PLOS ONE
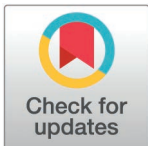
The impact of postoperative glucocorticoids on complications after head and neck cancer surgery with free flap reconstruction: A retrospective study

Tao Luo☯, Ren Zhou☯, Yu Sun🔟*

Department of Anesthesiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

☯ These authors contributed equally to this work.
* dr_sunyu@163.com

Abstract

Background

After head and neck cancer surgery with free flap reconstruction, the use of glucocorticoids is often required to alleviate inflammation and edema. However, the impact of glucocorticoid on postoperative complications and cancer progression remains unclear.

Methods

This retrospective cohort study included 711 elderly patients who underwent head and neck cancer surgery with free flap reconstruction at Shanghai Ninth People's Hospital from January 1, 2014, to December 31, 2022. Patients were categorized based on postoperative glucocorticoid usage into a high-dose steroid group (n = 307) and a control group (n = 404). The study focused on the impact of postoperative GC use on postoperative complications and long-term oncological outcomes.

Results

Multivariate analysis indicated that compared to the control group, the high-dose steroid group had a significant increase in postoperative complications, including atelectasis (OR: 3.83, 95% CI: 1.27–14.11, P = 0.025), postoperative hyperglycemia (OR: 1.54, 95% CI: 1.14–2.08, P = 0.006), and flap complications (OR: 4.61, 95% CI: 3.31–6.47, P < 0.001). These complications often required extended hospital stays (β: 1.656, 95% CI: 1.075-2.236, P < 0.001). Additionally, the high-dose steroid group had a higher rate of unplanned readmissions within one year (OR: 5.61, 95% CI: 3.87–8.25, P < 0.001). The increased readmission rates were notably due to difficulties swallowing requiring percutaneous gastrostomy (OR: 3.62, 95% CI: 1.97–6.98, P < 0.001), recurrence (OR: 9.34, 95% CI: 5.02–19.05, P < 0.001), and metastasis (OR: 4.78, 95% CI: 2.58-9.44, P < 0.001).

Conclusion

The use of high-dose postoperative glucocorticoids is associated with increased post-operative complications, higher readmission rates, and poorer oncological outcomes in patients. The results advocate for cautious use and dosage management of perioperative glucocorticoids in head and neck surgeries to optimize patient outcomes.

Introduction

Head and neck cancer (HNC), predominantly comprising squamous cell carcinoma (SCC), remains a significant clinical challenge due to its high incidence, mortality, and morbidity after treatment [1,2]. The complexity of treatment increases with the necessity for reconstructive surgeries such as free flap reconstruction (FFR) to restore functional and aesthetic deficits following extensive tumor resections [3,4]. Management strategies have steadily integrated advances in surgical, chemotherapeutic, and radiotherapeutic realms, nevertheless, improvements in prognosis and quality of life post-treatment are still greatly needed [5].

As surgical techniques advance, there is a growing recognition that the metabolic and systemic responses to cancer can influence treatment outcomes. In this context, glucocorticoids (GCs), while traditionally deployed for their potent anti-inflammatory and immuno-suppressive properties, represent a dual-edged sword in cancer care [6]. GCs bear a particular significance due to their intricate roles in not only mediating stress response and metabolic modulation but also potentially affecting tumorigenic processes directly and indirectly [7–10].

Currently, the interplay between GCs, inflammation, cancer biology, and surgical outcomes remains inadequately understood. The variability in individual glucocorticoid synthesis and metabolic processing within the tumor microenvironment, modulated by enzymes such as 11β-hydroxysteroid dehydrogenase types 1 and 2, further complicates this challenge [11,12]. These differences could influence local and systemic effects, including immune modulation, glucose metabolism, and the inflammatory cascades pivotal for both cancer progression and postoperative recovery.

Recent studies underscore the pervasive activation of the glucocorticoid system in both regional tissues and systemic levels in patients with HNC. Such systemic elevation has been correlated with poor therapeutic outcomes and heightened corticosteroid-induced regulatory mechanisms that might foster tumor progression and resistance to therapies [12–14]. Moreover, emerging evidence suggests that the perioperative administration of systemic GCs could impact immediate surgical outcomes and increase higher short-term mortality in head and neck cancer patients undergoing FFR, potentially implicated by perturbed wound healing, and postoperative hyperglycemia [15–17]. However, these studies are limited by small sample sizes, and research on the impact of GCs on long-term complications remains scarce in patients undergoing head and neck cancer surgery with free flap reconstruction (HNS-FFR).

This study aims to refine our understanding of how exogenous glucocorticoid administration intersects with these complex biological processes, particularly in the setting of HNS-FFR. We plan to investigate the multidimensional impacts of GCs administered during the postoperative period in a retrospective cohort of head and neck cancer patients, focusing on their potential to alter postoperative complications, the rate of unplanned readmissions within a year, and the risk of cancer recurrence and metastasis which may be the first time in the in clinical practice. Such insights will be fundamental for optimizing therapeutic strategies and tailoring perioperative care to improve both oncologic and functional outcomes in this challenging patient population.

Materials and methods

Study design and participants

This retrospective cohort study enrolled elderly patients who were admitted to Shanghai Ninth People's Hospital, affiliated with Shanghai Jiao Tong University School of Medicine, from January 1, 2014 to December 31, 2022. The study adhered to the STROBE guidelines (see S1 Checklist). Approval was obtained from the center's ethics committee (Ethics Reference: SH9H-2024-T315-1), and, due to its retrospective nature, the requirement for informed consent was waived. Data collection for research purposes began on September 2, 2024, following approval from the consent of the Ethics Committee. Authors had access to information that could identify individual participants during data collection. But prior to statistical analysis, information that could identify individuals was removed.

Inclusion criteria were: (1) aged 60 years or older, (2) diagnosed with a head and neck malignant tumor, and (3) underwent initially elective radical surgery such as maxillectomy, partial glossectomy, or partial buccal resection followed by free-flap reconstruction under general anesthesia.

Exclusion criteria included: (1) long-term use of GCs, (2) long-term use of immunosuppressants or being in an immunosuppressed state, (3) previous head and neck radiotherapy, and (4) missing data. Detailed registration information is shown in S1 Fig.

Data sources and variables

Data were sourced from the Union Digital Medical Record Browser (Version 2012.4; Unionnet Co., Ltd., Shanghai, China) digital medical records. Extracted data underwent a dual-check process and data cleaning to eliminate outliers and duplicate records.

Collected demographic medical record information included gender, age, weight, height, smoking and drinking habits, American Society of Anesthesiologists (ASA) physical status classification, history of chemotherapy, hypertension, diabetes, chronic heart failure, and chronic obstructive pulmonary disease (COPD).

Surgical information collected encompassed the primary lesion location, pathological type, TNM stage, free flap site, lymph node dissection extent (none/unilateral/bilateral), intraoperative transfusion, and respiratory management after surgery (tracheotomy/tracheal intubation).

Outcome and complication data

The primary outcomes of interest in this study were postoperative complications during hospital stay and unplanned readmissions within one year.

The postoperative complications collected included glycemic control (random blood glucose values ≥ 180 mg/dl) [18]; the Clavien-Dindo classification of surgical complications (S1 Table) [19]; respiratory system complications, including pneumonia, atelectasis, pulmonary embolism, and respiratory failure [20]; flap complications, such as flap infection, postoperative bleeding, flap dehiscence, seroma/fistula formation, partial flap necrosis, and flap crisis; and digestive system complications including liver dysfunction, acute pancreatitis, and intestinal obstruction. Other complications noted were cardiac insufficiency, cerebral embolism, acute kidney injury (AKI) (an absolute increase in plasma creatinine of 26.5 μmol/L within 48 h or a 1.5-fold increase in creatinine within 7 days) [21], deep vein thrombosis, postoperative delirium, and electrolyte imbalance.

Data on postoperative outcomes also included reasons for unplanned readmissions within one year, such as difficulty swallowing requiring percutaneous gastrostomy, lung infection, delayed healing at the surgical site, recurrence, and metastasis.

Secondary outcomes included length of ICU stay, postoperative hospital stay, unplanned reoperations, and mortality.

Statistical analysis

Statistical analysis was performed using SPSS (version 26; IBM Corp., Armonk, NY, USA). A total of 560 mg of methylprednisolone was used as the cut-off value [22]. First, we measured and compared the incidence of each complication between the two groups. We then performed multiple regression to assess differences between different cohorts. Different regression analyses were used based on different types, using OR and β presentations respectively. Postoperative complications during hospital stay, unplanned reoperation, postoperative hospital stay, and unplanned readmissions within a year were compared between the two groups. The control group (less than the cut-off value) was used as a reference level for comparison. Age, gender, BMI, ASA score, history of smoking and drinking, and chemotherapy were taken as covariates. Subgroup analyses were performed according to cancer sublocus, pathological type, and T stage, and covariates were age, gender, alcohol consumption, diabetes, chemotherapy, end-organ damage (Clavien-Dindo classification grade 4), and blood transfusion. A two-tailed P value < 0.05 indicated statistical significance.

Results

Demographics

The study cohort comprised 711 patients, with 404 in the control group and 307 in the high-dose steroid group. Table 1 summarizes the demographic information of both groups. The groups were comparable in all respects except for the history of diabetes. The prevalence of diabetes was significantly lower in the high-dose steroid group compared to the control group (8.8% vs 24.8%, P < 0.0001).

Surgical characteristics

The surgical characteristics of both groups are summarized in Table 2. Tongue cancer was the most common type of HNC (33.1%), and SCC accounted for approximately 90.6% of cases. The most common type of free flap used was the anterolateral thigh flap (50.0%). The high-dose steroid group was more likely to use this type of flap (55% vs 49.8%) and had a higher volume of intraoperative blood transfusion (P = 0.0347). Approximately 70.0% of patients underwent a prophylactic tracheotomy immediately after surgery.

Outcome variables

The most common postoperative complications during hospitalization for patients undergoing HNS-FFR were pulmonary complications (43.3%), followed by digestive complications (37.7%), flap complications (34.5%), and electrolyte imbalances (34.5%) (see S2 Table).

Multivariate analysis (Table 3) revealed that, compared to the control group, the high-dose steroid group had a higher risk of postoperative complications (OR: 3.76, 95% CI: 2.11-7.13, P < 0.001), more difficulty in controlling blood glucose (OR: 1.54, 95% CI: 1.14-2.08, P = 0.006), and a higher incidence of atelectasis (OR: 3.83, 95% CI: 1.27-14.11, P = 0.025). Notably, the rates of flap infection and seroma/fistula formation were significantly higher (OR: 5.52, 95% CI: 3.79-8.16, P < 0.001; and OR: 4.98, 95% CI: 3.2-7.92, P < 0.001, respectively). Partial flap necrosis (OR: 1.96, 95% CI: 1.16-3.37, P = 0.013) and flap dehiscence (OR: 2.52, 95% CI: 1.17-5.75, P = 0.021) were also more common in the high-dose steroid group. These complications often necessitated longer hospital stays (β: 1.656, 95%CI (1.075-2.236), P < 0.001).

Table 1. Baseline clinical characteristics.

characteristic	Control group (N = 404)	High-dose steroid group (N = 307)	P value
Duration of use (day)[b]	4.27 (2.67)	8.96 (3.18)	**<0.0001**
Dosage of glucocorticoids[b]	294.26 (167.52)	1213.94 (481.50)	**<0.0001**
Gender[a]			0.6808
Female	148 (36.6)	107 (34.9)	
Male	256 (63.4)	200 (65.1)	
Age [b]	68.23 (6.44)	68.74 (6.39)	0.292
Weight [b]	62.19 (11.47)	62.12 (10.58)	0.9357
Height [b]	164.91 (8.00)	165.63 (7.57)	0.3485
BMI [b]	22.87 (3.45)	22.80 (3.34)	0.8556
Smoke [a]			0.666
No	273 (67.6)	213 (69.4)	
Yes	131 (32.4)	94 (30.6)	
Drink [a]			0.7935
No	306 (75.7)	236 (76.9)	
Yes	98 (24.3)	71 (23.1)	
ASA [a]			0.7874
1	23 (5.7)	15 (4.9)	
2	347 (85.9)	265 (86.3)	
3	33 (8.2)	27 (8.8)	
4	1 (0.2)	0 (0.0)	
Chemotherapy [a]			0.6801
No	335 (82.9)	259 (84.4)	
Yes	69 (17.1)	48 (15.6)	
Diabetes [a]			**<0.0001**
No	304 (75.2)	280 (91.2)	
Yes	100 (24.8)	27 (8.8)	
CHF [a]			0.6034
No	385 (95.3)	289 (94.1)	
Yes	19 (4.7)	18 (5.9)	
COPD [a]			0.7184
No	382 (94.6)	293 (95.4)	
Yes	22 (5.4)	14 (4.6)	

[a]: Data are presented as n (%) for categorial values;

[b]: Data are presented as mean (standard deviation) for continuous variables; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; CHF: Chronic heart failure; COPD: Chronic obstructive pulmonary disease.

https://doi.org/10.1371/journal.pone.0319655.t001

The high-dose steroid group also had a higher rate of unplanned readmissions within one year (OR: 5.61, 95% CI: 3.87-8.25, P < 0.001) compared to the control group. The increased readmission rates were particularly due to difficulties swallowing that required percutaneous gastrostomy (OR: 3.62, 95% CI: 1.97-6.98), recurrence (OR: 9.34, 95% CI: 5.02-19.05), and metastasis (OR: 4.78, 95% CI: 2.58-9.44) (P < 0.001).

Subgroup analysis indicated that the adverse effects of high-dose steroid use on non-planned readmissions within one year were consistent across different primary lesion location, pathological types, and T stages, with interaction P-values indicating no significant trends (0.309, 0.115, and 0.564 respectively, S3 Table).

Table 2. Surgical information.

characteristic	Control group (N = 404)	High-dose steroid group (N = 307)	P value
Primary lesion location [a]			0.5482
cheek	96 (23.8)	77 (25.1)	
tongue	134 (33.2)	101 (32.9)	
gingiva	83 (20.5)	72 (23.5)	
others	91 (22.5)	57 (18.6)	
Pathological type [a]			0.9697
SCC	365 (90.3)	279 (90.9)	
ACC	22 (5.4)	16 (5.2)	
others	17 (4.2)	12 (3.9)	
T [a]			0.1221
1	36 (8.9)	26 (8.5)	
2	200 (49.5)	177 (57.7)	
3	63 (15.6)	45 (14.7)	
4	105 (26.0)	59 (19.2)	
N [a]			0.0818
0	174 (43.1)	160 (52.1)	
1	120 (29.7)	79 (25.7)	
2	99 (24.5)	64 (20.8)	
3	11 (2.7)	4 (1.3)	
M [a]			0.5505
0	400 (99.0)	306 (99.7)	
1	4 (1.0)	1 (0.3)	
Free flap type [a]			**0.0414**
anterolateral thigh flap	201 (49.8)	169 (55.0)	
radial forearm flap	125 (30.9)	69 (22.5)	
others	78 (19.3)	69 (22.5)	
CLND [a]			0.3296
none	21 (5.2)	9 (2.9)	
unilateral	327 (80.9)	254 (82.7)	
bilateral	56 (13.9)	44 (14.3)	
Blood transfusion [b]	1.25 (1.55)	1.51 (1.67)	**0.0347**
Respiratory condition [a]			0.6825
Tracheostomy	288 (71.3)	224 (73.0)	
Intubation	116 (28.7)	83 (27.0)	

[a]: Data are presented as n (%) for categorial values;

[b]: Data are presented as mean (standard deviation) for continuous variables; SCC: Squamous cell carcinoma; ACC: Adenocarcinoma; CLND: Cervical lymph node dissection.

https://doi.org/10.1371/journal.pone.0319655.t002

Discussion

The understanding of the impact of corticosteroid administration on elderly patients undergoing HNS-FFR is limited. Therefore, in this study, we investigated the association between postoperative glucocorticoid administration and short-term postoperative complications, as well as unplanned readmissions within one year. The results indicate that while GCs may offer significant perioperative benefits, the use of high-dose glucocorticoids is associated with an increase in postoperative complications, poor metabolic control, and deteriorated oncological outcomes.

Table 3. Multivariate Analysis of High-dose Steroid Group Compared to Control Group.

Complication	OR/β, 95% CI	P value
Any complication	3.76 (2.11,7.13)	**< 0.001**
Blood glucose control	1.54 (1.14,2.08)	**0.006**
Pneumonia	1.3 (0.96, 1.76)	0.091
Atelectasis	3.83 (1.27, 14.11)	**0.025**
Pulmonary embolism	1.59 (0.34, 8.23)	0.547
Respiratory failure	0.5 (0.13, 1.52)	0.246
Pulmonary complications	1.3 (0.96, 1.76)	0.091
Flap infection	5.52 (3.79, 8.16)	**< 0.001**
Postoperative bleeding	1.87 (0.79, 4.62)	0.156
Flap dehiscence	2.52 (1.17, 5.75)	**0.021**
Seroma/Fistula formation	4.98 (3.2, 7.92)	**< 0.001**
Partial flap necrosis	1.96 (1.16, 3.37)	**0.013**
Flap crisis	0.94 (0.36, 2.36)	0.892
Flap complications	4.61 (3.31, 6.47)	**< 0.001**
Hepatic insufficiency	1.16 (0.85, 1.58)	0.361
Acute pancreatitis	2.72 (0.26, 59.22)	0.417
Ileus	0.74 (0.02, 20.58)	0.839
Digestive complications	1.23 (0.91, 1.68)	0.182
Cardiac insufficiency	0.88 (0.54, 1.43)	0.619
Cerebral embolism	4.51 (1.07, 30.62)	0.063
AKI	0.75 (0.15, 3.12)	0.7
Electrolyte imbalances	0.99 (0.72, 1.36)	0.931
DVT	1.07 (0.45, 2.53)	0.871
Postoperative delirium	1.17 (0.74, 1.83)	0.504
Unplanned surgery	1.49 (0.75, 3.02)	0.256
PHS [a]	1.656 (1.075,2.236) [b]	**< 0.001**
NPR	5.61 (3.87, 8.25)	**< 0.001**
Difficulty swallowing	3.62 (1.97, 6.98)	**< 0.001**
Recurrence	9.34 (5.02, 19.05)	**< 0.001**
Metastasis	4.78 (2.58, 9.44)	**< 0.001**
Lung infections	2.12 (0.91, 5.19)	0.088
Delayed healing	1.94 (0.77, 5.14)	0.165

[a]: Linear regression analysis;

[b]: β value (95%CI); AKI: Acute kidney injury; DVT: Deep vein thrombosis; PHS: Postoperative hospital stay; NPR: Non-planned readmissions within the first year.

https://doi.org/10.1371/journal.pone.0319655.t003

Postoperative pulmonary complications (PPC) represent a significant issue in head and neck cancer surgeries, associated with high morbidity and mortality rates in patients undergoing HNS-FFR [23,24]. Our study observed that PPCs occur in up to 43.3% of postoperative head and neck cancer cases, aligning with previous findings [25]. Notably, patients in the high-dose steroid group exhibited a significantly higher incidence of postoperative atelectasis compared to the control group (OR: 3.83, 95% CI: 1.27-14.11, P = 0.025), and a trend towards statistical significance was also seen for pulmonary infections (P = 0.091). This increased susceptibility to infections such as pneumonia may be attributed to the immunosuppressive effects of high-dose glucocorticoids [26], which can exacerbate the immunodeficiency already present in patients with HNC [27]. Additionally, increased daily and cumulative doses of GCs

heighten the risk of skeletal muscle weakness, including the muscles essential for respiration and cough reflex [28,29]. This muscle weakness impairs the patient's ability to clear respiratory secretions, leading to mucus accumulation in the airways and resultant obstructive atelectasis.

Interestingly, we found that the high-dose steroid group was more susceptible to postoperative hyperglycemia (OR: 1.54, 95% CI: 1.14-2.08, P = 0.006), despite a higher prevalence of diabetes in the control group. This may be attributable to a higher proportion of patients with postoperative liver dysfunction in the high-dose steroid group (38.1% vs. 34.9%). Research shows that acute exposure to GCs can reduce the ability of adipocytes and hepatocytes to bind insulin, leading to insulin resistance [30]. Liver dysfunction undoubtedly exacerbates this phenomenon. Additionally, the cumulative dosage of steroids further contributes to the occurrence of hyperglycemia [31]. It is noteworthy that substantial observational evidence indicates that hyperglycemia in hospitalized patients, regardless of a diabetes diagnosis, is associated with adverse outcomes [18,32].

GCs are known for their anti-inflammatory properties, which may impede the inflammatory phase critical for wound healing. Successful progression and resolution of the inflammatory response are essential for proper wound healing. We observed that the high-dose steroid group had significantly increased risks of flap fistula formation (OR: 4.98, 95% CI: 3.2-7.92, P < 0.001), partial flap necrosis (OR: 1.96, 95% CI: 1.16-3.37, P = 0.013), and flap dehiscence (OR: 2.52, 95% CI: 1.17-5.75, P = 0.021). These findings highlight the detrimental effects of GCs on surgical recovery and wound integrity, consistent with previous studies [33]. This may be due to GCs interfering with various stages of the inflammatory response, preventing the smooth progression of each phase [34]. Moreover, GCs can also inhibit wound healing by suppressing the migration of keratinocytes [35]. Therefore, moderate use of GCs may be a crucial component in transitioning from inflammation to wound healing.

Patients receiving GCs appear particularly susceptible to infections [26]. Our study found that patients in the high-dose steroid group had a higher risk of flap infections compared to the control group (OR: 5.52, 95% CI: 3.79-8.16, P < 0.001). Kainulainen's study, which found an increased incidence of infections among oral cancer patients undergoing microvascular reconstruction treated with dexamethasone [15], seems to corroborate our findings. This could be due to high-dose corticosteroid-induced hyperglycemia increasing the risk of surgical site infections [17]. Additionally, delayed wound healing has been shown to elevate the risk of postoperative infections [33]. It is important to note that due to suppressed cytokine release, which reduces inflammation and febrile responses, patients on GCs usually have more challenges identifying infections early [36].

We also discovered that patients in the high-dose steroid group had significantly increased risks of recurrence and metastasis (OR: 9.34, 95% CI: 5.02-19.05, P < 0.001; and OR: 4.78, 95% CI: 2.58-9.44, P < 0.001, respectively), which is particularly concerning. The immunosuppressive properties of GCs act as a double-edged sword. While GCs can beneficially suppress the inflammatory responses that might exacerbate tissue damage during surgery, they can also inhibit the immune surveillance mechanisms necessary for detecting and destroying residual cancer cells [13,37]. This immunosuppression is especially significant in head and neck cancer patients, where the immune environment is already compromised by the tumor itself [27]. Additionally, glucocorticoid administration may exacerbate the immune evasion strategies employed by cancer cells, such as upregulation of immune checkpoints, known to facilitate immune escape in head and neck squamous cell carcinoma from host immunity [38]. Studies suggest that systemic GCs can enhance energy metabolism, potentially increasing the survival capacity of cancer cells during radiotherapy and chemotherapy both in vitro and in vivo [7,8,39]. This may be due to the fact that the sustained treatment with exogenous GCs activates

immunosuppressive transcription factors in dendritic cells, leading to the subversion of the anti-tumor immune responses induced by cancer therapies, and subsequent treatment failure [13,37]. Indeed, GCs have also been found to induce therapy resistance in solid tumors, including prostate, ovarian, and breast cancers [40]. Overall, the use of high-dose glucocorticoids postoperatively in head and neck cancer patients certainly warrants careful reconsideration.

Limitations

This study has several limitations. Primarily, its retrospective design and single-center setting may limit the generalizability of the results. Fortunately, the database we used took effective measures to ensure data quality, and the sample size of our study was relatively large. Secondly, the inherent biases associated with retrospective analyses and the potential presence of unaccounted confounding variables may have affected outcomes. In addition, this study focused solely on unplanned readmissions within 1 year, excluding longer-term complications, which may have led to an underestimation of the true data and restricted our ability to assess the long-term effects and sustainability of the observed outcomes. Longitudinal studies with extended follow-up periods would provide more insight into the persistence of these effects over time. Future research should address these limitations by incorporating more diverse samples, improving data collection precision, and accounting for additional confounding variables. A larger sample size and multicenter designs would enhance the generalizability and reliability of the findings. Furthermore, prospective studies are needed to better define the causal relationships and to explore the mechanisms behind these observations.

Conclusion

Postoperative overdose of GCs has a higher rate of complications, prolonged hospital stay, and an increased risk of recurrence and metastasis. In conclusion, while the perioperative administration of GCs in HNS-FFR can be beneficial for managing inflammation and stress responses, excessive use appears to compromise not only immediate surgical recovery but also long-term oncologic outcomes. These insights highlight the importance of tailored glucocorticoid regimens based on thorough preoperative assessments and intraoperative findings to optimize both immediate and long-term patient outcomes.

Supporting information

S1 Fig. Schematic flowchart.
(DOCX)

S1 Checklist. STROBE checklist.
(DOCX)

S1 Table. Clavien-Dindo classification.
(DOCX)

S2 Table. Postoperative data and complications.
(DOCX)

S3 Table. Subgroup analysis.
(DOCX)

Acknowledgments

Not applicable.

Author contributions

Data curation: Tao Luo.

Methodology: Ren Zhou.

Supervision: Yu Sun.

Validation: Yu Sun.

Writing – original draft: Tao Luo.

References

1. Mody MD, Rocco JW, Yom SS, Haddad RI, Saba NF. Head and neck cancer. Lancet. 2021;398(10318):2289–99. Epub 2021/09/26. https://doi.org/10.1016/S0140-6736(21)01550-6 PMID: 34562395

2. Hedberg ML, Grandis JR. 33 - The Molecular Pathogenesis of Head and Neck Cancer. In: Mendelsohn J, Gray JW, Howley PM, Israel MA, Thompson CB, editors. The Molecular Basis of Cancer (Fourth Edition). Philadelphia: W.B. Saunders; 2015. p. 491-8.e2.

3. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92. Epub 2020/11/28. https://doi.org/10.1038/s41572-020-00224-3 PMID: 33243986; PMCID: PMCPMC7944998

4. Futran ND, Alsarraf R. Microvascular free-flap reconstruction in the head and neck. JAMA. 2000;284(14):1761–3. Epub 2000/10/12. https://doi.org/10.1001/jama.284.14.1761 PMID: 11025806

5. Caudell JJ, Torres-Roca JF, Gillies RJ, Enderling H, Kim S, Rishi A, et al. The future of personalised radiotherapy for head and neck cancer. Lancet Oncol. 2017;18(5):e266–73. Epub 2017/05/01. https://doi.org/10.1016/S1470-2045(17)30252-8 PMID: 28456586

6. Muscari I, Fierabracci A, Adorisio S, Moretti M, Cannarile L, Thi Minh Hong V, et al. Glucocorticoids and natural killer cells: A suppressive relationship. Biochem Pharmacol. 2022;198:114930. Epub 2022/02/13. https://doi.org/10.1016/j.bcp.2022.114930 PMID: 35149054

7. Seyfried TN, Shelton LM, Mukherjee P. Does the existing standard of care increase glioblastoma energy metabolism?. Lancet Oncol. 2010;11(9):811–3. Epub 2010/07/17. https://doi.org/10.1016/S1470-2045(10)70166-2 PMID: 20634134

8. Zhang C, Beckermann B, Kallifatidis G, Liu Z, Rittgen W, Edler L, et al. Corticosteroids induce chemotherapy resistance in the majority of tumour cells from bone, brain, breast, cervix, melanoma and neuroblastoma. Int J Oncol. 2006;29(5):1295–301. Epub 2006/10/04. PMID: 17016664

9. Pitter KL, Tamagno I, Alikhanyan K, Hosni-Ahmed A, Pattwell SS, Donnola S, et al. Corticosteroids compromise survival in glioblastoma. Brain. 2016;139(Pt 5):1458–71. Epub 2016/03/30. https://doi.org/10.1093/brain/aww046 PMID: 27020328; PMCID: PMCPMC5006251

10. Shields LBE, Shelton BJ, Shearer AJ, Chen L, Sun DA, Parsons S, et al. Dexamethasone administration during definitive radiation and temozolomide renders a poor prognosis in a retrospective analysis of newly diagnosed glioblastoma patients. Radiat Oncol. 2015;10:222. Epub 2015/11/02. https://doi.org/10.1186/s13014-015-0527-0 PMID: 26520780; PMCID: PMCPMC4628380

11. Cirillo N, Prime SS. Keratinocytes synthesize and activate cortisol. J Cell Biochem. 2011;112(6):1499–505. Epub 2011/02/24. https://doi.org/10.1002/jcb.23081 PMID: 21344493

12. Cirillo N, Morgan DJ, Pedicillo MC, Celentano A, Lo Muzio L, McCullough MJ, et al. Characterisation of the cancer-associated glucocorticoid system: key role of 11β-hydroxysteroid dehydrogenase type 2. Br J Cancer. 2017;117(7):984–93. Epub 2017/08/11. https://doi.org/10.1038/bjc.2017.243 PMID: 28797028

13. Yang H, Xia L, Chen J, Zhang S, Martin V, Li Q, et al. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. Nat Med. 2019;25(9):1428–41. Epub 2019/09/11. https://doi.org/10.1038/s41591-019-0566-4 PMID: 31501614

14. Bernabé DG, Tamae AC, Miyahara GI, Sundefeld MLM, Oliveira SP, Biasoli ÉR. Increased plasma and salivary cortisol levels in patients with oral cancer and their association with clinical stage. J Clin Pathol. 2012;65(10):934–9. Epub 2012/06/27. https://doi.org/10.1136/jclinpath-2012-200695 PMID: 22734006

15. Kainulainen S, Törnwall J, Koivusalo AM, Suominen AL, Lassus P. Dexamethasone in head and neck cancer patients with microvascular reconstruction: No benefit, more complications. Oral Oncol. 2017;65:45–50. https://doi.org/10.1016/j.oraloncology.2016.12.008 PMID: 28109467

16. Kainulainen S, Aro K, Koivusalo A-M, Wilkman T, Roine RP, Aronen P, et al. Perioperative Dexamethasone Is Associated With Higher Short-Term Mortality in Reconstructive Head and Neck Cancer

Surgery. J Oral Maxillofac Surg. 2020;78(10):1835–45. Epub 2020/06/17. https://doi.org/10.1016/j.joms.2020.05.004 PMID: 32540321

17. Offodile AC 2nd, Chou H-Y, Lin JA-J, Loh CYY, Chang K-P, Aycart MA, et al. Hyperglycemia and risk of adverse outcomes following microvascular reconstruction of oncologic head and neck defects. Oral Oncol. 2018;79:15–9. Epub 2018/03/31. https://doi.org/10.1016/j.oraloncology.2018.02.009 PMID: 29598945

18. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32(6):1119–31. Epub 2009/05/12. https://doi.org/10.2337/dc09-9029 PMID: 19429873 PMCID: PMCPMC2681039

19. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13. Epub 2004/07/27. https://doi.org/10.1097/01.sla.0000133083.54934.ae PMID: 15273542; PMCID: PMCPMC1360123

20. Smith DK, Freundlich RE, Shinn JR, Wood CB, Rohde SL, McEvoy MD. An improved predictive model for postoperative pulmonary complications after free flap reconstructions in the head and neck. Head Neck. 2021;43(7):2178–84. Epub 2021/03/31. https://doi.org/10.1002/hed.26689 PMID: 33783905; PMCID: PMCPMC8197740

21. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204. Epub 2013/02/12. https://doi.org/10.1186/cc11454 PMID: 23394211; PMCID: PMCPMC4057151

22. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis. 1989;11(6):954–63. Epub 1989/11/01. https://doi.org/10.1093/clinids/11.6.954 PMID: 2690289

23. Shestak KC, Jones NF, Wu W, Johnson JT, Myers EN. Effect of advanced age and medical disease on the outcome of microvascular reconstruction for head and neck defects. Head Neck. 1992;14(1):14–8. Epub 1992/01/01. https://doi.org/10.1002/hed.2880140104 PMID: 1624289

24. Lai C-J, Shih P-Y, Cheng Y-J, Lin C-K, Cheng S-J, Peng H-H, et al. Incidence and risk factors of postoperative pulmonary complications after oral cancer surgery with free flap reconstruction: A single center study. J Formos Med Assoc. 2024;123(3):347–56. Epub 2023/09/23. https://doi.org/10.1016/j.jfma.2023.09.003 PMID: 37739911

25. Shaw LM, Iseli TA, Wiesenfeld D, Ramakrishnan A, Granger CL. Postoperative pulmonary complications following major head and neck cancer surgery. Int J Oral Maxillofac Surg. 2021;50(3):302–8. Epub 2020/07/20. https://doi.org/10.1016/j.ijom.2020.06.011 PMID: 32682644

26. Pofi R, Caratti G, Ray DW, Tomlinson JW. Treating the Side Effects of Exogenous Glucocorticoids; Can We Separate the Good From the Bad?. Endocr Rev. 2023;44(6):975–1011. Epub 2023/05/30. https://doi.org/10.1210/endrev/bnad016 PMID: 37253115 PMCID: PMCPMC10638606.

27. Kuss I, Hathaway B, Ferris RL, Gooding W, Whiteside TL. Decreased absolute counts of T lymphocyte subsets and their relation to disease in squamous cell carcinoma of the head and neck. Clin Cancer Res. 2004;10(11):3755–62. Epub 2004/06/03. https://doi.org/10.1158/1078-0432.CCR-04-0054 PMID: 15173082

28. Perrot S, Le Jeune C. Steroid-induced myopathy. Presse Med. 2012;41(4):422–6. Epub 2012/02/14. https://doi.org/10.1016/j.lpm.2012.01.004 PMID: 22326665

29. Decramer M, de Bock V, Dom R. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1996;153(6 Pt 1):1958–64. Epub 1996/06/01. https://doi.org/10.1164/ajrccm.153.6.8665061 PMID: 8665061

30. Beaupere C, Liboz A, Fève B, Blondeau B, Guillemain G. Molecular Mechanisms of Glucocorticoid-Induced Insulin Resistance. Int J Mol Sci. 2021;22(2):623. Epub 2021/01/14. https://doi.org/10.3390/ijms22020623 PMID: 33435513; PMCID: PMCPMC7827500

31. Fardet L, Kassar A, Cabane J, Flahault A. Corticosteroid-induced adverse events in adults: frequency, screening and prevention. Drug Saf. 2007;30(10):861–81. Epub 2007/09/18. https://doi.org/10.2165/00002018-200730100-00005 PMID: 17867724

32. Ramos M, Khalpey Z, Lipsitz S, Steinberg J, Panizales MT, Zinner M, et al. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. Ann Surg. 2008;248(4):585–91. Epub 2008/10/22. https://doi.org/10.1097/SLA.0b013e31818990d1 PMID: 18936571

33. Snäll J, Kormi E, Koivusalo A-M, Lindqvist C, Suominen AL, Törnwall J, et al. Effects of perioperatively administered dexamethasone on surgical wound healing in patients undergoing surgery for zygomatic fracture: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;117(6):685–9. Epub 2014/05/21. https://doi.org/10.1016/j.oooo.2014.02.033 PMID: 24842445

34. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17(4):233–47. Epub 2017/02/14. https://doi.org/10.1038/nri.2017.1 PMID: 28192415 PMCID: PMCPMC9761406

35. Lee B, Vouthounis C, Stojadinovic O, Brem H, Im M, Tomic-Canic M. From an enhanceosome to a repressosome: molecular antagonism between glucocorticoids and EGF leads to inhibition of wound healing. J Mol Biol. 2005;345(5):1083–97. Epub 2005/01/13. https://doi.org/10.1016/j.jmb.2004.11.027 PMID: 15644206

36. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30. Epub 2013/08/21. https://doi.org/10.1186/1710-1492-9-30 PMID: 23947590 PMCID: PMCPMC3765115.

37. Ma Y, Yang H, Kroemer G. Endogenous and exogenous glucocorticoids abolish the efficacy of immune-dependent cancer therapies. Oncoimmunology. 2019;9(1):1673635. Epub 2020/02/01. https://doi.org/10.1080/2162402X.2019.1673635 PMID: 32002285 PMCID: PMCPMC6959448

38. Mei Z, Huang J, Qiao B, Lam AK-Y. Immune checkpoint pathways in immunotherapy for head and neck squamous cell carcinoma. Int J Oral Sci. 2020;12(1):16. Epub 2020/05/29. https://doi.org/10.1038/s41368-020-0084-8 PMID: 32461587 PMCID: PMCPMC7253444

39. Azher S, Azami O, Amato C, McCullough M, Celentano A, Cirillo N. The Non-Conventional Effects of Glucocorticoids in Cancer. J Cell Physiol. 2016;231(11):2368–73. Epub 2016/04/27. https://doi.org/10.1002/jcp.25408 PMID: 27115293

40. Herr I, Pfitzenmaier J. Glucocorticoid use in prostate cancer and other solid tumours: implications for effectiveness of cytotoxic treatment and metastases. Lancet Oncol. 2006;7(5):425–30. Epub 2006/05/02. https://doi.org/10.1016/S1470-2045(06)70694-5 PMID: 16648047