Aus dem Universitätsklinikum Münster

Klinik und Poliklinik für Mund- und Kiefer- Gesichtschirurgie

- Direktor: Univ.- Prof. Dr. med. Dr. med. dent. Dr. h. c. Ulrich Joos -

Voraussagemodell von Transfusionen bei der operativen Therapie oraler Plattenepithelkarzinome

INAUGURAL - DISSERTATION

zur
Erlangung des doctor medicinae
der Medizinischen Fakultät
der Westfälischen Wilhelms-Universität Münster

vorgelegt von

Jinaporntham, Suthin
aus Bangkok, Thailand
2005

Gedruckt mit der Genehmigung der Medizinischen Fakultät
der Westfälischen Wilhelms-Universität Münster

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Tag der mündlichen Prüfung: 10.10.2005

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Zusammenfassung

Voraussagemodell von Transfusionen bei der operativen Therapie oraler Plattenepithelkarzinome

Suthin Jinapporntham

Ziel: Feststellung der Transfusionshäufigkeit bei der kurativen operativen Therapie oraler Plattenepithelkarzinome und die Entwicklung eines voraussagbaren Transfusionsmodells (Transfusion Prediction Model/TPM)

Material und Methoden: Es wurden von 150 Patienten mit einem oralen Plattenepithelkarzinom retrospektiv Daten gesammelt. Ausgewertet wurden insgesamt 17 deskriptive Variablen der Patienten. Um den TPM entwickeln zu können, wurden jedoch nur 10 präoperativ erhobene Variablen durch eine logistische Regression analysiert.

Ergebnisse: Insgesamt wurden 41 (27,3%) Patienten transfundiert. Die Medianzahl der transfundierten Erythrozytenkonzentrate war 2,0 (Variable 1-7). Das Verhältnis zwischen Bereitstellung zu Transfusion war 4,7:1. Die logistischen Regressionsanalysen ermittelten die Neck dissection und die Rekonstruktionsverfahren als die bedeutsamsten Variablen für den Bedarf einer Transfusion. Basierend auf diese beiden Variablen wurde ein TPM entwickelt. Mit dem TPM kann die Voraussage getroffen werden, dass Patienten die keine oder nur einseitige Neck dissection ohne Rekonstruktion benötigten, die niedrigsten Risiken hatten, eine perioperative Transfusion zu bekommen (1,7%-4,5%). Patienten, die eine beidseitige Neck dissection aber keine Rekonstruktion benötigten, besaßen ein mäßiges Risiko (11,2%). Patienten, die eine Rekonstruktion bekamen, besaßen die höchsten Risiken (22,7%-67,2%). Nach dem TPM wurde eine Richtlinie für die präoperative Vorbereitung der Transfusion erstellt.

Schlussfolgerung: Durch die Benutzung des TPM, ist eine medizinisch und wirtschaftlich sichere präoperative Planung für den Bedarf einer Transfusion möglich. Um die Genauigkeit des TPM prüfen zu können, sollte eine prospektive Studie folgen.

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Department of Cranio- and Maxillofacial Surgery

University Hospital of Muenster

- Director: Prof. Dr. Dr. Dr. h. c. U. Joos -

Transfusion Prediction Model for Surgical Treatment of Oral Squamous Cell Carcinoma

Inaugural - Dissertation

in partial fulfillment of the
requirements for the degree of
Doctor medicinae

Faculty of medicine
University of Muenster

by

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from Bangkok, Thailand
2005

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Abstract

Transfusion Prediction Model for Surgical Treatment of Oral Squamous Cell Carcinoma

Suthin Jinaporntham

Purpose: To determine the need for perioperative allogeneic blood transfusion in patients with oral squamous cell carcinoma who underwent curative surgical procedures and to develope a Transfusion Prediction Model (TPM).

Material and Method: Data from 150 patients with oral squamous cell carcinoma who were treated surgically during 1998-2002 were retrospectively collected. Data included 17 variables were descriptively analyzed to describe the population. In order to develope the TPM, only 10 variables available prior to surgery were analyzed with logistic regression analyses.

Results: Overall, 41(27.3%) patients required blood transfusion. The median number of units transfused was 2.0 (range 1-7 units). Crossmatch to transfusion ratio was 4.7:1. Logistic regression analyses showed the need for neck dissection and the need for reconstruction were most significantly associated with transfusion requirement. Based on these 2 variables, the TPM was developed. The TPM predicted that patients who received no or unilateral neck dissection without any reconstruction had low risk of requiring transfusion (1.7%-4.5%). Patients with bilateral neck dissection without reconstruction had moderate risk (11.2%), and patients who received reconstruction had high risk (22.7%-67.2%) of requiring blood transfusion. Based on this TPM, a guideline for preoperative transfusion planning was developed.

Conclusion: With the use of TPM, an appropriate and cost-effective transfusion planning is possible. However, a new prospective study to prove the accuracy of the TPM should be accomplished.

For my parents

`` I dressed him, God healed him. ´´

Ambroise Paré (1510-1590)

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1. Introduction

1.1. Historical Perspective

Since the prehistoric time of mankind, blood has been recognized as a vital element and the excessive blood loss from wounded animal or enemy was generally accepted to cause death [81]. The role of blood as a mystical vital element is referred to in Lecivitus 17:11 which reads, “The life of the flesh is in the blood. “, while the Chinese Neiching (circa 1000 B.C.) claims the blood contains the soul [45]. Egyptians took blood baths as a recuperative measure, and Romans drank the blood of fallen Gladiators in an effort to cure epilepsy [46]. The ancient Greeks believed that blood was formed in the heart and was circulated through the veins to the rest of the body where it was consumed. Arteries were part of an independent system transporting air from the lungs. Although Erasistratos (circa 270 B.C.) had imagined the heart as a pump and Galen (131-201 A.D.) finally proved that arteries contain blood, communication with the venous system was still not discovered. Blood, formed in the liver, merely passed through the blood vessels and heart on its way, as a one way route, to the periphery [81]. These teaching concepts remained in place for 1400 years. It was not until 1682 that William Harvey discovered the circulatory system of blood [145], which is still our contemporary concept until today.

The realization that blood moved in a circulatory stream led to experiments on vascular infusion. In 1642, George von Wahrendorff injected wine [54], and in 1656, Christopher Wren and Robert Boyle injected opium and other drugs intravenously into dogs [82]. Being inspired from the experiments from Christopher and Robert Boyle, Richard Lower began his experiments on intravenous injections of drugs and substances into living animals [143]. In 1665, he performed the first transfusion of bloods from the carotid artery of one dog to the jugular vein of another dog [57]. This experiment led to the transfusion of animal blood into humans. The first animal-to-human blood

transfusion was conducted by a physician of King Louis XIV Jean Baptist Denis. A 15- year-old boy who had been weakened by repeated phlebotomies received direct transfusion of a lamb's blood on June15, 1667 [80]. According to the letter by Denis, the child was cured and apparently survived the heterologous transfusion without any evident unfavorable effects. Soon after that, Lower and Edmund King transfused a man with sheep's blood in England on November 3, 1667 and the man survived the transfusion well [31, 79].

Although the first two subjects transfused by Denis were not adversely affected, the third and fourth recipients both died. The death of the third subject was attributable to other causes. However, the forth case, following an initial transfusion of calf's blood in an effort to cure his maniacal behavior without any improvement, the patient received a second transfusion 2 days later [56]. He developed a classic transfusion reaction and died 2 months later. Denis was charged with murder but he was exonerated by testimony that the patient's wife had given him a soup with a powder in it, which, when given to a cat, caused death [30]. French physicians determined that transfusion was unsound and the Parliament of Paris passed a law on January 10, 1670, making blood transfusion illegal. Later, when two men died from transfusion in Rome, a special proclamation by the Pope banned the practice of transfusion in almost all parts of Europe. The English quietly discontinued all transfusion studies and would not begin them again until the early 1800s. These events put an end to practice of blood transfusion for 150 years [137].

The beginning of modern transfusion research and therapy took place in 1818 by the London obstetrician James Blundell at Guy's hospital. The frequency of postpartum hemorrhage and death distressed him, so that he began experimenting with transfusing blood in animals. He demonstrated that a syringe could be effectively used to perform transfusion, that the lethal effects of arterial bleeding could be reversed by the transfusion of either venous or arterial blood, that the injection of 20 cc. air into the vein of a small dog was not fatal, but that transfusion across species was lethal to the recipient [32]. Thus,

Blundell was the first to state that only human blood should be use for human transfusion. This latter conclusion was confirmed in France by Dumas and Prevost, who demonstrated that the infusion of heterologous blood into an exanguinated animal produced only temporary improvement and was followed by death within 6 days [16]. Blundell is credited with carrying out the first human-to-human transfusion on September 26, 1818. The patient was in terminal stage due to pyloric obstruction caused by carcinoma. Despite initial apparent improvement, the patient died 2 days later [41]. Blundell's technique of blood transfusion was repeated on other patients and was variably successful, with approximately 50% of patients surviving the procedure [17]. In all, Blundell performed 10 transfusions, of which 5 were successful. Four of the unsuccessful transfusions were performed on moribund patients. The fifth was performed on a patient with puerperal sepsis. Four of the successful transfusions were given for postpartum hemorrhage and the fifth was administered to a boy who bled following amputation [115]. Thus, transfusion in the latter half of the 19th century was neither safe nor efficient. There were still many attempts to render transfusion a more predictable procedure. In 1869, Braxton-Hicks performed a number of transfusions in women with obstetrical bleeding. Many of them were in terminal stage, and ultimately all died [65]. Frustration with blood as a transfusion product led to even more bizarre innovations. From 1873 to 1880, cow, goat, and even human milk were transfused as a blood substitute [97]. Fortunately, these practices were discontinued as Bull advocated the use of saline solutions for blood volume replacement in stead of the more dangerous and unpredictable transfusion of blood [19].

In 1900, Karl Landsteiner observed that the sera of some individuals agglutinated the red cells of others. This study, published in 1901 in the Wiener Klinische Wochenschrift [70], revealed for the first time the cellular differences in individuals from the same species, i.e., the identification of blood groups. With the identification of blood group A, B, and O by Landsteiner in 1901 and of group AB by De castello and Sturli [29], the stage was set for the performance

of safe transfusion. However, at that time, the effective transfer of blood from one individual to another remained a very difficult procedure. Clotting, uncontrolled, quickly occluded transfusion devices were still frustrating.

In 1905, Alexis Carrel introduced the technique of end-to-end vascular anastomosis with a triple-threaded suture. This procedure brought the ends of vessels in close apposition and preserved luminal continuity, thus avoiding leakage or thrombosis [22]. This technique was adapted by Walker Carrel [134] and others to the performance of blood transfusion. Crile, one of surgical pioneers, introduced the use of an intraluminal metal cannula to facilitate the placement of sutures of end-to-end vascular anastomosis in 1907 [26], and Bernheim used a two-pieced cannula to connect the artery to the vein [12]. Because all of these procedures usually culminated in the sacrifice of the two vessels and were often very difficult or even unsuccessful, they were not performed frequently. Moreover, there was still disadvantage that the performer could not know the amount of blood he had transfused or when to stop the transfusion unless the donor collapsed [104].

Despite these difficulties, direct transfusion via arteriovenous anastomosis, for the first time, efficiently transferred blood from one individual to another. However, there was also a report of fatal hemolytic reactions that were undeniably caused by direct transfusion [108]. The relationship of these fatal reactions to Landsteiner's discovery was still not recognized until Reuben Ottenberg demonstrated the importance of compatibility testing. He learned the Landsteiner's discovery and began pretransfusion compatibility testing in 1907 [102]. He continued his studied of transfusion and published the report that demonstrated the important of preliminary blood testing for prevention of fatal hemolytic transfusion reactions in 1913 [105]. He also observed the relative unimportance of donor antibodies and, consequently, the universal utility of type O blood donors [103].

Despite the introduction of compatibility testing by Ottenberg, transfusion could not be performed frequently as long as arteriovenous anastomosis remained the procedure of choice. New techniques, such as Unger's two syringe method introduced in 1915 [131], eventually put an end to transfusion by arteriovenous anastomosis.

The Rhesus (Rh) system was discovered by Landsteiner and Wiener [71] in connection with an unusual transfusion reaction reported by Levine and Stetson in 1939 [75]. This discovery became one of the major advances in public health. The M, N, and P systems were described in the period between 1927 and 1947 [28].

It was not until the development of anticoagulants that blood transfusion become commonplace and direct transfusion from one individual to another were rendered obsolete. Early reports from Hustin [58] and Agote [1] in 1914 and 1915 were followed by the work of Lewisohn in 1915 that recommended the optimal citrate concentration for anticoagulation, which allowed blood to be stored for prolonged period [76]. The work of Weil then demonstrated the use of refrigerated blood combined with the addition of sodium citrate enabled the banking of blood and obviated the need for direct transfusion [140]. Subsequently, Rous and Turner developed the anticoagulant solution that was used during World War I [116, 113]. Despite its very large volume, this solution remained the anticoagulant of choice until the development of an acid-citrate-dextrose (ACD) solution by Louti and Mollison during World War II [78].

Separation of blood into its components led to component and derivative therapy, which began during World War II, when Edwin J. Cohn and his colleagues developed the cold ethanol method of plasma fractionation [25]. As result of their work, albumin, gamma-globulin and fibrinogen became available for clinical use. The introduction of plastic bags and equipments by Gibson and colleagues [47] allowed the convenient separation of blood

components and thus replaced the use of glass systems. These developments rendered the blood component separation and blood component therapy more practical and became commonplace. The introduction of automated cell separators provided even greater capabilities in this area.

Clotting factor concentrates for the treatment of patients with hemophilia and other hemorrhagic disorders were also developed during the postwar era. Although antihemophilic globulin had been described in 1937 [106], unconcentrated plasma was only the therapeutic material until Pool discovered that factor VIII could be harvested in the cryoprecipitable fraction of blood [109]. This resulted in the development of cryoprecipitate, which was introduced in 1965 for the treatment of hemophilia. Pool showed that cryoprecipitate could be made in a closed-bag system and urged its harvest from as many donations as possible. The development of cryoprecipitate and other concentrates was the great advancement in the care of patients with hemophilia and other hemorrhagic disorders.

In the early of the 20^{th} century, transfusion has become safe and easy. The introduction of new anticoagulants and modern technologies led to the era of modern blood banking. Blood banks were founded in Europe and in the North America and the number of blood transfusions increased exponentially everywhere.

1.2. Concern for Blood Safety

Although blood transfusion has saved countless lives, they can themselves also cause significant complications and even death. The transfusion risks are following.

1.2.1. Transfusion Reactions

Hemolytic transfusion reactions are serious complication and can be fatal. Most of them were caused by ABO-incompatibility, which occurs at a frequency of 1:27,000 to 1:135,207 [77, 60, 6]. About 2.11-7.06% of these cases were fatal [77, 6, 141, 23]. The frequency of fatality due to ABO-Incompatibility has been estimated to be 1:800,000 units of blood [120], compared with approximately 1:2,000,000 transfusion for transmission of HIV [49]. The FDA reported a mistransfusion-related death rate that was more than 2 times greater than that due to all infectious hazards combined, and the U.K. surveillance system reported an adverse event rate attributed to mistransfusion that was 10 times higher than the rate attributed to infectious disease transmission [95]. Approximately 50% of the errors are clinical errors such as incorrect identification of the recipient, sample collection error, and incorrect ABO-bedside testing [120]. Ahrens et al. reported incorrect ABO-bedside testing [2] as the most frequent clinical error, as also from many reports. The reported incidence of laboratory errors is extremely variable from 8 - 31% [6, 120,123,35, 89, 8, 124].

Febrile nonhemolytic transfusion reactions are generally not life threatening, with the estimated frequency at 0.5 % per unit of blood component transfused [135, 87]. Immediate allergic reactions, usually urticaria, occur in 1-3% of recipients of plasma infusion [50]. Anaphylactic shock has an incidence of 1:20,000 to 1:50,000 transfusions [135]. The transfusion-associated Graft-versus-Host disease is very rare adverse reaction to blood transfusion in some immunocompromised patients [51].

1.2.2. Transmission of Infectious Agents

The first reports of transfusion-transmitted hepatitis appeared in 1943 by Beeson [10], Morgan and Williamson [91]. After that, intensive investigations were done to identify the existence of hepatitis viruses, leading to the

subsequent definition of hepatitis A virus (HAV) [37] and hepatitis B virus (HBV) [27]. The recent discovery of hepatitis C virus (HCV) [24] filled the gap made by non-A non-B diseases. The implementation of third generation hepatitis B surface antigen screening test led to a marked reduction in transfusion-transmitted hepatitis B [34]. The transmission of hepatitis B has been further reduced through effective screening tests for viral antibodies. In the 1980s the incidence of posttransfusion hepatitis decreased to 1-3% from 10% in the 1970 [86]. The implementation of a test for HCV antibody in 1990 has further decreased the risk of posttransfusion hepatitis C [3], which is the predominant cause of transfusion-associated hepatitis.

Hepatitis A transmission by blood transfusion is very rare due to the lack of a chronic carrier state and the presence of symptoms that would exclude blood donation during the brief viremic phase of the illness. The risk is estimated to be 1:1,000,000 units [33].

The first report of transfusion-associated HIV infection in a 20-month-old infant in 1983 [5] prompted blood banks to implement donor education and self-exclusion from blood donation. After the introduction of HIV antibody testing in 1985, only about 5 cases of transfusion-associated HIV infection were reported per year during the subsequent 5 years, compared with 714 cases reported in the year before HIV testing [121]. After the beginning of HIV antigen testing in 1995, only 2 blood donors (P24 antigen positive / anti-HIV negative) were found after 1 year of screening, of approximately 6,000,000 donations [125]. In recent years, blood centers have implemented nucleic acid amplification test (NAT) of minipools from blood donations to reduce HIV and HCV transmission during the window period of infection. Current estimated risk per unit of blood in the post-NAT era is approximately 1:1,900,000 for HIV and 1:1,600,000 for HCV [49, 21, 7]. In contrast to the success at risk reduction of HIV and HCV, the risk of HBV transmission remains approximately 1:50,000 to 1:150,000 in western countries.

In 1999, the West Nile Virus (WNV) infection was detected as an epidemic meningitis and encephalitis in the USA. Blood transfusion was one of the new modes of infection recognized in 2002 [117]. There were 23 cases of transfusion-associated WNV from 14 donors between August 2002 and January 2003 [107]. The mean risk of WNV by transmission was estimated to be 146 to 1,233 per million donations [13].

Cytomegalovirus (CMV) infection may be very severe in immunocompromised patients after transfusion of blood containing the virus or in patients scheduled for transplantation. CMV antibody testing is the gold standard to identify potentially infectious donors [52].

The greatest risk of transfusion-associated bacterial infection is the contamination of platelets. Culture surveillance suggests that bacterial contamination of platelet concentrates and apheresis platelets occurs in approximately 1:1,000 to 1:2,000 units [144, 73].

Other infectious agents such as Epstein-Barr virus, Leishmaniasis, Lyme disease, Brucellosis, Malaria, Babesiosis, Toxoplasmosis, Chagas disease are rarely transmitted via transmission [48].

1.2.3. Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury is an acute respiratory distress syndrome that occurs within 4 hours after transfusion and is characterized by dyspnea and hypoxemia due to noncardiogenic pulmonary edema. Although the actual incidence is not well known and its occurrence is almost certainly underreported, its estimated frequency is approximately 1: 5,000 transfusions [110]. In a recent review, 11 cases of transfusion-related acute lung injury were recognized over 12 years [136]. 10 of 11 cases required mechanical respiratory support and 5 patients died. In 10 cases the transfused unit was plasma, with an observed incidence of 1: 7900 units. The authors concluded that transfusion-

related acute lung injury is the most common serious adverse event in their hospital.

1.2.4. Transfusion-Induced Immunosuppression

Immunosuppressive effects of blood transfusions were noted as early as 1973 by Opelz et al. [99], when renal allograft survival was found to be substantially improved in patients who had received preoperative blood transfusions. The authors postulated that this effect is secondary to immunosuppression induced by exposure to antigen expressed by transfused white blood cell, therefore decreased graft rejection. It has been widely accepted that allogeneic blood transfusion can improve renal allograft survival following transplantation [100, 98]. In 1980, Fischer et al. [40] demonstrated transfusion-induced suppression of cellular immunity in prospective study among renal transplant patients. After transfusion of 1 unit of allogeneic blood, mitogenic response and cell mediated hypersensitivity were reduced. Additional transfusions produced a more profound effect, suggesting a dose response. In contrast, patients receiving autologous blood did not show impaired cellular immunity. In contrast, allogeneic blood transfusions during surgery have not been shown to affect subsequent renal allograft survival [100]. Fernandez et al. [38] found significant immunosuppression among patients undergoing surgery for peripheral vascular disease who received transfusions compared with a similar group who did not. Among patients receiving blood, T4 lymphocyte counts decreased, and no rebound increase in the proliferation response occurred up to 90 days postoperatively.

The possible association between allogeneic blood transfusions and cancer recurrence was first suggested by Gantt [44] in 1981, who raised concern that patients undergoing curative surgery for a malignancy might be affected adversely by the immunosuppressive effects of allogeneic blood transfusion which were administered perioperatively. He also suggested that immunosuppression may cause shorter survival and disease-free interval in

cancer patients. Since then, many reports have described the effects of perioperative allogeneic blood transfusions on tumor recurrence and/or overall prognosis in patients with a malignancy who are undergoing curative cancer surgery. In 1982, Burrows and Tartter [20] reported an increased rate of recurrent colon cancer in a series of 58 transfused patients compared with 65 nontransfused patients. At each tumor stage, patients receiving transfusions had a significantly higher recurrence rate. Foster et al. [42] noted that overall survival in patients treated for colon cancer was significantly higher in patients who had not received allogeneic transfusions when compared with patients who had. The relative risk of death due to cancer in patients with versus without transfusions was 2.3 when controlled for age, sex, stage, histologic grading, and cancer location. Blumberg et al. [14] performed a retrospective study in patients with colon carcinoma. They found that recurrence developed in 9% of 68 patients who did not receive transfusions when compared with a 43% incidence of recurrence in 129 patients who received transfusion. In 1985, Hyman et al. [59] noted a significant decrease in survival time in patients underwent resection for lung cancer who received allogeneic blood transfusion when compared with patients in the same group who did not receive transfusion. Recently, Langley et al. [72] suggested that blood transfusion may have a significant adverse effect on late survival after esophageal resection for carcinoma in a study of 234 consecutive patients. In addition, several studies have shown increased tumor recurrence with perioperative allogeneic blood transfusion in patients with cancer of lung [129], breast [130], and soft tissue sarcomas of the extremities [114].

Some clinical investigators could not found the relationship between perioperative blood transfusion and increased tumor recurrence or decreased survival rate. Foster et al. [43] did not found any correlation between transfusion and survival in patients treated for breast carcinoma. Nozoe et al. [96] failed to demonstrate the significance of allogeneic blood transfusion on decreased survival in 259 patients with esophageal carcinoma. Vente et al. [132] have performed a prospective study in 158 patients with colorectal cancer who were

transfused and 54 patients who were not. He could not confirm the deleterious effect of perioperative blood transfusion on survival. Similarly, Ota et al. [101] could not found significant difference in five- and ten-year survival rate between patients with colon carcinoma who received perioperative blood transfusion and patients who did not.

In head and neck cancers, there were several reports on adverse effect of allogeneic blood transfusion on tumor recurrence and survival rate. Johnson et al. [64] retrospectively analyzed 179 patients with stage III squamous cell carcinoma of the head and neck who underwent surgery. He found that blood transfusion may have a detrimental effect to survival rate. Jackson and Rice [62] reviewed 100 consecutive patients with head and neck cancer and found that the recurrence rate for all cancers of the larynx was 14% for those who did not receive blood and 65% for those who did. For cancer of oral cavity, pharynx, and nose or sinus, the recurrence rate was 31% without transfusion and 71% with transfusion. Jones and Weissler [66] performed a multivariate analysis of blood transfusion and 15 other variables using recurrence as the dependent variable in stage III to IV cancer of head and neck. They found margin status and allogeneic blood transfusion to be the significant predictors of recurrence. Wooley et al. [142] performed a multivariate logistic regression to determine the effect of transfusion on recurrence of squamous cell carcinoma of the supraglottic larynx or hypopharynx in 143 patients with stage II to IV. They found transfusion, number of pathological nodes, and preoperative hematocrit were significantly related to recurrence. They also performed a meta-analysis of the data from their study and five published studies and found a significant effect of blood transfusion on recurrence of head and neck cancer. In a study of 207 patients who underwent surgical resection of head and neck squamous cell carcinoma, Barra et al. [9] found in their multivariate analysis that transfusion was related to a higher risk of tumor recurrence. Alun-Jones et al. [4] found significance between allogeneic blood transfusion and recurrence in 69 patients who had laryngeal cancer without nodal metastasis. Recently, Taniguchi and Okura [128] investigated the effect of perioperative allogeneic

transfusion on survival in stage II to IV squamous cell carcinoma of the oral cavity in consecutive 105 patients undergoing primary tumor resection and neck dissection. They found that, among 16 variables, the number of positive nodes and transfusion of 3 units or more of red blood cell were independent prognostic indicators on survival in multivariate analysis.

Some other studies, in contrast, have not confirmed the association between blood transfusion and recurrence in head and neck cancer patients. Von Doesten et al. [133] found transfusion status to be not significant after multivariate analysis. However, transfusion was found to be a significant predictor of postoperative infection. Boeck et al [18] found that patients requiring transfusion had a shorter survival than those who did not, but when adjusted for tumor size and lymph node metastasis, transfusion lost its significance. Similarly, McCulloch et al. [85] evaluated the role of blood transfusion in 166 patients with head and neck cancer who were treated with surgery and postoperative radiotherapy. Blood transfusion was among many variables, which were significant to survival. However, they failed to show the significant relationship between blood transfusion and survival in stepwise multivariate models. Sturgis et al. [126] also showed in his backward stepwise multivariate regression model that transfusion have no influence on recurrence of head and neck cancer.

The risk of bacterial infection in patients after surgery who received allogeneic blood transfusion has been reported to be 25% to 30% compared to 5% to 10% of patients received autologous blood [15]. Robbins et al. [112] reported a significant relationship between wound infection in head and neck surgical patients who undergoing clean-contaminated procedures who required blood transfusion. Weber et al. [139] found transfusion to be independently associated with an increased risk of postoperative pulmonary infections in multivariate analysis. Murphy et al. [94] showed a dose response between the number of allogeneic units transfused and postoperative infections among coronary bypass patients. In a case controlled study comparing infection rates

for patients receiving allogeneic versus autologous transfusions for the same surgical procedures, Mezrow et al. [88] found a significant difference in rates of positive cultures in the former group (16%) , compared to 4% in the latter group. In contrast, Boeck et al. [18] reviewed the infection rates among 151 patients underwent laryngectomy and found that the infection rates were not significantly different between patients who received transfusion and patients who did not. Von Doersten et al. [133] found that allogeneic transfusion was associated with an increased infection rate, but this failed to be significant in logistic regression analysis.

1.3 Transfusion Needs in Surgery

A multimodal approach to managing blood loss in surgical patients was described by Krause and Heymann in 1910 [68]. They suggested several means for managing hypovolemia caused by surgical blood loss, including the administration of caffeine for its cardiostimulant and diuretic properties. They also advocated the use of digitalis as an inotrope and epinephrine as a vasoconstrictor. Intravenous physiologic salt solutions were used to restore intravascular volume, and extremity tourniquets were applied to autotransfuse patients. As a last resort for treating anemia secondary to blood loss, direct transfusion was performed between two persons from the radial artery of the donor via cannula to the cephalic vein of the recipient. The end points for termination of the direct transfusion were either donor faintness or a decrease in the donor's systolic blood pressure to 100 mmHg.

In contemporary head and neck surgery, blood transfusion and the use of parenteral antibiotics have greatly decreased surgical morbidity and allowed the surgeon increased latitude in resecting advanced cancers. Describing the management of blood replacement in head and neck surgery, Hayes Martin [83] advocated no predetermination of the amount of blood to be given; however, blood replacement was to commence as soon as the operation got underway or as directed by the anesthesiologist based on the patient's

blood pressure and systemic factors. Though Martin admitted that this was an expensive practice, he believed that the patient's sense of well being, wound healing, and early discharge from the hospital were promoted by a replacement of blood equal to the loss. Total replacement might entail one transfusion for a standard neck dissection or up to 4 to 5 liters of blood for more extensive operations. In major procedures that include resection of a primary tumor in the upper aerodigestive tract and simultaneous neck dissection, blood transfusion may be required in more than 50% of patients [119, 36].

McCulloch et al. [84] reviewed 77 patients underwent major surgical resection for head and neck cancer. They reported that maxillectomy / midface procedure showed the highest average blood use (1.8 +/- 1.0 units), followed by composite resection (1.4 +/- 1.4 units) and laryngectomy (1.3 +/- 2.2 units), while isolated neck dissection required averagely 0.4+/- 0.9 unit. Leong and Chew [74] studied blood loss and transfusion in 63 patients underwent major head and neck surgical procedures. They reported the average blood use during composite resection in head and neck tumor surgery and maxillectomy to be 2.3 and 1.4 units accordingly.

In routine practice, surgeon usually orders blood for perioperative use according to experience of the institute where he works without knowing exactly the historic data of transfusion requirements for each specific surgical procedure. This leads to excessive amount of blood typing and cross matching because surgeon tends to feel safe for the patients, when he orders too much units of blood instead of not enough. As the modern operative and anesthesiologic techniques to reduce intraoperative blood loss are usually applied in the contemporary surgical procedures and more strict criteria for perioperative blood transfusion than in the past are followed, the administration of blood has decreased. Frequently, this leads to more excessive amounts of blood cross matched. As blood typing and cross matching places a specified number of units of allogeneic blood on reserve for an individual patient, these cross matched units cannot be transfused into another as long as they are still

on reserve for a specific patient. To meet the vast reserve demands, blood bank inventories must increase. As shown in the study from Jennings [63], the longer a unit of blood remains on reserve, the less likely it will be transfused and the greater the probability it will become outdated and be discarded. This wasteful practice should be avoided to save the limited medical resources.

2. Purpose

This study aims to determine the need for perioperative allogeneic blood transfusion in patients with squamous cell carcinoma of the oral cavity who underwent curative surgical procedures and to develope a Transfusion Prediction Model (TPM). With this model, the surgeon can predict the likelihood of receiving perioperative blood transfusion in certain patients and can make a decision together with the anesthesiologist regarding the general conditions of the patient on preparing for managements of perioperative blood loss. Furthermore, the surgeon can also educate the patient about the likelihood of receiving perioperative blood transfusion and according risks of allogeneic blood and the alternatives to allogeneic blood transfusion such as acute normovolemic hemodilution, as the current regulations in blood transfusion of the University Hospital of Muenster [122] do not recommend the use of preoperative autologous blood donation in tumor patients. By being educated, patients can make a decision regarding the need and possibility for acute normovolemic hemodilution or the likelihood of receiving allogeneic blood. Furthermore, the routine type and screen or type and crossmatch procedures can be limited only to those patients who are likely to need blood transfusions.

3. Materials and Methods

The data from all consecutive patients with squamous cell carcinoma of the oral cavity who underwent curative surgical procedures at the Department of Cranio- and Maxillofacial Surgery, University of Muenster during 1998-2002 were retrospectively collected.

3.1. Including criteria

1. primary squamous cell carcinoma of the oral cavity
2. primary surgical treatment without any other preoperative treatment, such as preoperative radiotherapy or chemotherapy
3. curative surgery
4. complete documentation of patient's data

3.2. Excluding criteria

1. recurrent or metastatic squamous cell carcinoma
2. other types or sites of tumors
3. palliative surgery
4. patient with any other previous treatments such as radiotherapy or chemotherapy
5. missing of important data

The attending surgeons were all faculty from the department. In all patients, the preoperative diagnoses were confirmed by biopsy and subsequent pathohistologic examination.

3.3. Data collection and definition

All data were collected retrospectively from anesthetic records and patient's charts by using ***Excel 2000*** program. The data include the followings.

1. patient's age at the time of surgery
2. gender
3. weight in kilogram at the time of surgery
4. associated diseases and debilitating factors
   - cardiovascular diseases
   - pulmonary diseases
   - endocrinological diseases
   - gastrointestinal diseases
   - urogenital diseases
   - alcohol abuse
   - smoking
   - others
5. tumor site
   - anterior floor of the mouth
   - posterior floor of the month
   - alveolar process
   - hard and soft palate
   - pharynx, tonsil, retromolar region
6. tumor size : according to pathological TNM classification (UICC)
   - pT1
   - pT2
   - pT3
   - pT4
7. lymph node involvement: according to pathological TNM classification (UICC)
   - pNx
   - pNo

- pN1
- pN2
- pN3

8. duration of surgery
9. tracheostomy
   - without tracheostomy
   - primary tracheostomy ; defined as an intraoperative tracheostomy
   - secondary tracheostomy ; defined as an postoperative tracheostomy
10. type of tumor resection
   - without bony resection
   - with partial mandibulectomy / maxillectomy without continuity defect
   - with partial mandibulectomy / maxillectomy with continuity defect
11. type of immediate reconstruction
   - local closure without flap reconstruction
   - partial thickness skin graft
   - local flap
   - distant flap
   - microvascular free flap
12. neck dissection
   - without neck dissection
   - unilateral neck dissection
   - bilateral neck dissection
13. preoperative hemoglobin (g/dl) and hematocrit levels (%)
14. amount of cross matched packed red cell (unit)
15. amount of transfusion (unit)
   - packed red cell
   - platelets concentrate
   - fresh frozen plasma
16. period of transfusion
   - preoperative
   - intraoperative
   - postoperative

17. presence of informed consent for blood transfusion
    - by anesthesiologist
    - by surgeon

Normal hemoglobin levels in this setting for males were 14 -18 g/dl and for females were 12 -16 g/dl. A perioperative blood transfusion was defined as the transfusion of allogeneic blood before**,** during surgery or within the hospital stays. The decision for transfusion was made by either attending surgeon or anesthesiologist. A general guideline for transfusion of packed red cell was a hemoglobin level under 8 g/dl with deteriorated cardiovascular status in spite of adequate intravascular volume. However, multiple factors were also considered such as age and underlying diseases of the patient.

3.4. Statistical considerations

All 17 variables were descriptively analyzed to describe the population. When undertaking the analyses to determine influential variables in predicting the need for transfusion, only 10 variables available before the surgical procedure were examined. They include age, gender, weight, associated diseases, tumor site, tumor size, type of tumor resection, type of immediate reconstruction, neck dissection and preoperative hemoglobin level. The relationship between these variables and blood transfusion need was evaluated with step back logistic regression model using a p-value of less than 0.05 as significant. The significant variables from the last step of the first logistic regression were analyzed further in second and third logistic regression using also a p-value of less than 0.05 as significant. The logistic regression program allowed calculation of the probability of transfusion need based on the significant predictive variables. Finally, the predictability of the significant variables was also quantified by using the area under the Receiver Operating Characteristic curve (ROC area). Data were processed using ***SPSS / PC+ version 12.***

4. Results

4.1. Biographic data

Age and gender

From the total amount of 150 patients, age range was 33 – 89 years with the mean age of 61 years. One hundred and three patients (68.7%) were male and 47 (31.3%) were female (Table 1).

Age (year)	Gender		total
	male	female	
30-39	1	3	4 (2.7%)
40-49	14	6	20 (13.3%)
50-59	27	8	35 (23.3%)
60-69	48	15	63 (42.0%)
>=70	13	15	28 (18.7%)
total	103 (68.7%)	47 (31.3%)	150 (100.0%)

Table 1. Age and gender

Weight

The weight of patients at the time of surgery ranged from 45 – 116 kg., with the mean weight of 73.5 kg.

Associated diseases and debilitating factors

The most frequent associated diseases were cardiovascular diseases (46%), followed by pulmonary (20.7%), and endocrinological diseases (15.3 %), respectively. About 75 % of the patients had history of smoking, while 56 % had alcohol abuse (Figure 1).

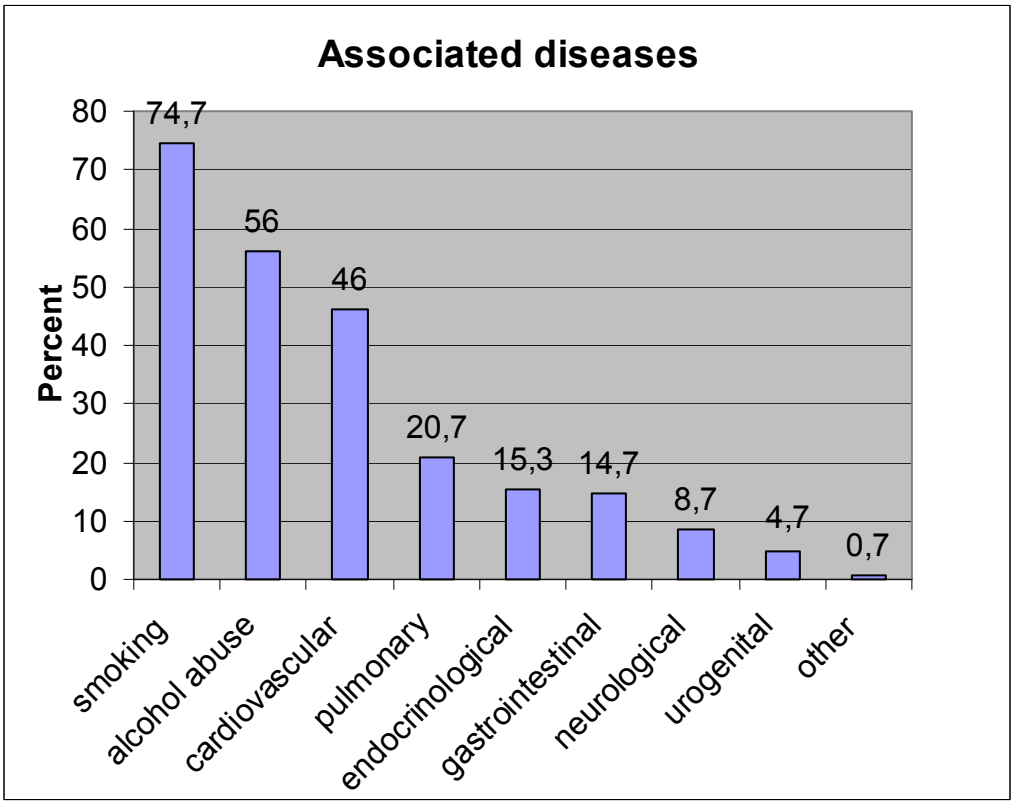

Figure 1. Associated diseases and debilitating factors (n =150)

4.2. Tumor data

Tumor site

The most common primary tumor sites were the anterior floor of the mouth (39.3%) and the posterior floor of the mouth (34.7%), followed by the

tongue, the alveolar process, pharynx/tonsil/retromolar area. The least common sites were palate and buccal mucosa (Figure 2).

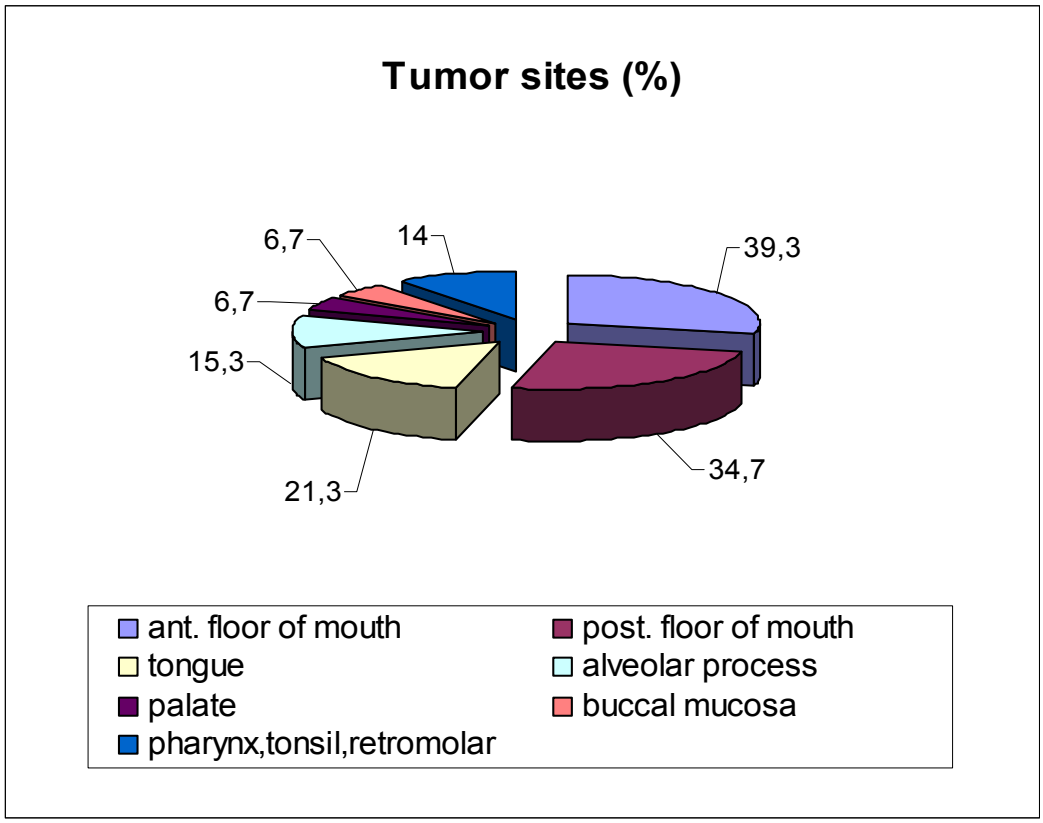

Figure 2. Tumor site

Pathological TNM stage

The majority of the patients had T1 – T2 tumors (80.7%), while 29 patients had T3 – T4 tumors (19.4%). Ninety patients were neck stage N0 (60 %), 22 were N1 (14.7%), 12 were N2 (8.0%), while there was no patient with N3 disease and 26 patients (17.3%) did not receive neck dissection (Table 2).

	N0	N1	N2	N3	Nx	total
T1	51	8	0	0	17	**76**
T2	25	8	5	0	7	**45**
T3	2	1	3	0	1	**7**
T4	12	5	4	0	1	**22**
total	**90**	**22**	**12**	**0**	**26**	**150**

Table 2. Number of patients according to pathological TNM stage

4.3. Operation data

Duration of surgery

The procedures were longer than 6 hours in 44 % of the patients while 15.3% of the patients experienced the procedures that took 2 hours or shorter (Table 3).

Duration (minute)	**Number of patient**	**%**
< 60	8	5.3
60 - 119	15	10.0
120 - 239	32	21.3
240 - 359	26	17.3
360 - 479	25	16.7
> 480	44	29.3
total	**150**	**100.0**

Table 3. Duration of surgery

Tracheostomy

Primary tracheostomy was performed in 14 patients (9.3%) and secondary tracheostomy in 22 patients (14.7%). The majority or 114 patients (76%) were not received tracheostomy (Figure 3).

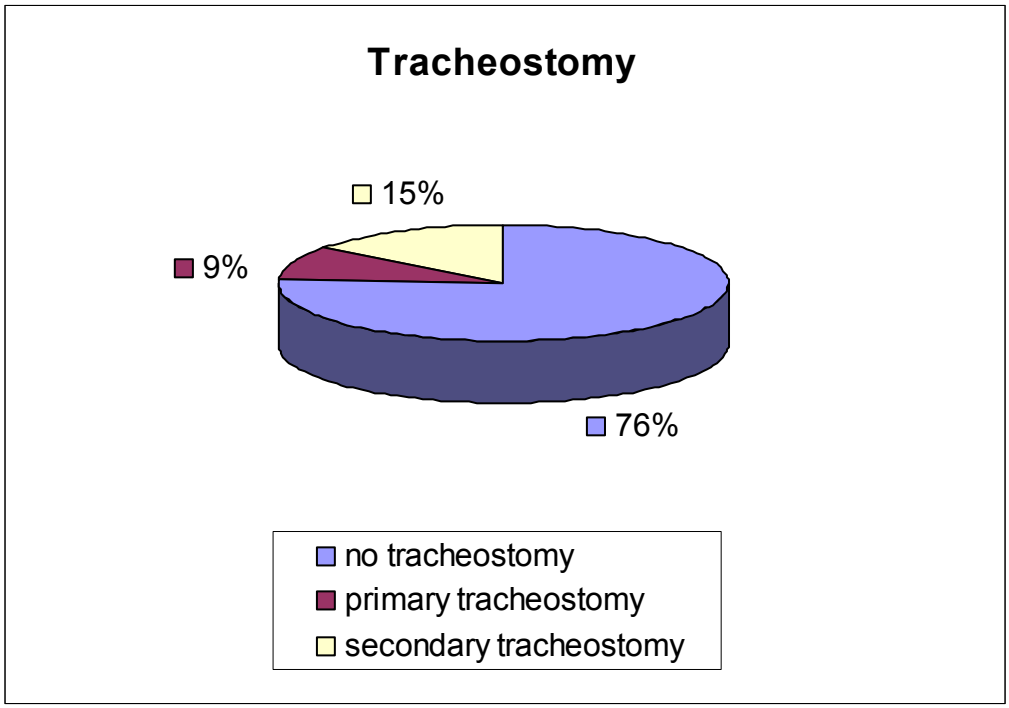

Figure 3. Need for tracheostomy

Type of tumor resection

Tumor resection without jaw bone resection was performed in 43 patients (28.7%), while jaw resection without continuity defect was performed in 38 patients (25.3%). Forty six percent of patients received jaw resection with continuity defect (Figure 4).

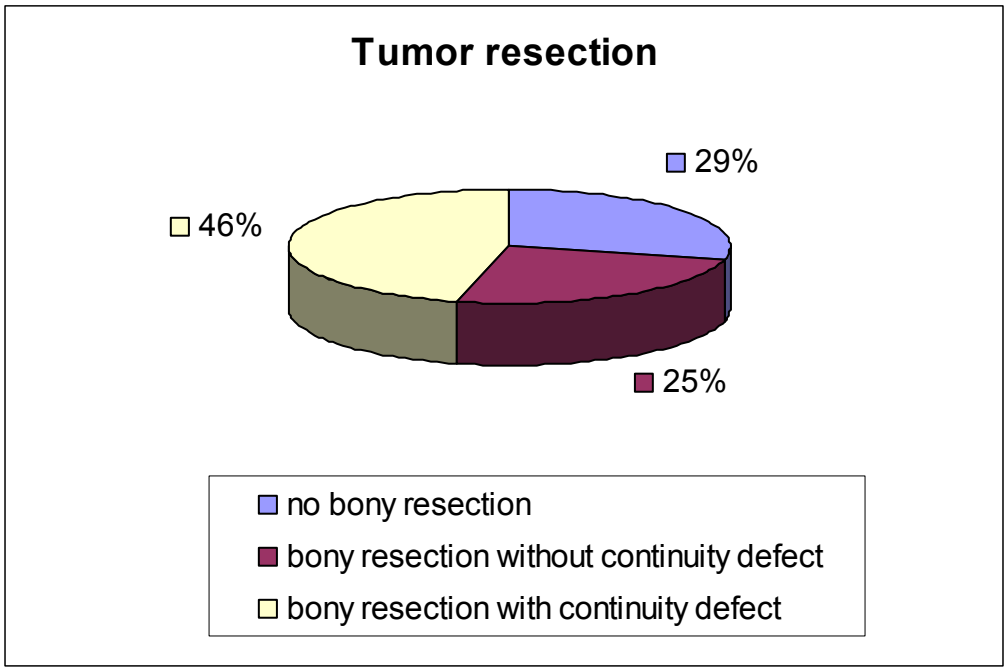

Figure 4. Type of tumor resection

Type of reconstruction

All of the continuity defects of the mandible were maintained and stabilized with titanium reconstruction plates. All of the bony defects in maxilla were left open and subsequently treated with obturator prosthesis.

The soft tissue defects were locally closed without any reconstruction in 70 patients (46.7%), followed by microvascular free flaps in 53 patients (35.3 %), local flaps in 15 patients (10.0%), partial thickness skin grafts in 10 patients (6.7%), and distant flaps in 2 patients (1.3%).(Figure 5)

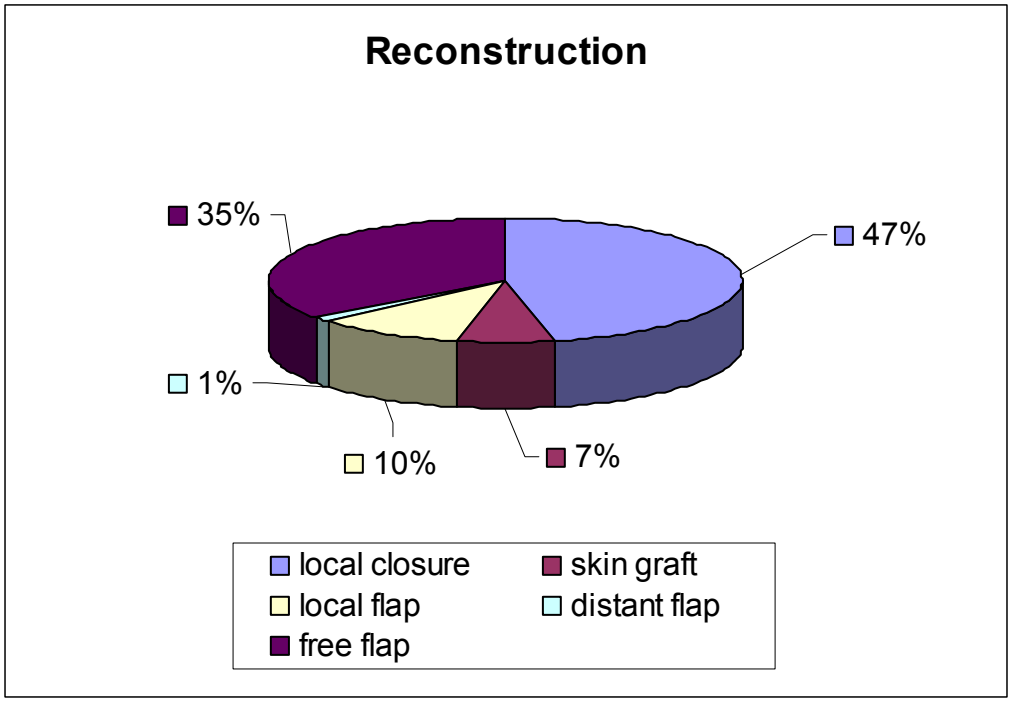

Figure 5. Type of reconstruction

Neck dissection

Unilateral neck dissection was performed in 93 patients (62%), while 27 patients (8 %) were received bilateral neck dissections. In 30 patients (20%), the neck dissection was not necessary (Figure 6).

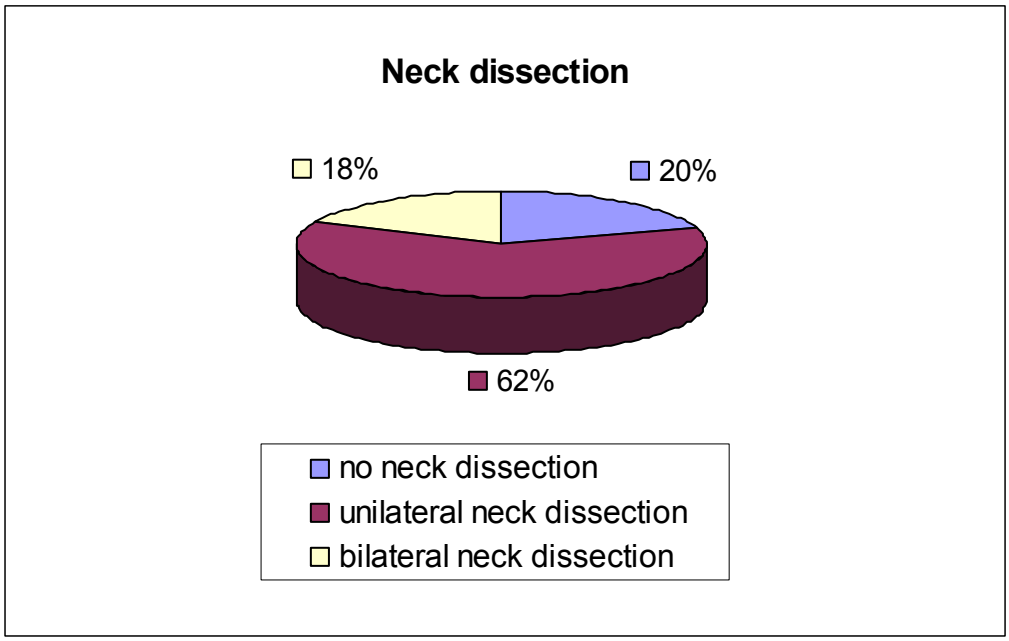

Figure 6. Need for neck dissection

4.4. Laboratory data

Preoperative hemoglobin level

From 150 patients, 35 (23.3%) had preoperative hemoglobin under normal values. Among them, 32 were male and 3 were female (Table 4).

Hemoglobin level (Hb)	Male	Female	Total
normal Hb	71 (47.4%)	44 (29.3%)	115 (76.7%)
under normal Hb	32 (21.3%)	3 (2.0%)	35 (23.3%)
Total	103 (68.7%)	47 (31.3%)	150 (100.0%)

Table 4. Preoperative hemoglobin level

4.5. Transfusion Data

Transfusion requirements

The overall transfusion rate for all blood products was 41 (27.3%) of 150 patients. All of them were transfused with packed red cell, 3 of them were additionally transfused with fresh frozen plasma and 1 patient received 1 unit of platelets concentrate additionally (Table 5, 6).

Blood products	Number of patients	Unit
packed red cell	41 (27.3%)	108
fresh frozen plasma	3 (2.0%)	13
platelets concentrate	1 (0.7%)	1

Table 5. The overall transfusions for all types of blood products

Type of transfusion	Number of patients	Percent of total patients	Percent of transfused patients
PRC only	37	24.6	90.3
PRC + FFP	3	2.0	7.3
PRC + Plt	1	0.7	2.4
Total	41	27.3	100.0

Table 6. Number of patients transfused with varying blood products;
PRC = packed red cell, FFP = fresh frozen plasma, Plt = platelets concentrate

The total amount of transfused packed red cell was 108 units, making an average amount of red cell transfusion of 2.6 units per patient transfused. Blood typing and cross matching were performed in 135 patients, while only 41 patients (30.4%) were transfused. Among patients who received blood transfusion, 28 were transfused with 2 units, 6 were with 4 units, 3 were with 3 units, and 1 was with 1 unit of blood, only 3 patients needed more than 4 units of blood. (Table 7) The total amount of preoperatively cross matched packed red cell was 501 units, while only 108 units were transfused, making the crossmatch to transfusion ratio of 4.7:1.

Amount (unit)	Number of patient	%
0	109	72.7
1	1	0.7
2	28	18.7
3	3	2.0
4	6	4.0
5	1	0.7
6	1	0.7
7	1	0.7
total	**150**	**100.0**

Table 7. Transfusion requirement (units of packed red cell)

Period of transfusion

From 41 patients who were transfused with red blood cell, 28 received transfusion postoperatively, 8 intraoperatively and 3 were transfused both intra- and postoperatively. In 2 patients, the data were missing.

Informed consent for blood transfusion

One hundred and forty seven patients were informed from the anesthesiologists about the probability of perioperative allogeneic blood transfusion. Only 21 of them were additionally informed by the surgeons. In 3 patients, the consent forms were missing. (Figure 7)

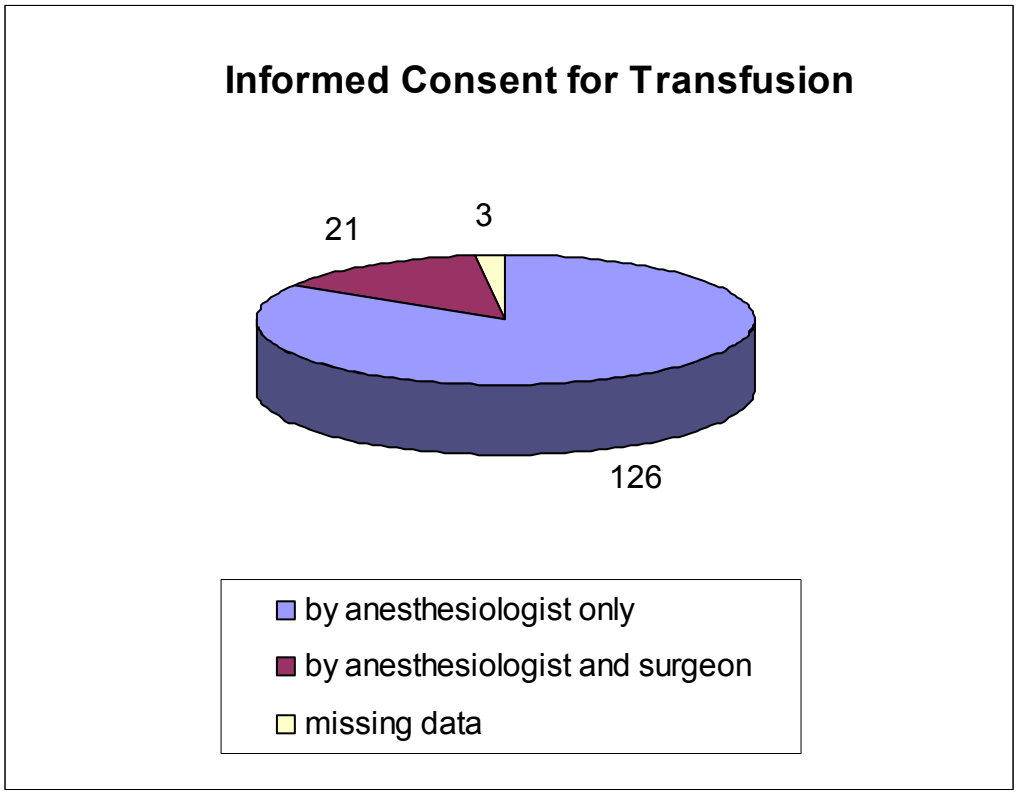

Figure 7. Number of patients who were informed about transfusion by anesthesiologist, anesthesiologist and surgeon

4.6. Transfusion Prediction Model (TPM)

The 10 variables with several further subcategories, which could be acquired before surgery, were analyzed with the step back logistic regression to determine the significance as predictive factors for the transfusion requirement. After each step of the first logistic regression, the variable or subcategory which was least significant was deleted from the list of variables, and the others were analyzed further in the next step. After 20 steps of the first logistic regression, only weight, type of immediate reconstruction and neck dissection were determined as significant ($p < 0.05$). (Table 8)

Variables	p-value
age	>0.05
gender	>0.05
weight	0.04
associated diseases	>0.05
tumor sites	>0.05
tumor size	>0.05
type of tumor resection	>0.05
type of reconstruction	0.00
-skin graft	0.99
-local flap	0.99
-distant flap	0.99
-microvascular free flap	0.99
need for neck dissection	0.02
hemoglobin level	>0.05

Table 8. Result of the first logistic regression analysis

As the subcategories of immediate reconstruction did not have any significance on the transfusion requirement, as shown in Table 8, this variable was newly named as the need for reconstruction and then divided only into two subcategories; with or without soft tissue reconstruction. These three significant variables, weight, neck dissection and immediate reconstruction, were then put into the second logistic regression analysis to testify their significance. Using a p-value of less than 0.05 as significant, weight of the patient has lost its significance, while neck dissection and reconstruction were still considered as significant factors after the second logistic regression (Table 9). These 2 factors were then put into the third logistic regression analysis to testify their significance again and to provide the calculation of the Transfusion Prediction Model (TPM). After the third logistic regression, using also a p-value of less than 0.05 as significant, the need for neck dissection and the need for reconstruction were still considered as influential factors for blood transfusion requirement. Among these 2 variables, the need for reconstruction showed higher significance than the need for neck dissection (Table 9).

Variables	p-value
weight	0.353
need for reconstruction	0.000
need for neck dissection	0.047

Table 9. Result of the second and third logistic regression analyses

The logistic regression program yielded the following Transfusion Prediction Model (TPM):

$$Risk = \exp(z) / [1 + \exp(z)]$$

when z = - 4.025 + 2.805 * (immediate reconstruction) + 0.969 * (neck dissection).

The variables took the following values:

immediate reconstruction : 0 = no , 1 = yes
neck dissection : 0 = no , 1 = unilateral , 2 = bilateral

The predicted probability for transfusion was calculated from the logistic regression equation and the results are shown in Table 10.

Type of reconstruction	**Neck dissection**		
	no	unilateral	bilateral
without reconstruction	1.7%	4.5%	11.2%
with reconstruction	22.7%	43.7%	67.2%

Table 10. Transfusion Prediction Model (TPM) shows the calculated probability for transfusion based on multivariate analysis with logistic regression model.

From the calculated probability for transfusion, it showed that patients who required bilateral neck dissection and immediate reconstruction will have the greatest probability of requiring a perioperative blood transfusion (67.2%). Patients who required neither neck dissection nor immediate reconstruction will have the lowest probability (1.7%) to receive blood transfusion.

Additionally, the values of sensibility were plotted against the values of 1-specificity for construction of the Receiver Operating Characteristic (ROC) curve as shown in Figure 8. The area under the ROC curve (ROC area) for the neck dissection and the need for reconstruction were 0.674 and 0.771 respectively.

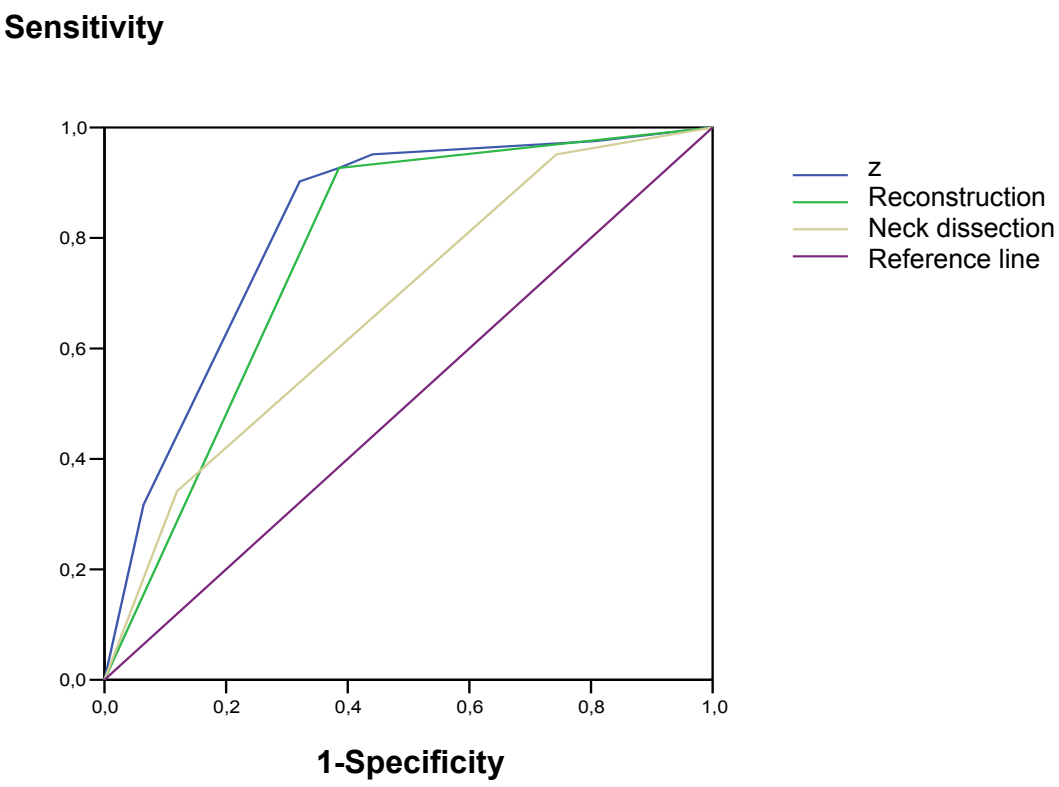

Figure 8. The ROC curve for neck dissection and reconstruction

5. Discussion

5.1. Transfusion requirements

In this study, the overall transfusion rate was 27.33%. It is lower than in the study from Taniguchi and Okura [128], who found the transfusion rate in their study to be 61% of 105 patients. However, all patients in their study had stage II - IV oral squamous cell carcinoma. Weber [138] found the overall transfusion rate in patients with all stages of various head and neck tumors to be 11.57% of 436 patients. However, the majority of them (77%) did not receive reconstruction and 30.7% did not receive neck dissection. Recently, Habler et al. [53] performed a prospective study on preoperative hemodilution in patients who underwent major maxillofacial surgery. Forty six from 84 tumor patients (55%), who received major resection, bilateral neck dissection and immediate reconstruction, were transfused.

A crossmatch to transfusion ratio of 4.7: 1 in this study is considered as very high when compared to other studies. McCulloch et al. [84] reported a crossmatch to transfusion ratio of 2.8: 1 in 77 patients with major surgical resections for head and neck carcinoma, while Leong and Chew [74] found this ratio to be 3.1: 1 in their retrospective study with 63 patients undergoing a variety of head and neck cancer operations. At a crossmatch to transfusion ratio of 4.7: 1, there remains a substantial amount of waste, that is, nearly 5 units of blood are cross matched and removed from the available blood pool for every unit transfused. In this era of limited medical resources, this wasteful practice is unacceptable.

From 135 patients who underwent blood typing and cross matching for allogeneic blood, only 41 (30.37%) of them were transfused. That means, about 70% of these procedures were wasteful.

From 41 patients who received allogeneic blood transfusion, the majority of them (68.3%) received 2 units of blood. This is comparable to the study from McCulloch et al. [84], who found in their study that 65% of their patients required less than 2 units of bloods. Similarly, Weber [138] found in his study that 36 (75.6%) of 51 patients who required transfusion, were transfused with 2 or fewer units of blood. Krupp et al [69] also found in their study that the majority (56.25%) of their patients with all stages of head and neck tumors, who required transfusion, were transfused with 2 units of blood. This information make the preoperative autologous blood donation a possible alternative to allogeneic blood use, providing that the patients meet the requirements for autologous blood donation and the preoperative time interval allow the procedure possible. However, the current regulations in blood transfusion of the University Hospital of Muenster [122] do not recommend the use of preoperative autologous blood donation in tumor patients. These regulations, however, should be reevaluated in the aspect of performing preoperative autologous blood donation due to many reasons. First, there are a lot of evidences of the deleterious effect of allogeneic blood transfusion on survival and recurrence in tumor patients in varying studies, as mentioned previously [44, 20, 42, 14, 59, 72, 129, 130, 114, 64, 62, 66, 142, 9, 4, 128]. Second, there are several studies, which reported a positive effect of autologous blood transfusion on survival and recurrence rate in tumor patients with varying settings when compared with allogeneic blood transfusion. Motoyama et al. [93] found the survival advantage of using autologous blood transfusion for esophageal cancer when compared with patients who received allogeneic blood transfusion. In another study from Motoyama et al. [92], they concluded in their study that use of autologous instead of allogeneic blood transfusion during esophagectomy prolonged disease-free survival among patients with recurrent esophageal cancer. Takemura et al. [127] recently reported immunologic effects of allogeneic versus autologous blood transfusion in patients undergoing radical esophagectomy. They found postoperative decrease of CD4+ lymphocyte count and NK cell activity in patients who received blood transfusion, however these abnormalities were returned to normal two weeks later in patients who received

autologous blood transfusion, but not in patients who received allogeneic blood. They also found a higher rate of infectious complications in allogeneic transfusion than in autologous transfusion group. In head and neck cancer surgery, Moir et al. [90] found a recurrent rate of 59% in head and neck cancer patients who received allogeneic blood transfusion compared with recurrent rates of 33% and 35% in those who had received autologous blood and those who did not receive transfusion at all in the same patient group. They also concluded that autologous blood should be used during head and neck cancer surgery if possible when transfusion is necessary. Third, the tumor patients should also have the same opportunity as other patients to use autologous blood to avoid risks from allogeneic blood, if the situation allows.

There are several authors who reported the use of autologous blood in head and neck tumor surgery [90, 118, 55]. Several found the majority of their tumor patients could have met all criteria for preoperative autologous blood donation. Leong and Chew [74] found 62% of their patients met the criteria for preoperative autologous blood donation and 50% of the patients' total transfusion requirements could have been covered by predeposited blood. In a similar study, McCulloch et al. [84] reviewed 77 patients undergoing head and neck surgical procedures. In their study, 85% of patients met the criteria for autologous blood donation, and 65% could have met all their perioperative blood needs through autologous donation. The authors concluded that preoperative autologous blood donation is an effective alternative to allogeneic transfusion in most head and neck surgical procedures. In the study from Weber [138], 52% of the patients receiving allogeneic transfusion could have met all their transfusion requirements through autologous donation.

5.2. Transfusion Prediction Model (TPM)

In this study, only the need for neck dissection and the need for reconstruction were found to be significant variables contributing to transfusion requirement. Several investigators had also investigated the factors that may have influence on transfusion requirement and they found varying results. Rashiq et al. [111] found age, gender, weight, hemoglobin level, ASA status and revision surgery to be the predictors for the blood transfusion in total joint arthroplasty. Karkouti et al. [67] created a multivariable model consisting of age, gender, weight, and hemoglobin level for predicting the need for blood transfusion in patients undergoing coronary bypass graft surgery. Benoist et al. [11], using multivariate analysis, defined age, body mass index, hemoglobin level, ASA status, and additional surgical procedures as significant risk factors for perioperative blood transfusion in patients with colorectal carcinoma. In contrast, Ferraris and Gildengorin [39], found only bleeding time and red cell volume were the best predictors for blood use among 12 variables.

In this study, the multivariate logistic regression analysis demonstrated the need for reconstruction and the need for neck dissection to be significant in predicting the transfusion requirement. Other studies, which were performed in patients with head and neck tumors, found that similar factors were associated with an increased risk for transfusion. Von Doersten et al. [133] found that a low preoperative hemoglobin level, pharyngeal tumor site, and stage III disease were predictors of the need for blood transfusion. Boeck et al. [18] found a low preoperative hemoglobin level, higher-stage tumors and the need for neck dissection to be significant for transfusion requirement. Weber [138] investigated preoperative clinical and laboratory variables to predict the transfusion requirement in patients underwent major oncologic procedures for all stages of various head and neck tumors and reported tumor size, flap reconstruction, and a low preoperative hemoglobin level as significant variables in predicting the transfusion requirement . In this study, in contrast to those

studies, tumor site, tumor size, and a low preoperative hemoglobin level were not proved to have significant relationship to the needs of blood transfusion.

The ability of the TPM to predict the risk of requiring transfusion was quantified by the area under the Receiver Operating Characteristic curve (ROC area). The ROC area can range from 0.5 (not more predictive than a coin flip) to 1.0 (perfect discrimination). A value over 0.7 can be interpreted as fair, and over 0.8 as good. When considering the ROC area in this study, which was 0.67 for the need of neck dissection and 0.77 for the need for reconstruction, one can assume the ability of TPM to be fair in predicting the transfusion requirement.

5.3. Potential uses of the Transfusion Prediction Model in clinical practice

The risk of blood transfusion calculated from the TPM could be applied to daily clinical practice in many aspects.

According to the regulations in blood transfusion of the University Hospital of Muenster, surgeon must include the probability and risks of blood transfusion in the preoperative consent form, if the risk of requiring blood transfusion is 10% or higher for any surgical procedures [122]. According to the TPM, it might be necessary for surgeons to inform oral cancer patients about the probability and associated risks of transfusion when bilateral neck dissection or any type of immediate reconstruction is anticipated.

Until currently, there is only a crude suggestion in the Department of Cranio-and Maxillofacial Surgery, University Hospital of Muenster that surgeon should order 2 units of packed red cell per one side of anticipated neck dissection. This led to a general practice of routine crossmatch for 2 units in patients who would undergo a unilateral neck dissection, and 4 units in those who would receive bilateral neck dissection, whether a reconstruction would be performed or not. This practice may have led to a high crossmatch to

transfusion ratio in this study, as the TPM has shown that the need for reconstruction was more significant than the need for neck dissection in predicting of transfusion requirement.

From the data of transfusion requirements in this study together with the result from TPM, a guideline for preparing of blood for perioperative use in patients with oral squamous cell carcinoma should be developed.

If the risk for requiring transfusion is low, that is, less than 10%, it may be not necessary to perform blood typing and screening. For patients who have a moderate risk for transfusion (between 10% and 20%), a preoperative type and screen should be performed. When the risk of requiring blood transfusion is high (20% or greater), preoperative planning should include type and crossmatch for 2 units of packed red cell, acute normovolemic hemodilution, or a preoperative autologous blood donation for 2 units of blood, if the regulations in blood transfusion allow (Table 11).

Type of reconstruction	**Neck dissection**		
	no	unilateral	bilateral
without reconstruction	no type & screen	no type & screen	type & screen
with reconstruction	type and crossmatch or ANH or PABD*	type and crossmatch or ANH or PABD*	type and crossmatch or ANH or PABD*

Table 11. Preoperative transfusion planning based on TPM;
ANH = acute normovolemic hemodilution
PABD = preoperative autologous blood donation
* = if the regulations in blood transfusion allow

If the regulations allow a preoperative autologous blood donation in tumor patients, it should be performed in those patients, who have risk for transfusion of 20% or greater, to avoid discarding of these autologous units. In this case, TPM would be very useful to identify this group of patients.

6. Conclusion

In contemporary oral and maxillofacial cancer surgery, blood transfusions have expanded surgeons' ability to safely resect oral cancer and perform major reconstructive procedures. Nevertheless, blood transfusions also possess many risks such as transfusion reactions, transmission of infections, and immunosuppressive effects, which may lead to higher recurrence rate and short disease-free interval. These adverse effects of allogeneic blood transfusion have led surgeons and anesthesiologists to become more cautious in their use of transfusion. Intraoperative techniques for reduction of blood loss, strict guidelines for blood transfusion, acute normovolemic hemodilution and use of autologous blood donation are among the methods used to decrease the need of allogeneic blood. In the current situation of cost constraint and resource conservation, it is necessary to develope a predictive model to determine the risk for transfusion. With this model, the routine type and screen or type and crossmatch procedure can be limited only to those patients who are likely to require transfusion. Moreover, if the acute normovolemic hemodilution or autologous blood donation should be performed, this predictive model could be useful in selecting appropriate group of patients for these procedures according to cost-effectiveness basis.

In this retrospective study including 150 patients undergoing surgical treatment for oral squamous cell carcinoma, the need for neck dissection and the need for reconstruction were found to be the influential factors for requiring blood transfusion, as shown by logistic regression analysis. As a result, a TPM was developed to assist in preoperative planning for blood transfusion. With this model, it is possible to identify patients who have low, intermediate and high risk for requiring blood transfusion, making an appropriate and cost-effective preoperative planning for blood transfusion possible.

In order to prove, and if necessary, improve the accuracy of this predictive model, it is necessary to compare the predicted transfusion rate with

the actual transfusion rate in a new prospective study of patients undergoing oncologic procedure for oral squamous cell carcinoma. If the TPM proves to be accurate, it may aid clinician in more cost-effective preoperative planning for blood transfusion.

References

1. Agote L (1915) Nuevo procediemento para la transfusion del sangre. An Inst Mod Clin Med (Buenos Aires) 2: 24-30
2. Ahrens N, Pruss A, et al (2005) Failure of bedside ABO testing is still the most common cause of incorrect blood transfusion in the Barcode era.Transfus Apheresis Sci (article in press)
3. Alter MJ (1994) Review of serologic testing for hepatitis C. Arch Pathol Lab Med 118: 342-345
4. Alun-Jones T, Clarke PJ, Morrisey S, et al (1991) Blood transfusion and laryngeal cancer. Clin Otolaryngol 16: 240-244
5. Ammann JA, Cowan MJ, Wara DW, et al (1983) Acquired immunodeficiency in an infant: possible transmission by means of blood products. Lancet 1: 956-958
6. Andreu G, Morel P, et al (2002) Hemovigilance network in France: Organization and analysis of immediate transfusion incident reports from 1994 to 1998. Transfusion 42: 1356-1364
7. AuBuchon JP, Birkmeyer JD, Busch MP (1997) Safety of the blood supply in the United States: Opportunities and controversies. Ann Intern Med 127: 904-909
8. Baele PL, De Bruyere M, et al (1994) Bedside transfusion errors. A prospective survey by the Belgium SAnGUIS Group. Vox Sang 66: 117-121
9. Barra S, Barzan L, Maione A, et al (1994) Blood transfusion and other prognostic variables in the survival of the patients with the cancer of the head and neck. Laryngoscope 104: 95-98
10. Beeson PB (1943) Jaundice occurring one to four months after transfusion of blood or plasma: report of seven cases. JAMA 121: 1332-1334
11. Benoist S, Panis Y, Pannegeon V, et al (2001) Predictive factors for perioperative transfusions in rectal resection for cancer: A multivariate analysis of a group of 212 patients. Surgery 129(4): 433-439

12. Bernheim BM (1917) Blood transfusion: hemorrhage and the anemia. JB Lippincott ,Philadelphia: p259
13. Biggerstaff BJ, Peterson LR (2003) Estimated risk of transfusion of the West Nile virus through the blood transfusion in the US.,2002.Transfusion 43: 1053-1059
14. Blumberg N, Agarwal MM, Chuang C (1985) Relation between recurrence of the colon and blood transfusion. Br Med J 290: 1037-1039
15. Blumberg N, Heal JM (1990) Transfusion-induced immunomodulation and its possible role in cancer recurrence and perioperative bacterial infection. Yale J Biol Med 63: 429-433
16. Blundell J (1818) Experiments on the transfusion of blood by the syringe. Med-Chir Trans 9: 56-92
17. Blundell J (1819) Some account of a case of obstinate vomiting in which an attempt was made to prolong life by the injection of blood into the veins. Med-Chir Trans 10: 296-311
18. Boeck M, Grevers G, Koblitz M, et al (1990) Influence of blood transfusion on recurrence, survival and postoperative infections of laryngeal cancer. Acta Otolaryngol 110: 155-160
19. Bull WT (1884) On the intra-venous injection of saline solutions as a substitute for transfusion of blood. Med Rec 25:6-8
20. Burrows L, Tartter P (1982) Effect of blood transfusions on colonic malignancy recurrence rate. Lancet 2: 662
21. Busch MP, Kleinman SH, Nemo GJ (2003) Current and emerging infectious risks of blood transfusion. JAMA 289: 959-962
22. Carrel A (1905) The transplantation of organs; a preliminary communication. JAMA 45:1645-1645
23. Caspari G, Alpen U, Greinacher A (2002) The risk of transfusion to the wrong patient in Germany. Transfusion 42: 1238-1239
24. Choo QL, Kuo G, et al (1989) Isolation of a cDNA clone derived from a blood-borne non-A non-B viral hepatitis genome. Science 244: 359-362
25. Cohn EJ (1947) The separation of blood into fractions of therapeutic value. Ann Intern Med 26: 341-352

26. Crile GW (1907) The technique of direct transfusion of blood. Ann Surg 46: 329-332
27. Dane DS, Cameron CH, Briggs M (1970) Virus-like particles in serum of patients with Australia-antigen associated hepatitis. Lancet 1: 695-700
28. Daunibd LK (1980) The story of our blood groups. In: Wintrobe MM, ed, Blood: Pure and eloquent. McGraw-Hill, New York: p690-717
29. Decastello A, Sturil A (1902) Ueber die Isoagglutinine im Serum gesunder und kranker Menschen. Muench Med Wochenschr 49:1090-1095
30. Denis J (1668) An extract of a letter…touching a late cure of an inveterate phrenisy by the transfusion of blood. Philos Trans R Soc Lond 3: 617-623.
31. Denis J (1667) A letter concerning a new way of curing sundry diseases by transfusion of blood. Philos Trans R Soc Lond 2: 489-504.
32. Denis J (1668) An extract of a printed letter….touching the differences risen about the transfusion of blood. Philos Trans R Soc Lond 3: 710-715.
33. Dodd RY (1994) Adverse consequences of blood transfusion: Quantitative risk estimates. In: Nance ST (Ed) Blood Supply: Risks perceptions, and prospects for the future. Bethesda, American Association of Blood Banks, p1-24
34. Domen RE (1995) Paid-versus-volunteer blood donation in the United States: A historical review. Trans Med Rev 9: 53-59
35. Dujardin PP, Salmi LR, Ingrand P (2000) Errors in interpreting the pretransfusion bedside compatibility test: An experimental study. Vox Sang 78: 37-43
36. Ell S R, Stell PM (1991) Blood transfusion and survival after laryngectomy for laryngeal carcinoma. J Laryngol Otol 105: 293-294
37. Feinstone SM, Kapikian AZ, Purcell RH (1973) Hepatitis A detection by immune electron microscopy of a virus like antigen associated with acute illness Science 182: 1026-1028
38. Fernandez LA, McSween JM, You CK, et al(1992) Immunologic changes after blood transfusion in patients undergoing vascular surgery. Am J Surg 163: 263-269

39. Ferraris VA, Gildengorin V (1989) Predictors of excessive blood use after coronary bypass grafting. A multivariable analysis. Thorac Cardiovasc Surg 101(1): 174-176
40. Fischer E, Lenhard V, Seifert P, et al (1980) Blood transfusion induced suppression of cellular immunity in man. Hum Immunol 3: 187-194
41. Foreign Department (1828) Transfusion and infusion. Lancet 2: 324-326.
42. Foster RS, Costanza MC, Foster JC, et al (1985) Adverse relationship between blood transfusions and survival after colectomy for colon cancer. Cancer 55: 1195-1201
43. Foster RS, Foster JC, Costanza MC (1984) Blood transfusion and survival after surgery for breast cancer. Arch Surg 119: 1138-1140
44. Gantt CL (1981) Red blood cells for cancer patients. [Letter] Lancet 2: 363
45. Garrison FH (1928) An introduction to the history of medicine.WB Saunders, Philadelphia: p50
46. Garrison FH (1928) An introduction to the history of medicine. WB Saunders, Philadelphia. p74
47. Gibson JG II, Sack T, Buclkez ES Jr (1952) The preservation of whole ACD blood, colleted, stored and transfused in plastic equipment. Surg Gynecol Obstet 95:113-119
48. Goodnough LT (2003) Risks of blood transfusion (Scientific reviews). Crit Care Med 31(12) suppl :678-686
49. Goodnough LT, Shander A, Brecher ME (2003) Looking to the future. Lancet 361: 161-169
50. Greenberger PA (1996) Plasma anaphylaxis and immediate type reactions. In: Rossi EC, Simon RL, Moss GS, Gould SA (Eds) Principle of transfusion medicine. Williams &Wilkins,Baltimore, 2nd ed: p765-766
51. Greenberger PA (1996) Transfusion-associated graft-versus-host disease. In: Rossi EC, Simon RL, Moss GS, Gould SA (Eds) Principle of transfusion medicine. Williams &Wilkins, Baltimore, 2nd ed: p 785-786
52. Gunter KC, Luban NLC (1996) Transfusion-transmitted Cytomegalovirus and Epstein-Barr virus diseases. In: Rossi EC, Simon RL, Moss GS, Gould

SA (Eds) Principle of transfusion medicine. Williams &Wilkins, Baltimore, 2nd ed: p717-728

53. Habler O, Schwenzer K, Zimmer K, et al (2004) Effects of standardized acute normovolemic hemodilution on intraoperative allogeneic blood transfusion in patients undergoing major maxillofacial surgery. Int J Oral Maxillofac Sur 33: 467-475
54. Harvey W (1628) Exertitatio Anatomica de Mortu Cordis et Sanguinis in Animalibus. Guilielmi Fitzeri, Frankfurt, 1628
55. Herzon FS (1978) Autotransfusion in Otolaryngology. Arch Otolaryngol 104: 608-609
56. Hoff EC, Hoff PM (1936) The life and times of Richard Lower, physiologist and physician (1631-1691). Bull Hist Med 4: 517-535.
57. Holingsworth MW (1928) Blood transfusion by Richard Lower in 1665. Ann Hist Med 10:13-225.
58. Hustin A (1914) A principe d'une nouvelle methode de transfusion. J Med Bruxelles12: 436
59. Hyman NH, Foster RS, De Meules JE, et al (1985) Blood transfusions and survival after lung cancer resection. Am J Surg 149: 502-508
60. Ibojie J, Urbaniak SJ (2000) Comparing near misses with actual mistransfusion events: A more accurate reflection of transfusion errors. Br J Haematol 108: 458-460
61. Ingrand P, Surer-Pierres, et al (1998) Reliability of the pretransfusion bedside compatibility test: Association with transfusion practice and training. Transfusion 38: 1030-1036
62. Jackson RM, Rice DH (1989) Blood transfusion and recurrence in head and neck cancer. Ann Otol Rhinol Laryngol 98 : 171-173
63. Jennings JB (1968) An analysis of a hospital blood bank whole blood inventory control policies. Transfusion 8:335-342
64. Johnson JT, Taylor FH, Thearle PB (1987) Blood transfusion and outcome in stage III head and neck carcinoma. Arch Otolaryngol Head Neck Surg 113: 307-310

65. Jones HW, Mackmull G (1928) The influence of James Blundell on the development of blood transfusion. Ann Hist Med 1928 20: 242-248.
66. Jones KR, Weissler MC (1990) Blood transfusion and other risk factors for recurrence of cancer of the head and neck. Arch Otolaryngol Head Neck Surg 116: 304-309
67. Karkouti K, Cohen MM, McCluskey SA, et al (2001) A multivariable model for predicting the need for blood transfusion on patients undergoing first-time elective coronary bypass graft surgery. Transfusion 41:1193-1203
68. Krause F, Heymann E (1910) Surgical operations of the head. Allied Book Co., New York
69. Krupp NL, Weinstein G, Chalian A, et al (2003) Validation of a Transfusion Prediction Model in head and neck cancer surgery. Arch Otolaryngol Head Neck Surg 129: 1297-1302
70. Landsteiner K (1901) Ueber Agglutinationserscheinungen normalen menschlichen Blutes. Wien Klin Wochenschr 14: 1132-1134
71. Landsteiner K, Wiener AS (1940) An agglutinable factor in human blood recognized by immune sera for rhesus blood. Proc Soc Exp Biol Med 43: 233
72. Langley SM, Alexiou C, Bailey DH, et al (2002) The influence of perioperative blood transfusion on survival after esophageal resection for carcinoma. Ann Thorax Surg 73 (6):1704-1709
73. Leiby DA, Kerr KL, Campos JM, et al (1997) A retrospective analysis of microbial contaminants in outdated random-donor platelets from multiple sites. Transfusion 37: 259-263
74. Leong HK, Chew CT (1991) Blood loss and transfusion in head and neck tumour surgery. Ann Acad Med Singapore 20 (5): 604-609
75. Levine P, Stetson RE (1939) An unusual case of intragroup agglutination. JAMA 113:126-127
76. Lewisohn R (1915) A new and greatly simplified method of blood transfusion. Med Rec 87:141-142
77. Linden JV, Wagner K, et al (2000) Transfusion errors in New York State: An analysis of 10 years experience. Transfusion 40: 1207-1213

78. Loutit JF, Mollison PL (1943) Advantages of a disodium-citrate-glucose mixture as a blood preservative. Br Med J 2: 744-745
79. Lower R (1667) An account of the experiment of transfusion practised upon a man in London. Philos Trans R Soc Lond 2: 557-559
80. Lower R (1666) The success of the experiment of transfusing the blood of one animal into another. Philos Trans R Soc Lon 1: 352
81. Majno G (1975) The healing hand. Cambridge, MA: Harvard University Press: p1
82. Maluf NSR (1954) History of blood transfusion. J Hist Med 9: 59-107.
83. Martin H (1957) Surgery of head and Neck Tumors. Hoeber-Harper Book Co., New York
84. McCulloch TM, VanDaele DJ, Hillel A (1995) Blood transfusion as a risk factor for death in stage III and IV operative laryngeal cancer. Arch Otolaryngol Head Neck Surg 121: 1227-1235
85. McCulloch TM , Glenn MG , Riley D , et al (1989) Blood use in head and neck tumor surgery. Arch otolaryngol Head Neck Surg 115:1314-1317
86. Menitove JE (1991) Transfusion practices in the 1990s. Annu Rev Med 42: 297-309
87. Menitove JE, McElligott MC, Aster RH (1982) Febrile transfusion reaction: what blood component should be given next? Vox Sang 42: 318-321
88. Mezrow CK, Bergstein I, Tartter PI (1992) Postoperative infections following autologous and allogeneic blood transfusions. Transfusion 32: 27-30
89. Migeot V, Ingrand LR, et al (2002) Reliability of bedside ABO testing before transfusion. Transfusion 42: 1348-1355
90. Moir MS, Samy RN, Hanasono MM, et al (1999) Autologous and heterologous blood transfusion in head and neck cancer surgery. Arch Otolaryngol Head Neck Surg 125 (8): 684-688
91. Morgan HW, Williamson DA (1943) Jaundice following administration of human blood products. Br Med J 1: 750-753
92. Motoyama S, Okayama M, Kitamura M, et al (2004) Use of autologous instead of allogeneic blood transfusion during esophagectomy prolongs

disease-free survival among patients with recurrent esophageal cancer. Surg Oncol 87 (1): 26-31

93. Motoyama S, Saito R, Kamata S, et al (2002) Surgical advantage of using autologous blood transfusion during surgery for esophageal cancer. Surg Today 32 (11): 951-958
94. Murphy PF, Connery C, Hicks GL, et al (1992) Allogeneic blood transfusion as a risk factor for postoperative infection after coronary artery bypass graft operations. J Cardiovasc Surg (Torino)104: 1092-1099
95. American Association of Blood Bank (2001) Noninfectious serious hazards of transfusion-Association Bulletin ¼. Bethesda
96. Nozoe T, Miyazaki M, Saeki H, et al (2001) Significance of allogenic blood transfusion on decreased survival in patients with esophageal carcinoma. Cancer 92 (7): 1913-1918
97. Oberman HA (1969) Early history of blood substitutes-transfusion of milk. Transfusion 9: 74-77
98. Opelz G (1989) The role of HLA matching and blood transfusions in the cyclosporine era. Transplant Proc 21: 609-612
99. Opelz G, Sengar DDS, Mickey MR, et al (1973) Effect of blood transfusion on subsequent kidney transplants.Transplant Proc 5: 253-259
100. Opelz G, Terasaki PI (1978) Improvement of kidney-graft survival with increased numbers of blood transfusions. N Engl J Med 299:799-803
101. Ota D, Alvarez L, Lichtiger B, et al (1985) Perioperative blood transfusion in patients with colon carcinoma. Transfusion 25: 392-394
102. Ottenberg R (1908) Transfusion and arterial anastomosis. Ann Surg 47: 486-505
103. Ottenberg R (1911) Studies in Isoagglutination.I Transfusion and the question of intravascular agglutination. J Exp Med 13: 425-438
104. Ottenberg R (1937) Reminiscences of the history of blood transfusion.. J Mt Sinai Hosp 4:264-271
105. Ottenberg R, Kaliski DJ (1913) Accidents in transfusion: their prevention by preliminary blood examination: based on an experience of 128 transfusions. JAMA 61:2138-2140

106. Patek AJ, Tazlor FHL (1973) Hemophilia II: Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of hemophilic blood. J Clin Invest 16:113-124
107. Pealer LN, et al (2003) Transmission of West Nile virus: a primer for the clinician. Ann Intern Med 137: 173-179
108. Pepper W, Nisbet V. (1907) A case of fatal hemolysis following direct transfusion of blood by arteriovenous anastomosis. JAMA 49: 385-389
109. Pool JG, Shannon AE (1965) Production of high-potency concentrates of antihemophilic globulin in a closed-bag system. N Engl J Med 273:1443-1447
110. Popovsky MA, Moore SB (1985) Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 25: 573-577
111. Rashiq S, Shah M, Chow AK, et al (2004) Predicting allogeneic blood tranfusion use in total joint arthroplasty. Anesth Analog 99(4): 1239-1244
112. Robbins KT, Favrot S, Hanna D, et al (1990) Risk of wound infection in patients with head and neck cancer. Head Neck 12: 143-148
113. Robertson OH (1918) Transfusion with preserved red blood cells. Br Med J 1: 691-695
114. Rosenberg SA, Seipp CA, White DE, et al (1985) Perioperative blood transfusions are associated with increases rates of recurrence and decreased survival in patients with high-grade soft tissue sarcoma of the extremities. J Clin Oncol 3: 698-709
115. Rossi EC, Simon TL, Moss GS (1991) Transfusion in Transition. in: Principle of Transfusion Medicine. EC Rossi, RL Simon and GS Moss (Eds). Williams &Wilkins, Baltimore: p1-11
116. Rous P, Turner JR (1916) The preservation of living red blood cells in vitro. J Exp Med 23: 219-248
117. Sampathkuman P (2003) West Nile virus: Epidemiology, clinical presentation, diagnosis, and prevention. Mayo Clin Proc 78: 1137-1156
118. Sands CJ, Wood RP, Van Schoonhoven PV (1968) Autologous Blood Transfusions in Head and Neck Surgery. Arch Otolaryngol 88: 103-105

119. Sataloff RT, Brown ACD, Sheets EE, et al (1987) A controlled study of hypotensive anesthesia in head and neck surgery. Ear Nose Throat J 66: 479-485
120. Sazama K (1990) Reports of 355 transfusion-associated deaths: 1976 through 1985. Transfusion 30: 583-590
121. Selik RM, Ward JW, Buehler JW (1993) Trends in transfusion-associated acquired immune deficiency syndrome in the United States, 1982-1991.Transfusion 33: 890-893
122. Sibrowski W (2004) Transfusionsvorschrift 2004/2005 des Universitaetsklinikum Muenster
123. Stainsby D, Cohen H, et al (2003) Summary of annual report 2001-2002. Key observations and recommendations. Manchester SHOT Office
124. Stainsby D, Williamson L, et al (2004) 6 years of short reporting-its influence on UK blood safety. Transfus Apheresis Sci 31: 123-131
125. Stramer SL, Grasse JR, Brodsky JP, et al (1997) US blood donor screening with p24 antigen (Ag): One year experience.Transfusion 37(suppl): 1S
126. Sturgis EM, Congdon DJ, Mather FJ, et al (1997) Perioperative transfusion, postoperative infection, and recurrence of head and neck cancer. South Med J 90(12): 1217-1224
127. Takemura M, Osugi H, Takada N, et al (2003) Immonologic effects of allogeneic versus autologous blood transfusion in patients undergoing radical oesophagectomy. Eur Surg Res 35(2):115-122
128. Tanigushi Y, Okura M (2003) Prognostic significance of perioperative blood transfusion in oral cavity squamous cell carcinoma. Head Neck 25 (11): 931-936
129. Tartter PI, Burrows L, Kirschner P (1984) Perioperative blood transfusion adversely affects prognosis after resection of stage I (subset NO) non-oat cell lung cancer. J Thorax Cardiovasc Surg 88: 659-662
130. Tartter PI, Burrows L, Papatestas AE, et al (1985) Perioperative blood transfusion has prognostic significance for breast cancer. Surgery 97: 225-229
131. Ubger Lj (1915) A new method of syringe transfusion. JAMA 64:582-584

132. Vente JP, Wiggeers T, Weidema WF, et al (1989) Perioperative blood transfusions in colorectal cancer. Eur J Surg Oncol 15(4): 371-374
133. Von Doersten P, Cruz RM, Selby JV, et al (1992) Transfusion, recurrence, and infection in head and neck cancer surgery. Otolaryngol Head Neck Surg 106: 60-67
134. Walker LG (1973) Carrel's direct transfusion of a five day old infant. Surg Gynecol Obstet 137: 494-496
135. Walker RH(1987) Special report: transfusion risks. Am J Clin Pathol 88: 374-378
136. Wallis JP, Lubenko A, Wells AW, et al(2003) Single hospital experience of TRALI. Transfusion 43: 1053-1059
137. Walton MT (1974) The first blood transfusion: French or English? Med Hist 18: 360-364.
138. Weber RS (1995) A model for predicting transfusion requirements in head and neck surgery. Laryngoscope 105: 1-17
139. Weber RS, Hankins P, Rosenbaum B, et al (1993) Nonwound infections following head and neck oncologic surgery. Laryngoscope 103: 22-27
140. Weil R (1951) Sodium citrate in the transfusion of blood. JAMA 64: 425-426
141. Williamson LM, Lowe S, et al (1999) Serious hazards of transfusion (SHOT) initiative: Analysis of the first two annual reports. BMJ 319:16-19
142. Wooley AL, Hogikyan ND, Gates GA, et al (1992) Effect of blood transfusion on recurrence of head and neck carcinoma: Retrospective review and meta-analysis. Ann Otol Rhinol Laryngol 101: 724-730
143. Wren C (1665) An account of the rise and attempts, of a way to conveigh liquors immediately into the mass of blood. Philos Trans R Soc Lond 1: 128-130
144. Yomtovian R, Lazarus HM, Goodnough LT, et al (1993) A prospective microbiologic surveillance program to detect and prevent the transfusion of bacterially contaminated platelets. Transfusion 33: 902-909
145. Zimmerman LM, Howell KM (1932) History of blood transfusion. Ann Med Hist 4: 415-433

Acknowledgement

I would like to thank all the people, who made it possible for me to accomplish this dissertation during my training period in the Department of Cranio- and Maxillofacial Surgery, University Hospital of Muenster.

- I would like to deeply thank the director of the department Prof. Dr. Dr. Dr. h. c. Joos and my supervisor Associate Prof. Dr. Dr. J. Kleinheinz, who greatly supported me during my training and preparing this dissertation and provided a very friendly working atmosphere
- My secondary mentor Associate Prof. Dr. T. Stamm for his kindness in supporting me during preparing this dissertation
- Dr. rer. Nat. Gerhard Burkhardtsmaier for his kind assisting in statistical analysis
- Patricia Hoppe, Jörg Wünnenberg, Alberto Mager, Susanne Gehrke, Christoph Gärtner, Jörg Schulte-Lünzum, Birgit Kruse-Lösler and other colleagues in the Department of Cranio- and Maxillofacial Surgery for their kind supports
- My patents for their love, unconditional supports and teaching
- Last, but not least, my wife Achara and my son Panwassa, who wonderfully supported my heart during this hard time of working. Without them, it might not be possible for me to get through this hard period of my life.

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Appendix

Pathological TNM Classification for oral squamous cell carcinoma (UICC)

Primary tumor (pT)

pTx = primary tumor cannot be assessed

pT0 = No evidence of primary tumor

pTis = Carcinoma in situ

pT1 = Tumor 2 cm or less in greatest dimension

pT2 = Tumor more than 2 cm but not more than 4 cm in greatest dimension

pT3 = Tumor more than 4 cm in greatest dimension

pT4 = (lip) Tumor invades adjacent structures(e.g. through cortical bone, tongue, skin of neck)

(oral cavity) Tumor invades adjacent structures (e.g. through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, skin)

Regional lymph nodes (pN)

pNx = Regional lymph nodes cannot be assessed

pN0 = No regional lymph node metastasis

pN1 = Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

pN2 = Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

pN2a = Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension

pN2b = Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

pN2c = Metastasis in bilataral or contralateral lymph nodes, none more than 6 cm in greatest dimension

pN3 = Metastasis in a lymph node more than 6 cm in greatest dimension

Distant metastasis (M)

Mx = Presence of distant metastasis cannot be assessed

M0 = No distant metastasis

M1 = Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage 2	T2	N0	M0
Stage 3	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage 4	T4	N0	Mo
	T4	N1	M0
	AnyT	N2	M0
	AnyT	N3	M0
	AnyT	AnyN	M1