Radiotherapy and Oncology 195 (2024) 110258

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

Dosimetric parameters predict radiation-induced temporal lobe necrosis in nasopharyngeal carcinoma patients: A systematic review and *meta*-analysis☆

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ARTICLE INFO

Keywords:
Temporal lobe necrosis
Nasopharyngeal carcinoma
Radiotherapy
Dosimetric parameters

ABSTRACT

This systematic review examines the role of dosimetric parameters in predicting temporal lobe necrosis (TLN) risk in nasopharyngeal carcinoma (NPC) patients treated with three-dimensional conformal RT (3D-CRT), intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). TLN is a serious late complication that can adversely affect the quality of life of NPC patients. Understanding the relationship between dosimetric parameters and TLN can guide treatment planning and minimize radiation-related complications.

A comprehensive search identified relevant studies published up to July 2023. Studies reporting on dosimetric parameters and TLN in NPC patients undergoing 3D-CRT, IMRT, and VMAT were included. TLN incidence, follow-up duration, and correlation with dosimetric parameters of the temporal lobe were analyzed.

The review included 30 studies with median follow-up durations ranging from 28 to 110 months. The crude incidence of TLN varied from 2.3 % to 47.3 % and the average crude incidence of TLN is approximately 14 %. Dmax and D1cc emerged as potential predictors of TLN in 3D-CRT and IMRT-treated NPC patients. Threshold values of >72 Gy for Dmax and >62 Gy for D1cc were associated with increased TLN risk. However, other factors should also be considered, including host characteristics, tumor-specific features and therapeutic factors.

In conclusion, this systematic review highlights the significance of dosimetric parameters, particularly Dmax and D1cc, in predicting TLN risk in NPC patients undergoing 3D-CRT, IMRT, and VMAT. The findings provide valuable insights that can help in developing optimal treatment planning strategies and contribute to the development of clinical guidelines in this field.

Nasopharyngeal carcinoma (NPC) is a prevalent disease in Southeast Asia, particularly in southern China, and is closely associated with Epstein-Barr virus infection [1]. Radiotherapy (RT) is an essential part of NPC treatment but careful planning is required as RT can cause damage

☆ This paper was written by members and invitees of the International Head and Neck Scientific Group (https://www.IHNSG.com).

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https://doi.org/10.1016/j.radonc.2024.110258
Received 14 December 2023; Received in revised form 18 March 2024; Accepted 21 March 2024
Available online 26 March 2024

to surrounding healthy tissues, including the temporal lobe [2–4]. Temporal lobe necrosis (TLN) is a potentially debilitating irreversible late complication following RT for NPC. It manifests with symptoms such as dizziness, headaches, cognitive impairment, and seizures [5,6]. TLN can be diagnosed through imaging techniques like magnetic resonance imaging (MRI) and computer tomography (CT). In general, edema without enhancement is evidence of radiation-induced injury, while radionecrosis typically shows signs of enhancement. Necrosis or cysts is usually considered as a late stage of TLI [7–9]. Despite various therapeutic approaches, none have been able to prevent or halt the progression of TLN effectively. In a cohort study, early intervention by initiating bevacizumab or corticosteroid treatment within 3 months after diagnosing radiation-induced brain necrosis decreased the risk of all-cause mortality in patients with head and neck cancer. This implies the importance of early diagnosis of TLN [10]. Prevention is a most pragmatic and effective strategy for managing TLN.

The incidence of TLN after RT varies significantly and is influenced by factors such as RT technique, dose-volume parameters, use of concurrent systemic therapy, and TLN evaluation methods [4,11–13]. Advanced RT techniques like Intensity-Modulated Radiation Therapy (IMRT) have improved dose distribution but still pose a risk to the temporal lobe due to its proximity to the nasopharynx. The optimal dose-volume constraints for the temporal lobe in NPC patients receiving different RT techniques, including three-dimensional conformal RT (3D-CRT), IMRT, and Volumetric modulated arc therapy (VMAT), are not well-established. Understanding these constraints is crucial for minimizing the risk of radiation-induced brain injury and improving the quality of life for NPC patients. The aim of this systematic review is to summarize radiation dose-volume predictive factors for TLN in NPC patients and analyze data using clinical-dosimetric models and artificial intelligence models to propose appropriate constraints for RT planning, potentially enabling safe dose escalation.

Methods

Literature search and eligibility criteria

A comprehensive literature search was conducted in the EMBASE, Medline, Cochrane and PubMed databases on July 25, 2023, to identify relevant articles reporting the outcome of TLN in patients treated with RT for NPC. The systematic review was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.

The search strategy included relevant keywords such as radiotherapy, temporal lobe necrosis, and nasopharyngeal carcinoma and their synonyms or variations. The detailed search strategy can be found in Table S1. After removing duplicates, the titles and abstracts of the remaining articles were screened for relevance to the topic. Inclusion and exclusion criteria were predetermined.

A study was considered eligible when all the following inclusion criteria were satisfied, 1) population: patients with newly diagnosed non-metastatic NPC, 2) treatment modality: 3D-CRT, IMRT or VMAT, 3) outcomes: reporting the incidence of treatment-related TLN or TLI and discussing dose-volume constraints of the temporal lobe, 4) study design: not limited.

Articles meeting any of the following criteria were excluded: 1) non-English reports, 2) systematic reviews and *meta*-analyses, 3) case reports, 4) letters, comments, replies, and editorials, 5) animal and laboratory studies, 6) studies lacking adequate radiation dose-volume analysis, 7) studies focusing on recurrent NPC, 8) studies using two-dimensional RT (2D-RT), radiosurgery, proton beam therapy, or intracavitary mold brachytherapy techniques, 9) conference abstracts that had overlapping patient cohorts and reported the same outcomes as the full articles. Specifically, studies on re-irradiation and historically 2D-RT, which are known to have a relatively high incidence of TLN, were excluded. Patients treated with proton therapy and brachytherapy were also excluded due to potential differences in biological effect doses across different RT techniques.

Two authors (JD and JL) independently assessed the articles for eligibility based on the predefined criteria. Any discrepancies were resolved through consensus between the authors (JD and JL). Unsolved discrepancies were settled by consulting a third blind reviewer (CW).

Data extraction and quality assessment

Data extraction was performed from the eligible studies, capturing the following information: 1) bibliographic details, 2) patient characteristics, 3) RT technique, dose and schedule, 4) concurrent therapy, 5) duration of follow-up, 6) latency period to TLN, 7) definition of TLN or TLI and the diagnostic method used, 8) incidence of TLN or TLI, 9) clinical risk factors, 10) predictive dose-volume parameters, 11) proposed dosimetric cut-off values, and comparative measures such as odds ratios (ORs), relative risk (RR), and hazard ratios (HRs) for the risk of TLN or TLI.

The quality of evidence was independently assessed and systematically evaluated by two authors (JD and JL) using the Newcastle-Ottawa Scale (NOS) for quality assessment. The NOS [14,15] is widely used for *meta*-analysis of cohort studies and can also be modified based on a special subject. Each domain was rated to determine the overall quality of evidence and any disagreements between the authors were resolved through consensus.

Statistical analysis

In this systematic review, various dosimetric predictors of radiation-induced TLN or TLI were qualitatively summarized based on the available literature. Most studies used the crude incidence rate to evaluate the occurrence of TLN or TLI. The crude incidence rate was calculated by dividing the total number of cases in a given time period by the total number of persons in the population. The relationships between fractionation, follow-up time and the crude incidence of TLN were visualized using a bubble plot. To evaluate the predictive value of the dose/volume parameters, ORs or HRs from each included study were pooled and *meta*-analyzed using a random-effects model. The random-effects *meta*-analysis approach assumes that different studies estimate various, but related, intervention effects. It weights the studies relatively equally, compared to a fixed-effect model, in the presence of heterogeneity. Results generated via the random-effects model are generally viewed as the "average intervention effect" [16]. Heterogeneity between studies was assessed using the I^2 statistic, considering significance if I^2 exceeded 75 %. All statistical analyses were performed using R software.

Results

The study selection process is presented in a PRISMA flow diagram (Fig. 1), illustrating the steps involved in identifying eligible articles. Initially, a total of 672 articles were identified from the literature search, and after removing duplicates, 360 records remained. Following the screening of titles, abstracts and full texts, 30 studies (26 articles and 4 abstracts) met the inclusion criteria for the systematic review. These studies included a total of 30,191 patients with NPC who underwent curative-intent RT.

Among the included studies, 18 provided comparative data on radiation dose-volume parameters, which are summarized in Table 1. Additionally, 12 studies presented information on normal tissue complication probability (NTCP), radiation dosimetric nomograms, radiomics or dosiomics models related to TLN, of which the findings are summarized in Table 2.

The characteristics of the selected studies are summarized in Tables 1 and 2. All included studies were published between 2010 and 2023. The majority of the studies were conducted in the endemic region of South Asia, with two studies conducted in the United States [17,18]. One study

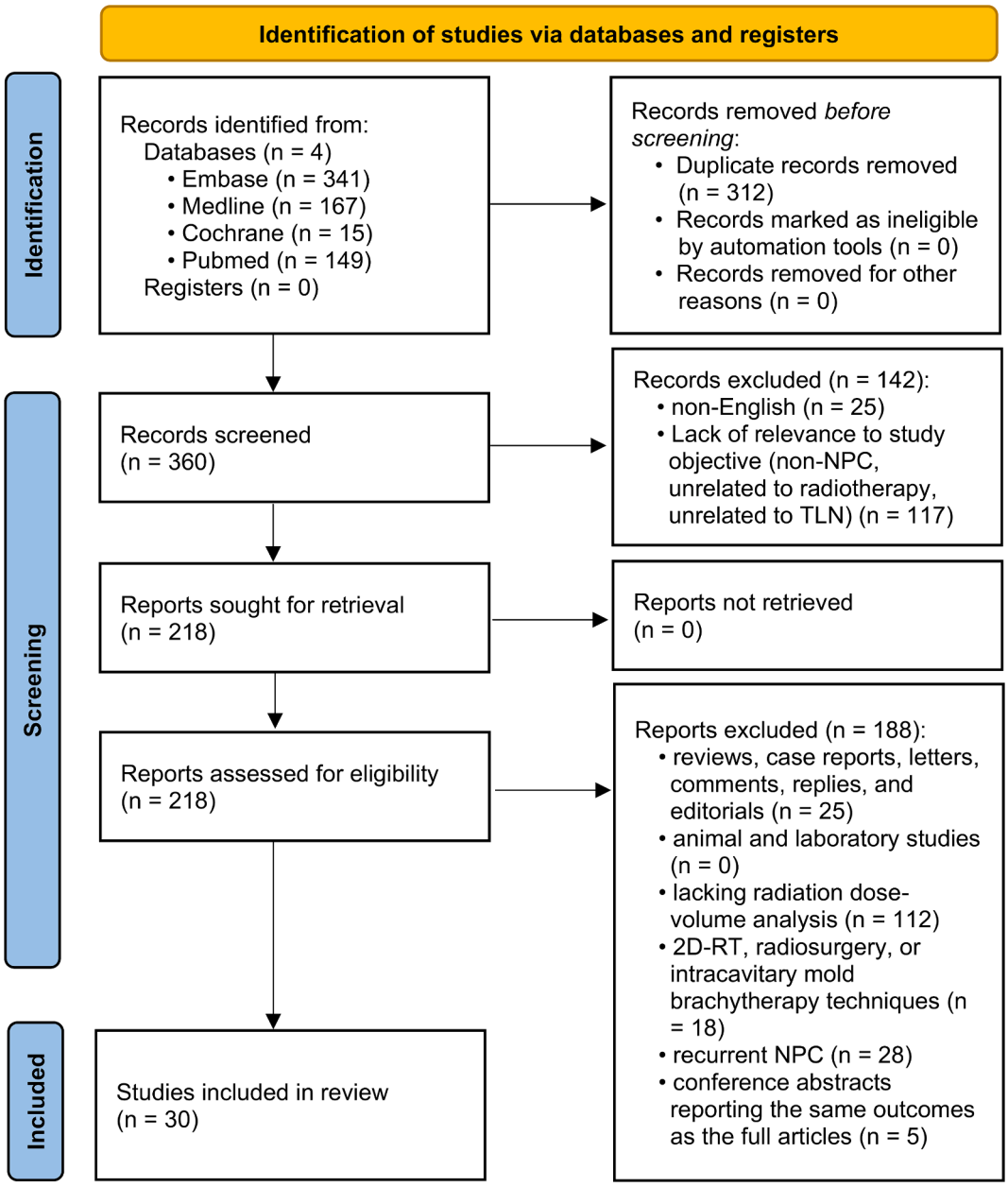

Fig. 1. PRISMA flow diagram.

was retrospective and prospective [19], the rest were retrospective. The quality assessment indicated a moderate risk of bias due to the retrospective and observational nature of the studies. As all the studies included were cohort studies, the NOS was used to assess the quality of evidence (Table S2).

IMRT, which is the most common radiation technique in clinical practice, was used in all studies. In one study, both IMRT and VMAT were utilized [20]. The radiation dose varied from 66 to 76 Gy, delivered in 30 to 38 fractions, with individualized schedules based on staging.

MRI was used as the standard diagnostic method for TLN in 27 studies. Among these studies, 21 provided detailed diagnostic criteria (Table S3), while three studies did not specify the diagnostic method [20–22]. Although there were discrepancies in the diagnostic criteria, the definitions of TLN and TLI remained consistent. TLI is defined as radiation-induced brain damage with or without necrotic lesion on postcontrast T1-weighted images, while TLN is evolved from TLI with a typical sign of a necrotic core [23,24].

The median follow-up duration ranged from 28 to 110 months, with 22 studies having a median observation time of over 3 years. The correlation between median incidence and observation time is shown in Fig. S1, indicating a positive relationship between the crude incidence of TLN and follow-up duration. The median latency period to TLN was reported in over 50 % of the studies and ranged from 27 to 48 months. A three-year observation time is not long enough to detect all TLN, as it usually occurs at least 30 months post-RT (Tables 1 and 2). To better assess TLN, monitoring the disease for at least five year is suggested.

Nineteen studies proposed thresholds for stratifying TLN occurrence into high- and low-risk groups, considering both dosimetric and clinical factors. The crude incidence of TLN was reported in 25 of 30 studies [17,19–23,25–43]. Since the definitions of TLN and TLI are often indistinct, TLI is considered equivalent to TLN in most cases. In studies that reported both TLI and TLN rates, the TLI rate was used to calculate the average crude incidence of TLN. When the patient cohorts overlapped and the incidence values were exactly the same in more than two

Table 1
Studies on radiation dose-volume parameters of post-radiation TLN/TLI in patients with NPC.

Study	Number of total patients for dosimetric analysis	Crude incidence of TLN/TLI	RT technique and dose to GTVp	Median follow-up time	Median latency to TLN	Diagnostic method	Concurrent therapy	Clinical factor associated to TLN/TLI	Proposed dosimetric parameter	Proposed cutoff point for dosimetric parameter	Relative effect	Incidence of TLN (low-risk vs high-risk group with proposed dosimetric cut-off point)
Hara 2010[18]	TLN: 8 of 16 (14 NPC, 2 skull base tumors), control: 8	NR	IMRT + SRS IMRT: 45–66 Gy/ 1.8–2.2 Gy, SRS boost: 8–20 Gy in 1-3F	TLN: 44 mo, control: 47.4 mo	NR	MRI	NR	NR	V55, V45, V35, V25, V15	IMRT: V55 < 1.3 ml, v45 < 4 ml, V35 < 9 ml, V25 < 18 ml, V15 < 40 ml	NA	NA
Su 2012[25]	870	40/870, 4.60 %	IMRT, 68 Gy/30F	40 mo	30 mo	MRI	Chemo for III-IV stage	NR	Dmax, D1cc	Dmax < 68 Gy, D1cc < 58 Gy	NA	NA
Su 2013[26]	870	40/870, 4.60 %	IMRT, 68 Gy/30F	40 mo	30 mo	MRI	Chemo for III-IV stage	NR	relative V40 (rV40), absolute V40 (aV40)	rV40 ≤ 11 %, aV40 ≤ 11 cc	NA	rV40: 2.5 % v.s. 27.5 %, aV40: 2.7 % v.s. 39.1 %
Sun 2013*[27]	506	20/506, 3.95 %	IMRT, 68 Gy/30F	65.5 mo	33.6 mo	MRI	Chemo for T3-4	NR	D0.5 cc	D0.5 cc < 69 Gy	RR = 0.84, (CI 0.76–0.93)	NR
Lang 2014**[28]	148	59/148, 39.86 %	IMRT	NR	NR	MRI	NR	NR	D1cc, Dmax	D1cc ≤ 61 Gy, Dmax ≤ 70 Gy	NA	NA
Zeng 2014[21]	789	59 of 789, 7.48 %	IMRT, 68 Gy/30F	65 mo	34 mo	NR	chemo for IIB and above stage	T stage, N stage, chemo	Dmax	Dmax ≤ 65.77 Gy	HR = 1.26 (CI 1.18–1.35)	5-yr TLI rate: 0.8 % v.s. 27.1 %
Zhou 2014[29]	86 (paired cohorts)	43/ 1887***, 2.28 %	IMRT, T1-2: 66 Gy/30F, T3-4: 70.4 Gy/ 32F	28 mo	30 mo	MRI	chemo or chemo + C225	C225	V45	V45 < 15.1 cm^3	OR = 1.13 (CI 1.06–1.21)	NA
Lu 2016[32]	3314	189/3314, 5.70 %	IMRT	NR	NR	MRI	NR	NR	Dmean, D3cc, D6cc, V20, V30, V40, V50, V60	NR	NA	NA
Miao 2017[22]	749	38/749, 5.07 %	IMRT	48.8 mo	NR	NR	NR	NR	D9cc, D0.5 cc	D0.5 cc: TD5 = 73.66 Gy, D9cc: TD5 = 58 Gy	D0.5 cc OR = 1.147 (CI 1.102–1.193)	NA
Feng 2018[33]	695	59 of 695, 8.49 %	IMRT, 66–67 Gy/ 30-33F	73 mo	38 mo	MRI	chemo	T stage, chemo, diabetes	D2cc, fraction size	Fraction size < 2 Gy, D2cc < 60.3 Gy	D2cc HR = 3.755, Fraction size < 2 Gy HR = 2.819	D2cc: 1.38 % vs 7.91 %, Fraction size < 2 Gy: 1.38 % vs 7.91 %
Lu 2018[23]	4186	TLI: 217/ 4186, 5.18 %, TLN: 80/ 4186, 1.91 %	IMRT, 68–70 Gy (fraction dose: 2.27–2.33 Gy)	70 mo	27 mo	MRI	chemo	NR	Dmin, Dmean, Dmax, D0.25 cc, D0.5 cc, D1cc, V70Gy	edema/enhancement/ necrosis: Dmean: 16.96/23.96/ 28.07 Gy Dmax: 72.25/73.75/ 74.87 Gy D0.25 cc: 70.09/70.79/ 72.22 Gy D0.5 cc: 68.80/69.34/ 70.43 Gy D1cc: 66.77/68.49/ 69.65 Gy V70Gy: 0.27/0.34/1.13 cc	NA	NA

(*continued on next page*)

Table 1 (*continued*)

Study	Number of total patients for dosimetric analysis	Crude incidence of TLN/TLI	RT technique and dose to GTVp	Median follow-up time	Median latency to TLN	Diagnostic method	Concurrent therapy	Clinical factor associated to TLN/TLI	Proposed dosimetric parameter	Proposed cutoff point for dosimetric parameter	Relative effect	Incidence of TLN (low-risk vs high-risk group with proposed dosimetric cut-off point)
Huang 2019****[34]	506 (all T4 stage)	63/506, 12.45 %	IMRT, 70.4 Gy/32F	40.1 mo	NR	MRI	chemo, C225 or nimotuzumab	NR	D1cc, V20	D1cc ≤ 71.14 Gy, V20c ≤ 42.22 cc	D1cc sHR = 1.5 (CI 1.212–1.856), V20 sHR = 1.072 (CI 1.009–1.139)	5-year cumulative incidence: D1cc 13.2 % vs 62.2 %, V20 17.9 % vs 44.1 %
Wu 2019****[36]	T3: 144, T4: 73	T3: 2.78 %, T4: 30.14 %	IMRT, 74 Gy/37F	T3: 89.5 mo, T4: 97 mo	48 mo	MRI	chemo	T stage, pre, post-CCRT NLR, TCRβ repertoire subtypes	no independently predictive dosimetric factors	NA	NA	NA
Gou 2019****[37]	200 (all T3-4 stage)	17/200, 8.5 %	IMRT, 70–74 Gy/33F	71 mo	43.5 mo	MRI	Chemo, C225 or nimotuzumab	NR	GTVnx volume, Dmax	GTVnx volume: 93 cc, Dmax: 78 Gy	GTVnx volume OR = 1.035 (1.006–1.065), Dmax OR = 1.006 (CI 1.002–1.009)	NA
He 2020[20]	627	35/627, 5.58 %	IMRT and VMAT, T1-2: 70 Gy/33F, T3-4: 74 Gy/33F	NR	NR	NR	chemo	NR	D2, Dmax, Dmean, V45, V50, V54, V60	NA	NA	NA
Du 2021[39]	220	76/220, 34.55 %	IMRT, 68–72 Gy/30-33F	TLI: 33.3 mo, non-TLI: 61 mo	NR	MRI	chemo	T stage	D0.6 cc and V70Gy of TL; D1.2 cc, V72Gy, V70Gy, V71Gy and V73Gy of half-brain	TL: D0.6 cc ≤ 68.99 Gy, V70Gy ≤ 0.45 cc; half-brain: D1.2 cc ≤ 67.49 Gy, V72Gy ≤ 0.6 cc, V70Gy ≤ 0.86 cc, V71Gy ≤ 0.72 cc, V73Gy ≤ 0.48 cc	NA	NA
Zhang 2021[17]	506 (IMRT group)	20/506, 3.95 %	IMRT and protons, IMRT: 68 Gy/30F	66 mo	34 mo	MRI	chemo	NR	V25, V30, V40, V45, V50, V55, V60, V65, V70, D1%	V25 < 23.33 %, V30 < 19.23 %, V35 < 15.09 %, V40 < 10.53 %, V45 < 8.54 %, V50 < 7.11 %, V55 < 5.27 %, V60 < 2.72 %, V65 < 1.44 %, V70 < 0.38 %, D1%<69.07 Gy	NA	NA
Chen 2022****[41]	169 (all T4 stage)	22/169, 13.02 %	IMRT, 66–70.95/30-35F	110 mo	37.3 mo	MRI	chemo	NR	D2%	D2% ≤ 74.5 Gy	NA	5-year cumulative incidence of TLN: 2.0 % vs 25.2 %

Abbreviation: TLN: temporal lobe necrosis, TLI: temporal lobe injury, GTVp: primary gross tumor volume, mo: month, chemo: chemotherapy, NA: not applicable, NR: not reported, OR: odds ratio, HR: hazard ratio, C225: cetuximab, sHR = subdistribution hazard ratio, NLR: neutrophil-to-lymphocyte ratios, TL: temporal lobe.

*: Patients with unilateral TLN were included.

**: conference abstract.

***: A total of 1,887 patients with newly diagnosed NPC who underwent definitive IMRT were recorded. Among them, 43 patients who developed TLN were included in the TLN group for dosimetric analysis. The control group consisted of 43 NPC patients who did not develop TLN after treatment.

****: Patients with locally advanced NPC were included.

studies, the same rate was only counted once [25,26]. The average crude incidence of TLN was found to be 14.48 % (range, 2.28 %–47.29 %). Additionally, the TLN rate exceeded 20 % in 4 studies [28,39,42,43]. The variation in incidence is partly attributed to the inclusion criteria of certain studies, where only patients with advanced-stage disease were recruited [34,36,37,41,43]. Differences in RT techniques and previous therapies among institutions may have also contributed to the variation.

Dosimetric data from CT-based treatment planning systems were extracted in all studies. Seventeen of 18 studies [18,20–23,25–29,32,37,39,41,42,44,45] reported the association between temporal lobe radiation dose-volume parameters and the subsequent risk of TLN. Various dosimetric parameters were evaluated, including maximum dose of the temporal lobe (Dmax), mean dose of the temporal lobe (Dmean), minimum dose of the temporal lobe (Dmin), minimum dose received by 0.25 cc volume (D0.25 cc), D0.5 cc, D0.6 cc, D1cc, D2cc, D3cc, D6cc, D9cc, absorbed dose in 1 % of the volume (D1), absorbed dose in 2 % of the volume (D2), percentage of the temporal lobe volume receiving a dose over 20 Gy (V20), V25, V30, V40, V45, V50, V55, V60, V65, V70, relative V40 (rV40), absolute V40 (aV40), nasopharynx gross tumor volume (GTVnx) and fraction size. Additionally, one study evaluated the dosimetry of the half-brain, proposing D1.2 cc, V72Gy, V70Gy, V71Gy and V73Gy of the half-brain as potential predictors [39].

Among these dose-volume metrics, Dmax was the most extensively proposed dosimetric predictor of TLN in patients with NPC in six studies [20,21,23,25,28,37]. For example, in a study by Su et al., Dmax of the temporal lobe was estimated in 870 patients and an incidence of TLN of 4.60 % was observed. No TLN was observed in patients with Dmax below 64 Gy, but a 2.6 % increment in TLN per Gy of Dmax was seen when it exceeded 64 Gy, as determined by linear regression analysis. Furthermore, Dmax of the injured temporal lobe was significantly higher than that of the non-injured temporal lobe [25]. Similarly, another study suggested a cutoff of 70 Gy for Dmax and the incidence of TLN increased by 4.6 % per Gy when Dmax exceeded 69 Gy [28]. An optimal threshold of 65.77 Gy for Dmax was determined in a retrospective study involving 460 temporal lobes from 789 NPC patients. When Dmax exceeded the cutoff point, the 5-year incidence of TLN increased from 0.8 % to 27.1 % [21]. Lu et al. reviewed 4186 NPC cases and defined temporal lobe toxicity endpoints, such as edema, enhancement and necrosis, based on MRI features. The proposed cutoff values for Dmax were 72.25 Gy, 73.75 Gy and 74.87 Gy for edema, enhancement and necrosis, respectively [23]. Gou et al. analyzed dosimetric factors in 200 NPC patients with advanced T stage treated with IMRT and recommended a cutoff point of 78 Gy for Dmax [36]. The correlation between Dmax and TLN was found to be statistically significant ($p < 0.001$) [20]. There was a relatively wide recommendation of safe Dmax constraints between 64 and 75 Gy. It should be noted that the dosimetric criteria for Dmax may vary among studies because different guidelines and protocols were followed. For example, the RTOG protocol recommends D0.03 cc of the PTV, while an Italian guideline recommends D1cc [46]. Moreover, Yu et al. recommended that Dmax should be within 3 % of the target volume [47] and the ICRU 83 report suggested reporting D2% instead of Dmax [48]. The international guideline on dose prioritization in NPC recommends a dose limit of D0.03 cc $\leq$ 65 Gy for T1-2 tumors and $\leq$ 70 Gy for T3-4 tumors for the temporal lobe [49].

Four studies proposed D1cc as a dosimetric predictor of TLN in patients with NPC after definitive RT [23,25,28,34]. Su et al. suggested that keeping D1cc below 52–58 Gy can reduce the 5-year incidence of TLN to less than 5 %, while Lang et al. recommended a D1cc $<$ 60 Gy as relatively safe dose limit for the temporal lobe [28]. Lu et al. determined the optimal threshold of D1cc for edema, enhancement and necrosis as 66.77 Gy, 68.49 Gy and 69.65 Gy, respectively [23]. A study described a statistically significant relationship between D1cc and TLN in patients with T4 stage disease, with a 5-year cumulative incidence of TLN of 13.2 % for D1cc $\leq$ 71.14 Gy and 62.2 % for D1cc $>$ 71.14 Gy [34].

In addition to D1cc, several other parameters, such as the D_V (the absorbed dose in V volume), were found to be directly related to clinically significant TLN. These parameters include D0.25 cc, D0.5 cc, D0.6 cc, D2cc, D3cc, D6cc, D9cc, D1 and D2 of temporal lobe, and D1.2 cc of half the brain [39] (tabulated in Table 1). Three studies observed a positive correlation between TLN and D0.5 cc. One study, which compared 20 patients with unilateral TLN, found D0.5 cc to be the only independent predictor of TLN. The recommended dose tolerance for D0.5 cc was determined as 69 Gy [27]. TD5/5 refers to a radiation dose that would result in a 5 % risk of severe complications within 5 years post-irradiation. One study suggested TD5/5 of D0.5 cc as 73.66 Gy [22]. Lu et al. proposed dose tolerance values of 68.80 Gy, 69.34 Gy and 70.43 Gy for D0.5 cc in radiation-induced edema, enhancement and necrosis, respectively [23]. Aside from Dv, a total of 12 vol-based parameters (V_D), which represent the percentage of the temporal volume receiving doses above a certain threshold (D Gy), have been identified as having value in sparing the temporal lobe from radiation doses (Table 1). Among these parameters, V40, V45, V50, V60 and V70 have been assessed in more than three studies. Of note, constraints for V70 were derived to be 0.27 cc, 0.34 cc and 1.13 cc for protecting the temporal lobe from edema, enhancement and necrosis, respectively [23]. Another study proposed V70 with the highest AUC of 0.814 among all the temporal lobe parameters, with a cutoff value of 0.45 cc [39]. Given the fact that “hot spots” (high doses delivered to small volumes), such as Dmax, D0.25 cc, D0.5 cc, D0.6 cc, D1cc, and V70, are commonly observed to affect the prevalence of TLN, which may be clinically relevant, the number of focal high doses should be minimized during treatment planning if high doses are unavoidable.

V40 has been reported to be positively correlated to TLN in three studies [17,26,32]. The recommended threshold values for rV40 are less than 10 %, and for aV40, it is below 5 cc [26]. Zhang et al. compared a late toxicity called “temporal lobe enhancement” between IMRT and proton therapy. They proposed tolerance V40 $<$ 10.53 % for IMRT. These values were higher in the IMRT group compared to the proton therapy group [17]. Three studies suggested that Dmean was a predictive dosimetric factor for TLN in patients with NPC [20,23,32]. Receiver operating characteristic analysis was performed to determine the cutoff values of Dmean for radiation-induced edema, enhancement and necrosis, resulting in values of 16.96 Gy, 23.96 Gy and 28.07 Gy, respectively [23].

It’s worth noting that one study suggested the prescribed fraction size ($>$2 Gy) as an independent predictor of TLN, supported by both univariate and multivariate analyses [33]. Additionally, another study [21] found a higher incidence of TLN in patients treated with IMRT compared to those treated with 2D-RT, speculating that the larger fractional dose used in IMRT may contribute to the increased rate of TLN. Both Lawrence et al. [50] and Lee et al. [51] speculated that brain tissue was more susceptible to higher fraction sizes. The correlation between the incidence of TLN and fraction size is displayed in Fig. S2. Since locally advanced disease is associated with a larger target volume and, inevitably, a higher dose to a larger volume of critical organs at risk, which could confound the effects on fraction size, studies on patients with locally advanced NPC were highlighted with red dots on Fig. S2 [34,36,37] to indicate their inclusion. By excluding the confounding effect from these three studies with locally advanced disease, we also observed a tendency of a higher incidence of TLN with a larger fraction size (Fig. S2, blue dots). However, fraction sizes greater than 2 Gy per fraction are commonly used in most institutions nowadays, raising concerns about whether the current fractionation model might increase the occurrence of TLN. In terms of the occurrence of TLN, fraction sizes greater than 2 Gy are not recommended.

Radiation-related TLN is a complex condition influenced by various factors. Apart from dosimetric parameters, patient and tumor-specific characteristics, therapeutic approaches, radiological factors and biomarkers all contribute significantly to the development of TLN. Seventeen studies have examined the relationship between TLN and 11

Table 2
Studies on NTCP models or radiation dosimetric nomograms of post-radiation TLN/TLI in patients with NPC.

Study	Number of total patients	TLN/TLI events (%)	Median follow-up (month)	Median latency to TLN/TLI (month)	Diagnostic method	RT technique and dose	Concurrent therapy	Clinical and radiological factor associated to TLN/TLI	Predictive dosimetric parameter	Proposed cutoff
Original NTCP model										
Zeng 2015 [30]	351	29 of 351, 8.26 %	76	33	MRI	IMRT, 68 Gy/30F	chemo	T stage, chemo	D1cc	NR
Kong 2016 [31]	179	17/179, 9.50 %	63.5	43	MRI	IMRT, 68–75 Gy/32-34F	chemo for II-IVb stage	T stage	Dmax, D1cc	NR
Wang 2019 [35]	749	38/749, 5.07 %	48.8	39.5	MRI	IMRT for T1-2, IMRT + SIB for T3-4, T1-2: 66 Gy/30F, T3-4: 70.4 Gy/32F	chemo for IIB and above stage	T stage	D0.5 cc, D10	NR
Dosiomics risk models										
Yang 2023 [19]	5599	701/5599, 12.52 %	training: 36, validation: 38, prospective: 31, external test: 37	training: 38, validation: 39, prospective: 30, external: 40	MRI	IMRT, 66–72 Gy/28–33F	chemo	age	dosiomics signature, D1cc	D1cc < 61.9 Gy
Nomogram										
Zhang 2019 [42]	194	59/194, 30.41 %	NR	NR	MRI	IMRT	chemo	T stage, chemo	Dmax, D1cc	NR
Guan 2020 [38]	391	77/391, 19.69 %	42	36.5	MRI	IMRT, 68–76 Gy/30-33F	chemo	T stage, NLR	Dmax, D1cc	Dmax ≤ 75 Gy, D1cc ≤ 67 Gy
Wen 2021 [40]	8194	TLI: 989/8194, 12.1 %, TLN: 491/8194, 5.9 %	66.8	36	MRI	IMRT, 66–72 Gy/25-37F	chemo for IIB and above stage	Age, T stage	D0.5 cc	D0.5 cc < 65.06 Gy
Bin 2022* [43]	99	44/99, 44.44 %	training: 49.9, validation: 53.4	NR	MRI	IMRT, 68–76 Gy/30-38F	chemo	age, RadscoreT1 and RadscoreT2	Dmax, D1cc	Dmax < 72 Gy, D1cc < 68.2 Gy
Hou 2022 [54]	203	96/203, 47.29 %	50	NR	MRI	IMRT, 70–76 Gy/30–33F	chemo	age, differentiation, rad-score	Dmax, Dmean	NR
Radiomics model										
Bao 2022 [55]	216	108/216, 50 %	TLI: 33.3, non-TLI: 61	NR	MRI	IMRT, 70–76 Gy/30-33F	chemo	Radiomics feature, age, T stage	Dmax of left TL ≥ 68 Gy AUC = 0.936, Dmax of right TL ≥ 68 Gy AUC = 0.911**	Dmax of left TL < 68 Gy, Dmax of right TL < 68 Gy
Bao 2022 [56]	216	108/216, 50 %	TLI: 29.9, non-TLI: 58.7	NR	MRI	IMRT, 70–76 Gy/30-33F	chemo	Radiomics feature, T stage	None	NA
Bao 2022 [57]	214	107/214, 50 %	TLI: 33.4, non-TLI: 61.4	NR	MRI	IMRT, 70–74 Gy/30-33F	chemo	radiomics feature, T stage	PGTVnx, left TL Dmax, right TL Dmax***	NA

Abbreviation: TLN: temporal lobe necrosis, TLI: temporal lobe injury, GTVp: primary gross tumor volume, mo: month, chemo: chemotherapy, NA: not applicable, NR: not reported, OR: odds ratio, HR: hazard ratio, C225: cetuximab, sHR = subdistribution hazard ratio, NLR: neutrophil-to-lymphocyte ratios, TL: temporal lobe.
*: Patients with locally advanced NPC were included.
**: No independent dosimetric parameters was found but AUC of Dmax was high.
***: The significant difference was only detected by univariate analysis.

clinical factors (Tables 1 and 2). These factors include age, T category, N category, chemotherapy, targeted therapies (cetuximab or nimotuzumab), diabetes, neutrophil-to-lymphocyte ratios (NLR), TCR_{β} repertoire subtypes, radiological features and tumor differentiation. Chemotherapy is widely used in patients with advanced NPC. It is worth noting that in some studies [21,29,33], multivariate analysis showed that the use of systemic therapy was associated with TLN incidence. Therefore, chemotherapy or cetuximab may potentially affect the development of TLN.

Among these clinical factors, the T category was the most commonly observed. TLN development is rare in early stages, but studies have reported a higher incidence of TLN, ranging from 2.8 % to 54.1 %, in patients with T3-4 NPC compared to that in patients with T1-2 disease (refer to Fig. S3 and Table S4). Additionally, two studies identified the biomarker NLR as a prognostic factor for TLN, suggesting that the tumor immune microenvironment may play a crucial role in chronic TLN pathogenesis. Moreover, discrepancies in the use of concurrent therapies, such as chemotherapy and targeted therapy, were observed among the studies. Some studies reported that chemotherapy or cetuximab influenced TLN development [21,29,30,37,42].

The NTCP model is established to describe the correlation between dosimetric parameters and the probability of radiation-related toxicities. Several studies have investigated the relationship between TLN risk and NTCP models [30,31,35]. The least absolute shrinkage and selection operator (LASSO) has been widely used to effectively address the multicollinearity problem and has exhibited valid predictions regarding the incidence of radiation toxicities [52,53]. One NTCP model based on LASSO regression analysis utilized DVH data from 132 newly diagnosed NPC patients and identified D1cc and Dmax as relevant variables [31]. The TD5/5 values for TLN occurrence were 69.0 ± 1.6 Gy for Dmax and 62.8 ± 2.2 Gy for D1cc. Zeng et al. developed an NTCP model using unconditional logistic regression analysis, which included 16 DVH-based variables and four clinical variables [30]. D1cc was identified as an independent predictor, with a TD5/5 of 62.83 Gy. Furthermore, a prediction model that considered both dosimetric and clinical factors demonstrated that physical dose parameters (D0.5 cc and D10) selected by LASSO regression could reliably predict TLN [35]. Interestingly, Yang et al. developed a dosiomics risk model that incorporated clinical variables, dosiomics signatures and DVH parameters using a database of 2503 NPC patients [19]. Through LASSO-Cox regression, D1cc was identified as an independent predictor, with a TD5/5 of 61.9 Gy. The model was validated by a prospective and external test cohort and exhibited a powerful capacity to stratify patients into low-risk and high-risk groups, outperforming traditional clinical models. The probability curves of predicted and actual 3-year temporal lobe injury-free survival rates showed a high degree of overlap, indicating the strong predictive power of the novel model.

Five studies focused on the development of nomograms, with D1cc and Dmax being the most frequently included variables. Zhang et al. established a nomogram with a C-index of 0.8036 (concordance index, used to measure the discriminability of the nomograms), incorporating Dmax, D1cc, T category, and concurrent chemotherapy [42]. Guan et al. constructed a nomogram that included Dmax, D1cc, T category and NLR, which was validated by an external test cohort. The nomogram exhibited good discriminative power in both the primary (AUC = 0.847) and validation cohorts (AUC = 0.811) [38]. Wen et al. developed a nomogram based on 5-year follow-up data from a large cohort of 8194 NPC patients, where D0.5 cc was the most powerful predictor, with a TD5/5 of 65.06 Gy [40]. Another nomogram was generated based on clinical and radiomics data to predict TLN in patients with T4 NPC [43]. LASSO regression was used to evaluate DVH parameters, and Dmax (<72 Gy) and D1cc (<62.83 Gy) were selected as variables for the nomogram. The nomogram demonstrated good predictive performance with a C-index of 0.85 and 0.82 in the training and validation cohorts, respectively. Hou et al. developed a nomogram model that combined all independent predictors from clinical and radiomics models [54]. The nomogram exhibited better predictive performance (AUC = 0.87) than the clinical or radiomics models alone. Several studies have focused on nomograms that combined radiomics features and clinical factors, with three studies from the same institution potentially enrolling overlapping patient cohorts, all demonstrating excellent predictive power [55–57]. Although dosimetric parameters were not selected as variables due to a lack of independent predictive value, Dmax was considered a relevant factor for TLN. All the nomograms displayed good internal predictive power, but external validation studies are still lacking.

Given the fact that D1cc and Dmax were the most frequently mentioned parameters that may affect TLN, a random-effect model was applied for *meta*-analysis. Fig. 2 and Fig. 3A present the results of several studies reporting radiation-induced TLN. The pooled OR for D1cc was 1.86 (95 % CI: 1.03, 3.36, $I^2 = 77$ %, P < 0.01) (Table S5) and the pooled OR for Dmax was 1.41 (95 % CI: 0.88, 2.27, $I^2 = 82$ %, P < 0.01) (Table S6). Furthermore, the HR was analyzed, and the pooled estimate using the random-effects model is shown in Fig. 3B, indicating moderate heterogeneity ($I^2 = 48$ %, p = 0.14). The pooled HR for Dmax on the risk of TLN in patients with NPC receiving definitive RT was 1.22 (95 % CI: 1.17, 1.26, Fig. 3B). Both D1cc and Dmax of the temporal lobe exhibited considerable heterogeneity among the included studies, which could potentially be attributed to several factors. These factors included

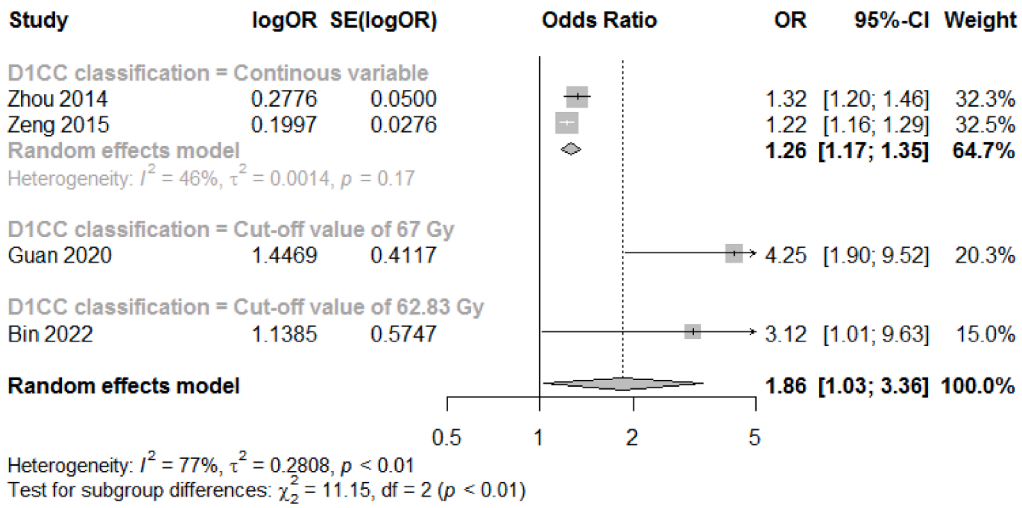

Fig. 2. Subgroup *meta*-analysis showing the association of D1cc and radiation-induced temporal lobe necrosis. Studies were included only if the reported odds ratios were adjusted in multivariable analyses.

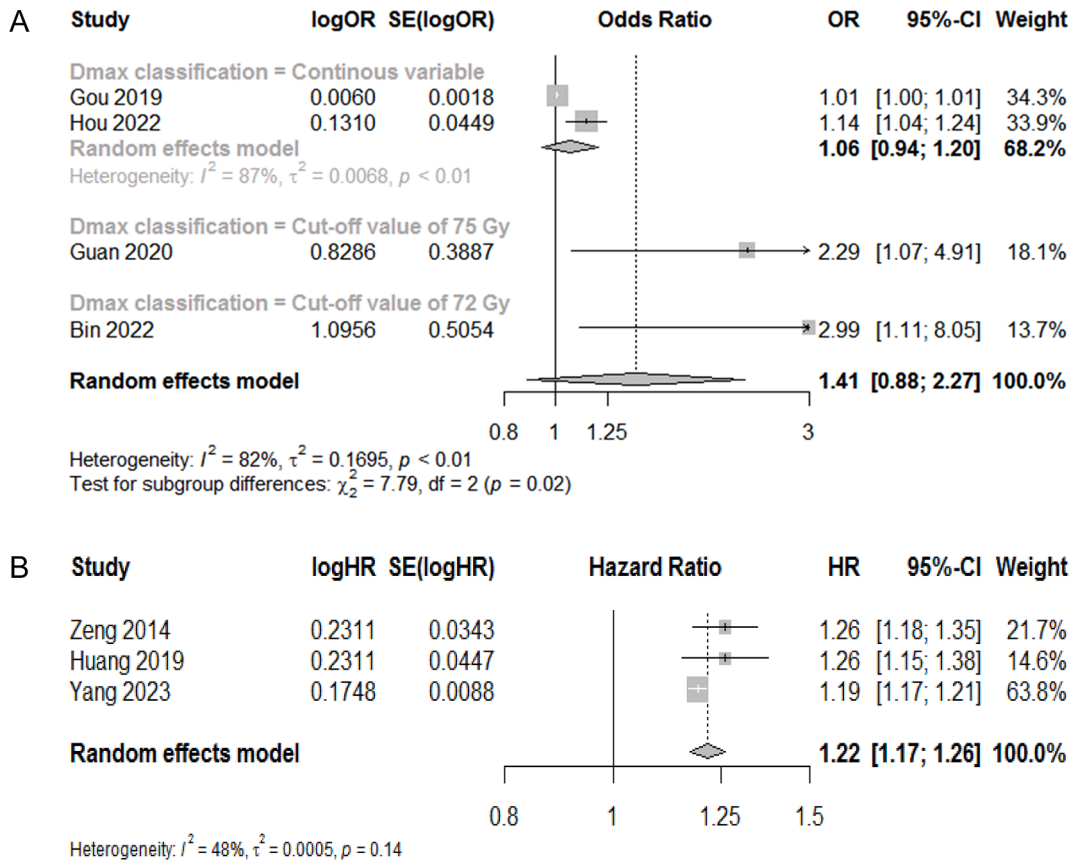

Fig. 3. (A) Subgroup *meta*-analysis for OR and (B) *meta*-analysis for HR showing the association of Dmax and radiation-induced temporal lobe necrosis, respectively.

variations in proposed cutoff values across the studies and the combination of dichotomized and continuous variables for analysis, variation in concurrent therapy regimens (such as the use of cetuximab in three studies [29,34,37]), variation in patient characteristics (including the enrollment of only T4 stage patients in two studies [34,43]), and differences in fraction size across different institutions. Since the results were heterogeneous, randomized studies are needed to confirm the hypothesis. Nevertheless, this review highlights the impact of dosimetric parameters on TLN, suggesting that the temporal lobe is vulnerable to a high dose delivered in a small volume.

Discussion

This systematic review provides valuable insights into the relationship between dosimetric parameters and the prevalence of TLN in patients with NPC treated with curative-intent RT. The findings indicate that the dosimetric parameters Dmax and D1cc are potentially valuable in predicting TLN, with threshold values of ≤72 Gy and ≤62 Gy, respectively. Since there is a positive correlation between temporal lobe DVH parameters and TLN, it is crucial to establish clinically useful standards that guide physicians in estimating radiation-related complications in current treatment paradigms.

These findings are particularly relevant to NPC, which is an endemic head and neck cancer in Southeast Asia, with RT being the primary treatment modality. Although advancements in RT techniques have significantly improved the precision of treatment, enabling dose escalation, prioritization, and conformity, they still result in unavoidable exposure of adjacent structures to relatively high radiation doses. For example, in a prospective study comparing IMRT with 2D-RT, the percentage of temporal lobe neuropathy treated with IMRT remained relatively high at 13.1 %, although it showed improvement compared to 21 % with 2D-RT (p = 0.01) [13]. Similar findings were reported by Zhou et al., with the crude incidence of TLN in NPC patients treated with IMRT being 7.5 %, representing a 3.3 % improvement compared to 10.8 % with 2D-RT [58]. In the 2D-RT era, Lee et al. [51] converted various fractionation schedules into BED and found that the BED ($\alpha/\beta = 3$ Gy) ranged from 103 to 121 Gy. A total dose of 64 Gy at 2 Gy per fraction ($BED_{Gy3} = 104$ Gy) would result in a 5 % TLN rate in 10-year survivors. According to the full-course radiation dose recommended by the NCCN guideline, 70–70.2 Gy at 1.8 to 2 Gy per fraction, or 69.96 Gy at 2.12 Gy per fraction, the BED ($\alpha/\beta = 3$ Gy) is 116.7 and 119.4 Gy, respectively. We also transformed the total dose of the included studies (excluding those studies reporting the total dose given as a range) into BED ($\alpha/\beta = 3$ Gy), ranging from 114.4 to 129.3 Gy. Most reported BED values fell within this range, with the outliers (129.3 Gy) coming from studies that only enrolled locally advanced NPC [20,37]. Notably, emerging evidence has revealed that the prevalence of TLN may be affected by RT techniques. He et al. [20] reported a lower incidence of TLN in patients treated with VMAT compared to IMRT. Shao et al. demonstrated that radiation damage induced by IMRT and VMAT affected different regions of the brain, with IMRT mainly impacting the region close to the temporal pole [59]. The discrepancy in the incidence of TLN between IMRT and VMAT is the result of different patterns of dose deposition. In addition, proton beam therapy, recognized as a state-of-the-art radiotherapy technique, has received widespread acknowledgement for its potential to further reduce radiation-related toxicities [60,61]. However, TLN is a late toxicity, and the existing literature on the use of proton beam therapy has not provided a sufficiently long follow-up period to accurately determine the incidence of TLN. Furthermore, uncertainties persist regarding the relative biological effectiveness of proton therapy. Specifically, in a study by Zhang et al. [17] involving 566 NPC patients, double-scattering proton therapy (60 patients) and IMRT (506 patients) were compared at Massachusetts General Hospital. The study found that the tolerance doses for temporal lobe radiographic changes with proton

treatments were lower than those for photon treatments, despite achieving similar dose distributions through both techniques. Consequently, proton therapy exhibited a higher incidence of temporal lobe radiographic changes (10 %) compared to IMRT (4 %). The authors suggested that the relative biological effectiveness (RBE) for temporal lobe enhancement was 1.18 at D1%, deviating from the previously established value of 1.1, which was based on *in vitro* cell culture systems and animal models. They also proposed a dose limit of D1% < 58.56 Gy for proton therapy and <69.07 Gy for photon therapy. In contrast, Liu et al. found no statistically significant difference in the cumulative risk of TLN between proton beam therapy (86 patients) and VMAT (112 patients) in 198 patients with NPC undergoing curative-intent radiotherapy [62]. However, it is important to note that these findings were based on a relatively small number of patients recruited from a single institution, highlighting the need for further large-scale, multicenter studies.

Our findings align with the aforementioned observations. The incidence of TLN in NPC patients treated with IMRT varies across studies, with reported rates ranging from 2.3 % to as high as 47.3 %. These studies have reported median follow-up durations of 28 to 110 months and the average crude incidence of TLN is approximately 14 %. The majority of studies included in the analysis had follow-up periods exceeding 3 years. Despite the routine adoption of IMRT, the relatively high crude incidence also highlights the ongoing risk of TLN as a significant late complication. Most TLN is asymptomatic and diagnosed by radiological finding (Table S7). Therefore, regular MRI surveillance is crucial for the early detection of TLN during follow-up. Interestingly, Cicone et al. longitudinally monitored the evolution of brain metastases with brain radionecrosis by using a novel method, 6-^{18}F-fluoro-l-dopa (^{18}F-FDOPA)-PET/CT, and found that it has better diagnostic accuracy in discriminating tumor progression and brain necrosis compared to routine MRI. ^{18}F-FDOPA-PET/CT could serve as a complementary method during long-term follow-up [63].

It is worth noting that international guidelines recommend a dose of 70 Gy in 35 fractions to the clinical target volume (CTV) of the nasopharynx [64]. However, the studies included in this review used institutional guidelines, resulting in fraction sizes generally greater than 2 Gy in most cases. Fraction size (>2 Gy) has been proposed as a predictor for TLN [33]. For example, Lee et al., using the 2D-RT technique, reported a 10-year actuarial incidence of TLN of 4.6 % for "conventional" fractionation (60 Gy with 2.5 Gy per fraction), which increased to 18.6 % for a hypofractionation scheme (50.4 Gy with 4.2 Gy per fraction) [51]. Similarly, a fraction size of 2.34 Gy per fraction was considered unsafe due to a relatively high risk of TLN in a prospective IMRT trial [65]. As a result, dose prioritization guidelines have been suggested, including dose limits for the planning organ at risk volume (PRV) of the temporal lobe. These guidelines propose a temporal lobe D0.03 cc PRV dose <65 Gy for T1-2 tumors and <70 Gy for T3-4 tumors, as well as a Dmax < 72 Gy for T3-4 tumors, with fraction sizes not exceeding 2 Gy [49]. However, achieving optimal OAR constraints in clinical practice, especially when prioritizing planning target volume over the temporal lobe, can be challenging. While these recommendations support the findings of this study regarding the dose to the Dmax of the temporal lobe, several studies have reported that V40 [17,26,32] and Dmean [20,23,32] was correlated to incidence of TLN, implying that limiting moderate dose delivered to a large area may confer reducing incidence of TLN. It is important to acknowledge that factors other than dosimetric parameters and T categories, such as host characteristics, tumor-specific features and therapeutic factors, may also significantly contribute to the development of TLN, highlighting the limitations of these guidelines.

It is important to acknowledge certain limitations and heterogeneity among the studies reviewed. One of the shortcomings is the information bias as most studies are retrospective design except one containing both retrospective and prospective cohorts [19]. TLN diagnosis relied primarily on clinical and radiological characteristics without confirmation through pathology in all studies. The use of imaging modalities for TLN diagnosis may not always be accurate, particularly in the early stages of the condition. TLN and tumor recurrence can present similar symptoms and radiological features, potentially leading to misclassification of patients with TLN. Most studies only reported the crude incidence of TLN, which does not take into account patients who were lost to follow-up or have passed away. This may underestimate the true incidence of TLN. As TLN is a late toxicity, the follow-up time ranging from 27 to 48 months may be insufficient.

Delineating the exact boundaries of the temporal lobe can also be challenging due to anatomical variability, methodological differences in imaging techniques and the lack of a clear and universally accepted definition for the temporal lobe [66–68]. Standardizing the delineation of the temporal lobe can help improve the accuracy and comparability of future studies.

Lastly, the constraints, nomograms, and NTCP models proposed in the reviewed studies were derived from a single cohort of patients. External validation of these models in independent cohorts is essential to assess their generalizability and reliability.

In conclusion, this systematic review highlights and summarizes the dosimetric parameters in predicting the risk of TLN in NPC patients treated with IMRT. The findings suggest that Dmax and D1cc are potential predictors of TLN. However, it is essential to consider other factors, including the volume receiving a moderate dose, host characteristics, tumor-specific features, and therapeutic factors, as they may also contribute to the development of TLN. Additionally, the exploration of innovative radiation techniques, such as proton therapy, may also hold promise in reducing TLN incidence. The latency of TLN is usually over 2 years so long-term MRI surveillance and diligent patient monitoring are recommended to facilitate early detection. Overall, this review provides valuable insights into the understanding of TLN in NPC patients and sets the stage for future studies and the formulation of clinical guidelines in this field.

Contributors

WN and AF with the help of the steering committee members designed and supervised the study.

NW and AL obtained funding.

JD, CW and JL searched and selected the studies.

JD and JL collected and checked data.

JD, CW and WN did the statistical analyses and wrote the draft, with revisions from the other investigators.

Role of the funding source

This work did not receive direct funding. W.T. Ng and A.M.W. Lee are supported by Shenzhen Key Medical Discipline Construction Fund (No. SZXK014), Shenzhen Science and Technology Program (Grant No. KQTD20180411185028798); Department of Clinical Oncology, Shenzhen Key Laboratory for cancer metastasis and personalized therapy, The University of Hong Kong-Shenzhen Hospital (Acknowledgement: ZDSYS20210623091811035); the Shenzhen Fundamental Research Program, China (CYJ20210324114404013) and Sanming Project of Medicine in Shenzhen, China (SZSM202211017).

CRediT authorship contribution statement

Jun Dong: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Wai Tong Ng:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Charlene H.L. Wong:** Software, Methodology, Formal analysis, Data curation. **Ji-Shi Li:** Methodology, Investigation, Data curation. **Heleen Bollen:** Supervision, Conceptualization. **James C.H. Chow:** Supervision, Conceptualization. **Avraham Eisbruch:** Supervision, Conceptualization. **Anne W.M. Lee:** Supervision, Funding acquisition, Conceptualization. **Victor H.F. Lee:** Supervision,

Conceptualization. **Sweet Ping Ng:** Supervision, Conceptualization. **Sandra Nuyts:** Supervision, Conceptualization. **Robert Smee:** Supervision, Conceptualization. **Alfio Ferlito:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110258.

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