ORIGINAL ARTICLE

Complications in Head and Neck Surgery

A Meta-analysis of Postlaryngectomy Pharyngocutaneous Fistula

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Objective: To summarize the potential risk factors for postlaryngectomy pharyngocutaneous fistula.

Data Sources: Observational studies in the English-language literature about postlaryngectomy pharyngocutaneous fistula from January 1, 1970, to March 31, 2003. Studies were identified through a MEDLINE search with relevant key words; additional studies were identified through references.

Study Selection: We included studies about the site of primary malignancy, type of procedure, and type of closure; studies had to have been based on individual-level data, with a comparison group for each risk factor evaluated.

Data Extraction: Data required to calculate the relative risk of fistula associated with commonly reported risk factors were abstracted from the studies, and a meta-analysis using a random-effects approach was performed to estimate a summary relative risk of fistula for each risk factor. The statistical significance of heterogeneity of effects among studies was assessed.

Data Synthesis: Of 65 studies identified, 26 met the inclusion criteria. Significant risk factors identified in the pooled analysis included postoperative hemoglobin level less than 12.5 g/dL, prior tracheotomy, preoperative radiotherapy, and preoperative radiotherapy and concurrent neck dissection. The degree of heterogeneity of effects among studies was significant for postoperative hemoglobin level, preoperative radiotherapy, concurrent neck dissection, and comorbid illness. The severity of fistula was greater in patients with a history of radiotherapy.

Conclusions: This meta-analysis identified several significant risk factors for postlaryngectomy pharyngocutaneous fistula. The clinical implications of these findings and the potential sources of heterogeneity of effects among studies are discussed.

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Wound complications after head and neck surgery are associated with increased patient morbidity, hospitalization, and resource utilization. Multiple risk factors have been implicated. However, studies in which complication rates after head and neck surgery are reported may be limited by small sample sizes, variability in the type of surgery performed, the tumor site and stage, the type of reconstruction performed, and the definition of *complication*.

To simplify our analysis, we limited it to a review of studies about pharyngocutaneous fistula (PCF) after total laryngectomy. Total laryngectomy is a standard operation, and PCF can be considered a "binary" complication as the patient does or does not have a fistula. The literature addressing postlaryngectomy PCF is extensive. The reported incidence of PCF ranges from 3%[1] to 65%.[2] Multiple risk factors have been investigated, including tumor stage, tumor site, concurrent neck dissection, preoperative or postoperative hemoglobin level, comorbid illness, prior tracheotomy, use of prophylactic antibiotics, type of suture material used, type of drain used, type of closure, duration of surgery, and preoperative radiotherapy. Through a meta-analysis of observational studies about PCF, this article summarizes the available evidence about risk factors contributing to PCF.

METHODS

DATA SOURCES

A search of the English-language literature was performed using MEDLINE. The search period was from January 1, 1970, to March 31,

Table 1. Significant Risk Factors for Pharyngocutaneous Fistula Identified in Single Articles

Variable	Source	Findings
Type of suture material used	Soylu et al,[3] 1998	Lower fistula rate when polyglactin 910 (Vicryl) suture is used for pharyngeal closure compared with catgut ($P<.05$)
Perioperative antibiotics	Johansen et al,[4] 1988	Drop in fistula rate when patients are given preoperative metronidazole ($P<.001$)
Positive surgical margins	Chee and Siow,[5] 1999	Fistula rate higher when positive surgical margins are present ($P=.02$)
Pharyngeal myotomy	Ikiz et al,[6] 2000	Fistula rate higher in patients undergoing pharyngeal myotomy ($P=.001$)
Blood transfusion	Hier et al,[7] 1993	Increased fistula rate in patients receiving perioperative blood transfusion ($P=.006$)
Type of radiotherapy	Virtaniemi et al,[8] 2001	Increased fistula rate in patients treated with a combination of cobalt-roentgen radiotherapy compared with photons ($P=.03$)

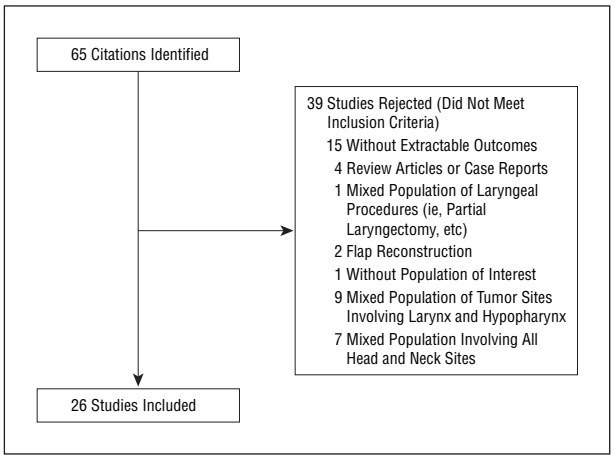

Figure 1. Study attrition flow sheet.

2003. The following search terms were used to identify relevant articles: *fistula*, *pharyngocutaneous fistula*, *cutaneous fistula*, *laryngectomy*, *postoperative complications*, *radiation therapy*, and *wound healing* (Boolean operators were used to narrow searches). Additional studies were identified through article references.

LITERATURE SCREENING AND STUDY SELECTION

Only those studies meeting strict inclusion criteria were selected. The inclusion criteria were as follows: (1) Site (only primary cancers of the larynx, excluding primary cancers of the hypopharynx or other sites in the aerodigestive tract). (2) Procedure (only total laryngectomy, excluding partial laryngectomy, laryngectomy with pharyngectomy [partial or total], and laryngectomy with glossectomy). (3) Closure (only primary pharyngeal closure, excluding any form of flap reconstruction). (4) Only studies presenting individual-level data were included. (5) Only studies in which risk factors were reported for PCF relative to a comparison group were included (ie, a study that presented PCF rates in patients receiving preoperative radiotherapy would be excluded if a comparison group of patients without radiotherapy was excluded from the analysis).

ABSTRACTION OF VARIABLES

Risk factors, or variables, examined in each article meeting the inclusion criteria were recorded in a spreadsheet. To be included in the meta-analysis, a variable had to be present in more than 1 article. Variables that were significant but were examined in a single article were also tabulated (**Table 1**).

STATISTICAL ANALYSIS

For each variable, a relative risk (RR) was calculated for each study in which data were reported for that variable. Combined summary estimates of effect for each risk factor were then calculated from a random-effects model using the method of DerSimonian and Laird.[9] The statistical significance of heterogeneity of effects among studies was assessed using the χ^2 method described by Mantel et al.[10] These analyses were performed using commercially available software (Stata, version 7.0; StataCorp LP, College Station, Tex).

RESULTS

Figure 1 is a flowchart outlining the systematic review process. Sixty-five studies presenting data on risk factors contributing to PCF formation were identified (a complete list of all studies reviewed is available from the authors). Of these studies, 26 met the inclusion criteria. The 10 variables abstracted from the 26 studies were as follows: preoperative radiotherapy, dose of radiotherapy (<6000 rad vs ≥6000 rad [<60 vs ≥60 Gy]), concurrent neck dissection, site (supraglottis, glottis, or subglottis), systemic illness, time from radiotherapy to surgery (<3 vs ≥3 months), prior tracheotomy, preoperative radiotherapy and concurrent neck dissection, stage (T1 and T2 vs T3 and T4), and postoperative hemoglobin level (<12.5 vs ≥12.5 g/dL). **Table 2** lists the 26 studies, the overall fistula rate reported in each study, and the variables analyzed in each study.

Table 3 gives the pooled analysis of the effect of each variable on the formation of PCF. The heterogeneity of effects among studies is also summarized. The results given in Table 3 are graphically shown in **Figure 2**. Four of 10 potential risk factors evaluated in the pooled analysis were significant, including the following: postoperative hemoglobin level less than 12.5 g/dL (RR, 2.10; $P=.006$), prior tracheotomy (RR, 1.60; $P=.03$), preoperative radiotherapy (RR, 2.28; $P<.001$), and preoperative radiotherapy and concurrent neck dissection (RR, 2.96; $P=.002$). Pooled estimates of the effects of radiotherapy dose (RR, 0.95; $P=.79$), time from radiotherapy to surgery (RR, 0.94; $P=.71$), comorbid illness (RR, 2.26; $P=.13$), tumor site (RR, 1.31; $P=.12$), tumor stage (RR, 0.88; $P=.35$), and concurrent neck dissection (RR, 1.12; $P=.55$) were not statistically significant. The degree of heterogeneity of effects among studies was significant for postoperative hemoglobin level and for preoperative radiotherapy. Concurrent neck dissection and comorbid

Table 2. Fistula Rates and Variables Studied in the 26 Studies in the Meta-analysis

Source	Fistula Rate, No./ Total No. (%)	Variables Studied
Aprigliano,[11] 1990	57/625 (9.1)	XRT
Bresson et al,[2] 1974	97/148 (65.5)	XRT, St
Cavalot et al,[12] 2000	32/293 (10.9)	XRT, ND, CI, T, HGB
Chee and Siow,[5] 1999	11/69 (15.9)	XRT
Cummings et al,[13] 1977	25/155 (16.1)	XRT, XRTD
Fradis et al,[14] 1995	7/56 (12.5)	XRT, ND, St, XRTD
Gall et al,[15] 1977	10/233 (4.3)	XRT, S
Hier et al,[7] 1993	24/126 (19.0)	XRT, St
Horgan and Dedo,[16] 1979	20/135 (14.8)	XRT, ND, T, HGB, XRTD, Ti
Ikiz et al,[6] 2000	8/92 (8.7)	XRT, ND, T, St
Johansen et al,[4] 1988	34/106 (32.1)	XRTND, S
Joseph and Shumrick,[17] 1973	8/23 (34.8)	XRT, XRTND, XRTD, Ti
Kent et al,[18] 1985	5/66 (7.6)	XRT, ND, CI, S, St
Krouse and Metson,[19] 1992	5/109 (4.6)	XRT, CI
Lavelle and Maw,[20] 1972	64/170 (37.6)	XRT, ND, XRTND, T, HGB, S, St, XRTD, Ti
McCombe and Jones,[21] 1993	84/357 (23.5)	XRT, ND, CI, St
Natvig et al,[22] 1993	21/180 (11.7)	XRT, ND, XRTND, Ti
Papazoglou et al,[23] 1994	28/310 (9.0)	XRT, ND, CI, S, St
Robbins et al,[24] 1972	2/23 (8.7)	XRT, ND, S, St, Ti
Sarkar et al,[25] 1990	30/110 (27.3)	XRT, ND
Sheman and Spiro,[26] 1986	7/60 (11.7)	XRT, ND
Soylu et al,[3] 1998	37/295 (12.5)	XRT, ND, T, St
Stell and Cooney,[27] 1974	17/111 (15.3)	XRT
Thawley,[1] 1981	4/155 (2.6)	XRT, S
Virtaniemi et al,[8] 2001	20/133 (15.0)	XRT, ND, S, St
Wei et al,[28] 1980	27/121 (22.3)	XRT, ND, HGB, Ti

Abbreviations: CI, comorbid illness; HGB, postoperative hemoglobin level; ND, concurrent neck dissection; S, tumor site; St, tumor stage; T, prior tracheotomy; Ti, time from radiotherapy to surgery; XRT, preoperative radiotherapy; XRTD, radiotherapy dose; XRTND, preoperative radiotherapy with concurrent neck dissection.

Table 3. Combined Summary Estimates of Effect for Variables and Significance of Heterogeneity of Effects Among Studies

Variable	RR (95% Confidence Interval)	RR *P* Value	Heterogeneity of Effects *P* Value
Patient			
Comorbid illness	2.26 (0.80-6.45)	.13	<.001
Postoperative hemoglobin level	2.10 (1.24-3.55)	.006	.05
Disease			
Tumor site	1.31 (0.93-1.83)	.12	.29
Tumor stage	0.88 (0.68-1.14)	.35	.14
Treatment			
Preoperative XRT	2.28 (1.59-3.25)	<.001	<.001
XRT dose	0.95 (0.64-1.41)	.79	.30
Time from XRT to surgery	0.94 (0.66-1.32)	.71	.40
Neck dissection	1.12 (0.78-1.59)	.55	.003
XRT and neck dissection	2.96 (1.51-5.80)	.002	.45
Prior tracheotomy	1.60 (1.05-2.44)	.03	.21

Abbreviations: RR, relative risk; XRT, radiotherapy.

illness did not demonstrate an overall increase in RR; however, the degree of heterogeneity of effects was also significant for these variables.

Table 1 lists the variables in single articles that were found to be significant in those studies[3-8] but were excluded from the pooled analysis because only the single article discussed the variable in question. Six studies,[2,6,8,13,21,23] summarized in **Table 4**, included data on the severity of fistula, comparing patients with and without preoperative radiotherapy. A pooled analysis could not be performed because of the lack of standardized presentation of these data among studies; however, the overall severity of fistula was greater among patients who underwent preoperative radiotherapy.

COMMENT

Wound complications (ie, infection, flap necrosis, and fistula) after head and neck surgery are associated with increased hospitalization, resource utilization, and patient anxiety and morbidity.[29-31] These complications may impede rehabilitation and delay additional postoperative therapy. Multiple factors contributing to increased risk of wound complications have been implicated, including prior radiotherapy, chemoradiotherapy, malnutrition, duration of surgery, anemia, tobacco use, medical comorbidity, and others. However, studies about complication rates are often limited by small sample sizes, as well as by variability in the type of surgery performed, the tumor site and stage, and the method of reconstruction. In addition, the definition of *complication* varies among studies.[31-35]

This article presents a meta-analysis of the current literature about postlaryngectomy wound complications. Meta-analysis is a statistical method in which separate studies that are considered to be combinable are statistically integrated. This statistical tool was originally described as a means of studying the pooled effects of multiple randomized controlled trials.[36-38] However, meta-analysis of observational studies is as commonly performed. When a highly structured and systematic method of data collection and analysis is used and when the studies analyzed include binary outcomes (eg, disease vs no disease, dead vs alive, or fistula or no fistula), it is considered a reliable means of performing a systematic review of observational studies.[39]

We chose studies about postlaryngectomy PCF because of the standard surgical approach to laryngectomy and the binary nature of PCF (a patient has or does not have a fistula). This allows for combining similar observational studies in which a binary outcome measure is reported. There is an extensive literature about postlaryngectomy PCF rates; the reported incidence of PCF ranges from 3%[1] to 65%.[2] The inclusion criteria outlined in the "Methods" section were used to create a homogenous pool of studies that could be statistically combinable.

The pooled analysis of the 10 abstracted variables from the 26 included studies shows that postoperative hemoglobin level, prior tracheotomy, preoperative radiotherapy, and preoperative radiotherapy and concurrent neck dissection are associated with increased RR of postlaryngectomy PCF formation. Although postoperative

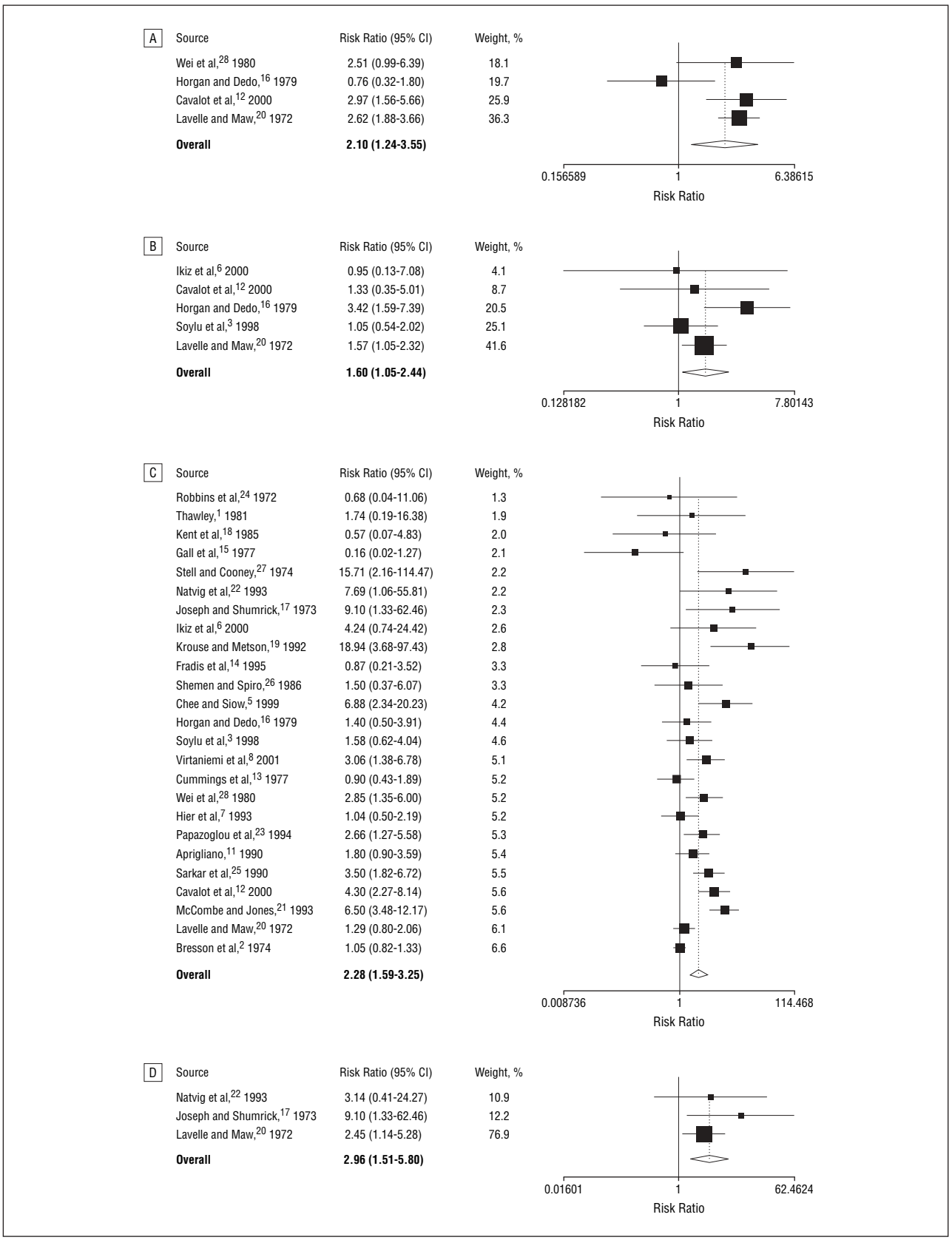

Figure 2. Graphical representation of the relative risk calculations for the studies and the overall relative risk for the following variables, which were significant risk factors for the formation of pharyngocutaneous fistula (PCF): postoperative hemoglobin level lower than 12.5 g/dL (A), prior tracheotomy (B), preoperative radiotherapy (C), and preoperative radiotherapy and concurrent neck dissection (D). A relative risk of 1 indicates that the variable does not increase the risk of fistula formation. The size of the black squares represents the weight (shown numerically as "Weight, %") of each study in the pooled analysis. Diamonds indicate overall risk ratio; size of diamonds, confidence interval (CI). Dotted lines indicate where each study fell with respect to the overall risk ratio.

hemoglobin level and preoperative radiotherapy represent significant RRs in the pooled analysis, there is also significant heterogeneity of effects among studies (ie, several studies[1-3,6,13-15,18,20,24] did not demonstrate an association between these factors and the risk of PCF formation). On the other hand, while increased risk of PCF was not shown to be associated with concurrent neck dissection and comorbid illness, the heterogeneity of effects among studies was significant. These findings suggest that other variables excluded from the analysis likely play a role in increasing the risk of PCF. These confounding variables may include pharyngeal closure technique, type of suture material used, timing and type of postoperative oral feeding, duration of surgery, nutritional status, and others. Table 1 lists some of the variables that were found to be significant in single studies[3-8] but could not be included in the meta-analysis because they were discussed only in single articles; the effect of these variables and possibly others that were not studied must be considered when interpreting the findings from the meta-analysis.

Although preoperative radiotherapy is associated with an increased risk of PCF, other radiotherapy-associated variables such as radiotherapy dose and time from radiotherapy to surgery did not demonstrate an increased RR. Given the known effects of radiotherapy on normal tissue, these findings seem counterintuitive.[40] In the acute phase, during the delivery of radiotherapy, cells that are regularly or rapidly dividing are killed, leading to acute toxic effects such as dermatitis or mucositis. The second, or chronic, phase of radiotherapy injury results from the effects of radiotherapy on the microvasculature of tissue, namely, subintimal fibrosis, endarteritis, and thrombus formation. This leads to tissue that is hypovascular, hypocellular, and hypoxic. Oxygen tension measurements in an irradiated tissue field demonstrate significant hypoxia in the center of the field, with a shallow gradient of improvement in oxygen tension as measurements are taken closer to the periphery.[41] These effects can be appreciated 6 months after treatment and persist for the lifetime of the patient. Given the known delayed effects of radiotherapy, it would seem that the longer the time after completion of radiotherapy that laryngectomy is performed, the higher the risk of PCF formation. However, the meta-analysis did not support this theory. If the time from radiotherapy to surgery could be more concisely stratified, an association may be better appreciated.

One finding that was consistent across all studies[2,6,8,13,21,23] discussing the severity of PCF was the increased severity of fistula in patients who underwent preoperative radiotherapy vs those who did not (Table 4). The results from these studies, although not combinable, suggest that if an irradiated patient develops a fistula, the duration and severity of the fistula will be greater.

Table 4. Severity of Fistula in Patients With and Without Preoperative Radiotherapy

Source	Comment
Virtaniemi et al,[8] 2001	Patients with preoperative XRT developed fistulas earlier ($P = .047$), fistulas took longer to heal ($P = .06$), and fistulas were larger ($P = .049$) compared with patients without preoperative XRT
Papazoglou et al,[23] 1994	More patients with preoperative XRT required surgical closure of their fistula
Cummings et al,[13] 1977	Patient undergoing high-dose preoperative XRT who developed fistula took longer to develop fistula and longer to heal
McCombe and Jones,[21] 1993	50% Of patients with preoperative XRT developed "severe" fistula compared with 11% of patients without preoperative XRT
Ikiz et al,[6] 2000	Patients with preoperative XRT with fistula required flap closure
Bresson et al,[2] 1974	Higher percentage of patients with preoperative XRT with fistula required surgical closure ($P<.05$)

Abbreviation: XRT, radiotherapy.

CONCLUSIONS

When strict inclusion criteria are used, meta-analysis of observational studies about postlaryngectomy PCF is a valid method of identifying risk factors contributing to wound complications in head and neck surgery. Postoperative hemoglobin level lower than 12.5 g/dL, prior tracheotomy, preoperative radiotherapy, and preoperative radiotherapy and concurrent neck dissection are associated with an increased risk of PCF formation. Overall, it seems as if the severity and duration of fistula in patients who underwent preoperative radiotherapy are greater than those in patients who did not. Further risk factor identification would be facilitated by larger studies examining multiple potential risk factors in a homogeneous surgical population.

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