



Radiotherapy for locally advanced head and neck cancer in elderly patients: results and prognostic factors a single cohort

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ABSTRACT

Background: The objective of this study was to assess the treatment outcomes and prognostic factors of elderly patients with locally advanced head and neck cancer (LAHNC) undergoing radiotherapy (RT).

Materials and methods: A retrospective cohort from a single institution, from 2000 to 2015, including patients older than 65 years old with LAHNC (stage III–IVa) treated by RT combined or not with chemotherapy (CRT). Univariate and multivariate analysis (MVA) were performed to identify prognostic factors associated with overall survival (OS), cancer-specific survival (CSS), and locoregional control (LRC). A p-value < 0.05 was considered significant.

Results: 220 patients with LAHNC and > 65 years of age were identified. The median follow-up was 3.8 years, the 3/5 years estimated OS, CSS, and LRC rate was 40%/30%, 49%/34%, 76%/45%, respectively. In the univariate analysis, clinical stage (III vs. IVa/b, p = 0.01), tumor stage (T1/2 vs. T3/4, p = 0.035), Karnofsky performance status (KPS, 60–70, p = 0.03) and tumor site (other than vs. hypopharynx, p = 0.0001) were associated with lower OS. Patients with clinical stage (III vs. IVa/b, p = 0.01), tumor stage (T1/2 vs. T3/4, p = 0.015), N stage (N0/1 vs. N2/3, p = 0.04), (KPS 60–70, p = 0.04) and tumor site (other than vs. hypopharynx, p = 0.0001) had worst CSS. For the LRC, clinical stage (III vs. IVa/b, p = 0.02), tumor stage (T1/2 vs. T3/4, p = 0.02), treatment type (CRT vs. RT, p = 0.02), RT technique (IMRT vs. 2DRT/3DRT, p = 0.0001), and tumor site (other than vs. hypopharynx, p = 0.02) were significant. In the MVA, KPS maintained significant for OS and CSS. For LRC, clinical stage (Iva/b, p = 0.007), tumor stage (T3/4, p = 0.047) and radiotherapy technique other than IMRT (p = 0.0001) were significant.

Conclusion: The OS, CSS, and LRC were associated with several prognostic factors. The clinical performance was the main marker of OS and CSS. Chemoradiation should be offered to selected elderly patients using IMRT to improve LRC.

Key words: head and neck cancer; elderly; radiotherapy; outcomes

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Introduction

In the world, head-and-neck squamous cell carcinoma (HNSCC) is the seventh most common cancer, resulting in about 300,000 deaths per year [1]. Head-and-neck squamous cell carcinoma is a heterogeneous group of malignancies originating from the upper aero-digestive tract [2]. It is classified into early and locally advanced disease in clinical practice. The early disease includes tumors with clinical stages I and II, representing 40% of the cases, while locally advanced disease (stage III/IVa) represents the other 60% [3]. Early disease is treated by surgery or radiotherapy alone, with both treatment modalities producing cure rates of around 80% [2–4]. The locally advanced HNSCC requires a multimodality approach to produce better survival rates. However, even offering chemoradiation alone or chemoradiation after surgery, the 5-year overall survival rarely exceeds 60% [5].

The elderly population account for half of the diagnosed cases of HNSCC [6]. The older patients are at risk of undertreatment due to their natural frailty, associated comorbidities, and the fear of treatment-related severe toxicity [7, 8]. Observational studies have demonstrated a higher probability of elderly HNSCC patients not receiving a curative treatment than younger patients [9]. Data from these studies comparing < 60 versus > 70 years shows a significant difference (90% vs. 60%) in receiving the standard treatment [9]. In the last decades, age has been adopted as the main driver for selecting patients to receive a non-standard treatment. This practice is observed even for elderly patients with similar morbidity and clinical conditions as younger patients [9].

In the majority of prospective trials, patients older than 70 years have consistently been excluded. Less than 3.5% of studies worldwide are currently ongoing in patients older than 65 years [10]. The reduced inclusion of elderly patients in clinical trials is a significant clinical problem. The lack of evidence-based data to select older patients to receive the standard treatment puts them at constant risk of being undertreated [11]. The paucity of randomized clinical trials to drive the radiotherapy treatment in elderly HNSCC makes retrospective studies a valuable oncological outcome source [8].

Based on this context, we designed a retrospective study to evaluate the oncologic outcomes and prognostic factors in elderly HNSCC treated by radiotherapy combined or not with chemotherapy.

Material and methods

A cohort study was designed to evaluate the overall survival of elderly patients with HNSCC treated in a single institution. To gather a large sample of head and neck cancer (HNC) patients with adequate follow-up time, we included patients treated in the last fifteen years. Our institution is linked to the State Department of Health, which receives cancer data from hospitals in the state through regional centers called Cancer Hospital Registries (CRH). To guarantee an adequate follow up, we crosscheck the data from our database with the data from CHR. In the CHR, individuals diagnosed and treated at the hospital are checked for the rest of their life through annual follow-ups, after identifying and collecting information in the medical records.

Analysis process

The information was filtered, limiting the treatment period from 2000 to 2017, and Head and Neck Cancer cases that refer to ICDs “C00 to C14” and “C30 to C32” according to the 10th International Statistical Classification of Diseases and Related Health Problems (ICD-10). We included only patients older than 65 years with the histological diagnosis of cancer from head and neck with a clinical staging III–IVb treated with radiotherapy or chemoradiation alone. Regarding the radiotherapy schedule, only conventional fractionation was included. During the long period, different radiation techniques were employed; therefore, conventional (2DRT), conformational (3DRT) and intensity-modulated radiotherapy (IMRT) techniques were included. We excluded patients with metastatic disease (clinical stage IVC), patients treated with induction chemotherapy, or chemotherapy without cisplatin or patients treated with hyperfractionation or hypofractionation radiotherapy. The analyses performed were based on the information contained in the database, such as age, sex, clinical performance (KPS), the morphology of the disease, topography, clinical stage, tumor/lymph node stage, chemotherapy treatment, performed, follow-up

time and death. The cases were categorized by the primary treatment type employed: Radiotherapy alone (RT); and chemoradiation (CRT). Patients submitted to radiotherapy in the period between 2000–2008 were treated using conventional treatment technique (2DRT) with doses varying from 68 Gy to 70 Gy. Since 2009, conformational radiotherapy (3DRT) and IMRT treatments were applied to most of the patients with the same doses. A linear accelerator treated all patients. The radiotherapy treatment volumes followed the treatment guidelines according to the site of the disease current at the period. The chemotherapy was based on cisplatin every three weeks with 100 mg/m² in the majority of the cases and, when necessary, weekly cisplatin with 30 mg/m².

Statistical analysis

The survival analysis was counted from the end of radiotherapy treatment until death or last information. The survival analysis was performed by the Kaplan-Meier estimator method. The Cox stepwise method was used for the multivariate analysis. The hazard ratio (HR) was calculated with the regression model that allows the evaluation of the independent variables as well as their relevance in a set of other parameters. The significant prognostic factors ($p < 0.05$) identified by the log-rank test in the univariate analysis were moved to the multivariate analysis. A p -value < 0.05 and 95% confidence interval (CI) was considered statistically significant. Statistical analysis was performed with IBM SPSS 24.0 software.

Results

In our database during the period between 2000–2015, a total of 990 patients were treated by RT due to HNSCC. After excluding 770 patients aged < 65 years, we identified 220 patients ≥ 65 years with the diagnosis of HNC with LAHNC (clinical stage III to IVb). The disease distribution by anatomical site was the oral cavity (36.4%), oropharynx (19.6%), hypopharynx (14.6%), and larynx (25.4%), as demonstrated in Table 1. The most frequent histological subtype was squamous cell carcinoma (SCC) (96%). The mean age was 72 years (66–96 years), with a predominance of males (81%). In the entire cohort, the median follow-up was of 3.8 years (1 to 11 years). The overall survival (OS), cancer-specific

Table 1. Characteristic of patients included in the study

Variables	All cohort N (%)
Age (median)	72 (66–96)
Gender	
Male	178 (81%)
Female	42 (19%)
Clinical stage	
III	61 (38%)
IVa/b	159 (62%)
KPS	
90–100	46 (21%)
80	70 (32%)
60–70	104 (47%)
Tumor site	
Oral cavity	80 (36.4%)
Oropharynx	43 (19.6%)
Hypopharynx	32 (14.6%)
Nasopharynx	9 (4%)
Larynx	56 (25.4%)
Histology	
Squamous cell carcinoma	211 (96%)
Others	9 (4%)
Chemotherapy	
Yes	92 (32%)
No	128 (58%)
Radiotherapy technique	
2DRT/3DRT	114 (51.8%)
IMRT	106 (47.2%)
RT dose (median)	69.9 Gy (68–72 Gy)
Follow-up time after treatment [yrs]	3.8 years

KPS — Karnofsky performance status; 2DRT — conventional radiotherapy; 3DRT — conformational radiotherapy; IMRT — intensity-modulated radiotherapy; RT — radiotherapy

survival (CSS), and local-regional control (LRC) at 3/5 years were 40%/30%, 49%/34%, and 76%/45%, respectively, Figures 1–3. In the univariate analysis, the clinical stage (III vs. IVa/b, $p = 0.01$), tumor stage (T1/T2 vs. T3/4, $p = 0.035$), KPS (60–70 vs. ≥ 70 , $p = 0.03$) and tumor site (other sites vs. hypopharynx, $p = 0.0001$) were associated with lower OS rates, as demonstrated in Table 2. The clinical stage (III vs. IVa/b, $p = 0.01$), tumor stage (T1/2 vs. T3/4, $p = 0.015$), N stage (N0/N1 vs. N2/3, $p = 0.04$), KPS (60–70 vs. ≥ 70 , $p = 0.04$) and tumor site (other sites vs. hypopharynx, $p = 0.0001$) were associated with lower CSS rates. For the LRC, clinical stage

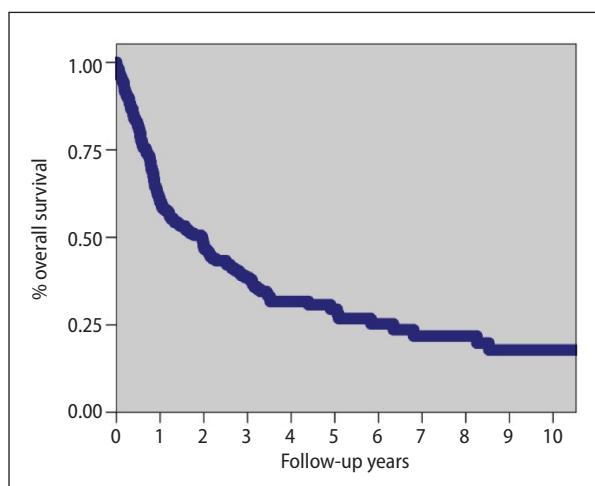


Figure 1. Overall survival (OS) estimation curve of the entire cohort

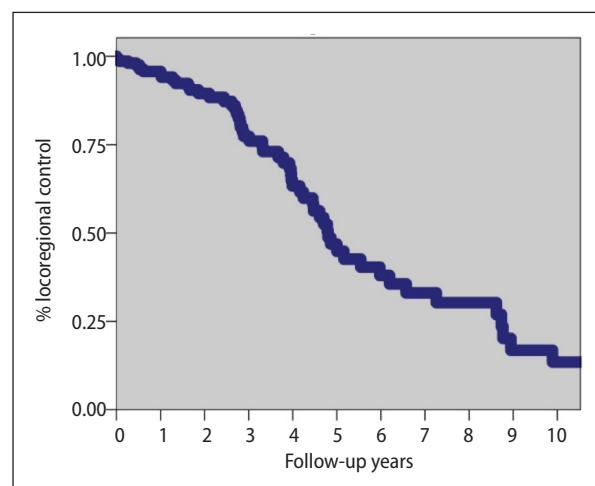


Figure 3. Locoregional control (LRC) estimation curve of the entire cohort

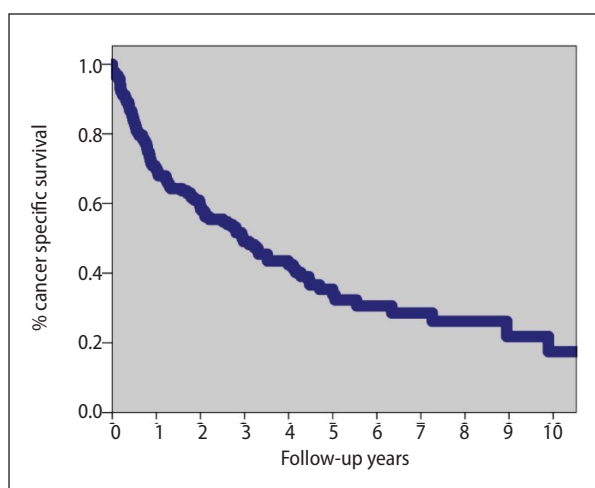


Figure 2. Cancer specific survival (CSS) estimation curve of the entire cohort

(III vs. IVa/b, $p = 0.02$), tumor stage (T1/2 vs. T3/4, $p = 0.02$), treatment type (CRT vs. RT, $p = 0.02$), RT technique (IMRT vs. 2DRT/3DRT, $p = 0.0001$), and tumor site (other sites vs. hypopharynx, $p = 0.02$) were associated with lower LRC rates. In the multivariate analysis, the KPS was the only significant factor associated with better OS (KPS 60–70, HR = 1.31, 95% CI: 1.09–1.31, $p = 0.033$) and CSS (KPS 60–70, HR = 1.28, 95% CI: 1.12–1.36, $p = 0.034$) (Tab. 3). For LRC, clinical stage (Iva/b, HR = 6.4, 95% CI: 1.6–22.4, $p = 0.007$), tumor stage (T3/4, HR = 3.3, 95% CI: 1.1–12.3, $p = 0.047$) and no IMRT (HR = 4.8, 95% CI: 2.4–9.7, $p = 0.0001$) maintained statistical significance, as demonstrated in Table 3.

Discussion

The elderly are a considerable part of patients with a diagnosis of HNC. The treatment of such a fragile population, with reduced overall survival due to the advanced age and several comorbidities, is a great challenge in clinical practice [7, 9]. We designed a large single-center cohort including only elderly patients with LAHNC treated with radiotherapy with or without chemotherapy to evaluate the outcomes and prognostic factors associated with the patient, tumor, and treatment characteristics to better understand the disease behavior of this specific subgroup of patients.

The 5-year OS of 30% in the present study was lower than 55% in patients < 60 years treated with chemoradiation in our previous publication [12]. These outcomes agree with other series that included exclusively elderly HNC [5, 13, 14]. Lusinchi and colleagues described the Gustave Roussy experience on 331 elderly patients (≥ 70 years) with HNC treated with radical RT (65–70 Gy) in 84%. Overall, the LRC at three years was 71% for patients treated with a radical dose [14]. In our cohort, the 3/5 y OS, CSS, and LRC rates were 40%/30%, 49%/34%, and 76%/45%, respectively.

We searched for significant prognostic factors to guide the treatment. In the univariate analysis, recognized prognostic factors such as clinical stage, T stage, clinical performance, and tumor site were related to overall survival and cancer-specific survival. However, chemoradiation was associated with better LRC, but not with OS or CSS. The lack

Table 2. Univariate analysis of factors related to overall survival (OS), cancer specific survival (CSS) and locoregional control (LRC)

Variable	N Total	OS 3 years	p value	CSS 3 years	P value	LRC 3 years	p value
Age							
65–70 y	103	42%	0.68	51%	0.89	80%	0.32
70–75 y	64	36%		47%		81%	
75–80y	31	35%		46%		76%	
> 80 y	22	33%		15%		66%	
Gender							
Male	178	36%	0.56	48%	0.16	75%	0.42
Female	42	48%		52%		77%	
Clinical stage							
III	61	49%	0.01	53.8%	0.01	85.2%	0.023
IVa–b	159	33%		37.4%		71.2%	
Tumor stage							
T1–2	64	49%	0.035	58%	0.015	82%	0.04
T3–4	156	30%		45%		71%	
N stage							
N0	60	46%	0.12	58%	0.04	85%	0.10
N1	51	40%		53%		81%	
N2/3	109	32%		39%		72%	
KPS							
90–100	46	49.7%	0.03	56%	0.04	91%	0.61
80	70	30%		47%		85%	
60–70	104	16%		22%		78%	
Treatment							
RT	128	37%	0.96	48%	0.63	61.4%	0.02
CRT	92	38%		50%		81.2%	
RT technique							
2D RT/3D RT	72	39%	0.90	46%	0.95	62.5%	0.0001
IMRT	156	36%		51%		83.5%	
Tumor site							
Larynx	56	31%	0.0001	42%	0.002	75%	0.024
Hypopharynx	32	19%		39%		34%	
Oral cavity	80	33%		44%		73%	
Oropharynx	43	63%		68%		80%	
Nasopharynx	9	21%		27%		40%	
Treatment period							
2000–2005	48	34%	0.16	46	0.74	72	0.68
2006–2010	70	40%		50		84	
2011–2015	102	46%		48		81	

KPS — Karnofsky performance status; RT — radiotherapy; CRT — radiotherapy combined with chemotherapy; 2DRT — conventional radiotherapy; 3DRT — conformational radiotherapy; IMRT — intensity-modulated radiotherapy

of benefit for OS with CRT was probably due to the high rate of patients aged between 65–70 years

and KPS 70–80 who received the combined treatment guided mainly by the age. In this scenario,

Table 3. Multivariate analysis of significant factors for overall survival (OS), cancer specific survival (CSS) and locoregional control (LRC)

Variable	Strata	Multivariate analysis		
		HR	95% CI	p
Clinical stage	III (ref) IVa/b	OS: Ref 1.6	Ref 0.5–4.3	0.34
		CSS: Ref 1.16	Ref 0.3–3.9	0.80
		LRC: Ref 6.4	Ref 1.6–22.4	0.007
Tumor stage	T1/2 (ref) T3/4	OS: Ref 0.71	Ref 0.2–1.9	0.50
		CSS: Ref 1.23	Ref 0.3–4.8	0.76
		LRC: Ref 3.3	Ref 1.1–12.5	0.047
Tumor site	Other (ref) Hypopharynx	OS: Ref 0.95	Ref 0.8–1.1	0.59
		CSS: Ref 1.13	Ref 0.9–1.36	0.24
		LRC: Ref 4.4	Ref 0.8–22	0.07
N stage	N0 (ref) N1 N2/3	OS: NA	NA	0.73
		CSS: Ref 1.1	Ref 0.5–1.7	
		LRC: NA	NA	
Chemoradiation	Yes (ref) No	OS: NA	NA	0.90
		CSS: NA	NA	
		LRC: Ref 1	Ref 0.5–1.9	
IMRT	Yes (ref) No	OS: NA	NA	0.0001
		CSS: NA	NA	
		LRC: Ref 4.8	Ref 2.4–9.7	
KPS	90–100 (ref) ≤ 80	OS: Ref 1.31	Ref 1.12–1.66	0.033
		CSS: Ref 1.28	Ref 1.16–1.72	0.034
		LRC: NA	NA	

HR — hazard ratio; CI — confidence interval; IMRT — intensity-modulated radiotherapy; KPS — Karnofsky performance status; NA — non available

although CRT produced an improvement in tumor LRC, the patients died from other non-cancer causes, i.e., they did not have enough survival time

to benefit from the combined treatment. Our data is in agreement with a retrospective analysis from the SEER database. In this analysis, evaluating

4,042 elderly HNC patients, CRT's benefit disappeared between patients with 71–80 years [15]. The authors conclude that age alone is not a useful parameter to decide about chemotherapy. In this topic, our data point out that the age should not be used isolatedly to deny chemotherapy, and that the clinical performance is a good driver to make that decision mainly if combined with the other prognostic factors.

The absence of the CRT benefit for survival can be explained by several reasons. The leading causes for the reduced survival of elderly HNC patients and the absence of benefits observed here are directly associated with the advanced age. The majority of our patients (> 50%) were older than 70 years. In a cohort like ours, other competitive non-cancer causes lead to death. In the entire cohort, non-cancer-related deaths were 2.3 times more likely than cancer deaths. Other studies have reinforced that patients older than 70 do not benefit from chemoradiation [16–18]. For instance, Takenaka et al. pointed out that over 75 years was associated with a higher incidence of non-cancer death (HR = 2.59) [18]. Although our results are in line with these studies, it is essential to note that indirect causes related to chemoradiation, e.g., aspirations and fatal bronchopneumonia due to poor laryngeal function, could also be a cause of non-cancer death. Therefore, all these data show that only highly select elderly HNSCC patients can benefit from the combined treatment.

The LRC is a crucial endpoint for HNC, mainly for elderly patients. Tumor local control has a direct relationship with a better quality of life. Patients who achieve local control have less cancer-related pain and a reduced need for additional treatment. The univariate analysis identified tumor stage, CRT, IMRT, and tumor site as significant factors for LRC. The IMRT can deliver highly conformal radiation treatment for locally advanced tumors as compared to older radiation techniques while avoiding critical structures to receive an excessive dose. The higher conformation dose with IMRT possibly resulted in a lower radiation dose at the organ at risk, reducing the treatment breaks, which probably translated into a statistically significant difference for LRC with IMRT [19]. Although not employed to this group of patients, IMRT with IGRT can reduce the treatment toxicity using more strict margins, which is an attractive tool to employ in combination with

chemotherapy to improve the therapeutic index in such a fragile population [19].

The finding of significant prognostic factors has great importance for clinical practice. In complex or challenging scenarios like that, where the radiation oncologist and clinical oncologist have to decide between providing survival gain or increasing treatment toxicity, prognostic information is necessary. Based on our findings, it is possible to drive the decision about the combined treatment combining the KPS with other prognostic factors. For instance, patients with high clinical performance (KPS 90–100), with tumor stage T3/4, or clinical stage IVa/b, could be treated with CRT and IMRT to maximize the chance of LRC and try to improve the survival, once the KPS was the most substantial prognostic factor associated with OS and CSS. On the other hand, patients with KPS ≤ 80, with T3/T4 or clinical stage IVa/b could be treated by RT alone with IMRT to guarantee a better chance of LRC, once the survival benefit in this subgroup is absent due to low KPS.

Although our study agrees with several studies in the literature, it has limitations inherent to its design. First, we cannot analyze the influence of comorbidities and biological tumor characteristics, such as p16 status for all patients included in this study. Second, we do not provide an evaluation of toxicity and quality of life to give a general overview of the impact of treatment in such a population. However, even with these deficiencies, our outcomes are valid, and the prognostic factors identified here can be useful to guide the decision regarding the treatment, keeping in mind these limitations.

Conclusion

Our cohort achieved similar OS, CSS, and LRC to other series evaluating the outcomes of RT for LAHNC in elderly patients. Our analysis identified several prognostic factors related to the primary endpoints. These prognostic factors are useful to drive the decision in a complex and challenging clinical scenario involving fragile patients. In our data, CRT had no benefit for OS and CSS, probably due to the competing factors of non-cancer mortality. The KPS associated with other prognostic factors could be used to guide the decision on combined treatment rather than age solely.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

All authors participated the study design, data extraction and analysis.

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