was seen concerning PTV ther coverage. The median D95 of the PTV elect was significantly lower in the experimental arm than in the standard arm (p<0.001). A significant reduction of the V50 of all swallowing structures was observed in the experimental group.

We retrieved follow up information of 150, 132, 117 and 107 patients at 6, 12, 18 and 24 months respectively.

Statistically significant less dysphagia at 6 months was seen in the experimental arm (p=0.017); at 12 and 18 months this difference between both groups was however not present. At 24 months we noticed less dysphagia in the experimental arm, this failed to reach statistical significance (p=0.065). Concerning late stiffness of the neck we did not see any statistical significant difference, but observed less severe stiffness at all time-points in the experimental arm.

After two years follow up, we did not observe significant differences in loco-regional control, disease free or overall survival.

Conclusion
Dose de-escalation to the elective nodal sides might result in less dysphagia while tumour control remains unaltered. Impact on late xerostomia and quality of life in both patient groups will be investigated further.
PHASE II RANDOMIZED TRIAL OF TWO POST-OPERATIVE REIRRADIATION PROTOCOLS AFTER SALVAGE SURGERY IN HEAD AND NECK CARCINOMA: ANALYSIS OF ACUTE TOXICITY

Philippe Gorphe, MD, Francois Janot, MD, Pierre Boisselier, MD, Anne Laprie, MD, Etienne Bardet, MD, Philippe Schultz, MD, PhD, Dominique de Raucourt, MD, Stephane Temam, MD, PhD, Yungan Tao, MD, Pierre Blanchard, MD, Ellen Benhamou, MD, Jean Bourhis, MD, PhD; Institut Gustave Roussy Villejuif France, Centre Val d'Aurelle Montpellier France, Institut Claudius Regaud Toulouse France, Centre René Gauducheau Nantes France, CHRU Strasbourg France, Centre Francois Baclesse Caen France, CHUV Lausanne Suisse

Background: Full-dose re-irradiation combined with chemotherapy has been shown to improve disease-free survival after salvage surgery (J Clin Oncol, 26:5518-23, 2008). As toxicity is a major issue in re-irradiation protocols, the GETTEC (Groupe dEtude des Tumeurs de la Tête et du Cou) and the GORTEC (Groupe dOncologie et de Radiothérapie Tête Et Cou) performed a multicentric randomized phase 2 trial, so as to compare acute toxicity of two different reirradiation protocols

Material/Methods: Between June 2010 and December 2013, 56 head and neck cancer patients were treated with salvage surgery and then randomly assigned to two reirradiation protocols at the dose of 60 Gys. Patients in the reference arm received once daily fractionation (2 gys) and planned split course over 12 weeks combined with concomitant 5FU and hydroxyurea (Vokes protocol). Patients in the experimental arm received twice daily fractionation (1.2 Gys) over 5 weeks combined with concomitant Cetuximab. Eligibility criteria were: recurrence or a second primary in an area previously irradiated up to at least 45 Gy, no major sequels due to the first course of radiotherapy and a good general condition, no distant metastasis, salvage surgery with a macroscopically complete resection, able to start adjuvant treatment within 8 weeks of salvage surgery. A 2 steps Simon plan was designed, with 9 patients in each arm at the first step, and 19 additional patients at the second step.

Preliminary results: Twenty eight patients were randomized to each arm. Analysis at the first step showed that 7/9 patients in the reference arm and 2/9 in the experimental arm experienced grade 3 or 4 acute toxicity. High grade acute toxicity in the reference arm was mainly mucosal with dysphagia, major asthenia and one hand-foot syndrome. There was only one mucosal and one cutaneous major toxicity in the experimental arm.

Conclusions: Analysis of acute toxicity of this phase 2 randomized trial is currently underway, and acute toxicity for the 56 patients will be reported at the Head and Neck meeting in July 2014. However late toxicity and disease free survival are the major issues in reirradiation protocols, which needs to assess more patients. Continuation in a large phase 3 trial is under discussion, despite difficulties in enrolling patients.
**S401 DOES CLINICAL TRIAL ENROLLMENT AFFECT TREATMENT RELATED TOXICITY AND OUTCOMES IN PATIENTS WITH HPV/P16+ OROPHARYNGEAL CANCER TREATED WITH DEFINITIVE CHEMORADIATION?**

**Megan Mezera, MD, MS, Craig Silverman, MD, Rebecca Redman, MD, Jeffrey Bumpous, MD, Kevin Potts, MD, Neal Dunlap, MD; James Graham Brown Cancer Center, University of Louisville**

**Purpose**

The goal of this study is to evaluate the effect on treatment outcomes and toxicity of clinical trial enrollment in HPV/p16 positive oropharyngeal (OP) cancers treated with definitive chemoradiotherapy.

**Materials/Methods**

271 consecutive head and neck cancer patients with known HPV/p16 status treated between 2009-2012 were retrospectively reviewed. Ninety-four were identified as having OP cancers, of which 62 had HPV/p16+ tumors. Fifteen of the patients were enrolled in cooperative group studies for HPV/p16+ OP cancer. Ninety-five percent of patients were treated with intensity modulated radiation therapy (IMRT) with or without systemic therapy. Treatment related toxicity and outcomes were evaluated.

**Results**

The median follow-up time was 24 months. Patients treated on protocol were well matched with those treated off protocol in terms of age, sex, race, T stage, N stage, radiation dose to the primary site, and systemic therapy regimen. Elective nodal irradiation dose was significantly lower in patients treated on protocol (52.5 Gy vs. 56 Gy, p = 0.0012). The estimated 3-year overall survival for the cohort was 87%. There was no difference in 3-year survival for patients treated on protocol versus those treated off protocol (82% vs. 90%, p = 0.439). There were higher rates of neck nodal failure in the on protocol group (23% vs. 0%, p = 0.008), but non-significant lower rates of distant metastasis (0% vs. 8.5%, p = 0.533). 3-year progression free survival (PFS) was 79% for the cohort, with a slightly higher mean PFS for those treated off protocol (39.0 months vs. 26.8 months, p = 0.101). There was a trend toward decreased grade 3 or higher acute toxicity in patients treated on protocol (13% vs. 37.5%, p = 0.088). On protocol patients had significantly lower rates of long-term feeding tube requirements (0% vs. 8%, p = 0.044). There was no direct correlation with chemotherapy type or nodal irradiation dose.

**Conclusions**

At our institution, patients with HPV/p16+ OP cancers treated on protocol may have reduced rates of both acute and late toxicity compared with patients treated off protocol. Due to the lower elective nodal irradiation doses required on protocol, there may be a higher rate of elective nodal failure in protocol patients. Due to the limited size of our cohort, more comprehensive analyses should be performed to determine if these trends hold true.
SIGNIFICANT IMPACT OF CRITICAL WEIGHT LOSS DURING (CHEMO)RADIOTHERAPY ON QUALITY OF LIFE AND DISEASE SPECIFIC SURVIVAL IN HEAD AND NECK CANCER PATIENTS: ANALYSIS OF RISK FACTORS AND DEVELOPMENT OF A PREDICTIVE MODEL.

Simone E Eerenstein, MD, PhD, Jacqueline A Langius, RD, Anne M van Dijk, Sanne Bakker, Patricia Doornaert, MD, Irma M Verdonck-de Leeuw, PhD, Peter J Weijts, PhD, C. René Leemans, PhD; Department of Otolaryngology-Head and Neck Surgery, Dept. Nutrition and Dietetics, Internal Medicine, The Hague University of Applied Sciences, Academy of Health, Dept. Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands

Background: Pre-treatment weight loss (WL) is associated with both the important treatment outcome measurements quality of life (QoL) and survival. Although severe WL during treatment is frequent in head and neck cancer (HNC) and nutritional interventions are usual, little is known about risk factors predicting WL and the effects of WL during treatment on these outcome measurements.

Purpose / objective: First, to assess the independent association between WL during treatment and deterioration in QoL, 5-year overall survival (OS) and disease specific survival (DSS). Second, to assess risk factors to predict critical WL during treatment and to build a predictive model to identify patients at risk of severe weight loss during treatment.

Material/methods: WL-data on 1340 patients were collected before and during (adjuvant) curative-intent radiotherapy. Patients were categorized into 4 categories: <=0%, 0.1-5%, 5.1-10% and >10% WL. Critical WL was defined as >5% during radiotherapy or >7.5% WL until week 12. QoL-data were collected (QLQ-C30 and QLQ-H&N35 modules) in 533 patients. Association between WL and changes in QoL and survival was analyzed (confounder-adjusted) by linear and Cox's regression analysis. Multivariate logistic regression was used to analyze predictive factors for critical WL during treatment.

Results: WL pre-radiotherapy was: 70% <=0%, 16% had 0.1-5%, 9% had 5.1-10% and 5% had >10%. Five-year OS for these groups were 71%, 59%, 47% and 42% respectively (p<0.001) with five-year DSS of 86%, 86%, 81% and 71% respectively (p<0.001). Adjusted for potential confounders, >10% WL before radiotherapy remained significantly associated with worse OS and DSS (HR 1.7; 95%CI 1.2-2.5; p=0.002 and HR 2.1; 95% CI 1.2-3.5; p=0.007). WL of >10% during radiotherapy, when adjusted for disease-specific symptoms and tube-feeding, was significantly associated with global QoL, social eating, and social contact (P < 0.05). Five-year OS and DSS rates for critical WL during radiotherapy were 62% and 82%, compared with 70% and 89% for patients without critical WL (P =0.01; P = 0.001). After adjustment, critical WL during radiotherapy remained significantly associated with worse DSS (HR 1.7; 95% CI 1.2-2.4; P = 0.004). Critical WL during treatment occurred in 50% of patients. Main predictors were RT on ipsilateral (OR 3.19; 95% CI 1.90-5.37; P<0.001), or bilateral lymph nodes (OR 4.05; 95% CI 2.61-6.29;P<0.001), higher RT-dose on primary tumor (OR 2.10; 95%CI 1.52-2.89;P<0.001), 3D-RT instead of IMRT (OR 1.70; 95% CI 1.23-2.36; P=0.001), WHO grade 2 and 3 (OR 0.55; 95% CI 0.37-0.83; P=0.004) and younger age (OR 0.84; 95% CI 0.74-0.97; P=0.010 per 10 years).

Conclusion: Critical WL during and directly after (chemo)RT has a significant impact on QoL and 5-year DSS. Risk factors for critical WL during treatment were RT of the ipsilateral and bilateral neck, higher WHO-grade, younger age, higher RT-dose and RT-technique. The developed practical predictive model could help identify patients at risk of severe WL during treatment and in need of nutritional intervention.
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