# RESEARCH



# Hypothyroidism following immunotherapy predicts more postoperative complication in oral squamous cell carcinoma

Wenwen Zhang<sup>1\*</sup>, Ping Lu<sup>1</sup>, Xing Li<sup>2</sup> and Qigen Fang<sup>3</sup>

# Abstract

**Objective** To evaluate the impact of hypothyroidism that develops following immunotherapy on surgical outcomes in patients diagnosed with oral cancer.

**Methods** Patients with surgically treated oral cancer following neoadjuvant immunochemotherapy were retrospectively enrolled. Impact of hypothyroidism on postoperative complication were analyzed.

**Results** In total, 303 patients were enrolled. In comparison to patients with normal thyroid function, patients with subclinical or overt hypothyroidism did not exhibit a significantly increased risk of surgical site infection, but both conditions were associated with a higher risk of fistula formation and wound debridement. The cohort suffering from subclinical hypothyroidism exhibited odds ratios (ORs) of 1.88 [95% confidence interval (CI): 1.12–5.47] for fistula development and 1.95 [95% CI: 1.27–6.98] for wound debridement. Patients with overt hypothyroidism had a 2.03-fold higher risk of fistula formation (95% CI: 1.35–6.24) and a 2.17-fold higher risk of wound debridement (95% CI: 1.20–7.53). The rate of wound debridement escalated to 40.0% when both hypothyroidism and diabetes were present simultaneously; in contrast, it diminished to 20.0% in cases of isolated hypothyroidism, 12.1% in individuals with diabetes alone, and a mere 5.2% in patients devoid of both conditions. The incidence of fistula formation was most pronounced in patients with coexisting diabetes and hypothyroidism, followed closely by 6.7% in those with solely hypothyroidism. The occurrence of fistulas was remarkably rare among patients with only diabetes or those lacking both factors.

**Conclusions** Hypothyroidism induced by neoadjuvant immunotherapy exerts a considerable negative impact on the formation of fistulas and wound debridement in patients with locally advanced oral cancer, an effect that may be exacerbated by the presence of diabetes.

Keywords Hypothyroidism, Neoadjuvant immunotherapy, Oral cancer, Fistula, Wound debridement

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# Introduction

Oral squamous cell carcinoma (SCC) is the most prevalent malignancy among all head and neck cancers, with half or more of these cases presenting in a locally advanced stage at the commencement of therapy, primarily due to lymph node metastasis [1]. Traditionally, complete excision has remained the primary treatment modality, often followed by adjuvant radiotherapy or chemoradiation [2, 3].

While conventional neoadjuvant chemotherapy regimens that focus on platinum-based agents have not demonstrated a significant enhancement in survival rates for oral SCC [4], they have been associated with a notable increase in the likelihood of mandible preservation, approaching 50% [5]. As our comprehension of immune checkpoint pathways deepens, immunotherapy has emerged as a superior alternative to traditional chemoradiotherapy, contributing to extended overall survival in patients with recurrent or metastatic head and neck SCC [6, 7]. Consequently, immunotherapy has become the frontline treatment for such cases. The incorporation of immunotherapy into neoadjuvant protocols has garnered considerable interest, with a series of clinical trials showing that neoadjuvant immunotherapy, with or without the addition of chemotherapy, can achieve an impressive objective response rate that exceeds 95%. Furthermore, pathologic complete response rates of 30% or higher, along with major pathologic response rates nearing 70%, have been documented [8, 9].

However, the occurrence of immune-related adverse events (irAEs) demands significant attention, as conditions such as immune-related pneumonia can pose fatal risks to patients. Hypothyroidism emerges as the most frequently encountered adverse event, affecting up to approximately 70% of individuals undergoing immunotherapy [10]. It is well recognized that patients with hypothyroidism face an elevated incidence of postoperative fistula following salvage oropharyngectomy [11] and are more prone to flap compromise and the necessity for postoperative debridement in cases of osteoradionecrosis requiring free flap reconstruction [12], but prior radiotherapy may complicate the situation considerably. A recent extensive study reveals that hypothyroidism is associated with a 12.2% increase in the odds of readmission due to issues such as wound dehiscence, fistula formation, infection, and electrolyte imbalances [13]. Nonetheless, this study is significantly limited by its variability in surgical procedures.

Therefore, our objective was to evaluate the impact of hypothyroidism that develops following immunotherapy on surgical outcomes in patients diagnosed with oral SCC.

# **Patients and methods** Ethical approval

This study received approval from the Zhengzhou University Institutional Research Committee, and written informed consent for medical research was obtained from all patients prior to the initiation of treatment. All methodologies were executed in accordance with the relevant guidelines and regulations.

# Study design

To fulfill our objective, a retrospective review of medical records of patients with surgically treated primary oral SCC between January 2020 and December 2024 at a tertiary hospital was conducted. The sole inclusion criterion was the administration of neoadjuvant immunochemotherapy, but patients with hypothyroidism confirmed prior to neoadjuvant therapy were excluded. Data concerning demographics, treatment, and pathology were meticulously extracted.

# **Study variables**

Both albumin levels and thyroid function were assessed in all patients before, during, and after neoadjuvant therapy. Overt hypothyroidism is defined by a thyroidstimulating hormone (TSH) concentration exceeding the normal range (0.27-4.2 mIU/L) alongside a free thyroxine (FT4) concentration falling below the laboratory reference range (12-22 pmol/L). Subclinical hypothyroidism is characterized by an elevated TSH concentration while FT4 levels remain within the reference range [14]. Body mass index (BMI) was calculated from the patient's weight and height, with a normal range established at 18.5 to 23 for individuals of Asian descent [15]. The normal range for albumin levels was determined to be between 40 and 55 g/L. Perioperative blood glucose level maintained from 8.0 to 10.0 mmol/L for diabetes patients.

Free flap failure was defined as a free flap that succumbs to complete necrosis due to loss of perfusion. Free flap compromise was characterized as flaps displaying evidence of reduced or total loss of perfusion, originating from either arterial or venous sources, necessitating operative microvascular revision. Conversely, free flap salvage referred to a flap that, having experienced diminished or complete loss of perfusion, underwent a microvascular revision in which vascular flow was successfully reestablished.

The primary outcome variable assessed was the influence of hypothyroidism on surgical outcomes, which encompassed surgical site infection, free flap failure, free flap compromise, free flap salvage, total necrosis of pedicled flaps, partial necrosis of pedicled flaps, wound debridement, fistula development, and 30-day readmission.

### **Treatment program**

For individuals suffering from subclinical hypothyroidism, supplementation with levothyroxine was not administered. However, patients with overt hypothyroidism typically received an initial dose of Levothyroxine ranging from 25 to 50 micrograms daily, which was subsequently tailored in accordance with the results of thyroid function tests. Moreover, the restoration of normal thyroid function prior to surgery was not an absolute prerequisite.

The treatment protocols comprised the administration of cisplatin at a dosage of 75 mg/m<sup>2</sup> on days 1 and 2, docetaxel at 75 mg/m<sup>2</sup> on days 1 and 8, and pembrolizumab or other PD-1 inhibitors at 200 mg on day 4 of each three-week cycle for two or three cycles. Surgical intervention was scheduled within one to four weeks following the completion of the six-week neoadjuvant regimen. Surgical strategies and resection margins were predefined based on baseline evaluations prior to neoadjuvant therapy and remained unchanged regardless of treatment response. Postoperative antibiotic therapy was routinely sustained for a minimum of five days.

# Statistical analysis

A univariate analysis was executed employing chi-square and Fisher's exact test for categorical variables. Significant variables in the univariate analyses were further analyzed in a multivariable logistic regression. Two-sided tests were carried out, with a p-value of less than 0.05 indicating statistical significance. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). All statistical analyses were conducted using R 3.4.4.

# Results

# **Baseline data**

In total, 303 patients were enrolled in the study, with a mean age of  $55 \pm 14$  years. The cohort comprised 238 males (78.5%) and 65 females (21.5%). Among these individuals, 142 (46.9%) were identified as smokers and 88 (29.0%) as drinkers. Diabetes was present in 63 patients (20.8%). Low albumin levels were observed in 101 patients (33.3%). The BMI was categorized as low in 54 patients (17.8%), normal in 201 patients (66.3%), and high in 48 patients (15.8%). The cancer staging revealed 189 patients (62.4%) diagnosed with stage III and 114 patients (37.6%) with stage IV. Among the reconstructive procedures, free flaps were applied in 180 patients (59.4%), while pedicled flaps were used in 123 patients (40.6%). Hypothyroidism was diagnosed in 60 patients (19.8%), of whom 22 cases were classified as overt and the remainder as subclinical. In comparison with patients exhibiting normal thyroid function, individuals characterized by subclinical and overt hypothyroidism demonstrated a higher propensity for positivity of anti-Tg antibodies

Table 1	Univariate and	alysis of the	impact	of hypothyroid	ism on
surgical	outcomes				

Complication	Hypothyroidism			р
	No ( <i>n</i> =243)	Sub- clinical (n=38)	Overt ( <i>n</i> =22)	
Surgical site infection	21	7	4	0.084
Free flap failure	5	1	0	0.765
Free flap compromise	10	3	2	0.415
Free flap salvage	5	2	2	0.119
Total necrosis of pedicled flap	1	0	0	1.000
Partial necrosis of pedicled flap	10	6	3	0.241
Wound debridement	15	10	8	< 0.001
Fistula	4	4	4	0.001
30-day readmission	10	3	2	0.415

 Table 2
 Univariate analysis of the impact of diabetes on surgical outcomes

Complication	Diak	р	
	No ( <i>n</i> = 240)	Yes (n=63)	
Surgical site infection	20	12	0.014
Free flap failure	4	2	0.445
Free flap compromise	10	5	0.208
Free flap salvage	6	3	0.347
Total necrosis of pedicled flap	0	1	0.111
Partial necrosis of pedicled flap	13	6	0.200
Wound debridement	17	16	< 0.001
Fistula	6	6	0.021
30-day readmission	10	5	0.323

(p = 0.011) and anti-TPO antibodies (p < 0.001). (Supplementary Table 1)

A total of 32 patients experienced surgical site infections, yielding an incidence rate of 10.6%. Wound debridement was performed in 33 patients (10.9%), while fistulas developed in 12 patients (4.0%). Additionally, 15 patients (5.0%) underwent readmission within 30 days. Among those who received free flap reconstruction, 15 flaps encountered vascular crises, with 10 cases of venous compromise and 5 cases of arterial compromise, of which 9 were ultimately salvaged. In the cohort undergoing pedicled flap procedures, complete necrosis was observed in one patient, with partial necrosis documented in 19 patients.

# Univariate analysis

Tables 1, 2, 3 and 4 illustrate the univariate analysis concerning the influence of hypothyroidism, diabetes, albumin, and BMI on surgical outcomes, and the impact of additional factors on these complications was detailed in Supplementary Tables 2–5. Those significant factors were further analyzed in a multivariable logistic regression.

Neither albumin levels nor BMI demonstrated any significant effect on the occurrence of surgical

 Table 3
 Univariate analysis of the impact of albumin on surgical outcomes

Complication	Alt	р	
	Low ( <i>n</i> = 101)	Normal ( <i>n</i> = 202)	_
Surgical site infection	12	20	0.597
Free flap failure	3	3	0.465
Free flap compromise	6	9	0.574
Free flap salvage	3	6	0.687
Total necrosis of pedicled flap	1	0	0.157
Partial necrosis of pedicled flap	8	11	0.402
Wound debridement	13	20	0.558
Fistula	3	9	0.757
30-day readmission	6	9	0.574

 Table 4
 Univariate analysis of the impact of BMI on surgical outcomes

Complication	BMI			р
	Low ( <i>n</i> = 54)	Normal (n=201)	High ( <i>n</i> =48)	
Surgical site infection	5	22	5	0.962
Free flap failure	2	3	1	0.584
Free flap compromise	4	8	3	0.531
Free flap salvage	2	5	2	0.674
Total necrosis of pedicled flap	0	1	0	1.000
Partial necrosis of pedicled flap	3	14	2	0.783
Wound debridement	5	24	4	0.735
Fistula	2	7	3	0.683
30-day readmission	2	3	2	0.362

complications (all p > 0.05). Conversely, hypothyroidism exhibited a substantial association with the formation of fistulas (p = 0.001) and the necessity for wound debridement (p < 0.001), yet it did not significantly affect other adverse outcomes, but exhibited a tendency to influence the incidence of surgical site infections (p = 0.084). Moreover, patients with diabetes were more prone to experience surgical site infections (p = 0.014), the need for wound debridement (p < 0.001), and the development of fistulas (p = 0.021), while showing no correlation with other events (all p > 0.05).

### Multivariable analysis

A multivariable analysis of independent predictors was conducted regarding surgical site infections, fistula formation, and wound debridement (Table 5, Supplementary Table 6). In comparison to patients with normal thyroid function, those afflicted with subclinical or overt hypothyroidism did not evince an augmented risk of surgical site infection. Nonetheless, the cohort with subclinical hypothyroidism exhibited ORs of 1.88 [95% CI: 1.12–5.47] for the formation of fistula and 1.95 [95% CI: 1.27-6.98] for wound debridement, whereas patients with overt hypothyroidism had a 2.03-fold higher risk of fistula formation (95% CI: 1.35-6.24) and a 2.17-fold higher risk of wound debridement (95% CI: 1.20-7.53). When compared to patients without diabetes, those characterized by diabetes demonstrated ORs of 2.92 (95% CI: 1.57-7.44) for surgical site infections, 3.14 (95% CI: 1.53-8.56) for fistula development, and 2.69 (95% CI: 1.27-8.99) for wound debridement. However, smoking status did not impinge upon the three outcome variables.

# Subgroup analysis

Both hypothyroidism and diabetes exhibited independent effects on fistula formation and wound debridement, prompting a subgroup analysis of the interplay between these two factors, as illustrated in Fig. 1. The rate of wound debridement escalated to 40.0% when both hypothyroidism and diabetes were present simultaneously; in contrast, it diminished to 20.0% in cases of isolated hypothyroidism, 12.1% in individuals with diabetes alone, and a mere 5.2% in patients devoid of both conditions. The incidence of fistula formation was most pronounced in patients with coexisting diabetes and hypothyroidism, followed closely by 6.7% in those with solely hypothyroidism. The occurrence of fistulas was remarkably rare among patients with only diabetes or those lacking both factors.

Factor	S	urgical site infection	Fistula		Wound debridement	
	p	OR [95%CI]	p	OR[95%CI]	p	OR[95%CI]
Hypothyroidism						
No		ref		ref		ref
Subclinical	0.343	1.78 [0.73-3.65]	0.017	1.88 [1.12-5.47]	0.004	1.95[1.27-6.98]
Overt	0.289	1.89 [0.64–5.58]	0.011	2.03 [1.35-6.24]	0.002	2.17 [1.20–7.53]
Diabetes						
No		ref		ref		ref
Yes	0.006	2.92 [1.57–7.44]	0.020	3.14 [1.53-8.56]	0.026	2.69 [1.27-8.99]
Smoker						
No		ref		ref		ref
Yes	0.326	1.99 [0.64–6.90]	0.417	2.31 [0.57–7.42]	0.398	2.28 [0.59–7.06]



Fig. 1 Incidence of fistula formulation and wound debridement in patients with hypothyroidism or diabetes

# Discussion

Our most significant finding was that, in the context of locally advanced oral SCC, hypothyroidism that arises during neoadjuvant immunochemotherapy is markedly associated with both wound debridement and fistula formation, with the adverse effects not being contingent upon the specific type of hypothyroidism. Moreover, the detrimental influence of hypothyroidism appears to be exacerbated by the presence of diabetes. This study represents the first of its kind to examine the implications of hypothyroidism following neoadjuvant immunochemotherapy in oral SCC and reveals the necessity for heightened vigilance to prevent fistula formation and wound debridement.

Hypothyroidism can sometimes manifest asymptomatically with minimal clinical ramifications; however, when left untreated, it poses a significant risk for morbidity and, ultimately, mortality. A substantial body of literature has examined the impact of hypothyroidism on surgical outcomes. Ang et al. [16] conducted a review encompassing seven studies with a total of 1,132 patients with hypothyroidism and 11,753 euthyroid individuals undergoing percutaneous coronary intervention. Although both cohorts exhibited no differences in the incidence of myocardial infarction, major adverse cardiovascular and cerebrovascular events, or heart failure, the hypothyroid group displayed a significantly elevated risk of cardiovascular mortality, all-cause mortality, and repeat revascularization. Rosko et al. [17] sought to delineate the effects of hypothyroidism on postoperative wound healing in 182 patients undergoing salvage laryngectomy, revealing a fistula rate of 47% among hypothyroid patients compared to 23% in their euthyroid counterparts. Multivariate analysis indicated that patients experiencing hypothyroidism in the postoperative period had a 3.6-fold increased risk of fistula formation. Moreover, those with hypothyroidism faced an 11.4-fold greater likelihood of requiring reoperation (24.4% vs. 5.4%) than their euthyroid peers, with the risk for both fistula and reoperation escalating in accordance with rising TSH levels. Specifically, each doubling of TSH corresponded to an approximate 12.5% incremental increase in the absolute risk of fistula and a 10% increase in the absolute risk of reoperation. In the context of total hip arthroplasty [18], patients with hypothyroidism exhibited a higher prevalence of postoperative acute anemia and incurred

greater mean hospital costs compared to the non-hypothyroid group. Li et al. [19] reported that, although no significant differences were noted in terms of mortality, organ system complications, wound dehiscence, or other postoperative metrics between patients with and without hypothyroidism in breast reconstruction, the hypothyroid cohort did possess a heightened risk for hemorrhage and hematoma. Collectively, these studies underscore that hypothyroidism is a predictor of increased postoperative adverse events. However, it is essential to acknowledge that in the studies referenced, hypothyroidism was often attributed to chronic autoimmune thyroiditis or prior radiotherapy. In the former scenario, the immune system erroneously targets the thyroid gland, precipitating chronic inflammation and cellular degradation; concurrently, an influx of lymphocytes infiltrates the thyroid, progressively undermining the integrity of the thyroid tissue [20]. In the latter case, radiotherapy induces the destruction of thyroid cells via ionizing radiation, resulting in their dysfunction or annihilation. Moreover, radiotherapy can impair the blood vessels and adjacent tissues of the thyroid gland, compromising blood circulation and further exacerbating the impairment of thyroid functionality [21]. Notably, hypothyroidism may also arise as a side effect of immunotherapy, a prominent focus in cancer treatment. Consequently, the potential for a similar detrimental influence resulting from immunotherapyinduced hypothyroidism remains ambiguous.

In this study, we incorporated several well-established indicators for assessing postoperative complications and discovered that hypothyroidism is a predictor of an increased risk of fistula formation and wound debridement, with comparable probabilities observed between subclinical and overt forms of the condition. This finding is significant for several reasons. First, immunotherapy has emerged as an essential component in the initial management of locally advanced oral SCC [22]. While current literature has predominantly examined the incidence and patterns of adverse events, with conclusions suggesting that neoadjuvant immunotherapy does not delay surgical schedules [23], our study provides the inaugural evidence of the adverse effects of hypothyroidism on wound healing, thus offering valuable insights for clinical management in these scenarios. Secondly, overt hypothyroidism tended to introduce additional complications; typically, higher TSH levels are associated with greater difficulties in healing compared to lower levels, and overt forms of hypothyroidism are linked to an increased risk of complications [24]. This discrepancy may be elucidated by the fact that, unlike previous studies, thyroid function was rigorously monitored during immunotherapy. Even when free T4 levels did not return to the normal range, the timely administration of levothyroxine mitigated the detrimental effects commonly associated with overt hypothyroidism. Thirdly, subclinical hypothyroidism was similarly correlated with an increased incidence of surgical complications. Potential explanations may involve disruptions to the immune response, impairments in angiogenesis, or a deceleration of metabolism following immunotherapy [25].

In addition to hypothyroidism, factors such as albumin levels, smoking, diabetes, and BMI also significantly influence wound healing. In a cohort of 415 patients undergoing free tissue transfer [26], type 2 diabetes was identified as an independent risk factor for increased infectious complications, a finding that aligns with our analysis. Low albumin levels were correlated with the need for a second flap procedure [12], while a higher prevalence of abdominal aortic aneurysm among obese patients has been documented [27]; smoking resulted in a 2.49 times higher overall complication rate [28]. However, these results appear to contradict our findings. Potential explanations might include the relatively mild severity of hypoproteinemia in our study, as well as the fact that the most significant negative impact of BMI was attributed to prolonged operation times due to intraoperative exposure difficulties. Another noteworthy finding from our study was the interaction between hypothyroidism and diabetes; the incidence of adverse events, particularly wound debridement, was significantly heightened in the presence of both conditions. This carries substantial clinical implications, given the widespread prevalence of diabetes and the critical need for meticulous perioperative management in affected patients.

We must acknowledge several limitations in the current study: firstly, there is an inherent bias associated with retrospective research; secondly, our sample size may be inadequate, potentially reducing the statistical power of our findings confirmed by Bootstrap analysis, a substantial cohort from a multicenter investigation was imperative; lastly, our analysis was confined to a single institution, highlighting the necessity for external validation.

In conclusion, hypothyroidism induced by neoadjuvant immunotherapy exerts a considerable negative impact on the formation of fistulas and wound debridement in patients with locally advanced oral cancer, an effect that may be exacerbated by the presence of diabetes.

# Supplementary Information

The online version contains supplementary material available at https://doi.or g/10.1186/s12885-025-14070-7.

Supplementary Material 1		
Supplementary Material 2		
Supplementary Material 3		
Supplementary Material 4		
Supplementary Material 5		

Supplementary Material 6

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None declared.

# Author contributions

Study design: WZ, PL, XL, QF. Manuscript writing: WZ, PL, XL, QF. Studies selecting: WZ, PL, XL, QF. Data analysis: WZ, PL, XL, QF. Study quality evaluating: WZ, PL, XL, QF. Manuscript revising: WZ, PL, XL, QF. The final manuscript was read and approved.

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### Data availability

All data generated or analyzed during this study are included in this published article. And the primary data could be achieved from the corresponding author.

# Declarations

### Ethics approval and consent to participate

This study was approved by Zhengzhou University Institutional Research Committee, and written informed consent for medical research was obtained from all patients prior to initial treatment. All methods were performed in accordance with relevant guidelines and regulations.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare no competing interests.

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