Perioperative Dexamethasone Is Associated With Higher Short-Term Mortality in Reconstructive Head and Neck Cancer Surgery

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Purpose: Studies of the effects of perioperative dexamethasone (DEX) during oncologic surgery are scarce. The first aim of the present study was to clarify whether perioperative DEX affects the short-term mortality in patients with head and neck cancer (HNC). The second aim was to analyze the causes of death and predictors affecting long-term mortality.

Patients and Methods: The present prospective, double-blind randomized, controlled study included patients with HNC who had undergone microvascular reconstruction from 2008 through 2013. The patients were randomized into 2 groups: the receipt of perioperative DEX for 3 days (study group) or no DEX (control group). The patients' data and cause of death were registered until the end of 2017. The primary cause of death was used in the analyses.

Results: A total of 93 patients were included in the present study: 51 in the DEX group (study group) and 42 in the NON-DEX group (control group). Altogether 38 patients died during a median follow-up period of 5.3 years. During the first year, more deaths had occurred in the DEX group than in the NON-DEX group: at 1 month, 4% versus 0%; at 6 months, 14% versus 0%; and at 12 months, 22% versus 5% ($P = .043$). The overall survival rate for all patients was 59%. HNC was the primary cause of death for most of the patients who died. On univariate analysis, the deceased patients had more advanced disease (higher T classification, $P = .002$; higher stage, $P = .008$), a greater need for a gastrostoma ($P = .002$), more often received postoperative chemotherapy ($P = .005$), and more often had locoregional ($P = .025$) or distal ($P < .001$) metastases. In the multivariate Cox model, the most important long-term predictors of death were the presence of

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The present study was supported by the Helsinki University Hospital Research Fund.

Conflict of Interest Disclosures: None of the authors have any relevant financial relationship(s) with a commercial interest.

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Received July 23 2019

Accepted May 2 2020

0278-2391/20/30457-2

https://doi.org/10.1016/j.joms.2020.05.004

distant metastases ($P < .001$), a Charlson comorbidity index (CCI) of 5 to 9 ($P < .001$), and the use of perioperative DEX ($P = .004$).

Conclusions: The use of perioperative DEX was associated with higher short-term mortality after reconstructive HNC surgery. The most important long-term predictors of death were the receipt of DEX, the presence of distant metastases, and a CCI of 5 to 9. These findings do not encourage the routine use of perioperative DEX for these patients.

J Oral Maxillofac Surg 78:1835-1845, 2020

Surgery for advanced head and neck cancer (HNC) will often be mutilating, and the large defects that result from tumor resection will require reconstruction with free flaps. The complexity of the surgery with the possible complications influences the survival of patients with HNC. The 5-year disease-specific survival of patients with head and neck squamous cell cancer (HNSCC) has improved during previous decades from 55 to 66%.[1,2] However, the overall survival (OS) at 5 years has been lower, reported to be ~50 to 60%.[3-5] With an aging population, the patients with HNC undergoing surgery have also been aging, with an increasing burden of comorbidities.

The occurrence of postoperative complications after free flap reconstruction for HNC impairs survival.[6-8] Perioperative glucocorticoids (GCs), mainly dexamethasone (DEX), have been widely used in HNC surgery because of their anti-inflammatory effects, and numerous patients with HNC have received GCs for the prevention of pain, swelling, nausea, and vomiting during their perioperative treatment. However, the safety of GCs has remained unclear. Only a few studies have evaluated the influence of perioperative DEX on the oncologic surgery outcomes. de Oliveira et al[9] did not find a significant association between the perioperative administration of DEX and tumor recurrence in 260 patients undergoing for ovarian cancer. Yu et al[10] studied the effects of perioperative DEX in 515 patients with rectal cancer who had undergone radical surgery. They reported that patients who had received DEX had significantly lower 3-year disease-free survival and OS.[10]

We have previously shown that the use of perioperative DEX increases the incidence of major complications in patients with HNC undergoing microvascular reconstruction, which could also have affected patient survival.[11] Thus, the purpose of the present study was to investigate whether the use of perioperative DEX would influence the short-term survival of patients with HNC. The second aim was to assess the causes of death and the factors associated with mortality during long-term follow-up of patients who had undergone surgery and reconstruction for HNC.

Patients and Methods

STUDY DESIGN

To address the research purpose, we designed and implemented a prospective, randomized, double-blind, controlled study. The study population included all patients who presented for evaluation and management of HNC at the Department of Oral and Maxillofacial Surgery and Department of Plastic Surgery, Helsinki University Hospital, from December 2008 to February 2013. These patients were followed until the end of 2017. To be included in the study cohort, adult patients with HNC had to have required microvascular reconstruction. Patients were excluded if they had a history of liver or kidney dysfunction, glaucoma, peptic ulcer, psychosis from the use of steroids, an allergy to any constituent of the DEX preparation used, or refused to provide written informed consent. The multidisciplinary head and neck tumor board of Helsinki University Hospital determines the treatment for all patients with HNC in our catchment area of 1.6 million people. The present study followed the Declaration of Helsinki regarding the medical protocol and ethics. The regional ethical review board of Helsinki University Hospital, Finland, approved the present study, which was registered with EudraCT (registry no. 2008-000892-11). All included patients had provided written informed consent before randomization.

STUDY VARIABLES

For the survival analysis, the primary predictor variable was the treatment group, classified as DEX or NON-DEX, according to whether the patient had received DEX. The patients were followed until the end of 2017, and the cause of death for the deceased patients was obtained from the death certificates of Statistics Finland. In Finland, the cause of death is classified as immediate, intermediate, or contributing and categorized as "disease," "occupational," "trauma," "medical complications," "homicide," "suicide," "war," or "unclear." The classification for the cause of death was determined using the Finnish Cause of Death Registry.[12] An intermediate cause of death refers to a condition that has led from the underlying cause to an immediate cause of death. The primary (intermediate) cause of death was used to divide the deaths into 3

Table 1. PATIENT DATA

Variable	Group		Total (n = 93)	*P* Value*
	DEX (n = 51)	NON-DEX (n = 42)		
Gender				.878†
Female	19 (37.3)	15 (35.7)	34 (36.6)	
Male	32 (62.7)	27 (64.3)	59 (63.4)	
BMI‡ (kg/m^2)				.331§
Median	25.5	24.5	24.9	
Range	15.8-42.7	17.0-32.6	15.8- 42.7	
ASA class				.344†
1	3 (5.9)	3 (7.1)	6 (6.5)	
2	10 (19.6)	13 (31.0)	23 (24.7)	
3	27 (52.9)	22 (52.4)	49 (52.7)	
4	11 (21.6)	4 (9.5)	15 (16.1)	
History of alcohol use‖				.038*†
Major	8 (15.7)	13 (31.7)	21 (22.8)	
Moderate	23 (45.1)	21 (51.2)	44 (47.8)	
No	20 (39.2)	7 (17.1)	27 (29.3)	
History of smoking¶				.583†
Yes	19 (37.3)	18 (42.9)	37 (39.8)	
No	32 (62.7)	24 (57.1)	56 (60.2)	
CCI				.363†
0-1	24 (47.1)	25 (59.5)	49 (52.7)	
2-4	19 (37.3)	10 (23.8)	29 (31.2)	
5-9	8 (15.7)	7 (16.7)	15 (16.1)	
Age at surgery (yr)				.537§
Median	65.4	64.7	65.2	
Range	39.2-92.8	34.2-87.6	34.2-92.9	
Airway access for mechanical ventilation				.047*†
Intubation	30 (58.8)	16 (38.1)	46 (49.5)	
Tracheostomy	21 (41.2)	26 (61.9)	47 (50.5)	
PEG				.228†
Yes	19 (37.3)	23 (54.8)	42 (45.2)	
No	28 (54.9)	16 (38.1)	44 (47.3)	
Later	4 (7.8)	3 (7.1)	7 (7.5)	
Reconstruction type				.745†
Bone	5 (9.8)	5 (11.9)	10 (10.8)	
Soft tissue	46 (90.2)	37 (88.1)	83 (89.2)	
Primary lesion site				.699†
Maxilla	9 (17.6)	6 (14.3)	15 (16.1)	
Mandible	14 (27.5)	12 (28.6)	26 (28.0)	
Tongue	13 (25.5)	14 (33.3)	27 (29.0)	
Floor of mouth	8 (15.7)	3 (7.1)	11 (11.8)	
Buccal mucosa	5 (9.8)	4 (9.5)	9 (9.7)	
Tonsil	1 (2.0)	2 (4.8)	3 (3.2)	
Palate	1 (2.0)	0 (0.0)	1 (1.1)	
Larynx, hypopharynx	0 (0.0)	1 (2.4)	1 (1.1)	
Flap type				.440†
ALT	15 (29.4)	17 (40.5)	32 (34.4)	
Forearm flap	31 (60.8)	20 (47.6)	51 (54.8)	
Other#	5 (9.8)	5 (11.9)	10 (10.8)	
Neck dissection				.207†
Unilateral	45 (88.2)	33 (78.6)	78 (83.9)	
Bilateral	6 (11.8)	9 (21.4)	15 (16.1)	
Neck dissection level				.201†
Sentinel lymph node biopsy	7 (13.7)	3 (7.1)	10 (10.8)	

Table 1. Cont'd

Variable	Group		Total (n = 93)	*P* Value*
	DEX (n = 51)	NON-DEX (n = 42)		
1-3	18 (35.3)	10 (23.8)	28 (30.1)	
1-4/5 or radical	26 (51.0)	29 (69.0)	55 (59.1)	

Data presented as n (%) or median and range.

Abbreviations: ALT, anterolateral thigh perforator flap; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; DEX, dexamethasone; NON-DEX, no dexamethasone; PEG, percutaneous endoscopic gastrostomy.

* Statistically significant ($P < .05$).

† Pearson χ^2 test.

‡ Data missing for 1 patient.

§ Kruskal-Wallis rank sum test.

‖ Alcohol use was defined as moderate if drinking was weekly or less and major if it occurred daily, data missing for 2 patients.

¶ Patients were defined as smokers if they had smoked before surgery.

Four deep circumflex iliac artery bone flaps, 1 fibular flap, 1 latissimus dorsi muscle flap, 2 scapular plus latissimus dorsi muscle flap, 1 scapular plus parascapular flap.

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categories: HNC, non-HNC, and other. Additional variables were collected from the patients' medical records: free flap type, tumor location, tumor stage, American Society of Anesthesiologists class, Charlson comorbidity index (CCI), body mass index (BMI), alcohol use, smoking (smoking status was recorded at primary surgery but not during follow-up), postoperative intensity-modulated radiotherapy (~60 to 66 Gy to the primary site and neck) and/or chemotherapy, number of complications, number of surgeries, and possible tumor recurrence or metastasis. Surgical complications were classified according to the Dindo-Clavien classification, and all patients with major complications required additional surgery within 3 weeks.[13,14]

DATA COLLECTION

The patients were randomly allocated into 2 groups: DEX and NON-DEX. The patients in the study group received DEX (Oradexon; Famar L'Aigle, France) 10 mg intravenously 3 times daily for the first day, 2 times daily the second day, and 1 time the third day, for a total dose of 60 mg. The patients in the control group did not receive any DEX (NON-DEX group). Randomization was performed by a person not participating in the study. The information regarding patient allocation was provided in a sealed envelope to the anesthesiologist, who administered all doses to the patients. The surgeons did not know the patients' assignments to the groups.

STATISTICAL ANALYSIS

Descriptive statistics are reported as the mean ± standard deviation, median, or percentage. The statistical significance of the differences between the 2 groups was tested using the χ^2 test or independent samples *t* test. The analysis of short-term survival for the DEX and NON-DEX groups was performed using univariate analysis. The factors associated with long-term death were assessed using univariate and multivariate Cox proportional hazard models, and the results are reported as hazard ratios. The variables selected for the multivariate model were those with statistical significance in the univariate model and/or with clinical relevance using the least absolute shrinkage and selection operator.[15] In addition, a Kaplan-Meier plot was used to compare the survival between the 2 groups. Two-sided *P* values < .05 were regarded as statistically significant. A power analysis to determine the number of patients required for each group had been performed in our previous study of the same patient cohort.[11] Statistical analysis was performed using SPSS for Windows, version 22 (IBM Corp, Armonk, NY) and R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).[16]

Results

DEMOGRAPHIC DATA

Initially, 110 consecutive patients with HNC were included in the present study and randomized into 2 groups, with 55 in each group. After the inclusion criterion assessment, 13 patients were excluded from the study population. An additional 4 patients were excluded; 3 because of intraoperative cancellation of free flap reconstruction and 1 because of the administration of an additional dose of DEX. Thus, 93 patients were included in the present study. Of the 93 patients,

Table 2. COMPARISON OF STUDY VARIABLES AND SURVIVAL DATA (MEDIAN FOLLOW-UP, 5.3 YEARS)

Variable	Survived (n = 55)	Died (n = 38)	Total (n = 93)	*P* Value[*]
Group				.259[†]
DEX	27 (49.1)	24 (63.2)	51 (54.8)	
NON-DEX	28 (50.9)	14 (36.8)	42 (45.2)	
Gender				.628[†]
Female	19 (34.5)	15 (39.5)	34 (36.6)	
Male	36 (65.5)	23 (60.5)	59 (63.4)	
BMI[‡] (kg/m^2)				.284[§]
Median	24.7	25.6	24.9	
Range	16.0-39.4	15.8-42.7	15.8-42.7	
ASA class				.621[†]
1	5 (9.1)	1 (2.6)	6 (6.5)	
2	14 (25.5)	9 (23.7)	23 (24.7)	
3	28 (50.9)	21 (55.3)	49 (52.7)	
4	8 (14.5)	7 (18.4)	15 (16.1)	
History of alcohol use[‖¶]				.137[†]
Major	13 (23.6)	8 (21.6)	21 (22.8)	
Moderate	30 (54.5)	14 (37.8)	44 (47.8)	
No	12 (21.8)	15 (40.5)	27 (29.3)	
History of smoking[#]				.704[†]
Yes	21 (38.2)	16 (42.1)	37 (39.8)	
No	34 (61.8)	22 (57.9)	56 (60.2)	
CCI				.082[†]
0-1	32 (58.2)	17 (44.7)	49 (52.7)	
2-4	18 (32.7)	11 (28.9)	29 (31.2)	
5-9	5 (9.1)	10 (26.3)	15 (16.1)	
Age at surgery (yr)				.522[§]
Median	64.7	66.0	65.2	
Range	39.2-87.7	34.2-92.8	34.2-92.8	
Airway access for mechanical ventilation				.238[†]
Intubation	30 (54.5)	16 (42.1)	46 (49.5)	
Tracheostomy	25 (45.5)	22 (57.9)	47 (50.5)	
PEG				.002[*†]
Yes	19 (34.5)	23 (60.5)	42 (45.2)	
No	34 (61.8)	10 (26.3)	44 (47.3)	
Later	2 (3.6)	5 (13.2)	7 (7.5)	
Reconstruction type				.534[†]
Bone	5 (9.1)	5 (13.2)	10 (10.8)	
Soft tissue	50 (90.9)	33 (86.8)	83 (89.2)	
Primary lesion site				.428[†]
Maxilla	8 (14.5)	7 (18.4)	15 (16.1)	
Mandible	11 (20.0)	15 (39.5)	26 (28.0)	
Tongue	17 (30.9)	10 (26.3)	27 (29.0)	
Floor of mouth	8 (14.5)	3 (7.9)	11 (11.8)	
Buccal mucosa	7 (12.7)	2 (5.3)	9 (9.7)	
Tonsil	2 (3.6)	1 (2.6)	3 (3.2)	
Palate	1 (1.8)	0 (0.0)	1 (1.1)	
Larynx, hypopharynx	1 (1.8)	0 (0.0)	1 (1.1)	
Flap type				.053[†]
ALT	17 (30.9)	15 (39.5)	32 (34.4)	
Forearm flap	35 (63.6)	16 (42.1)	51 (54.8)	
Other[**]	3 (5.5)	7 (18.4)	10 (10.8)	
Neck dissection				.283[†]
Unilateral	48 (87.3)	30 (78.9)	78 (83.9)	
Bilateral	7 (12.7)	8 (21.1)	15 (16.1)	

Table 2. Cont'd

Variable	Survived (n = 55)	Died (n = 38)	Total (n = 93)	*P* Value*
Neck dissection level				.506†
Sentinel lymph node biopsy	6 (10.9)	4 (10.5)	10 (10.8)	
1-3	19 (34.5)	9 (23.7)	28 (30.1)	
1-4/5 or radical	30 (54.5)	25 (65.8)	55 (59.1)	
pT classification††	2.07 ± 1.36	2.97 ± 1.21	2.44 ± 1.37	.002*‡‡
Stage§§				.008*†
1	24 (43.6)	4 (10.8)	28 (30.4)	
2	4 (7.3)	3 (8.1)	7 (7.6)	
3	5 (9.1)	4 (10.8)	9 (9.8)	
4	22 (40.0)	26 (70.3)	48 (52.2)	
Postoperative radiotherapy				.076†
No	32 (58.2)	15 (39.5)	47 (50.5)	
Yes	23 (41.8)	23 (60.5)	46 (49.5)	
Postoperative chemotherapy‖‖				.005*†
No	47 (85.5)	22 (59.5)	69 (75.0)	
Yes	8 (14.5)	15 (40.5)	23 (25.0)	
Major complication				.096†
No	48 (87.3)	28 (73.7)	76 (81.7)	
Yes	7 (12.7)	10 (26.3)	17 (18.3)	
During follow-up				
Second primary				.414†
No	47 (85.5)	30 (78.9)	77 (82.8)	
Yes	8 (14.5)	8 (21.1)	16 (17.2)	
Distant metastasis				<.001*†
No	54 (98.2)	26 (68.4)	80 (86.0)	
Yes	1 (1.8)	12 (31.6)	13 (14.0)	
Locoregional metastasis				.025*†
No	51 (92.7)	29 (76.3)	80 (86.0)	
Yes	4 (7.3)	9 (23.7)	13 (14.0)	

Data presented as n (%), median and range, or mean ± standard deviation.

Abbreviations: ALT, anterolateral thigh perforator flap; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; DEX, dexamethasone; NON-DEX, no dexamethasone; PEG, percutaneous endoscopic gastrostomy.

* Statistically significant at $P < .05$.

† Pearson χ^2 test.

‡ Data missing for 1 patient.

§ Kruskal-Wallis rank sum test.

‖ Alcohol use defined as moderate if drinking was weekly or less and major if daily.

¶ Data missing for 2 patients.

Patients were defined as smokers if they had smoked before surgery.

** Four deep circumflex iliac artery bone flaps, 1 fibular flap, 1 latissimus dorsi muscle flap, 2 scapular plus latissimus dorsi muscle flap, 1 scapular plus parascapular flap.

†† Data missing for 2 patients.

‡‡ Linear model analysis of variance (Mann-Whitney *U* test for 2 groups).

§§ Data missing for 2 patients.

‖‖ Data missing for 2 patients.

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51 had received DEX, and 42 had not received DEX (control group). The discrepancy in the size of the 2 groups resulted from the effects of chance in the randomization process. Most (92%) of the tumors were HNSCC. The only statistically significant difference between the 2 groups at baseline in the preoperative data was the proportion of those reporting major alcohol use (DEX, 16%; NON-DEX, 32%; $P = .038$). Alcohol use was defined as moderate if alcohol consumption was weekly or less and major if it occurred daily. Perioperative management of the airway was different between the 2 groups ($P = .047$). None of the patients had radiologically diagnosed distant metastasis before primary surgery. The demographic data and their associations with the treatment group are listed in Table 1. Of the 93 patients, 18% developed

a major complication. The second primary HNC rate was 17% (16 patients). The second primary HNC had been diagnosed 32 to 3363 days (median, 612 days) postoperatively. Locoregional metastasis on the neck developed in 13 patients (14%). It had been diagnosed 52 to 1982 days (median, 600 days) postoperatively. Distant metastasis developed in 13 patients (14%) and had been diagnosed 32 to 1982 days (median, 244 days) postoperatively (Table 2). In addition, 4 patients developed another cancer besides HNC during follow-up.

SHORT-TERM SURVIVAL

Of the 93 patients, 2 died within 33 days, both in the DEX group. During the first 6 months postoperatively, 7 patients died in the DEX group but none in the NON-DEX group. After 1 year, 11 patients died in the DEX group and 2 in the NON-DEX group (χ^2 test, P = .043; Fig 1). Of the 7 patients in the DEX group who died during the first 6 months, 5 (71%) developed postoperative complications. Of these 5 patients, 2 required numerous operations because of the rapid spread of cancer, 1 developed pneumonia, 1 developed local infection, and 1 developed venous thrombosis. The primary cause of death was HNC for all the patients who died during the first 12 months postoperatively.

LONG-TERM SURVIVAL

For the whole cohort, the median follow-up period was 5.3 years (range, 0.07 to 9 years). The OS for all patients was 59% (55 of 93). The primary cause of death was HNC for most of the patients who died in the whole cohort (30 of 38; 79%). Three patients died of a non-HNC cause (1 of prostate cancer, 1 of colon cancer, and 1 of bladder cancer). Five patients died of another cause (4 of cardiovascular disease and 1 of preoperatively undiagnosed alcoholic liver cirrhosis). Although more patients died in the DEX group during the follow-up period, using the Kaplan-Meier curve and log-rank test, no statistically significant differences were found in long-term survival between the 2 groups (Fig 2).

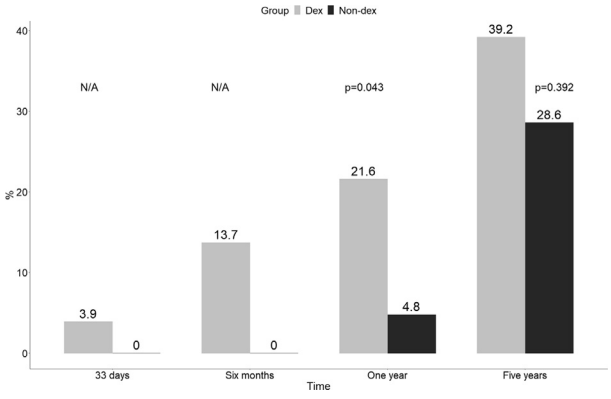

FIGURE 1. Bar graph showing the percentage of deceased patients at different points during follow-up stratified by treatment group. Dex, dexamethasone group; Non-dex, control group; N/A, statistical methods not available.

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During the long-term follow-up, the patients who died were more likely to have had more advanced decease (higher T classification, P = .002; higher stage, P = .008), to need a gastrostoma (P = .002), to have received postoperative chemotherapy (P = .005), and to have locoregional (P = .025) or (P < .001) distant metastases more often during follow-up (Table 2).

For the initial multivariate Cox model, we identified 13 confounders. Three variables (ie, chemotherapy, BMI, alcohol use) had 1 or 2 missing observations that we provided using random imputation. After adjustment, in contrast to the univariate analysis results, the use of DEX predicted for an excess risk of mortality (P = .004). Also, the results from the reduced model suggested that the other statistically significant long-term predictors of death and poor OS during follow-up were a CCI of 5 to 9 and the presence of distant metastasis. The global Schoenfeld test results indicated that the proportional hazard assumption held in the multivariate Cox model[17,18] (Table 3).

Discussion

The first purpose of the present prospective, randomized, double-blind, controlled study was to investigate the association between the perioperative use of DEX and short-term survival after free flap surgery in patients with HNC. The second aim was to clarify the cause of death and long-term predictors affecting long-term mortality. To the best of our knowledge, the present study is the first to examine the effect of GCs on mortality in patients undergoing major microvascular reconstruction. We hypothesized that DEX might also have an effect on the short-term survival of patients with cancer because it can cause major complications and also induces immunosuppression.

Our previous study had shown a greater number of complications in those patients who received perioperative DEX.[19] In the present study, the use of perioperative DEX was associated with higher short-term mortality. All patients who died within 6 months postoperatively and 85% of those who died within 12 months postoperatively had been in the DEX group. Almost all the patients who died within 1 year postoperatively developed postoperative complications. In the present study, the most important predictors associated with long-term mortality were receipt of DEX, a CCI of 5 to 9, and the presence of

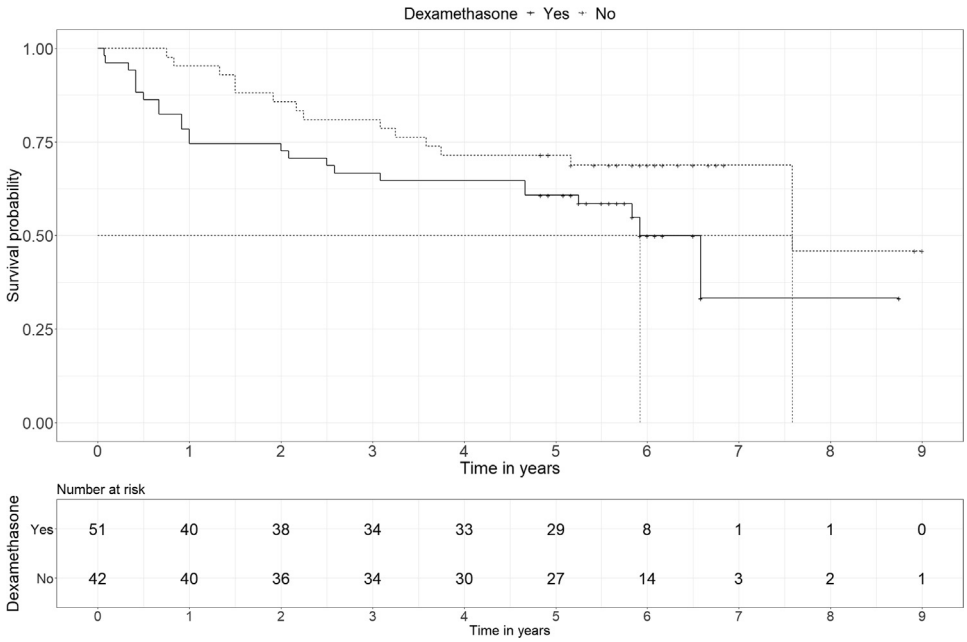

FIGURE 2. Kaplan-Meier overall survival curve for patients in dexamethasone (DEX) and non-dexamethasone (NON-DEX) groups: 24 events (hazard ratio, 0.115) occurred in the DEX group and 14 (hazard ratio, 0.0673) in the NON-DEX group; log-rank statistic was 0.094 for the whole follow-up period and 0.019 for the first 12 months.

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distant metastases. Also, those patients who died were more likely to have had a more advanced initial oncologic disease stage.

The use of free flaps has enabled radical ablative surgery. Radical surgery with negative surgical margins has been an independent predictor of local recurrence and patient survival.[4,20] In the present study, we did not analyze the effect of surgical margin status on patient death. The multidisciplinary head and neck tumor board of Helsinki University Hospital provides recommendations for the treatment of all patients with HNC in our institution. In our cohort, none of the deceased patients required additional surgery or developed recurrence at the primary site. Most patients with HNC requiring free flaps will have more advanced-stage disease. This could be expected to influence patient survival, independent of the reconstructive method used.

Our results support the hypothesis that perioperatively administered DEX can be harmful to patients because it can increase the occurrence of postoperative complications and, thus, result in more serious side effects. Impaired wound healing is a considerable disadvantage of GCs and can increase the risk of postoperative complications. Another concern is that DEX might have an effect on patient survival because it induces immunosuppression and can suppress cell proliferation and promote resistance to apoptosis in tumor cells.[21,22] Khuri et al[23] studied the determinants of 30-day postoperative mortality and long-term survival after 8 different types of major surgery, including vascular reconstructive surgery, in the US Veterans Administration.[23] That study showed that the most important determinant of decreased postoperative survival was the occurrence of complications within 30 days postoperatively. Imai et al[24] evaluated the effect of preoperative GC administration during major surgery for HNC as a part of the Enhanced Recovery After Surgery program and compared the outcomes with those of a control group who had undergone surgery before implementation of the protocol and had not received GCs. They did not find an increase in the number of complications related to GC use. However, in that retrospective study, the number of patients had been limited to 28.[24] de Cassia Braga Ribeiro et al[25] studied the clinical factors and morbidity and mortality of 530 patients with oral and oropharyngeal cancer. They and found that the occurrence of local complications (wound infection) and systemic complications independently worsened 5-year OS ($P < .001$).[25] In our cohort, after adjustment for confounding factors, we observed a difference in long-term survival between the 2 groups, which was evident throughout follow-up (Table 3, Fig 2). In our institute, we have already discontinued the use of perioperative DEX for patients with HNC, because the results from our previous study indicated that its use causes more harm than benefit.[11,19]

Knowledge of the cause of death after microvascular reconstruction in patients with HNC has been

Table 3. FACTORS AFFECTING LONG-TERM MORTALITY (MEDIAN FOLLOW-UP, 5.3 YEARS)

		HR (95% CI; *P* Value)	
Overall Survival	n	Multivariable	Multivariable Reduced
Group			
DEX	51	Ref	Ref
NON-DEX	42	0.22 (0.09-0.56; .001)	0.31 (0.14-0.69; .004*)
pT classification†			
1	38	Ref	Ref
2	15	3.07 (0.77-12.26; .111)	2.58 (0.74-9.03; .137)
3	3	5.16 (0.83-32.00; .078)	3.13 (0.56-17.59; .196)
4	37	4.22 (1.47-12.09; .007)	2.56 (0.98-6.71; .055)
PEG			
Yes	42	Ref	Ref
No	44	0.22 (0.06-0.74; .015)	0.37 (0.14-1.04; .059)
Later	7	2.74 (0.61-12.34; .188)	2.09 (0.58-7.51; .256)
Major complication			
No	76	Ref	Ref
Yes	17	0.94 (0.30-2.90; .910)	1.59 (0.65-3.89; .312)
CCI			
0-1	49	Ref	Ref
2-4	29	3.79 (1.14-12.59; .029)	1.57 (0.64-3.83; .322)
5-9	15	7.29 (2.33-22.83; .001*)	5.82 (2.26-14.98; <.001*)
History of alcohol use†§			
Major	22	Ref	Ref
Moderate	44	0.81 (0.26-2.51; .721)	0.84 (0.32-2.18; .722)
No	27	2.35 (0.74-7.45; .146)	1.53 (0.54-4.34; .421)
Postoperative radiotherapy			
No	47	Ref	Ref
Yes	46	0.83 (0.27-2.59; .752)	NA
Age at surgery (yr)	65.3 ± 11.0	1.00 (0.96-1.05; .848)	NA
Gender			
Female	34	Ref	Ref
Male	59	0.72 (0.28-1.80; .478)	NA
BMI (kg/m^2)	25.6 ± 4.9	1.05 (0.96-1.14; .277)	NA
During follow-up			
Second primary			
No	77	Ref	Ref
Yes	16	0.51 (0.14-1.77; .286)	NA
Distant metastasis			
No	80	Ref	Ref
Yes	13	16.10 (5.13-50.52; <.001*)	10.41 (3.99-27.13; <.001*)
Locoregional metastasis			
No	80	Ref	Ref
Yes	13	2.82 (1.00-7.94; .050)	NA
Postoperative chemotherapy‖			
No	69	Ref	Ref
Yes	23	1.83 (0.51-6.54; .352)	NA

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; NA, not applicable; NON-DEX, no dexamethasone; PEG, percutaneous endoscopic gastrostomy.

* Statistically significant ($P < .05$).

† Data missing for 1 patient.

‡ Alcohol use defined as moderate if drinking was weekly or less and major if daily.

§ Data missing for 2 patients.

‖ Data missing for 2 patients.

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limited. Tanaka et al[26] analyzed the data from 1249 patients with HNC who had been treated with free flaps. They found a short-term (30-day) mortality of 0.88%; however, the long-term survival was not analyzed.[26] Lahtinen et al[27] retrospectively analyzed the survival and cause of death in 146 patients with head and neck free flap reconstruction at a median follow-up of 3 years. HNC was the primary cause of death in most (73%) patients,[27] in line with the results from the present study (79%). Our patient cohort had a 5.9-year OS of 59%, which is relatively good. Lidman and Niklasson[28] studied 139 patients with reconstructive HNC and found a 5-year OS of 57%. In that study, the cause of death, however, had been studied only for those who died within 2 months after surgery.[28] de Vicente et al[29] analyzed 98 patients with HNC patients (49 with free flap reconstruction) and reported an OS rate of 59% at 5 years.[29]

The strength of the present study was that it was double-blind, randomized, and prospective, although the number of patients remained relatively small. The median follow-up time was more than 5 years, which also provided the long-term results of HNC mortality in patients requiring microvascular reconstructive surgery.

In conclusion, in our study, the perioperative use of DEX was associated with higher short-term mortality in patients with HNC undergoing microvascular reconstruction. All the patients who died during the first 6 months, and most of those who died during the first 12 months, received perioperative DEX and had postoperative complications. The most important long-term predictors of death were receipt of DEX, the presence of distant metastases, and a CCI of 5 to 9. Thus, we have concluded that it is not safe to use perioperative DEX during reconstructive HNC surgery. Also, the potential harm of the use of perioperative DEX should be investigated for other surgically treated cancers in randomized prospective studies.

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