



ORIGINAL ARTICLE

Outcomes, toxicity profiles, and prognostic factors of unresectable head and neck cancer treated with chemoradiotherapy

Matheus de Aquino Moreira Guimarães^{1*}, Tatiane Motta Cardoso¹, Flávio Nogueira Segato¹, Leandro Machado Colli¹, Liane Rapatoni¹, Fernanda Maris Peria¹

¹Universidade de São Paulo (USP), Faculdade de Medicina de Ribeirão Preto (FMRP), Hospital das Clínicas (HC), Departamento de Imagens Médicas, Hematologia e Oncologia Clínica, Ribeirão Preto, SP, Brasil.

Financial support: None.
Conflicts of interest: No conflicts of interest declared concerning the publication of this article.
Submitted: January 06, 2022.
Accepted: February 11, 2022.

The study was carried out at Hospital das Clínicas (HC), Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), São Paulo, SP, Brasil.

Abstract

Introduction: Head and neck cancer (HNC) is a heterogeneous group of neoplasms that can have a poor prognosis when diagnosed in advanced stages. The optimized treatment for locally advanced and unresectable lesions is mainly based on radiotherapy associated with chemotherapy (cisplatin 100mg/m²), however, at the expense of a high toxicity index. **Objective:** Evaluate whether chemoradiotherapy (CRT) – the gold-standard treatment for locally advanced head and neck cancer (HNC) – is effective in the study population. **Methods:** This is a retrospective study aimed at determining the efficacy of definitive CRT in patients with unresectable HNC treated between the 2012 and 2018 in a single institution. The following outcomes were evaluated: objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and toxicity profiles. **Results:** Fifty-two (52) patients diagnosed with HNC between 2012 and 2018 met the inclusion criteria. The ORR was 84.6%, with 50% showing complete response. Median PFS and OS were 35.3 and 52 months, respectively. Analysis of the toxicity profiles revealed that 69.2% of the patients presented grade 3-4 toxicity. Completion of two or more cycles of cisplatin-based therapy (HR 3.57 [95% CI 1.25–10.25]; p < 0.001), grade 3-4 toxicity (HR 0.27 [95% CI 0.09–0.8] – p < 0.02), and Charlson comorbidity index (CCI) (HR 3.23 [95% CI 1.26–8.29]; p < 0.001) were significantly associated with survival. Regarding toxicity, prophylactic low-level laser therapy (HR 0.48 [95% CI 0.27–0.86]; p < 0.001 for those without this practice) and body mass index (BMI) (HR 0.27 [95% CI 0.09–0.76]; p < 0.01) showed statistical significance. **Conclusion:** CRT was effective to treat HNC in the study population, with PFS and OS comparable to those reported in larger sample studies and lower toxicity grade. Some clinical characteristics have been identified as prognostic and/or predictive factors.

Keywords: head and neck cancer; toxicity; chemotherapy; cisplatin.

How to cite: Guimarães MAM, Peria FM, Cardoso TM, Segato FN, Colli LM, Rapatoni L. Outcomes, toxicity profiles, and prognostic factors of unresectable head and neck cancer treated with chemoradiotherapy. Arch Head Neck Surg. 2022;51:e20220004. <https://doi.org/10.4322/ahns.2022.0004>

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Introduction

The term “head and neck cancer” (HNC) refers to a heterogeneous group of malignant tumors affecting the upper aerodigestive tract, including the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, salivary glands, and paranasal cavities¹. HNC accounts for 888 thousand new cases and 453 thousand deaths a year worldwide². It has a high incidence in Brazil, with estimates of 15,190 cases of oral cavity cancer and 7,650 cases of larynx cancer for 2020³.

One of the most common histologic subtypes of HNC is squamous cell carcinoma (SCC), which accounts for 90% of cases. The main risk factors for SCC are smoking and alcohol consumption. However, there has been a progressive increase of SCC induced by the human papilloma virus (HPV) in patients not exposed to the usual etiological factors, especially in the oropharynx. This has led to an epidemiologic shift in disease stage and prognosis, but with no important changes in treatment strategies^{1,4}.

The appropriate treatment depends on tumor stage and presence of lymph nodes and metastasis (tumor-node-metastasis - TNM), as reported in the 8th American Joint Committee on Cancer (AJCC) manual⁵. Management of these patients usually requires a multidisciplinary approach, and early-stage tumors, i.e., tumors in clinical stage I-II, should be considered for local treatment, such as surgery and/or radiotherapy (RT), whereas more-advanced lesions require a combination of surgery and adjuvant RT or chemoradiotherapy (CRT), according to the risk factors for recurrence detected in the surgical specimen.

Chemotherapy can be the definitive treatment in two situations: in organ-sparing treatment, with more robust studies in the larynx as the primary site, and in locally advanced, unresectable disease. Finally, in patients with metastatic disease and poor prognosis, systemic treatment includes the combination of cytotoxic chemotherapy (CT) and anti-epidermal growth factor receptor (EGFR) therapy or immunotherapy, or immunotherapy alone^{1,6}.

With emphasis on locally advanced, unresectable disease, CRT is the treatment of choice whenever available⁷. However, there are few studies in the literature comparing the efficacy of different RT regimens and radiosensitization with chemotherapeutic agents. The regimen of choice is the combination of RT (70 Gy in 35 fractions) and cisplatin (100 mg/m², D1, D22, D43)⁷⁻⁹. Adelstein et al.¹⁰, in a phase 3 trial conducted with 295 patients with unresectable HNC, randomized patients to the aforementioned CRT regimen vs. RT (70 Gy) and reported improvement in three-year projected overall survival (OS) for patients enrolled in the combined therapy (23% compared with 37% for RT), despite a higher occurrence of grade ≥ 3 toxicity (77% vs. 47% of patients). Because of adverse events, 30% of the patients did not receive the three CT doses as planned.

Therefore, despite evidence on the efficacy of CRT as a definitive treatment, more attention should be paid to treatment toxicity. Moreover, randomized studies on CRT had strict inclusion criteria that limited the external validity of the findings and their application in daily clinical practice, in patients with impaired nutritional status, and poor performance status and clinical and social support. Thus, we conducted a retrospective analysis of HNC patients undergoing CRT with high-dose cisplatin to determine the efficacy and toxicity of this therapy in our institution.

Methods

We conducted a retrospective review of the medical records of patients with HNC, histology of unresectable epidermoid carcinoma, clinical stage III-IVB, treated with CRT in our institution between 2012 and 2018, and who received at least one cycle of cisplatin (100 mg/m²). Patients who underwent definitive treatment for refusing surgery or as an attempt to spare the tumor-affected organ, patients with synchronous neoplasms, and patients with primary nasopharyngeal or salivary gland tumors were excluded from the survey. The data collected included information on clinical status, treatment, toxicity (CTCAE 5.0¹¹), and response rates (according to the Response Evaluation Criteria in Solid Tumors [RECIST]¹²), progression-free survival (PFS), and overall survival (OS). Acute toxicity was evaluated before each cycle and 30 days after treatment and chronic toxicity was registered during subsequent follow-up. PFS was defined as the interval between the beginning of treatment and disease progression, whereas OS was defined as the interval between the beginning of treatment and death. This study was approved by the Ethics Committee of the aforementioned Institution under protocol no. 20696619.60000.5440.

The Cox proportional-hazards model was used to assess the relationship between survival time and the qualitative variables¹³. Correlations between the clinical variables and treatment-related toxicity were assessed using the Poisson regression model, with a robust error variance, and crude and adjusted logarithm link function¹⁴. Variables with $p \leq 0.20$ in the crude model were included in the adjusted model. For analysis of the association of the neutrophil/lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR) with outcomes and toxicity, patients were assigned to two groups: one with values above the mean and one with values below the mean. Kaplan-Meier curves were constructed for PFS and OS. All graphs were constructed using the R 4.0.0 software and the analysis was performed using the SAS 9.4 system. A significance level of 5% ($p < 0.05$) was adopted for all statistical analyses.

Results

Demographic characteristics

Fifty-two (52) patients were included in the study. Mean age was 53 years, and most patients were men (90.4%), smokers or former smokers (84.7%), current or former alcohol users (90.4%), and had the oropharynx as the primary tumor site (59.6%). For tumors in the oropharynx, 19.4% of the specimens showed positive immunohistochemical staining with antibodies to HPV, 42.0% showed negative staining, and 38.7% were not tested. Only 3.8% of the patients had unresectable stage III epidermoid carcinoma, 32.7% had stage IVB, and 63.5% stage IVA. Weight loss >5% of the usual weight before diagnosis in 50% of the patients. In the performance status assessment, 72% of the patients had a Karnofsky performance score (KPS) of 90-100. Other characteristics of the sample are described in Table 1. Mean NLR was 4.14 and mean PLR was 215.57.

Table 1. Demographic characteristics of head and neck cancer (HNC) patients treated with chemoradiotherapy between 2012 and 2018.

Characteristics	N: 52
Age - N (%)	
Mean (range) - years	53 (31 - 70)
<60 years	42 (80.77)
≥60 years	10 (19.23)
Sex - N (%)	
Male	47 (90.4)
Female	5 (9.6)
Smokers - N (%)	
Current	24 (46.2)
Former	20 (38.46)
Never	8 (15.4)
Alcohol users - N (%)	
Current	13 (25)
Former	34 (65.4)
Never	5 (9.6)
Primary site - N (%)	
Oral cavity	5 (9.6)
Oropharynx	31 (59.6)
Larynx	4 (7.7)
Hypopharynx	4 (7.7)
Nasal cavity and sinuses	5 (9.6)
Hidden site	3 (5.8)
Histological degree - N (%)	
1	6 (11.5)
2	31 (59.6)
3	7 (13.5)
Not available	8 (15.4)
P16 Immunohistochemistry and HPV testing in oropharynx tumors - N (%)	
Positive	6 (19.4)
Negative	13 (42)
Inconclusive	12 (38.7)
Stage - N (%)	
III	2 (3.8)
IVA	33 (63.5)
IVB	17 (32.7)
BMI (Kg/m²) - N (%)	
<18.5	8 (15.4)
18.5 - 24.9	28 (53.9)
>24.9	16 (30.8)
Weight loss in the six months prior to diagnosis - N (%)	
0 - 5%	26 (50)
5,1 - 10%	11 (21.2)
>10%	15 (28.8)
Karnofsky performance score - N (%)	
70 - 80	15 (28.8)
90 - 100	37 (71.2)
Charlson comorbidity index - N (%)	
0	18 (34.6)
1 - 2	30 (57.7)
≥3	4 (7.7)

N: number; BMI: Body Mass Index; III: Stage III; IVA: Stage IV A; IVB: Stage IV B.

Treatment data

Mean interval between diagnosis and treatment onset was 91 days. Only one patient did not complete RT because of toxicity. Mean radiation dose was 6,950 (6,600 – 7,560) cGy, delivered in 37 (25-42) fractions over a mean period of 70 (44-126) days. Regarding CT, only 42.3% of the patients concluded all cycles, and 19.2% of them completed only one cycle. Low-level laser therapy was performed concomitantly with CT as prophylactic treatment in 28.8% of the patients.

Response rate, PFS, and OS

An objective response rate (ORR) of 84.6% was observed, with a complete response rate (CR) of 50%; 7.7% had stable disease and 7.7% had progressive disease despite combined treatment. Thus, based on the response rate, 11.5% of the patients could undergo salvage surgery.

Median PFS was 35.3 months (95% CI 27.28–43.78), with a one-year non-progression rate of 0.65 (0.52–0.78) and a five-year non-progression rate of 0.34 (0.2–0.48). Median OS was 52 months (95% CI 41.32–62.8), with one-year and five-year survival rates of 0.83 (0.72–0.93) and 0.44 (0.28–0.60), respectively. The Kaplan Meier curves are shown in Figures 1 and 2.

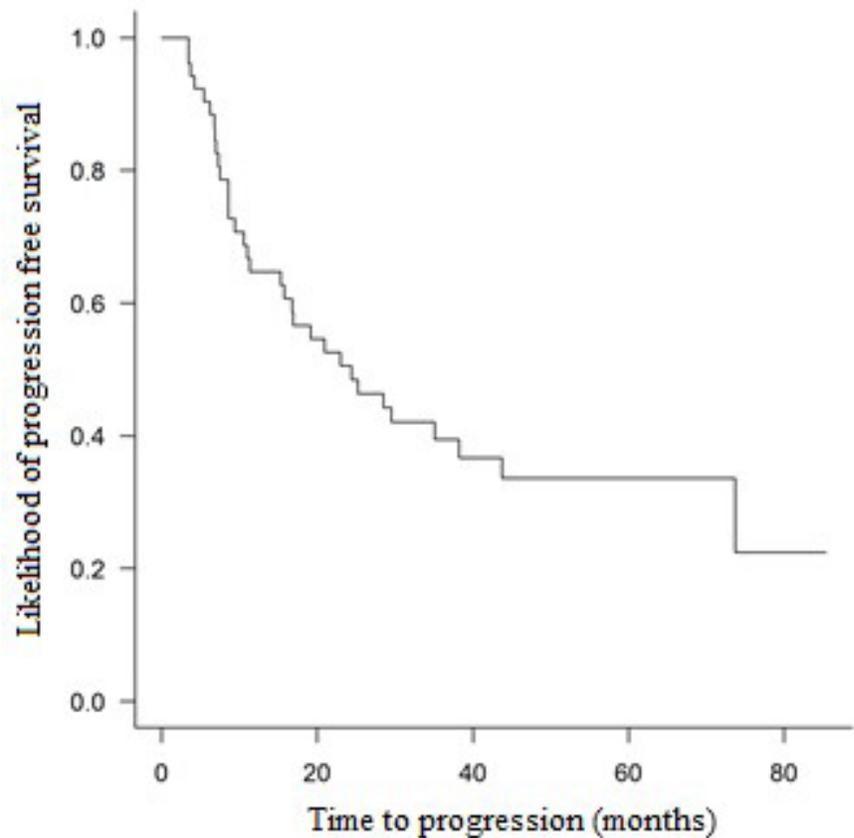


Figure 1. Progression-free survival (PFS) in the general population.

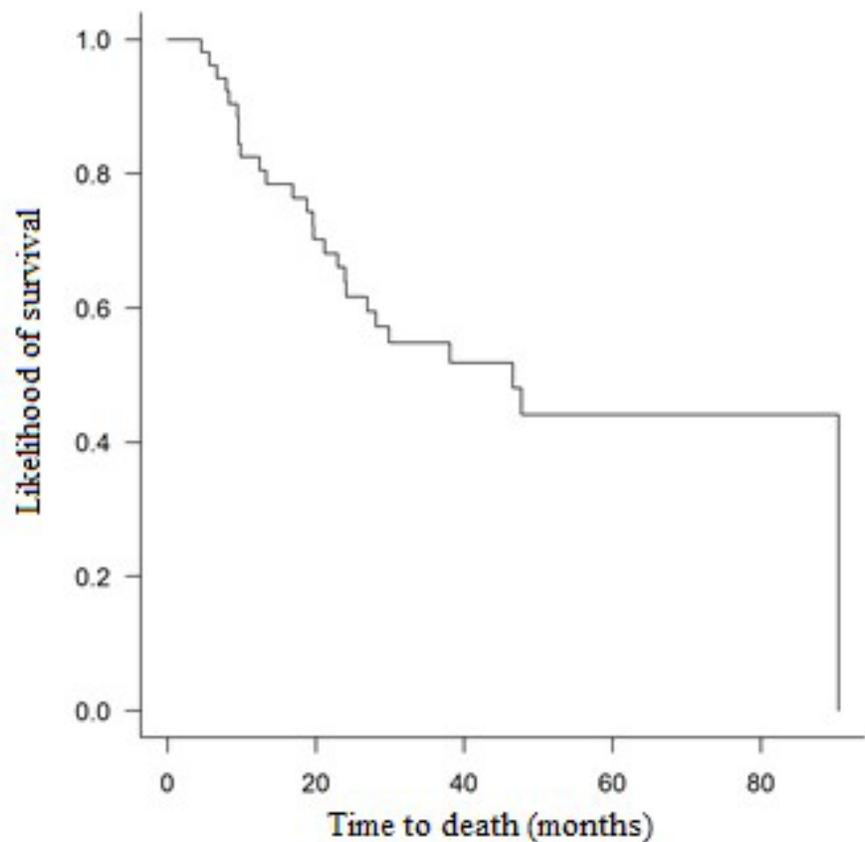


Figure 2. Overall survival (OS) in the general population.

Analysis of the correlation of clinical and treatment data with PFS and OS revealed that the number of CT cycles (1 vs. 2-3 cycles) and development of grade 3-4 toxicity were significantly correlated with mortality, with hazard ratio (HR) of 3.57 (1.25–10.25) ($p < 0.001$) for patients undergoing one CT cycle, and HR=0.27 (0.09–0.8) ($p < 0.02$) for patients with grade 3-4 events.

Statistically significant results were also found in the Charlson comorbidity index (CCI) scores, specifically in comparisons between 0 vs. 1-2 points (HR 3.23 [1.26–8.29], $p < 0.001$) and 1-2 points vs. ≥ 3 points (HR 0.08 [0.01–0.69], $p < 0.02$) (Table 2).

Toxicity

Acute toxicity was experienced by all patients: 90.4% grade 1 toxicity, 84.6% grade 2, and 69.2% grade 3 (Table 3). The most common acute toxicity was weight loss (86.5%), whereas acute renal failure was the most common grade 3 toxicity. No deaths or grade 4 toxicity were reported. Some patients experienced recurrent grade 3 toxicity over the four time points of analysis; it was observed in two or more time points in 21.2% of the patients and in three time points in 5.8% of them. Late toxicity was experienced by 51.9% of the patients, and only 3.8% of them had grade ≥ 3 toxicity. Persistent

Table 2. Progression-free survival (PFS) and overall survival (OS) analyses by variables.

Variable	Progression-free survival (PFS)				Overall survival (OS)			
	Crude		Adjusted		Crude		Adjusted	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (<60 vs. ≥60)	0.92 (0.38 - 2.25)	0.86			0.72 (0.29 - 1.81)	0.49		
Sex (F vs. M)	2.36 (0.8 - 6.97)	0.12	2.54 (0.72 - 8.95)	0.15	2.33 (0.68 - 7.92)	0.18	1.93 (0.5 - 7.38)	0.34
Smokers (Never vs. Former)	0.65 (0.18 - 2.3)	0.50	0.72 (0.19 - 2.72)	0.63	0.94 (0.25 - 3.5)	0.93		
Smokers (Never vs. Current)	0.47 (0.14 - 1.6)	0.23	0.59 (0.16 - 2.15)	0.42	0.68 (0.19 - 2.39)	0.55		
Smokers (Former vs. current)	0.73 (0.35 - 1.51)	0.39	0.82 (0.37 - 1.83)	0.62	0.72 (0.31 - 1.69)	0.45		
Alcohol users (Never vs. Former)	0.51 (0.12 - 2.16)	0.36			0.7 (0.16 - 3.03)	0.64		
Alcohol users (Never vs. Current)	0.56 (0.12 - 2.6)	0.46			1.12 (0.22 - 5.78)	0.90		
Alcohol users (Former vs. Current)	1.1 (0.5 - 2.41)	0.81			1.59 (0.59 - 4.3)	0.36		
Primary site (non-oro-pharynx vs. Oropharynx)	0.86 (0.41 - 1.78)	0.68			1.33 (0.6 - 2.94)	0.48		
Clinical stage (III/IVA vs. IVB)	1.6 (0.72 - 3.57)	0.25	1.53 (0.65 - 3.61)	0.34	1 (0.43 - 2.31)	0.99		
BMI (<18.5 vs. 18.5 - 24.9)	0.79 (0.29 - 2.1)	0.63			0.93 (0.31 - 2.83)	0.90		
BMI (<18.5 vs. ≥25)	1.15 (0.37 - 3.55)	0.81			1.09 (0.32 - 3.73)	0.89		
BMI (18.5 - 24.9 vs. ≥25)	1.46 (0.64 - 3.35)	0.37			1.17 (0.47 - 2.91)	0.73		
Δ weight in 6 months (0 - 5% vs. 5 - 10%)	0.72 (0.31 - 1.66)	0.44	0.99 (0.36 - 2.73)	0.99	0.89 (0.31 - 2.54)	0.83		
Δ weight in 6 months (0 - 5% vs. >10%)	1.78 (0.74 - 4.31)	0.20	2.44 (0.87 - 6.84)	0.09	0.91 (0.37 - 2.23)	0.84		
Δ weight in 6 months (5 - 10% vs. >10%)	2.48 (0.88 - 6.97)	0.09	2.46 (0.81 - 7.51)	0.11	1.02 (0.33 - 3.13)	0.97		
KPS (70/80 vs. 90/100)	1.3 (0.62 - 2.73)	0.49			1.31 (0.56 - 3.05)	0.53		
Comorbidities (0 vs. 1 - 2)	1.19 (0.57 - 2.5)	0.64			1.9 (0.83 - 4.35)	0.13	3.23 (1.26 - 8.29)	0.01
Comorbidities (0 vs. ≥3)	1.37 (0.3 - 6.21)	0.68			1.15 (0.25 - 5.3)	0.85	0.26 (0.03 - 1.93)	0.19
Comorbidities (1 - 2 vs. ≥3)	1.15 (0.27 - 4.94)	0.85			0.61 (0.14 - 2.72)	0.52	0.08 (0.01 - 0.69)	0.02
Time to treatment (0 to 60 vs. 61 to 90)	1.4 (0.57 - 3.43)	0.46			2.16 (0.85 - 5.48)	0.10	1.89 (0.7 - 5.12)	0.21
Time to treatment (0 - 60 vs. >90)	1.22 (0.5 - 2.95)	0.66			2.56 (0.95 - 6.91)	0.06	2.2 (0.73 - 6.68)	0.16
Time to treatment (61- 90 vs. >90)	0.87 (0.4 - 1.92)	0.73			1.18 (0.44 - 3.2)	0.74	1.17 (0.39 - 3.51)	0.78
Number of cycles (1 vs. 2/3)	1.34 (0.55 - 3.27)	0.52			1.98 (0.79 - 4.98)	0.15	3.57 (1.25 - 10.25)	0.02
Grade 3-4 toxicity (No vs. Yes)	0.63 (0.29 - 1.35)	0.23	0.6 (0.22 - 1.61)	0.31	0.52 (0.21 - 1.31)	0.17	0.27 (0.09 - 0.8)	0.02
Salvage surgery (No vs. Yes)	1.08 (0.38 - 3.07)	0.89			4.13 (0.56 - 30.6)	0.17	11.27 (0.73 - 174)	0.08
NLR	1.02 (0.88 - 1.17)	0.81			1.07 (0.92 - 1.25)	0.35		
PLR	1.02 (0.99 - 1.05)	0.22	1.04 (1 - 1.08)	0.05	1 (0.97 - 1.04)	0.92		

HR: Hazard ratio; F: Female; M: Male; BMI: body mass index; KPS: Karnofsky performance scale; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

Table 3. Acute toxicity of any grade.

Acute toxicity	Grade - N (%)				
	Any	Grade 1	Grade 2	Grade 3	Grade 4
	100%	47 (90.4%)	44 (84.6%)	36 (69.2%)	-
Weight loss	45 (86.5%)	36 (69.2%)	29 (55.8%)	10 (19.3%)	-
Nausea	35 (67.3%)	22 (42.3%)	16 (30.8%)	4 (7.7%)	-
Mucositis	29 (55.8%)	17 (32.7%)	15 (28.8%)	8 (18.4%)	-
Creatinine elevation	25 (48%)	16 (30.8%)	13 (25%)	5 (9.6%)	-
Vomiting	24 (46.2%)	14 (26.9%)	12 (23%)	3 (5.8%)	-
Radiation skin injury	21 (40.4%)	19 (36.5%)	6 (11.5%)	-	-
Neutropenia	17 (32.7%)	-	11 (21.2%)	8 (18.4%)	-
Acute renal failure	15 (28.8%)	-	-	15 (28.8%)	-
Weakness	14 (26.9%)	5 (9.6%)	8 (18.4%)	1 (1.9%)	-
Anemia	9 (17.3%)	-	7 (13.5%)	3 (5.8%)	-
Anorexia	7 (13.5%)	5 (9.6%)	2 (3.8%)	-	-
Infection	5 (9.6%)	1 (1.9%)	4 (7.7%)	-	-
Thrombocytopenia	3 (5.8%)	2 (3.8%)	-	1 (1.9%)	-
Diarrhea	3 (5.8%)	2 (3.8%)	1 (1.9%)	-	-
Hearing loss	3 (5.8%)	1 (1.9%)	2 (3.8%)	-	-
Pain	2 (3.8%)	1 (1.9%)	1 (1.9%)	-	-
Dysphagia	2 (3.8%)	1 (1.9%)	1 (1.9%)	-	-
Neuropathy	1 (1.9%)	-	1 (1.9%)	-	-
Xerostomia	1 (1.9%)	1 (1.9%)	-	-	-
Dysphonia	1 (1.9%)	1 (1.9%)	-	-	-

Another point worth mentioning is the lack of evaluation of the association between HPV and PFS or OS in our study. Oncogenic HPV infections in HNC are associated with better outcomes; however, 38.7% of our sample were not submitted to immunohistochemical analysis due to limited availability of histopathological specimens. We then decided not to perform the analyses of PFS and OS, as the statistical power of these results would be low.

With respect to acute toxicity, despite the high prevalence (69.2%) of patients with toxicity grade ≥ 3 , this is lower than that reported in previous studies (from 77 to 89%^{10,27,28}). Retrospective studies are subjected to (under)reporting bias of adverse events and respective grades, mainly events related to subjectivity. The severe weight loss and high prevalence of acute renal failure may be explained by the fact that these data were obtained from clinical practice in public facilities that, unlike well-designed clinical investigations, lack

increase in creatinine was observed in 27% of the patients, with 15.4% of them presenting chronic kidney disease (creatinine clearance <60mL/min/1.73m²), 5.8% xerostomia, 3.8% radiation skin injury, 3.8% hearing loss, and 1.9% secondary infection. In the adjusted model of clinical variables (Table 4), prophylactic low-level laser therapy and body mass index (BMI) were associated with development of acute grade ≥3 toxicity, with HR of 0.48 (95% CI 0.27–0.86) (*p*<0.01) for patients with prophylaxis and HR of 0.27 (95% CI 0.09–0.76) (*p*< 0.01) for those with BMI <18.5 Kg/m² compared with BMI ≥25 Kg/m².

Table 4. Analyses of grade 3-4 toxicity by variables.

Comparisons	Crude		Adjusted	
	ORR (95% CI)	<i>p</i> -value	ORR (95% CI)	<i>p</i> -value
Age (<60 vs. ≥60)	0.83 (0.57 - 1.21)	0.34		
Sex (F vs. M)	1.18 (0.73 - 1.90)	0.51		
Smokers (Never vs. Former)	0.71 (0.34 - 1.51)	0.38		
Smokers (Never vs. Current)	0.67 (0.32 - 1.38)	0.28		
Smokers (Former vs. Current)	0.93 (0.65 - 1.35)	0.71		
Alcohol users (Never vs. Former)	1.09 (0.67 - 1.76)	0.73		
Alcohol users (Never vs. Current)	1.49 (0.76 - 2.90)	0.24		
Alcohol users (Former vs. Current)	1.37 (0.79 - 2.35)	0.26		
Primary site (Non-oropharynx vs. Oropharynx)	0.94 (0.64 - 1.37)	0.75		
Clinical stage (III/IVA vs. IVB)	0.86 (0.60 - 1.23)	0.40		
BMI (<18.5 vs. 18.5–24.9)	0.53 (0.21 - 1.32)	0.17	0.46 (0.14 - 1.58)	0.22
BMI (<18.5 vs. ≥25)	0.46 (0.18 - 1.16)	0.10	0.27 (0.09 - 0.76)	0.01
BMI (18.5 - 24.9 vs. ≥25)	0.88 (0.63 - 1.23)	0.45	0.58 (0.27 - 1.23)	0.15
Δ weight in 6 months (0-5% vs. 5-10%)	1.55 (0.88 - 2.73)	0.13	1.08 (0.32 - 3.63)	0.91
Δ weight in 6 months (0-5% vs. >10%)	1.59 (0.96 - 2.62)	0.07	1.52 (0.71 - 3.26)	0.28
Δ weight in 6 months (5-10% vs. >10%)	1.02 (0.50 - 2.10)	0.95	1.41 (0.49 - 4.05)	0.52
KPS (70/80 vs. 90/100)	0.70 (0.42 - 1.17)	0.18	0.55 (0.29 - 1.07)	0.08
Comorbidities (0 vs. 1-2)	0.91 (0.61 - 1.34)	0.63		
Comorbidities (0 vs. ≥3)	1.33 (0.47 - 3.75)	0.59		
Comorbidities (1 - 2 vs. ≥3)	1.47 (0.54 - 4.00)	0.45		
Clearance (60-90 vs. >90)	1.12 (0.78 - 1.61)	0.55		
Hb (≥12.5 vs. <12.5)	0.98 (0.68 - 1.42)	0.92		
Albumin (≥3.5 vs. <3.5)	1.83 (1.25 - 2.68)	<0.01	1.88 (0.91 - 3.89)	0.09
Prophylactic low-level laser therapy	0.72 (0.52 - 0.99)	0.04	0.48 (0.27 - 0.86)	0.01
Time to treatment (0 to 60 vs. 61 to 90)	1.03 (0.61 - 1.71)	0.92		
Time to treatment (0 - 60 vs. >90)	0.89 (0.55 - 1.43)	0.63		
Time to treatment (61- 90 vs. >90)	0.87 (0.58 - 1.30)	0.49		
NLR	0.88 (0.75 - 1.02)	0.10	0.80 (0.55 - 1.16)	0.24
PLR	0.98 (0.95 - 1.00)	0.05	1.00 (0.95 - 1.05)	0.97

F: Female; ORR: Objective response rate; M: Male; BMI: body mass index; KPS: Karnofsky performance scale; Hb: Hemoglobin; NLR: neutrophil-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; CI: confidence interval.

Discussion

The ORR was 84.6%, with a CR rate of 42.3%, and 11.5% of the patients eligible for salvage surgery. These findings agree with those reported by Aldestein et al.¹⁰, who found 40.2% of CR and 21% of salvage surgery. However, median OS in their study was 19.1 months (no description of PFS), lower than that observed in our study (median PFS of 35.3 months and median OS of 52 months). On the other hand, corroborating our findings, a retrospective analysis of 2,200 Veterans Health Administration patients with HNC showed a median OS of 49 months, and Xiang et al.¹⁵ reported a median OS of 54 months. Therefore, although we have found a longer survival rate compared with that of the pivotal study by Aldestein et al.¹⁰, our data are compatible with those reported in large sample studies. PFS was not evaluated in the studies by Aldestein et al.¹⁰, Bauml et al.¹⁶ and Xiang et al.¹⁵, but a meta-analysis by Mohamed et al.¹⁷ reported a two-year PFS rate of 62%. These results are similar to ours, since their two-year PFS rates are similar to our value of 65% at the end of the first year. However, our results show that the combination of CT and RT promoted a good long-term disease control.

With respect to the analysis of the correlation of clinical characteristics and treatment with survival, the correlation between number of CT cycles and survival has been previously demonstrated. In the RTOG 0129 trial, similar outcomes were observed in patients receiving two or three cycles of cisplatin, with no difference in tumor control, PFS, or OS. However, patients receiving only one cycle of cisplatin had poorer outcomes¹⁸. These findings corroborate those of other studies that suggested that a cisplatin dose ≥ 200 mg/m² should be administered throughout the treatment¹⁹, with a standard-dose⁷ of 300 mg/m². Although we did not assess correlations between the number of cycles received and the occurrence of toxicity, we presume that the risk of adverse events is related to the number of cycles of cisplatin and, thereby, the occurrence of toxicity was related to survival. To infer that toxicity *per se* is associated with longer survival contradicts the assumption that CT with two or more cycles of cisplatin results in better outcomes, since adverse effects are the main limitations to deliver adequate doses of cisplatin.

The relationship between CCI and survival has been explored in previous studies on HNC and other tumors²⁰⁻²². Our results agree with the literature in showing a greater risk of death for higher CCI scores (0 vs. 1-2 points). In contrast, patients with CCI of 1-2 points had poorer outcomes compared with those with CCI ≥ 3 points and, in contrast to what was expected, no difference in the risk of death was observed between CCI scores 0 and ≥ 3 . We believe that the disparities observed in comparisons including patients with CCI score ≥ 3 were caused by a sampling bias due to the small number of patients assigned to this group (only 7.7% of the study population).

Although there was no other association between the variables and PFS or OS, other predictive factors have been previously described: weight loss $>5\%$ of baseline weight²³, hypoalbuminemia²⁴, NLR and PLR^{25,26}, and clinical stage of disease¹. Thus, the smaller sample size and the lower statistical power may explain the discrepancy between our findings and those reported in other studies.

adequate clinical, social and nutritional support, and hence malnutrition- and dehydration-related toxicity may be more common.

The correlation between prophylactic low-level laser therapy and toxicity was explored with decreased risk of mucositis with this practice²⁹. However, our data show an opposite relationship. We hypothesize that laser therapy is not actually related to increased toxicity, but that there has been a greater notification of adverse events, probably because the prophylactic treatment was associated with dental support on a regular basis, making it possible to identify and describe toxicity profiles possibly neglected and/or underreported until then.

Finally, a lower toxicity grade in the population with a lower BMI in the comparison $<18.5 \text{ kg/m}^2$ vs. $\geq 25 \text{ kg/m}^2$ was not expected, since malnutrition is associated with increased adverse events in the literature³⁰. In addition, the relationship between BMI and toxicity is not maintained between comparisons of other categories of BMI.

Conclusion

Definitive treatment of HNC patients with a regimen combining RT and cisplatin 100 mg/m^2 was effective, with PFS and OS comparable to those of larger sample studies, and lower early and late toxicity profiles compared with those of pivotal studies. In addition, two or more cycles of cisplatin, grade 3-4 toxicity, and CCI were correlated with OS, and prophylactic low-level laser therapy and BMI were associated with grade 3-4 toxicity.

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***Correspondence**

Matheus de Aquino Moreira Guimarães
Universidade de São Paulo (USP),
Faculdade de Medicina de Ribeirão
Preto (FMRP), Hospital das Clínicas (HC),
Departamento de Imagens Médicas,
Hematologia e Oncologia Clínica,
Ribeirão Preto, SP, Brasil
Rua Tenente Catão Roxo, 3900, 7º andar,
sala 731 - Vila Monte Alegre, Ribeirão
Preto - SP, 14015-010.
Tel: (16) 36021000, ramal 5624.
Email: matheusamguimaraes@gmail.com

Authors information

MAMG, TMC, FNS and LR - MD,
Clinical Oncologist, Hospital das
Clínicas, Faculty of Medicine of
Ribeirão Preto, University of São
Paulo (HCFMRP-USP). FMP and LMC
- PhD, Clinical Oncologist, Hospital
das Clínicas, Faculty of Medicine of
Ribeirão Preto, University of São Paulo
(HCFMRP-USP).

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