The Laryngoscope

Bleeding Complications After Transoral Robotic Surgery: A Meta-Analysis and Systematic Review

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Objective: Postoperative hemorrhage is the most common complication of transoral robotic surgery (TORS), the severity of which can range from minor bleeding treated with observation to catastrophic hemorrhage leading to death. To date, little is known about the incidence, risk factors, and management of post-TORS hemorrhage.

Study Design: Systematic Review and Metanlysis.

Methods: A systematic review of the published literature using the Cochrane Handbook for Systematic Reviews of Interventions was performed and examined TORS, postoperative hemorrhage, and the use of prophylactic transcervical arterial ligation (TAL).

Results: A total of 13 articles were included in the analysis. To date, there have been 332 cases of hemorrhage following a total of 5748 TORS. The pooled median post-TORS hemorrhage rate was 6.47%. The overall incidence of minor and major hemorrhage was 5.29% and 2.90%. Patients with prior radiation (relative risk [RR] = 1.46, 95% confidence interval [CI] = 1.00–2.12), large tumors (RR = 2.11, 95% CI = 1.48–2.99), and those requiring perioperative coagulation (RR = 2.25, 95% CI = 1.54–3.28) had significantly higher relative risks of hemorrhage. There was no significant difference in the relative risk of overall hemorrhage with TAL. Looking at major hemorrhage, patients undergoing TAL had a large but insignificant relative risk reduction in post-TORS hemorrhage (RR = 0.40, 95% CI = 0.15–1.07).

Conclusion: The incidence of post-TORS hemorrhage is low (5.78%), and for major hemorrhage requiring emergent embolization, TAL, or tracheotomy to control hemorrhage it is even lower (2.90%). Large tumors, perioperative anticoagulation, and prior radiation were associated with significantly increased risk of post-TORS hemorrhage. TAL does not reduce the overall incidence of post-TORS hemorrhage but may lead to fewer severe hemorrhages.

Key Words: Hemorrhage, TORS, transoral robotic surgery, complications, bleeding, transcervical arterial ligation.

Level of Evidence: III

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INTRODUCTION

Transoral surgery with neck dissection has become increasingly accepted as a primary treatment modality for early-stage oropharyngeal cancer.[1–4] The recently completed eastern cooperative oncology group (ECOG) 3311 trial (NCT01898494) was designed to study the efficacy of transoral robotic surgery (TORS) and concurrent selective neck dissection as a primary treatment modality for intermediate-risk oropharyngeal cancer; its results when published may allow for de-escalation of adjuvant therapy.[5] Since food and drug administration (FDA) approval of TORS for tumor (T)1 and T2 head and neck malignancy in 2009 and its increased use in the treatment of select oropharyngeal cancers, there has been careful evaluation of oncologic outcomes as well as the morbidity and mortality associated with robotic-assisted surgery.[6]

Hemorrhage is one of the most common complications following TORS and is the cause of 30% of readmissions.[7,8] The severity of post-TORS hemorrhage can range from minor bleeding treated with observation to catastrophic hemorrhage leading to emergent tracheotomy for airway management and even death. A large survey study of self-reported complications following TORS on a total of 2,015 patients revealed a catastrophic bleed rate of 3.5% and mortality rate of 0.3%.[8] To date, various groups have identified factors associated with postoperative bleeding, including larger primary tumors, greater extent of surgery, prior radiation, and perioperative anticoagulation.[2–4]

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Additional supporting information may be found in the online version of this article.

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However, no consensus on risk factors for post-TORS hemorrhage or its management currently exists in the literature.

In an effort to prevent catastrophic bleeding and deaths, some groups have proposed transcervical arterial ligation (TAL) of either the external carotid artery or its branches to reduce the arterial blood flow to the surgical bed.[2–4,9,10] This intervention takes little extra time for the experienced surgeon when performing concurrent neck dissection.[11] However, there is great variation as to how (which branches are ligated) and when (i.e., with neck dissection prior to TORS, concurrently, or during staged neck dissections in the weeks following TORS) TAL is performed. During the ECOG 3311 trial, this intervention became mandatory after one of the initial meetings of the data and safety monitoring committee.[5] Since then, some single-institution studies have shown that TAL is associated reduction in the rate of severe bleeding according to the mayo postoperative bleeding severity classification,[2,3] but thus far no group has shown an overall change in the post-TORS bleeding rate.[2] Here. we present a systematic review of the literature and meta-analysis of the literature to better understand the risk factors for post-TORS hemorrhage, management strategies, and efficacy of TAL as an intervention to prevent bleeding.

METHODS

A systematic review of the published literature examining TORS, postoperative hemorrhage, and the use of prophylactic TAL was conducted. The study methodology was based upon the Cochrane Handbook for Systematic Reviews of Interventions.[12] A review protocol was written prior to data collection using the preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA-P).[13] PUBMED/MEDLINE, web of science, and cochrane clinical trails databases were searched from January 1, 2009, to March 30, 2019, for English language articles using the MeSH terms "Trans-oral Robotic Surgery," "TORS," "Transcervical Arterial Ligation," and "Hemorrhage" (Appendix 1). Authors W.S. and M.T. independently screened titles and abstracts identified for eligibility. References of the identified publications were checked for additional relevant publications. Data extraction was performed by authors W.S. and M.T. and included the following: study design, level of evidence, patient demographics, number of bleeding events, time to hemorrhage, severity of hemorrhage, surgical site, indication for surgery, T stage, use of TAL, prior irradiation, extent of resection, perioperative anticoagulation or antiplatelet therapy, and surgeon experience (<50 cases).

Studies eligible for inclusion were cohort studies of patients with aerodigestive squamous cell carcinoma (SCC) treated with TORS who reported rates of postoperative hemorrhage and complications (Appendix 2). Only articles published after 2009, the year that TORS received FDA approval, were included. If there were two studies published by the same institution using the same database, then the largest, most relevant study data was used in the final analysis. Studies were excluded if they were animal studies, cadaveric studies, case reports, small case series (<10 patients), unavailable in English, or did not have a significant proportion of patients undergoing TORS for treatment of upper aerodigestive tract SCC. Only studies with data specific to the use of the TAL to prevent post-TORS hemorrhage were included in the final analysis. The selection process for this review is outlined in Figure 1.

A study bias assessment was performed on studies included in the final analysis by two separate authors (W.S. and M.T.) according to the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies.[14] The NOS involves a star system in which a study is judged based on three broad perspectives: 1) the selection of the study group, 2) comparability of the groups, and 3) ascertainment of the outcome of interest. Higher quality studies can be awarded up to nine stars in the NOS. See Table I. Disagreements on the assessment of bias between reviewers were resolved during repeat assessment, face-to-face discussion, and by establishing a consensus regarding bias. The level of evidence presented in each study was determined with guidelines established by the Center for Evidence-Based Medicine.[15] See Table I.

The primary outcome was post-TORS hemorrhage. Secondary outcomes were major and minor post-TORS hemorrhage. For the purposed of our study, major bleeding was defined as postoperative bleeding requiring operative intervention with ligation of named vessels or intravascular embolization. Minor postoperative bleeding was defined as bleeding events in which patients reported bleeding, presented to the emergency room, or were admitted for observation, as well as those managed operatively with simple transoral monopolar cautery. TAL was defined as ligation of the external carotid artery and/or any of its branches to the resection bed. Additional subgroup analyses were performed to assess the impact of factors associated with postoperative hemorrhage on post-TORS hemorrhage rates. These included previous radiation/surgery, surgeon experience (<50 cases vs. > 50 cases), tumor size, and use of perioperative anticoagulation or antiplatelet therapy. T1 and T2 tumors, or cases with one to two subsites resected, were considered to be small tumors. T3 and T4 tumors, or cases with three subsites resected, were considered large tumors. Anticoagulation/antiplatelet therapy consisted of therapeutic aspirin therapy, platelet inhibitors, therapeutic heparin, vitamin K inhibitors, and direct thrombin inhibitors. Tertiary outcomes were the use of embolization, the need for emergent tracheotomy, the need for emergent TAL, and death. The method for transcervical arterial ligation, if used, was examined and categorized as ligation of the main trunk of the external carotid artery or ligation of its individual branches. Finally, the effect of TAL on the overall incidence of bleeding and severity of bleeding was analyzed.

All outcome variables were dichotomous. Total number of patients and number of events for all cases of post-TORS hemorrhage were obtained and input into Excel 365 (Microsoft Corp., Redmond, WA). Meta-analysis of risk ratio (RR) was conducted using MetaXL version 5.3 (EpiGear International Pty Ltd, Queensland, Australia). A random effects model was constructed using the DerSimonian & Laird method (1986), which allows for heterogeneity to be assessed through the Q score, which is then used to calculate I^2. Studies were weighted using an inverse variance method; therefore, studies with smaller variance are weighted more highly in analysis. Forest plots and funnel plots (to assess publication bias) were also constructed through MetaXL (EpiGear International Pty Ltd, version 5.3).

RESULTS

Initial electronic search revealed 1,760 studies; of those, 1,736 were excluded based on screening of the title by W.S. Review of the abstracts was performed by both W.S. and M.T., after which eight articles were identified as duplicates. One study was excluded because it only included patients undergoing TORS for benign disease.[16] Two

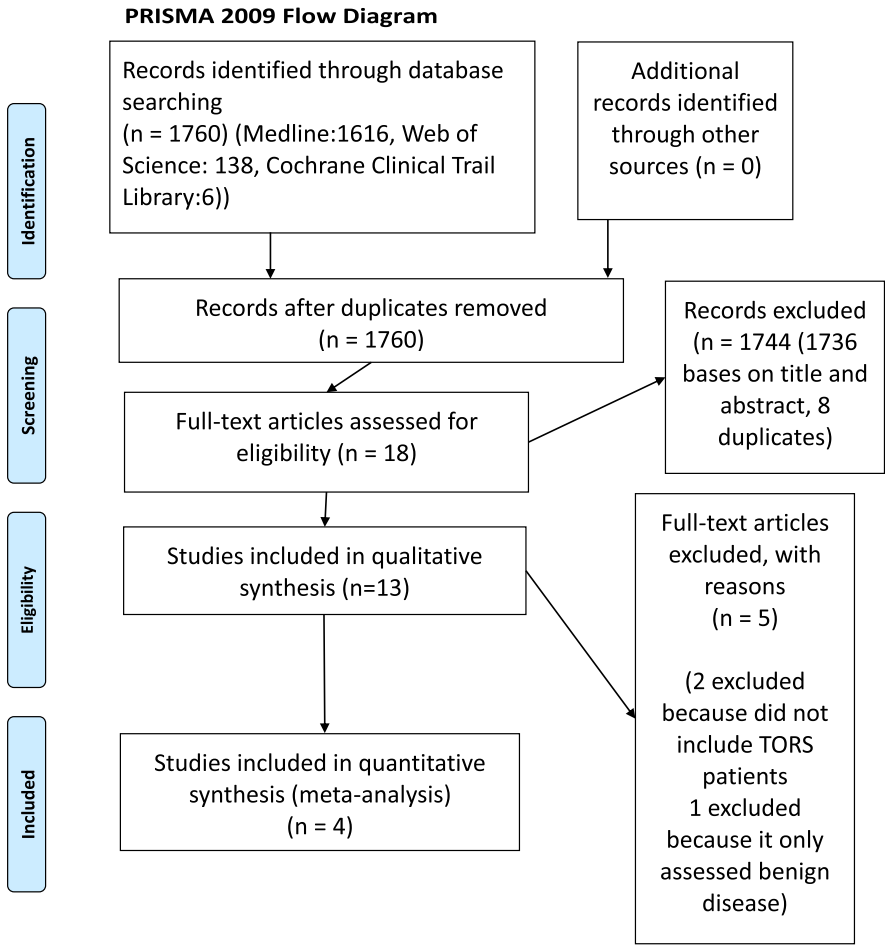

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis literature search flowchart. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE I.
NewCastle Ottawa Scale Cohort Bias Assessment.

Article	Representativeness	Selection of Control	Ascertainment of Exposure	Outcome of Interest Not Present at Start	Comparability of Controls	Assessment of Outcome	Follow-up Long Enough	Adequacy of Follow-up	Overall Bias
Pollei et al.[†,‡,§]	*	*	*	*		*	*	*	******* (7/9)
Kubik et al.[†,‡,§,‖,¶]	*	*	*	*		*	*	*	******* (7/9)
Hay et al.[†,§]	*	*	*	*		*	*	*	******* (7/9)
Gleysteen et al.[†,‡,‖,¶]	*	*	*	*		*	*	*	******* (7/9)
Aubry et al.[‡,§,‖]		*	*	*		*	*	*	****** (6/9)
Asher et al.[‡,‖]		*	*	*		*	*	*	****** (6/9)
Chia et al.[¶]			*	*					** (2/9)
Topf et al.[‖]	*	*	*	*		*	*	*	******* (7/9)

Studies were ranked according to the selection of the study group (4 stars), comparability of the groups (2 stars), and ascertainment of the outcome of interest (3 stars).
[†]Bias assessment based on TAL ligation as exposure.
[‡]Bias assessment based on radiation history as exposure.
[§]Bias assessment based on large tumor size as exposure.
[‖]Bias assessment based on anticoagulation as exposure.
[¶]Bias assessment based on <50 cases as exposure.
TAL = transcervical arterial ligation.

TABLE II.
Study Demographics.

Study	N	Age	Site	Indication	Technique	Identification of Bleeds	COE‖	Comments
Pollei	906	59 mean	100% oropharynx	97.8% SCC†, 2.2% other neoplasm	TLM‡ 53%, TORS§ 29.7%, handheld electrocautery 12.9%	Review of medical record w/minimum 30 days follow-up	III	*Only reported bleed rate with surgery and radiation so this was included in analysis, retrospective single institution cohort study
Kubik	265	59 mean	Unknown	100% SCC†	100% TORS§	Review of medical record w/minimum 30 days follow-up	III	*Retrospective single institution cohort study
Hay	122	57 median	100% oropharynx	97.6% malignant, 2.4% benign	100% TORS§	Review of medical record w/minimum 30 days follow-up	III	*Retrospective single institution cohort study
Gleysteen	201	60 median	100% oropharynx	100% SCC†	100% TORS§	Review of medical record w/minimum 30 days follow-up	III	*Retrospective multi-institution cohort study
Zenga	509	59.8 mean	66.4% oropharynx, 4.72% oral cavity, 28.89% unknown	66% malignant, benign 7%, other 26%	100% TORS§	Data extracted from multiple databases with bleeding identified by ICD-9 codes 998.11 or 459.0.	III	*Retrospective cohort study of readmission database
Parhar	950	X	Unknown	Unknown	100% TORS§	Data collected from National Readmission Database (bleeding extracted from reasons for readmission).	III	*Study reported total readmission rate and not bleed rate (12.5% overall readmission rate) retrospective cohort study of readmission database.
Aubry	178	61.4 mean	47.19% larynx, 24.16% hypopharynx, 28.65% oropharynx	94.94% malignant, 5.06% benign	100% TORS§	Review of medical record w/minimum 30 days follow-up	III	*Retrospective single institution cohort study
Lörincz	35	65 median	100% oropharynx	100% SCC	100% TORS§	Review of medical record w/minimum 30 days follow-up	III	*Retrospective single institution cohort study
Winter	32	57 mean	100% oropharynx	100% T1 SCC†	100% TORS§	Review of medical record w/minimum 30 days follow-up	III	*Retrospective single institution cohort study
Chia	2015	X	Unknown	Unknown	100% TORS§	Survey with self-reported data	III	*Retrospective cohort study that assess complications based on surgeon report, subject to significant recall bias
Asher	147	59.6 mean	82.99% oropharynx, 17.00% larynx, 6.12% other	92.5% SCC†, 7.5% other malignancy	100% TORS§	Review of medical record w/minimum 30 days follow-up	III	*Retrospective multi-institution cohort study
Topf	297	60.9 mean	91% oropharynx, 4% hypopharynx, 2% larynx, 2% unknown	100% SCC†	100% TORS§	Review of medical record w/minimum 30 days follow-up	III	*Retrospective single institution cohort study
Richmond	91	59 median	100% oropharynx	86.8% malignant	100% TORS§	Review of medical record w/minimum 30-days follow-up	III	*Retrospective single institution cohort study
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COE = class of evidence; ICD-9 = International Classification of Diseases, Ninth Revision; TLM = transoral laser microsurgery; TORS = transoral robotic surgery; SCC = squamous cell carcinoma.

TABLE III.
Bleeding Rates Analysis.

Study	Time to Hemorrhage (POD)	Overall Bleeding Rate	Minor/Mild Bleeding Rate	Major/Severe Bleeding Rate	Perioperative Anticoagulation	Tumor Size	Learning Curve (% < 50 Cases)	TAL*
Pollei	Mean 10	5.41	3.64	1.77	X	36.4% T1, 41.6% T2, 14.9% T3, 7.20% T4	X	14.79%
Kubik	Median 6	13.21	7.17	6.03	23.40%	44.15% T1, 29.06% T2, 10.19% T3	52.08%	27.92%
Hay	Median 8	19.67	15.57	5.74	X	44.26% T1, 38.52% T2, 3.28% T3	X	29.51%
Gleysteen	Median 5	6.47	2.49	3.98	35.32%	X	49.75%	25.87%
Zenga	Median 9	8.06	5.89	2.16	X	X	X	X
Parhar	Median 13 for all readmissions	4.00	X	X	X	X	X	X
Aubry	Mean 9 days	18.54	X	X	23.03%	28.65% T1, 56.18% T2, 8.99% T3, 1.12% T4	X	X
Lörincz	Median 4.5	5.71	X	X	X	54.29% T1, 42.86% T2, 2.86% T3	X	X
Winter	Unknown	6.25	X	X	X	100% T0	X	X
Chia	Unknown	3.08	X	X	X	X	44.17%	X
Asher	Median 8	7.48	X	X	32.65%	33.33% T1, 44.22% T2, 10.20% T3, 2.04% T4	X	X
Topf	Median 6 (all readmissions)	5.28	X	X	25.93%	42% T1, 42% T2, 12% T3, 1% T4, 3% TX	X	23.91%
Richmond	Unknown	6.59	X	X	X	20% T0, 76% T1/T2, 4% T3	X	X
		Mean:5.76	Mean: 5.29%	Mean: 2.90%				
	Median:8 days	Median: 6.47%	Median: 5.89%	Median: 3.98%				

POD = postoperative day; T = tumor; TAL = transcervical artery ligation.

additional studies were excluded because they represented earlier studies with duplicate data.[17,18] Only four studies used TAL as an intraoperative intervention to prevent or reduce the severity of post-TORS hemorrhage.[2–4,9] Among these, only one study described a method of intraoperative hemostasis (clips vs. bipolar vs. monopolar cautery) during TORS and neck dissection without TAL.[9] The selection process is presented in Figure 1. Table II presents the individual details of the 13 studies selected for inclusion in the systematic review.[2–4,7–10,19–24]

Post-TORS Hemorrhage and Management

There have been 332 cases of hemorrhage after TORS reported in the literature following a total of 5,748 TORS cases (5.78%). The post-TORS hemorrhage rate among studies ranged from 3.1% to 19.7%. The pooled mean post-TORS bleeding rate was 5.78%, with a pooled median post-TORS bleeding rate of 6.47%. Overall, the median time to hemorrhage following TORS was on postoperative day 8. Minor versus major bleeding was examined in five of 13 studies. In studies that assessed bleeding severity, minor and major hemorrhages occurred postoperatively in 106 and 58 patients for an overall incidence of 5.29% (2.49%–5.57%) and 2.90% (1.77%–6.03%), respectively.

In terms of management of post-TORS hemorrhage in the literature, 125 (37.35%) of these events were observed, and 207 (62.65%) required operative or endovascular intervention. No patient required use of transoral laser or robotic-assisted surgery for control. The use of emergent tracheotomy for airway management during post-TORS hemorrhage was rare and was performed on only 41 (0.71%) patients. Similarly, emergent TAL was performed in only 22 patients (0.38%), and angioembolization of the external carotid branches was required in 61 patients (1.06%) for effective bleeding control. Lastly, there have been only 10 patient deaths (0.17%) due to catastrophic hemorrhage reported in the literature during the 10 years since FDA approval.

Factors Associated With Post-TORS Hemorrhage

Subgroup analysis found a significant increase in post-TORS bleeding associated with a history of prior radiation, large primary tumors, and perioperative anticoagulation (Table III). Five studies including a total of 226 patients with prior treatment assessed post-TORS bleeding in the salvage setting.[3,9,10,21] The pooled overall post-TORS bleeding rate was 13.66% for subjects with a history of prior radiation compared to a 7.48% rate without prior radiation. Prior radiation was associated with a significantly increased relative risk of hemorrhage after TORS (relative risk [RR] = 1.45, 95% confidence interval [CI] = 1.00–2.12). Three studies including a total of 144 salvage patients further assessed major hemorrhage in

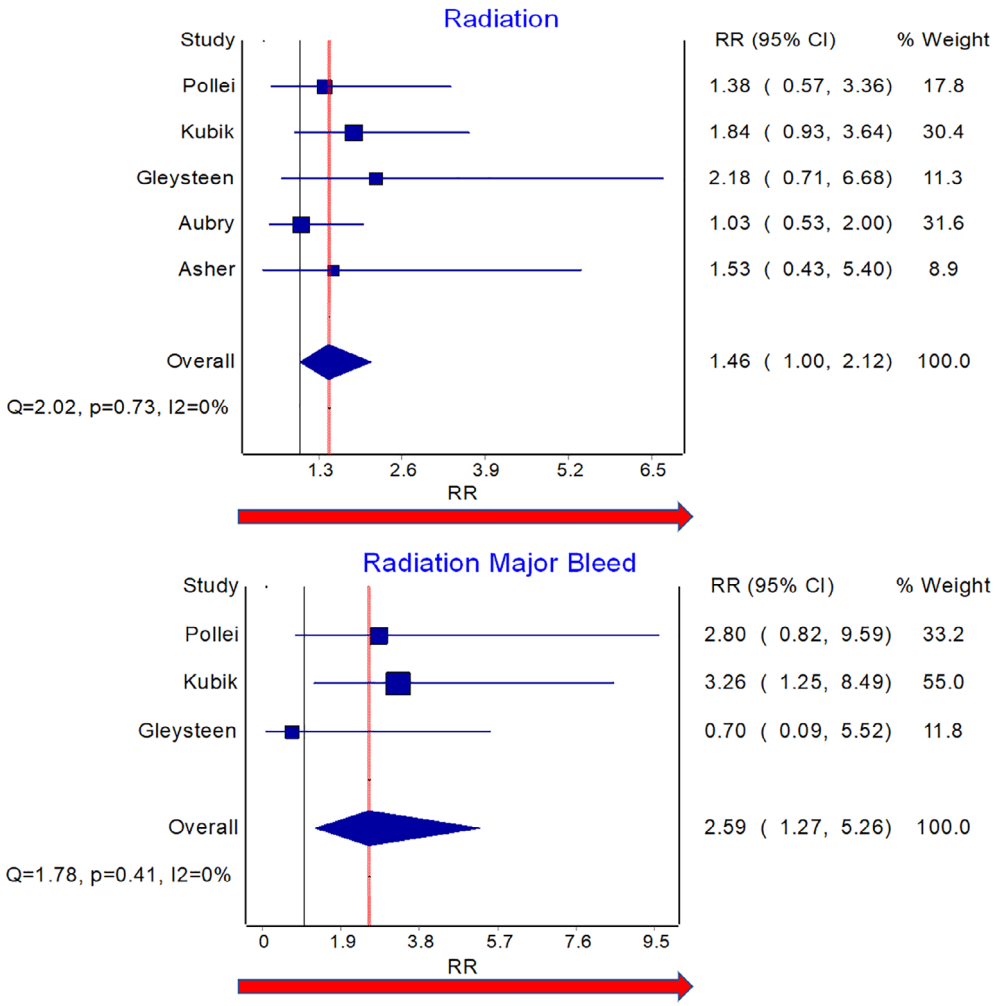

Fig. 2. Forest plot of prior radiation associated with post-TORS hemorrhage. RR of post-TORS hemorrhage in patient with prior radiation versus none. Red arrow indicates direction in increasing hemorrhage rate (top) RR of major/severe post-TORS hemorrhage in patients with prior radiation versus none. Red arrow indicates direction in increasing hemorrhage rate (bottom). RR = relative risk; TORS = transoral robotic surgery. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

patients by radiation status.[2,3,9] The overall rate of major post-TORS hemorrhage was 6.94% and 2.44% with and without prior radiation. This increased risk in the group with prior radiation was significant (RR = 2.59, 95% CI = 1.27–5.26) (Fig. 2).

An additional four studies including a total of 271 T3 and T4 patients assessed differences in post-TORS bleeding rates by tumor size.[2–4,21] The pooled post-TORS bleeding rate was 13.8% for the group with large tumors versus 7.9% for small tumors and demonstrates a significant increase of post-TORS bleeding for those patients with large tumors (RR = 2.11, 95% CI = 1.48–2.99). Finally, there were five studies including 299 anti-coagulated patients that examined post-TORS bleeding rates associated with use of perioperative anticoagulation/antiplatelet therapy.[3,9,10,19,21] The pooled overall post-TORS bleeding rate was 18% for those patients on perioperative anticoagulation/antiplatelet therapy compared to 9.1% for those not on perioperative anticoagulation/antiplatelet therapy, which was a significant relative risk increase (RR = 2.25, 95% CI = 1.54–3.28) (Fig. 3). Finally, three studies with a total of 2481 patients assessed surgeon learning curve as a factor related to post-TORS hemorrhage.[3,8,9] Pooling data across these studies found no significant difference in the rate of post-TORS hemorrhage associated with a surgeon experience of < 50 cases versus > 50 cases (RR = 1.38, 95% CI = 0.83–2.32) (Fig. 4).

TAL as Prevention for Post-TORS Bleeding

Four studies including a total of 1,494 patients assessed the use of TAL as intervention to prevent post-TORS hemorrhage. Of this group, 296 patients underwent TAL compared to 1,198 patients who did not. The exact method of TAL was defined as ligation of the entire external carotid artery (ECA) system in three studies[3,9,18]; however, the specific ECA branch or extent of ligation was not reported in the last study.[2] The overall post-TORS hemorrhage rates with and without TAL was similar at 8.8% and 7.9%, for which there was no

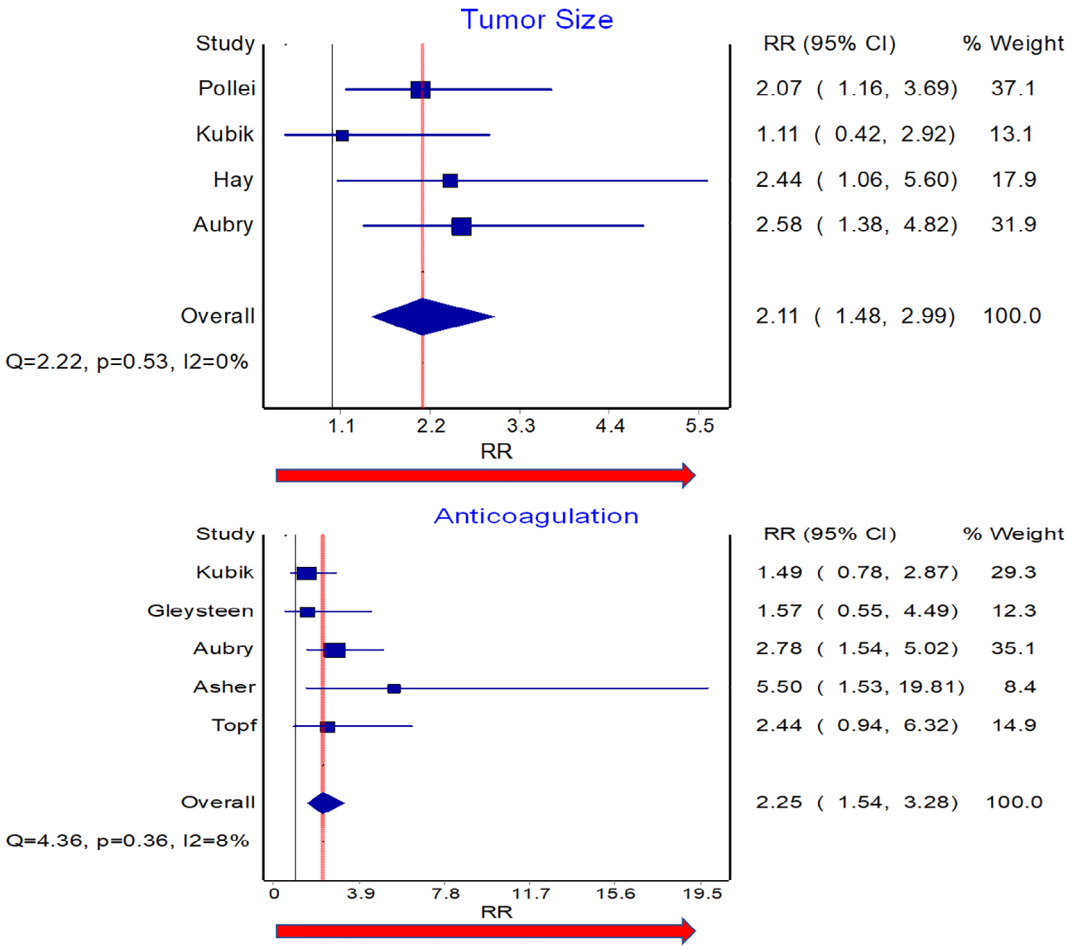

Fig. 3. Forest plot of anticoagulation and tumor size associated with post-TORS hemorrhage. RR of post-TORS hemorrhage in patients receiving perioperative anticoagulation versus none. Red arrow indicates direction in increasing hemorrhage rate (top) RR of post-TORS hemorrhage in patients with large versus small tumor size. Red arrow indicates direction in increasing hemorrhage rate (bottom). RR = relative risk; TORS = transoral robotic surgery. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

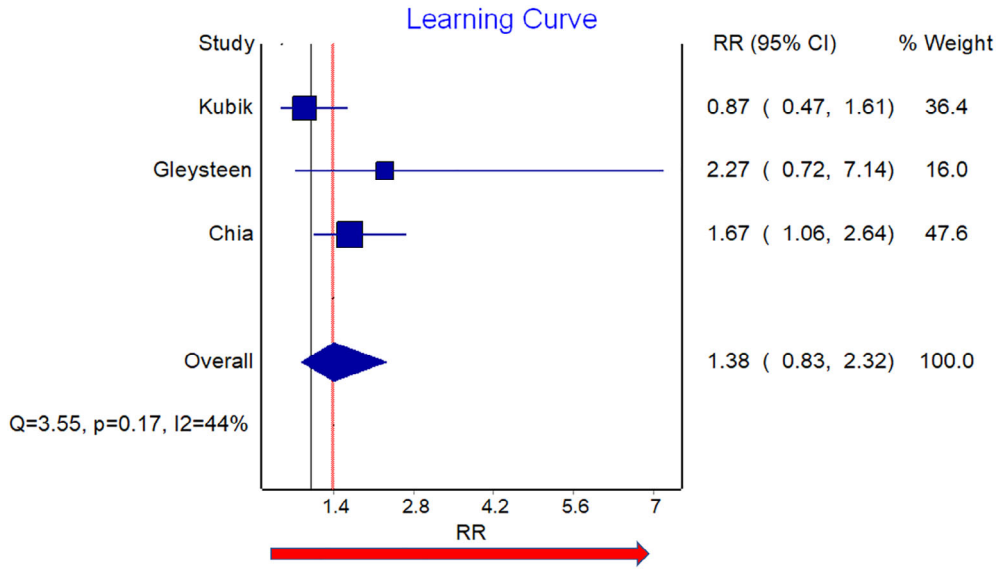

Fig. 4. Forest plot comparison of surgeon experience association with post-TORS hemorrhage. RR of post-TORS hemorrhage in patients whose surgeons had <50 cases versus > 50 cases. Red arrow indicates direction in increasing hemorrhage rate. RR = relative risk; TORS = transoral robotic surgery. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

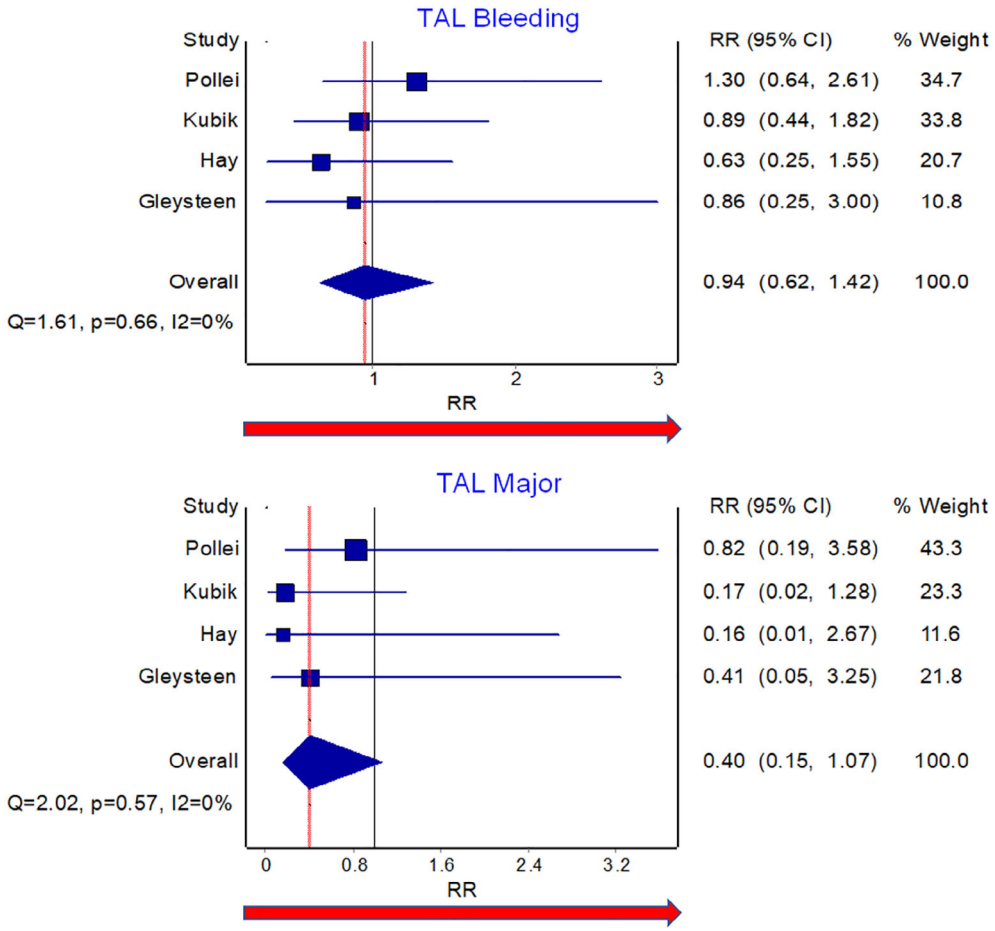

Fig. 5. Forest plot comparison of TAL associated with post-TORS hemorrhage. RR of post-TORS hemorrhage in patient with prophylactic TAL versus none. Red arrow indicates direction in increasing hemorrhage rate (top). RR of major/severe post-TORS hemorrhage in patients with prophylactic TAL versus none. Red arrow indicates direction in increasing hemorrhage rate (bottom). RR = relative risk; TAL = transcervical arterial ligation; TORS = transoral robotic surgery. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

significant difference in the relative risk between the two groups (RR = 0.95, 95% CI = 0.62–1.42). However, when major bleeding events were examined, those patients not undergoing TAL had an increased rate of major post-TORS hemorrhage (3.6% vs. 1.4%). This difference was not statistically significant (RR = 0.40, 95% CI = 0.15–1.07) but suggests a potential protective effect of TAL on major bleeding events. The meta-analysis is shown in Figure 5. Looking at the incidence of severe bleeds in institutions where TAL has been routinely adopted, the vast majority of severe bleeds have occurred in those patients who did not undergo TAL (91.7%, or 22 of 24). The incidence of emergent tracheotomy, embolization, cardiac arrest, and death without TAL were 11 (0.74%), 17 (1.13%), 2 (0.13%), and 1 (0.07%). There was only one report of the use of embolization after TAL, with no reported emergent tracheotomies, cardiac arrests, or deaths.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis examining post-TORS hemorrhage rates, risk factors, and management strategies. It is also the first systematic review and meta-analysis examining the effect of TAL on post-TORS hemorrhage rates. Overall, most studies on post-TORS hemorrhage fall under category III level of evidence due to their lack of controlling of confounders or lack of reporting on follow-up. Ten of the 13 studies included were single or multi-institutional retrospective cohort studies in high-volume academic centers, which limits the generalizability of these findings. Two studies were based on statewide databases,[7,22] capturing the experiences few states (New York, California, and Florida in one study). One study was a national survey of TORS surgeons and used self-reported data in their analysis, which is subject to recall bias and underreporting of minor hemorrhages and complications.[8] It should also be noted that two large studies were excluded from our final analysis because they provided duplicate data. In 2016, Mandal et al. used the University of Pittsburgh Medical Center database to examine post-TORS hemorrhage rates and included patients who underwent TORS for malignant and benign indications.[17] Later, Kubik et al. used the same database to analysis the effect of TAL on post-TORS hemorrhage in patients undergoing TORS in the treatment of

oropharyngeal SCC.[3] In 2015, Hay et al. used the Memorial Sloan Kettering database to look at factors related to post-TORS hemorrhage.[18] Later in 2017, Hay et al. used the same database to analyze the effect of TAL on post-TORS hemorrhage rates.[4] Still, we believe this study provides the best available evidence on post-TORS hemorrhage and provides useful information to surgeons performing TORS.

A major limitation of this study is the lack of information available on the method of intraoperative hemostasis during the initial TORS procedure reported in the literature. Only one of 13 studies specifically described a routine practice.[9] Methods for intraoperative control of bleeding encountered during TORS resections include clipping, suture ligation, bipolar cautery, and monopolar cautery, which may have significant impact on the rate of post-TORS bleeding. Therefore, future studies should plan to collect data and report on intraoperative hemostasis techniques.

Patients with history of prior radiation or surgery had a significant relative risk increase of major post-TORS hemorrhage (RR = 2.59, 95% CI = 1.27–5.26). This extends the window for postoperative bleeding beyond the typical 2 to 3 weeks.[2,3,9] Furthermore, radiation leads to poor wound healing and prolonged time to mucosalization.[25] This makes sense because radiation fibrosis can lead to more difficult dissection, increased intraoperative hemorrhage, and poor ability to isolate vessels. Given that TAL led to a 60% relative risk reduction of severe hemorrhage in the studies analyzed, prophylactic TAL may be advised. If concurrent neck dissection is planned, strong consideration should be given to performing TAL. If no concurrent neck dissection is indicated, one might consider other strategies, such as preoperative embolization, prophylactic tracheostomy for airway control, or reconstruction of the TORS defect, as measures to prevent death related to catastrophic bleeding.[26]

We also found that use of perioperative anticoagulation or antiplatelet therapy is associated with significantly increased risk of post-TORS hemorrhage with a relative risk of 2.25 (95% CI = 1.54–3.28). This data emphasizes the importance of proper patient selection and should help guide the surgeon in providing adequate preoperative counseling on the risks of post-TORS hemorrhage when such agents are used. These findings, however, are limited because hemorrhage associated with use of medication classes and specific agents could not be examined. Furthermore, there was no data available on dosages of these medications. For this reason, we are unable to identify specific agents or dosages (prophylactic vs. therapeutic) that pose a greater threat of postoperative TORS bleeding. In those instances when patients are undergoing prophylactic or elective anticoagulation, one might consider holding antiplatelet or anticoagulant therapy perioperatively. If anticoagulation is medically necessary, the surgeon might consider TAL during neck dissection. One might also give more thought to reconstruction as opposed to healing by secondary intention, which eliminates minor hemorrhage from the granulating wound.[27–30]

Additionally, the incidence of post-TORS hemorrhage was significantly higher in patients undergoing surgery for large primary tumors. Whereas only a small subset of patients undergoing TORS have large tumors, patients with large tumors had a bleeding incidence that was nearly twice as high as small tumors (13.8% vs. 7.9%). It makes intuitive sense that the incidence of hemorrhage is higher with more extensive resections. Large tumors are more likely to require deeper resection into either the tongue base or parapharyngeal space. Anatomically, this puts the wound closer to the main branches of the facial, lingual, and ascending pharyngeal arteries. Patients with large tumors would easily benefit from TAL because these patients are likely to have cervical metastases and to undergo neck dissection.[31] TAL can therefore be performed with minimal additional risk or operative time.[11]

Only four single-institution studies looked at TAL as a possible intervention that might decrease post-TORS hemorrhage rates. In those studies, the method of ligation was not standardized among surgeons and was poorly defined. It should also be mentioned that some TORS surgeons do not perform TAL because retrograde flow and collateral circulation from the contralateral carotid system have been shown to maintain sufficient blood supply to a ligated or occluded external carotid artery.[32] This may be the reason that we did not find any reduction in the overall post-TORS hemorrhage rate after TAL. Additionally, the relatively limited number of interventions (207 of 5748) and the overall paucity of major bleeding events (24 of 1198) may also explain why the obvious reduction in severe post-TORS bleeding events (2 of 24, 8.3% with TAL vs. 22 of 24, 91.7% without TAL) was not significant (RR = 0.40, 95% CI = 0.15–1.07). Finally, none of the four studies were able to assess the effects of TAL independent of radiation, tumor size, and anticoagulation. Still, we believe that our findings are important because they identify specific patients who are at increased risk of severe post-TORS hemorrhage and thus may benefit from TAL.

Hemorrhage is the most common complication following TORS, and this study provides important information regarding the severity and management of hemorrhage after TORS. Post-TORS bleeding rates in high-volume centers, performed on appropriately selected patients, lead to rates of postoperative hemorrhage similar to those of noncancer-related adult tonsillectomy (5.76%).[33,34] Some patients with post-TORS hemorrhage may be observed (2.16%), whereas others will require examination under anesthesia and control of hemorrhage in the operating room (3.62%). The important thing to note is that any otolaryngologist can control the majority of these hemorrhages with traditional methods. Not one hemorrhage required laser or robotic assistance for control. The risk of catastrophic bleeding, such as hemorrhage requiring emergent tracheotomy (0.71%), embolization (1.06%), postoperative vessel TAL (0.38%), or resulting in death (0.17%) is relatively low.

Interventions to prevent catastrophic post-TORS hemorrhage would be valuable to surgeons performing TORS. In the emergency setting, the risks of tracheotomy

and embolization are grave. The incidence of major complications in emergent tracheotomy is 20%, and mortality rate is 2%.[35,36] Similarly, the risk of neurovascular complications following emergent embolization for carotid hemorrhage is 8% to 14%.[37,38] However, the currently reported overall mortality rate for elective tracheostomy is 1.6%,[35] and there is an overall stroke rate of 1.4% for external carotid artery embolization.[38] These risks and the low rate of major post-TORS hemorrhage (1.4%) make prophylactic embolization and/or tracheotomy difficult to justify but might be considered for certain high-risk patients. Reconstruction of oropharyngeal defects, although possible, can be technically difficulty.[26,39] Currently, it is only used in select situations such as large palatal defects, loss of volume of the tongue base, fistula, or exposure of the carotid artery.[8,40] It may allow reduction in secondary bleeding by covering the defect and preventing formation of granulation tissue; however, the data at this time is limited, with the largest series only consisting of 20 patients.[39]

To date, the only reported complication following TAL is first bite syndrome (6%).[11] According to our results, prophylactic TAL has led to a large but insignificant decrease in the relative risk of major post-TORS bleeding (RR = 0.38, 95% CI = 0.14–1.04).[2,3,9,18] Based on the data from this study, one would have to perform 45 neck dissections with TAL in order to prevent one major post-TORS hemorrhage requiring operative control of hemorrhage, emergent tracheostomy, TAL, embolization, cardiac arrest, or death. Post-hoc power calculation assuming a major bleed rate of 3.6% for the non-TAL group and 1.4% for the prophylactic TAL group found a sample size 1,578 patients with 789 patients in each group would be necessary to eliminate the null hypothesis for an 80% study power. However, cofactors such as radiation status, tumor size, and anticoagulation will increase this number of patients needed if not controlled for in the specific study. A multi-institutional study specifically designed to examine the role of prophylactic TAL in reducing post-TORS hemorrhage might provide more insight to the benefits of prophylactic TAL in the future.

CONCLUSION

The overall incidence of post-TORS hemorrhage (5.78%) in high-volume centers is low. The combined incidence of major hemorrhage requiring emergent embolization, TAL, or tracheotomy to control hemorrhage is even lower (2.90%). Large primary tumors, perioperative anticoagulation/antiplatelet therapy, and prior radiation were associated with significantly increased rates of post-TORS hemorrhage. TAL does not reduce the overall incidence of post-TORS hemorrhage but may lead to fewer major post-TORS hemorrhages.

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