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Association of Preoperative Depression and Clinical Outcomes After Head and Neck Free Flap Reconstruction

Sindhura Sridhar, BS[1], Daniel P. Larson, BS[2], Brooke B. Swain, BS[2], Heezy Suh, BA[2], Daniel R. S. Habib, BA[2], Kelly Vittetoe, MD[1], Donald Sengstack, MS[3], Michael C. Topf, MD, MSCI[1], and Melanie D. Hicks, MD[1]

Abstract

Objective. Comorbid depression is a significant negative predictor of survival in patients with head and neck cancer (HNC). Prior studies have shown a prevalence of up to 40.1%; however, depression is often underdiagnosed in this patient population.

Study Design. Retrospective cohort.

Setting. Single-institution database.

Methods. Patients who underwent free flap reconstruction for HNC at our institution (January 2019-December 2023) were retrospectively reviewed. The primary outcome was overall survival (OS). Secondary outcomes included length of stay, discharge disposition, 30-day readmissions, and post-operative radiotherapy (PORT) delay. Kaplan-Meier and multivariate Cox proportional hazards models estimated the effect of preoperative depression on OS. Multivariate regression models examined the association of preoperative depression with secondary outcomes.

Results. 645 patients were included. Preoperative depression was present in 158 patients (24%) and 150 patients (23%) were on preoperative antidepressants. There was no difference in OS in depressed patients compared to nondepressed patients (adjusted hazard ratio [aHR] 1.07, 95% confidence interval [CI] 0.76-1.51). Preoperative antidepressant use was independently associated with discharge to rehabilitation or skilled nursing facilities compared to discharge home (adjusted odds ratio [aOR] 1.82, 95% CI 1.07-3.06). There were no associations of preoperative depression with length of stay, 30-day readmission rates, or PORT delay.

Conclusion. Preoperative antidepressant use is associated with greater likelihood of discharge to rehabilitation facilities after free flap reconstruction. Preoperative depression was present at one-half the estimated rate in our patients, highlighting the need for improved preoperative screening and intervention.

Keywords

depression, free flap, head and neck cancer, mental health

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Head and neck cancer (HNC) can be a physically and psychologically debilitating disease, with treatment often including extensive surgical resection with free flap reconstruction. While surgical advances have improved functional and aesthetic outcomes, the psychosocial burden on patients remains underexamined. Patients who require free flap reconstruction often have advanced-stage disease that results in higher postoperative morbidity.

Patients with HNC are disproportionately affected by depression, with a recent cohort study using population-level data showing a prevalence of 40.1% of depression in HNC patients compared to 22.3% in other cancers[1] yet frequently goes undiagnosed. A recent study of patients with HNC undergoing free flap reconstruction found that up to 22% had unrecognized depression or anxiety at the time of surgery, despite preoperative screening using validated instruments such as the PHQ-9.[2]

In the broader cancer population, depression has been associated with worse overall survival (OS), due to both biological factors, such as increased systemic

[1]Department of Otolaryngology—Head and Neck Surgery, Vanderbilt University Medical Center, Nasvhille, Tennessee, USA
[2]Vanderbilt University School of Medicine, Nasvhille, Tennessee, USA
[3]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nasvhille, Tennessee, USA

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Corresponding Author:
Michael C. Topf, MD, MSCI, Department of Otolaryngology–Head and Neck Surgery, Vanderbilt University Medical Center.
Email: Michael.topf@vumc.org

inflammation, and behavioral factors, such as worse adherence to treatment.[1,3] Depression has also been linked to longer hospital stays and perioperative complications such as delirium.[1,4] In the postoperative period, patients with depression are frequently found to have significantly worse psychological distress and decreased quality of life.[5,6] However, the data specific to HNC and free flap patients are sparse.

To investigate these gaps, we conducted a retrospective review of patients undergoing free flap reconstruction for HNC at a tertiary academic center. We assessed whether preoperative depression and antidepressant use were associated with survival and other clinical predictors of patient prognosis. Although there is data showing that preoperative psychiatric conditions in HNC patients lead to suboptimal recovery and rehabilitation,[7] few studies have examined their effect on critical clinical endpoints. Furthermore, there is a high level of heterogeneity in the literature with regard to how depression is defined and identified.

Methods

This study was approved by the Vanderbilt University Medical Center Institutional Review Board (#241879). A retrospective review of patients who underwent free flap reconstruction for HNC at our institution between January 01, 2019 and December 31, 2023 was conducted. Patients were identified using Current Procedural Terminology (CPT) codes for free flap reconstruction (20955, 15733, 15757, 20969, 15739, 15756, 15756HN, 15758, 15758H and neck dissection or exploration (38724, 35701, 31390, 31365, 31395, 38720, 41155, 42426, 41153, 41150, 21047, 38700); patients with at least 1 free flap code and 1 neck dissection code were included in the study. Patients who underwent free flap reconstruction for oncologic tumor resection or related indications (osteo- or soft tissue radionecrosis, afunctional larynx, etc.) were included. Patients who underwent free flap reconstruction for non-HNC or non-oncologic reasons, or who did not undergo free flap reconstruction were excluded.

Patient demographic data, comorbidities, oncologic history, preoperative and postoperative psychiatric diagnoses and medication use, surgical details, postoperative adjuvant treatment, and clinical outcomes including length of stay, discharge disposition, and 30-day readmission, and date of last known follow up or date of death were collected. Depression and anxiety diagnoses were identified in the medical record using International Classification of Diseases (ICD)-9 and -10 codes for depression (ICD-10 codes: F32.A, F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.8, F32.89, F32.9, F33.0, F33.1, F33.2, F33.3, F33.4, F33.41, F33.42, F33.8, F33.9, F43.23; ICD-9 codes: 296.20, 296.22, 296.23, 296.24, 296.30, 296.32, 296.33, 296.34, 309.0, 309.1, 309.28, 311) and anxiety (ICD-10 codes: F41.0, F41.1, F41.8, F41.9, F43.22, F43.23; ICD-9 codes: 300.00, 300.01, 300.02, 300.09, 309.24, 309.28). Patients were classified as having preoperative depression if an ICD-9 or -10 code for depression was present in the medical record between the date of diagnosis and prior to the date of surgery. Preoperative antidepressant use was classified as use of a selective serotonin reuptake inhibitor (SSRI), Serotonin-Norepinephrine Reuptake Inhibitor (SNRI), monoamine oxidase inhibitor (MAO-I), tricyclic antidepressant (TCA), atypical antidepressant, or other medication indicated to treat depression (including atypical antipsychotics and lithium) after the date of diagnosis and prior to the date of surgery.

All statistical analysis was performed using R (R version 4.5.0, https://www.r-project.org/). The primary outcome was OS. Secondary outcomes included length of hospital stay, discharge destination (home vs rehabilitation facility or skilled nursing facility), 30-day readmission, and post-operative radiotherapy (PORT) delay (in patients who received adjuvant radiotherapy), defined as date of first radiation treatment greater than 6 weeks after the date of surgery. The cohort was further delineated by indication for surgery: primary resection, salvage surgery, or other oncologic-related reason (osteoradionecrosis, afunctional larynx, etc.). Comorbidities in the preoperative depression/antidepressant use cohorts were compared using Chi-squared analysis or Fisher's exact analyses when expected counts were less than 5. The effect of preoperative depression and antidepressant use on OS was assessed for each cohort subset using Kaplan-Meier analysis and corresponding multivariate Cox proportional hazards models controlling for age, sex, and Charlson comorbidity index (CCI). American Joint Committee on Cancer (AJCC) 8th edition pathological tumor staging and adjuvant radiation were included as covariates in survival analyses for the primary resection subset. Multivariate linear and logistic regression models were used to examine the association of preoperative depression with secondary outcomes.

Results

Demographics

Six hundred forty-five patients were included in the study. The cohort had a mean age of 64.0 years (median 65, range 14-101) and included 477 males (69%). 389 patients (60%) underwent surgery for primary treatment of their malignancy, 208 (32%) underwent salvage surgery, and 48 (8%) underwent free flap reconstruction for other oncologic-related reasons. Patients underwent a variety of free flap procedures, including 325 (50%) radial forearm free flaps, 123 (19%) osteocutaneous radial forearm free flaps, 114 (18%) anterolateral thigh free flaps, 34 (5%) fibula free flaps, 24 (4%) osteocutaneous scapular free flaps, 18 (3%) latissimus dorsi free flaps, and 11 (2%) other flap types. Three hundred seventy-two patients (58%) had T3 or T4 disease, and 200 patients (31%) had nodal metastasis. Two hundred one patients

(31%) underwent preoperative (chemo)radiation, and 227 patients (35%) received adjuvant radiation. Complete demographic and clinical characteristics of the cohort are displayed in **Table 1**.

Prevalence of Psychiatric Diagnoses and Medication Usage

Preoperative depression was identified in 158 patients (24%) and preoperative anxiety was identified in 160 patients (25%), identified using the ICD-9 and -10 codes for depression and anxiety described in the Methods (**Table 2**). One hundred fifty patients (23%) were on an antidepressant medication preoperatively, including 90 (14%) on an SSRI, 30 (5%) on an SNRI, 13 (2%) on a TCA, 28 (4%) on an atypical antidepressant, 17 (3%) on an atypical antipsychotic, and 2 (0.3%) on lithium. Psychiatric services were consulted for 32 patients (5%) during their hospital stay. One hundred twenty-nine patients (20%) were prescribed an SSRI or SNRI during their hospital stay, including 12 who were not previously on antidepressants.

Table 1. Demographics of Overall Cohort

Characteristic	N (%)
Age (mean [±SD])	64.0 (11.8)
Sex	
Female	198 (31)
Male	477 (69)
Race	
White	591 (92)
Hispanic	1 (0)
Black	34 (5)
Asian	4 (0)
Other	9 (1)
CCI (mean [±SD])	5.0 (2.5)
Indication for surgery	
Primary resection	389 (60)
Salvage surgery	208 (32)
Other	48 (8)
ORN/Mandibular reconstruction	22 (3)
Fistula repair	6 (1)
Afunctional larynx	3 (0)
Pharyngeal reconstruction	5 (1)
Wound dehiscence/plate exposure	1 (0)
Flap type	
RFFF	325 (50)
OCRFFF	123 (19)
ALTFF	114 (18)
FFF	34 (5)
Scapula	24 (4)
Latissimus	18 (3)
Other	11 (2)
Pathological T stage (pT)	
1	29 (4)
2	67 (10)
3	110 (17)
4	262 (41)
Pathological N stage (pN)	
0	245 (38)
1	56 (9)
2	65 (10)
3	79 (12)
Adjuvant treatment	
Chemotherapy	135 (21)
Radiation	227 (35)

Comorbidities in Depressed Versus Nondepressed Patients

Prior to evaluating clinical outcomes, a comparison of comorbidities in the patient cohorts with and without preoperative depression and antidepressant use was performed (Supplemental Table S1, available online). In both the preoperative depression and antidepressant use cohorts, there was a significantly greater proportion of patients with congestive heart failure (CHF), dementia, chronic obstructive pulmonary disease (COPD), moderate-to-severe liver disease, and diabetes mellitus (DM). In the antidepressant use cohort, there was also a greater proportion of patients with a prior cerebrovascular accident (CVA). There was no significant difference in obesity (defined as BMI $\geq$ 30), mild liver disease, complicated DM, or chronic kidney disease (CKD).

Survival and Clinical Outcomes

Median OS was 494 days (range 0-2252). There was no difference in OS between patients with and without

Table 2. Psychiatric Characteristics of Overall Cohort

Characteristic	N (%)
Depression	223 (35)
Anxiety	214 (33)
Preoperative depression	158 (25)
Preoperative anxiety	150 (23)
Preoperative antidepressant use	
SSRI	90 (14)
SNRI	30 (5)
MAO Inhibitor	0 (0)
Tricyclic antidepressant	13 (2)
Atypical antidepressant	28 (4)
Lithium	2 (0)
Quetiapine	13 (2)
Aripiprazole	4 (0)
Psychiatric consult while inpatient	21 (3)
Antidepressant prescribed while inpatient	
SSRI	94 (15)
SNRI	35 (5)

preoperative depression/antidepressant use (median OS 489.5 days vs 494 days, adjusted hazard ratio [aHR] 1.07, 95% confidence interval [CI] 0.76-1.51), regardless of indication for surgery (**Figure 1**, **Table 3**).

Median length of stay (LOS) was 6 days (range 0-75). There was no difference in LOS between patients with and without preoperative depression/antidepressant use (median 6 vs 6 days, coefficient 0.46, 95% CI −0.54-1.47) (**Table 4**). Most patients were discharged to home/self-care (317 patients, 49%) or home-health services (227 patients, 35%). Other discharge destinations included skilled nursing facilities, rehabilitation facilities, and long-term care. Patients with preoperative depression/antidepressant use were more likely to be discharged to a skilled nursing or rehab facility compared to discharge home (adjusted odds ratio [aOR] 1.82, 95% CI 1.07-3.06). A supplemental table has been included with complete univariate and multivariate regression analysis for all collected covariates for discharge disposition (Supplemental Table S2, available online). One hundred eleven patients (17%) were readmitted within 30 days of discharge. There were no associations of preoperative depression/antidepressant use with 30-day readmission rates.

Two hundred twenty-seven patients (35%) received adjuvant radiation, of whom 157 (69%) had PORT delay. Patients with preoperative depression/antidepressant use had decreased likelihood of PORT delay (aOR 0.48, 95% CI 0.23-0.99). In patients with preoperative depression who received adjuvant radiation, there was no association of PORT delay with treated versus untreated depression (aOR 1.03, 95% CI 0.26-3.69).

Discussion

Patients with HNC are at increased risk of comorbid depression,[1] but the effects of depression on clinical outcomes are understudied. In this single-institution retrospective cohort study, we investigated the association of preoperative depression with survival (OS) and key clinical outcomes including length of stay, discharge location, 30-day readmissions, and PORT delay in patients who underwent free flap reconstruction for HNC. Preoperative depression was present in 24% of our cohort. Patients with preoperative depression and/or antidepressant use were more likely to have certain medical comorbidities, including CHF, dementia, COPD, moderate-to-severe liver disease, and DM. Contrary to some recent publications,[8-11] our results showed that preoperative depression and antidepressant use is not associated with survival, length of stay, and 30-day readmissions. We found that depression was associated with increased likelihood of discharge to rehabilitation or skilled nursing facilities. In addition, in patients who received adjuvant radiation, depression was interestingly associated with decreased PORT delay.

Although the comorbidity of mental health disorders in HNC patients is well-known, it is difficult to capture and study together in this population due to the variability in how depression is identified. In prior literature investigating the effects of depression on survival in HNC patients, depression is variably defined. Prospective studies implement a variety of screening measures, including the patient health questionnaire-9 (PHQ-9), Hamilton depression rating scale (HDRS), Beck Depression Inventory (BDI), Center for Epidemiological Studies—Disease (CES-D), and the Hospital Anxiety and Depression Scale (HAS).[8-10,12] Retrospective studies have primarily used ICD-9, ICD-10, Current Procedural Terminology (CPT), and other predefined codes to identify depression,[11,13,14] each using a variable set of codes to encapsulate depression within this group. The rates of depression in these published studies range from 8.9% to 25.4%,[11,13-15] much lower than the reported 40% in larger scale studies on HNC patients.[1-9] In our cohort, 31% (200 patients) had either a preoperative depression diagnosis or used antidepressants preoperatively. These values are likely still an underestimation of the true prevalence in this patient population given the retrospective nature of the study and the reliance of adequate diagnosis coding in patient charts.

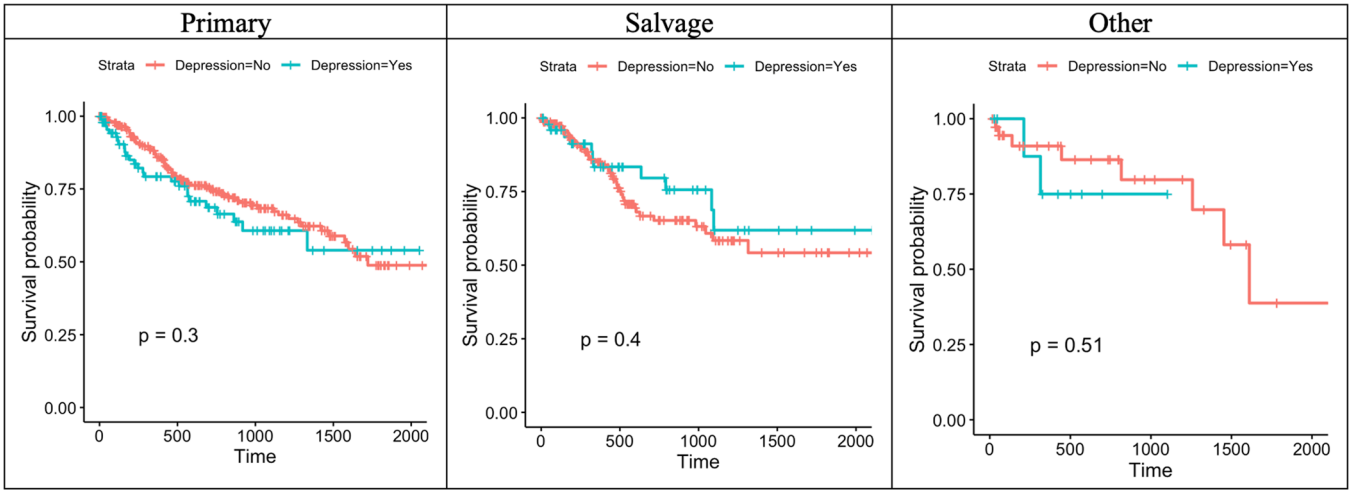

Figure 1. Kaplan-Meier curves for overall survival of patients with and without preoperative depression.

Table 3. Cox Proportional Hazards Regression for Overall Survival

	Overall (HR [95% CI])	Primary resection (HR [95% CI])	Salvage (HR [95% CI])	Other (HR [95% CI])
Depression				
Preop depression diagnosis				
N	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Y	1.07 (0.74-1.54)	1.18 (0.72-1.92)	0.81 (0.41-1.60)	1.83 (0.30-11.06)
Depression ± any antidepressant				
N	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Y	1.07 (0.76-1.51)	1.33 (0.83-2.12)	0.78 (0.42-1.45)	2.43 (0.48-12.32)
Any preop antidepressant				
N	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Y	1.08 (0.75-1.56)	1.27 (0.77-1.09)	0.94 (0.50-1.78)	1.58 (0.29-8.77)
Covariates				
Age	1.00 (0.98-1.01)	0.99 (0.97-1.01)	0.98 (0.95-1.02)	0.98 (0.89-1.07)
Sex				
Male	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Female	0.88 (0.63-1.23)	0.84 (0.54-1.33)	1.10 (0.58-2.09)	0.49 (0.12-2.04)
CCI	1.11 (1.05-1.19)[a]	1.13 (1.03-1.23)[a]	1.16 (1.04-1.29)[a]	0.98 (0.74-1.29)
pT				
1	N/A	1 [ref]	N/A	N/A
2	N/A	1.00 (0.27-3.69)	N/A	N/A
3	N/A	1.39 (0.40-4.83)	N/A	N/A
4	N/A	1.83 (0.54-6.17)	N/A	N/A
Adjuvant Radiation				
N	N/A	1 [ref]	N/A	N/A
Y	N/A	0.60 (0.38-0.96)	N/A	N/A

Abbreviations: CI, confidence interval; CCI, Charlson comorbidity index; HR, hazard ratio.
[a]Denotes statistically significant result.

Table 4. Regression Analyses for Clinical Outcomes in Overall Cohort

	Length of stay (coef [95% CI])	Discharge disposition (OR [95% CI])	30-Day readmissions OR [95% CI])	PORT delay OR [95% CI])
Depression				
Preop depression				
N	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Y	0.93 (−0.14-2.00)	1.66 (0.98-2.78)	0.82 (0.49-1.34)	0.65 (0.31-1.40)
Depression ± any antidepressant				
N	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Y	0.46 (−0.54-1.47)	1.54 (0.93-2.53)	0.63 (0.39-1.01)	0.48 (0.23-0.99)[a]
Any preop antidepressant				
N	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Y	0.69 (−0.41-1.79)	1.82 (1.07-3.06)[a]	0.76 (0.45-1.26)	0.49 (0.23-1.10)
Covariates				
Age	0.00 (−0.04-0.04)	1.08 (1.05-1.10)[a]	1.01 (0.99-1.03)	0.98 (0.94-1.03)
Sex				
Male	1 [ref]	1 [ref]	1 [ref]	1 [ref]
Female	0.29 (−0.70-1.29)	1.02 (0.61-1.67)	1.18 (0.76-1.82)	2.41 (1.04-6.35)
CCI	0.12 (−0.08-0.33)	1.03 (0.93-1.13)	1.01 (0.92-1.10)	1.12 (0.93-1.40)

PORT Delay was only assessed for patients who received adjuvant radiation.
Abbreviations: CI, confidence interval; CCI, Charlson comorbidity index; HR, hazard ratio; OR, odds ratio.
[a]Denotes statistically significant result.

The inconsistency of how depression is defined within current literature contributes to the variability in observed effects in the prevalence of depression and impacts on survival and other clinical outcomes. Several studies have demonstrated an association between depression and worse OS,[10,16-19] in contrast to our findings. To retrospectively identify as many patients as possible within our cohort that were affected by depression, we used 32 ICD-9 and -10 codes and used preoperative antidepressant use as a surrogate indicator for depression. It is possible that our broader definition identified patients with a wider spectrum of depression severity, leading to a higher prevalence of depression in our cohort but also resulting in not enough dissimilarity between the two analysis groups (preoperative depression vs no preoperative depression) to capture differences in survival.

In current literature, few studies account for differences in severity and treatment of depression, including patients who may have clinical depression but who have not initiated pharmacologic treatment, variabilities in time of treatment (as common antidepressants can take months to have significant effects), well- versus poorly-controlled depression, and patients who were previously on pharmacologic treatment for depression and may be still "at-risk" for worse outcomes. Despite the difficulties in fully capturing depression in this population, it is valuable to standardize how depression is diagnosed in the literature to more consistently evaluate outcomes. Understanding these relationships may inform the need for standardized preoperative mental health screening and support targeted interventions to improve outcomes in this vulnerable population. These associations are particularly important in a population where timely recovery, return to baseline function, and minimizing unnecessary healthcare utilization are essential for optimal prognosis and quality of life.

The results of this study highlight important opportunities for improved perioperative risk stratification and targeted preoperative intervention for patients with depression. In our patient cohort, patients with preoperative depression or antidepressant use were more likely to have additional chronic disease burden, including CHF, COPD, liver disease, or DM, compared to patients without depression. Although preoperative antidepressant use was independently associated with increased likelihood of discharge to rehabilitation facilities, several comorbid conditions were also associated with increased likelihood of discharge to rehabilitation facilities on univariate analysis (Supplemental Table S2, available online). Depression is comorbid not only with HNC, but also with other chronic diseases that commonly affect HNC patients and may contribute to worse perioperative outcomes.

Early identification and prophylactic treatment of depression may confer survival and prognostic benefits for these patients.[13,20-22] In 2 randomized controlled trials, Lydiatt et al showed that prophylactic antidepressant initiation decreased development of depression in nondepressed patients.[23,24] Prophylactic psychotherapy may also play a beneficial role in treatment of patients with HNC.[20-22] Additionally, a recent study by Gallagher et al also demonstrated decreased mortality in HNC patients treated with antidepressants and/or psychotherapy.[13] Although there is limited literature examining the long-term outcomes of antidepressant and/or psychotherapy in the HNC patient population, these studies demonstrate that there is clinical benefit to early intervention in the HNC patient population. Psychiatric comorbidities have been shown to affect treatment compliance, treatment response, and OS;[22,25] intervention may not only reduce the psychiatric burden of HNC, but may improve overall oncologic prognosis.

This study has several important limitations related to chance, bias, and confounding. First, although our cohort was relatively large, the number of patients with documented preoperative depression was small (n = 158), which may have limited our statistical power to detect subtle but clinically relevant differences in survival or postoperative outcomes. Second, as a retrospective study relying on electronic health record data, it is vulnerable to bias through misclassification. Depression was identified through ICD coding, which likely underestimates true prevalence in this cohort, relative to published estimates up to 40%; this may have introduced nondifferential misclassification, biasing results towards the null hypothesis. We attempted to mitigate this limitation by including both diagnosis codes and antidepressant prescriptions as proxies, but this approach does not capture untreated or subclinical depression. The only way to capture untreated or subclinical depression is to reliably screen all patients for depression in the preoperative setting. Third, unmeasured confounding remains a concern. Although we adjusted for known covariates including age, sex, comorbidity burden, pathological T stage, and receipt of adjuvant radiation, we were unable to account for other variables that may influence both depression and clinical outcomes, such as substance use, functional status, or socioeconomic factors. Finally, the single-center nature of this study may limit generalizability, though our institution's high surgical volume and diverse patient base provide some reassurance. Taken together, these limitations do not invalidate the findings, but they underscore the need for additional investigation.

Ultimately, preoperative depression was present at approximately one-half the estimated rate in our patients, potentially highlighting the need for improved and standardized screening at major institutions that treat a large volume of HNC patients. Future research should focus on prospective cohort studies incorporating validated preoperative mental health screening tools such as the PHQ-9 or GAD-7. Standardized assessments would provide more accurate prevalence estimates and better characterization of depression severity, further allowing

for improved statistical analysis of the relationship between preoperative depression and clinical outcomes. In addition, examining patient-reported outcomes, functional status, and long-term quality of life measures could provide a more comprehensive understanding of the impact of depression on recovery after free flap reconstruction. Interventional studies assessing whether preoperative mental health optimization improves surgical outcomes are also warranted. Finally, multicenter collaborations would enhance generalizability and provide greater statistical power to explore subgroup effects, such as differences by tumor site, treatment modality, and psychiatric medication class. Demonstrated results could dictate provider screening practices and possibly improve clinical outcomes through psychiatric intervention.

Conclusion

This single-institution retrospective cohort study of patients with HNC who underwent free flap reconstruction showed minimal differences in OS between patients with and without preoperative depression, although differences were observed in discharge disposition and rates of PORT delay, indicating that preoperative depression may be an indicator of patients at-risk for worse prognosis after treatment. Further study is needed to characterize depression in this population and provide more insight into the complex interactions of mental health disorders with clinical and sociodemographic factors that impact oncologic treatment.

Author Contributions

Sindhura Sridhar, BS, study design, data collection and analysis, manuscript writing and revision; **Daniel P. Larson, BS**, data collection, manuscript writing, manuscript revision; **Brooke B. Swain, BS**, data collection, manuscript revision; **Heezy Suh, BA**, data collection, manuscript revision; **Daniel R.S. Habib, BA**, data collection, manuscript revision; **Kelly Vittetoe, MD**, study design, manuscript revision; **Donald Sengstack, MS**, data collection, manuscript revision; **Michael C. Topf, MD, MSCI**, supervision, study design, manuscript revision; **Melanie D. Hicks, MD**, supervision, study design, manuscript revision.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

ORCID iD

Sindhura Sridhar https://orcid.org/0009-0009-3649-3920
Daniel R. S. Habib https://orcid.org/0000-0003-0504-9076
Kelly Vittetoe https://orcid.org/0000-0002-9683-5242
Michael C. Topf https://orcid.org/0000-0002-1022-4417

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