Risk factors of thrombosis in a single method of microsurgical head and neck reconstruction: A multi-institutional study of 773 reconstructions with a free jejunal graft after total pharyngo-laryngo-esophagectomy for hypopharyngeal cancer

Narushi Sugiyama, MD[1], Soshi Takao, MD, PhD[2], Etsuji Suzuki, MD, PhD[2], Yoshihiro Kimata, MD, PhD[1]

[1]Department of Plastic and Reconstructive Surgery, Okayama University Hospital, Okayama, Japan

[2]Department of Epidemiology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

Acknowledgments

The authors are very grateful to Dr. Mitsuru Sekido, Dr. Hirotaka Asato, Dr. Hiroyuki Sakurai, Dr. Minoru Sakuraba, Dr. Seiich Yoshimoto, Dr. Masahiro Nakagawa, Dr. Ikuo Hyodo, Dr. Tomoyuki Kurita, Dr. Sei Yoshida, and Dr. Katsumi Tanaka for data collection. The authors also thank Dr. Hiroshi Furukawa, Dr. Takuya Iida, Dr. Keijiro Hori, Dr. Atsumori Hamahata, Dr. Kazuyoshi Kawabata, and Dr. Wataru Shimbashi for the approval of the Institutional Review Board. The authors are very grateful for the support provided by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

Correspondence and reprint requests:

Narushi Sugiyama, MD

Department of Plastic and Reconstructive Surgery

Okayama University Hospital

2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

Tel: +81-86-235-7214

E-mail: narusi-s@ka2.so-net.ne.jp

Running title: Risk factors of free jejunal graft thrombosis

Key words: risk factor, thrombosis, microsurgery, head and neck reconstruction, multivariate analysis

Abstract

Background: The risk factors for thrombus formation in anastomotic vessels in free-flap head and neck reconstruction have been previously reported. However, the evidence is inconsistent.

Methods: In total, 773 patients who underwent free jejunal graft reconstruction after pharyngo-laryngo-esophagectomy for hypopharyngeal cancer were enrolled at 12 institutions in Japan from 1995 to 2006. Both the resection area and the applied reconstruction method were constrained to overcome the limitations of previous studies. After the exclusion of recurrent cases, odds ratios and 95% confidence intervals for thrombosis were calculated in a multivariate logistic regression analysis.

Results: Postoperative anastomotic thrombosis developed in 23 (3.0%) patients. In the multivariate analysis, the odds ratio for thrombosis per 100-mL increase in blood loss was 1.24 (95% confidence interval: 1.02–1.51), even after controlling for other risk factors.

Conclusions: Our results show that the blood loss volume is an independent risk factor for thrombosis in free tissue grafts.

Introduction

Free tissue grafting is currently the standard therapy in patients undergoing reconstruction after head and neck cancer resection. The most serious complication in free tissue grafting is total necrosis of the graft tissue caused by thrombosis in the vascular anastomosis. According to recent reports that included large numbers of cases, total necrosis of the graft flap occurs in 0.8% to 5.4% of head and neck reconstructions.[1-7] Although total necrosis is uncommon, it is a major burden for affected patients. The risk factors for thrombosis in head and neck reconstruction include secondary reconstruction,[6] malnutrition,[8] concurrent chemoradiotherapy,[4] vein grafting, and salvage surgery after flap necrosis.[9] However, the methodologies used in those studies were not comparable in terms of resection areas, reconstruction materials, and their analyses, which resulted in inconsistencies regarding their conclusions. In addition, very few studies of head and neck reconstruction have considered other risk factors for anastomotic thrombosis in a multivariate model.

In head and neck reconstruction surgeries, free jejunal graft reconstruction after pharyngo-laryngo-esophagectomy is a relatively simple reconstructive procedure, and little variation is present in the operative procedure and technique. These features make it well suited for the analysis of postoperative outcomes. Thus, to conduct a more accurate assessment of the risk factors for anastomotic thrombosis in head and neck reconstruction, we limited the included resections to pharyngo-laryngo-esophagectomy for hypopharyngeal cancer and the reconstruction method to free jejunal graft reconstruction in the present study. In addition, we concomitantly adjusted for possible risk factors for thrombosis in the vessel anastomosis.

Patients and methods

The study population comprised 773 patients who underwent free jejunal graft reconstruction after pharyngo-laryngo-esophagectomy for hypopharyngeal cancer at 12 university hospitals and cancer centers in Japan from January 1995 to December 2006 (Table 1).

Only those patients who underwent free jejunal graft reconstruction after pharyngo-laryngo-esophagectomy for hypopharyngeal cancer were included in the study. Patients who underwent simultaneous operations for other cancers (e.g., thoracic esophageal cancer) were excluded from the study. Patients who underwent salvage procedures due to previous free flap failure were also not included in the study.

The outcome of interest was the presence of postoperative thrombosis in anastomotic vessels, including both the artery and vein. The variables considered as risk factors were age (continuous), sex, onset (primary vs. recurrent), preoperative complications (diabetes mellitus and cardiovascular disorder; present or absent), history of irradiation (present or absent), preoperative chemotherapy (present or absent), blood loss volume (continuous), operation time (quartile), neck dissection procedure, administration of thromboprophylaxis, and institution type. In addition, a dichotomous variable for cardiovascular disorders was created to determine whether the patient had hypertension, angina, myocardial infarction, and/or cerebral infarction or a history thereof. A history of head and neck irradiation was considered both primary disease and another disease. Any irradiation range overlapping the cervical area and any irradiation dose were considered. Preoperative chemotherapy included only chemotherapy for primary disease. All types of chemotherapy agents (e.g. 5-fluorouracil, cisplatin, etc.) were included. Neck dissection procedures were assessed as no dissection, radical neck dissection, or other (non-radical neck dissection). Thromboprophylaxis was assessed as no use of thromboprophylaxis, use of prostaglandin E1 (PGE1) only, use of PGE1 and other agents, or use of other agents. Twelve participating institutions were categorized as either university hospitals or cancer centers.

After describing the univariate relationships between possible risk factors and the presence of thrombosis, we examined multivariate relationships using logistic regression models. In the univariate analysis, we entered the operation time and blood loss volume as both continuous variables and categorical variables to determine whether their associations were

linear or nonlinear. Before multivariate analysis, correlation coefficients between each variable were checked to address the issue of multicollinearity.

Based on the results of the univariate analysis, previous reports, and clinical experiences, we selected variables for the multivariate analysis. Sex and age were selected because they are basic demographic factors. Because data on the sex of 264 patients were missing, we adjusted for sex only in the fully adjusted model. In recurrent cases, factors such as a history of surgery or irradiation might affect the risk of thrombosis, and these variables were not necessarily independent. Thus, recurrent cases were excluded (n = 96) and only primary cases were analyzed (n = 614). Cardiovascular disorder was selected because atherosclerosis might affect the risk of thrombosis. Because there were no cases of thrombosis among the patients with diabetes mellitus, we did not adjust it. A history of irradiation and preoperative chemotherapy were selected because the tissue damage that they induce might affect the risk of thrombosis. Although no neck dissection was positively associated with thrombosis in the univariate analysis, we thought that recurrence was a confounder between thrombosis and no neck dissection. There was little difference between radical neck dissection and non-radical neck dissection in the univariate analysis, and neck dissection was not selected for the multivariate analysis. Thromboprophylaxis was selected because it might decrease the risk. Patients with thromboprophylactic agents other than PGE1 were excluded because of the small number of such patients (n = 35). Operation time and blood loss volume were selected because they might be associated with systemic invasiveness and surgical technique. Based on the results of the univariate analysis, operation time was entered as a categorical variable to address a potential nonlinear relationship, whereas blood loss volume was entered as a continuous variable in the multivariate models. Institution was selected because it might be associated with the therapeutic strategy and surgical procedure.

We calculated odds ratios (ORs) and their 95% confidence intervals (CIs) for thrombosis. A p value of <0.05 (two-sided test) was considered statistically significant. The

statistical analysis was conducted using SPSS 22.0 (IBM Corp., Armonk, NY, USA). The present study used data collected in a past survey entitled "Research for establishing plastic and reconstructive surgery for surgical cancer therapy" supported by a Grant-in-Aid for Cancer Research (grant 17-5) from the Ministry of Health, Labour and Welfare of Japan.[10] Permission for use of the data was newly obtained from the Institutional Review Boards of all participating institutions.

Results

Table 2 shows the preoperative demographic data of the patients. Anastomotic thrombosis developed in 23 (3.0%) of the 773 patients. The mean age of the patients at reconstructive surgery was 64.0 years (standard deviation [SD], 9.2 years). The sex distribution was as follows: male, 55.2%; female, 10.6%; and unknown, 34.2%. Table 3 shows the surgical variables of the patients. The mean operation time was 592 min (SD, 197 min). The mean blood loss volume was 582 mL (SD, 343 mL).

Table 4 shows the crude ORs for thrombosis associated with preoperative demographic data. The OR of recurrent vs. primary cases was 2.68 (95% CI: 1.01–7.08). Table 5 shows the crude ORs for thrombosis associated with surgical variables. There were no significant results except for two categories that included a small number of patients: no neck dissection vs. non-radical neck dissection (OR = 4.95, n = 25) and other form of thromboprophylaxis vs. no prophylaxis (OR = 17.57, n = 10).

The absolute values of the correlation coefficients between each variable were ≤0.5 (data not shown). As shown in Table 6, the OR for thrombosis per 100-mL increase in blood loss was 1.24 (95% CI: 1.02–1.51), even after controlling for other risk factors (Model 3). In Model 3, patients at university hospitals (n = 49) were excluded for convergence of logistic regression analysis. Although not statistically significant, the adjusted ORs associated with cardiovascular disorder, history of irradiation, preoperative chemotherapy, and

thromboprophylaxis were 0.48, 0.82, 1.49, and 2.93, respectively (Model 3).

Discussion

To our knowledge, this is the first study to show that the blood loss volume is an independent risk factor for thrombosis in free tissue grafts after controlling for other already known risk/preventive factors. To achieve a rigorous evaluation of the risk factors for anastomotic thrombosis, only those patients who underwent free jejunal graft reconstruction after pharyngo-laryngo-esophagectomy for hypopharyngeal cancer were enrolled in the study. However, the details of the surgical procedures varied among the institutions (e.g., recipient vessel, jejunal anastomosis procedure, etc.).

Yoshimoto et al.[4] also reported a higher prevalence of thrombosis with an increasing blood loss volume based on a univariate analysis. However, the relationship was not significant. Furthermore, their study included patients with a wide variety of head and neck cancers, and the reconstructions were carried out with different materials. In the present study, in addition to the strict inclusion criteria regarding the resection area and reconstruction method, we conducted a multivariate analysis and simultaneously adjusted for other risk factors. This approach would account for our significant results. Another study reported an association between perioperative hemorrhage and stroke or myocardial infarction[11]; our results are similar to these. However, the mechanism by which a larger blood loss volume leads to a greater risk of thrombosis is unclear. A large blood loss volume is likely to reduce blood pressure and exacerbate systemic problems, which in turn may cause thrombosis. The surgical technique may also be an unmeasured confounding factor. A larger blood loss volume may be associated with a more complex case or poorer surgical technique; a longer operation time may also be associated with these factors. However, the ORs for operation time showed a reverse trend. A longer operation time tended to be associated with a lower risk. Thus, we believe that the blood loss volume is an independent risk factor. Efforts to reduce the blood loss volume must be made. In addition, when the blood

loss volume increases, appropriate thromboprophylaxis and carful monitoring should be considered.

An unexpected finding was that the prevalence of thrombosis was nearly identical between patients who were administered PGE1 as a preventive therapy and those who did not receive any form of thromboprophylaxis; in fact, the prevalence was slightly higher in the former group. Although the effect estimate was not significant, our findings still show that PGE1 is a "risk" factor for thrombosis. However, reverse causation must be considered given that patients administered PGE1 were likely to have been those at a high risk of thrombosis. In addition, there were large differences in the administration of PGE1 to patients at the different institutions. Thus, while in some institutions almost all patients are prophylactically given PGE1, in others it is used only rarely. Therefore, reverse causation cannot fully explain our results. In a report on head and neck reconstruction using free tissue transfer, Riva et al.[7] also reported that PGE1 did not confer an antithrombotic effect. Davies[12] evaluated patients who underwent free flap surgery and reported no difference in the prevalence of thrombosis between the group administered thromboprophylaxis and the non-administration group. However, during replantation, the treated group had a significantly lower prevalence of thrombosis.[12] Thromboprophylaxis is considered to be unnecessary in free flap grafting because the condition of the blood vessels is better than in replantation. Furthermore, the vessels of the head and neck region have a large flow volume, which allows blood flow to be easily maintained even if the volume decreases (unlike in the extremities); therefore, the risk of thrombosis is considered to be relatively low. Thus, while PGE1 administration after free tissue grafting is unnecessary in patients who undergo typical head and neck reconstructions, thromboprophylaxis (whether with PGE1 or other agents) should be considered for patients at a high risk of thrombosis.

The risk factors for thrombosis have been evaluated in several studies. Yoshimoto et al.[4] identified concurrent chemoradiotherapy as a risk factor for thrombosis. Although we did not examine concurrent chemoradiotherapy in the present study, chemotherapy and a history of

irradiation were examined separately, and neither was found to be a significant risk factor for thrombosis. Because we did not include information about the area of irradiation or irradiation dose, the degree of effect on the recipient vessel could not be taken into account. Normally, the surgeon confirms the status of the recipient vessel before anastomosis; if the status is poor because of the effect of irradiation, a different vessel is selected. Thus, because there may have been a large selection bias, it was difficult to examine the true effect of irradiation. Our finding that age was not a risk factor for thrombosis is in line with the results reported in other studies.[4,6,9,13] In contrast, age is a significant risk factor for postoperative complications such as infection and fistula formation.[2] While age may not be a risk factor for thrombosis, head and neck reconstruction is not necessarily safe for elderly patients. The operation time was also not a significant risk factor for thrombosis, in agreement with several previous reports.[4,9] In fact, our results suggest an association between a longer operation time and a lower risk of thrombosis. In their study of breast reconstruction using free tissue grafts, Masoomi et al.[13] reported that complications involving peripheral vascular disorders and secondary reconstruction were risk factors for thrombosis. Contrary to expectations, an association of hypertension, diabetes mellitus, and preoperative chemotherapy with a lower risk of thrombosis was demonstrated. In the present study, after collective assessment of hypertension, cardiovascular disorders, and peripheral vascular disorders, these were not found to be significant risk factors.

Although no neck dissection was positively associated with thrombosis in the univariate analysis, it was also positively associated with recurrence; 16 of 25 cases of no neck dissection were recurrent. Recurrence can presumably act as a confounder between thrombosis and no neck dissection. Use of thromboprophylactic agents without PGE1 was also positively associated with thrombosis in the univariate analysis. Although it is difficult to interpret the findings from the available data, these patients used heparin and/or urokinase. Those with such strict thromboprophylactic management might have had a higher risk of thrombosis.

There are several limitations of our study. First, the number of events was relatively

low compared with the number of variables; thus, the results may be biased. Second, the sex of a relatively large number of patients (n = 264; 34.2%) was unknown. The large amount of missing data hindered estimations of the direction and magnitude of biases that may have affected the results. Third, the structure of our data was not considered; patients were nested within surgeons, who were in turn nested within institutions. Indeed, surgical technique may have been an important unmeasured confounder, and there may have been large differences between institutions with respect to cancer treatment strategies, procedural details, and perioperative management. We could only take into account the dichotomized institutional type because of the relatively large number of institutions. These relationships should be examined in more sophisticated statistical analyses such as those using multilevel models. Fourth, by reanalyzing previously collected data, some important risk factors for thrombosis were not included in the dataset (e.g., malnutrition, perioperative blood pressure, transfusion, and administration of agents promoting thrombosis). These factors should be considered in future studies.

Conclusion

Our findings suggest that the blood loss volume is a significant risk factor for thrombosis, even after adjusting for other risk factors. Further studies are needed to determine the effects of systemic management (such as perioperative blood pressure and transfusion) on anastomotic thrombosis.

References

1. Suh JD, Sercarz JA, Abemayor E, et al. Analysis of outcome and complications in 400 cases of microvascular head and neck reconstruction. Arch Otolaryngol Head Neck Surg 2004;130:962–966.
2. Clark JR, McCluskey SA, Hall F, et al. Predictors of morbidity following free flap reconstruction for cancer of the head and neck. Head Neck 2007;29:1090–1101.
3. Yoshimoto S, Kawabata K, Mitani H. Analysis of 59 cases with free flap thrombosis after reconstructive surgery for head and neck cancer. Auris Nasus Larynx 2010;37:205–211.
4. Yoshimoto S, Kawabata K, Mitani H. Factors involved in free flap thrombosis after reconstructive surgery for head and neck cancer. Auris Nasus Larynx 2010;37:212–216.
5. Singh B, Cordeiro PG, Santamaria E, Shaha AR, Pfister DG, Shah JP. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg 1999;103:403–411.
6. Nakatsuka T, Harii K, Asato H, et al. Analytic review of 2372 free flap transfers for head and neck reconstruction following cancer resection. J Reconstr Microsurg 2003;19:363–368.
7. Riva FMG, Chen Y-C, Tan N-C, et al. The outcome of prostaglandin-E1 and dextran-40 compared to no antithrombotic therapy in head and neck free tissue transfer: Analysis of 1,351 cases in a single center. Microsurgery 2012;32:339–343.
8. Shum J, Markiewicz MR, Park E, et al. Low prealbumin level is a risk factor for microvascular free flap failure. J Oral Maxillofac Surg 2014;72:169–177.
9. Bozikov K, Arnez ZM. Factors predicting free flap complications in head and neck reconstruction. J Plast Reconstr Aesthet Surg 2006;59:737–742.
10. Sugiyama N, Kimata Y, Sekido M, et al. A multi-institutional study of reconstruction for laryngopharyngoesophagectomy. Toukeibu Gan 2006;32:486–493.
11. Kamel H, Johnston SC, Kirkham JC, et al. Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. Circulation 2012;126:207–212.
12. Davies DM. A world survey of anticoagulation practice in clinical microvascular surgery. Br J Plast Surg 1982;35:96–99.
13. Masoomi H, Clark EG, Paydar KZ, et al. Predictive risk factors of free flap thrombosis in breast reconstruction surgery. Microsurgery 2014;34:589–594.

Table 1. List of participating institutions

Division of Plastic and Reconstructive Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
Department of Plastic and Reconstructive Surgery, Hokkaido University Graduate School of Medicine
Division of Plastic and Reconstructive Surgery, National Cancer Center Hospital East
Department of Plastic and Reconstructive Surgery, The University of Tokyo
Division of Plastic Surgery, Saitama Cancer Center
Department of Plastic and Reconstructive Surgery, Tokyo Women's Medical University
Department of Head and Neck, Cancer Institute Hospital of Japanese Foundation for Cancer Research
Division of Plastic and Reconstructive Surgery, Shizuoka Cancer Center Hospital
Department of Head and Neck Surgery, Aichi Cancer Center Hospital
Division of Head and Neck Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases
Department of Otorhinolaryngology, Faculty of Medicine, Kyushu University
Department of Plastic and Reconstructive Surgery, Graduate School of Medical and Dental Science, Nagasaki University

Table 2. Distribution of the 773 study patients by preoperative demographic variables, Japan (1995–2006)

	No thrombosis n = 738		Thrombosis n = 23		Total* n = 773	
	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Sex						
Male	405	(54.9)	15	(65.2)	427	(55.2)
Female	80	(10.8)	2	(8.7)	82	(10.6)
Missing data	253	(34.3)	6	(26.1)	264	(34.2)
Age (years), mean / SD	64.0	9.3	64.5	8.6	64.0	9.2
Missing data	0	(0.0)	0	(0.0)	0	(0.0)
Onset						
Primary	589	(79.8)	15	(65.2)	614	(79.4)
Recurrence	88	(11.9)	6	(26.1)	96	(12.4)
Missing data	61	(8.3)	2	(8.7)	63	(8.2)
Cardiovascular disorder						
No	519	(70.3)	14	(60.9)	542	(70.1)
Yes	215	(29.1)	9	(39.1)	227	(29.4)
Missing data	4	(0.5)	0	(0.0)	4	(0.5)

Diabetes mellitus						
No	676	(91.6)	23	(100.0	705	(91.2)
Yes	58	(7.9)	0	(0.0)	64	(8.3)
Missing data	4	(0.5)	0	(0.0)	4	(0.5)
History of irradiation						
No	510	(69.1)	15	(65.2)	531	(68.7)
Yes	218	(29.5)	7	(30.4)	231	(29.9)
Missing data	10	(1.4)	1	(4.3)	11	(1.4)
Preoperative						
No	553	(74.9)	14	(60.9)	575	(74.4)
Yes	167	(22.6)	8	(34.8)	179	(23.2)
Missing data	18	(2.4)	1	(4.3)	19	(2.5)

Abbreviation: SD: standard deviation.

*The “Total” column includes missing data on postoperative thrombosis.

Table 3. Distribution of the 773 study patients by surgical variables, Japan (1995–2006)

	No thrombosis n = 738		Thrombosis n = 23		Total* n = 773	
	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Neck dissection						
No	22	(3.0)	3	(13.0)	25	(3.2)
Non-radical neck dissection	508	(68.8)	14	(60.9)	532	(68.8)
Radical neck dissection	208	(28.2)	6	(26.1)	216	(27.9)
Thromboprophylaxis						
No	205	(27.8)	5	(21.7)	211	(27.3)
PGE1 only	491	(66.5)	14	(60.9)	514	(66.5)
PGE1 and others	23	(3.1)	1	(4.3)	24	(3.1)
Others	7	(0.9)	3	(13.0)	11	(1.4)
Missing data	12	(1.6)	0	(0.0)	13	(1.7)
Operation time (min), mean / SD	589	192	571	168	592	197
Categorized operation time (min)†						
<470	184	(24.9)	7	(30.4)	191	(24.7)
≥470, <554	182	(24.7)	5	(21.7)	189	(24.5)
≥554, <660	193	(26.2)	5	(21.7)	199	(25.7)

≥660	168	(22.8)	6	(26.1)	181	(23.4)
Missing data	11	(1.5)	0	(0.0)	13	(1.7)
Blood loss volume (mL), mean / SD	576	337	685	392	582	343
Categorized blood loss volume (mL)‡						
<326	183	(24.8)	4	(17.4)	188	(24.3)
≥326, <509.5	179	(24.3)	4	(17.4)	187	(24.2)
≥509.5, <746.5	179	(24.3)	8	(34.8)	188	(24.3)
≥746.5	176	(23.8)	7	(30.4)	187	(24.2)
Missing data	21	(2.8)	0	(0.0)	23	(3.0)
Institution§						
University hospital	251	(34.0)	6	(26.1)	267	(34.5)
Cancer center	487	(66.0)	17	(73.9)	506	(65.5)
Missing data	0	(0.0)	0	(0.0)	0	(0.0)

Abbreviations: PGE1: prostaglandin E1; SD: standard deviation.

*The “Total” column includes missing data on postoperative thrombosis.

† Operation time was categorized in quartiles.

‡ Blood loss volume was categorized in quartiles.

§ The 12 participating institutions were categorized as either university hospitals or cancer centers.

Table 4. Crude odds ratios for thrombosis associated with preoperative demographic variables, Japan (1995–2006)

	Total	Thrombosis				
	No. of patients	No. of patients	(%)	OR	(95% CI)	p
Sex						
Male	427	15	(3.5)	1.00		
Female	82	2	(2.4)	0.68	(0.15–3.01)	0.61
Age (years)	761			1.01	(0.96–1.05)	0.79
Onset						
Primary	614	15	(2.4)	1.00		
Recurrence	96	6	(6.3)	2.68	(1.01–7.08)	0.05
Cardiovascular disorder						
No	533	14	(2.6)	1.00		
Yes	224	9	(4.0)	1.55	(0.66–3.64)	0.31
Diabetes mellitus						
No	699	23	(3.3)			
Yes	58	0	(0.0)		N/A	
History of irradiation						
No	525	15	(2.9)	1.00		

Yes	225	7	(3.1)	1.09	(0.44–2.72)	0.85
Preoperative chemotherapy						
No	567	14	(2.5)	1.00		
Yes	175	8	(4.6)	1.89	(0.78–4.59)	0.16

Abbreviations: CI: confidence interval; N/A: not applicable; OR: odds ratio.

Table 5. Crude odds ratios for thrombosis associated with surgical variables, Japan (1995–2006)

	Total	Thrombosis			
	No. of patients	No. of patients (%)	OR	(95% CI)	p
Neck dissection					
No	25	3 (12.0)	4.95	(1.32–18.49)	0.02
Non-radical neck dissection	522	14 (2.7)	1.00		
Radical neck dissection	214	6 (2.8)	1.05	(0.40–2.76)	0.93
Operation time (per hour)	750		0.97	(0.84–1.12)	0.66
Categorized operation time (min)*					
<470	191	7 (3.7)	1.00		
≥470, <554	187	5 (2.7)	0.72	(0.23–2.32)	0.58
≥554, <660	198	5 (2.5)	0.68	(0.21–2.18)	0.52
≥660	174	6 (3.4)	0.94	(0.31–2.85)	0.91
Blood loss volume (per 100 mL)	740		1.09	(0.98–1.21)	0.13
Categorized blood loss volume (mL)†					
<326	187	4 (2.1)	1.00		
≥326, <509.5	183	4 (2.2)	1.02	(0.25–4.15)	0.98
≥509.5, <746.5	187	8 (4.3)	2.05	(0.61–6.91)	0.25
≥746.5	183	7 (3.8)	1.82	(0.52–6.32)	0.35
Thromboprophylaxis					

No	210	5	(2.4)	1.00		
PGE1 only	505	14	(2.8)	1.17	(0.42–3.29)	0.77
PGE1 and others	24	1	(4.2)	1.78	(0.20–15.93)	0.61
Others	10	3	(30.0)	17.57	(3.49–88.57)	<0.01
Institution‡						
University hospital	257	6	(2.3)	1.00		
Cancer center	504	17	(3.4)	1.46	(0.57–3.75)	0.43

Abbreviations: CI: confidence interval; OR: odds ratio; PGE1: prostaglandin E1.

*Operation time was categorized in quartiles.

† Blood loss volume was categorized in quartiles.

‡ The 12 participating institutions were categorized as either university hospitals or cancer centers.

Table 6. Adjusted odds ratios for thrombosis associated with preoperative demographic data and surgical variables, Japan (1995–2006)*

	Model 1 ‖				Model 2¶				Model 3#			
	No. of patients				No. of patients				No. of patients			
	n = 545	OR	(95% CI)	p	n = 527	OR	(95% CI)	p	n = 323	OR	(95% CI)	p
Operation time (min)†												
<470	125	1.00			119	1.00			110	1.00		
≥470, <554	142	0.93	(0.19–4.49)	0.93	140	0.86	(0.18–4.17)	0.85	97	0.87	(0.16–4.74)	0.87
≥554, <660	148	0.54	(0.09–3.30)	0.50	145	0.54	(0.09–3.37)	0.51	85	0.37	(0.05–2.87)	0.34
≥660	130	0.39	(0.04–3.96)	0.43	123	0.35	(0.03–4.00)	0.40	31	0.24	(0.01–4.26)	0.33
p for trend			0.72				0.36				0.25	
Amount of bleeding (per 100 mL)		1.22	(1.03–1.44)	0.02		1.20	(1.01–1.42)	0.03		1.24	(1.02–1.51)	0.03

Thromboprophylaxis‡												
No	166	1.00			165	1.00			138	1.00		
PGE1 only	379	2.87	(0.66–12.48)	0.16	362	3.04	(0.68–13.55)	0.14	185	2.93	(0.57–15.08)	0.20
Institution§												
University hospital	167	1.00			157	1.00						
Cancer center	378	6.08	(0.65–56.90)	0.11	370	5.42	(0.45–65.40)	0.18			N/A	
Sex												
Male									263	1.00		
Female									60	0.59	(0.07–5.11)	0.63
Age (years)						1.02	(0.95–1.09)	0.57		1.04	(0.96–1.13)	0.34
Cardiovascular disorder												
No					383	1.00			234	1.00		
Yes					144	1.08	(0.29–4.05)	0.91	89	0.48	(0.08–2.85)	0.42
History of irradiation												
No					404	1.00			281	1.00		

Yes	123	0.40	(0.04–4.03)	0.43	42	0.82	(0.08–8.60)	0.87
Preoperative chemotherapy								
No	420	1.00			295	1.00		
Yes	107	2.13	(0.28–16.47)	0.47	28	1.49	(0.11–19.49)	0.76

Abbreviations: CI: confidence interval; N/A, not applicable; OR: odds ratio; PGE1: prostaglandin E1.

*Only primary cases were analyzed.

† Operation time was categorized in quartiles.

‡ Patients with thromboprophylactic agents other than PGE1 were excluded.

§ The 12 participating institutions were categorized as either university hospitals or cancer centers.

‖ Surgical variables were adjusted in Model 1.

¶ Sex was not adjusted in Model 2 because of the large amount of missing data.

#Patients in university hospitals (n = 49) were excluded for convergence of logistic regression analysis.