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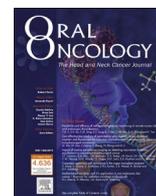
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Patterns of alcohol use among early head and neck cancer survivors: A cross-sectional survey study using the alcohol use disorders identification test (AUDIT)

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ABSTRACT

Objective: Alcohol use among survivors of head and neck cancer (HNC) negatively impacts patient outcomes and is an important risk factor for recurrent and second primary tumors. Despite recommendations from several cancer societies, alcohol consumption remains a common problem in this population.

Methods: A cross-sectional study was performed with the Alcohol Use Disorders Identification Test (AUDIT) Self-Report questionnaire. Patients with HNC completed surveys at pre-treatment and follow-up appointments every 3–6 months for at least 2-years after treatment.

Results: 796 surveys were available for analysis. Most participants were male (75.7%) and had either oropharyngeal (34.5%) or laryngeal (16.7%) cancer. The percentage of alcohol drinkers decreased from 56.1% at pre-treatment to 40.4% at 0–3 months post-treatment, but then increased and surpassed baseline levels by 24 + months post-treatment (64.4%, $p = 0.0079$). Concurrently, moderate drinkers (AUDIT = 1–3) decreased from 34.2% at pre-treatment to 25.2% at 0–3 months post-treatment, but then increased and surpassed baseline levels at 24 + months post-treatment (39.7%, $p = 0.0129$). Trends among heavy (AUDIT > 3), and heaviest (AUDIT > 6) drinkers were similar, but not statistically significant. At 24 + months post-therapy, we observed a statistically significant increase in female users (39.1% to 63.2%, $p = 0.0213$) and moderate drinkers < 55 years old (43.4% to 61.9%, $p = 0.0184$).

Conclusion: Alcohol consumption in survivors of HNC transiently decreases in the immediate months after treatment, but then increases and remains largely stable by 24 months. This pattern is particularly concerning and highlights the need for timely interventions.

Introduction

Alcohol-related cancers are a significant public health problem; in the United States, 3.5% of all cancer deaths are attributable to alcohol use.[1] Alcohol use is a risk factor for the development of head and neck cancer (HNC) in particular, including oral, pharyngeal, and laryngeal malignancies.[2,3] In fact, tobacco and alcohol use account for the development of 75% of oral cancers.[4] Research indicates that alcohol consumption has not only been linked to the development of primary HNC, but that continued alcohol use results in cancer recurrence.

Available data also show that those who continue to consume alcohol following a HNC diagnosis are at increased risk of second primary malignancies. A multicenter study including close to 100,000 HNC survivors found that about 13% of second primary tumors (SPT) were alcohol-related cancers.[5] Another multicenter study of over 4,000 individuals with HNC found that consumption of >1 drink per day increased the risk of second primary malignancies among those with laryngeal cancer (hazard ratio (HR) = 2.11, 95% CI: 1.13–3.94).[6] In a third of cancers of the upper aerodigestive tract,[7] continued consumption of alcohol post-diagnosis was associated with a 1.3 times

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greater risk of SPT. This same study found that consumption of >14 drinks per week was associated with a 50% increase in SPT risk. Aside from higher risk of SPTs, continued alcohol use among HNC survivors is linked to a number of negative outcomes, include higher risk of gastrostomy tube feeding [8] and jaw osteoradionecrosis. [9] Furthermore, continued alcohol use is associated with undesirable socioeconomic outcomes including unemployment [10] and work disability. [11] The absence of alcohol use by HNC survivors is significantly associated with better quality of life. [12,13]

The American Society of Clinical Oncology, among a number of other organizations, have called for reduction or avoidance of alcohol in HNC survivors. [14] Despite these strong recommendations, HNC survivors continue to use alcohol. A recently published extensive literature review from our institution identified few studies of alcohol use among HNC survivors in the early post-treatment setting, [15] when patients are perhaps most amenable to modifying their behavior. Moreover, the existing studies have many limitations as they are mostly international cohorts, outdated with data collection ranging from 1959 to 2006, and they group together all upper aerodigestive tract cancers without specifically focusing on HNC. Therefore, we sought to quantify alcohol use in a contemporary, representative American patient population focusing on the first 24 months after completion of treatment.

Materials and methods

Study design and participants

A cross-sectional study was conducted at a single multi-site cancer center to assess temporal changes in the prevalence and trends of alcohol use among HNC patients. The study cohort consisted of adults over 18 years who were diagnosed with HNC, including all subsites, who were scheduled to receive or had received radiation therapy (RT). A paper questionnaire was distributed to patients at the time of check-in to their radiation medicine appointment; all forms were completed and collected before the patient met with the clinician. A waiver of informed consent for medical record review was obtained from the Institutional Review Board (IRB) for this Health Insurance Portability and Accountability Act (HIPAA) compliant study.

Data collection

As part of current practice, HNC patients received standard symptom assessment surveys at each visit starting from pre-treatment until 24 + months. Data collected was divided into eight time points which included pre-intervention; four 3-month post-treatment intervals (0–3; 4–6; 7–9; 10–12); two 6-month intervals (13–18; 19–24) and 24 + months. Beginning in December 2017, the 10-item Alcohol Use Disorders Identification Test (AUDIT) [16] Self-Report questionnaire was included for all eligible patients during their consultation (pre-radiation treatment) and follow-up radiation oncology visits. [17,18]

Patient demographics such as gender, age, and clinical details (site of cancer, smoking history, and amount (packs-year)) were obtained via retrospective review of medical records. All recorded results were entered and stored with the research electronic data capture (REDCap), an internet-based electronic data capture software system. [19]

The primary outcome measures of presence and severity of alcohol use were assessed using the AUDIT. The AUDIT is a validated 10-item questionnaire which includes domains on alcohol consumption, drinking behaviors, and alcohol-related problems. Total scores range from 0 to 40, with higher scores indicating greater alcohol use severity. Modified total AUDIT score cut-offs were categorized into quartiles (scores 0, 1–3, 4–6, and > 6). Patients were categorized in the lowest category (non-drinkers) if they reported never drinking at that moment, followed by moderate, heavy and heaviest users. These modifications were based on past criteria [20,21] and deemed suitable for a population with lower than average alcohol consumption.

Table 1
Characteristics of Study Participants (N = 608).

Characteristics	n (%)
Age (median [range])	64 [24–95]
Age Group	
<55	113 (18.6)
55–64	201 (33.1)
65–74	179 (29.4)
>75	115 (18.9)
Gender	
Male	460 (75.7)
Female	148 (24.3)
Primary site	
Oropharynx	210 (34.5)
Larynx	102 (16.7)
Oral Cavity	87 (14.3)
Salivary Gland	44 (7.2)
Neck/Nodal	35 (5.8)
Sinonasal	28 (4.6)
Skin	25 (4.1)
Nasopharynx	22 (3.6)
Hypopharynx	17 (2.8)
Cervical esophagus	14 (2.3)
Pharynx, overlapping	7 (1.1)
Other H & N site	8 (1.3)
Unknown	12 (2.0)
Treatment Received	
Radiation only	125 (20.6)
Radiation + Chemotherapy	271 (44.6)
Radiation + Surgery	121 (19.9)
Radiation + Chemotherapy + Surgery	91 (14.9)
Time period	
Pre-treatment	164 (27.0)
Follow up treatment (months)	
0–3	151 (24.8)
4–6	109 (17.9)
7–9	73 (12.0)
10–12	65 (10.7)
13–18	72 (11.8)
19–24	89 (14.6)
24+	73 (12.0)

Statistical analysis

This study utilized descriptive analyses to compare alcohol use across time. Analyses were restricted to patients who had complete AUDIT surveys. In accordance with statistical guidelines, incomplete surveys were excluded if >10% of data was missing. [22]

Continuous variables were summarized as mean with standard deviation (SD) or median with range according to the normality of distribution. Frequency (percentage) was used for categorical data. Cochran-Armitage trend test was used to assess changes in the proportions of severity over time, and Fisher exact or Pearson χ^2 analyses were used when appropriate. The Cochran-Armitage trend test was also used to analyze whether there were variations in the trends for alcohol use in age- and gender- stratified groups. All statistical tests were two-sided with statistical significance defined as a p-value < 0.05. All statistical analyses were analyzed with GraphPad Prism 8 (GraphPad Software, San Diego, CA).

Results

From December 2017 until February 2019, a total of 1,754 surveys were distributed among eligible patients. Approximately 888 were returned (50.6% response rate) from two separate hospital-based outpatient radiation oncology clinics. Of these, 796 surveys completed by 608 patients were eligible for analysis.

Survey respondents' demographic and clinical characteristics are presented in Table 1. Approximately 460 (75.7%) of the participating

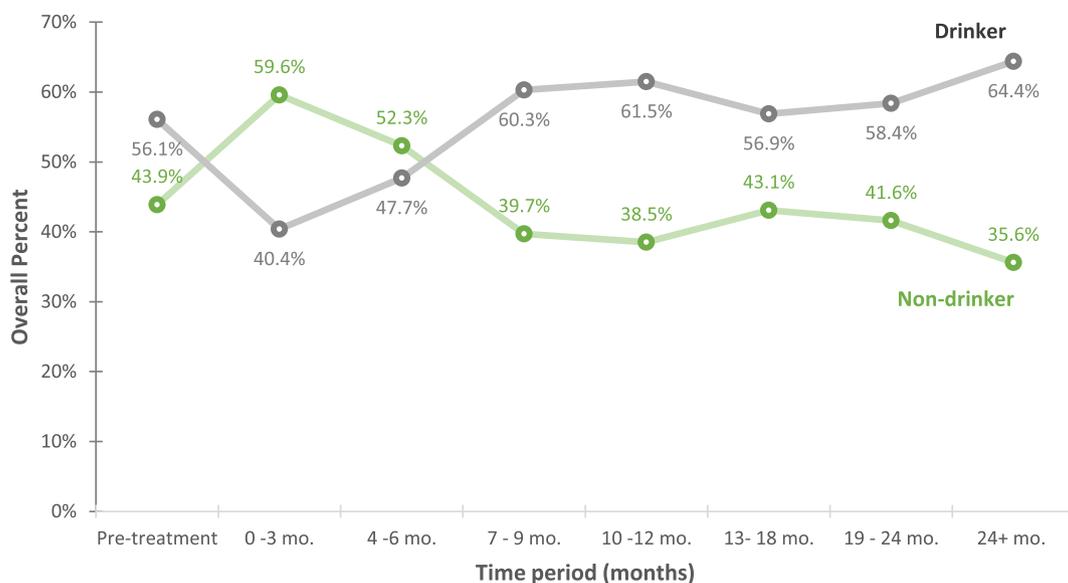


Fig. 1A. Temporal trends in alcohol use among HNC survivors (pre-treatment – 24 + months) comparing Non-drinker (AUDIT = 0) (green) and drinker (AUDIT > 0) (gray). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

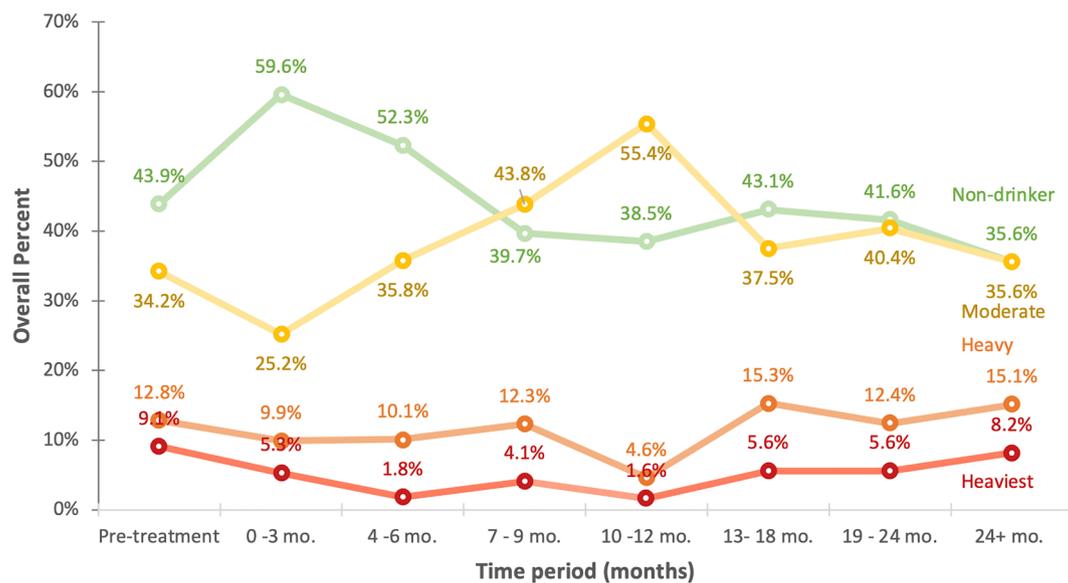


Fig. 1B. Temporal trends in alcohol use comparing AUDIT categories. Non-drinker (AUDIT = 0); Moderate (AUDIT = 1 – 3), Heavy (AUDIT = 4 –6); Heaviest (AUDIT > 6) drinkers. Note. Cochran-Armitage χ^2 test for trend: non-drinkers ($p = 0.0079$); moderate drinkers ($p = 0.0129$); heavy drinkers ($p = 0.5254$); heaviest drinkers ($p = 0.6225$).

patients were male, with a median age of 64 years (range: 24.0 – 95.0). Most patients had either cancer of the oropharynx (34.5%), larynx (16.7%) or oral cavity (14.3%).

Temporal trends of alcohol use are shown in Figure 1. At pre-treatment, 56.1% (n = 92) of participants were drinkers, which decreased to 40.4% (n = 61) at 0–3 months post-treatment. During the subsequent months, the percentage of drinkers increased and surpassed baseline by 24 + months post-treatment (64.4%, n = 47). Overall, the proportion of drinkers showed a statistically significant increase from pre-treatment to 24 + months ($p = 0.0079$). Fig. 1B illustrates the temporal changes in drinking for specific AUDIT categories. All three groups demonstrated declining proportions in the immediate months after treatment, but then increased and were close to or had surpassed baseline levels by 24 + months. Moderate drinkers had increased from 34.2% (n = 56) at pre-treatment to 35.6% (n = 26) at 24 + months ($p = 0.0129$). The overall changes for heavy and heaviest drinkers were not

significant ($p = 0.5254$ and $p = 0.6225$, respectively).

Comparing participants by gender (Appendix A) revealed males were more likely to report alcohol use than females, n = 350 (81.6%) vs n = 79 (18.4%) ($p = 0.02$). When focusing on only females (N = 79), the proportion of nondrinkers fell over time. Specifically, there was a decrease from 60.9% (N = 28) at pre-treatment to 36.8% (N = 7) at 24 + months ($p = 0.0213$). With regards to age, the proportion of alcohol users significantly declined with age over time ($p = 0.0001$) (Appendix B). Alcohol use was highest among participants <55 years old and decreased to 37.6% by 75 + years. Among moderate users <55 years old, alcohol use significantly increased from 43.4% (N = 10) at pre-treatment to 58.8% (N = 10) at 24 + months ($p = 0.0184$). Finally, there were some associations between the type of treatment received and alcohol use patterns in this sample; there was an increase in the proportion of moderate users in the radiation + surgery group ($p = 0.002$), as well as in the radiation + chemotherapy + surgery group ($p =$

0.0011) (Appendix C). No other substantial trends in moderate, heavy or heaviest alcohol use over time were noted.

Discussion

This cross-sectional study of over 600 patients was designed to quantify alcohol use within 2-years following completion of radiation therapy for head and neck cancer. The following results are noteworthy: First, a majority of patients (56.1%) used alcohol at the time of treatment initiation, indicating that alcohol use continues to be a common practice after diagnosis with head and neck malignancies. Second, while most individuals (59.6%) reported no alcohol use in the immediate post-treatment period of 0–3 months, the percentage of drinkers increased above pre-treatment levels by 1-year post-treatment (61.5%). The initial decline in alcohol use was transient as more and more patients resumed alcohol consumption. This U-shaped pattern was similar regardless of baseline consumption level (i.e., for moderate, heavy, and heaviest use) and was largely sustained through the end of the study period at 24 + months despite varying fluctuations. The increase in post-treatment alcohol use was especially notable in female patients and moderate users < 55 years of age, the reasons for which are unknown at this time.

The reported alcohol use levels among our cancer population are similar to those reported by other investigators. For example, Potash *et al* reported that 12 months after diagnosis, 44.5% of survivors of HNC were still drinking, 21.4% of whom were heavy users, as assessed with the MAST questionnaire.[23] A similar U-shaped pattern of alcohol consumption was found in a large sample (N = 973) of patients with HNC from the United Kingdom.[24] Baseline alcohol consumption was at 54%, 35% at 4-months post-diagnosis, and 41% at 12-months post-diagnosis, confirming the temporal pattern of decline and then rise in consumption found in the present investigation.

Survivors of head and neck cancer should be discouraged from any alcohol use post-treatment, and these consumption levels are particularly concerning, highlighting the need for timely intervention. Our data, and that of other investigators, suggests that the time period of 3–4 most post-treatment, prior to the documented rise in alcohol consumption, may be an important interval to target alcohol cessation interventions, with the goal of avoiding a return to baseline drinking levels. These efforts should complement pre-treatment interventions as patients may be even more receptive before the onset of treatment. Future studies should prospectively compare the different time periods of the care continuum to identify the most effective period to target alcohol cessation.

Our study finds that the proportion of patients who reach or surpass baseline levels of alcohol consumption stays relatively stable by 2 years post-treatment. This stability in long-term alcohol consumption has

been confirmed in a small sample of 165 survivors of HNC in Germany who were surveyed 5 years post-diagnosis.[25] Sixty-two percent of survivors considered themselves current drinkers, 26% of whom consumed alcohol at least 4 times per week. Overall, only 13% of all patients became abstinent, suggesting that the likelihood of unaided alcohol cessation is very low after treatment for HNC. Similar prevalence of long-term alcohol use after 5 years were found by other reports.[26]

The rationale underlying these trends in alcohol use is currently unknown. The fact that patients continued to drink despite the strong deterrent of a cancer diagnosis and its subsequent treatment suggests that the reasons are complex and multifaceted. A lack of knowledge may play a role; studies suggest that HNC survivors are often unaware of the relationship between alcohol and HNC, and do not receive adequate information from their providers about the impact of alcohol on their disease course. In one study, between 15 and 50% of those surveyed did not recall having received any recommendation regarding alcohol consumption.[27] Education about, and raising awareness of, the risks of alcohol consumption among HNC survivors is a necessary first step to achieve alcohol reduction and cessation. One study, using an educational pamphlet, showed that knowledge of alcohol abuse as a risk factor for cancer increased from 15% to 27% from pre- to post-reading.[28] Further, it is possible that alcohol use may have increased post-treatment as a method of self-guided analgesia as pain from the primary malignancy and side effects of treatment is highly prevalent in HNC survivors.[29] However, anecdotally, the study authors did not observe this pattern in their clinics. Future analyses should investigate the reasons for continued alcohol use in HNC survivors.

Few publications have aimed to reduce alcohol use specifically in the HNC population. One study consisting of a tailored smoking, alcohol, and depression nurse-administered intervention of cognitive behavioral therapy and medications, found that alcohol consumption decreased overall, but the number of problem drinkers did not change.[30] A randomized controlled trial of 105 individuals with HNC, focused on tobacco cessation, showed that participants smoked less, but consumed more alcohol.[31] Survivors may have substituted alcohol for tobacco.

There are several limitations of this study. Our data relies on recall and self-report which might introduce biases. However, self-report tools with adequately designed questions, such as the AUDIT questionnaire, have been shown to be appropriate methods to measure alcohol use in adult HNC populations.[15] Identification of objective biomarkers to complement these subjective measures would be helpful in future studies. Non-reporting bias may have been introduced by the suboptimal response rate of 50% for the AUDIT questionnaire, which likely resulted from variable survey uptake among the physician practices. However, we do not believe there was a systematic bias in regard to survey responding based on alcohol consumption levels. A second limitation is

Table A1

Alcohol use percentage categorized by severity (nondrinker, moderate, heavy and heaviest use) and **gender** across time.

	Pre-treatment	Post-treatment (months)							p-value
		0–3	4–6	7–9	10–12	13–18	19–24	24+	
N (total)	164	151	109	73	65	73	89	72	
Total Female	46 (28.0)	29 (19.2)	20 (18.3)	15 (20.5)	14 (21.5)	14 (19.2)	14 (15.7)	19 (26.4)	
Non-drinkers (0)									
Female	28 (60.9)	18 (62.1)	12 (60.0)	10 (66.7)	5 (35.7)	4 (28.6)	8 (57.1)	7 (36.8)	0.0213 †
Male	44 (37.3)	72 (59.0)	45 (50.6)	19 (33.3)	19 (37.3)	27 (45.8)	29 (38.9)	19 (35.8)	0.0894
Moderate (1–3)									
Female	10 (21.7)	9 (31.0)	7 (35.0)	4 (26.7)	8 (57.1)	8 (57.1)	3 (21.4)	8 (42.1)	0.0583
Male	46 (39.0)	29 (23.8)	32 (36.0)	27 (47.4)	28 (54.9)	19 (32.2)	33 (44.0)	21 (39.6)	0.0699
Heavy (4–6)									
Female	4 (8.7)	2 (6.9)	1 (5.0)	1 (6.7)	1 (7.1)	2 (14.3)	2 (14.3)	4 (21.1)	0.1053
Male	17 (14.4)	13 (10.7)	10 (11.2)	8 (14.0)	2 (3.9)	9 (15.3)	9 (12.0)	7 (13.2)	0.9055
Heaviest (>6)									
Female	4 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.1)	0 (0)	0.1737
Male	11 (9.3)	8 (6.6)	2 (2.2)	3 (5.3)	2 (3.9)	4 (6.8)	4 (5.3)	6 (11.3)	0.9893

Table B1

Alcohol use percentage categorized by severity (nondrinker, moderate and heavy use) and age groups across time.

	Pre-treatment	Post-treatment (months)							p-value
		0–3	4–6	7–9	10–12	13–18	19–24	24+	
Non-drinkers (0)									
<55	6 (26.1)	13 (56.5)	9 (45.0)	3 (23.1)	1 (11.1)	4 (26.7)	4 (19.0)	5 (29.4)	0.0864
56–64	21 (40.4)	26 (49.1)	14 (41.2)	11 (40.7)	9 (37.5)	14 (48.3)	17 (51.5)	6 (27.3)	0.7794
65–74	18 (38.3)	33 (66.0)	19 (55.9)	12 (50.0)	7 (38.9)	6 (33.3)	8 (38.1)	11 (42.3)	0.1529
≥75	27 (64.3)	18 (72.0)	15 (71.4)	3 (33.3)	7 (50.0)	7 (63.6)	8 (57.1)	4 (57.1)	0.2751
Moderate (1–3)									
<55	10 (43.4)	4 (17.4)	8 (40.0)	5 (38.5)	6 (66.7)	5 (33.3)	13 (61.9)	10 (58.8)	0.0184 †
56–64	18 (34.6)	16 (30.2)	18 (52.9)	14 (51.9)	14 (58.3)	10 (34.5)	10 (30.3)	8 (36.4)	0.8890
65–74	18 (38.3)	13 (26.0)	10 (29.4)	9 (37.5)	10 (55.6)	9 (50.0)	9 (42.9)	8 (30.8)	0.3477
≥75	10 (23.8)	5 (20.0)	3 (14.3)	4 (44.4)	6 (42.9)	3 (27.3)	4 (28.6)	3 (42.9)	0.1519
Heavy (>3)									
<55	7 (30.4)	6 (26.1)	3 (15.0)	5 (38.5)	2 (22.2)	6 (40.0)	4 (19.1)	2 (11.8)	0.3934
56–64	13 (25.0)	11 (20.8)	2 (5.9)	2 (7.4)	1 (4.2)	5 (17.2)	6 (18.2)	8 (36.4)	0.8529
65–74	11 (23.4)	4 (8.0)	5 (14.7)	3 (12.5)	1 (5.6)	3 (16.7)	4 (19.0)	7 (26.9)	0.4730
≥75	5 (11.9)	2 (8.0)	3 (14.3)	2 (22.2)	1 (7.1)	1 (9.1)	2 (14.3)	0 (0)	0.7419

Table C1

Alcohol use percentage categorized by severity (nondrinker, moderate and heavy use) and treatment received across time.

	Pre-treatment	Post-treatment (months)							p-value
		0–3	4–6	7–9	10–12	13–18	19–24	24+	
Non-drinkers (0)									
<i>Rad only</i>	25 (54.3)	25 (96.1)	12 (63.2)	3 (33.3)	5 (50.0)	4 (57.1)	7 (46.7)	2 (25.0)	0.0223 †
<i>Rad + Chemo</i>	21 (32.3)	66 (89.2)	26 (53.1)	12 (42.9)	13 (48.1)	17 (42.5)	20 (43.5)	17 (39.5)	0.0123 †
<i>Rad + Surgery</i>	21 (53.8)	25 (89.3)	9 (47.4)	7 (46.7)	2 (18.2)	3 (33.3)	4 (36.4)	4 (26.7)	0.0005 ††
<i>Rad + Chemo + Surgery</i>	8 (61.5)	19 (82.6)	10 (45.5)	7 (33.3)	5 (27.8)	8 (42.1)	5 (35.7)	4 (30.8)	0.0017 ††
Moderate (1–3)									
<i>Rad only</i>	16 (34.8)	1 (3.8)	6 (31.6)	5 (55.6)	4 (40.0)	3 (42.9)	5 (33.3)	2 (25.0)	0.4595
<i>Rad + Chemo</i>	25 (38.5)	6 (8.1)	17 (34.7)	12 (42.9)	11 (40.7)	12 (30.0)	17 (37.0)	14 (32.6)	0.1623
<i>Rad + Surgery</i>	11 (28.2)	2 (7.1)	8 (42.1)	5 (33.3)	9 (81.8)	4 (44.4)	5 (45.5)	10 (66.7)	0.0002 ††
<i>Rad + Chemo + Surgery</i>	2 (15.4)	4 (17.4)	8 (36.4)	10 (47.6)	12 (66.7)	9 (47.4)	9 (64.3)	6 (46.2)	0.0011 ††
Heavy (4–6)									
<i>Rad only</i>	4 (8.7)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)	2 (13.3)	0 (0)	0.9189
<i>Rad + Chemo</i>	12 (18.5)	2 (2.7)	5 (10.2)	3 (10.7)	2 (7.4)	8 (40.0)	6 (13.0)	9 (20.9)	0.1275
<i>Rad + Surgery</i>	3 (7.7)	1 (3.6)	2 (10.5)	2 (13.3)	0 (0)	2 (22.2)	2 (18.2)	1 (6.7)	0.3807
<i>Rad + Chemo + Surgery</i>	2 (15.4)	0 (0)	4 (18.2)	3 (14.3)	1 (5.6)	1 (5.3)	1 (7.1)	3 (23.1)	0.6541
Heaviest (>6)									
<i>Rad only</i>	1 (2.2)	0 (0)	1 (5.3)	0 (0)	1 (10.0)	0 (0)	1 (6.7)	4 (50.0)	0.0005 ††
<i>Rad + Chemo</i>	8 (12.3)	0 (0)	1 (2.0)	1 (3.6)	1 (3.7)	3 (7.5)	3 (6.5)	3 (7.0)	0.8761
<i>Rad + Surgery</i>	4 (10.3)	0 (0)	0 (0)	1 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)	0.0662
<i>Rad + Chemo + Surgery</i>	1 (7.7)	0 (0)	0 (0)	1 (4.8)	0 (0)	1 (5.3)	1 (7.1)	0 (0)	0.8491

Abbreviation: Rad: Radiation treatment; Chemo: Chemotherapy.

† represents $p > 0.05$.†† represents $p > 0.01$.

the cross-sectional nature of our assessment. The large majority of patients were interviewed once at a particular point in time of their survivorship trajectory. Thus, the patterns of alcohol consumption and cessation reported herein are not based on longitudinal data, collected from the same cohort of patients. Further, since most patients in this study had primary tumors of the oropharynx, larynx, and oral cavity, the results may not be as applicable to other subsites of the head and neck, such as salivary gland, nasopharynx, and paranasal sinuses. There was also limited information on the types of alcohol drinks consumed since the AUDIT questionnaire does not include this item.

Conclusion

Alcohol consumption in survivors of HNC can be characterized by a U-shape curve, demonstrating that consumption transiently decreases in the immediate months after treatment, but then increases and remains largely stable by 24 months. This pattern of post-treatment alcohol use is particularly concerning and highlights the need for timely interventions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A

See [Table A1](#)

Appendix B

See Table B1

Appendix C

See Table C1

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