Vascular Events in Patients with Head and Neck Cancer: a Systematic Review and Meta-Analysis

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BACKGROUND

- Head and neck cancer (HNC) makes up roughly 4% of all cancers.[1] HNC causes significant morbidity, often secondary to oncologic resection, radiation, chemotherapy, or a combination of the three.
- Vascular events, including myocardial infarction (MI), cerebrovascular accident (CVA, stroke), deep vein thromboses (DVT), pulmonary embolism (PE), and hemorrhage, are devastating, often fatal, conditions that are highly prevalent nationally and globally.
- Thrombotic events are even more common in patients with cancer,[4,5] with an estimated rate of thrombotic events such as DVT of about 10% in all patients with cancer with an increased risk of death from DVT/PE.[5,7]
- The mechanism of cancer-related hypercoagulability is not completely understood; however, it is known that the production of procoagulants like tissue factor and inflammatory proteins plays a role.[8]
- In patients with HNC specifically, MI and stroke have been reported to be more common than the general population.[9,10] Possible differences have also been noted between HNC subsites, with nasopharyngeal and hypopharyngeal cancers having the highest risk for stroke and MI, respectively.[9]
- Reported rates of DVT in patients with HNC are variable but have mostly been reported to be around 3%.[11-13] Some studies suggest that there is a difference in vascular event rates between different HNC treatment modalities.[9,14] Radiation therapy (RT) has been reported to increase the risk of stroke in patients with HNC.[15] RT has also been reported to increase the risk for hemorrhage in patients with HNC.[16]
- The use of anticoagulation is inconsistent when it comes to chemoprophylaxis in patients with HNC, and its use in the postoperative period after head and neck surgery can be controversial due to balancing the risks of thrombosis versus bleeding.[19]
- We performed this systematic review and meta-analysis to investigate the prevalence of vascular events. Additionally, we investigated the effects of primary treatment modality and the use of prophylactic anticoagulation in this population.

METHODS

- This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Individual search strategies are detailed in supplemental data.
- Studies reporting vascular events of any type in patients with head and neck cancer were included. Abstracts were screened separately by two reviewers (NPM and KAD) to identify relevant articles.
- Vascular event outcomes and demographic data were extracted independently by two reviewers (NPM and KAD). Outcomes were extracted by HNC subsite when available.
- Meta-Analysis of continuous measures was perfomed using Comprehensive Meta-Analysis version 4(Biostat Inc, Englewood, NJ, USA). Meta-analysis of proportions and comparison of proportions were performed using MedCalc (MedCalc Software, Ostend, Belgium).

RESULTS

Table 1: Meta-Proportions of vascular event incidence in HNC patients

Vascular Event	Number of Subjects (n)	Incidence (%)	95% Confidence Interval (%)
DVT	625,644	1.2	0.9 – 1.5
PE	562,345	0.6	0.4 – 0.8
MI	762,344	2.0	1.6 – 2.5
CVA	842,494	2.7	2.1 – 3.4
TIA	16,697	2.9	1.9 – 4.3
IJVT	373	12.1	2.3 – 28.1
Major Bleed	188,271	3.2	2.2 – 4.4
Arterial Thrombosis	279	1.9	0.1 – 9.0
Overall Events	1,184,160	4.3	3.7 – 4.9

Table 2: Meta-Proportions of vascular event incidence in HNC patients on DVT chemoprophylaxis

Vascular Event	Number of Subjects (n)	Incidence (%)	95% Confidence Interval (%)
DVT	4,475	1.1	0.4 – 2.1
PE	3,383	1.1	0.4 – 2.2
MI	72	4.8	1.2 – 12.4
CVA	866	2.8	1.8 – 4.2
Major Bleed	1,863	2.4	0.6 – 5.3
Overall Events	5,580	4.6	2.7 – 7.0

Table 3: Comparison of proportions of vascular event incidence between overall group and group receiving DVT chemoprophylaxis

Vascular Event	Difference (%)	95% Confidence Interval (%)	p Value
DVT	0.1	-0.3 – 0.3	0.6053
PE	0.6	0.2 – 1.0	<0.0001*
MI	2.8	-0.3 – 10.4	0.0938
CVA	0.1	-0.8 – 1.3	0.8552
Major Bleed	0.8	-0.02 – 1.4	0.0538
Overall Events	0.3	-0.2 – 0.9	0.2299

Table 4: Meta-Proportions of vascular event incidence in HNC patients undergoing surgery as primary treatment modality

Vascular Event	Number of Subjects (n)	Incidence (%)	95% Confidence Interval (%)
DVT	620,899	1.0	0.8 – 1.4
PE	522,157	0.7	0.5 – 0.9
MI	690,845	1.5	1.0 – 2.0
CVA	587,936	0.9	0.7 – 1.3
IJVT	298	16.0	3.2 – 35.9
Major Bleed	323	2.3	1.3 – 3.6
Overall Events	917,250	2.6	2.2 – 3.0

Table 5: Meta-Proportions of vascular event incidence in HNC patients undergoing RT as primary treatment modality

Vascular Event	Number of Subjects (n)	Incidence (%)	95% Confidence Interval (%)
MI	334	1.1	0.3 – 2.8
CVA	71,575	6.5	3.3 – 10.6
TIA	5,332	2.4	1.2 – 4.1
Major Bleed	37,713	4.7	4.5 – 4.9
Overall Events	76,790	8.4	5.5 – 11.7

Table 6: Meta-Proportions of vascular event incidence in HNC patients undergoing chemotherapy as primary treatment modality

Vascular Event	Number of Subjects (n)	Incidence (%)	95% Confidence Interval (%)
DVT	213	2.9	0.1 – 9.9
PE	65	2.1	0.1 – 9.0
MI	634	2.3	1.3 – 3.8
CVA	17,442	5.1	3.8 – 6.6
TIA	85	13.7	7.3 – 22.8
Major Bleed	401	2.0	0.9 – 3.9
Overall Events	18,739	5.1	3.7 – 6.6

Table 7: Comparison of proportions of vascular event incidence between primary treatment types

Vascular Event	Difference (%)	95% Confidence Interval (%)	p Value
DVT			
S vs C	1.9	0.3 – 5.1	0.0067*
PE			
S vs C	1.4	-0.2 – 8.4	0.1513
MI			
S vs R	0.4	-1.4 – 1.1	0.5585
S vs C	0.8	-0.1 – 2.3	0.0816
R vs C	1.2	-0.8 – 2.8	0.1854
CVA			
S vs R	5.5	5.4 – 5.7	<0.0001*
S vs C	4.1	3.8 – 4.5	<0.0001*
R vs C	1.4	1.0 – 1.8	<0.0001*
TIA			
R vs C	11.3	5.5 – 20.2	<0.0001*
Major Bleed			
S vs R	2.4	2.2 – 2.6	<0.0001*
S vs C	0.3	-1.6 – 1.3	0.7029
R vs C	2.7	0.8 – 3.7	0.0119*
Overall Events			
S vs R	5.8	5.6 – 6.0	<0.0001*
S vs C	2.5	2.2 – 2.8	<0.0001*
R vs C	3.3	2.9 – 3.7	<0.0001*

INCLUDED STUDIES AND DEMOGRAPHICS

A total of 146 studies were ultimately included in our meta-analysis. A PRISMA diagram outlining our search is shown in Figure 1. Studies were published from 1976 to 2023 and were conducted in 22 unique countries. Descriptions of the individual studies and selected patient characteristics can be found in supplemental data. Critical appraisal of studies indicated an acceptably low risk of bias (supplemental data). Potential sources of bias were most pronounced in bias arising from measurement of the exposure, bias in selection of participants, and bias arising from measurement of the outcome. A funnel plot with Egger's test (1.36, 95%CI: -0.42 to 3.14, p = 0.1315) demonstrated all studies lie within the funnel with little asymmetry, suggesting little risk for publication bias (supplemental data). There was a total of 1,184,160 patients included in our meta-analysis, including 72.2% males, with a mean age of 58.4 years (range: 17 to 104, 95%CI: 56.9 to 60.0, p = 0.00). Of 160,449 patients with reported race, 77.3% (95%CI: 70.6 to 83.4) were white, 7.8% (95%CI: 6.7 to 9.1) were Black, 17.5% (95%CI: 9.5 to 27.3) were another race or ethnicity, and 3.5% (95%CI: 0.5 to 9.2) were unknown. Primary HNC subsites consisted of Oral Cavity 31.2% (95%CI: 20.0 to 43.7), Oropharynx 13.4% (95%CI: 10.0 to 17.1), Hypopharynx 6.0% (95%CI: 3.9 to 8.5), Larynx 14.0% (95%CI: 10.4 to 18.1), Nasopharynx 13.4% (95%CI: 6.7 to 21.8), Salivary 1.9% (95%CI: 0.8 to 3.5), Sinus 1.5% (95%CI:1.0 to 2.2), Nasal Cavity 1.5% (95%CI: 0.8 to 2.5), Ear 0.03% (95%CI: 0.01 to 0.06), and other 5.7% (95%CI: 2.7 to 9.8). Of patients with reported staging, 7.5% (95%CI: 4.1 to 11.7) were AJCC stage I, 13.6% (95%CI: 10.9 to 16.5) were stage II, 20.6% (95%CI: 17.0 to 24.4) were stage III, 54.8% (95%CI: 48.5 to 61.0) were stage IV, and 2.9% (95%CI: 1.2 to 5.3) were unknown.

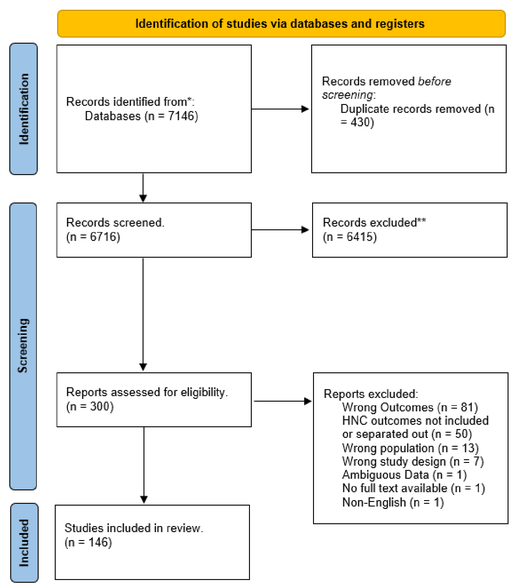

Figure 1: PRISMA Diagram of Included Studies

CONCLUSIONS

Vascular events occur in 4-5% of patients with HNC. Our data does not support the use of universal anticoagulation for chemoprophylaxis in these patients. Additionally, we found that RT could put patients at the highest risk for vascular events, especially CVA, followed by chemotherapy at intermediate risk, and surgery at lowest risk for vascular events. We did not appreciate a reduction in event frequency in those receiving DVT chemoprophylaxis; however, given our small sample size in the group that received chemoprophylaxis, we do not feel that we can make strong recommendations at this time and further prospective analyses are needed. We support close surveillance in this population, especially those who are primarily receiving non-surgical HNC therapy. Diligent optimization of risk factors for stroke must be a focus to minimize the risk of devastating injury, which likely requires the involvement of a multidisciplinary team.

REFERENCES and SUPPLEMENTAL DATA

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