Research Article

Risk Factors for Delayed Surgical Recovery and Massive Bleeding in Skull Base Surgery

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What Is It about?

The factors that delay surgical recovery and increase intraoperative hemorrhage in skull base surgery remain unknown. Our study revealed that massive blood loss, comorbidity, and postoperative complications are risk factors for delayed surgical recovery. Tumor invasion to the hard palate, the maxillary sinus, the pterygopalatine fossa, the base of the pterygoid process, the sphenoid sinus, the middle cranial fossa, and the cavernous sinus and a long operation time were associated with increased total hemorrhage. Meticulous preoperative planning, intraoperative surefire hemostasis are required for skull base surgery.

Keywords

Skull base surgery · Delayed surgical recovery · Intraoperative bleeding · Perioperative care · Postoperative complication

Abstract

Background: To determine factors that delay surgical recovery and increase intraoperative hemorrhage in skull base surgery. **Methods:** Factors related to delayed postoperative recovery were retrospectively reviewed in 33 patients who underwent open skull base surgery. Early and late recovery phases were assessed as “days required to walk around the ward (DWW)” and “length of hospital stay (LHS),” respectively. Intraoperative blood loss was calculated every hour and analyzed in 4 steps, i.e., craniotomy and intracranial manipulation, cranial fossa osteotomy, extracranial osteotomy, and reconstruction. **Results:** More than 4,000 mL of blood loss ($B = 2.7392$, $\text{Exp}[B] = 15.4744$; 95% CI 1.1828–202.4417) and comorbidity

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ty ($B = 2.3978$, $\text{Exp}[B] = 10.9987$; 95% CI 1.3534–98.3810) significantly prolonged the DWW; the occurrence of postoperative complications significantly delayed the LHS ($p = 0.0316$). Tumor invasion to the hard palate, the maxillary sinus, the pterygopalatine fossa, the base of the pterygoid process, the sphenoid sinus, the middle cranial fossa, and the cavernous sinus and a long operation time (> 13 h) were associated with increased total hemorrhage. The optimal cut-off hemorrhage volume associated with total massive blood loss in craniotomy and intracranial manipulation (AUC = 0.8364), cranial fossa osteotomy (AUC = 0.8000), and extracranial osteotomy (AUC = 0.8545) was 1,111, 750, and 913 mL, respectively. Persistent infection (6%) and neuropsychiatric disorder (6%) are direct causes of delayed LHS. **Conclusion:** Blood loss, comorbidity, and postoperative complications were risk factors for delayed surgical recovery. Meticulous preoperative planning, intraoperative surefire hemostasis, and perioperative holistic management are prerequisites for safe skull base surgery.

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Introduction

Craniofacial resection of malignant tumors with skull base invasion was first reported in 1954 and subsequently developed by Ketcham et al. [1, 2]. Currently, it is widely accepted as the “gold standard technique” for malignant tumors involving the skull base [3].

Recently transnasal endoscopic skull base surgery without craniotomy has been established for skull base tumors [4–7]. Its application was gradually expanded to benign or low-grade malignant tumors involving the pituitary gland, the pterygopalatine fossa, the infratemporal fossa, and the anterior cranial fossa [8]. However, many head and neck malignancies are locally advanced tumors involving the middle cranial fossa or orbital or pathologically high-grade tumors such as squamous cell carcinoma or sarcoma. Traditional “open” craniofacial resection remains an important surgical technique [9–13].

Skull base surgery with craniotomy requires highly specialized techniques of head and neck surgery, neurosurgery, and plastic surgery. It involves a long operation time and results in profuse hemorrhage because of intra- or extracranial bone resection and pterygoid venous plexus and cavernous sinus management.

Moreover, some patients exhibit delayed surgical recovery. Because the skull base is anatomically complex with a 3-dimensional structure, patients develop an abscess that forms a dead space postoperatively. Head and neck sarcomas such as rhabdomyosarcoma or osteosarcoma are specific to the skull base [14]. Multidisciplinary treatment is necessary for these sarcomas. Immediate postoperative chemotherapy should be administered postoperatively. Therefore, a rapid surgical recovery is required because of postoperative treatment.

Previously, many studies have reported postoperative complications of craniofacial resection [14–16]; however, the factors that delay surgical recovery after craniofacial resection remain unknown. Therefore, this study aimed to determine the factors that delay surgical recovery and increase intraoperative hemorrhage.

Materials and Methods

Study Population

From January 2012 to December 2018, one thousand nine hundred eighty-seven patients underwent surgery under general anesthesia at the National Cancer Center Hospital of Japan. Of these patients, 481 transferred to the intensive care unit postoperatively owing to postop-

erative critical care. Among them, definitive craniofacial resection was performed in 33 patients. These 33 patients with malignant tumors invading the skull base were considered eligible for this retrospective analysis.

The 2013 version of the World Health Organization criteria was used for the histological classification. Tobacco smokers were defined as individuals with heavy tobacco use (20 pack-years or more, i.e., 1 pack per day for 20 or more years), and alcohol drinkers were defined as individuals with heavy alcohol use (15 drinks or more per week for 15 or more years).

Treatment Strategies and Operative Procedure

Unresectability of the skull base was defined as invasion of the cavernous sinus, carotid artery, wide dura mater, cerebrum, and superior or lateral wall of the sphenoid sinus.

In this study, craniofacial resection was systematically performed in 4 steps as previously reported [17].

First, a coronal skin incision and the Weber-Fergusson skin incision were performed. Frontal craniotomy, frontotemporal craniotomy, or temporal craniotomy was performed depending on tumor invasion. After craniotomy, the frontal or temporal lobe and overlying dura were retracted. Tumors invading the dura mater, the olfactory nerve, the supraorbital fissure, the maxillary nerve, or the mandibular nerve were resected as necessary. In cases of dura resection, reconstruction was performed using the fascia lata or abdominal fascia as soon as possible.

Second, cranial fossa bone resection was performed via craniotomy. The anterior cranial fossa was resected by drilling a cribriform plate or orbital plate of the frontal bone, avoiding the tumor. Entering the frontal sinus, the ethmoid sinus, the sphenoid sinus, and the orbit became a good landmark. Resection of the inferior wall in the sphenoid sinus was assessed using a transnasal endoscope. The middle cranial fossa was resected from the lateral part of temporal craniotomy to the medial side by drilling. The superior orbital fissure, the foramen rotundum, and the foramen ovale became a good landmark. When drilling around the foramen rotundum, the sphenoid sinus was identified. Therefore, the middle cranial fossa osteotomy was connected to the anterior cranial fossa resection.

Third, extracranial osteotomy was performed. Partial or total maxillectomy was performed using lateral rhinotomy, the Weber-Fergusson incision, facial desmasking, and midfacial degloving. All of the patients underwent en bloc resection. Neck dissection was performed after tumor resection if necessary.

Fourth, reconstruction was performed. Pericranial flap reconstruction was performed in patients with an anterior cranial fossa defect without orbital exenteration or preoperative irradiation, and free-flap reconstruction through the rectus abdominis musculocutaneous flap or anterolateral thigh flap was performed in patients with larger postoperative defects or preoperative irradiation. A superficial temporal or facial artery was used in vascular anastomosis.

The first step was performed by a neurosurgeon (Y.M., aged ≥ 40 years), the second and third steps were performed by head and neck surgeons (K.K., G.O., and S.M., aged < 40 years; F.M. and S.Y., aged ≥ 40 years), and the fourth step was performed by a plastic surgeon (S.A. and S.M., aged ≥ 40 years).

Definition of Delayed Surgical Recovery and Massive Blood Loss

In this analysis, early and late delayed surgical recovery was defined as “days required to walk around the ward (DWW)” and “length of hospital stay (LHS)” longer than the 75th percentile in the analysis population, respectively. Massive blood loss is usually defined as the loss of 1 blood volume within a 24-h period [18, 19]. Because the normal blood volume is 70 mL/kg, massive blood loss in this study was alternatively defined as a blood loss of greater than 4,000 mL during the operation.

Assessment and Index of Delayed Surgical Recovery

Age (>65 years), body mass index (BMI; >25), performance status (PS; ≥ 1), smoking and drinking history, hemoglobin (<8 g/dL), hemoglobin A1c (>6.5%), albumin (<3.5 g/dL), comorbidities (hypertension, diabetes mellitus, asthma, or atrial fibrillation requiring medication), preoperative treatment, total blood loss (>4,000 mL), operation time (>13 h), type of osteotomy (middle cranial fossa resection), orbital exenteration, cavernous sinus resection, type of reconstruction (free-flap reconstruction), and surgical complications were analyzed as delayed surgical recovery indices.

Analysis of Factors of Increased Total Hemorrhage

Total hemorrhage was assessed based on 3 aspects, i.e., patient factor, tumor factor, and surgical factor. Age (>65 years), BMI (>25 kg/m²), hemoglobin (<8 g/dL), albumin (<3.5 g/dL), and preoperative treatment were classified by patient factor. The anatomical location of tumor invasion was assessed based on preoperative imaging studies and intraoperative findings. Invasion to the hard palate, the maxillary sinus, the pterygoid muscle, the pterygo-palatine fossa, the base of the pterygoid process, the orbital apex, the sphenoid sinus, the middle cranial fossa, the cavernous sinus, and the dura matter was assessed. The head-and-neck surgeon's age (<40 years), i.e., surgical experience, and operative time (>13 h) were assessed as surgical factors.

Hemorrhage Trend Analysis

We analyzed intraoperative hemorrhage trends in 16 patients with middle cranial fossa resection or anterior-middle cranial fossa resection because of highly invasive surgery accompanied by a massive hemorrhage, a long operation time, and an unified surgical procedure.

In this analysis, intraoperative blood loss was prospectively calculated every hour, and operation contents were recorded for all patients. Surgery was performed in 4 steps as previously described: craniotomy and intracranial manipulation, cranial fossa osteotomy, extracranial osteotomy, and reconstruction. Hemorrhage volume was calculated and analyzed at every step. To identify the intraoperative parameter of massive blood loss, we calculated the cut-off hemorrhage volume for each surgical step in total massive blood loss (>4,000 mL).

Postoperative Complication Analysis

Postoperative complications were assessed chronologically. The association between each complication and LHS was also analyzed.

Statistical Analysis

Early- and late-phase surgical recoveries were analyzed separately. Delayed surgical recovery between the risk groups was analyzed using Fisher's exact test and logistic regression analysis. Baseline variables with $p < 0.05$ in the univariate analysis were included in the multi-variable fixed-effects models.

For analysis of risk factors of increased total hemorrhage, Welch's t test was used. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off hemorrhage volume following each step for total massive blood loss (>4,000 mL).

Statistical analyses were performed using SPSS Statistics software (version 22.0.0, IBM, Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

Table 1. Patient characteristics

Characteristic	Value
Sex	
Male/Female	20/13
Age, years	50 (9–74)
Smoking status	
Smoker/Nonsmoker	12/21
Drinking status	
Drinker/Nondrinker	9/24
Performance Status	
0/1	29/4
BMI	20 (13–33)
LWW, median, days	6 (2–18)
LHS, median, days	20 (10–77)
Preoperative blood tests	
Hemoglobin, g/dL	13.4 (6.1–17)
Glycosylated hemoglobin, mmol/mol	5.7(5.2–7.4)
Primary tumor site	
Paranasal sinus/nasal cavity	11/11
Orbita/oral cavity	9/2
Histopathological type	
SCC/adenocarcinoma/OS/UUS	9/5/5/5
RMS/ACC/MM/ONB/ES	4/2/1/1/1
Preoperative treatment	
Positive/negative	9/24
Type of skull base resection	
Anterior cranial fossa resection	17
Middle cranial fossa resection	6
Anterior-middle cranial fossa resection	10
Orbital excenteration	
Positive/negative	16/17
Hard palate resection	
Positive/negative	11/22
Type of reconstruction	
ALT/RA/pericranial flap	10/16/7
Operation time	11 h 22 m (6 h 28 m–16 h 40 m)
Bleeding volume, mL	1,700 (124–6,183)

Values are presented as medians (range). BMI, body mass index; LWW, length of walking around ward; LHS, Length of hospital stay; SCC, squamous cell carcinoma; OS, osteosarcoma; UUS, undifferentiated/unclassified sarcoma; RMS, rhabdomyosarcoma; ACC, adenoid cystic carcinoma; MM, malignant melanoma; ONB, olfactory neuroblastoma; ES, Ewing sarcoma; ALT, anterolateral thigh flap; RA, rectus abdominis musculo-cutaneous flap.

Results

Patient Characteristics

Patient characteristics are shown in Table 1. The study population comprised 20 men and 13 women aged 9–74 years (median: 50 years). We observed 9 cases of squamous cell carcinoma, 5 adenocarcinomas, 5 osteosarcomas, 5 undifferentiated/unclassified sarcomas, 4 rhabdomyosarcomas, 2 adenoid cystic carcinomas, 1 malignant melanoma, 1 olfactory neuroblastoma, and 1 Ewing sarcomas. The extent of skull base resection was anterior cranial fossa resection in 17, middle cranial fossa resection in 6, and anterior-middle cranial fossa

Table 2. Univariate analysis of risk factors for delayed surgical recovery

Variable	DDW, n (%)		p value	LHS, n (%)		p value
	>9 days	≤9 days		>28 days	≤28 days	
Age (years)						
>65	3 (43)	4 (57)	0.6456	3 (43)	4 (57)	0.0929
≤65	7 (26)	19 (74)		3 (12)	23 (88)	
BMI						
>25	5 (50)	5 (50)	0.2148	5 (50)	5 (50)	0.0895
≤25	5 (21)	18 (79)		4 (17)	19 (83)	
Performance Status						
1	2 (20)	8 (80)	0.5672	3 (75)	1 (25)	0.0523
0	2 (8)	21 (92)		6 (21)	23 (79)	
Tobacco						
Smoker	3 (25)	9 (75)	0.7098	4 (33)	8 (67)	0.6905
Nonsmoker	7 (33)	14 (67)		5 (24)	16 (76)	
Alcohol						
Drinker	4 (44)	5 (56)	0.3999	2 (22)	7 (78)	1.0000
Nondrinker	6 (25)	18 (75)		7 (29)	17 (71)	
Hemoglobin (g/dL)						
<8	1 (33)	2 (67)	1.0000	2 (67)	1 (33)	0.1738
≥8	9 (30)	21 (70)		7 (23)	23 (77)	
HbA1c (g/dL)						
>6.5	1 (50)	1 (50)	0.5208	1 (50)	1 (50)	0.4773
≤6.5	9 (29)	22 (71)		8 (26)	23 (74)	
Albumin (g/dL)						
<3.5	2 (67)	1 (33)	0.2117	1 (100)	0 (0)	0.2727
≥3.5	8 (27)	22 (73)		8 (25)	24 (75)	
Comorbidity						
Positive	5 (71)	2 (29)	0.0161	2 (29)	5 (71)	1.0000
Negative	5 (24)	21 (76)		7 (27)	19 (73)	
Preoperative treatment						
Positive	3 (30)	7 (70)	1.0000	3 (33)	6 (67)	0.6769
Negative	6 (26)	17 (74)		6 (25)	18 (75)	
Blood loss (mL)						
>4,000	4 (80)	1 (20)	0.0214	2 (40)	3 (60)	0.5971
≤4,000	6 (21)	22 (79)		7 (25)	21 (75)	
Operation time (h)						
>13	4 (44)	5 (56)	0.3999	3 (33)	6 (67)	0.3092
≤13	6 (25)	18 (75)		3 (13)	21 (87)	
Type of osteotomy						
MCF resection	5 (31)	11 (69)	1.0000	7 (43)	9 (57)	0.0570
Others	5 (29)	12 (71)		2 (12)	15 (88)	
Orbital exenteration						
Positive	5 (29)	12 (71)	1.0000	7 (41)	10 (59)	0.1175
Negative	5 (31)	11 (69)		2 (13)	14 (87)	
Cavernous sinus resection						
Positive	2 (40)	3 (60)	0.6269	2 (40)	3 (60)	0.5971
Negative	8 (40)	20 (60)		7 (25)	21 (75)	
Free-flap reconstruction						
Positive	9 (35)	17 (65)	0.3968	9 (35)	17 (65)	0.1493
Negative	1 (14)	6 (86)		0 (0)	7 (100)	
Surgical complication						
Positive	4 (57)	3 (43)	0.1605	9 (39)	14 (61)	0.0316
Negative	6 (23)	20 (77)		0 (0)	10 (100)	

Table 3. Multivariate analysis of risk factors for delayed surgical recovery

Variable	B	Exp(B)	95% CI	p value
DWW				
Comorbidity	2.3978	10.9987	1.3534–89.3810	0.0249
Blood loss	2.7392	15.4744	1.1828–202.4417	0.0368

Table 4. Risk factors for increased total hemorrhage

Variable	Univariate analysis		
	t	d.f.	p value
Patient factors			
Age >65 years	0.54	14.8	0.5983
BMI >25	0.11	7.64	0.9127
Hemoglobin <8 g/dl	0.41	2.30	0.7151
Albumin <3.5 g/dL	0.79	2.44	0.4983
Preoperative treatment	0.16	15.4	0.8773
Tumor factors			
Hard palate	3.59	18.0	0.0021
Maxillary sinus	6.42	15.7	9.40E–06
Pterygoid muscle	1.24	10.1	0.2427
Pterygopalatine fossa	2.80	16.7	0.0125
Base of the pterygoid process	3.46	8.75	0.0074
Orbital apex	1.17	31.0	0.2524
Sphenoid sinus	2.76	9.40	0.0212
Middle cranial fossa	3.55	24.8	0.0016
Wide middle cranial fossa	2.21	4.67	0.820
Cavernous sinus	5.62	13.1	0.00008
Dura matter	0.51	14.5	0.6191
Surgical factors			
Surgeon's age <40 years	0.34	18.8	0.7387
Operation time >13 h	2.85	13.5	0.0132

resection in 10 patients. Orbital exenteration was performed in 16 patients. Free-flap reconstruction was performed in 26 patients (anterolateral thigh flap in 10 and rectus abdominis musculocutaneous flap in 16 patients), and pericranial flap reconstruction was performed in 7 patients.

In this study, the median DWW was 6 days (range: 2–18) and the median LHS was 20 days (range: 10–77). The 75th percentile value at DWW and LHS was 9 and 28 days, respectively. As a result, delayed surgical recovery was defined as DWW and LHS longer than 9 and 28 days, respectively.

Risk Factors of Delayed Surgical Recovery

In early-phase recovery, univariate analysis showed that the existence of comorbidity and massive blood loss (>4,000 mL) were significantly associated with prolonged DWW (Table 2). In the multivariate analysis, blood loss and comorbidity remained independent factors (Table 3).

In the late-phase recovery, univariate analysis showed that development of postoperative complications was significantly associated with prolonged LHS (Table 2).

Risk Factors of Increased Total Hemorrhage

Univariate analysis showed that tumor invasion to the hard palate, the maxillary sinus, the pterygopalatine fossa, the base of the pterygoid process, the sphenoid sinus, the middle

Fig. 1. Case presentation of the intraoperative bleeding trend in a patient who underwent middle cranial fossa resection, total maxillectomy, and ALT flap reconstruction. The total bleeding was 2,030 mL; the operation time was 11 h and 22 min.

Fig. 2. Box plot of the amount of bleeding according to surgical procedure. The median hemorrhage volumes for each step, i.e., craniotomy and intracranial manipulation, cranial fossa osteotomy, extracranial osteotomy, and reconstruction are 819, 604, 606, and 268 mL, respectively.

cranial fossa, and the cavernous sinus, and long operation time (>13 h), were significantly associated with increased total hemorrhage (Table 4).

Hemorrhage Trend Analysis

Figure 1 shows the actual intraoperative hemorrhage trend. Intracranial manipulation, cranial fossa osteotomy, and extracranial osteotomy had a hemorrhage peak, whereas some patients had mild continuous hemorrhage during reconstruction.

Figure 2 shows the calculated hemorrhage volume during each step in all 16 patients by a box plot. The median hemorrhage volume for each step, i.e., craniotomy and intracranial manipulation, cranial fossa osteotomy, extracranial osteotomy, and reconstruction, was 819, 604, 606, and 268 mL, respectively.

ROC curve analysis revealed that the optimal cut-off hemorrhage volume associated with massive blood loss (>4,000 mL) was 1,111 mL (AUC = 0.8364) in craniotomy and intracranial manipulation, 750 mL (AUC = 0.8000) in cranial fossa osteotomy, and 913 mL (AUC = 0.8545)

Fig. 3. Optimal cut-off hemorrhage volume for massive bleeding. ROC curve analysis to determine the cut-off hemorrhage volume by each step for massive hemorrhage (>4,000 mL). **a** During craniotomy/intracranial manipulation, the cut-off volume was 1,111 mL (AUC = 0.8364) and it was weakly associated with total hemorrhage. **b** During cranial fossa osteotomy, the cut-off volume was 750 mL (AUC = 0.8000). **c** During extracranial osteotomy, the cut-off volume was 913 mL (AUC = 0.8545). **d** During reconstruction, the cut-off volume was 546 mL (AUC = 0.6182). TPF, true positive fraction; FPF, false positive fraction.

in extracranial osteotomy. Regarding reconstruction, ROC curve analysis could not determine the optimal cut-off hemorrhage volume (AUC = 0.6182) (Fig. 3).

Postoperative Complication Analysis

In total, 27 perioperative complications were reported. Local infection was reported in 24% and central nervous system (CNS)-related complications was reported in 12% of the patients.

In Figure 4, each postoperative complication was plotted chronologically. In the early postoperative period (POD 0–5), Donner flap hematoma, thrombotic occlusion after anastomosis, and intracranial hypotension occurred. In the intermediate postoperative period (POD

Fig. 4. Postoperative complication trend. Postoperative complications were plotted chronologically. The red exes indicate a length of hospital stay of more than 28 days. The circles indicate a direct reason for a prolonged hospital stay.

5–20), local infection and wound dehiscence and bone exposure occurred. In the late postoperative period (POD 21 or later), depression and anxiety neurosis were observed.

Persistent infection (6%) and neuropsychiatric disorder (6%) are the direct causes of long-term hospitalization (>28 days LHS).

Discussion

Appropriate perioperative management is necessary for early recovery from surgery. The factors of recovery following surgical procedures were divided into 3 categories, i.e., preoperative, intraoperative, and postoperative factors. Age, sex, PS, BMI, comorbidity, and a preoperative blood test were classified as preoperative factors. Blood loss, operation time, and surgical procedure were classified as intraoperative factors. Surgical complication was classified as a postoperative factor.

Many outcomes, such as duration of hospital stay, morbidity, and mortality, or biologic or physiologic parameters, were reported for recovery from the surgery [20]. As the short-term recovery, physical activity or mobility were important outcomes [21]. In this study, early and late phases of recovery were assessed as DWW and LHS, respectively.

In patients with surgically resected esophageal cancer, preoperative PS, smoking history, preoperative weight loss, and postoperative chylothorax were reported as risk factors of delayed surgical recovery [22, 23]. In this study, blood loss and comorbidity were factors that delayed the early-phase recovery, whereas postoperative complications delayed late-phase recovery.

In this study, blood loss delayed early recovery from surgery. The surgeon should make an increased effort to decrease bleeding. The risk for increased total hemorrhage was significantly associated with anatomical tumor extensions, such as maxillary sinus invasion, hard palate invasion, and the invasion to the base of the pterygoid process, and a long operation time; however, patient factors, such as the patient's age and BMI, or surgical factors, such as the surgeon's age, i.e., surgical experience, were not associated with the risk. Unfortunately, multivariate analysis was difficult in the current study because of the small sample size. It is certain that surgical procedures like extra- or intracranial osteotomy are difficult to change or modify depending on tumor extension; however, it is possible to decrease total hemorrhage by meticulous preoperative planning for prolonged and tough skull base surgery. 3-D virtual surgical simulations contribute to preoperative planning for skull base surgery [24]. Systematic and efficient surgery may help in minimizing intraoperative bleeding. We also objectively analyzed the cut-off hemorrhage volume following each of the 4 surgical steps for total massive blood loss (>4,000 mL). During surgery, if the hemorrhage volume reaches these cut-off values, the surgeon should perform the surgery cautiously.

The pterygoid plexus veins and the cavernous sinus may be the 2 main sources of persistent bleeding. To reduce bleeding originating from the pterygoid plexus, we attempted various methods. First, ligation of the internal maxillary artery before extracranial osteotomy reduced the bleeding [17]. Second, when drilling out the middle cranial fossa, the superior part of the pterygoid plexus was also approached. To avoid plexus damage, a diamond drill was used to penetrate the cranial fossa. Third, the pterygoid plexus was connected with the cavernous sinus through the foramen ovale. Coagulation of larger vessels in the foramen ovale reduced bleeding from the pterygoid plexus. Finally, prolonged operative procedures induced a deficient clotting factor. Immediate clotting factor replacement is necessary for safe skull base surgery.

Bleeding from the cavernous sinus is also persistent. In the case of tumor invasion near the cavernous sinus, approaching this area is inevitable. However, we should avoid the cavernous sinus if possible. For instance, to cut the optic nerve in the optic canal, the dull posterior from the anterior clinoid process near the cavernous sinus should be kept intact.

During reconstruction, massive bleeding did not easily occur; however, 2 patients experienced rebleeding from the pterygoid plexus. Therefore, surefire hemostasis and optimal clotting factor replacement during each surgical step is important, particularly before reconstruction.

In this study, LHS was significantly long in patients experiencing postoperative complications. Postoperative complications are reported to experience wound infection (19–20% of the patients) and CNS-related complications (13–20% of the patients) [13–15]. In our analysis, wound complications occurred in 30% and CNS-related complications in 15% of the patients, which was consistent with findings reported in previous studies. Adverse events were quite different chronologically. Operative procedure resulted in early-phase adverse events (POD 0–5), wound infection caused intermediate phase adverse events (POD 5–20), and neuropsychiatric disorders caused late-phase adverse events (POD 21 or later).

Wound infection and neuropsychiatric disorders were the direct reason for long-term hospitalization. Postoperative recipient-site infection and facial fistula were reported to occur mainly in patients with a low BMI [25]. Optimal reconstruction without having a dead space and immediate assessment for fluid retention are necessary to decrease postoperative complications. Neuropsychiatric disorders often afflict patients with head and neck cancer (reported in 18% of patients diagnosed with depression during treatments) [26]. Early identification and treatment for neuropsychiatric disorder are recommended [27]. Skull base surgery with total maxillectomy or orbital exenteration induced severe deformity and changed the body image which had an impact on the patients' long-term quality of life [28].

The usefulness of cosmetic treatments combined with routine cancer care has been previously reported [29]. At our institute, preoperative routine consultations to psychotherapists and psychiatrists are recommended for mental care. Moreover, patients with a skull base malignancy can develop complications months or years after the completion of treatment. It is important to continue to follow up for several years [30].

The main limitation of the study was selection bias because of the retrospective study with a small sample size. Moreover, skull base surgery being a highly invasive and time-consuming surgery, several factors might be related to delayed surgical recovery or increased intraoperative hemorrhage. Unmeasured confounding is probably substantial. In the analysis of increased total bleeding, multivariate analysis was difficult because of the small sample size. As a result, confounding factors might cause bias for a result. Further studies are needed to assess the factors associated with delayed surgical recovery in skull base surgery.

In conclusion, massive blood loss and existence of comorbidities are early-phase risk factors of delayed surgical recovery, whereas the occurrence of postoperative complications is a late-phase risk factor. The optimal cut-off hemorrhage volume associated with total massive blood loss in craniotomy and intracranial manipulation, cranial fossa osteotomy, and extracranial osteotomy was 1,111, 750, and 913 mL, respectively. Wound infection and neuropsychiatric disorder are the direct causes of delayed LHS (>28 days LHS). Meticulous preoperative planning, intraoperative surefire hemostasis, and perioperative holistic management are required for safe skull base surgery.

Statement of Ethics

This study was approved by our institutional ethics committee (2010-077) and conducted in accordance with the Declaration of Helsinki.

Disclosure Statement

The authors declare that they have no conflict of interests.

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Author Contributions

Kenya Kobayashi: study design and data interpretation. Fumihiko Matsumoto and Seiichi Yoshimoto: study design, data interpretation, and revision of this paper. Yasuji Miyakita, Masaki Arikawa, Go Omura, Satoko Matsumura, Atsuo Ikeda, Azusa Sakai, Kohtaro Eguchi, Yoshitaka Narita, Satoshi Akazawa, and Shimpei Miyamoto: data interpretation and revision of this paper.

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