Perioperative Risk Factors for One-Year Mortality in Patients With Free-Flap Reconstruction Due to Cancer of the Head and Neck

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Purpose: Head and neck cancer requiring free-flap reconstruction is associated with relatively high mortality. We aimed to evaluate perioperative risk factors for 1-year mortality in this patient group.

Methods: This is a single-center retrospective analysis of 204 patients operated during 2008 to 2018.

Results: A total of 47 (23.0%) patients died within 1 year. In univariate analysis, there were no differences in the intraoperative course between 1-year survivors and nonsurvivors. Among the 1-year nonsurvivors, preoperative albumin level was lower (39 [36 to 43] vs 42 [39 to 44], $P = .032$) and the Sequential Organ Failure Assessment admission score was higher (4 [3 to 5] vs 3 [2 to 4], $P = .003$) than those of the 1-year survivors. Among the nonsurvivors, the preoperative and postoperative levels of leukocytes were higher (7.6 [6.7 to 9.5] vs 6.9 [5.5 to 8.4], $P = .002$; 11.4 [9.0 to 14.2] vs 8.7 [7.2 to 11.3], $P < .001$). The highest odds ratios for 1-year mortality in multivariate analysis were American Society of Anesthesiologists A classification greater than 2 (3.9 CI 1.4 to 10.5), male gender (4.0 CI 1.5 to 11), and increase in leukocyte count (1.3 CI 1.1 to 1.5).

Conclusions: One-year nonsurvivors had higher American Society of Anesthesiologists classification and were more often men. The postoperative inflammatory markers were higher in nonsurvivors, while the intraoperative course did not have a significant impact on the 1-year mortality.

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Free-flap transfer is a standard method in reconstruction of large defects in major head and neck cancer surgery. Head and neck cancer is accompanied with high long-term mortality; 5-year survival is approximately 50 to 60%.[1-4] In our previous article assessing the long-term outcomes and causes of deaths after free-flap surgery (FFS) for cancer of the head and neck, we found patient-related factors including low body mass index and advanced American Society of Anesthesiologists (ASA) classification as the most significant risk factors for poor long-term mortality. However, intraoperative factors and surgical complications did not have impact on outcome. This indicates that patient-related factors play an important role in unfavorable outcomes.[5]

Previous studies have shown the high rate of complications and poor long-term outcome in this patient group.[1,5-8] The impact of complications on outcomes has also been shown; medical complications in immediate postoperative phase may lead to compromise long-term outcomes including quality-of-life and mortality. Risk factors for medical complications include mostly patient-related factors.[7] However, the risk factors for poor short-term outcome are not well studied. We determined to analyze retrospectively the possible recordable perioperative factors to recognize the possible risk factors for 1-year mortality in the early phase of the patient care.

Methods

This retrospective study was conducted in Oulu University Hospital, and it is a substudy of our previous study analyzing the long-term mortality and causes of deaths in patients operated with FFS due to cancer of the head and neck.[5] The study protocol was accepted by hospital administration (239/2016). Owing to the retrospective study design, no statement from the local ethics committee was obtained.

PATIENTS

This study included 204 patients who underwent head and neck cancer surgery with free-flap reconstruction in Oulu University Hospital in 2008 to 2018. The patients are operated in the head and neck surgery unit by a multidisciplinary surgical team. Immediate postoperative care is routinely provided at the intensive care unit.

DATA EXTRACTION

The data extraction is described in our previous article.[3] Preoperative factors including patient demographics, laboratory values, and tumor staging were retrieved from the medical records. The ASA classification was used to estimate preoperative risks, and Charlson comorbidity index was used to determine the severity of chronic diseases. Laboratory values of the first postoperative day and severity of illness scores (Sequential Organ Failure Assessment; Acute Physiology and Chronic Health Evaluation II) on initial postoperative phase were retrieved from electronic patient data management system of the hospital's intensive care unit. The retrieved data consisted of facts obtainable at intensive care unit discharge. The survival data were retrieved from the causes of death registry of Statistics Finland.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software (SPSS for Windows, version 22.0. [IBM Corp., 2013, Armonk, NY, USA]). Proportional data are presented in numbers and percentages, and continuous variables are presented in medians and 25th to 75th percentiles. Continuous variables were tested using nonparametric Mann-Whitney test, and proportional data were tested using Pearson χ^2 test. Logistic regression analysis was used to estimate odds ratios (OR) for factors related to 1-year mortality. All the categorical and continuous variables with univariate significance <0.1 were included into the model. Continuous variables were categorized using local reference values when possible.

Results

PATIENT DEMOGRAPHICS AND PREOPERATIVE FACTORS

Of the 204 patients, 47 patients (23.0%) died within 1 year from the operation. Median survival time of the 1-year nonsurvivors was 218 days (119 to 299). A total of 8 patients died within 3 months from the operation and 1 of them within 30 days.

Most of the 1-year nonsurvivors were men (n = 36 (76.6%), *P* = .004) and were more often recorded as ASA 3 to 4 (n = 38 (80.9%) versus 85 (54.1%), *P* = .001) compared with the 1-year survivors. Preoperative leukocyte and C-reactive protein (CRP) levels were higher in nonsurvivors than in survivors (7.6 [6.7 to 9.5] x 10^9/L vs 6.9 [5.5 to 8.4] x 10^9/L, *P* = .002 and 16 [12 to 39]mg/L vs 5 [3 to 20] mg/L, *P* = .013), and the albumin levels were lower (39 [36 to 43] g/L vs 42 [39 to 44]g/L, *P* = .019). A total of 30 (85.7%) 1-year non-survivors had tumor stage 3 or 4 in contrast to 75 (64.1%) survivors (*P* = .015). There were no other differences between survivors and nonsurvivors in patient demographics or preoperative data (Table 1.).

INTRAOPERATIVE AND POSTOPERATIVE FACTORS

There were no differences in the intraoperative variables between 1-year survivors and nonsurvivors. The

Table 1. PATIENT DEMOGRAPHICS AND PREOPERATIVE VALUES

	1-Yr Survivors N = 157	1-Yr Nonsurvivors N = 47	Missing Data (1-Yr survivors/1-Yr Nonsurvivors)	*P* Value
Male gender	83 (52.9)	36 (76.6)		.004
Age	65 [57 to 75]	69 [62 to 76]		.061
ASA>2	85 (54.1)	38 (80.9)		.001
CCI>1	47 (29.9)	20 (42.6)		.106
Smoking	64 (40.8)	23 (49.9)		.320
Alcohol abuse	49 (31.2)	16 (34.0)		.715
Body mass index	24.2 [20.9 to 27.4]	24.4 [20.7 to 26.7]		.716
Tumor stage				.060
T1	7 (6.0)	1 (2.9)	40/12	
T2	35 (29.9)	4 (11.4)		
T3	26 (22.2)	14 (40.0)		
T4	49 (41.9)	16 (45.7)		
Hemoglobin (g/L)	132 [121 to 143]	131 [114 to 146]	16/3	.778
Thrombocytes (10^9/L)	277 [220 to 330]	279 [224 to 355]	4/0	.615
Leucocytes (10^9/L)	6.9 [5.5 to 8.4]	7.6 [6.7 to 9.5]	23/4	.002
CRP (mg/L)	5 [3 to 20]	16 [12 to 39]	117/31	.013
Creatinine mmol/L	63 [55 to 71]	67 [49 to 78]	6/1	.790
Albumin g/L	42 [39 to 44]	39 [36 to 43]	29/12	.019
Tumor				.742
Tongue	62 (9.7)	15 (31.9)		
Maxilla	18 (11.5)	4 (8.5)		
Mandible	20 (12.6)	8 (17.0)		
Larynx	15 (9.6)	8 (17.0)		
Melanoma	12 (7.7)	5 (10.6)		
Palatinal	10 (6.4)	3 (6.4)		
Buccal mucosa	14 (9.0)	2 (4.3)		
Parotic gland	4 (2.6)	2 (4.3)		
Lymphoma	1 (0.6)	0	1/0	

Abbreviations: ASA, American Society of Anesthesiologists classification; CCI, Charlson Comorbidity Index; CRP, C-reactive protein.

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Sequential Organ Failure Assessment scores in immediate postoperative phase were higher in nonsurvivors (4 [3 to 5] vs 3 [2 to 4], $P = .003$). The first postoperative day leukocytes were higher in nonsurvivors (11.4 vs 8.9 [7.3 to 12.2], $P = .001$). The increase between preoperative and postoperative leukocyte count was higher in the nonsurvivors (1.8 [0.7 to 3.4] vs 2.4 [1.3 to 5.7], $P = .037$) (Table 2).

LOGISTIC REGRESSION ANALYSIS

As per the logistic regression analysis, independent factors associated to 1-year mortality were ASA classification greater than 2, male gender, and increase in leukocyte count between preoperative and postoperative measurement (Table 3).

UNIVARIATE COMPARISON BETWEEN MALE AND FEMALE PATIENTS

Male patients were more often smokers (53.9% vs 27.5%, $P < .001$), had more alcohol abuse (43.5 vs 15.0%, $P < .001$), and had higher 1 postoperative day CRP (74 [51 to 96] mmol/L vs 59 [38 to 85] mmol/L, $P = .040$). The male patients were younger than female patients (63 [57 to 73] vs 68 [63 to 78], $P = .03$), and they had lower Acute Physiology and Chronic Health Evaluation II scores (11 [10 to 14] vs 13 [11 to 16], $P < .001$). There were no other differences between male and female patients.

Discussion

The main finding of the present study is that the most significant risk factors for 1-year mortality after FFS for cancer of the head and neck are patient-related, including male gender, advanced ASA classification and also increased inflammatory markers on the first postoperative day. We did not find any significant intraoperative factors that were independently related to 1-year mortality; moreover, none of the recorded chronic diseases were related to unfavorable outcome during the first year from the operation.

Table 2. INTRAOPERATIVE AND POSTOPERATIVE FACTORS

	1-Yr Survivors N = 157	1-Yr Nonsurvivors N = 47	*P* Value
Duration of operation (min)	610 [530 to 682]	635 [549 to 707]	.821
Intraoperative blood loss (mL)	580 [350 to 950]	600 [370 to 1,040]	.318
Blood transfusion	70 (44.6)	25 (53.2)	.299
Intraoperative fluid administration (mL)	5,400 [4,400 to 6,900]	5,400 [4,400 to 6,250]	.936
Fluid administration per body weight	82.6 [62.5 to 106.3]	78.5 [65.9 to 110.4]	.982
Free flap			.05
RFA	60 (38.5)	10 (21.7)	
ALT	46 (29.5)	23 (50.0)	
LD	1 (0.6)	3 (6.5)	
Scapula	6 (3.8)	3 (6.5)	
Fibula	20 (12.8)	5 (10.9)	
Lateral arm	14 (9.0)	0	
Other	9 (5.8)	2 (4.3)	
SOFA	3 [2 to 4]	4 [3 to 5]	.003
APACHE II	12 [10 to 15]	13 [11 to 15]	.057
1.POD hemoglobin (g/L)	99 [94 to 107]	98 [93 to 108]	.539
1. POD leucocytes (10^9/L)	8.7 [7.2-11.3]	11.4 [9.0-14.2]	<.001
Increase in leucocytes (10^9/L)	1.8 [0.7-3.4]	2.4 [1.3-5.7]	.037
1.POD CRP (mmol/L)	61 [43 to 87]	78 [47 to 111]	.044
Increase in CRP mmol/L	55 [32 to 75]	40 [21 to 66]	.410
1 POD (creatinine mmol/L)	56 [48 to 68]	55 [49 to 75]	.390
ICU LOS (d)	0.9 [0.8 to 1.7]	0.8 [0.7 to 1.1]	.184

Abbreviations: ALT, anterolateral thigh; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRP, C-reactive protein; ICU LOS, intensive care unit length of stay; LD, latissimus dorsi; POD, postoperative day; RFA, radial forearm; SOFA, Sequential Organ Failure Assessment.

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In our previous study, we reported raised inflammatory markers to be a risk factor for 6-month mortality, but when assessed in relation to long-term outcomes, these factors did not have a significant impact.[5] Inflammatory markers as risk factors for short-term outcomes are new findings in this patient group; however, this has been reported previously in other patient groups.[9] Nonsurvivors had higher preoperative CRP levels and leukocyte levels which may reflect also the tumor size. We found differences in postoperative leukocyte count and in the increase in the leukocyte levels before and after the operation. This may indicate stronger response to the surgical insult. On the other hand, there was a statistically not significant difference in postoperative CRP levels; CRP was lower in nonsurvivors, which could reflect disability to respond to the surgical stress. We have previously reported that medical complications are associated to poor long-term outcome in this patient group.[3] Although not shown in the present study or in our previous studies, one could hypothesize that the same factors that result in inadequate inflammatory response may lead to medical complications in this patient group. In the current results, tumor stage was not associated to short-term mortality. This is an expected finding because we analyzed the first year from the operation. However, the inflammatory response can be linked to the tumor size and further studies are needed in this patient group.

Table 3. ORS AND 95% CONFIDENCE INTERVALS FOR 1-YEAR MORTALITY AS PER LOGISTIC REGRESSION ANALYSIS

Factor	OR (95% CI)	*P* Value
ASA 1 to 2	1	.006
ASA 3 to 4	3.9 (1.4 to 10.5)	
Female	1	.007
Male	4.0 (1.5 to 11.1)	
Preoperative albumin (continuous)	0.9 (0.8 to 1.0)	.054
Increase in leukocyte count (continuous)	1.3 (1.1 to 1.5)	.003

Abbreviations: ASA, American Society of Anesthesiologists classification; CI, confidence interval; OR, odds ratio.

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Male gender was associated with significantly increased OR for 1-year mortality. We are not able to explain this finding using the factors that were obtainable for this study, but the same phenomenon has been reported before.[10,11] We performed a univariate analysis to make comparisons between the genders without achieving any clear explanations to our findings; smoking and alcohol abuse were more common in men, but on the other hand, Acute Physiology and Chronic Health Evaluation II scores were lower. The significantly raised OR for 1-year mortality that was related to advanced ASA classification was not a surprising finding of this study. The ASA classification is a known and widely used scoring with ability to predict postoperative risk, even with its limiting factors; it is based on a highly subjective evaluation and is easily predisposed for personal interpretation.[12,13]

CLINICAL IMPACT

The present study evaluated the available risk factors for adverse outcome after FFS for cancer of the head and neck at the first postoperative day. We have previously reported factors associated to poor long-term outcomes, but these factors, including medical complications with onset of more than 4 days postoperatively, cannot be used in predicting outcome during the immediate postoperative phase. In the present patient cohort, most of the deaths occurred after 3 months from the operation, indicating that the surgical insult leading to increased inflammation was not necessarily directly related to the deaths. In our previous analysis of the same patient cohort, increased long-term mortality was found in those facing medical complications detected more than 4 days postoperatively.[5] This indicates that patient-related factors play a major role in survival, and as per present results, preventive measures should be aimed to patients with ASA 3 to 4 and on those with increased inflammatory markers. By that, part of the medical complications and poor outcome could be prevented.

LIMITATIONS

Owing to the retrospective study design, we were not able to include all the preoperative laboratory markers into the study which would have enhanced the results concerning the inflammatory response. The limited number of patients compromised the logistic regression analysis. Further analysis of CRP values would have been of interest. There was a trend toward lower increase in postoperative CRP in nonsurvivors. Unfortunately, there were missing data in the preoperative values limiting the reliability of this analysis.

In conclusion, 1-year nonsurvivors had higher ASA classification and were more often men. The postoperative inflammatory markers were higher in nonsurvivors, while the intraoperative course did not have significant impact on the 1-year mortality.

References

1. McMahon J, Handley TPB, Bobinskas A, et al: Postoperative complications after head and neck operations that require free tissue transfer - prevalent, morbid, and costly. Br J Oral Maxillofacial Surg 55:809, 2017
2. Klosterman T, Siu E, Tatum S: Free flap reconstruction experience and outcomes at a low-volume institution over 20 years. Otolaryngology–Head Neck Surg 152:832, 2015
3. Lahtinen S, Koivunen P, Ala-Kokko T, et al: Complications and outcome after free flap surgery for cancer of the head and neck. Br J Oral Maxillofacial Surg 56:684, 2018
4. Clark JR, McCluskey SA, Hall F, et al: Predictors of morbidity following free flap reconstruction for cancer of the head and neck. Head & Neck 29:1090, 2007
5. Lahtinen S, Koivunen P, Ala-Kokko T, et al: Short- and long-term mortality and causes of death after reconstruction of cancers of the head and neck with free flaps. Br J Oral Maxillofacial Surg 57: 21, 2019
6. Patel RS, McCluskey SA, Goldstein DP, et al: Clinicopathologic and therapeutic risk factors for perioperative complications and prolonged hospital stay in free flap reconstruction of the head and neck. Head & Neck 32:1345, 2010
7. Jones NF, Jarrahy R, Song JI, et al: Postoperative medical complications???-not microsurgical complications???-negatively influence the morbidity, mortality, and true costs after microsurgical reconstruction for head and neck cancer. Plast Reconstr Surg 119:2053, 2007
8. Bianchi B MD, Copelli C, MD, et al: Free flaps: Outcomes and complications in head and neck reconstructions. J Cranio-Maxillo-Facial Surg 37:438, 2009
9. De Magistris L, Paquette B, Orry D, et al: Preoperative inflammation increases the risk of infection after elective colorectal surgery: Results from a prospective cohort. Int J Colorectal Dis 31:1611, 2016
10. Al-Taki M, Sukkarieh HG, Hoballah JJ, et al: Effect of gender on postoperative morbidity and mortality outcomes: A retrospective cohort study. The Am surgeon 84:377, 2018
11. Harten J, McCreath BJ, McMillan DC, et al: The effect of gender on postoperative mortality after emergency abdominal surgery. Gend Med 2:35, 2005
12. Hackett NJ, De Oliveira GS, Jain UK, Kim JYS: ASA class is a reliable independent predictor of medical complications and mortality following surgery. Int J Surg 18:184, 2015
13. Hopkins TJ, Raghunathan K, Barbeito A, et al: Associations between ASA physical status and postoperative mortality at 48 h: A contemporary dataset analysis compared to a historical cohort. Perioper Med (London, England) 5:29, 2016