# Increased risk of stroke in young head and neck cancer patients treated with radiotherapy or chemotherapy

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## ARTICLE INFO

## SUMMARY

*Background:* Chemo-radiotherapy-induced carotid stenosis and cerebrovascular events in head and neck cancer patients can cause severe disability and death. We aimed to estimate the risk of stroke in such patients over a six-year follow-up period.
*Patients and methods:* The study cohort consisted of head and neck cancer patients ($n$ = 10,172). Cox proportional hazard model was used to compare the stroke-free survival rate between the patients treated with radiotherapy or chemotherapy, surgery alone, and surgery with adjuvant therapy after adjusting for possible confounding factors.
*Results:* At the end of follow-up, 384 patients had strokes: 126 (4.3%) from the surgery alone group, 167 (3.8%) from the radiotherapy or chemotherapy group, and 91 (3.2%) from the surgery with adjuvant therapy ($P$ = 0.222). Head and neck cancer patients aged less than 55 years treated with radiotherapy or chemotherapy conferred a 1.8-fold higher risk for stroke (95% CI, 1.22–2.56; $P$ = 0.003) after adjusting for patient characteristics, co-morbidities, geographic region, urbanization level, and socio-economic status. There was no statistical difference in stroke risk between different treatment modalities in head and neck cancer patients aged 55 years and more.
*Conclusions:* Young head and neck cancer patients treated with radiotherapy or chemotherapy have higher risks for stroke. Different treatment strategies should be considered in such patients.
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## Introduction

Head and neck cancer accounts for about 3–5% of all cancers in the United States.[1,2] Organ-preserving strategies using either radiotherapy alone or concurrent chemo-radiotherapy (CCRT) with or without target therapy have been increasingly integrated into first-line therapy for head and neck cancer with loco-regionally advanced stage or oropharyngeal cancer.[3–5]

Several studies suggest that neck irradiation or cisplatin-based chemotherapy for cancer increase the incidence of stroke.[6–9] Dorresteijn et al. report that the relative risk of ischemic stroke in patients with early stage laryngeal cancer and parotid gland tumor after radiotherapy is 10 times that of an age- and gender-matched population of patients aged < 60 years.[10] In head and neck cancer patients aged ⩾ 65 years, the incidence of cerebrovascular events within 10 years of diagnosis is 33% for those treated with radiotherapy alone, compared to 25% for those treated with surgery.[11] However, the risk for developing stroke in all head and neck cancer patients treated with radiotherapy or chemotherapy remains unclear.[12,13]

This study seeks to determine the incidence of stroke in such patients identified through the National Health Insurance (NHI) Research Database in Taiwan. This allows for a comparison of risk of stroke between head and neck cancer patients who underwent

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different treatment modalities, and provides a chance to outline long-term follow-up suggestions for head and neck cancer patients treated by radiotherapy or chemotherapy.

## Material and methods

### Database

This study used the 2001–2007 National Health Insurance Research Database (NHIRD), published by Taiwan's National Health Research Institutes. The NHIRD covered the medical benefit claims for approximately 97% of the Taiwanese population, and contains a registry of board-certified physicians and contracted medical facilities. The database does not contain information on tobacco use, dietary habits, and body mass index. Since this data consists of de-identified secondary data released to the public for research, this study was exempted from full review by the Institutional Review Board.

The study cohort consisted of patients with head and neck cancer (identified according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 140.0–148.9) aged 20 years and more who had undergone surgery, radiotherapy, chemotherapy, chemo-radiotherapy, or surgery with adjuvant therapy in 2001 and 2002. Patients with any type of stroke (ICD-9-CM 430–438) diagnosed before or during the index admission were excluded. A total of 10,172 patients with head and neck cancer were identified.

### Measurements

The primary dependent variable in the study was stroke. Using administrative data to identify all patients who developed stroke (ICD-9-CM codes 430–438), each patient was tracked from initial treatment in 2001 and 2002 for a six-year period. Patients were then linked to the death data covering the years 2001–2007 to calculate the stroke-free survival time, with cases censored if the patients died from non-stroke causes during follow-up. We compared the outcomes for patients who underwent surgery alone, radiotherapy/chemotherapy/chemoradiotherapy, or surgery with adjuvant therapy. The three groups were analyzed separately to account for the likelihood that patients who undergo radiotherapy or chemoradiotherapy may receive higher radiation dose or other predisposing factors for stroke, such as chemotherapy regimen, than the patients undergoing surgery with or without adjuvant therapy. Age of 55 was used to divide the patients as young and old head and neck cancer patients according to the American Heart Association scientific statement on cardiovascular risk factors.[14]

The independent variables were gender, co-morbidities, geographic area of residence, urbanization level, and socio-economic status. Details on co-morbid medical disorders, including hypertension, diabetes, coronary artery disease, hyperlipidemia, and atrial fibrillation, were extracted from the claims data at the time of index discharge and were associated with stroke. This study used enrollee category (EC) in insurance as a proxy measure of socio-economic status, which was an important prognostic factor for stroke.[15] The head and neck cancer patients were classified into four sub-groups: EC 1 (civil servants, regular or full-time paid personnel with a government affiliation), EC2 (employees of privately owned institutions, EC3 (self-employed individuals, members of the farmers; or fishermen's association, and other employees), and EC4 (veterans, substitute service draftees, and members of low-income families).[16]

Geographic region and urbanization level were reportedly associated with stroke and were therefore included.[17–19] The level of

urbanization was recorded as urban, and sub-urban (urbanization level 1–3), or rural (urbanization level 4–7).

### Statistical analysis

The SAS statistical package (version 9.2; SAS Institute, Inc., Cary, NC, USA), and SPSS (version 15, SPSS Inc., Chicago, IL,

**Table 1**
Head and neck cancer site by treatment groups.

| Cancer site | Total (n = 10,172) | Treatment groups | | |
|---|---|---|---|---|
| | | Surgery alone (n = 2901) | RT/CT/CRT (n = 4391) | Surgery with adjuvant therapy (n = 2880) |
| | No. (%) | No. (%) | No. (%) | No. (%) |
| Oral cavity | 6124(60) | 2549(42) | 1177(19) | 2398(39) |
| Oropharynx | 511(5) | 69(14) | 318(62) | 124(24) |
| Hypopharynx | 801(8) | 92(11) | 558(70) | 151(19) |
| Nasopharynx | 2105(21) | 16(1) | 2079(99) | 10(0.5) |
| Nasal cavity and sinus | 226(21) | 27(12) | 175(78) | 23(10) |
| Salivary gland | 352(4) | 130(37) | 60(17) | 162(46) |
| Other | 54(0.5) | 18(33) | 24(44) | 12(22) |

RT, radiotherapy; CT, chemotherapy; CRT, chemoradiotherapy.

**Table 2**
Demographic characteristics for head and neck cancer patients by treatment modality.

| Variables | Surgery alone (n = 2901) n (%) | RT/CT/CRT (n = 4391) n (%) | Surgery with adjuvant therapy (n = 2880) n (%) | P value |
|---|---|---|---|---|
| Gender | | | | <0.001 |
| Male | 2550(87.9) | 3598(81.9) | 2618(90.9) | |
| Female | 351(12.1) | 793(18.1) | 262(9.1) | |
| Age, yr. | | | | <0.001 |
| <45 | 746(25.7) | 1299(29.6) | 828(28.8) | |
| 45–54 | 932(32.1) | 1440(32.8) | 1042(36.2) | |
| 55–64 | 653(22.5) | 866(19.7) | 615(21.4) | |
| 65–74 | 426(14.7) | 559(12.7) | 308(10.7) | |
| >75 | 144(5.0) | 227(5.2) | 87(19.0) | |
| Tumor characteristics | | | | <0.001 |
| Localized/locoregional | 2782(95.9) | 3744(85.3) | 2732(94.9) | |
| Distant metastasis | 119(4.1) | 647(14.7) | 148(5.1) | |
| Hypertension | | | | 0.613 |
| Yes | 137(4.7) | 228(5.2) | 150(5.2) | |
| No | 2764(95.3) | 4163(94.8) | 2730(94.8) | |
| Diabetes | | | | 0.101 |
| Yes | 166(5.7) | 227(5.2) | 183(6.4) | |
| No | 2735(94.3) | 4164(94.8) | 2697(93.6) | |
| Coronary heart disease | | | | 0.015 |
| Yes | 51(1.8) | 44(1.0) | 45(1.6) | |
| No | 2850(98.2) | 4347(99.0) | 2835(98.4) | |
| Hyperlipidemia | | | | 0.057 |
| Yes | 8(0.3) | 18(0.4) | 3(0.1) | |
| No | 2893(99.7) | 4373(99.6) | 2877(99.9) | |
| Atrial fibrillation | | | | 0.977 |
| Yes | 6(0.2) | 10(0.2) | 6(0.2) | |
| No | 2895(99.8) | 4381(99.8) | 2874(99.8) | |
| Enrollee category | | | | <0.001 |
| EC 1–2 | 1152(39.7) | 1918(43.7) | 1133(39.3) | |
| EC 3–4 | 1749(60.3) | 2473(56.3) | 1747(60.7) | |
| Geographic | | | | <0.001 |
| Northern/Central | 1822(62.4) | 3047(68.9) | 1901(65.7) | |
| Southern/Eastern | 1100(37.6) | 1378(31.1) | 993(34.3) | |
| Urbanization | | | | 0.472 |
| Rural | 876(30.0) | 1280(28.9) | 871(30.1) | |
| Urban and suburban | 2046(70.0) | 3145(71.1) | 2023(69.9) | |

RT, radiotherapy; CT, chemotherapy; CRT, chemoradiothearpy; EC, enrolled category.