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Author manuscript

Radiother Oncol. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

Radiother Oncol. 2020 April ; 145: 95–100. doi:10.1016/j.radonc.2019.12.023.

Lymphopenia During Radiotherapy In Patients With Oropharyngeal Cancer

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Abstract

Purpose/Objective: Radiation-induced lymphopenia has been associated with poor survival outcomes in certain solid tumors such as esophageal, lung, cervical and pancreatic cancers. We aim to determine the effect of treatment-related lymphopenia during radiotherapy on outcomes of patients with oropharyngeal cancer.

Materials/Methods: A retrospective analysis of all patients who completed definitive radiotherapy for oropharyngeal cancer at The University of Texas MD Anderson Cancer Center and had blood counts taken during radiotherapy from 2002 to 2013 were included. Patient, tumor and treatment characteristics, clinical outcomes and lymphocyte counts during radiotherapy were recorded. Lymphopenia was graded according to the CTCAE v4.0. Survival rates were estimated using the Kaplan-Meier method and compared with log-rank tests.

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Conflict of interest: None.

Results: 850 patients were evaluated. The median age was 57 years. The majority of the cohort had pl6/HPV-positive disease (71%), 8% had HPV-negative disease and 21% were unknown. The median radiation total dose was 70 Gy. 45% of patients had induction chemotherapy, and 87% had concurrent chemotherapy. 703 (83%) patients developed ≥grade 3 (G3) lymphopenia and 209 (25%) had grade 4 (G4) lymphopenia during radiotherapy. The median follow-up was 59 months; the 5-year overall survival rate was 81%. There were no significant differences in overall survival rates nor in disease control rates, in those who developed G3/G4 lymphopenia compared with those who did not. No significant effect of lymphopenia on survival was observed when analyzed according to pl6/HPV status.

Conclusion: In this large cohort of patients with oropharyngeal cancer, the development of lymphopenia during radiotherapy did not impact outcomes.

Keywords

oropharyngeal cancer; lymphopenia; radiotherapy

Introduction

Radiation-induced lymphopenia has been associated with poor survival outcomes in certain solid tumors such as lung [1–3], esophageal [4], cervical [5,6] and pancreatic cancers [7]. Lymphoid cells are highly radiosensitive; radiation doses (<1 Gy) have been demonstrated to deplete and induce cell death in lymphocytes [8–10]. The mechanism underlying this correlation remains unknown. It has been postulated that a reduction in lymphocytes may have resulted in a decrease in systemic tumor surveillance. Hence, tumor cells that entered the systemic circulation can successfully evade the immune system. Therefore, a reduction of lymphocyte count may portend a possible higher risk of regional and metastatic disease, and subsequently poorer survival outcomes.

Radiotherapy remains the mainstay treatment modality for the majority of patients with oropharyngeal cancer. As the human papillomavirus (HPV) has been established as the major cause of oropharyngeal cancer [11,12], there are hypotheses that the immune system plays a major role in the transformation of latent HPV infection to malignancy [13]. Therefore immune-modulation may be a factor in the curability and outcomes of patients with oropharyngeal cancer [14]. Here, we investigated the association of lymphocyte depletion during radiotherapy with outcomes in a large cohort of patients with oropharyngeal cancer.

Methods

The records of patients who completed curative-intent radiotherapy (minimum dose of 50 Gy) for oropharyngeal cancer and had blood counts taken during radiotherapy from 2002 to 2013 were reviewed. All patients received curative-intent radiation dose. Patients with distant metastatic disease (Ml) at diagnosis were excluded.

Patient, tumor and treatment characteristics, clinical outcomes and serial absolute lymphocyte counts (ALCs) pre, during (weekly) and 6 to 12 weeks post-radiotherapy were

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recorded. All patients had at least two intra-treatment ALCs recorded after week 1 of treatment. Patients with no ALC recorded pretreatment and/or during treatment, and those with chronic lymphocytic leukemia were excluded. The disease was staged according to the American Joint Committee on Cancer staging system (7^{th} edition). Lymphopenia was graded according to the CTCAE v4.0. This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center.

Statistical analysis

Pre-, during and post-treatment ALCs were compared using paired T-test. Overall survival (OS) was calculated with the Kaplan-Meier method from the date of completion of radiotherapy to date of death. Locoregional control was measured from the date of completion of radiotherapy to date of first locoregional failure. Freedom from distant metastasis was calculated from the date of completion of radiotherapy to date of first distant disease. For all survival calculations, patients were without events were censored at last follow up time.

Lymphopenia was characterized as either grade (G) 3 [ALC $0.2 – 0.5 \times 10^9$/L) or G4 (ALC $< 0.2 \times 10^9$/L). The nadir value during radiotherapy was used. Survival and disease control rates were estimated using the Kaplan-Meier method and the relationship between lymphopenia and survival was evaluated with log-rank tests. The Cox regression model was used to analyse lymphopenia as a continuous variable. Multivariable regression analyses were performed to account for potential confounders. Variables that had p-value of <0.10 on univariate analysis are included in the multivariable model. Statistical analyses were performed using JMP vl4.0 (SAS Institute Inc.). A p-value of <0.05 was deemed statistically significant.

Results

Patient characteristics

A total of 850 patients were eligible for analysis (Figure 1). Patient demographics, disease and treatment characteristics are described in Table 1. The median age was 57 years (range: 28 – 87 years) and 87% of patients were males. The most common primary sites were base of tongue (55%) and tonsil (43%). Most patients (71%) had HPV-associated oropharyngeal cancer and more than half of the cohort were never smokers or previous light smokers (<10 pack year). The majority (99%) had locally advanced oropharyngeal cancer (AJCC stage III - IV) and 87% received concurrent chemotherapy. The median prescribed dose was 70 Gy (range: 50 – 74 Gy). The median follow-up was 59 months.

Changes in ALC during radiotherapy

The median pretreatment ALC was 1.7 (range: 0.3 – 4.8]; only 5 patients had pretreatment G3 lymphopenia. Those who received induction chemotherapy had a lower baseline ALC than those who did not (1.58 vs 1.74, $p < .001$]. On regression analysis, there was no significant correlation between those who had induction chemotherapy with the subsequent development of G3 or higher (p=0.054], or G4 lymphopenia (p=0.959) during radiotherapy. However, there was an inverse association between those who had concurrent chemotherapy with G3 or higher ($p<0.0001$) and G4 lymphopenia ($p=0.0002$). Table 2 shows the results of univariate and multivariate analyses between variables with lymphopenia.

There was a significant drop ($p<0.0001$) in ALC during radiotherapy when comparing ALC for each timepoint with baseline, and also between each consecutive treatment weeks. Figure 2 shows the overall kinetics of ALCs during the course of radiotherapy. Seven hundred three patients (83%) developed ≥ grade 3 (G3) lymphopenia including 209 (25%) with grade 4 (G4) lymphopenia during radiotherapy. Significant recovery of ALC was observed at 6 to 12 weeks post-treatment ($p<0.0001$).

Lymphopenia and clinical outcomes

At the time of analysis, 183 patients have died. Overall, 141 patients developed disease recurrence. The 5-year and 10-year OS rate for the cohort were 81.3% and 69.8%. The 5 and 10-year relapse free survival were 83.2% and 82%. There were no significant differences in overall survival rates nor in disease control rates, in those who developed G3 or G4 lymphopenia compared with those who did not (Figure 3 - 5). In addition, no significant effect of lymphopenia on survival was observed when analyzed according to pl6/HPV status, those who had received induction chemotherapy, and those who had concurrent chemotherapy. Table 3 shows the results of univariate and multivariate analyses for factors associated with overall survival and freedom from disease recurrence. Factors associated with overall survival included age at diagnosis ($p=0.003$), smoking status ($p=0.004$) and tumor (T] stage, whilst smoking status was the only independent factor associated with freedom from recurrence. Lowest ALC during treatment did not emerge as a significant factor in the analyses.

Discussion

Our study shows that the development of lymphopenia during radiotherapy is common in patients with oropharyngeal cancer and it does not impact subsequent patient outcomes. Despite the development of lymphopenia during treatment, our data suggests that this is likely temporary as some lymphocyte recovery is seen at 6 to 12 weeks post-treatment.

There is an increasing body of literature illustrating the development of treatment-related lymphopenia during radiotherapy in the treatment of several malignancies [3,5–7,15,16]. Our study showed that this is a common event as more than 80% of our cohort developed grade 3 or higher lymphopenia during treatment. Although the mechanism of radiation-induced lymphopenia in irradiation of non-marrow containing organs remains poorly understood, it has been proposed: [1) at each fraction of treatment the circulating lymphocytes receive a radiation dose capable of inducing cell death in lymphocytes; and/or (2) the circulating lymphocytes accumulate DNA damage during each fraction, and over the course of multiple fractions of radiation the lymphocytes accumulate a lethal dose [17]. The gradual drop in ALC over the course of treatment suggests the latter mechanism is more likely. In patients with oropharyngeal cancer, it may possible that low dose to the circulating lymphocytes particularly with a large field of treatment and also dose to large vessels such as the carotid arteries may contribute to the development of intra-treatment lymphopenia.

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Several investigations have reported that patients who developed lymphopenia (typically ≥ Grade 3) during radiotherapy had poorer clinical outcomes. This has been studied in patients with cervical cancer [5,6], high-grade glioma [16,18,19], small cell [3] and non-small cell lung cancer [1,2,18] and pancreatic adenocarcinoma [7,18]. Campian et al [15] reported in a cohort of 56 patients with head and neck cancer (70% had oropharyngeal cancer), those with HPV-negative disease (n=22) who developed Grade 3 or higher treatment-related lymphopenia 2 months after commencing radiotherapy had significantly poorer disease-free survival. The study may have had a different outcome than ours because it included non-oropharyngeal head and neck cancer which has a different disease biology than oropharyngeal cancer. Jensen et al [20] demonstrated in 114 patients with oropharyngeal cancer, Grade 4 lymphopenia during treatment was associated with poorer overall survival. Contrary to these studies, our data with 850 patients with oropharyngeal cancer demonstrated that the development and degree of lymphopenia during treatment did not affect patients' subsequent clinical outcomes, regardless of HPV status.

The reason behind why treatment-related lymphopenia had minimal or no effect on outcomes in oropharyngeal cancer may be difficult to elucidate. One reason may be that the effect of quality radiotherapy treatment is highly paramount for improved outcomes [21–23] and other factors unrelated to the quality of radiotherapy have minimal effect. It is unarguably true that the immune system plays a crucial role in the development and recurrence of cancer. However the ALC is a crude measure of immune function - lymphocytes have both immune suppressing and immune effector functions. Additionally, a threshold level of lymphocytes may be adequate for anti-tumor immunity. Finally, we only measured circulating lymphocytes and do not know the status of the immune microenvironment in the patients' tumors before, during, and after therapy.

Our study has its inherent limitations secondary to the design of a retrospective study. Blood counts were historically obtained to monitor for chemotherapy toxicity, therefore the majority of our patients had locally advanced disease and therefore likely to have had bilateral neck irradiation and chemotherapy (induction and/or concurrent). It would be interesting to investigate the degree and impact of lymphopenia in those who had unilateral radiotherapy (with or without chemotherapy). Furthermore, about one-fifth of our cohort did not have available HPV status data as routine HPV testing only came into effect in 2010, limiting the analysis according to HPV status.

Conclusion

In this large cohort of patients with oropharyngeal cancer, the development of lymphopenia during radiotherapy did not impact subsequent patient outcomes.

Acknowledgments

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Dr. Ng received funding from the Australian Postgraduate Award, the Royal Australian and New Zealand College of Radiologists (RANZCR) Research Grant and Radiological Society of North America (RSNA) Fellow Grant. Drs. Lai, Mohamed and Fuller receive funding support from the National Institutes of Health (NIH)/National Institute

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for Dental and Craniofacial Research (NIDCR) (1R01DE025248-01 /R56DE025248-01). Drs. Mohamed and Fuller were previously funded via the National Science Foundation (NSF), Division of Mathematical Sciences, Joint NIH/NSF Initiative on Quantitative Approaches to Biomedical Big Data (QuBBD) Grant (NSF DMS-1557679) and are currently supported by the NIH National Cancer Institute (NCI)/Big Data to Knowledge (BD2K) Program (1R01CA214825-01). Dr. Fuller received/(s) grant and/or salary support from the NIH/NCI Head and Neck Specialized Programs of Research Excellence (SPORE) Developmental Research Program Career Development Award (P50CA097007-10); the NCI Paul Calabresi Clinical Oncology Program Award (K12 CA088084-06); a General Electric Healthcare/MD Anderson Center for Advanced Biomedical Imaging In-Kind Award; an Elekta AB/MD Anderson Department of Radiation Oncology Seed Grant; the Center for Radiation Oncology Research (CROR) at MD Anderson Cancer Center Seed Grant; and the MD Anderson Institutional Research Grant (IRG) Program. Dr. Fuller has received speaker travel funding from Elekta AB. Supported in part by the NIH/NCI Cancer Center Support (Core) Grant CA016672 to The University of Texas MD Anderson Cancer Center (P30 CA016672).

Disclosures: Dr. Ng is funded by the Australian Postgraduate Award, the Royal Australian and New Zealand College of Radiologists (RANZCR) Research Grants and the Radiological Society of North America (RSNA) Fellow Grant Dr. Fuller received funding support from the National Institutes of Health, the NCI Paul Calabresi Clinical Oncology Program Award, the MD Anderson Institutional Research Grant (IRG) Program and the Andrew Sabin Family Fellowship. Dr. Fuller has received speaker travel funding from Elekta AB. Dr. Johnson has received research funding from PIQUR Therapeutics and Trovagene.

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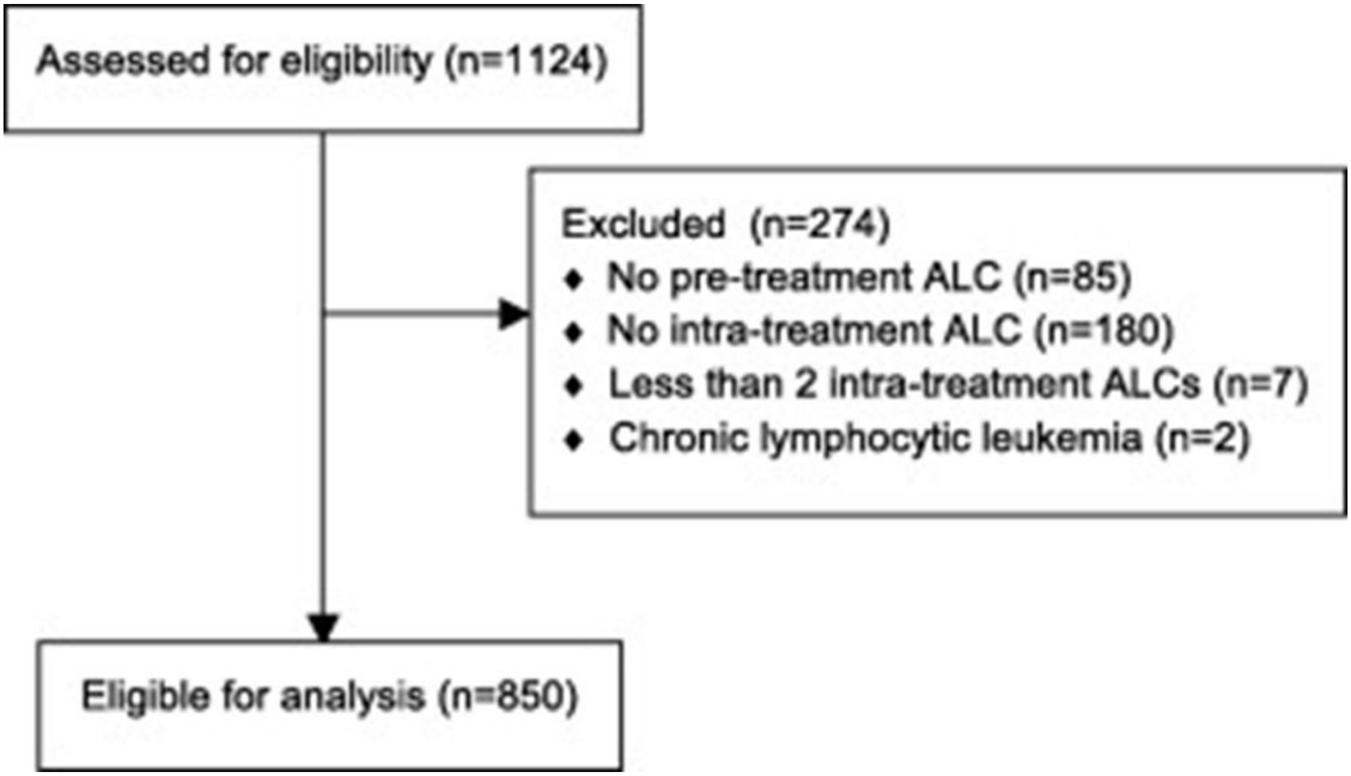

Figure 1.
CONSORT diagram.

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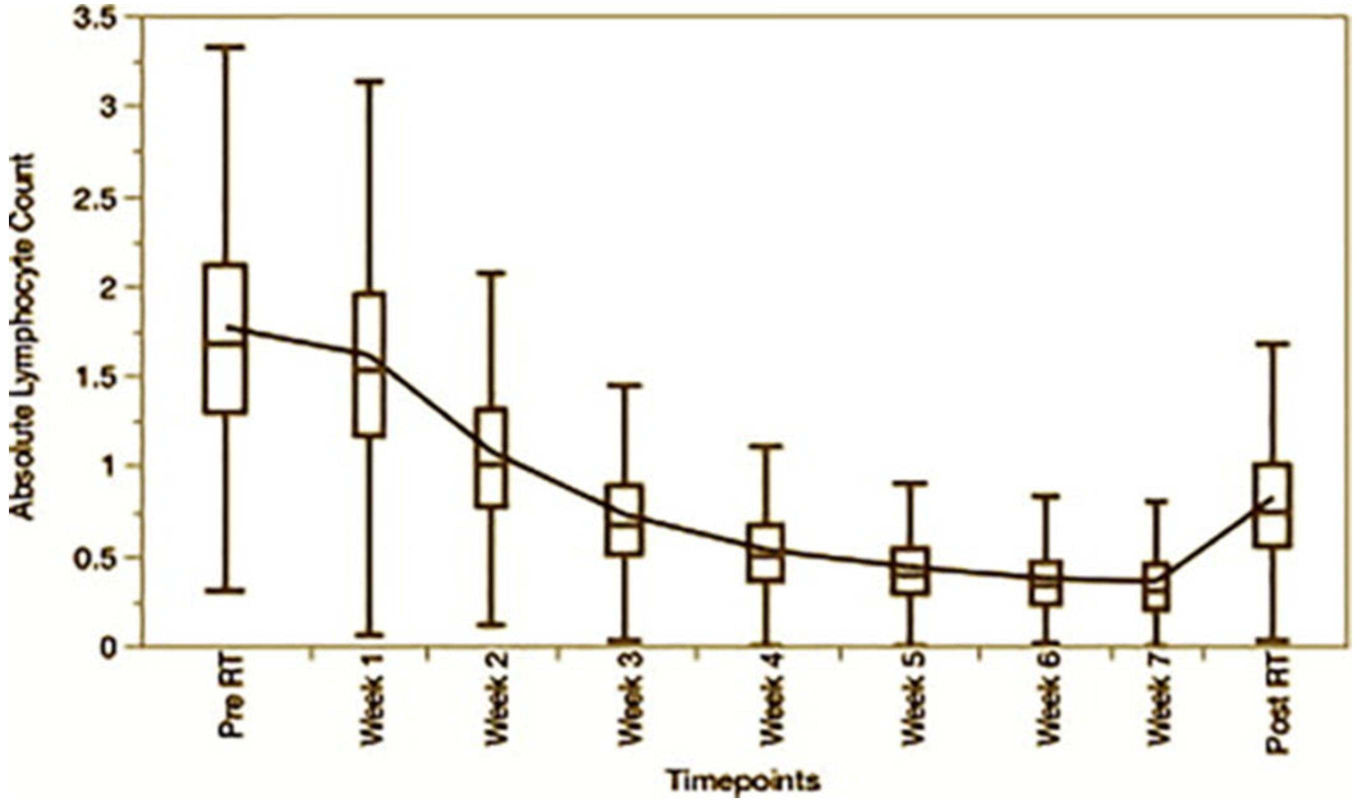

Figure 2.
Kinetics of absolute lymphocyte count (ALC) during radiotherapy.

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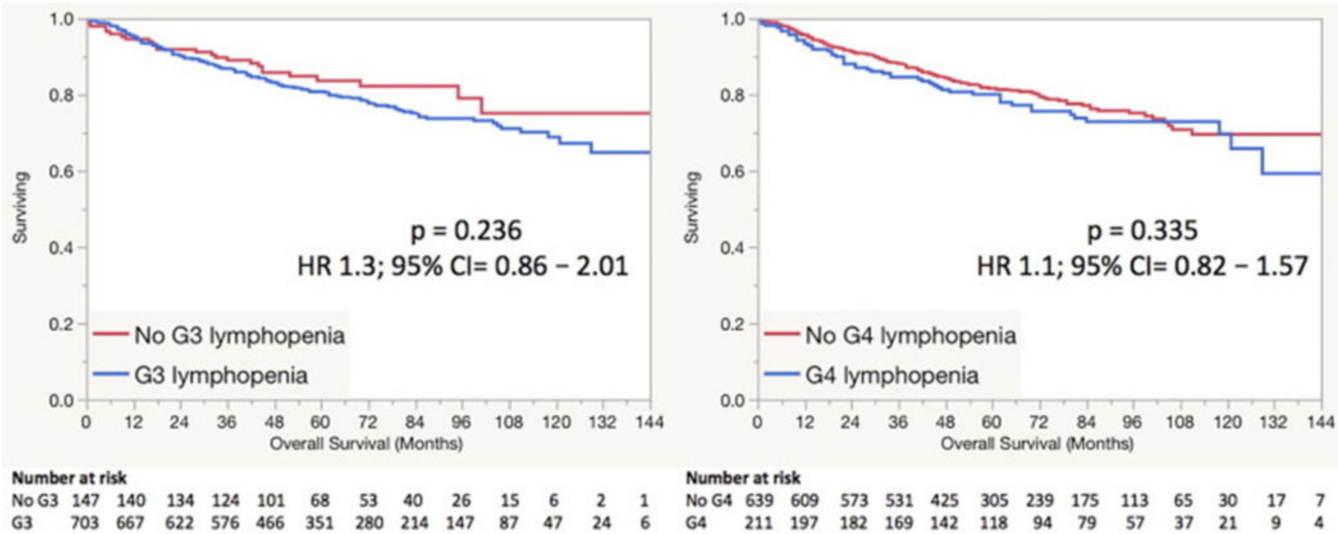

Figure 3.

Overall survival stratified by degree of lymphopenia

G3 - Grade 3; G4 - Grade 4.

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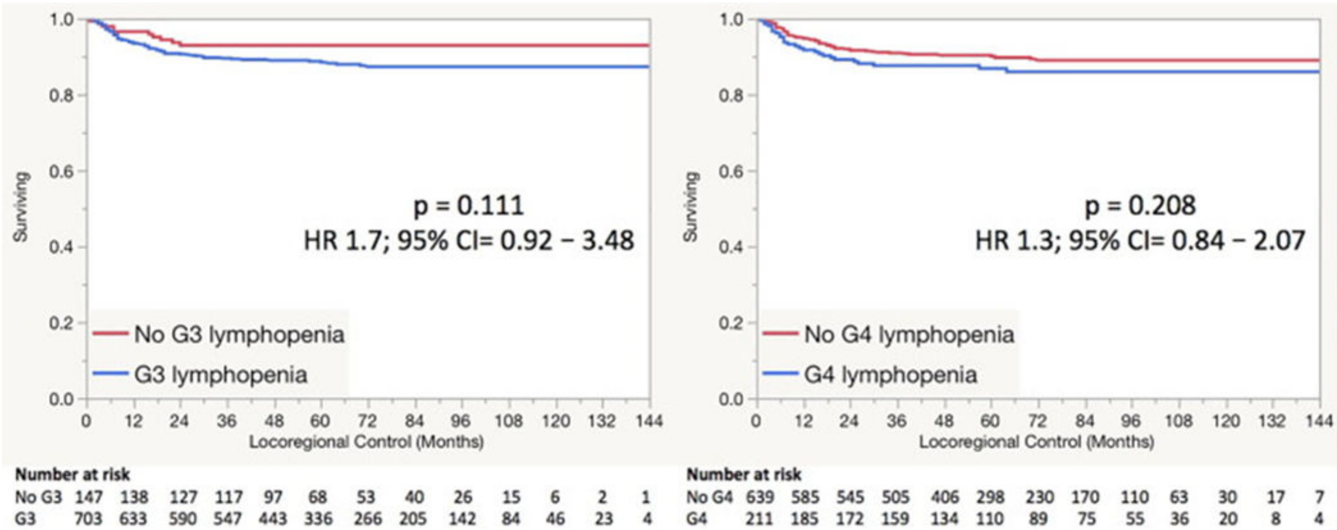

Figure 4.

Locoregional control stratified by degree of lymphopenia

G3 - Grade 3; G4 - Grade 4.

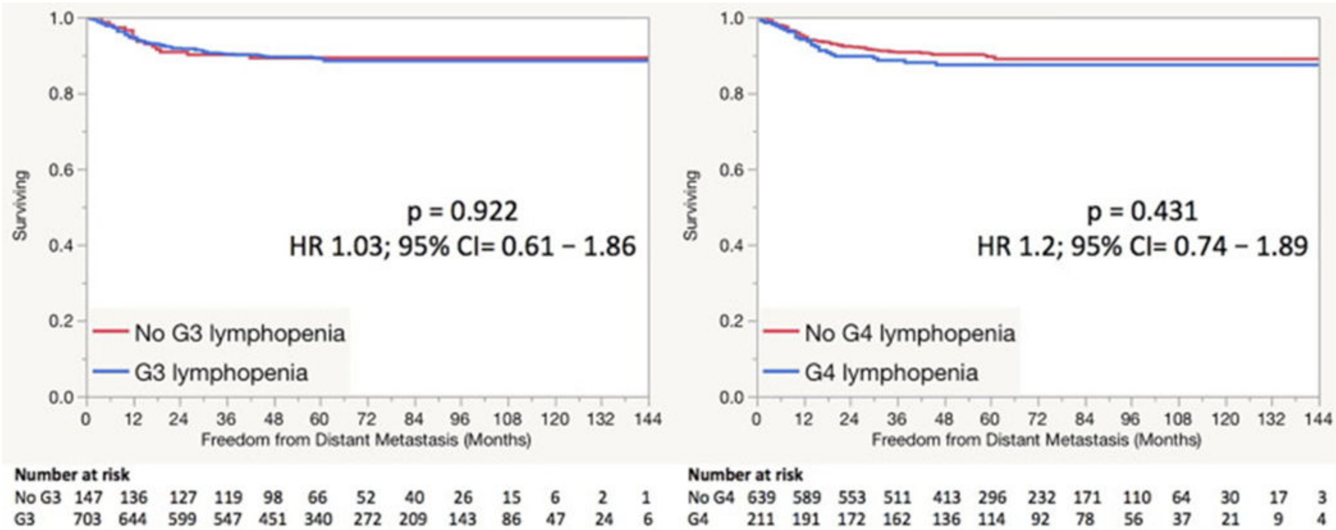

Figure 5.

Freedom from distant metastasis stratified by degree of lymphopenia

G3 - Grade 3; G4 - Grade 4.

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Table 1.

Patient, tumor and treatment characteristics.

Parameters	***N* = 850**	**%**
Age (years)	Median = 57	
	Range = 28–87	
Sex		
Male	743	87
Female	107	13
Site		
Base of tongue	465	55
Tonsil	368	43
Soft palate	10	1
Pharyngeal wall	7	1
HPV status		
Positive	604	71
Negative	71	8
Unknown	175	21
Smoking status		
Current	173	20
Former ≥10 pack years	215	25
Former <10 pack years	97	11
Never	365	43
Tumor (T) stage		
T1	156	18
T2	305	36
T3	209	25
T4	162	19
Tx	18	2
Nodal (N) stage		
N0	41	5
N1	74	8
N2a	51	6
N2b	424	50
N2c	212	25
N3	45	5
Nx	3	0.4
Overall AJCC 7th Stage		
I–II	11	1
III–IV	839	99
Induction chemotherapy		
Yes	384	45
No	466	55

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Parameters	***N* = 850**	**%**
Concurrent chemotherapy		
Yes	743	87
No	107	13
Radiation dose (Gy)	Median = 70	
	(Range = 50–74)	
Number of fractions	Median = 33	
	(Range = 28–42)	

HPV – human papillomavirus; AJCC – American Joint Committee on Cancer staging system

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Table 2.

Univariate and multivariate analyses for grade 3 and above lymphopenia and grade 4 lymphopenia.

Variables	≥G3 lymphopenia		G4 lymphopenia	
	Univariate (*p* value)	Multivariate (*p* value)	Univariate (*p* value)	Multivariate (*p* value)
Age	0.975		0.636	
Sex	0.349		0.893	
Smoking	0.512		0.335	
HPV status (positive)	0.166		0.0001	0.002 (HR 1.26; 95% CI: 1.17–1.64)
T stage (T3-T4)	0.0004	0.10	0.014	0.28
N stage	0.458		0.215	
Induction chemotherapy	0.054	0.354	0.959	
Concurrent chemotherapy (Yes)	<0.0001	<0.0001 (HR 0.46; 95% CI: 0.36–0.58)	0.0002	0.007 (HR 0.64; 95% CI: 0.45–0.87)
Radiation dose	0.007	0.883	0.0067	0.442

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Table 3.

Univariate and multivariate analyses for predictors of overall survival and freedom from recurrence.

Variables	Overall Survival		Freedom from Recurrence	
	Univariate (*p* value)	**Multivariate (*p* value)**	**Univariate (*p* value)**	**Multivariate (*p* value)**
Age	<0.0001	0.0029 (HR 1.03; 95% CI: 1.01–1.04)	0.091	0.123
Sex	0.147		0.404	
Smoking (Current smoker and Ex >10)	0.0001	0.004 (HR 1.54; 95% CI: 1.15–2.10)	0.012	0.049 (HR 1.4; 95% CI: 1.00–1.96)
HPV status (positive)	0.066	0.522	0.343	
T stage (T3-T4)	<0.0001	0.010 (HR 1.52; 95% CI: 1.10–2.10)	0.001	0.082
N stage	0.0009	0.067	0.01	0.372
Induction chemotherapy	0.231		0.101	
Concurrent chemotherapy	0.016	0.312	0.023	0.181
Lowest ALC during radiotherapy	0.570		0.124	