Elderly patients affected by head and neck squamous cell carcinoma unfit for standard curative treatment: Is de-intensified,

Elderly patients affected by head and neck squamous cell carcinoma unfit for standard curative treatment: is de-intensified, hypofractionated radiotherapy a feasible strategy?

Conflict of interest statement

None declared.

Abstract

Objectives: The aim of our work was to report on the clinical outcome of a moderately hyprofractionated radiotherapy regimen in elderly patients affected by head and neck squamous cell carcinoma (HNSCC).

Material and methods: HNSCC aged ≥ 65 deemed unsuitable for curatively-intended concurrent chemo-radiotherapy or high-dose radiotherapy by clinical judgement were further evaluated with the Geriatric 8 (G8) questionnaire and Charlson comorbidity index (CCI). In case of a G8 score ≤ 14, a de-intensified radiation schedule of 40 Gy delivered in 16 fractions was prescribed.

Results: Thirty-six patients were treated between 2011 and 2016. The median age of the cohort was 77.5 (range: 65-91 years) with a combined ECOG PS of 2-3 in 77.8% and CCI of ≥ 8 in 25% patients, respectively. At a median follow-up of 13 months (range 2 – 62 months), the 6-month and 1-year rates of loco-regional control and progression-free survival were 42%, 28% and 36% and 20%, respectively. At univariate analysis, log-rank test showed that age > 75 years (p=0.036), worse PS (ECOG ≥ 2; p=0.027), lower G8 score (<9; p=0.027) and PTV volume greater than 200 cc (p= 0.038) had a significant correlation with PFS. The negative impact of the PTV volume on PFS was the only parameter confirmed in the multivariate analysis (HR 2.68; 95% CI: 1.24-5.81, p=0.013). No grade 4-5 toxicity was observed, while 13/36 patients (36%) had G3 acute side effects.

Conclusion: the hypofractionated radiation schedule evaluated provides clinical benefit with low toxicity in frail, elderly patients affected by locally advanced HNSCC.

Keywords

Head and Neck Cancer; Comorbidity; Squamous cell carcinoma; Radiotherapy; Elderly; Unfit.

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents the sixth most common malignant tumor worldwide, with over 600.000 new cases diagnosed per year [1]. In last 15 years, human papilloma virus (HPV) infection has been recognized to account for a distinct epidemiologic trend occurring mainly in western countries, leading to a rising incidence of oropharyngeal cancer (OPC) particularly in male patients in their 5th decade of life [2,3]. Next to the pathogenesis of HPV-driven OPC [4], the development of HNSCC is still largely the result of a chronic exposure to tobacco and alcohol – induced field cancerization [5] of the upper aerodigestive mucosal tract. As a consequence, almost half of the patients are older than 65 years at diagnosis [6]. In next 20 years, the incidence of HNSCC is expected to increase by 64% in the elderly population [7]. Level 1 evidence [8, 9, 10] supports the use of multimodality treatment for the loco-regionally advanced disease which can be found in over 60% of cases: however, none of the intensified approaches addressed in clinical trials and metanalyses have demonstrated to provide clinical benefit in patients older than 65 years. Moreover, compared with younger subjects, elderly patients with head and neck cancer are more frequently burdened with treatment-induced severe acute toxicity [11, 12], multiple comorbidities [13] and non-cancer related death [14]. The aim of our work was to evaluate the feasibility and clinical benefit of a de-intensified hypofractionated radiotherapy in elderly patients deemed unfit for standard curative treatment, a group for whom at present no specific evidence-based recommendations [15, 16] are available.

Material and Methods

Patients

Following the definition of the National Institutes of Health [17], patients with age $\geq$ 65 years were defined as old. In case of locally advanced HNSCC for whom the multidisciplinary team recommended a curatively-intended non surgical treatment, a prospective evaluation of frailty was performed when the treating oncologist considered the elderly patient unfit for standard therapy by clinical judgement. First, the Geriatric 8 (G8) screening tool was administered in order to identify subjects potentially able to undergo an intensive therapy. By definition, a G8 score $\geq$ 14 was taken as a cutoff value for healthy patients suitable for standard treatment [18]. In case of a lower score, the individual burden of comorbidities was further investigated through the Charlson comorbidity index (CCI) [19]. Both tests were therefore used to support the clinical decision towards a de-intensified therapeutic approach. Patients affected by histologically proven, squamous cell carcinoma of any sub-site of the head and neck with an ECOG performance status of 1-3 could be included in our observational prospective study. Study design and study procedures were reviewed and approved by institutional ethics committee (‘‘Comitato Etico Area Vasta Centro’’). All patients provided informed consent before treatment.

Treatment characteristics

All patients underwent staging workup including computed tomography (CT) with contrast medium of the head and neck and chest or magnetic resonance (MR) of the head and neck with contrast medium combined with chest CT to rule out the presence of distant metastases. Positron emission tomography (PET) with ^{18}F – fluorodeoxyglucose was performed in selected cases. A CT scan (Light Speed 16; GE Healthcare Medical Systems, Milwaukee,WI, USA) was acquired at 3 mm slice width for radiation treatment planning. A personalized thermoplastic face mask was created for all patients. The gross tumor volume (GTV) consisted of the primary tumor and pathologic lymph nodes. A single clinical target volume (CTV) was made up by the GTVs plus a 1 cm margin. The first macroscopically unaffected lymphatic echelon was also included in the CTV. To take into account potential systematic and random errors, a 5 mm CTV to planning target volume (PTV) margin was chosen. A total dose of 40 Gy was delivered in 16 fractions of 2.5 Gy each. Radiotherapy was delivered by a linear accelerator (Elekta Synergy, Elekta, Crawley, UK) with a 3D-conformal technique or intensity modulated radiotherapy (IMRT). For the latter, a volumetric modulated arc therapy (VMAT) solution was chosen. All VMAT plans were calculated with Monaco software (Elekta, Crawley, UK). In selected cases with marginal or out-of-field recurrences, a second round of treatment with the same total dose and accelerated regimen (40 Gy/2.5 Gy fraction) was prescribed by the treating radiation oncologist, provided that a disease-free interval of at least 6 months was obtained and in accordance with cumulative dose constraints.

Outcome measures and statistical methods

A clinical evaluation at 25 days after treatment was scheduled for all patients to assess the resolution of radiation-induced side effects. Acute toxicity was scored according to CTCAE v. 4 [20]. Response assessment was performed at 2 months after treatment and every 3 months thereafter for the first 2 years, then every 6 months. Tumor response was evaluated according to Recist criteria [21]. A complete response (CR) was defined as no visible gross tumor, partial response (PR) as at least a 30% decrease, progressive disease (PD) as at least a 20% increase, and stable disease (SD) as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The primary outcome measure of the study was progression-free survival (PFS). PFS was defined as the time from the last day of radiotherapy to the date of the first of the following events:

- the first day when the RECIST criteria for PD were met
- salvage surgery or elective neck dissection performed after 15 weeks from the last day of treatment performed on the clinical or radiological evidence of progression;
- death for any cause

A pattern of failure analysis after de-intensifed RT was performed. Locoregional control (LRC) was defined as the time from the last day of radiotherapy to local and/or regional disease progression. Overall survival (OS) was defined as the time from the last day of

treatment to death from any cause.
Median LRC, PFS and OS were calculated. The relative estimates of LRC, PFS and OS at 6 and 12 months were estimated by the Kaplan-Meyer method, with corresponding 95% confidence intervals. The predictive impact of pretreatment variables was assessed with a log-rank test. The risk of disease progression and death was assessed through Cox regression model (both univariate and multivariate analyses) calculating the hazard ratio (HR) with corresponding 95% confidence intervals and p values. Baseline demographics, patients' characteristics and treatment features were summarized using descriptive statistics.

Results

Between December 2011 and July 2016, 36 patients received the described hypofractionated de-intensified RT schedule. Patients' characteristics are summarized in table 1. The median age of the cohort was 77.5 (range: 65-91 years), with a high prevalence of male subjects. Notably, the most involved subsite of primary tumor was the oral cavity with a prevalence of 50% (n = 18). In most cases, patients had advanced tumors with stage IVA and IVB disease (86.1%). Only five patients (13.9%) had stage ≤ III disease. None of 6 OPC had a HPV positive disease, therefore the global cohort was HPV negative. Only a minority of patients (6/36; 16%) had a percutaneous endoscopic gastrostomy (PEG) in place before RT start. According to the G8 questionnaire, all patients were considered vulnerable with an individual score below 14. The unsuitability of our cohort for intensive treatment was further highlighted by the frail general conditions and high comorbidity burden (combined ECOG PS of 2-3 in 77.8% and CCI of $\geq$ 8 in 25% of cases, respectively). A standard 3D conformal parallel or multiple field technique was used in 25/36 patients (69.4%) whereas VMAT was preferentially delivered from October 2014 on (11/36, 30.6%). RT was completed as scheduled in the majority of cases (33/36, 91.6%). In 3 patients the therapy was stopped prematurely (at 20 Gy in two cases and at 32.5 Gy in one case, respectively) due to worsening general conditions. The median length of treatment interruption was 1,02 day (range 0 to 10), with no need for RT breaks in 30/36 (83.3%) patients. As expected, the irradiated disease burden was rather heterogeneous in our cohort, with a median PTV volume of 191.4 cc (range: 31.87 – 608 cc). As reported in Table 2, no grade 4-5 acute side effects were observed, instead the incidence of grade 3 side effects was 36% (13/36 patients). The most common treatment-related toxicities were grade 1 oral mucositis and grade 1 dysphagia, both with an incidence of 36.1%. Early response assessment at 2 months after treatment was available for 33 of 36 patients (91.6%). An objective response rate of 66.6% was obtained, resulting from 4 complete responses (12.1%) and 18 partial responses (54.5%), respectively.
At a median follow-up of 13 months (range 2 – 62 months), the median loco-regional control was 5 months. The 6-month and 1-year rates of LRC were 42% and 28%, respectively. Regarding PFS, all but 3 cases developed a loco-regional recurrence as first event of treatment failure. Overall, the median PFS was 4 months, with 6-month and 1-year rates of 36% and 20%, respectively (figure 1). At univariate analysis, log-rank test

showed that age > 75 years (p=0.036), worse PS (ECOG ≥ 2; p=0.027), lower G8 score (<9; p=0.027) and PTV volume greater than 200 cc (p= 0.038) had a significant correlation with PFS. The negative impact of the PTV volume on PFS was the only parameter confirmed in the multivariate analysis (HR 2.68; 95% CI: 1.24-5.81, p=0.013; figure 2).
In 6/36 cases (16.6%), a second round of treatment was prescribed at a median disease-free interval from the end of first RT course of 6 months (range: 6-16).
The median OS of the whole cohort was of 12 months, with resulting 6-month and 1-year rates of 58% and 50%, respectively (figure 3). At time of analysis, 6 patients (16%) are alive, with a median OS of 26 months (range: 16-33).

Discussion

Multimodal treatment is standard of care in the curative setting of HNSCC on the basis of level 1 evidence. However, patients' age is a factor that needs to be carefully taken into account.
The individual patient data MACH-NC meta-analysis [8] showed that the concurrent addition of cisplatin-based chemotherapy to radiotherapy yielded a 6.5% improvement in 5-year OS (hazard ratio of death, 0.81; p <0.0001). At subgroup analysis, the benefit was shown to be diluted with increasing age (test for trend, p=0.003). In particular, no survival advantage could be observed for the patients aged 71 or more, which were also markedly underrepresented (8% out of total 17.346 subjects included from 93 trials). The individual patient data MARCH meta-analysis [9] demonstrated that altered fractionation was beneficial compared with conventional RT, with a 3.4% improvement in 5-year OS (HR of 0.92, p=0.003). Of note, hyperfractionation was shown to be the most effective option, with a 8% gain in survival. Again, the reported benefit was attenuated by increasing age, disappearing for patients older than 70 years (HR of 1.08; test for trend, p =0.007), which were about 14% out of total 6515 subjects included. Similarly, only 45/211 (21%) of the patients treated with cetuximab and radiotherapy in the experimental arm of the IMCL 9815 phase 3 trial [10] were older than 65 years, receiving no significant advantage from the combined treatment compared with RT alone at subgroup analysis.
Taking altogether, these data provide indirect evidence of a lack of benefit of standard intensified approaches in the treatment of elderly HNSCC patients. This assumption may be corroborated by further observations. First, the accrual of subjects with more than 65 years was historically very low in pivotal randomized phase 3 trials, thus hampering the generalizability of any incremental gain in this category. Second, the physiological loss of functional reserve [22] associated with aging may translate into severe toxicity [11] and suboptimal compliance to intensive treatment compared with younger adults, leading to a detrimental reduction in relative dose intensity of both radiation and systemic agents. Third, any potential improvement in survival may be blunted by the competing risk of non-cancer related death due to aging itself [23]. Whereas chronological age per se should not be viewed as a limiting factor towards the implementation of standard of care [24, 25], it is the individual burden of comorbidites to play a major role in the treatment decision-making of HNSCC. A meta-analysis on 22.932 patients showed that the presence of comorbidity

was significantly correlated with worse overall survival (HR of 1.38; 95% CI: 1.32–1.43) [13]. Since chronic exposure to tobacco and/or alcohol is the main etiopathogenetic factor implied in the development of HNSCC, it is recognized that a substantial proportion [26] of elderly HNSCC patients are vulnerable to a variable extent due to mainly concurrent cardiovascular, pulmonary and liver diseases. In recent years, a geriatric assessment intervention has been advocated to support cancer individualized treatment decision making in the elderly population [27, 28]. In order to single out subjects fit enought to be potentially amenable to receive intensive standard treatment, different screening tools have been proposed [29]. Among them, the G8 questionnaire was shown to be the most accurate in identifying the patients at highest risk of frailty. In particular, a systematic review of the literature [29] and a prospective non-interventional study [30] on 937 patients with cancer aged 70 or more showed that its sensitivity in detecting unfit elderly was of 87% and 86.5%, respectively. A pilot study [31] performed on 35 HNSCC patients aged 65 years or older confirmed that a G8-based screening assessment was able to discriminate vulnerable subjects more accurately than the MDT evaluation alone (detection increased from 20% to 40%; p=0.12).

Overall, no curatively-intended recommendation is specifically available for locally advanced HNSCC in elderly patients deemed unfit to receive standard treatment.

The use of de-intensifed radiation regimens has been mainly described in the context of clinical scenarios with clear palliative intent. Hypofractionated schedules such as 20 Gy in 5 consecutive fractions [32], 30 Gy in 5 fractions delivered over 3 weeks [33] and 14 Gy in 4 fractions given twice daily in 2 consecutive days [34, 35] were shown to be effective in yielding symptomatic relief and improved quality of life with minimal toxicity. The adoption of more protracted, moderately hypofractionated treatments was reported in few single center experiences when a prolonged locoregional control was pursued on top of a pure palliative purpose.

Over an 11-year time span, Al-Mamgani et al [36] treated 158 patients with the “Christie regimen” consisting of 50 Gy given in 16 fractions of 3.125 Gy. A standard 3D-conformal technique was used to enclose the macroscopic primary and nodal disease plus a 1 cm margin. A 73% ORR was obtained despite the occurrence of non-negligible acute toxicity (grade $\geq$ 3 dermatitis and mucositis of 45% and 65%, respectively). At a median follow-up of 16.4 months, the 1- and 3-year locoregional control rates were 62% and 32%, respectively. Between 2000 and 2005, Agarwal et al [37] treated 110 unresectable HNSCCs with a telecobalt machine delivering 40 Gy in 16 fractions, with possible escalation to 50 Gy in selected cases. Complete and partial responses were showed in 11 (10%) and 69 (63%) patients, respectively, with a resulting 73% ORR. At a median follow-up of 6 months, a 1-year PFS of 55.1% (95% CI: 40.3%–69.9%) was achieved. More recently, Bledsoe et al [38] reported on a split-course regimen consisting of two rounds of 30/36 Gy given at 3 Gy/fraction with a 3 to 5 weeks break between them. Between 2002 and 2010, 65 patients with advanced age, severe comorbidities, anticipated intolerance to standard treatment or oligometastatic disease received either a conventional 3-field approach or IMRT. Both courses were completed in 89% of cases. Excluding 26 recurrent/metastatic patients from the cohort, a 91% ORR was obtained at 3 months after treatment in 29/39 subjects (50% CR and 41% PR), with resulting median LRC and OS of

25.7 and 8.9 months, respectively. Notably, the median age of the cohort was 71 (range 42-101 years). An IMRT-simultaneous integrated boost (SIB) technique was used by Straube et al [39] in 27 patients for whom the multidisciplinary team prescribed a reduced-volume RT, mainly due to age, comorbidity burden or metastatic disease (9/27 had stage IVC). Out of 19 patients evaluable for response, an early 6-week ORR of 52.6% was achieved (1 and 9 patients achieved CR and PR, respectively).

Taking all data together, these moderately hypofractionated regimens are characterized by mid-term efficacy in securing loco-regional control with acceptable toxicity. However, the interpretation of the aforementioned studies is hampered by their significant heterogeneity in terms of patients' selection, to certain extent biased by the inclusion of recurrent/metastatic patients, elegibility to concurrent chemotherapy for some patients and variable symptomatic burden.

The results of our study are consistent with previous experiences in terms of early and mid-term efficacy. We also showed that a de-intensified, moderately hypofractionated regimen of 40 Gy in 16 fractions of 2.5 Gy each is an effective approach providing rapid disease regression (2-month ORR of 66.6%) with low toxicity and potential for sustained locoregional control in selected patients. When dealing with locally advanced HNSCC in the elderly, proper patients' selection is a crucial step in treatment decision-making [40]. To our knowledge, our single-center experience is the fist to report on the support of a geriatric screening tool such as the G8 questionnaire towards the adoption of a de-intensified radiation schedule in frail elderly patients. Compared with previous experiences, the poor long-term outcome data in our cohort may reflect the inclusion of patients with homogeneous, unfavorable features such as the low G8 score, high CCI, prevalent ECOG PS of 2 and the age cutoff of 65 years. In addition, the exclusion of patients with recurrent/metastatic disease from our cohort may be seen as another strenght towards an unbiased interpretation of the possible anticancer efficacy of a low dose hypofractionated regimen as ours. According to our analysis, a large disease volume in an elderly and frail patient is a factor associated with dismal prognosis. In particular, we can hypothesize that above 200 cc PTV volume a shorter hypofractionated regimen may be better suited in light of the limited life expectancy. Several limitations have to be taken into account in interpreting our data. First, a comprehensive geriatric assessment (CGA) was not performed due to logistic reasons. However, although cumbersome and time-consuming, the CGA is considered the gold standard instrument to tailor cancer treatment intensity in elderly patients [41]. We used the G8 questionnaire as a quick screening assessment that could aid the therapeutic decision together with the clinical evaluation and Charlson comorbidity score. Moreover, quality of life was not formally evaluated in our study. Potentially, this could have allowed us to highlight the benefit of a de-intensifed approach in a frail patients' population, further reinforcing the value of our strategy. Indirectly, the rate of early disease control and low toxicity might support our treatment in preventing rapid QoL deterioration due to disease progression. The small sample size of the cohort limits the generalizability of our findings. In the future, the results of the ongoing randomized ELAN phase 3 trial [42] testing the non-inferiority of hypofractionated split-course versus standard RT will provide valuable insight on this topic.

Conclusions

A de-intensified, moderately hypofractionated radiation schedule provides clinical benefit with low toxicity in frail, elderly patients affected by locally advanced HNSCC. In this setting, a PTV larger than 200 cc is an unfavorable prognosticator of response. The treatment of non-metastatic HNSCC patients unfit for intensive standard therapy remains a significant challenge in head and neck oncology, warranting future investigations.

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006;24:2137-2150
2. Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. J Clin Oncol 2006;24:2606–11. doi:10.1200/JCO.2006.06.1291.
3. Gillison ML, Castellsagué X, Chaturvedi A, Goodman MT, Snijders P, Tommasino M, et al. Eurogin Roadmap: Comparative epidemiology of HPV infection and associated cancers of the head and neck and cervix. Int J Cancer 2013;134:497–507. doi:10.1002/ijc.28201.
4. Weinberger PM, Yu Z, Haffty BG, Kowalski D, Harigopal M, Brandsma J, et al. Molecular Classification Identifies a Subset of Human Papillomavirus – Associated Oropharyngeal Cancers With Favorable Prognosis 2006;24. doi:10.1200/JCO.2004.00.3335.
5. Cancer Genome Atlas Network: Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015; 517:576-582. doi: 10.1038/nature14129.
6. The changing demographics of head and neck squamous cell carcinoma in the United States. Sikora AG, Toniolo P, DeLacure MD. Laryngoscope 2004;114(11):1915-23. doi: 10.1097/01.mlg.0000147920.66486.bc
7. Gugi J, Strojan P. Squamous cell carcinoma of the head and neck in the elderly. Reports Pract Oncol Radiother 2013;18:16–25. doi:10.1016/j.bjoms.2005.05.011.
8. Pignon JP, Maître A le, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14. doi:10.1016/j.radonc.2009.04.014.
9. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843–54. doi:10.1016/S0140-6736(06)69121-6.
10. Bonner J a, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. NEJM 2006;354:567–78. doi:10.1056/NEJMoa053422.
11. Pignon T, Horiot JC, Van den Bogaert W, Van Glabbeke M, Scalliet P. No age limit for radical radiotherapy in head and neck tumours. Eur J Cancer 1996;32A(12):2075-81.
12. Merlano MC, Monteverde M, Colantonio I, Denaro N, Lo Nigro C, Natoli G, et al. Impact of age on acute toxicity induced by bio- or chemo-radiotherapy in patients with head and neck cancer. Oral Oncol 2012;48:1051–7. doi:10.1016/j.oraloncology.2012.05.001.

13. Bøje CR. Impact of comorbidity on treatment outcome in head and neck squamous cell carcinoma - A systematic review. Radiother Oncol 2014;110:81–90. doi:10.1016/j.radonc.2013.07.005.
14. Mell LK, Dignam JJ, Salama JK, Cohen EEW, Polite BN, Dandekar V, et al. Predictors of competing mortality in advanced head and neck cancer. J Clin Oncol 2010;28:15–20. doi:10.1200/JCO.2008.20.9288.
15. Sarris EG, Harrington KJ, Saif MW, Syrigos KN. Multimodal treatment strategies for elderly patients with head and neck cancer. Cancer Treat Rev 2014;40:465–75. doi:10.1016/j.ctrv.2013.10.007.
16. Porceddu S V., Haddad RI. Management of elderly patients with locoregionally confined head and neck cancer. Lancet Oncol 2017;18:e274–83. doi:10.1016/S1470-2045(17)30229-2.
17. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. Cancer J Clin 1997;47:5-27
18. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23(8):2166-72. doi: 10.1093/annonc/mdr587.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.
20. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. 2009 May. Available at: http://evs.nci.nih.gov/.
21. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47. doi: 10.1016/j.ejca.2008.10.026
22. Balducci L, Colloca G, Cesari M, Gambassi G. Assessment and treatment of elderly patients with cancer. Surg Oncol 2010;19:117–23. doi:10.1016/j.suronc.2009.11.008
23. Huang SH, O'Sullivan B, Waldron J, Lockwood G, Bayley A, Kim J, et al. Patterns of care in elderly head-and-neck cancer radiation oncology patients: a single-center cohort study. Int J Radiat Oncol Biol Phys 2011;79(1):46-51. doi: 10.1016/j.ijrobp.2009.10.052.
24. Bhattacharyya N. A matched survival analysis for squamous cell carcinoma of the head and neck in the elderly. Laryngoscope. 2003;113(2):368-72
25. Moye VA, Chandramouleeswaran S, Zhao N, Muss HB, Weissler MC, Hayes DN, et al. Elderly patients with squamous cell carcinoma of the head and neck and the benefit of multimodality therapy. Oncologist. 2015 Feb;20(2):159-65. doi: 10.1634/theoncologist.2013-0325.
26. Bøje CR, Dalton SO, Primdahl H, Kristensen CA, Andersen E, Johansen J, et al. Evaluation of comorbidity in 9388 head and neck cancer patients: A national cohort study from the DAHANCA database. Radiother Oncol 2014;110:91–7. doi:10.1016/j.radonc.2013.11.009.
27. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. Oncologist. 2000;5(3):224-37.

28. Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, et al. Improving the evidence base for treating older adults with cancer: American Society of Clinical Oncology statement. J Clin Oncol 2015;33:3826–33. doi:10.1200/JCO.2015.63.0319.
29. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: A systematic review. Lancet Oncol 2012;13:e437–44. doi:10.1016/S1470-2045(12)70259-0.
30. Kenis C, Milisen K, Flamaing J, Wildiers H, Decoster L, Van Puyvelde K, et al. Performance of two geriatric screening tools in older patients with cancer. J Clin Oncol 2014;32:19–26. doi:10.1200/JCO.2013.51.1345.
31. Kenis C, Milisen K, Flamaing J, Wildiers H, Decoster L, Van Puyvelde K, et al. Performance of two geriatric screening tools in older patients with cancer. J Clin Oncol 2014;32:19–26. doi:10.1200/JCO.2013.51.1345.
32. Mohanti BK, Umapathy H, Bahadur S, Thakar A, Pathy S. Short course palliative radiotherapy of 20 Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study. Radiother Oncol 2004;71:275–80. doi:10.1016/j.radonc.2004.03.009.
33. Porceddu S V., Rosser B, Burmeister BH, Jones M, Hickey B, Baumann K, et al. Hypofractionated radiotherapy for the palliation of advanced head and neck cancer in patients unsuitable for curative treatment - “Hypo Trial.” Radiother Oncol 2007;85:456–62. doi:10.1016/j.radonc.2007.10.020.
34. Corry J, Peters LJ, D’Costa I, Milner AD, Fawns H, Rischin D, et al. The “QUAD SHOT” - A phase II study of palliative radiotherapy for incurable head and neck cancer. Radiother Oncol 2005;77:137–42. doi:10.1016/j.radonc.2005.10.008.
35. Lok BH, Jiang G, Gutiontov S, Lanning RM, Sridhara S, Sherman EJ, et al. Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers. Oral Oncol 2015;51:957–62. doi:10.1016/j.oraloncology.2015.07.011.
36. Al-mamgani A, Tans L, Van rooij PHE, Noever I, Baatenburg de jong RJ, Levendag PC. Hypofractionated radiotherapy denoted as the “Christie scheme”: an effective means of palliating patients with head and neck cancers not suitable for curative treatment. Acta Oncol 2009;48:562–70. doi:10.1080/02841860902740899.
37. Agarwal JP, Nemade B, Murthy V, Ghosh-Laskar S, Budrukkar A, Gupta T, et al. Hypofractionated, palliative radiotherapy for advanced head and neck cancer. Radiother Oncol 2008;89:51–6. doi:10.1016/j.radonc.2008.06.007.
38. Bledsoe TJ, Noble AR, Reddy CA, Burkey BB, Greskovich JF, Nwizu T, et al. Split-course accelerated hypofractionated radiotherapy (scahrt): A safe and effective option for head and neck cancer in the elderly or infirm. Anticancer Res 2016;36:933–40.
39. Straube C, Pigorsch SU, Scherb H, Wilkens JJ, Bier H, Combs SE. Reduced volume SIB-IMRT/IGRT to head and neck cancer in elderly and frail patients: outcome and toxicity. Radiat Oncol 2016;11:133. doi:10.1186/s13014-016-0711-x.
40. Orlandi E, Bossi P. Toward Personalized Cancer Care for Elderly Head and Neck

Cancer Patients. Int J Radiat Oncol 2017;98:965–6. doi:10.1016/j.ijrobp.2016.11.001.

41. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol. 2005 Sep;55(3):241-52. doi: 10.1016/j.critrevonc.2005.06.003
42. www.clinicaltrials.gov/NCT01864850

CAPTIONS

Figure 1: **Overall PFS for the entire population**

Figure 2: Impact of PTV volume on PFS

Figure 3: Overall survival for the entire population

Table 1: patients' characteristics

Table 2: acute treatment-related toxicity according to CTCAE v.4

Table_1

TABLE 1. Patients' characteristics.

Characteristic	No. of patients (%), n = 36
Median age, y (range)	77.5 (65-91)
Sex	
Male	21 (58.3%)
Female	15 (41,7%)
ECOG	
0	0
1	8 (22.2%)
2	19 (52.8%)
3	9 (25%)
CCI	
<4	0
4-7	27 (75%)
8-11	9 (25%)
G8	
11-13	4 (11%)
<11	32 (89%)
Location	
Oral cavity	18 (50%)
Oropharynx	6 (16.6%)
Larynx	6 (16.6%)
Other	6 (16.6%)
AJCC staging	
≤ III	5 (14%)
IVA	19(53%)
IVB	12 (33%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; AJCC American Joint Committee on Cancer 7th edition.

Table_2

TABLE 2. Acute treatment-related toxicity according to CTCAE version 4.03.

	No. (%) by toxicity grade		
Toxicity (CTCAE v 4.03)	**Grade 1**	**Grade 2**	**Grade 3**
Oral mucositis	13 (36.1%)	11 (30.5%)	7 (19.3%)
Dysphagia	13 (36.1%)	8 (22.2%)	6 (16.7%)
Radiation dermatitis	10 (27,8%)	10 (27.8%)	0

Abbreviations: CTCAE . 4.03 Common Terminology Criteria for Adverse Events version 4.03.

Figure_1

Figure.1 Overall PFS for the entire population

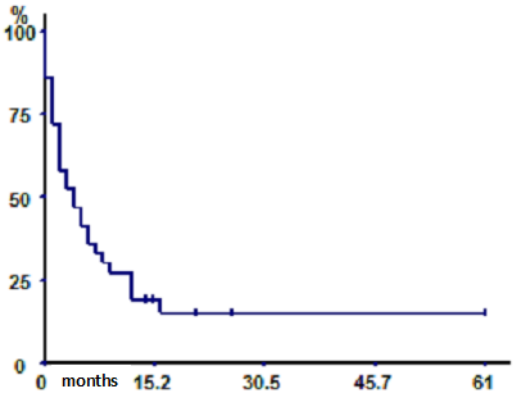
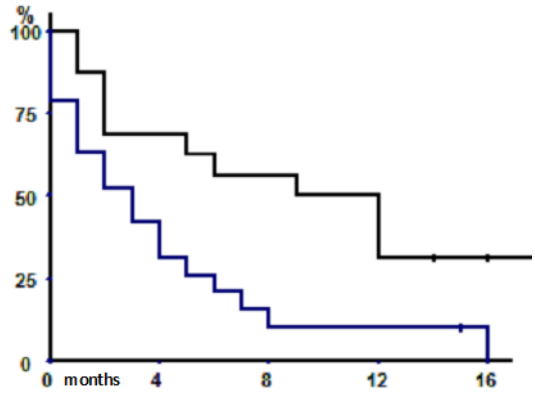


Figure_2

Figure. 2 Impact of PTV volume on PFS



Black line: PTV < 200cc; Blue line: PTV > 200cc

Figure_3

Figure. 3 Overall survival for the entire population