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Short- and long-term mortality and causes of death after reconstruction of cancers of the head and neck with free flaps

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Abstract

The use of free flaps to reconstruct cancers of the head and neck is accompanied by appreciable postoperative morbidity and high long-term mortality, but the causes of death and the impact of postoperative complications on survival have not been well studied. We have therefore analysed retrospectively the causes of death and survival of 146 such patients operated on between 2008 and 2016 of whom a total of 62 (43%) had died by the end of 2016. The cause of death was the primary disease in 45 of the 62. The median survival of those who died with the primary cancer as the cause of death did not differ from that of those who died of other causes. In a multivariate Cox model indicators of five-year mortality were male sex, low body mass index (BMI), American Society of Anesthesiologists (ASA) grade more than II, and late medical complications. Neither the size of the tumour nor any operative factors were independent risks for five-year mortality. Ten patients died within six months of operation, all of whom had higher postoperative C-reactive protein concentrations than those who survived for more than six months. The cause of death of most patients who died after free flap operations for head and neck cancer was the primary diagnosis. According to these results, patient-related factors (male sex, ASA grade more than II, low BMI, and low albumin concentration) have an important role in long-term survival, which highlights the importance of careful selection of patients for operative treatment.

Keywords: head and neck cancer; free flap surgery; long-term mortality; causes of deaths

Introduction

During the past decades, free flap transfer has become a standard way of surgically reconstructing large defects in patients with head and neck cancer. It is often accompanied by postoperative complications and high mortality, with five-year survival of between 43% and 66%.[1–5] We have previously reported the impact of postoperative complications on long-term survival after free flap reconstruction in patients with head and neck cancer, and showed increased mortality in patients with medical complications.[6]

Despite the high mortality, the number of studies that have reported causes of deaths after free flap reconstruction for these cancers is limited, and these causes are usually reported as secondary endpoints. In those studies early postoperative causes include respiratory, cerebrovascular, and gastrointesti-

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Table 1
Summary of previous studies.

First author and year	Group studied	End points	Main finding	Limitations
Salvatori, 2014	1178 Patients treated with free flaps after resection of the tumour	DSS	Mean DSS 44.4 months. 5-year survival 50.4% Nodal involvement decreased survival	Causes of deaths not analysed
de Vicente, 2012	98 Patients, 49 of whom were treated with free flaps after resection of the tumour	Survival	No difference in survival between the free flap and local flap groups	Limited number of patients
Lidman, 2008	131 Patients treated with free flaps after resection of the tumour	Postoperative outcome, including survival among patients with primary intraoral SCC (n = 79)	Five-year survival 58%	Only patients with primary intraoral SCC were included in the survival analysis Limited number of patients Causes of deaths analysed only for those who died <2 months' postoperatively
Tanaka et al, 2011	1294 Patients treated with free flaps after resection of the tumour	30-Day postoperative mortality; in-hospital mortality	30-Day postoperative mortality 0.88%. In-hospital mortality 1.84%. Recurrence of cancer was the most common cause of death in hospital	Only short-time mortality was analysed
Ch'ng et al, 2013	255 Patients treated with free flaps after resection of the tumour	Effect of postoperative complications on survival	Major postoperative complications reduced overall survival	Causes of deaths analysed only for those who died within 30 days postoperatively
Rogers et al, 2009	489 oral cancer patients treated with primary curative surgery	Overall and disease-specific survival	Free flaps associated with reduced overall and disease- specific survival	Causes of deaths not analysed

SCC = squamous cell carcinoma; DSS = disease specific survival.

nal diagnoses, as well as tumour-related causes.[7–9] Ch'ng et al reported that 65% of the deaths in their series of 255 patients during a two-year follow-up period were related to the primary disease, but they did not report the other causes of death.[8] We know of few detailed data on the causes of deaths and possible factors contributing to death after free flap reconstruction, and no studies that have compared causes of deaths among patients who did or did not have postoperative complications (Table 1).

We also found an absence of studies that focused on mortality and causes of deaths after free flap reconstructions in patients with head and neck cancer. Our aim, therefore, was to examine the short-term (less than six months) and long-term (six months or more) mortality and causes of deaths in a group of patients operated on in a single tertiary care centre between 2008 and 2016.

Methods

This retrospective study was done in Oulu University Hospital, Finland, which provides tertiary, university, hospital-level operative care to patients who require operations on the head and neck. The hospital administration approved the study protocol (239/2016), but as a result of local policy concerning retrospective studies, no statement was obtained from the hospital's ethics committee.

Group studied

We studied all patients who had microvascular free flap reconstruction for cancer of the head and neck from 2008–2016. We previously published a study of the same group that focused on postoperative complications[6] and, for the present study, patients operated on during 2016 were included.

Patients were identified from the records of the head and neck surgical unit. The data were collected from electronic medical records, anaesthetic charts, and the intensive care unit (ICU) database (Centricity Clinical Care Clinisoft, GE Healthcare). We extracted personal and clinical details of each patient, the type and classification of the tumour, the operative technique, and the short-term outcomes including duration of hospital stay and postoperative complications. The complications were classified as reported previously, including surgical complications (haematoma of the surgical site, infection, partial and total failure of the flap, and the need for re-operation) and medical complications (pneumonia, sepsis, myocardial infarction, stroke, pulmonary embolism,

Table 2
Personal and clinical data for the 146 patients operated on. Data are shown as number or number (range).

	Survived (n = 84)	Died (n = 62)	p value
Male sex	38	45	<0.001
Age (years)	65 (57–72)	68 (61–74)	0.075
ASA grade >II	38		0.02
CCI ≥ 1	34	29	0.45
BMI	24.1 (20.8–27.2)	22.7 (19.1–25.5)	0.030
Smoking	32	30	0.21
Alcohol misuse	13	16	0.12
Preoperative laboratory values:			
Albumin (g/L)	44 (42–45)	42 (39–44)	0.002
Haemoglobin (g/L)	134 (124–146)	127 (116–138)	0.022
Creatinine (μmol/L)	61 (55–71)	65 (53–75)	0.90
Postoperative laboratory values:			
Haemoglobin (g/L)	100 (93–108)	96 (92–105)	0.12
Creatinine (μmol/L)	54 (48–67)	55 (48–71)	0.29
White cells (x10^9)	9 (7.6–12.1)	10.0 (8.4–13-1)	0.089
CRP (mg/L)	65 (48–90)	73 (54–111)	0.099
APACHE II score	12 (9–15)	13 (11–15)	0.27
SOFA	3 (2–4)	3 (3–4)	0.005
Site:			
Oral cavity/tongue	33	27	
Maxilla	8	5	
Mandible	17	7	
Larynx	3	12	
Skin/melanoma	6	4	0.066
Palate	7	2	
Buccal mucosa	8	3	
Parotis	1	2	
Lymphoma	1	0	
T stage:			
T1	9	2	
T2	28	10	
T3	12	14	0.029
T4	31	33	
Free flap:			
Radial forearm	32	14	
Anterolateral thigh	19	25	
Latissimus dorsi	2	2	
Scapula	3	4	
Fibula	16	9	0.048
Lateral arm	8	2	
Iliac crest	3	1	
Transverse rectus abdominis	0	4	
Other	1	1	
Duration of operation (min)	607 (517–685)	634 (548–715)	0.20
Blood loss (ml/kg)	7.6 (5.1–14.0)	11.1 (7.1–17.8)	0.022
Perioperative fluids (ml/kg)	86.9 (59.9–108.1)	114.0 (88.4–145.1)	<0.001
Initiation of oncological treatment (days)	41(26–56)	50 (36–113)	0.035
Complications:	49	45	0.076
Early surgical	21	21	0.24
Late surgical	26	24	0.33
Early medical	21	31	0.002
Late medical	20	31	0.004
Success rate of flaps	77	59	0.41
Duration of stay in hospital (days)	10 (8–15)	15 (11–17)	<0.001
Died within six months	–	10	

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; BMI = body mass index; APACHE = Acute Physiology And Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment.

deep venous thromboembolism, or acute renal injury). Early complications were those detected during the first four postoperative days, and those recorded later were classified as late.[6] The American Society of Anesthesiologists (ASA) grade and Charlson Comorbidity Index (CCI) were used as indicators of chronic disease, and the Sequential Organ Failure Assessment (SOFA) score was used to describe the severity of illness on admission to the ICU. Laboratory values during the preoperative period and on the first postoperative day were used in the analyses.

Statistics Finland provided the data about causes of death, and the primary cause of death was used in the analysis. The causes were divided into two categories: "primary disease" was used if the cause of death reflected the diagnosis of the primary tumour, while "other cause" was used if the cause of death did not include cancer of the head and neck. Patients were followed up until the end of the year 2016 or at least 180 days after the operation. The median (range) follow-up time was 616 (297–1157) days and the time from the operation to the end of the year 2016 was 1114 (618–1157) days.

In Finland, the causes of deaths are categorised as "disease", "occupational causes", "trauma", "medical complications", "suicide", "homicide", "war", or "unclear". The classification for causes of death was made according to the Finnish Cause of Death Registry, which has previously been shown to be reliable.[10]

Statistical analysis

For the statistical analysis we used IBM SPSS Statistics for Windows (Version 22.0, IBM Corp). Summary data are presented as medians and 25th and 75th percentiles and proportional data as numbers and percentages. The non-parametric Mann–Whitney test was used to assess the significance of differences between medians across the groups, and for categorical data we used using Pearson's chi squared or Fisher's exact test, as appropriate. Kaplan–Meier survival curves were drawn to compare long-term mortality between the groups. Probabilities of less than 0.05 were accepted as significant. Variables giving probabilities of less than 0.02 on univariate analysis or with clinical interest (postoperative complications) were entered into a multivariate proportional hazards Cox model to assess risk factors for five-year mortality. The follow-up time was restricted to five years because of lack of additional information on the model after that (only two deaths). A potential risk factor was left in the model if the probability of it happening was less than 0.05, or if it had a significant effect on log likelihood value. The results of the Cox model are presented as hazard ratio (HR) with 95% CI.

Table 3
Causes of deaths for the 62 patients who died.

Diagnosis	No. of patients who died (n = 62)	No. who died/were operated on
Head and neck cancer:		
Oral cavity/tongue	17	17/60
Maxilla	5	5/14
Mandible	2	2/24
Larynx/pharynx	10	10/15
Melanoma	3	3/10
Palate	1	1/9
Buccal mucosa	5	5/12
Parotid gland	2	2/3
Other:		
Cardiovascular	9	–
Other cancers	3	–
Others	5	–

Results

A total of 166 operations were done on 146 patients during the study period, and 62 patients (43%) had died by the end of 2016. Patients who died were more likely to have had stage T4 tumours, the anterolateral thigh was more likely to have been used as the free flap, their recorded preoperative ASA grade and SOFA scores at ICU admission were more likely to have been higher, and the median body mass index (BMI) and haemoglobin and albumin concentrations were more likely to have been lower. Intraoperatively, patients who died were given more fluids and lost more blood. In addition, postoperative oncological treatment was initiated later among those who died, who also had more postoperative medical complications. They were also more likely to have had infections of the surgical site (25/62 compared with 13/84, $p = 0.001$) and pneumonia (24/62 compared with 14/84, $p = 0.003$) though there were no differences in the incidence of other recorded complications (data not shown). Ten of the patients who died did so within six months of the operation (Table 2).

Causes of death

In all cases the cause of death was classified as "disease". In 45 of the 62, the recorded cause was head and neck cancer. The highest rate was among those operated on for laryngeal/pharyngeal carcinoma (n = 10) and in those with parotid carcinoma (n = 2). The patients' personal and clinical details did not differ between those with the primary diagnosis as a cause of death and those who had other causes of death (data not shown). In those with tumours of stages T3-4, a total of 10 patients died of causes other than the primary tumour, in contrast to six of those with T1 or T2 tumours($p = 0.046$). The causes of death did not differ between those with or without postoperative complications (Table 3).

Table 4
Comparison of characteristics between those who survived for less than six months and those who survived six months or more. Data are given as number, number (%), or median (25–75 centile).

	Survived for six months or more (n = 136)	Survived for less than six months (n = 10)	p value
Age (years)	65 (59–74)	58 (49–74)	0.075
Male sex	71 (52)	9	0.020
ASA grade >II	73 (54)	8	0.106
CCI 1 or more	59 (43)	4	0.84
BMI	23.7 (20.6–26.9)	20.7 (16.7–26.6)	0.034
Preoperative laboratory values:			
Albumin (g/L)	43 (41–45)	38 (34–43)	0.002
Haemoglobin (g/L)	13.2 (12.1–14.3)	12.8 (11.9–15.2)	>0.9
Creatinine (μmol/L)	63 (55–71)	69 (48–81)	0.68
Postoperative laboratory values:			
Haemoglobin (g/L)	99 (92–107)	95 (89–107)	0.42
Creatinine (μmol/L)	55 (48–68)	53 (47–71)	0.84
White cells($\times 10^9$ L)	9.2 (7.8–12.7)	9.9 (9.2–11.4)	0.59
CRP (mg/L)	68 (51–91)	111 (98–128)	0.006
APACHE II	12 (10–15)	13 (10–13)	0.27
SOFA on admission	3 (2–4)	4 (3–4)	0.005
Initiation of oncological treatment (days)	43 (29–71)	83 (48–93)	0.035
Duration of stay in hospital (days)	12 (8–16)	23 (14–55)	<0.001
Free flap:			
Radial forearm	45 (33.1)	1	
Anterolateral thigh	41 (30.1)	3	
Latissimus dorsi	4 (2.9)	0	
Lateral arm	10 (7.4)	0	
Scapula	5 (3.7)	2	0.18
Fibula	22 (16.2)	3	
Iliac crest	3 (2.2)	1	
Transverse rectus abdominis	4 (2.9)	0	
Others	2 (1.5)	0	
Site of tumour:			
Oral cavity/tongue	55 (40.4)	5	
Maxilla	13 (9.6)	0	
Mandible	22 (16.2)	2	
Larynx/pharynx	13 (9.6)	2	
Skin	9 (6.6)	1	0.84
Palate	9 (6.6)	0	
Buccal mucosa	11 (8.1)	0	
Others	4 (2.9)	0	
T stage:			
T1	8 (6.3)	1	
T2	36 (28.1)	2	
T3	25 (19.5)	1	0.83
T4	59 (46.1)	5	
Duration of operation (min)	613 (540–701)	669 (534–754)	0.31
Blood loss (ml/kg)	8.8 (5.5–15.4)	8.8 (4.8–40.8)	0.48
Perioperative fluids (ml/kg)	93.2 (71.3–118.3)	145.1 (95.3–159.3)	0.044
Complication:	85 (62.5)	9 (90.0)	0.080
Early surgical	38 (27.9)	4 (40.0)	0.42
Late surgical	45 (33.1)	5 (50.0)	0.28
Early medical	44 (32.4)	8 (80.0)	0.002
Late medical	43 (31.6)	8 (80.0)	0.002

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; BMI = body mass index; APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment.

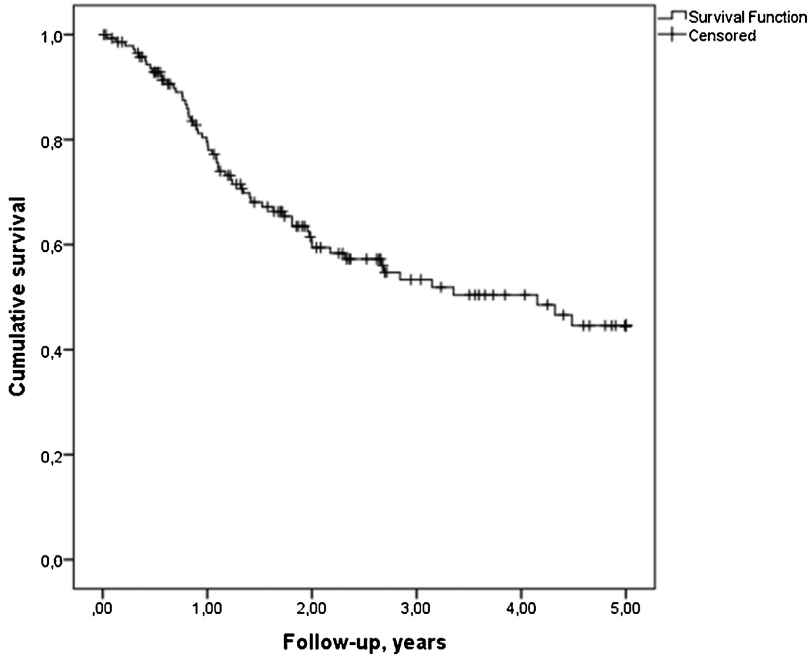

Fig. 1. Survival curve for the 146 patients who were operated on.

Comparison between those who survived for six months and those who did not

Ten of the patients operated on died within six months. These patients were more often male, had lower BMI and lower albumin concentrations, and higher SOFA scores at admission to the ICU. The postoperative concentrations of CRP were higher in those who survived less than six months. They stayed in hospital longer, and they had higher rates of early and late medical complications (Table 4).

Three patients who died within six months died of causes other than the primary tumour: two had myocardial infarctions and one developed peritonitis. Only one patient died within less than 30 days, the cause of death being pneumonia with myocardial infarction on the 15th postoperative day. All the patients who died and had been given the primary tumour as the cause of death survived for more than 90 days.

Long-term survival

Most of the deaths occurred within two years of the operation and a survival curve of the study group reaches a plateau at three years from the operation (Fig. 1). Only two of those who died survived beyond five years. The median (range) survival of those who died of the primary tumour was 396 (278–634) days in contrast to 428 (319–979) days for those who died of other causes ($p = 0.364$). A total of 45 patients died within two years. They had lower median (25–75 centile) preoperative concentrations of haemoglobin (130 g/L (11.9–14.0) compared with 138 g/L (126–151), $p = 0.023$), were given more fluids during operation (108.1 1 (93.7–138.1) ml/kg compared with 70.8 (49.2–91.2) ml/kg, $p < 0.001$), and the time from the operation to oncological treatment being given was longer (46 (35–93) compared with 32 (23–56) days, $p = 0.01$). No other details of patients, perioperative factors, or causes of deaths, differed among the groups (data not shown). A total of 60 patients died within five years of operation. In the multivariate analysis BMI below 20, ASA grade above II, male sex, low preoperative albumin concentration, and late medical complications were risk factors for death within five years of operation (Table 5).

Table 5
Multivariate hazard ratios and 95% CI for mortality at five years.

Variable	Hazard ratio (95% CI)	p value
Body mass index <20	1.90 (1.00 to 3.60)	0.049
American Society of Anesthesiologists grade >II	2.15 (1.20 to 3.85)	0.010
Male sex	2.71 (1.50 to 4.88)	0.001
Preoperative albumin concentration (g/L)	0.93 (0.87 to 1.00)	0.052
Late medical complication	1.82 (1.07 to 3.11)	0.027

Discussion

The main findings of our study include: first, that for most deaths the cause was the primary disease, while other causes were recorded in only seven cases. Patients' personal and clinical details, or disease-specific factors, had no impact on the cause of death. Secondly, there was no difference in survival between those who died of head and neck cancer and those who died of other causes. Thirdly, we found that late medical complications as well as patient-related risk factors (including male sex, low BMI, and increased ASA grade) were independent risk factors for mortality while stage of the tumour was not as important. To our knowledge this is the first study that has reported all causes of deaths in patients with head and neck cancer who were treated by free flap reconstruction, and includes postoperative complications as possible predisposing factors to death.

We found no differences in the causes of deaths as far as postoperative complications were concerned, and complication-related diagnoses were also uncommon as causes of death. Despite the high rate of complications, they were rarely related to the cause of death. In most cases the cause was given as the primary disease, and all the deaths were classified as "disease". Infections of the surgical site and pneumonia were more common among those who died, while other complications were equally distributed between those who lived and those who died. However, three deaths that occurred within 90 days of the operation were said to have been caused by other conditions and not by the primary diagnosis. Cardiac causes, infections, and gastrointestinal conditions could have been linked to complications, but two of the three patients died more than one month after the operation, which could indicate that the deaths were related to a lack of recovery capacity instead of postoperative complications.

We found that those who did not survive required more fluids and lost more blood during the operation than those who survived. The postoperative fluid overload and bleeding, and a need for transfusions during the operation, may compromise the initial postoperative course, and consequently the recovery. The excessive fluid management has previously been shown to be associated with postoperative morbidity in patients after free flap reconstructions for head and neck cancer.[11] Because most of the deaths occurred more than 180 days after the operation, the role of bleeding and fluid replacement can be questioned. The Cox regression analysis supports this finding, and we found no operative factors with increased hazard ratios for five-year mortality.

Postoperative CRP concentrations were also higher among those who died within 180 days. A total of three-quarters of those who survived less than 180 days had higher postoperative CRP concentrations than three-quarters of those who survived 180 days or more. This could indicate that the poor outcome might also be associated with inflammatory factors, which may play a part even later in the recovery phase, and could explain the difference in the need for fluids intraoperatively. According to recent studies, an increased perioperative CRP concentration predicts postoperative complications after free flap reconstruction for head and neck cancer, but the impact of the activated systemic inflammation on the postoperative outcome needs further study.[12] The postoperative systemic inflammatory response has been found to be associated with worsened disease-specific survival and long-term outcome after operations for colorectal cancer.[13]

Most of the patients had tumours staged as T3-4, which may partly explain the mortality and the rate of postoperative complications in these patients with advanced disease. However, Hsieh et al reported no difference in survival or recurrence of cancer in patients with advanced stage 4 oral squamous carcinoma that had been treated with or without free flap reconstruction.[14] Medical complications were more common among those who died in our group, and those who died also had lower albumin and haemoglobin concentrations and lower BMI than those who survived. In the multivariate analysis, BMI, male sex, and ASA grade had increased hazard ratios for five-year mortality as well as late medical complications. It is notable that the time from the operation to death in patients in whom the primary tumour was given as a cause of death did not differ from those with other causes of death. Also, surprisingly, an advanced tumour stage did not have increased hazard ratios for five-year mortality as reported previously elsewhere.[3,8] This may indicate that not only disease-specific, but also patient-related, factors are important when assessing the risk of death. Interestingly, surgical complications did not have an impact on the outcome. It seems that those who are recovering from surgical complications have sufficient capacity to survive, while those with medical complications may already have limited capacity preoperatively.

In line with our results, Ch'ng et al reported that major postoperative complications are an independent risk factor for decreased overall survival after free flap reconstructions for cancer of the oral cavity. Among those with major complications, medical complications were the most predominant.[8] Previous studies have reported low preoperative BMI, and low albumin and haemoglobin concentrations, to be risk factors for postoperative complications, but the impact of these on mortality requires further study.[15,16] However, it seems obvious that factors such as albumin concentration and low BMI as well as postoperative medical complications indicate the general health and nutritional state of the patient and have an impact on the patient's capacity to recover postoperatively.

Significance

We present what is to our knowledge the first study that has focused solely on mortality and causes of deaths in patients with head and neck cacer being treated by free flap reconstruction. We found a higher rate of deaths among those with medical complications, and also several patient-related risk factors for death, particularly for death within six months of operation. Free flap reconstruction for head and neck cancer is technically challenging and uses many resources, and also may cause psychological and physiological stresses for individual patients as a result of the considerable rate of postoperative complications. The rather poor outcome seems to be associated with patient-related factors such as nutrition, inflammatory factors, and chronic diseases. This increases the need for the right patients to be selected. Our finding that postoperative complications are not necessarily fatal supports this hypothesis; those who died had more complications and previous coexisting medical conditions than those who recovered, which may limit these patients' capacity for recovery.

There are some limitations in the present study. The relatively small number of patients who died decreases the generalisability of the results, which is significant among those who died within six months; we were not able to do a multivariate analysis in this group. To include more patients in the study, we would have needed to expand the duration of the study, which could have led to heterogeneity in the surgical techniques used. We were not able to use data about the socioeconomic status of the patients or the use of health care services after discharge from hospital, which can be considered as a limitation. The retrospective setting also has limitations in reporting possible unusual circumstances during the operation concerning the site of the tumour or technical challenges that may have had an impact on complications and, in the long-term, also on mortality. However, despite the retrospective design, we made a detailed analysis of the perioperative factors that contributed to complications using exact information recorded in the ICU database, electronic medical records, and anaesthetic charts.

Conclusion

Most of the patients who died after free flap reconstruction for head and neck cancer had the primary diagnosis as the cause of death. Most of the patients survived more than six months. In the multivariate analysis there were increased hazard ratios for five-year mortality in factors including male sex, low BMI, higher ASA grade, and late medical complications, while stage of the tumour and intraoperative factors were not associated with poor outcome. According to these results, patient-related factors play an important part in long-term survival, and this highlights the importance of careful selection of patients for operative care.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

As it was a retrospective investigation we required neither ethics approval nor patients' permission.

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