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Review Article

Carotid stenosis prevalence after radiotherapy in nasopharyngeal carcinoma: A meta-analysis

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ABSTRACT

Purpose: Radiotherapy (RT) is the most effective treatment for nasopharyngeal carcinoma (NPC) but may cause stenosis of the carotid arteries. This meta-analysis evaluates the prevalence of carotid stenosis after radiation therapy.

Materials and methods: Online search for studies reporting carotid stenosis in patients with NPC who received radiation therapy (RT) compared to NPC patients who did not receive RT and compared to healthy controls.

Results: Twelve studies were included for a total analysis of 1928 patients (837 received RT and 1091 were controls). RT patients showed a statistically significant higher incidence of overall stenosis (pooled risk ratio = 4.17 [2.44, 7.10], $p < 0.00001$) and an even greater incidence of significant stenosis (50% or more) (pooled risk ratio = 8.72 [3.53, 21.55], $p < 0.00001$). Analyzing by individual blood vessels showed that the RT patients had significantly higher incidence of stenosis in common carotid artery (CCA), external carotid artery (ECA), carotid bulb, CCA and internal carotid artery (ICA), and CCA/ICA/carotid bulb.

Conclusions: NPC patients who receive RT have increased risk of developing carotid stenosis, and should be screened after treatment.

Nasopharyngeal carcinoma (NPC) is among the most common head and neck cancers in southern China, affecting 15–50 per 100,000 people [1,2]. Because NPC is highly radiosensitive, radiotherapy (RT) is an effective treatment [3]. However, with the 5-year survival rate now above 50%, late complications such as those reported in our previous work (optic neuropathy, brachial plexus injury and brain necrosis) [4–6] are an increasing problem.

RT contributes to atherosclerosis of the irradiated vessels and increases the risk of vascular stenosis, which may lead to transient ischemic attacks (TIA) or ischemic stroke [7]. Radiation-induced carotid stenosis involves arterial wall thickening and plaque which are histologically similar to spontaneous atherosclerosis. However, carotid stenosis is more likely to occur in the irradiated area and can develop in patients without atherosclerosis risk factors [8,9].

RT is a well-documented independent risk factor for carotid stenosis in NPC patients [10]. A study by Lam et al. of 71 NPC patients after radiation therapy reported that 30% had carotid stenosis [11]. For comparison, in a population-wide screening of 22,636 asymptomatic individuals, the prevalence of carotid stenosis was only 4.2% [12].

This meta-analysis was designed to further examine the effects of radiation therapy for NPC on carotid stenosis risk. We also subdivided the results by blood vessel and region (common carotid artery (CCA), internal carotid artery (ICA), external carotid artery (ECA), and CCA/ICA/carotid bulb together).

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [13].

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Eligibility criteria

Eligible studies were case control studies and observational studies of extra-cranial carotid artery (ECCA) stenosis in patients who received radiation therapy (RT) as treatment for NPC. All studies compared RT-treated patients with a non-irradiated control group. We excluded case series and review articles.

Search strategy

On Nov 5th, 2017 we searched Medline, Web of Science, EMBASE, and the Cochrane library for the following terms: [“carotid stenosis” OR “plaque” OR “atherosclerosis” OR “occlusion”] AND [“Nasopharyngeal Carcinoma” OR “Nasopharyngeal Neoplasm” OR “Nasopharyngeal Tumor” OR “Nasopharyngeal Cancer”]. Results were limited to English language and human subjects but were not restricted by publication date or status. Bibliographies of included trials were searched for additional studies. A summary of the study selection process can be found in the PRISMA flow chart (Fig. 1).

The main outcome of interest for this review was the number of patients with carotid stenosis. Secondary outcomes of interest were blood vessels affected and the incidence of severe stenosis, as defined by the individual studies. Two authors (WL, YZ) independently evaluated the abstracts of prospective articles for these criteria, settling any discrepancies with a third author (SB), then obtained the full texts of all articles to be used.

Data collection

Two reviewers independently compiled the raw data in Microsoft Excel (WL, YZ). Any discrepancies in the extracted data were discussed between the authors and settled by consulting a third author (SB) if necessary. We recorded demographics of age and sex, co-morbid conditions, radiotherapy dose, time interval from RT to the first stenosis scan, number of abnormal scans, and the incidence and severity of stenosis in ECCAs. Cerebrovascular accidents (CVA), defined as stroke or transient ischemic attack (TIA), were also recorded whenever possible (Table 1).

Quality assessment and statistical analysis

Studies were scored with zero to nine stars using the modified Newcastle–Ottawa scale (NOS) [14], which has three domains: cohort selection, cohort comparability, and assessments of exposure and outcome. Meta-analysis was performed with Review

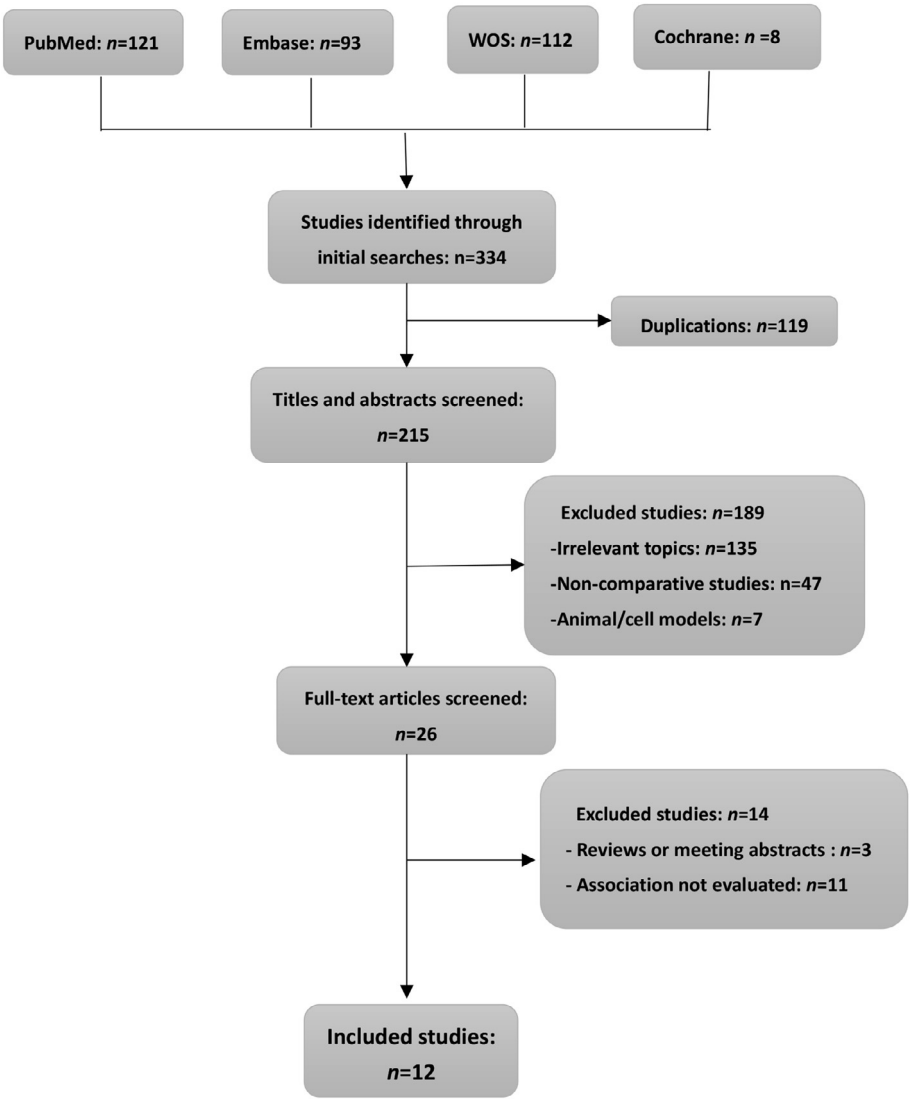

Fig. 1. Flow chart of study selection.

Table 1
Demographic characteristics of included studies.

Study	Year	Matching*	Population	Radiation dose (Gy)	Interval from radiotherapy (years)	Subjects (n)		Average age (years old)		Quality score
						Post-RT NPC	CTRL	Post-RT NPC	CTRL	
Zhou et al.	2015	1–9	China	66.0	5.7 (3–16)	72	50	54 (19–81)	54 (20–85)	★★★★★★★
Chu et al.	2015	NA	Hong Kong	NA	14.8 (2–30)	19	133	64.9 ± 11.6	64.9 ± 11.6	★★★★★
Yuan et al.	2014	1,2,10	Hong Kong	66.87 ± 3.45	≥4	69	76	52.6 ± 8.4	42.8 ± 15.5	★★★★★★★
Tai et al.	2013	1–7,11	China, Malaysia	66	6.4 ± 7.9	47	47	55.1 ± 12.4	55.0 ± 12.9	★★★★★★★
Ye et al.	2012	1,2,10	China	60–64	4.53 ± 1.69	91	29	38.29 ± 4.66	38.10 ± 5.35	★★★★★★★
Li et al.	2010	1,2,3,6,12,13	Taiwan	4500–8100 cGy	5	31	276	56 ± 7	64 ± 12	★★★★★
Lam et al.	2002	2,3,4,6	Hong Kong	56.6	4–11	71	142	53.6 (39–69)	60.6 (20–83)	★★★★★★★
Lam et al. (Ca)	2001	2,3,4,6	Hong Kong	56.4	4–20	71	51	53.6 (38–64)	48.8 (26–87)	★★★★★★
Lam et al. (H & N)	2001	3,6	Hong Kong	56.6	4–26	80	58	53.0 (38–69)	NA	★★★★★★
Cheng et al.	1999	NA	Hong Kong	5500 cGy	6.4 ± 5.5	85	108	59.3 ± 14.0	62.1 ± 10.3	★★★★★
Cheng et al.	1998	NA	Hong Kong	60–66	6.7	96	96	53.6	61.8 ± 10.5	★★★★★
Huang et al.	2013	1,2,4,6	Taiwan	68.4–78.6	4.0	105	25	52.43 ± 10.23	50.68 ± 11.49	★★★★★

NA = data not available; Post-RT NPC = post-radiotherapy nasopharyngeal carcinoma patients; CTRL = healthy controls or nasopharyngeal carcinoma patients without radiotherapy.

* Matching: 1 = age; 2 = gender; 3 = smoking; 4 = diabetes mellitus; 5 = hypertension; 6 = hypercholesterolemia; 7 = symptomatic ischemic heart disease; 8 = symptomatic cerebrovascular disease; 9 = clinical stage; 10 = conventional cardiovascular risk factors; 11 = ethnic; 12 = atrial fibrillation; 13 = alcohol use; Ca = Cancer; H & N = Head & Neck.

Manager 5.3 (Cochrane Collaboration, Oxford, UK), using relative risk (RR) to compare dichotomous variables and a 95% confidence interval.

Statistical heterogeneity between studies was evaluated using Cochrane's Q statistic with significance set at $p < 0.1$ and the total variation across studies was quantified using the I^2 index [15]. The fixed-effects model was used if $p > 0.1$ or $I^2 < 0.5$; otherwise, the random-effects model was used. We also used funnel plots to look for potential publication bias (Figs. 8 and 9).

Result

Literature search

The results of the study selection process are summarized in the PRISMA flow diagram (Fig. 1). The initial search returned 334 citations, with 215 remaining after removing duplicate citations and limiting the results to English language and human subjects. We evaluated the abstracts of those titles and narrowed the results to 26 full text articles. After assessing for eligibility criteria, 12 studies were used for this review. All included studies reported extra-cranial carotid stenosis in RT and control groups [11,16–26], and 10 studies reported significant (>50%) stenosis [11,16–20,23–26].

Characteristics of included studies

Table 1 shows characteristics of the twelve included studies. All were case-control or cross-sectional, with a total of 1928 subjects: 837 received radiation therapy for NPC and 1091 did not. Five studies used untreated NPC patients as controls [11,18–20,25], totaling 577 control patients, and seven studies used healthy people [16,17,21–24,26], totaling 514 healthy controls. Since nasopharyngeal carcinoma has not been evaluated as a possible independent risk factor for carotid stenosis, we pooled these results. However, we also did a subgroup analysis that excluded all healthy-control studies and looked only at NPC patients who either received RT or did not (Fig. 3).

As shown in Table 1, some studies matched their patients and control subjects better than others. Matching factors included age, gender, smoking, diabetes mellitus, hypertension, hypercholesterolemia, symptomatic ischemic heart disease, symptomatic cerebrovascular disease, clinical stage of NPC, conventional cardiovascular risk factors, ethnicity, atrial fibrillation, and alcohol use. The mean ages of RT patient cohorts ranged from 38.3 to 64.9 years and the mean ages of their corresponding controls ranged from 38.1 to 64.9 years, excluding one study which did not report control subjects' ages [18]. Only seven of the studies reported patients' sex [11,16–21,24–26]. Time intervals from RT to the first ultrasound scan varied widely. Our assigned quality scores are also in Table 1, ranging from 5 to 7 out of 9 possible stars.

Meta-analysis

Carotid stenosis

Eleven of the included studies (1808 patients) examined overall carotid stenosis [11,16–20,22–26]; Ye et al. reported stenosis in ICA but not other arteries [21]. Pooled results show a higher incidence of overall carotid stenosis in the RT group (402/746) than controls (162/1062), with significant difference (pooled risk ratio = 4.17 [2.44, 7.10], $p = 0.00001$) (Fig. 2).

To exclude potential risk factors arising from NPC itself, we analyzed the subgroup of studies that directly compared RT-treated NPC patients with untreated NPC patients [11,18–20,25]. These pooled results show a significantly higher incidence of overall carotid stenosis in patients who received RT (250/325) than in untreated patients (142/577; pooled risk ratio = 2.89 [1.74, 4.79], $p < 0.00001$) (Fig. 3).

Significant stenosis

Ten of the studies investigated significant (>50%) stenosis, with 1678 total patients [11,16–20,23–26]. 402 of 746 RT patients showed more than 50% stenosis compared to 162/1062 with significant stenosis in the control group. Pooled results show significantly greater incidence of significant stenosis after RT (pooled risk ratio = 8.72 [3.53, 21.55], $p = 0.00001$) (Fig. 4).

Analysis by blood vessel and area

To reduce heterogeneity, we subdivided the results by blood vessel and area affected. Of the 12 studies included, three each examined CCA [18,24,25], ICA [16,18,25] and ECA [11,23,25]; four studies examined CCA and ICA together [11,17,19,23]; one exam-

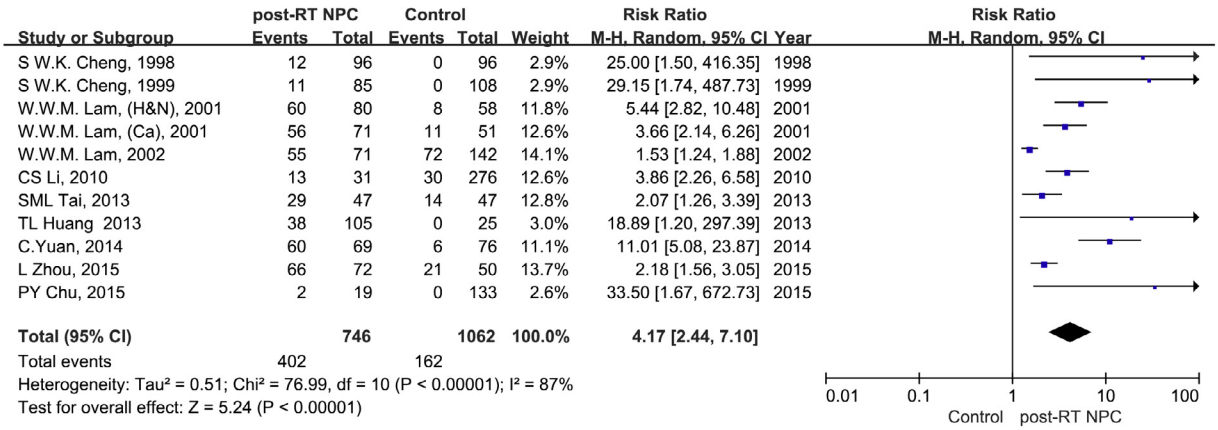

Fig. 2. Meta-analysis of RT for overall carotid stenosis (n).

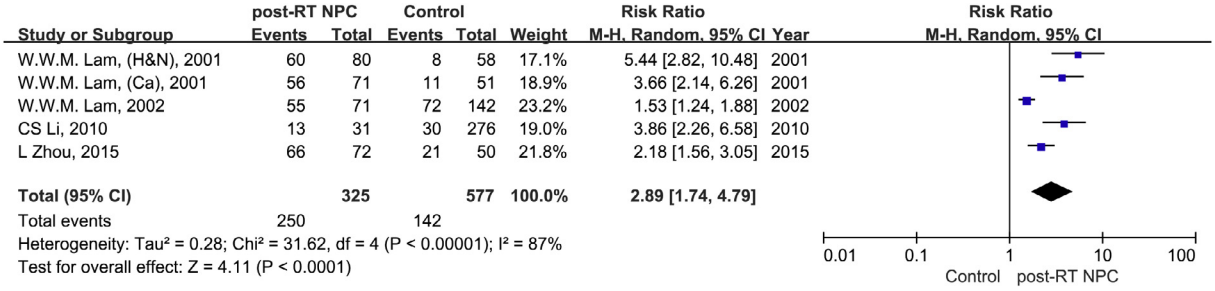

Fig. 3. Meta-analysis of RT for overall carotid stenosis with NPC patients as controls(n).

ined carotid bulb[18]; and one examined CCA, ICA, and carotid bulb together [19].

CCA Patients who received RT were more likely to show CCA stenosis (111/171) than controls (12/241), and the difference was significant (pooled risk ratio = 6.62 [3.89, 11.26], $p = 0.00001$) (Fig. 5).

The RT group seemed to show more significant stenosis (30/171) than the control group (8/241), but in pooled results this difference was not statistically significant (pooled risk ratio = 6.11 [0.79, 47.07], $p = 0.08$) (Fig. 6).

ICA The RT group seemed to have a higher incidence of ICA stenosis (117/248) than controls (22/204), but the difference among pooled results was not significant (pooled risk ratio = 9.98 [0.66, 151.76], $p = 0.1$) (Fig. 5).

However, the RT group showed a significantly greater incidence of significant ICA stenosis (48/248) than controls (3/204; pooled risk ratio = 9.80 [3.39, 28.38], $p < 0.0001$) (Fig. 6).

ECA The RT group showed a higher incidence of stenosis in ECA (89/190) than controls (5/148), and the difference was significant (pooled risk ratio = 9.37 [1.91, 45.94], $p = 0.006$) (Fig. 5).

The incidence of significant ECA stenosis was higher after RT (25/190) than controls (0/148), with significant difference (pooled risk ratio = 11.75 [2.24, 61.59], $p = 0.004$) (Fig. 6).

CCA and ICA More patients showed stenosis in ICA or CCA after RT (95/203) than controls (25/206), with a significant difference (pooled risk ratio = 3.15 [1.50, 6.61], $p = 0.003$) (Fig. 5).

40 of the 203 patients in the RT group showed >50% stenosis in ICA or CCA, compared to just 1/206 in the control group; this difference is significant (pooled risk ratio = 15.83 [3.82, 65.50], $p = 0.001$) (Fig. 6).

Carotid bulb Only one study investigated stenosis in the carotid bulb [18]. Overall stenosis was more likely in the RT group (46/80) than controls (7/58), and the difference was significant (pooled risk ratio = 4.76 [2.32, 9.79], $p < 0.0001$) (Fig. 5).

However, there was no significant difference in significant stenosis between RT patients (15/80) and controls (7/58; pooled risk ratio = 1.55 [0.68, 3.57], $p = 0.004$) (Fig. 6).

CCA/ICA/carotid bulb In the single study that examined CCA, ICA, and carotid bulb together [19], RT patients showed a higher incidence of stenosis (55/71) than controls (72/142). The difference was statistically significant (pooled risk ratio = 1.53 [1.24, 1.88], $p < 0.0001$) (Fig. 5). This study did not report significant stenosis rates.

Arteries on each side RT exposes the carotid arteries to a gradient of radiation depending on the treatment site, with more exposure on the ipsilateral side and less on the contralateral side. Because we could not measure the actual radiation dose to arteries on each side, we instead pooled the studies that examined arteries on each side individually [11,16,19,21,23,26]. These pooled results showed a higher incidence of stenosis in each vessel in RT patients (762/2082) than in controls (251/2274; pooled risk ratio = 4.32 [2.56, 7.29]) (Fig. 7).

Sensitivity analysis and publication bias

For carotid stenosis, all eleven studies that scored five or more stars on the modified Newcastle-Ottawa scale were included in sensitivity analysis (Table 2). As shown in Table 2, excluding any of these studies does not significantly change the outcome. Likewise, the sensitivity analysis of the ten studies of significant stenosis (Table 3) shows consistency in the significance of outcome.

Figs. 8 and 9 show funnel plots of the risk ratios for overall stenosis and significant stenosis calculated by the studies in this meta-analysis. The funnel plots suggest some possible publication bias.

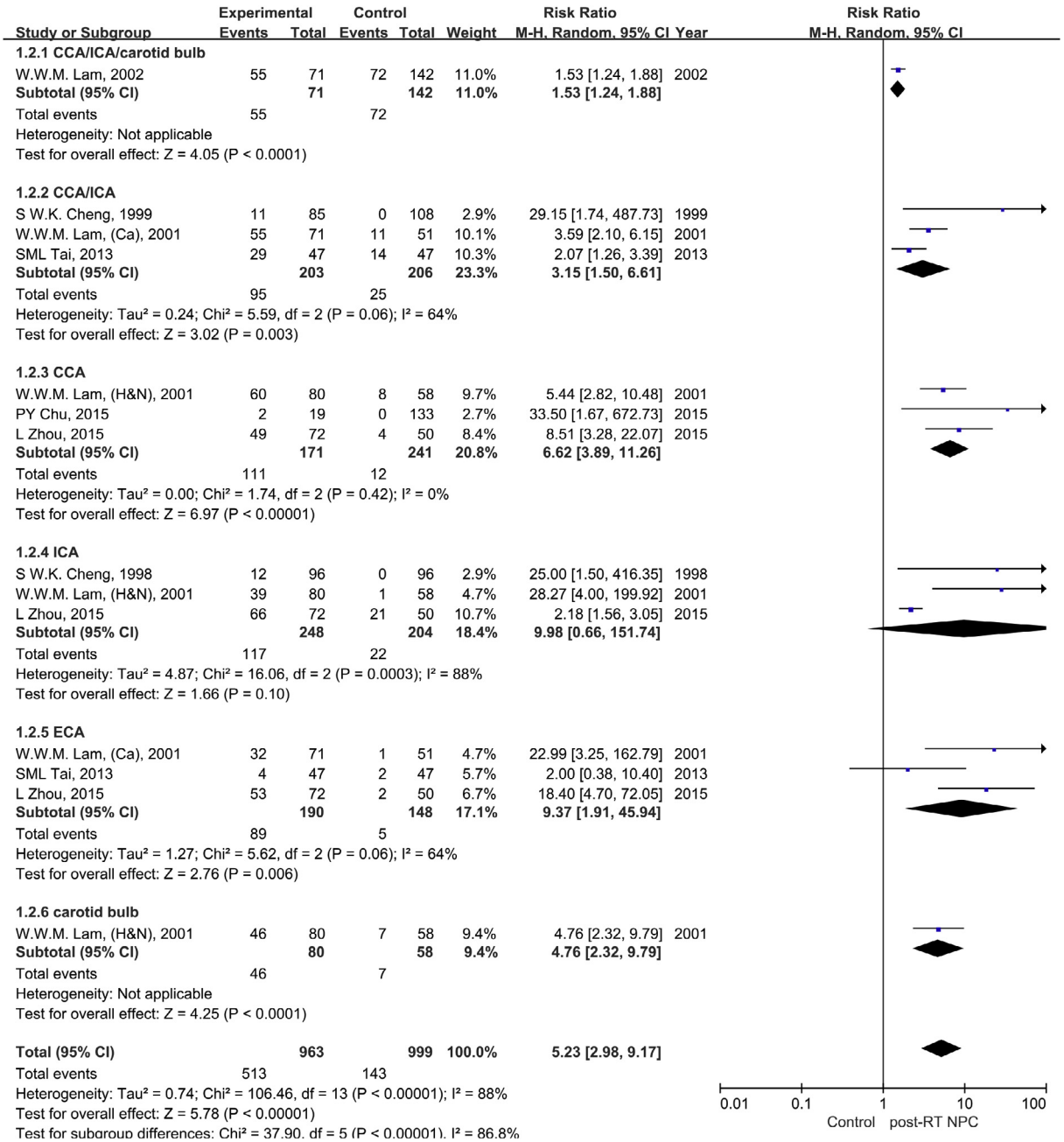

Fig. 4. Subgroup meta-analysis of RT for carotid stenosis (n).

Discussion

Radiation therapy has increased long-term survival of NPC patients but may also cause carotid stenosis, increasing NPC survivors' risk of TIA and stroke [11]. However, to the authors' knowledge, no large-scale study has yet analyzed carotid stenosis rates in NPC patients after receiving RT.

This review compiled 12 studies (1928 patients) which examined the effects of RT in NPC patients with overall number patients with carotid stenosis and significant stenosis being the main outcomes of interest, in 1928 total patients. Our review demonstrated an increased incidence of carotid stenosis in NPC patients after RT with the RR of 4.17 (95% CI, 2.44–7.10, $p = 0.00001$) (Fig. 2).

Since different blood vessels may be exposed to different levels of radiation during treatment, reports on the prevalence of stenosis could vary depending which arteries were studied [27]. Therefore, we subdivided study results by the arteries affected. In CCA, ECA, carotid bulb, and CCA and ICA together, RT patients showed significantly higher rates of stenosis than non-irradiated controls (Fig. 5). However, in ICA there was no significant difference between RT patients and controls. This may be from lack of homogeneity, since the I^2 value from these studies was 88%.

Ten studies had sufficient data for analysis of significant (>50%) stenosis, with 1678 total patients [11,16–20,23–26]. More patients in the RT group had significant stenosis than the controls (RR = 8.72 [3.53, 21.55]) (Fig. 4), but this difference was not statistically significant in CCA and carotid bulb (Fig. 6).

The principal limitation of this review is that it is based on observational data from case-control or cross-sectional studies. However, all studies included had a control group. Three of the

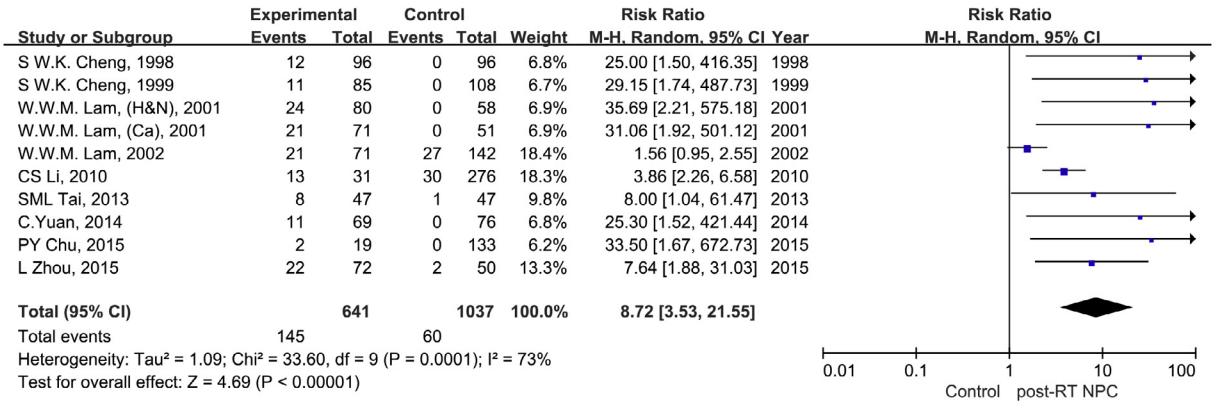

Fig. 5. Meta-analysis of RT for overall significant carotid stenosis (n).

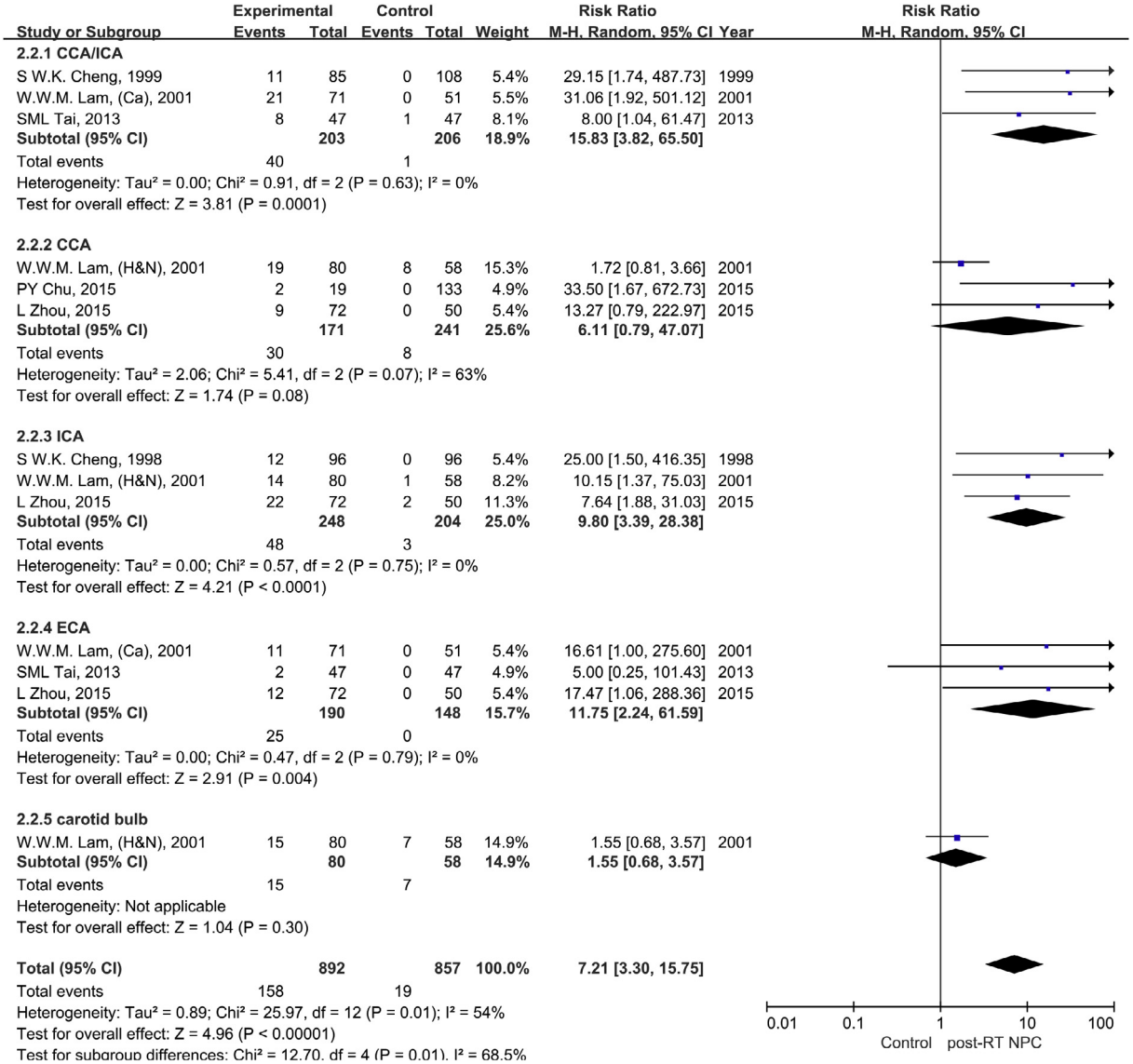

Fig. 6. Subgroup meta-analysis of RT for significant carotid stenosis (n).

12 studies used non-irradiated NPC patients as controls [11,18,25], seven studies used healthy people as controls [16,17,21–24,26], and two studies used ischemic stroke patients as controls [19,20]. From our perspective, NPC patients who have not received RT are the best controls since they have the most similar condition. Nine studies listed risk factors for which they controlled by match-

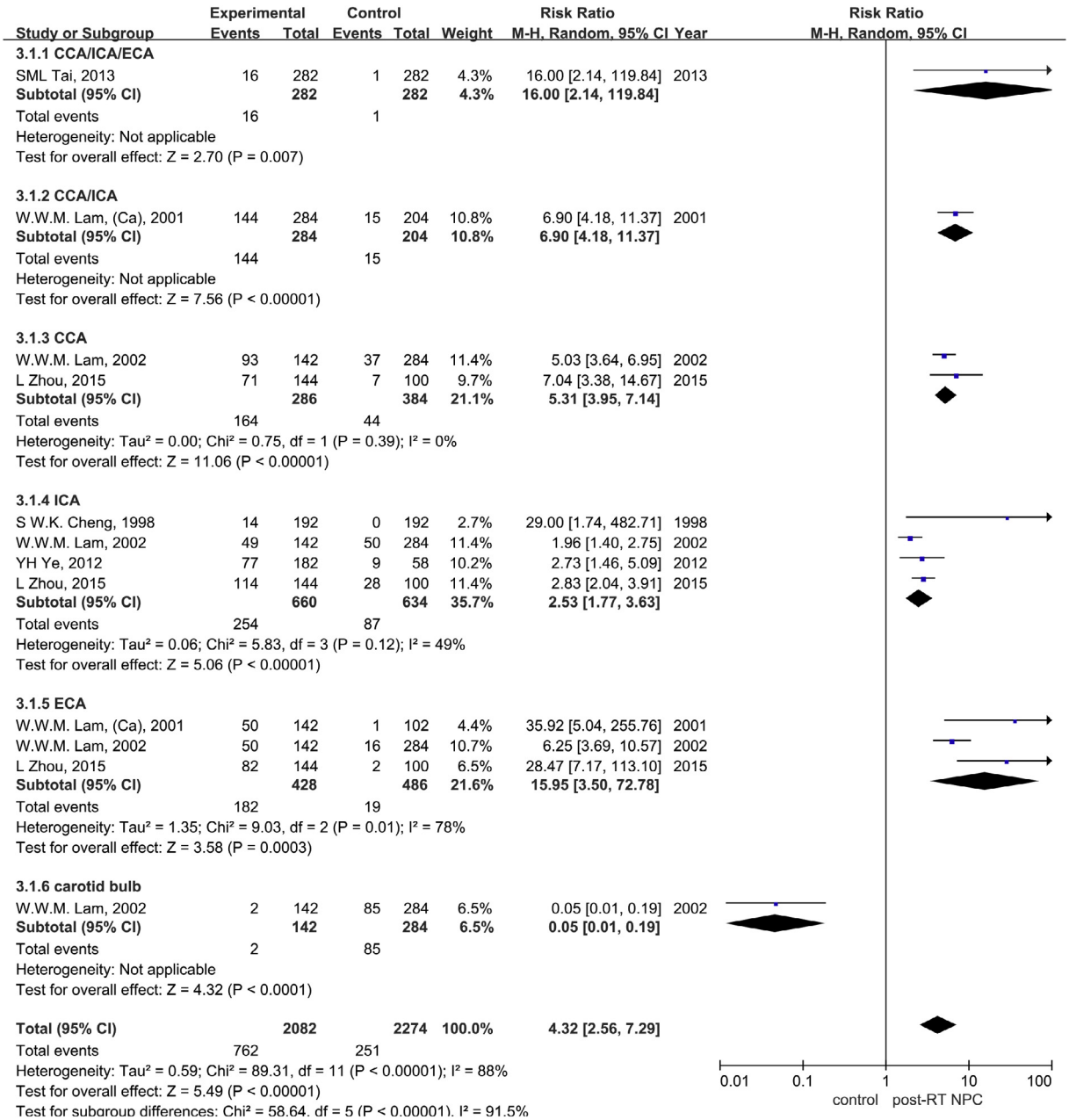

Fig. 7. Subgroup meta-analysis of RT for carotid stenosis (vessel).

Table 2
Sensitivity analysis of association between radiotherapy and carotid stenosis.

Study	Post-RT NPC (n)	CRTL (n)	RR (95% CI)	*p* value	Study heterogeneity			
					x^2	*df*	I^2,%	*p* value
Cheng, 1998	96	96	3.91 (2.31–6.62)	<0.00001	71.33	9	87	<0.00001
Cheng, 1999	85	108	3.89 (2.30–6.57)	<0.00001	70.85	9	87	<0.00001
Lam, (Ca), 2001	71	51	4.34 (2.39–7.87)	<0.00001	74.22	9	88	<0.00001
Lam, (H&N), 2001	80	58	3.97 (2.28–6.91)	<0.00001	66.55	9	86	<0.00001
Lam, 2002	71	142	4.64 (2.80–7.67)	<0.00001	35.76	9	75	<0.00001
Li, 2010	31	276	4.31 (2.37–7.85)	<0.00001	74.87	9	88	<0.00001
Tai, 2013	47	47	4.81(2.58–8.96)	<0.00001	79.44	9	89	<0.00001
Huang, 2013	105	25	3.94 (2.32–6.66)	<0.00001	71.25	9	87	<0.00001
Yuan, 2014	69	76	3.44(2.12–5.57)	<0.00001	51.29	9	82	<0.00001
Zhou, 2015	72	50	5.01 (2.54–9.89)	<0.00001	80.80	9	89	<0.00001
Chu, 2015	19	133	3.92 (2.30–6.67)	<0.00001	73.29	9	88	<0.00001
All studies	746	1062	4.17 (2.44–7.10)	<0.00001	76.99	10	87	<0.00001

Post-RT NPC = post-radiotherapy nasopharyngeal carcinoma patients; CTRL = healthy controls or nasopharyngeal carcinoma patients without radiotherapy.

Table 3
Sensitivity analysis of association between radiotherapy and significant carotid stenosis.

Study	Post-RT NPC (n)	CRTL (n)	RR (95% CI)	*p* value	Study heterogeneity			
					x^2	*df*	I^2,%	*p* value
Cheng, 1998	96	96	7.91 (3.16–19.76)	<0.00001	30.22	8	74	0.0002
Cheng, 1999	85	108	7.78 (3.13–19.35)	<0.0001	29.83	8	73	0.0002
Lam, (Ca), 2001	71	51	7.62 (3.11–18.68)	<0.00001	28.72	8	72	0.0004
Lam, (H&N), 2001	80	58	7.46 (3.08–18.08)	<0.00001	27.91	8	71	0.0005
Lam, 2002	71	142	12.60 (4.76–33.41)	<0.00001	17.35	8	54	0.03
Li, 2010	31	276	12.83 (3.41–48.18)	0.0002	34.1	8	77	<0.0001
Tai, 2013	47	47	8.98 (3.39–23.76)	<0.00001	32.81	8	76	<0.0001
Yuan, 2014	69	76	7.91 (3.16–19.77)	<0.00001	30.27	8	74	0.0002
Zhou, 2015	72	50	9.17 (3.37–24.96)	<0.0001	31.96	8	75	<0.0001
Chu, 2015	19	133	7.91 (3.13–19.79)	<0.0001	31.31	8	74	0.0001
All studies	641	1037	8.72 (3.53–21.55)	<0.00001	33.6	9	73	0.0001

Post-RT NPC = post-radiotherapy nasopharyngeal carcinoma patients; CTRL = healthy controls or nasopharyngeal carcinoma patients without radiotherapy.

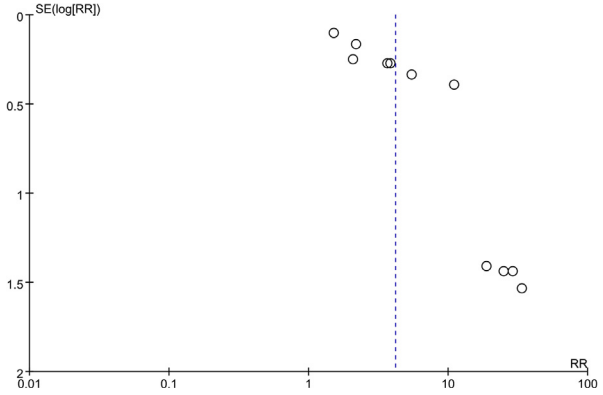

Fig. 8. Funnel plot of RT for overall carotid stenosis (n).

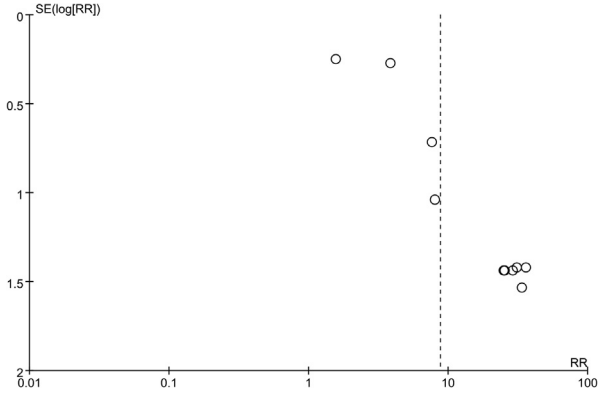

Fig. 9. Funnel plot of RT for overall significant carotid stenosis (n).

ing, while three studies did not [16,17,24]. Matching factors included age, gender, smoking, diabetes mellitus, hypertension, hypercholesterolemia, symptomatic ischemic heart disease, symptomatic cerebrovascular disease, clinical stage of NPC, conventional cardiovascular risk factors, ethnicity, atrial fibrillation, and alcohol use. Framingham stroke risk factors are most strongly associated with carotid stenosis after RT, so these are the most important factors to match between RT patients and controls [28]. Blinding and randomization are not described in the studies included.

The use of different imaging techniques between studies is another limitation. Ultrasound scanning is widely used to screen for carotid stenosis since it is safe, noninvasive and cost-effective. Ten of the 12 studies in this review used ultrasound to measure stenosis, but Zhou et al. used contrast-enhanced MR angiography and Chu et al. used computed tomographic angiography (CTA). These two latter imaging techniques are less operator-dependent than ultrasound and are considered to be more accurate, especially for arteries with an irregular lumen [29,30].

Studies in this meta-analysis used different radiotherapy methods, another limitation. Only one study used intensity-modulated radiation therapy (IMRT) [25], the most advanced technique [25,31,32]. The rest used either 2D or 3D conventional RT, or did not specify [16,17,20,22,24]. Different radiotherapy techniques confer different carotid stenosis risk: our most recent research shows that IMRT confers significantly less risk of significant carotid stenosis than 2D-RT [33]. Lastly, the patient cohorts varied between studies by age at treatment, radiation dose, time elapsed before the first stenosis scan, and other factors.

Radiation therapy can be a mixed blessing for NPC patients, since it treats their tumors but can bring long-term complications like radiation encephalopathy, radiation-induced lower cranial neuropathy, optic neuropathy, brachial plexus injury, cervicular vascular injury, and so on [34]. The exact mechanism for radiation-induced carotid stenosis is not clear [35], but injury to microvasculature may be the main cause of damage in the large arteries [7]. Endothelial cells in the intima layer and vava vasorum are considered the most radiation-sensitive cell type in the carotid artery [36,37]. Radiation can not only trigger inflammatory responses, but can also initiate proliferation, migration and differentiation of smooth muscle cells [38]. Collagen overproduction and extracellular matrix remodeling caused by the radiation eventually lead to the thickening and stiffening of the artery[7].

Generally speaking, this meta-analysis shows a strong association between radiation therapy and carotid stenosis. However, more precise analysis will require further study. Future well-designed studies are needed to confirm the association between radiation therapy and carotid stenosis and elucidate the mechanisms. In the meantime, the long-term complications of radiation therapy need to be publicized so that doctors and patients can make every effort to avoid them.

This meta-analysis shows a strong association between radiation therapy and increased prevalence of stenosis in patients with NPC. NPC patients who undergo radiation therapy should be thoroughly screened after treatment, to detect any developing stenosis before it becomes severe.

Author contributions

Conceived and designed the experiments: JL. Analyzed the data: WL, YZ, SB. Contributed materials/analysis tools: BZ, YX, YL, WF, SX, LY. Wrote the paper: WL, YZ, TA.

Conflicts of interests

All the authors have nothing to disclose in terms of employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or any funding.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.013.

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