



Radiation-induced carotid artery stenosis and brain necrosis for nasopharyngeal cancer need to be concerned

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INTRODUCTION

Radiotherapy (IMRT)-induced carotid artery stenosis (CAS) and brain necrosis (BN) are late life-threatening complications that can develop after treatment in patients with nasopharyngeal carcinoma (NPC). However, there are limited data reporting the risk and prevention strategies of CAS or BN in patients receiving radiotherapy for NPC.

AIM

The aim of this study was to examine the incidence and risk factors of radiation-induced carotid stenosis in a large real-world database, brought to the attention of junior radiation oncologists.

METHOD

We identified a cohort of HNC patients from the catastrophic illness patient dataset of Taiwan National Health Insurance Research Database (NHIRD) using ICD-9 or ICD-10 to investigate the incidences of radiotherapy induced carotid artery stenosis and brain necrosis as well as its risk factors among HNC patients between January 2005 and December 2018. The cohort of HNC patients was identified as an exposure and non-exposure group. Patients who received radiotherapy or did not receive radiotherapy were defined as exposure or non-exposure group, respectively. Propensity-score matching analysis was performed with a 1:1 ratio to reduce baseline difference between the two groups. The incidence and hazard ratios were quantified using Cox proportional hazards models.

REFERENCES

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- Liu CH, Chang JT, Lee TH, Chang PY, et al. Total plaque score helps to determine follow-up strategy for carotid artery stenosis progression in head and neck cancer patients after radiation therapy. PLoS One. 2021 Feb 12;16(2):e0246684.**

RESULTS

A total of 65,880 HNC patients were included in our study. Among them, there were 27194 patients who received radiotherapy and 38,686 patients who did not receive radiotherapy. After propensity score matching analysis, there were 19,964 patients identified as the exposed and non-exposed groups. We found 863 and 965 cases of CAS and 435 and 359 cases of brain nevrosis in the exposed and non-exposed groups, respectively. The incidence rates of CAS and BN were 8.57 and 8.61 cases/1000 person/year, and 4.26 and 3.13 cases/1000 person/year in the exposed and non-exposed groups, respectively. There was no significantly increased risk of CAS in exposure group compared with the non-exposure group (HR=1.05; 95% CI: 0.95-1.16, p=0.329). Patients with HNC who received radiotherapy had a significantly increased risk of brain necrosis compared with patients who did not receive radiotherapy (HR=1.29;95% CI: 1.11-1.5, p< 0.001) (Table 1). In a multivariate logistic regression model comparing the radiotherapy and non-radiotherapy groups, male patients aged 20-59 with grade 1 and 2 tumors or followed-up for more than 6 years were found to be associated with a significantly increased risk of CAS and RIBN (Table 2).

Table 1. Risk of Carotid Artery Stenosis and BN associated with radiotherapy and covariates									
Carotid Artery Stenosis									
Variable	N	PV	IR	cHR	(95% CI)	p-value	aHR	(95% CI)	p-value
Radiotherapy									
No	965	112077.72	8.61	1.00	(reference)	-	1.00	(reference)	-
Yes	863	100648.57	8.57	1.03	(0.94, 1.13)	0.525	1.05	(0.95, 1.16)	0.329
Gender									
female	250	35636.74	7.02	1.00	(reference)	-	1.00	(reference)	-
male	1578	377089.55	8.91	1.34	(1.17, 1.53)***	<0.001	1.44	(1.36, 1.60)***	<0.001
Age, year									
20-59	950	147311.82	6.45	1.00	(reference)	-	1.00	(reference)	-
60+	878	65414.46	13.42	2.13	(1.95, 2.34)***	<0.001	1.66	(1.51, 1.83)***	<0.001
Mean, (SD)				1.04	(1.04, 1.05)***	<0.001	1.03	(1.03, 1.04)***	<0.001
Primary site									
Oropharynx	13	1525.20	8.52	1.00	(reference)	-	1.00	(reference)	-
Nasopharyngeal	181	22256.50	8.13	0.89	(0.51, 1.57)	0.695	1.05	(0.58, 1.90)	0.862
Hypopharynx	37	4449.10	8.32	0.98	(0.52, 1.84)	0.943	0.94	(0.50, 1.76)	0.836
Larynx	13	1934.67	6.72	0.85	(0.39, 1.83)	0.671	0.67	(0.31, 1.44)	0.299
Oral cavity	8	3047.80	2.62	0.29	(0.12, 0.70)**	0.006	0.32	(0.15, 0.78)*	0.012
Other	1576	179513.01	8.78	0.89	(0.52, 1.54)	0.677	0.85	(0.49, 1.47)	0.561
Comorbidities									
Hypertension	694	58765.59	11.81	1.64	(1.48, 1.81)***	<0.001	1.17	(0.96, 1.38)**	0.002
Cerebrovascular events	35	1887.18	18.55	2.22	(1.58, 3.13)***	<0.001	1.37	(0.88, 1.93)	0.065
Hypertension	1035	78685.54	13.15	2.31	(2.16, 2.47)***	<0.001	1.71	(1.55, 1.89)***	<0.001
Coronary artery disease	456	34278.67	14.04	1.87	(1.68, 2.08)***	<0.001	1.12	(0.99, 1.26)	0.070
Atrial Fibrillation									
myocardial infarction	26	2589.32	10.04	1.36	(0.93, 2.01)	0.116	0.80	(0.53, 1.18)	0.260
Peripheral artery disease	35	2717.43	12.88	1.57	(1.12, 2.19)**	0.008	1.10	(0.79, 1.54)	0.574
Smoking	56	7481.59	7.49	0.95	(0.73, 1.24)	0.719	0.97	(0.74, 1.27)	0.838
The Charlson comorbidity index, CCI									
0-2	1251	157356.67	7.95	1.00	(reference)	-	1.00	(reference)	-
3+	577	55389.61	10.42	1.43	(1.29, 1.58)***	<0.001	1.09	(0.99, 1.21)	0.088
Tumor Grade									
1	144	24243.78	5.94	1.00	(reference)	-	1.00	(reference)	-
2	298	47113.45	6.33	1.09	(0.89, 1.33)	0.390	1.08	(0.88, 1.32)	0.450
3	88	12068.65	7.29	1.28	(0.98, 1.66)	0.072	1.20	(0.92, 1.58)	0.179
4	121	15524.15	7.79	1.36	(1.07, 1.73)**	0.012	1.36	(0.98, 1.88)	0.063
X	1177	113776.25	10.34	1.64	(1.38, 1.95)***	<0.001	1.60	(1.34, 1.91)***	<0.001
Brain Necrosis (BN)									
Variable	N	PV	IR	cHR	(95% CI)	p-value	aHR	(95% CI)	p-value
Radiotherapy									
No	359	114571.10	3.13	1.00	(reference)	-	1.00	(reference)	-
Yes	435	102141.81	4.26	1.46	(1.27, 1.68)***	<0.001	1.29	(1.11, 1.5)**	<0.001
Gender									
female	124	36211.08	3.42	1.00	(reference)	-	1.00	(reference)	-
male	670	180501.34	3.71	1.24	(1.02, 1.50)*	0.028	1.28	(1.06, 1.56)*	0.012
Age, year									
20-59	503	149255.57	3.37	1.00	(reference)	-	1.00	(reference)	-
60+	291	67456.84	4.31	1.33	(1.15, 1.54)***	<0.001	1.16	(0.99, 1.35)	0.067
Mean, (SD)				1.02	(1.01, 1.03)***	<0.001	1.01	(1.01, 1.03)***	<0.001
Primary site									
Oropharynx	7	1545.29	4.53	1.00	(reference)	-	1.00	(reference)	-
Nasopharyngeal	113	22433.71	4.95	1.05	(0.49, 2.24)	0.309	0.88	(0.39, 2.00)	0.760
Hypopharynx	18	4470.40	4.03	0.87	(0.36, 2.09)	0.759	0.83	(0.35, 1.98)	0.679
Larynx	6	1948.32	3.08	0.88	(0.30, 1.63)	0.822	0.73	(0.24, 2.17)	0.565
Oral cavity	10	3051.79	3.38	0.68	(0.36, 1.30)	0.432	0.77	(0.29, 2.02)	0.591
Other	642	183282.91	3.50	0.50	(0.24, 1.06)	0.069	0.56	(0.26, 1.18)	0.124
Comorbidities									
Diabetes	280	60331.79	4.56	1.49	(1.363, 1.70)**	<0.001	1.16	(1.01, 1.37)**	0.046
Hypertension	281	60341.79	4.66	1.51	(1.331, 1.70)**	<0.001	1.18	(1.01, 1.39)**	0.041
Cerebrovascular events	9	1968.25	4.57	1.27	(0.66, 2.44)	0.480	0.93	(0.48, 1.79)	0.822
Hypertension	395	81100.88	4.87	1.80	(1.57, 2.07)***	<0.001	1.60	(1.37, 1.88)***	<0.001
Coronary artery	158	33593.77	4.64	1.37	(1.15, 1.64)**	<0.001	0.94	(0.77, 1.14)	0.519
Atrial Fibrillation	16	2013.67	7.95	2.65	(1.62, 4.39)***	<0.001	1.89	(1.14, 3.14)*	0.014
Myocardial infarction	10	2635.58	3.79	1.42	(0.76, 2.65)	0.272	1.01	(0.55, 1.92)	0.984
Peripheral artery disease	14	2793.47	5.01	1.53	(0.90, 2.60)	0.112	1.23	(0.72, 2.09)	0.451
Smoking	32	7541.60	4.24	1.54	(1.08, 2.20)**	0.017	1.47	(1.03, 2.11)*	0.033

Table 2. Comparison of CAS and RIBN risks in radiotherapy and non-radiotherapy groups associated with all covariates												
Carotid Artery Stenosis												
Covariates	No			Yes			cHR	(95% CI)	p-value	aHR	(95% CI)	p-value
	N	PV	IR	N	PV	IR						
Sex												
female	153	18307.19	8.36	97	17329.54	5.60	0.68	(0.52, 0.87)**	0.003	0.67	(0.51, 0.88)**	0.004
male	812	93770.53	8.66	766	83319.02	9.19	1.11	(1.01, 1.22)*	0.045	1.12	(1.01, 1.25)*	0.029
Age, year												
20-59	474	77766.23	6.10	476	69545.60	6.84	1.17	(1.03, 1.33)*	0.015	1.21	(1.06, 1.38)**	0.006
60+	491	34311.49	14.31	387	31102.97	12.44	0.89	(0.78, 1.02)	0.095	0.91	(0.79, 1.05)	0.199
Primary site												
Oropharynx+Oml cavity+S	5	1691.48	2.96	16	2881.52	5.55	1.58	(0.57, 4.36)	0.375	1.19	(0.42, 3.38)	0.744
Nasopharyngeal	39	4310.18	9.05	142	17946.32	7.91	0.74	(0.51, 1.05)	0.094	0.70	(0.48, 1.00)	0.050
Hypopharynx	6	931.13	6.44	31	3517.98	8.81	1.29	(0.54, 3.10)	0.565	1.20	(0.5, 2.91)	0.682
Larynx	5	619.84	8.07	8	1314.83	6.08	0.73	(0.24, 2.23)	0.575	0.71	(0.23, 2.20)	0.552
Other	910	104525.10	8.71	666	74987.91	8.88	1.05	(0.95, 1.16)	0.326	1.08	(0.98, 1.20)	0.134
Comorbidities												
Hyperlipidemia	359	30881.39	11.63	335	27884.21	12.01	1.07	(0.92, 1.24)	0.403	1.08	(0.92, 1.26)	0.367
Cerebrovascular events	19	933.34	20.36	16	953.84	16.77	0.83	(0.42, 1.61)	0.578	0.53	(0.24, 1.19)	0.123
Hypertension	556	41429.13	13.42	479	37256.41	12.86	0.99	(0.87, 1.11)	0.823	1.01	(0.89, 1.15)	0.916
Coronary artery disease	259	17059.20	15.18	197	15419.47	12.78	0.86	(0.72, 1.04)	0.114	0.87	(0.72, 1.06)	0.179
Atrial Fibrillation	14	976.24	14.34	21	976.06	21.52	1.57	(0.8, 3.08)	0.194	1.48	(0.72, 3.06)	0.289
Myocardial infarction	18	1411.83	12.75	8	1177.48	6.79	0.54	(0.23, 1.23)	0.143	0.48	(0.19, 1.19)	0.111
Peripheryl artery disease	23	1401.08	16.42	12	1316.35	9.12	0.55	(0.27, 1.11)	0.096	0.42	(0.18, 0.98)*	0.045
Smoking	23	4011.90	5.73	33	3469.68	9.51	1.76	(1.03, 3.00)*	0.038	1.39	(0.78, 2.49)	0.261
Charlson comorbidity index, CCI												
0-2	651	82576.10	7.88	690	71780.58	8.02	1.05	(0.94, 1.18)	0.359	1.07	(0.95, 1.20)	0.264
3+	314	29501.62	10.64	263	25667.99	10.17	0.99	(0.84, 1.17)	0.928	1.01	(0.85, 1.20)	0.938
Tumor Grades												
1	75	15398.33	4.87	69	8845.46	7.80	1.59	(1.14, 2.2)**	0.008	1.50	(1.07, 2.10)*	0.018
2	110	20886.15	5.27	188	26227.29	7.17	1.36	(0.97, 1.91)*	0.011	1.28	(1.01, 1.62)*	0.042
3	26	3448.74	7.54	62	8619.91	7.19	0.92	(0.58, 1.45)	0.719	0.97	(0.60, 1.57)	0.804
4	28	3334.23	8.93	93	12389.93	7.51	0.70	(0.46, 1.08)	0.112	0.71	(0.46, 1.10)	0.124
5	726	87122.27	10.49	451	44655.98	10.12	1.00	(0.89, 1.13)	0.945	0.99	(0.88, 1.12)	0.927
Follow-up interval												
<6 years	707	69142.65	8.11	558	80585.86	6.92	0.88	(0.79, 0.98)*	0.023	0.89	(0.79, 1.00)	0.051
6+ years	258	24935.07	10.35	305	20963.31	15.20	1.47	(1.25, 1.74)**	<0.001	1.48	(1.24, 1.76)**	<0.001
Brain Necrosis												
Covariates	No			Yes			cHR	(95% CI)	p-value	aHR	(95% CI)	p-value
	N	PV	IR	N	PV	IR						
Sex												
female	57	18755.69	3.04	67	17455.39	3.84	1.31	(0.92, 1.86)	0.134	1.10	(0.75, 1.62)	0.615
male	302	95815.41	3.15	368	84685.92	4.35	1.50	(1.29, 1.75)**	<0.001	1.32	(1.13, 1.56)**	<0.001
Age, year												
20-59	210	79025.02	2.66	293	70240.55	4.17	1.69	(1.42, 2.02)**	<0.001	1.47	(1.22, 1.78)**	<0.001
60+	149	35546.08	4.19	142	31910.76	4.45	1.15	(1.01, 1.40)	0.244	1.04	(0.81, 1.32)	0.771
Primary site												
Oropharynx+Larynx+Oml c	3	2324.08	1.29	20	4221.31	4.74	3.33	(0.99, 11.21)	0.053	2.87	(0.83, 9.87)	0.095
Nasopharyngeal	19	4356.60	4.36	92	18057.11	5.09	0.87	(0.53, 1.43)	0.586	0.89	(0.54, 1.47)	0.651
Hypopharynx	3	930.26	3.22	15	350.12	4.24	1.25	(0.36, 3.40)	0.729	1.24	(0.35, 4.35)	0.782
Other	334	10690.13	3.12	308	76322.78	4.04	1.33	(1.14, 1.56)**	<0.001	1.31	(1.12, 1.53)**	<0.001
Comorbidities												
Hyperlipidemia	131	31811.07	4.12	150	28530.72	5.26	1.35	(1.07, 1.71)*	0.011	1.18	(0.91, 1.51)	0.207
Cerebrovascular events	4	981.00	4.08	5	987.25	5.06	1.46	(0.39, 5.84)	0.573	1.00	(0.21, 4.83)	0.996
Hypertension	190	42853.58	4.43	205	38247.29	5.36	1.29	(1.06, 1.57)*	0.012	1.16	(0.94, 1.43)	0.170
Coronary artery disease	81	17728.01	4.57	75	15864.75	4.73	1.10	(0.80, 1.50)	0.556	0.94	(0.67, 1.31)	0.701
Atrial Fibrillation	13	980.87	15.25	3	1032.80	2.90	0.23	(0.06, 0.79)	0.020	0.17	(0.04, 0.68)*	0.013
Myocardial infarction	5	1452.45	3.44	5	1183.13	4.23	1.50	(0.43, 5.21)	0.528	0.59	(0.12, 2.99)	0.525
Peripheryl artery disease	6	1475.87	4.07	8	1317.60	6.07	1.82	(0.63, 5.27)	0.272	1.58	(0.43, 5.83)	0.491
Smoking	15	4024.76	3.73	17	3516.84	4.83	1.46	(0.73, 2.93)	0.282	1.62	(0.78, 3.39)	0.197
The Charlson comorbidity index, CCI												
0-2	248	84411.51	2.94	322	75796.84	4.25	1.56	(1.33, 1.85)**	<0.001	1.37	(1.15, 1.64)**	<0.001
3+	111	30159.59	3.68	113	26344.48	4.29	1.25	(0.96, 1.63)	0.091	1.10	(0.83, 1.45)	0.509
Tumor Grades												
1	31	15779.88	1.99	35	8966.53	3.89	1.83	(1.13, 2.97)*	0.014	1.59	(0.96, 2.63)	0.073
2	54	21059.35	2.56	103	26043.83	3.89	1.50	(1.08, 2.08)*	0.016	1.47	(1.06, 2.06)*	0.022
3	9	3492.18	2.58	21	8749.98	2.40	0.87	(0.40, 1.90)	0.738	0.80	(0.35, 1.82)	0.592
4	17	3155.61	5.39	71	12443.13	5.71	0.77	(0.45, 1.31)	0.326	0.75	(0.43, 1.28)	0.291
5	248	71267.08	3.48	205	45510.84	4.50	1.33	(1.10, 1.60)**	0.003	1.27	(1.05, 1.54)*	0.012
Follow-up interval												
<6 years	165	82661.59	1.87	174	81239.71	2.14	1.20	(0.97, 1.48)	0.098	0.89	(0.71, 1.12)	0.333
6+ years	194	26309.51	7.37	261	20901.60	12.49	1.70	(1.42, 2.05)**	<0.001	1.67	(1.38, 2.03)**	<0.001