Literature Review of Criteria for Defining Recipient-Site Infection after Oral Oncologic Surgery with Simultaneous Reconstruction

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A literature review of criteria for defining recipient site infection following oral oncologic surgery with simultaneous reconstruction

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Running title: Review of SSI criteria in oral oncologic surgery

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Abstract

Background: The lack of uniformity of criteria for defining recipient site infection following oral oncologic surgery with simultaneous reconstruction is problematic, despite numerous studies on this issue. This study aimed to investigate the difference of criteria for defining recipient site infection following oral oncologic surgery with simultaneous reconstruction.

Methods: A Medline search was performed via PubMed using the following combination of key terms that were tagged in the title and/or abstract: "surgical site infection head neck", "surgical site infection oral cancer", "antibiotic prophylaxis head neck", and "surgical site infection oral carcinoma". Search results were filtered between 2005 and 2017. Articles in which there was no mention of criteria for definition of surgical site infection were excluded.

Results: The number of articles that met the inclusion criteria was 24. The lack of uniformity of criteria of defining recipient site infection in each article appeared to be mainly due to differences in whether orocutaneous fistula and superficial incisional infection were regarded as recipient site infection.

Conclusion: Reconsideration of categorization of orocutaneous fistula as infection, regardless of the etiology, and differentiation of superficial and deep incisional infections are necessary for correct assessment of recipient site infection in oral oncologic surgery.

Keywords: recipient site infection, oral cancer, simultaneous reconstruction, criteria, orocutaneous fistula, flap failure

INTRODUCTION

Surgical site infection (SSI) following oral oncologic surgery with a reconstructive procedure is the most common complication. This occurs because of a "clean-contaminated" surgical site [1], complex defects after extensive resection, and ischemic complications of a transferred flap. SSI prolongs the duration of hospital stay, increases medical costs, and may postpone initiation of adjuvant therapy, which in turn increases the risk of recurrence of cancer [2]. There have been numerous studies on SSI after head and neck oncologic surgery, but the reported incidence considerably varies. This variation could be due to differences in the enrolled study population (e.g., age, tumor site, and comorbidity, such as diabetes mellitus, radiotherapy, and reconstruction type). Additionally, the differences in criteria for defining SSI that are applied in each study are likely to relate to non-uniformity of the reported incidence. Notably, Yarlagadda et al. [3] described that comparison of the incidence of SSI following head and neck free flap reconstruction between studies is difficult because many studies did not list their criteria for SSI.

Although the Centers for Disease Control and Prevention (CDC) criteria are the most prevalent in diagnosis of SSI [4,5], criteria established by Johnson et al. [6] are frequently used in the head and neck region. In the CDC criteria, SSIs are classified into superficial incisional, deep incisional, and organ/space SSIs. Purulent drainage, organisms identified from aseptically-obtained specimens, spontaneous dehiscence with fever (>38°C) and/or localized pain or tenderness, and an abscess are indicators of diagnosis of SSI (Centers for Disease Control and Prevention. Surgical site

infection event. https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf). In the Johnson criteria, postoperative infection is graded on a scale of 0 to 5 as follows: 0, normal healing; 1–3, erythema or induration; 4, purulent drainage either spontaneously or by incisional drainage; and 5, orocutaneous fistula. Which criteria (CDC or Johnson) are adequate for recipient site infection following radical resection of oral cancer with flap reconstruction is still an unresolved issue. We performed a literature review to investigate which criteria for defining recipient site infection were applied in previous articles. We also discuss which diagnostic criteria are appropriate in this field.

MATERIALS and METHODS

A Medline search was performed via PubMed using the following combination of key terms that were tagged in the title and/or abstract: “surgical site infection head neck”, “surgical site infection oral cancer”, “antibiotic prophylaxis head neck”, and “surgical site infection oral carcinoma”. Search results were filtered for the literature between 2005 and 2017.

The articles that were identified had to meet the following inclusion criteria: human studies; studies including cases in which oral cancer resection with primary reconstruction was performed; explicit description of criteria applied for the definition of SSI; explicit description of the number of reconstructed cases; and studies published in the English language. The following exclusion criteria were applied: animal studies; no mention of criteria for the definition of SSI; no mention of disease location (because the percentage of patients with oral cancer was unknown); studies including only

surgeries of the larynx, thyroid, skull base, and major salivary gland; studies in which the surgical sites were clean in most cases; studies in which the number of reconstruction cases was small (<30% of all cases); and studies described by the same authors of which the purpose was different, but the enrolled study population was similar. We reviewed all clinical trials, and included prospective and retrospective studies. Review articles were excluded.

The titles of articles were screened for relevancy according to the above-mentioned inclusion criteria. If these criteria were met, the abstracts were screened according to the inclusion criteria. If the abstracts did not provide sufficient information, the full-text article was downloaded and retrieved. A few articles that might have met the inclusion criteria, but could not be downloaded as the full-text version, were excluded in this review. If information on recipient or donor site infection was not mentioned, distinction between recipient and donor site infections is not shown in the tables.

RESULTS

The search resulted in 1089 hits on PubMed. After reading the downloaded full-text, 24 articles met the above-mentioned inclusion criteria. The numbers of articles that applied criteria of Johnson, the CDC, and others were nine, nine, and six, respectively.

Table 1 shows a summary of studies that applied the Johnson criteria. In all of the studies, only grades 4 (purulent drainage) and 5 (orocutaneous fistula) of the Johnson criteria were defined as

SSI, and grades 1–3 (erythema or induration) were not regarded as SSI. In some studies, there was no mention whether flap failure was included in SSI, while three studies clearly specified that they regarded spontaneous or incisional purulent drainage caused by flap failure as SSI [7-9]. In one study, SSI was defined only when the microbial cultures were positive [10]. In one study, wound dehiscence or ischemic necrosis of wound edges requiring local care was not considered an infection [7]. Six of nine articles that applied the Johnson criteria were from Asian countries. Some reports were from the same department, including four from Taiwan [11-14] and two from France [8,9]. The other three reports from Asian countries were from Japan [7,10,15]. Although information on recipient or donor site infection was not mentioned in some studies, the highest incidence of postoperative SSI was 45% [9], and the lowest incidence of recipient site infection was 13% [15].

Table 2 shows a summary of the studies that applied the CDC criteria. In these studies, diagnosis of SSI was based on clinical findings, such as purulent drainage, an incision that was spontaneously dehisced or opened by the surgeon, and abscess formation, which were similar to the Johnson criteria. Although some studies did not mention whether superficial infection was regarded as SSI, one study clearly specified that only deep incisional infections based on the CDC criteria were considered as SSI [16]. The application criteria in the study by Pool et al. [17] were similar to the diagnostic criteria of deep incisional SSI. In only one study by Wagner et al. [18], SSIs were classified as superficial or deep. Notably, in three studies, orocutaneous fistula that did not meet the CDC criteria was not categorized as a SSI [3,17,19]. In contrast, one study that applied the CDC

criteria described that a fistula, which was defined as the presence of orocutaneous or pharyngocutaneous leakage, was considered as an SSI, regardless of the origin [20]. The highest incidence of postoperative SSI was 38.3% [21] and the lowest incidence of recipient site infection was 11.1% [22].

Table 3 shows a summary of studies that applied other criteria. Two studies applied both the Johnson and CDC criteria. In these two studies, SSIs were classified into incisional (deep or superficial) or space SSIs, and fistula was included in SSI [23,24]. A prospective study by Mücke et al. [25] defined SSI as only purulent discharge at the wound. Frederick et al. [26] defined SSI as only infection requiring surgical intervention. Avery et al. [27] applied Szilagyi classification for vascular surgery. The highest incidence of postoperative SSI was 62.1% [28] and the lowest one was 4%.

DISCUSSION

There have been numerous reports on SSI following head and neck cancer surgery. However, results, such as the incidence of SSI presented by different authors, appear to lack uniformity and are conflicting [2]. In addition to the heterogeneity of the study population included in each article, we focused on the lack of uniformity of criteria for defining SSI. Therefore, this literature review was conducted to determine the differences in SSI criteria. The most prevalent criteria for SSI are the CDC criteria. The Johnson criteria are also often applied in this field. Our review showed that, in studies that applied the Johnson criteria, only purulent drainage and orocutaneous fistula (regardless of

etiology) were categorized as SSI. In contrast, two studies that applied the CDC criteria did not regard orocutaneous fistula that did not meet the CDC criteria as SSI [17,19]. Moreover, in two studies that applied the CDC criteria, only deep incisional infections were regarded as SSI [16,17].

Head and neck fistula tends to occur following extensive resection for cancer, with a reported incidence ranging from 3–65% [29]. In a recent study in which almost all of the included cases were oral lesions (e.g., cancer, osteoradionecrosis, or ameloblastoma), the incidence of orocutaneous fistula following head and neck reconstructive surgery was 10% [30]. Additionally, the incidence of infection (no mention of definition criteria of SSI), dehiscence, and flap failure was 5%, 7%, and 1%, respectively [30]. In their study, a significant association was identified only between fistula formation and previous chemoradiotherapy. In a study by Guidera et al. [31], the incidence of orocutaneous fistula following oral cavity cancer resection and free flap reconstruction was 7% (4/54), of which three (75%) cases were associated with partial or total flap failure. In their study, there was no mention of the association between infection and orocutaneous fistula. Importantly, Johnson et al. [6] described “the cart before the horse” dilemma, where wound separation caused by tissue ischemia (e.g., suture line ischemia) or other technical difficulties precedes development of infection. Based on our experience, almost all formation of orocutaneous fistula after oral cancer resection with simultaneous flap reconstruction is followed by ischemic complications of a transferred flap. Orocutaneous fistula results in infection. In contrast, recipient site infection causes flap failure in only 1% of free flap reconstruction for intra-oral cancer [32]. Taken together, these findings suggest that

inclusion of orocutaneous fistula without considering the etiology in SSI is inadequate for properly evaluating recipient site infection in oral oncologic surgery with flap reconstruction. Therefore, orocutaneous fistula should be categorized as postoperative SSI with consideration of the etiology. This is because orocutaneous fistula generally occurs because of flap complications or ischemia of incisional wound edges in patients who undergo oral oncologic surgery with simultaneous reconstruction. **Only orocutaneous fistula caused by apparent infection such as abscess formation should be categorized as postoperative SSI.**

Subcutaneous tissue and fascia of the neck are thinner than those of the limbs and trunk. Recipient site infections after cervical neck dissection are difficult to be classified into superficial and deep infections. Candau-Alvarez et al. [16] only focused on deep incisional infection because infection after cervical neck dissection does not expand into other organs or spaces. Although a few studies distinguished superficial and deep incisional infections, they included donor site infection. In donor site infection, distinguishing the superficial and deep layers can be relatively easier than in the cervical neck. Another reason to make the diagnosis of postoperative superficial infection in recipient site difficult is a flap transfer. Larger flaps than the actual defect size should be transferred because the volume of transferred flaps is sequentially reduced [33]. A bulky flap occasionally causes ischemia of the suture line and spontaneous dehiscence, followed by serous discharge. This wound dehiscence generally heals conservatively without antibiotic therapy, but tends to be misdiagnosed as superficial infection in the recipient site by inexperienced doctors (e.g., young residents). Generally,

causes of recipient site infection following oral cancer surgery requiring neck dissection are formation of a hematoma, salivary leakage, and dead space due to a complex defect (i.e., problematic recipient site infection following oral cancer surgery with reconstruction always occurs under the subcutaneous layer). With regard to recipient site infection, differentiation of superficial and deep incisional infections appears to be unnecessary because of difficulty of clinical diagnosis **in some circumstances**.

Our literature review has some major limitations. This study aimed to complete the important studies with the recently publicized literature, therefore with no claim to completeness of the whole issue. The study populations in articles that were included in this review were heterogeneous. Types of diseases that were included in our review were not only oral malignancy, but also benign lesions or osteoradionecrosis. Moreover, hypopharyngeal or laryngeal carcinomas were included in some articles that were included in this review. We did not conduct a meta-analysis because of heterogeneity of the above-mentioned literature results. Regardless of these limitations, our review highlights an overlooked, but critical issue. Uniform, novel criteria of defining recipient site infection in oral oncologic surgery with reconstruction will hopefully be established in the future based on the proposal described in this literature review.

CONCLUSIONS

This literature review reveals the lack of uniformity of criteria of defining recipient site infection following oral oncologic surgery with simultaneous reconstruction. This non-uniformity of criteria is mainly due to differences in interpretation of orocutaneous fistula and superficial incisional infection. Categorization of orocutaneous fistula as SSI, regardless of etiology, does not contribute to correct assessment of postoperative SSI. Moreover, for evaluating recipient site infection, differentiation of superficial and deep incisional infections appears to be unnecessary in oral cancer surgery.

Conflicts of interest: None**.**

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Table 1 Summary of studies that applied the Johnson criteria

Reference	*n*	Disease location[a]	Reconstruction[a]	Associated variables[a]	Prophylactic antibiotics	Incidence of SSI[a]	Additional information of the definition of SSI
Wang et al., 2015 [11]	478	Oral cavity (76.8) Hypopharynx (12.8) Oropharynx (5.9) Neck (4.6)	PM (100)	Previous radiation (21.1) Salvage surgery (reason: ORN, failure of free tissue transfer, etc) (6.7)	NI	Recipient site (38.3) Total flap necrosis (4.4)	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI).
Akashi et al., 2015 [15]	100	Oral cavity (100)	RF (53) RA (25) Fibula (12) PM (7) Others (3)	Previous radiation (8)	NI	Recipient site (13) (early/late onset [6/7]) Non-wound infections (9)	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI). SSIs were divided into early (<14 days postoperatively) and late onset (14–30 days).
Hirakawa et al., 2013 [7]	277	Oral cavity (37.5) Hypopharynx (30) Larynx (24.2) Oropharynx (8.3)	Free flap (55.6) Pedicle flap (8.3)	Previous radiation/chemoradiation (58.8) Previous surgery (9.7) Flap failure (partial and total necrosis) (3.9)	Ampicillin-sulbactam	33.2 (in 7 flap failures, SSI was observed in 2 cases [28.6])	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI). Flap failure was included in SSI. Wound dehiscence or ischemic necrosis of wound edges requiring local care was not considered an infection.
Lin et al., 2012 [12]	894	Oral cavity (100)	Locoregional flap/STSG (48.7) PM (31.1) Free flap (18.2) Primary closure (2)	Previous surgery (19.4) Previous radiation (8.5)	Clindamycin or cefazolin	20.8	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI).

Liu et al., 2011 [13]	306	Oral cavity (100)	PM (36.6) STSG (19.9) Free flap (17.3) Primary closure (14.4) Locoregional flap (11.8)		Clindamycin or cefazolin	31	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI).
Sato et al., 2011 [10]	66	Oral cavity (100)	STSG (37.9) Primary closure (27.3) Artificial dermis (21.2) Free flap (13.6)	Preoperative systematic oral health care intervention (50) Previous radiation (16.7)	Cefazolin sodium or cefmetazole sodium	21	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI). Erythema, induration, or tenderness around the suture line was not included in SSI. SSI was defined only when the microbial cultures were positive.
Milet et al., 2010 [8]	261	Oral cavity (52.5) Hypopharynx (26.4) Larynx (20.3)	Flap reconstruction (44.1)	Previous radiation (33) Previous surgery (23) Older age (≥70 years) (11.1)	Amoxicillin and clavulanic acid	36.4	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI). Flap failure was included in SSI.
Liu et al., 2007 [14]	994	Oral cavity (100)	STSG (32.7) Primary closure (29.7) PM (23.4) Free flap (7.6) Locoregional flap (6.5)		Clindamycin or cefazolin	19.8	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI).
Penel et al., 2005 [9]	260	Oral cavity/oropharynx (51.9) Hypopharynx	Primary closure (55.8) Flap reconstruction (44.2) PM (34.2)	Previous radiation (35.4)	Clindamycin/ netromycin or amoxicillin, and clavulanic acid	45	Modified Johnson criterion (i.e., only grades 4 and 5 were regarded as SSI). Flap failure was included

	(26.1)	in SSI.
	Larynx (19.2)	

[a]Data are reported as percentage (%) of study patients.

NI = not informed, ORN = osteoradionecrosis, PM = pectoralis major musculocutaneous flap, RA = rectus abdominis musculocutaneous free flap, RF = radial forearm fasciocutaneous free flap SSI = surgical site infection, STSG = split thickness skin graft.

Table 2 Summary of studies that applied the CDC criteria

Reference	*n*	Disease location[a]	Reconstruction[a]	Associated variables[a]	Prophylactic antibiotics[a]	Incidence of SSI[a]	Additional information of the definition of SSI
Saunders et al., 2017 [22]	72	Oral cavity (75) Oropharynx (12.5) Hypopharynx/larynx (9.7) Outside upper digestive tract (2.8)	RF (47.2) Fibula (34.7) ALT (18.1)	Malignant/benign (84.7/15.3)	Cefazolin/metronidazole (69.4) Clindamycin (12.5) Cefazolin, levofloxacin, vancomycin, or a combination (18.1) All subjects received antibiotics for a minimum of 7 days	Recipient site (11.1) Donor site (1.4) Tracheobronchitis (1.4)	At least one of the following was required: purulent drainage, organism-positive culture, and a deliberate incisional opening. Additionally, at least one sign of infection needed to be present, including pain, swelling, erythema. or heat including donor or recipient site cellulitis and abscesses, necrotizing fasciitis or myositis, and tracheobronchitis.
Pool et al., 2016 [17]	266	Oral cavity (62) Oropharynx (10.1) Hypopharynx/larynx (15) Sinonasal (12.4) Salivary gland (0.4)	RF (45.9) ALT (27.8) Fibula (15.8) Scapula (9.0) Serratus (1.1) Others (1.5)	Previous radiation (84.6) Malignant/benign/ ORN (89.9/5.6/4.1)	Cefazolin Metronidazole Ampicillin-sulbactam Clindamycin	Overall (11.3) Orocutaneous fistula (2.6)	Although not clearly specified, only deep incisional infections of the CDC criteria were diagnosed as SSI. Orocutaneous fistula that did not meet the above-mentioned criteria was not categorized as SSI.
Wagner et al., 2016 [18]	117	Larynx/hypopharynx (26) Mandible/maxilla (36) Soft tissue oral cavity/oropharynx (29) External site (9)	Free flap (100)	Previous radiation (31.6)	Clindamycin/cefepime/ vancomycin (43.6) Clindamycin (13.7) Others (42.7)	Overall (31.6) (recipient site [25.6]/donor site [8.5]/incision site [6.8])	SSIs were classified as superficial or deep.
Yarlagadda et al., 2016 [3]	480	Oral cavity (53.5) Cutaneous/temporal (11.7) Larynx (10.2)	RF (73.8) Fibula (13.1) ALT (11.3) Others (1.9)	Malignant/benign/ ORN (87.7/6.3/6) Clean-contaminated (90.8)	Ampicillin-sulbactam (83) Clindamycin (9) Cefazolin (3) Others (5)	Recipient site (13.3) Donor site (4.6) Orocutaneous	At least one of the following was required: purulent drainage from the incision, an incision that spontaneously dehisced or was opened by the surgeon

		Oropharynx (9) Sinus/maxilla (9) Hypopharynx (6.7)		Previous radiation (35.4) Previous aerodigestive surgery (25) Previous neck/skin surgery (24.4)		fistula (2.7) (with infection [1.2]/without infection [1.5])	because of infection, diagnosis of abscess or other evidence of infection involving a deep incision detected at a physical examination, during an invasive procedure, or by a histopathological examination or imaging test, and diagnosis by a surgeon of SSI. SSIs accompanied by orocutaneous fistula were considered as SSIs. A patient who developed orocutaneous fistula without signs of infection, as defined by CDC criteria, was considered as having nonsurgical site infection.
Candau-Alvarez et al., 2015 [16][b]	40	Oral cavity (85) Nodal metastases (15)	Local flap (65) PM (12.5) Temporal (2.5) ALT (10) Fibula (7.5) Medial sural (2.5)	Previous radiation (0)	Amoxicillin and clavulanic acid	Overall (15)	Only deep incisional infections of CDC criteria were diagnosed as SSI.
Durand et al., 2015 [19]	504	Oral cavity/oropharynx/ hypopharynx/larynx (80) Cutaneous/temporal and sinus/maxilla (20)	RF (75) Fibula/ALT (23) Scapula or LD (2)	Clean-contaminated (91) Malignant/ORN/benign tumors and others (88/6/6)	Ampicillin-sulbactam (83.5) Clindamycin (8.3) Cefazolin (2.8) Vancomycin with/without others (1.8) Others (3.6)	Recipient site (13.3) (complete flap loss [1.5]) Donor site (4.4)	Same as criteria that were applied in the study by Yarlagadda et al. (2016), as shown above.
Kamizono et al., 2014 [20]	197	Oral cavity (51.3) Hypopharynx (22.8) Cervical esophagus	Jejunum (34) RA (33) ALT (15.2)	Previous neck surgery (22.3) Previous radiation	Cefmetazole (continued for 3 days after surgery)	Overall (21.3)	At least one of the following was required: purulent drainage from the incision, spontaneous dehiscence or

		(9.1) Mesopharynx (5.6) Larynx (5.1) Thyroid (3.0) Maxilla (2.5)	PM (8.6) Fibula (7.6) Scapla (3.6) Others (1)	(17.3)			deliberate opening of the incision with signs or symptoms of infection (pain, tenderness, localized swelling, redness, or heat), and organisms isolated from a culture of fluid from the incision. A small amount of leakage that did not interact with the skin was not regarded as an SSI. A fistula, defined as the presence of orocutaneous or pharyngocutaneous leakage, was considered as an SSI, regardless of the origin.
Ma et al., 2012 [34]	376	Oral cavity (100)	Local flap (43.4) Primary closure (28.5) Free flap/PM (28.2)	Older (≥65 years) (100) Previous radiation (25.3)	Cefotiam/metronidazole Ampicillin-sulbactam Clindamycin (continued for 3 days after surgery)	Overall (23.1) (minor and superficial [10.3]) Postoperative pneumonia (14.9)	The presence of purulent drainage from the wound or the presence of an orocutaneous or pharyngocutaneous fistula and recipient or donor site infections.
Lotfi et al., 2008 [21][c]	258	Mouth/lip/ submandibular gland (43) Oropharynx (25) Larynx (23) Hypopharynx/ esophagus (9)	Myocutaneous/ free flap (60) Local flap (9)	Previous radiation (12) Previous surgery and radiation (11) Previous oncologic surgery (10)	Clindamycin Clindamycin/amikacin Cefoxitin	Overall (38.8)	Occurrence of any of the following was required: purulent secretion from the incision or drain, isolation of the infectious agent in the fluid found in the wound, and diagnosis of infection by a physician. Infection at the tracheotomy site was not considered for diagnosis of SSI.

[a]Data are reported as percentage (%) of study patients.

[b]Prospective pilot study.

[c]Prospective cohort study.

ALT = anterolateral thigh flap, CDC = Centers for Disease Control and Prevention, LD = latissimus dorsi myocutaneous free flap, NI = not informed, ORN = osteoradionecrosis, PM = pectoralis major musculocutaneous flap, RA = rectus abdominis musculocutaneous free flap, RF = radial forearm fasciocutaneous free flap, SSI = surgical site infection.