Medical Oncology (2019) 36:42
https://doi.org/10.1007/s12032-019-1264-2

ORIGINAL PAPER

Individualized treatment of head neck squamous cell carcinoma patients aged 70 or older with radiotherapy alone or associated to cisplatin or cetuximab: impact of weekly radiation dose on loco-regional control

Liliana Belgioia[1,2] · Almalina Bacigalupo[2] · Francesco Missale[3,4] · Stefania Vecchio[5] · Ilaria Chiola[1] · Serena Callegari[1] · Elisa Verzanini[1] · Giorgio Peretti[3,4] · Renzo Corvò[1,2]

Received: 7 February 2019 / Accepted: 18 March 2019 / Published online: 29 March 2019

Abstract

The purpose of this study is to evaluate if, in elderly HNC patients, loco-regional control (LRC) is influenced by average weekly radiation dose (AWD). From 2009 to 2017, 150 consecutive HNC elderly patients were analyzed. AWD was calculated by dividing total dose in Gray by overall treatment time in weeks. Patients were divided in 2 groups: Group 1 (70–75 years) and Group 2 (> 75 years). Primary endpoint was LRC; secondary endpoints were overall survival (OS) and compliance to treatment. The median age was 76 years (range 70–92), the distribution of patients by age was 72 and 78 patients in Group 1 and in Group 2, respectively; overall median follow-up was 23 months. Optimal cut-off of AWD for LRC was 9.236 ($p=0.018$). Median OS was 73 months. In univariate survival analysis low PS ($p=0.005$), T3–T4 ($p=0.021$), Stage III–IV ($p=0.046$) and AWD^{Low} (< 9.236) ($p=0.018$) were significantly associated with lower LRC; low PS ($p<0.001$) and Group 2 ($p=0.006$) were also associated with lower OS. Considering patients treated with radiotherapy alone AWD^{Low} was significantly associated with lower LRC ($p=0.04$) whereas among patient treated with chemoradiotherapy AWD did not affected LRC ($p=0.18$). The multivariate analysis confirmed the significant value of PS for the prediction of LRC and OS ($p=0.035$ and $p<0.001$, respectively). In elderly patients an AWD of > 9.236 Gy was found to be beneficial for RT alone regimen. When radiotherapy alone is indicated in elderly patients an effort should be made to maintain an increased AWD in order to improve LRC.

Keywords Head neck cancer · Elderly · Average weekly dose · Loco-regional control · Chemoradiotherapy · Radical radiotherapy

Introduction

Head and neck carcinoma (HNC) is the sixth most common cancer worldwide and the majority of patients present with advanced stage disease thus requiring a multimodality approach [1]. Approximately 50% of the head and neck cancer population are elderly patients (aged > 65 years), and this rate is inevitably projected to increase over time, especially in developed countries [2].

Elderly HNC patients presented worse survival in comparison to younger patients and seem that they not benefit from intensified regimens including chemo or bioradiotherapy [3, 4].

However, these data emerged from clinical trials in which the proportion of elderly population represents less

✉ Liliana Belgioia
liliana.belgioia@unige.it

1 Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

2 Radiation Oncology Department, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

3 Department of Otorhinolaryngology, Head and Neck Surgery, University of Genoa, Genoa, Italy

4 IRCCS Ospedale Policlinico San Martino, Genoa, Italy

5 Medical Oncology Department, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

than 10% of the study population [5]; no data demonstrate that chronological age in itself is a determining factor and probably biological age should be considered for treatment decision [6]; on this basis, despite the increasing incidence of cancer in elderly, the standard of care in this subgroup of patients remains uncertain and, at date, the treatment is largely influenced by physician evaluation or single Institution guidelines. Recently, the interest in elderly HNC patients is increasing for different reasons but especially because seems that, if adequately selected, subgroup of these patients may present outcomes as good as those younger [7]. For patients not submitted to conservative or radical surgery, radiotherapy (RT) remains the mainstay for cure. Radiotherapy delivered with standard or altered fractionation may be less effective in frail patients or patients who need gap during the treatment [8]. An overall treatment time of radiotherapy longer than that planned may impair local control and, subsequently, decrease survival rate [9]. The risk of longer treatment time is higher in elderly due more severe toxicity and less compliance due to co-morbidity or logistics issues. Few experiences have reported, so far, the impact of Overall Treatment Time on local control in elderly. The investigation of the Average Weekly Dose (AWD), i.e., the actual radiation dose delivered during every week of radiotherapy, may be a predictive value of the quality of the treatment in order to obtain good outcomes. Here we retrospectively analyze the outcomes of a larger series of elderly HNC patients, treated with radiotherapy alone or associated to systemic therapy, with the additional aims to evaluate if loco-regional control is influenced by AWD as well as to assess if some subgroup of elderly may have similar prognosis to younger patients with HNC.

Materials and methods

This retrospective study was performed within the notification presented to the Ethics Committee of IRCCS Policlinico San Martino Hospital of Genoa (P.R 133REG2017).

Patients

Between February 2009 and January 2017, 514 patients were treated for head and neck malignancies (HNC) at the Department of Radiation Oncology at our Institute. We selected and retrospectively analyzed all patients with age ≥ 70 years old and histological proven squamous cell carcinoma of head and neck district (HNSCC). The choice of 70 years as starting age value for elderly was chosen since the difficulty in treatment decision increases in particular for old (70–75 years) (Group 1) and very old (> 75 years) (Group 2) patients compared to young old (< 70 years). Patients who underwent to re-irradiation or palliative treatment were excluded from our analysis. All patients were staged in accordance with the 2009 American Joint Committee on Cancer staging classification.

Treatment consisted of primary radiotherapy with or without chemotherapy or anti EGFR therapy, or adjuvant radiotherapy with or without systemic therapy after primary surgery. The diagnostic-therapeutic work-up included clinical examination, endoscopy, computed-tomography (CT) scan or MRI, and a multidisciplinary evaluation to plan the optimal treatment and follow-up strategy. All patients received a nutritional evaluation before and during radiotherapy.

Radiotherapy

Planning CT scan was performed in treatment position with an immobilization device consisting of a head and shoulder 5-points thermoplastic mask with slices of 2.5 mm. Gross tumor volume (GTV) was determined according to clinical examination, endoscopy, CT scan, MRI, or PET scan.

Radiation therapy was delivered with a High Tech linear accelerator (Clinac 2100 or Trilogy, Varian, Palo Alto, CA, USA) or by Helical Tomotherapy (Accuray, Sunnyvale, CA, USA). Three-dimensional conformational (3DCRT) and RapidArc radiotherapy were planned using Eclipse version 13.5.31 (Varian, Palo Alto, USA), rotational intensity modulated radiotherapy (IMRT) was performed using Helical Tomotherapy treatment planning system. Patients were treated with the following RT regimens: once daily radiation with sequential boost or simultaneous integrated boost.

Patients could receive a standard fractionation radiation schedule (2 Gy daily for a total of 66–70 Gy) or a moderately accelerated RT consisted of 2.12 Gy daily for a total dose of 66–69.9 Gy to the high-risk volume. In the majority of patients two clinical target volumes were identified (high and low risk), in selected patients an intermediate risk volume was contouring.

The average weekly dose (AWD) was calculated for each patient dividing the total dose in Gy by the total treatment time in calendar weeks.

Systemic therapy

Patients received cisplatin (CDDP) (dose: 100 mg/m2 every 3 weeks or 40 mg/m2 weekly) based chemotherapy or cetuximab (according to Bonner regimen) associated to radiotherapy at the discretion of a medical oncologist expert in HNC.

Endpoints and statistics

The primary endpoint of this observational study was loco-regional control (LRC) according to Average Weekly Dose of Radiotherapy. Loco-regional failure was defined as any progression or recurrence of disease at the primary site or in head and neck regional nodes. The secondary endpoints were overall survival and compliance to treatment evaluated as treatment breaks or interruption of planned treatment.

Associations between categorical variables were assessed by Chi Square test. Univariate survival analyses for LRC and OS were calculated using the Kaplan–Meier method and the differences in rates were assessed by log-rank test. Optimal cut-off of for LRC was searched by Cutoff finder [10] and it is defined as the point with the most significant (log-rank test) split; Hazard ratios (HRs) including 95% confidence intervals are calculated. Multivariate survival analysis was performed using Cox proportional hazard model and estimates were reported as hazard ratio (HR) with 95% Confidence Intervals (CI). GraphPad Prism Version 6.0 (San Diego, CA, USA), IBM SPSS Statistics version 24.0 and Cutoff Finder version 2.1 [10] were used for statistical analysis and graph drawing. For all tests a two-tailed p value < 0.05 was considered significant.

Results

150 consecutive elderly patients were included in the analysis, the median age was 76 years (range 70–92), the distribution of patients by age was 72 (48%) and 78 (52%) patients in Group 1 and in Group 2, respectively; overall median follow-up was 23 months (range 0–99). Patients characteristics of the whole population and categorized by age were represented in Table 1. Patients in group 1 (70–75 years) underwent to RT concomitant to systemic therapy and were treated with a IMRT technique more frequently than those in group 2 ($p = 0.000$ and 0.002, respectively), group 1 was associated to lower T stage ($p = 0.0192$) and high PS ($p = 0.037$), whereas no significant differences of N stage, overall Stage and finality of treatment were seen ($p > 0.05$). Globally, 58 (38.6%) patients received systemic therapy associated to RT: 26 patients received Cetuximab and 34 received chemotherapy (17 patients weekly CDDP and 17 CDDP q21).

As regards compliance evaluation, 38 (25.3%) patients interrupted RT treatment due to toxicity for a median time of 1 day (range 1–9), 20 and 18 patients were in group 1 and group 2, respectively ($p = 0.508$). The number of patients who had completed the full planned course of radiotherapy was 93%, 10 patients (4 in group 1 and 6 in group 2, $p = 0.74$) with mean age of 78 years (range 71–88) stopped the planned treatment: 1 died after 21.2 Gy and the others presented important cognitive and physical impairment.

Table 1 Patient characteristics of Group 1 and 2

Variable	All *n.* (%)	Group 1 (70–75 years) *n.* (%)	Group 2 (> 75 years) *n.* (%)	*p*
All	150 (100)	72 (48)	78 (52)	
Gender				0.345*
Male	113 (75)	57 (79)	56 (72)	
Female	37 (25)	15 (21)	22 (28)	
PS				0.037**
0	84 (56)	49 (68)	35 (44)	
1	49 (33)	18 (25)	31 (40)	
2	14 (9)	4 (6)	10 (13)	
3	3 (2)	1 (1)	2 (3)	
Primary site				0.003**
Oral cavity	23 (16)	5 (7)	18 (23)	
Oropharynx	47 (33)	28 (39)	19 (24)	
Larynx	62 (43)	26 (36)	36 (46)	
Hypopharynx	11 (8)	13 (18)	5 (7)	
T stage				0.019*
Tis-T2	58 (39)	35 (49)	23 (29)	
T3–T4	92 (61)	37 (51)	55 (71)	
N stage				0.068*
N0	62 (41)	24 (33)	38 (49)	
N+	88 (59)	48 (67)	40 (51)	
Stage				0.837*
0–II	28 (19)	14 (19)	14 (18)	
III–IV	122 (81)	58 (81)	64 (82)	
RT				1.000*
Adjuvant	37 (25)	18 (25)	19 (24)	
Radical	113 (75)	54 (75)	59 (76)	
RT techniques				0.002*
3DCRT	75 (50)	26 (36)	49 (63)	
IMRT	75 (50)	46 (64)	29 (37)	
RT schedule				1.000*
Standard	103 (69)	49 (68)	54 (69)	
Slight accelerated	47 (31)	23 (32)	24 (31)	
Systemic therapy				< 0.0001**
No	92 (61)	30 (42)	62 (80)	
Cetuximab	25 (17)	17 (23)	8 (10)	
Chemotherapy	33 (22)	25 (35)	8 (10)	
Treatment completed				0.747**
Yes	140 (93)	68 (94)	72 (92)	
No	10 (7)	4 (6)	6 (8)	

*P value estimated by by Fisher's exact test

**P value estimated by Chi square test

Survival analysis

The AWD was assessed for all but 10 patients (excluded because they did not complete RT). Among patients who completed the treatment (140 patients, 93%) univariate and multivariate survival analysis was performed; median overall survival was 73 months. The mean AWD was 9.28 ± 0.92, ranging from 3.84 to 12.07. Optimal cut-off of AWD for LRC was 9.236 ($p = 0.018$).

In univariate survival analysis low PS ($p = 0.005$), T3–T4 ($p = 0.021$), Stage III–IV ($p = 0.046$) and AWD^{Low} (< 9.236) ($p = 0.018$) were significantly associated with lower LRC; low PS ($p < 0.001$) and Group 2 ($p = 0.006$) were also associated with lower OS (Tables 2, 3). Figures showed LRC and OS by AWD (Fig. 1) and by PS (Fig. 2). Considering patients treated with radiotherapy alone AWD^{Low} was significantly associated with lower LRC ($p = 0.04$) whereas among patient treated with concomitant chemotherapy AWD did not affected LRC ($p = 0.18$)

Table 2 Univariate and multivariate survival analysis for loco-regional control (LRC)

Variable		Univariate survival analysis		Multivariate survival analysis	
	n. (%)	5-year LRC (%)	*p*	HR (95% CI)	*p*
Gender			0.403	–	–
Male	103 (74)	67.6		–	–
Female	37 (26)	62.1		–	–
Age Group			0.729	–	–
Group 1	68 (49)	67.9		–	–
Group 2	72 (51)	64.1		–	–
PS			0.005		0.032
0	82 (59)	76.4		1	
1	45 (32)	56.7		1.91 (0.97–3.75)	
2	13 (9)	33.6		3.10 (1.24–7.74)	
Primary site			0.886	–	–
Oral cavity	22 (17)	74.2		–	–
Oropharynx	42 (31)	71.3		–	–
Larynx	56 (42)	62.5		–	–
Hypopharynx	14 (10)	56.3		–	–
T stage			0.022		0.84
Tis-T2	55 (39)	79.4		1	
T3–T4	85 (61)	57.4		0.92 (0.41–2.05)	
N stage			0.605	–	–
N0	56 (40)	68.6		–	–
N+	84 (60)	64		–	–
Stage			0.012		0.11
0–II	27 (19)	90.9		1	
III–IV	113 (81)	60.1		2.95 (0.80–10.93)	
RT			0.500	–	–
Adjuvant	36 (26)	54.7		–	–
Radical	104 (74)	69.1		–	–
RT technique			0.432	–	–
3DCRT	68 (49)	70.9		–	–
IMRT	72 (51)	59.6		–	–
AWD			0.017		0.07
High	91 (65)	74.9		1	
Low	49 (35)	48.6		1.78 (0.96–3.30)	
CHT (Stage III–IV; radical)			0.0181	–	–
No	35 (43)	45.3		–	–
Cetuximab	20 (24)	71.2		–	–
Chemotherapy	27 (33)	81.1		–	–

Table 3 Univariate and multivariate survival analysis for overall survival (OS)

Variable		Univariate survival analysis		Multivariate survival analysis	
	n. (%)	5-year OS (%)	*p*	HR (95% CI)	*p*
Gender			0.169	–	–
Male	103 (74)	54.1		–	–
Female	37 (26)	42.7		–	–
Group			0.006		0.084
Group 1	68 (49)	63.4		1	
Group 2	72 (51)	40.8		1.62 (0.94–2.80)	
PS			< 0.0001		0.001
0	82 (59)	67.3		1	
1	45 (32)	39.3		1.79 (1.0–3.2)	
2	13 (9)	7.7		4.2 (2.0–8.8)	
Primary site			0.101	–	–
Oral cavity	22 (17)	31.1		–	–
Oropharynx	42 (31)	56.8		–	–
Larynx	56 (42)	58.1		–	–
Hypopharynx	14 (10)	34.7		–	–
T stage			0.097	–	–
Tis–T2	55 (39)	65.2		–	–
T3–T4	85 (61)	42.4		–	–
N stage			0.192	–	–
N0	56 (40)	62.5		–	–
N+	84 (60)	42.8		–	–
Stage			0.044		0.139
0–II	27 (19)	76.5		1	
III–IV	113 (81)	44.4		1.78 (0.83–3.78)	
RT			0.311	–	–
Adjuvant	36 (26)	33.6		–	–
Radical	104 (74)	55.39		–	–
RT technique			0.915	–	–
3DCRT	68 (49)	51.8		–	–
IMRT	72 (51)	49.3		–	–
AWD			0.096	–	–
High	91 (65)	55.6		–	–
Low	49 (35)	41.6		–	–
CHT (Stage III–IV; radical)			0.001	–	–
No	35 (43)	31.2		–	–
Cetuximab	20 (24)	36.8		–	–
Chemotherapy	27 (33)	81.9		–	–

(Fig. 1c, d). Moreover considering only stage III–IV patients treated with radical intent the adding of chemotherapy significantly impact on LRC and OS (Fig. 3). No correlation was found between AWD and total RT dose ($p = 0.68$). The multivariate analysis confirmed the independent significant value of PS for the prediction of both LRC and OS ($p = 0.035$ and $p < 0.001$, respectively) as showed in Tables 2, 3.

Discussion

Results of this analysis suggest that AWD should be a priority parameter to consider for elderly patients treated with radiotherapy not associated to systemic therapy as impact on LRC. Previously, also Dragovic et all analyzed 601 patients treated with different radiation regimens, with or without chemotherapy and detected a better loco-regional

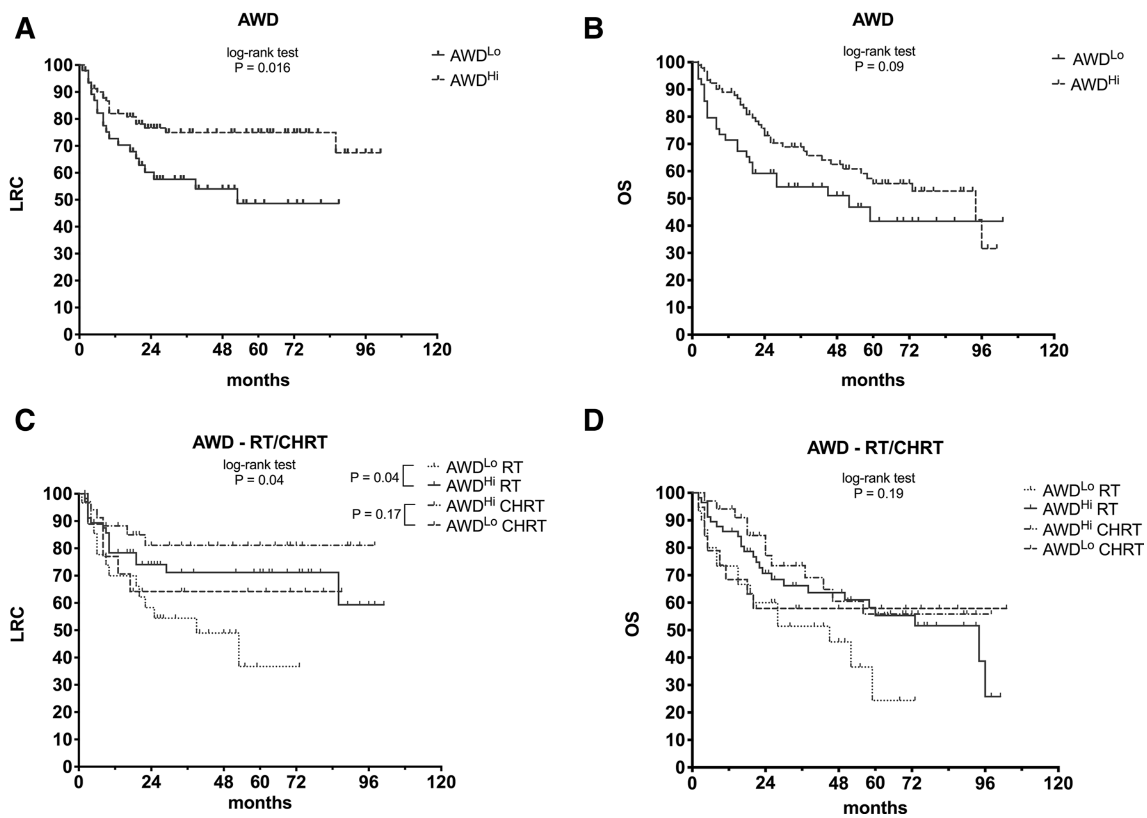

Fig. 1 Kaplan Meier curves for Loco-regional control (LRC) and Overall survival (OS) by AWD^{Low} vs AWD^{High} **a**: LRC for all patients, **b**: OS for all patients, **c**: LRC RT alone vs chemoradiotherapy (CHRT), **d**: OS RT alone vs chemoradiotherapy (CHRT)

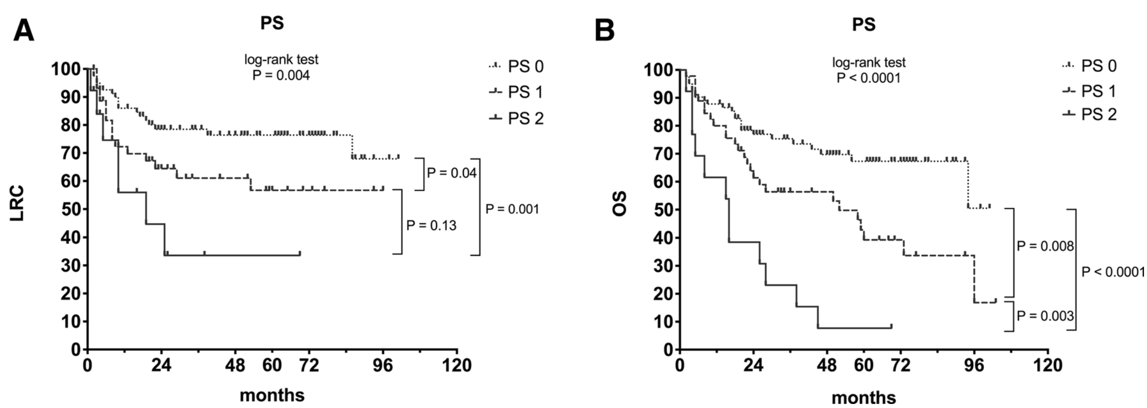

Fig. 2 Kaplan Meier curves for Loco-regional control (LRC) and Overall survival (OS) by PS

control in those patients that underwent to exclusive RT with AWD > 10 Gy, suggesting that maximizing the timeliness of AWD should be a high priority for these patients. As in our study, AWD was not identified as a crucial point for patients treated with chemoradiation regimen (both cisplatin than cetuximab), probably due to different mechanism of action of various chemotherapies and RT and to the possibility that chemotherapy may compensate for potential deleterious effects of breaks in RT [11]. The main difference of our analysis is represented by the selection of elderly patients that represent a critical population in which some data reported a major rate of treatment interruptions [12]; Dragovic et al. considered very different patients with a median age of 57 years and about 63% of whom received chemoradiotherapy.

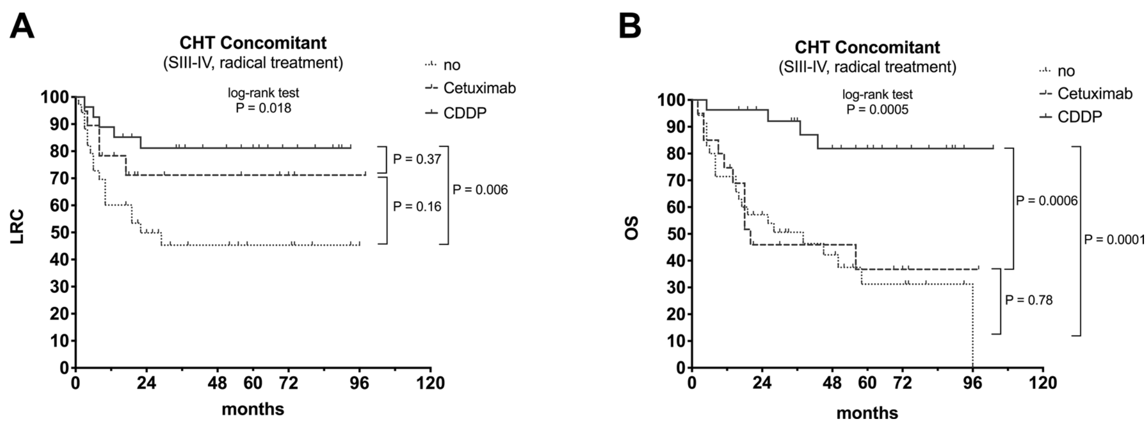

Fig. 3 Kaplan Meier curves for Loco-regional control (LRC) and Overall survival (OS) by systemic therapy in stage III–IV

In HNC it is recognized that the overall treatment time is an important prognostic factor influencing local control [13] so different radiotherapy fractionations have been studied hypothesizing that the more rapid delivery of treatment may be beneficial [14, 15]. At the same time prolonging radiation course with RT breaks is reported to result in a decrease in local control and survival [13].

At date the level of evidence on treatment of HNC elderly patients is still low both for radiotherapy and for the possible association with systemic therapy. In this context we should remind that the recent update of MARCH meta-analysis demonstrated in HNC patients a significant interaction between the effect on overall survival and altered fractionation regimens with an absolute difference of 8.1% for the hyperfractionated group (where the AWD is generally high); the survival benefit decreased when the age increased (reduction in treatment effect for progression free survival) but was otherwise consistent in all subgroups [16].

Moreover an important issue in elderly patients is the tendency towards less aggressive treatment reported by some investigators [17]; even if we do not have a comparison arm with younger patients, we also found that fewer patients in group 2 (older patients) were treated with combined therapy. This probably is related to different factors and especially to the literature evidence that adding systemic therapy including cetuximab to radiotherapy do not confers any advantages in elderly population [18–20]. Also the landmark trial of Bonner et al., detected a benefit of adding cetuximab to RT vs RT alone, demonstrated no improvement in patients > 65 years [21]. On the other hand offering aggressive radiotherapy to elderly patients is often hampered by the concern about tolerance and possible decreased normal tissue tolerance to RT [22]. Limited data are available to address the issue of tolerance in elderly patients; some studied reported that they can tolerate treatment as well as younger but generally are all small trials [23–25]. Interestingly in our experience patients with stage III–IV disease that received radiotherapy plus chemotherapy or cetuximab had a benefit in LRC and the adding of chemotherapy impact also on OS. In our opinion this datum, even if not derived from a randomized trial, is to underline as demonstrated that a subgroup of elderly patients could, not only, well tolerate combined treatment but also improve outcomes.

From our analysis emerged also the importance of PS, probably this might be explained by the fact that patients with worse PS did not received chemotherapy and this reflect its impact both on LRC than on OS.

At date, probably the real challenge is to identify which subgroup of elderly patients may benefit from a more aggressive therapy. Treatment decision should be based also on a complete geriatric evaluation that allows to integrate functional age into the decision making process. Different studies started to use the geriatric assessment in HNC [26–28] with the aim to divide patients in 3 main groups: fit, vulnerable, and frail; this categorization help to personalized therapies and identified patients that could receive "intensified" treatment (fit) and vulnerable patients that probably need of an implementation of supportive care strategies.

One limitation of the present study was that a detailed acute toxicity was not collected but we chose unplanned RT interruptions and non completion of RT as surrogate indicators; we did not detected any differences in the two groups of patients with an excellent compliance considering that 93% of the patients completed the planned radiotherapy course.

We further underline that the proportion of elderly patients in clinical trials is little and those included are not representative of all elderly population as they are extremely selected and fit for "intensive" treatment. Moreover literature data on elderly HNC patients derived all from trials initiated 20 to 50 years ago that enrolled mainly HPV negative patients with tobacco and alcohol abuse. It is known that the incidence of tobacco and alcohol related HNSCC is decreasing whereas the incidence of oropharyngeal SCC that are often HPV related and with better outcomes is increasing not only in younger patients but also in elderly: thus modern elderly HNC patients may represent a very different population than those analyzed in meta-analysis and data available do not find an easy application in clinical practice.

At last we have to consider also the evolution of radiotherapy techniques as IMRT that reduced toxicity rate [29, 30], so if we integrate all these observations it is possible that the therapeutic index of elderly HNC patients could increase in the next years.

Conclusion

The results of this retrospective analysis detected that an AWD > 9.236 Gy is beneficial for RT alone regimens. Also elderly HNC patients could have good outcomes with no evidence of impaired treatment tolerance. Moreover patients with locally advanced disease that underwent to combined radical treatment have better loco-regional control rates than patients treated with radiotherapy alone. Even if chronologic age should not be a contraindication for definitive RT further studies based on a better selection of patients are warranted in order to improve prognosis in older patients.

Author contributions LB, AB, FM, RC contributed to study concepts and design; IC, SC, EV data collection; LB, FM data analysis and interpretation; FM statistical analysis; LB manuscript preparation and editing; AB, RC, GP, SV manuscript review.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2008;83(4):489–501. https://doi.org/10.4065/83.4.489.
2. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol. 2009;27(17):2758–65. https://doi.org/10.1200/JCO.2008.20.8983.
3. Pignon JP, le Maître A, Bourhis J, MACH-NC Collaborative Group. Meta-analyses of chemotherapy in head and neck cancer (MACH-NC): an update. Int J Radiat Oncol Biol Phys. 2007;69(2 Suppl):S112–4. https://doi.org/10.1016/j.ijrobp.2007.04.088.
4. Belgioia L, Desideri I, Errico A, et al. Safety and efficacy of combined radiotherapy, immunotherapy and targeted agents in elderly patients: a literature review. Crit Rev Oncol Hematol. 2019;133:163–70. https://doi.org/10.1016/j.critrevonc.2018.11.009.
5. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA. 2004;291(22):2720–6. https://doi.org/10.1001/jama.291.22.2720.
6. Porceddu SV, Haddad RI. Management of elderly patients with locoregionally confined head and neck cancer. Lancet Oncol. 2017;18(5):e274–83. https://doi.org/10.1016/S1470-2045(17)30229-2.
7. Allal AS, Maire D, Becker M, et al. Feasibility and early results of accelerated radiotherapy for head and neck carcinoma in the elderly. Cancer. 2000;88(3):648–52.
8. Bourhis J, Overgaard J, Audry H, et al. Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet. 2006;368(9538):843–54. https://doi.org/10.1016/s0140-6736(06)69121-6.
9. Hoffstetter S, Marchal C, Peiffert D, et al. Treatment duration as a prognostic factor for local control and survival in epidermoid carcinomas of the tonsillar region treated by combined external beam irradiation and brachytherapy. Radiother Oncol. 1997;45(2):141–8.
10. Budczies J, Klauschen F, Sinn BV, Gyorffy B, Schmitt WD, Darb-Esfahani S, Denkert C. Cutoff finder: a comprehensive and straightforward web application enabling rapid biomarker cutoff optimization. PLoS One 2012;7(12):e51862. https://doi.org/10.1371/journal.pone.0051862.
11. Dragovic AF, Bonner JA, Spencer SA, et al. Impact of average weekly dose of radiation during radiotherapy alone or chemoradiotherapy in head and neck cancer. Head Neck. 2011;33(11):1551–6. https://doi.org/10.1002/hed.21634.
12. Rim CH, Yoon WS, Lee JA, et al. Factors predicting intolerance to definitive conventional radiotherapy in geriatric patients. Strahlenther Onkol. 2018. https://doi.org/10.1007/s00066-018-1318-y.
13. Maciejewski B, Preuss-Bayer G, Trott KR. The influence of the number of fractions and of overall treatment time on local control and late complication rate in squamous cell carcinoma of the larynx. Int J Radiat Oncol Biol Phys. 1983;9(3):321–8.
14. Peters LJ, Ang KK, Thames HD Jr. Accelerated fractionation in the radiation treatment of head and neck cancer. A critical comparison of different strategies. Acta Oncol. 1988;27(2):185–94.
15. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: dAHANCA 6 and 7 randomised controlled trial. Lancet. 2003;362(9388):933–40.
16. Lacas B, Bourhis J, Overgaard J, et al. MARCH Collaborative Group. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. Lancet Oncol. 2017;18(9):1221–37. https://doi.org/10.1016/s1470-2045(17)30458-8.
17. Juarez JE, Choi J, St John M, et al. Patterns of care for elderly patients with locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys. 2017;98(4):767–74. https://doi.org/10.1016/j.ijrobp.2017.01.209.
18. Magrini SM, Buglione M, Corvò R, et al. Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a Randomized Phase II Trial. J Clin Oncol. 2016;34(5):427–35. https://doi.org/10.1200/JCO.2015.63.1671.

19. Buglione M, Maddalo M, Corvò R, et al. Subgroup analysis according to human papillomavirus status and tumor site of a randomized phase ii trial comparing cetuximab and cisplatin combined with radiation therapy for locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys. 2017;97(3):462–72. https://doi.org/10.1016/j.ijrobp.2016.10.011.
20. Russi EG, Moretto F, Rampino M, et al. Acute skin toxicity management in head and neck cancer patients treated with radiotherapy and chemotherapy or EGFR inhibitors: literature review and consensus. Crit Rev Oncol Hematol. 2015;96(1):167–82. https://doi.org/10.1016/j.critrevonc.2015.06.001.
21. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010;11(1):21–8. https://doi.org/10.1016/S1470-2045(09)70311-0. (**Erratum. In: Lancet Oncol. 2010 Jan; 11(1):14**).
22. Baumann M. Is curative radiation therapy in elderly patients limited by increased normal tissue toxicity? Radiother Oncol. 1998;46(3):225–7.
23. Oguchi M, Ikeda H, Watanabe T, et al. Experiences of 23 patients ≥ 90 years of age treated with radiation therapy. Int J Radiat Oncol Biol Phys. 1998;41(2):407–13.
24. Italiano A, Ortholan C, Dassonville O, et al. Head and neck squamous cell carcinoma in patients aged ≥ 80 years: patterns of care and survival. Cancer. 2008;113(11):3160–8. https://doi.org/10.1002/cncr.23931.
25. Merlano M, Grimaldi A, Benasso M, et al. Alternating cisplatin-5-fluorouracil and radiotherapy in head and neck cancer. Am J Clin Oncol. 1988;11(5):538–42.
26. Neve M, Jameson MB, Govender S, et al. Impact of geriatric assessment on the management of older adults with head and neck cancer: a pilot study. J Geriatr Oncol. 2016;7(6):457–62. https://doi.org/10.1016/j.jgo.2016.05.006.
27. Pottel L, Lycke M, Boterberg T, et al. G-8 indicates overall and quality-adjusted survival in older head and neck cancer patients treated with curative radiochemotherapy. BMC Cancer. 2015;9(15):875. https://doi.org/10.1186/s12885-015-1800-1.
28. Pottel L, Lycke M, Boterberg T, et al. Serial comprehensive geriatric assessment in elderly head and neck cancer patients undergoing curative radiotherapy identifies evolution of multidimensional health problems and is indicative of quality of life. Eur J Cancer Care (Engl). 2014;23(3):401–12. https://doi.org/10.1111/ecc.12179.
29. Agnese D, Belgioia L, Bacigalupo A, et al. Prolonged complete remission after induction chemotherapy followed by chemoradiation with tomotherapy in metastatic nasopharyngeal cancer. Anticancer Res. 2014;34(9):5075–8.
30. Corvò R, Lamanna G, Vagge S, Belgioia L, et al. Once-weekly stereotactic radiotherapy for patients with oligometastases: compliance and preliminary efficacy. Tumori. 2013;99(2):159–63. https://doi.org/10.1700/1283.14186.