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Dosimetric comparison of volumetric-modulated arc therapy (VMAT) and fixed field intensity-modulated radiotherapy (IMRT) in patients with nasal tumor: a meta-analysis

W.G. Feng, W. Ma, Sh.P. Li, Y.X. Guo, W. Du, H.Y. Cai*

Department of Radiotherapy, Gansu Provincial Hospital, Lanzhou, Gansu 73000, China

► ***Original article***

Corresponding author:
H.Y. Cai, Ph.D.,
E-mail: *gschy333@163.com*

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ABSTRACT

***Background*:** In recent years, volumetric-modulated arc therapy (VMAT) and fixed field intensity-modulated radiotherapy (IMRT) have been used as the two mainstream radiotherapy techniques for the treatment of nasal tumors. In this study, we compared effectiveness of these two radiotherapy techniques in the treatment of nasal tumors through analysis of relevant literature and meta-analysis. ***Materials and Methods*:** A search was performed on PubMed, Web of Science, Embase, and Cochrane Library databases on April 2022 to identify all related literature in line with pre-determined eligibility criteria. The included/excluded studies were screened manually and relevance data were extracted. Forest plots were plotted and analyze, Egger's asymmetry tests and sensitivity analysis were conducted using software Stata 16.0. ***Results*:** Eight studies were included in the meta-analysis. We found no significant difference in $D_{2\%}$ and $D_{98\%}$ of the Planning Target Volumes (PTV) between VMAT and IMRT. In contrast, the conformity index (CI) and the homogeneity index (HI) were significantly different between the two groups. Further analysis revealed no significant differences in dose sparing for all analyzed organs at risk (OARs) between VMAT and IMRT techniques. In addition, the monitor unit (MUs) of VMAT plan was significantly lower than that of the IMRT plan. ***Conclusions*:** VMAT has better local tumor control rate compared with IMRT, but it does not significantly reduce maximum dose (Dmax) or mean dose (Dmean) of OARs. We suggest that VMAT plan may be a better radiation therapy technology in the treatment of nasal tumors.

INTRODUCTION

Nasal tumors may be intranasal-arising from the tissues inside the nasal cavity such as the epithelial lining, cartilage, bone, lymphoid tissues or extra nasal -arising from the nasal planum or other tissues covering the nose. With the continuous progress of society and economy, people's living standards continue to improve, the level of medical treatment has also been developed, and the treatment of nasal tumors has also been improved. Radiotherapy is one of the mainstay treatment for nasal tumors [1-4]. Radiation treatment techniques for nasal tumors include three-dimensional conformal radiation therapy (3DCRT) [5, 6], IMRT [7], and VMAT [8, 9] among others. Radiotherapy for nasal neoplasms can cause radiation reactions in the tissues surrounding the neoplasms and adjacent tissues and organs. IMRT and VMAT can increase the dose conformal degree of tumor target area, significantly reduce the dose of surrounding normal tissues, and protect surrounding normal tissues and organs [10-12].

Fixed field IMRT is the most commonly used radiotherapy technique and represents a major breakthrough in the treatment of tumors in the last century [13, 14]. It divides each radiation field into many small fields. During the plan-making stage, radiation beams are assigned to different weights according to the shape and depth of the target area, as well as the anatomical relationship with the OARs. This is done to improve the tumor dose and uniformity, and lower the dose of exposure to the surrounding normal tissues. VMAT is a new form of intensity-modulated radiotherapy technique [15, 16]. Compared fixed field IMRT, VMAT allows the speed of motion of the accelerator arm, the Angle of the multi-leaf collimator (MLC), the position and speed of the MLC leaves, and the dose rate of the machine to be automatically changed as needed during radiation therapy.

Currently, whether VMAT has a dosimetric advantage over the fixed field IMRT in the treatment of nasal tumors is controversial. In this meta-analysis, we compared the effectiveness of VMAT and IMRT plan to provide guidance for clinical selection of appropriate radiotherapy technique.

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MATERIAL AND METHODS

Search strategy

We obeyed the suggestions of the PRISMA statement [17], although this meta-analysis was concerned with observational studies. The PubMed, Web of Science, Embase, and Cochrane Library databases were searched by us without restrictions on years and status of publication, by using the following keywords: "nasal," "sinus," "intensity modulated radiotherapy," "IMRT," "volumetric modulated arc radiotherapy," "VMAT," and "Rapid arc." Literature searches were limited to English. The last searched data was in April 2022.

The searching terms incorporated these keywords were as follows: ((nasal) OR (sinus)) AND (((intensity modulated radiotherapy) OR (IMRT)) AND ((volumetric modulated arc therapy) OR (VMAT) OR (Rapid arc))). The search strategy was appropriately adjusted according to different databases and confirmed after multiple pre-retrieval tests. To collect more eligible studies, we also searched the keywords using the Google Scholar search engine. Any disagreements or contradictions were resolved through consultation.

Study selection

Two reviewers selected and evaluated relevant studies according to the following criteria: 1) Patients diagnosed with nasal tumor; studies with cervical node metastasis were excluded; 2) Studies comparing VMAT with IMRT plans were included but those involving combined treatments were excluded; 3) Studies that provided the following dosimetric data were included: MUs, PTV index estimated, brainstem, chiasm, bilateral lens, bilateral optic nerve, and spinal cord; Data without mean and standard deviation (SD) were excluded; 4) Meeting articles, posters, review papers, and relapse studies were excluded; and 5) None of the cases had distant metastasis or had received prior radiotherapy.

Data extraction

Two researchers independently completed data extraction. Differences of opinion were resolved through discussion, and a third researcher participates when necessary to reach a consensus on this matter. All data below were extracted from selected studies: 1) Basic information of IMRT and VMAT plan, including first author, country, the treatment planning system (TPS), year of publication, prescription dose, radiotherapy technique, etc. 2) Data for MUs, PTV($D_{98\%}$, $D_{2\%}$, CI and HI), brainstem (Dmax), chiasm (Dmax), bilateral lens (Dmax), bilateral optic nerves (Dmax), bilateral eyes (Dmax), gland parotid (Dmean) and spinal cord (Dmax). $D_{98\%}$ dose received by 98% of the volume is near-minimum dose, and $D_{2\%}$ dose received by 2% of the volume is near-maximum dose.

The specific principles were as follows: If Coplanar VMAT (co-VMAT) plan and No coplanar VMAT (NC-VMAT) plan exist in the paper, co-VMAT would be chosen. According to plan quality, the co-VMAT is superior to NC-VMAT [18]. All data were selected from plans using 6-MV photon beams.

Statistical analysis

The extracted data were analyzed through forest plots, publication bias, and sensitivity analysis. VMAT was used as the experimental group and IMRT was used as the control group. For measurement data, the pooled weight mean difference (WMD) or standardized mean difference (SMD), and 95% confidence intervals (95% CIs) were calculated. I^2 was used to analyze heterogeneity among included studies. If there was heterogeneity (I^2>50%), a random-effect model was applied for analysis and sensitivity analysis was performed to evaluate the stability of the meta-analysis results. If I^2<50%, a fixed-effect model was used for analysis. The Egger's test was employed to evaluate publication bias. All the data were analyzed using RevMan software (Version 5.3, Cochrane Collaboration) and Stata software (Version16.0, Stata Corporation). The Egger's asymmetry tests and the sensitivity analyses were conducted using the Stata software. P<0.05 was considered statistical significant.

RESULTS

Literature search and basic characteristics

The total number of relevant studies in the initial search of PubMed, Web of Science, Embase, and the Cochrane Library were 421, 39, 50, and 3, respectively. Finally, a total of 8 full-text references were included after literature screening according to inclusion/exclusion criteria. The flowchart of the retrieved studies is shown in figure 1. Eight studies included 108 patients; a total of 108 VMAT plans and 108 IMRT plans were evaluated in the meta-analysis. Basic information, including such as the first author, year of publication, country, TPS, and other details, were summarized in table 1 [18-25].

Comparison of VMAT and IMRT

$D_{98\%}$ and $D_{2\%}$ of PTV did not display any significant differences between the VMAT and IMRT plans (P>0.05) [table 2 and figure 2(c, d)]. The conformity index (CI) of PTV tends to 1, the conformity is better. Whether both CI<1 and CI>1, CI had significantly increased for VMAT than IMRT for radiotherapy (P=0.001 and P=0.005) [table 2 and figure 2(a)]. HI of PTV showed significant differences between the VMAT and IMRT plans (P=0.04) [table 2 and figure 2(b)].

For the dosimetric comparison of OARs and MUs, forest plots are shown in figure 3. There were no significant differences between the VMAT and IMRT

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plans regarding radiation dose of OARs (P>0.05) (Table 2). However, compared with IMRT, MUs of VMAT were significantly lower (P<0.001) (table 2).

It is difficult to estimate the publication bias of this meta-analysis because of the limited number of studies included. For the part of parameters in Table 2, Egger's tests were applied to evaluate publication bias. There was no publication bias for other parameters except MUs. In addition, if I^2>50%, sensitivity analysis was carried out, and all results are shown in figure 4. Comparing VMAT plans to IMRT plans, the meta-analysis results for the dosimetric parameters were not significantly affected by removing any literature included, which showed that every single study did not affect the stability of pooled study estimate.

Table1. Main features of the studies for dosimetric comparison.

First author, Year	Country	TPS	N	Prescribed dose	Radiation technology	obervational index						
						PTV	Brainstem	Optic chiasm, Bilateral optic nerve, Bilateral lens	Bilateral eye	Bilateral parotid	Spinal cord	MUs
Ning ZH 2014 [18]	China	Monaco	10	68Gy/33f, 59Gy/28f	co-VMAT, NC-IMRT	$D_{2\%}$, $D_{98\%}$, CI, HI	$D_{2\%}$	D_{max}	$D_{2\%}$			Y
Sang Y 2020 [19]	China	Raystation	18	66Gy/30f, 60Gy/30f, 54Gy/30f	co-VMAT, co-IMRT	CI, HI	D_{max}	D_{max}			D_{max}	Y
Raturi VP 2021 [20]	Japan	Raystation	12	65Gy/26f	NC-VMAT, NC-IMRT	$D_{2\%}$, $D_{98\%}$, CI, HI	D_{max}	D_{max}			D_{max}	Y
Nguyen K 2013 [21]	Houston (USA)	Pinnacle	10	60Gy/30f, 57Gy/30f, 54GY/30f	NC-VMAT, NC-IMRT		D_{max}	D_{max}		D_{mean}	D_{max}	Y
Lu JY 2016 [22]	China	Eclipse	14	60Gy/30f	co-VMAT, NC-IMRT	$D_{2\%}$, $D_{98\%}$, CI, HI	$D_{2\%}$	$D_{2\%}$	$D_{2\%}$	D_{mean}	$D_{2\%}$	Y
Liu XF 2019 [23]	China	Eclipse	24	50Gy/25f	co-VMAT, co-IMRT	$D_{2\%}$, $D_{98\%}$, CI, HI	D_{max}	D_{max}	D_{max}	D_{mean}	D_{max}	Y
Jeong Y 2014 [24]	Korea	Eclipse	10	60Gy/30f	co-VMAT, NC-IMRT	CI, HI	D_{max}	D_{max}	D_{max}	D_{mean}		Y
Cakir A 2019 [25]	Turkey	Eclipse	10	50Gy	co-VMAT, NC-IMRT	$D_{2\%}$, $D_{98\%}$, CI, HI	D_{max}	D_{max}	D_{max}		D_{max}	

Notes: N = IMRT sample size = VMAT sample size. Abbreviations: TPS = the treatment planning system, f = fractional; co-VMAT = coplanar volumetric-modulated arc therapy; NC-IMRT = No coplanar intensity-modulated radiation therapy; NC-VMAT = No coplanar volumetric-modulated arc therapy; co-IMRT = coplanar intensity-modulated radiation therapy; CI = conformity index; HI = homogeneity index; $D_{98\%}$ = near-min dose; $D_{2\%}$ = near-max dose; D_{max} = maximum dose; D_{mean} = mean dose; MUs = monitor units; Y=Yes.

Table 2. Comparison of PTV and OARs between VMAT and IMRT.

research projects	number[study]	analysis model	I^2(%)	SMD	95%CI	P-value	Egger's test
CI(<1)	5[18-20,22,23]	random	65.1	0.02(W)	[0.01,0.04]	0.001	
HI	7[18-20,22-25]	random	93.4	1.45	[-2.83,-0.07]	0.04	0.067
$D_{98\%}$	5[18,20,22,23,25]	random	95.2	0.73	[-1.06,2.51]	0.42	
$D_{2\%}$	5[18,20,22,23,25]	random	81	-0.13	[-0.93,0.66]	0.75	
brainstem D_{max}	8[18-25]	random	73.8	-0.31	[-0.86,0.24]	0.285	0.158
chiasm D_{max}	8[18-25]	fixed	23.1	0.00	[-0.27,0.27]	0.981	0.284
Ipsi len D_{max}	8[18-25]	random	91.7	-0.48	[-1.55,0.58]	0.374	0.357
Cont len D_{max}	8[18-25]	random	89	-0.23	[-1.12,0.66]	0.611	0.918
Ipsi optic nerve D_{max}	8[18-25]	fixed	46	-0.06	[-0.33,0.21]	0.655	0.059
Cont optic nerve D_{max}	8[18-25]	fixed	46.8	-0.01	[-0.28,-0.26]	0.933	0.462
Ipsi eye D_{max}	5[18,22-25]	random	70.1	0.05	[-0.60,0.71]	0.88	
Cont eye D_{max}	5[18,22-25]	random	79.2	0.11	[-0.68,0.89]	0.79	
Ipsi parotid D_{mean}	4[21-24]	fixed	0	0.07	[-0.30,0.43]	0.709	
Cont parotid D_{mean}	4[21-24]	fixed	0	0.19	[-0.18,0.55]	0.315	
spinal cord	6[19-23,25]	fixed	0	-0.06	[-0.36,0.24]	0.684	0.460
MUs	7[18-24]	random	95.3	-4.49	[-6.67,-2.31]	<0.0001	0.004

Notes: W = WMD. Abbreviations: CI = conformity index; HI = homogeneity index; $D_{98\%}$ = near-min dose; $D_{2\%}$ = near-max dose; D_{max} = maximum point dose; D_{mean} = mean dose; Ipsi = ipsilateral; Cont = contralateral.

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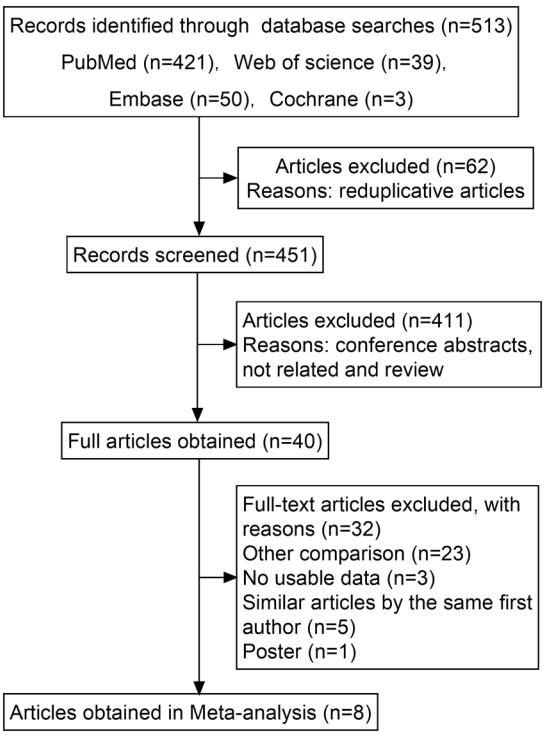

Figure 1. The flowchart of Literature screening.

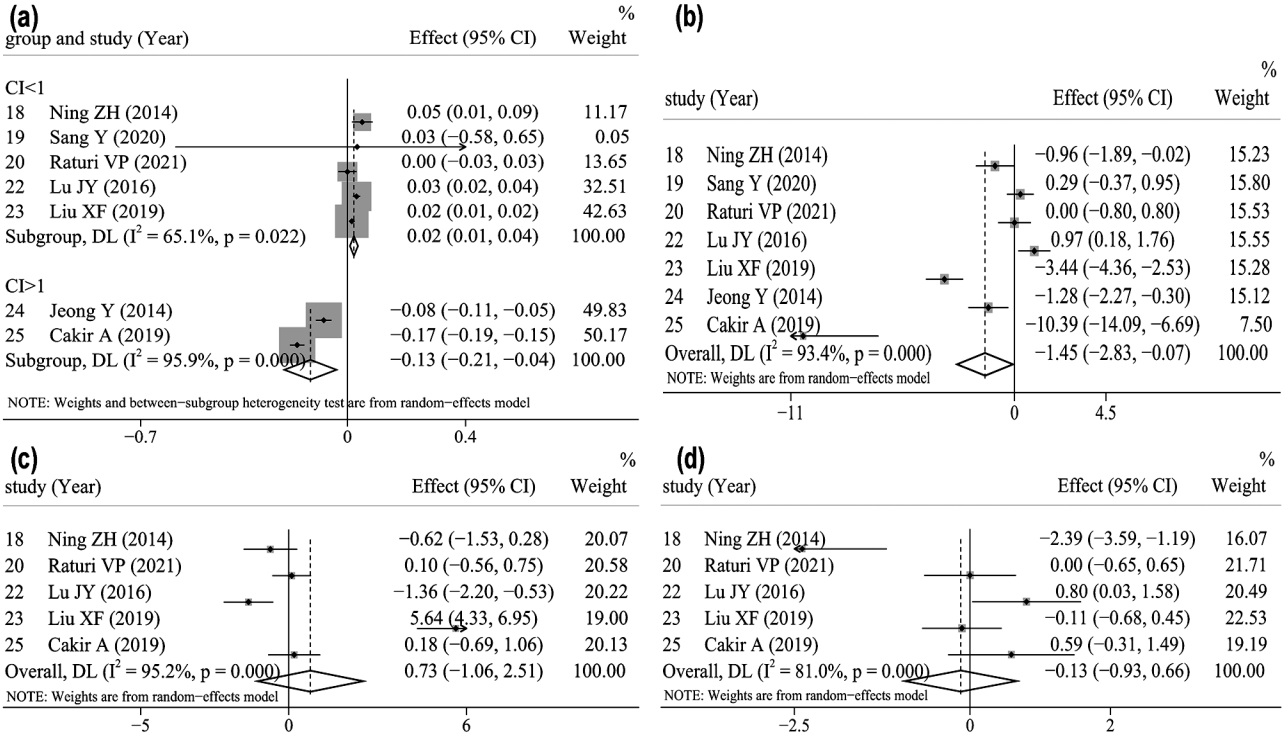

Figure 2. Forest plot of PTV index between VMAT and IMRT plans. **(a)** CI, **(b)** HI, **(c)** D98%, **(d)** D2%.

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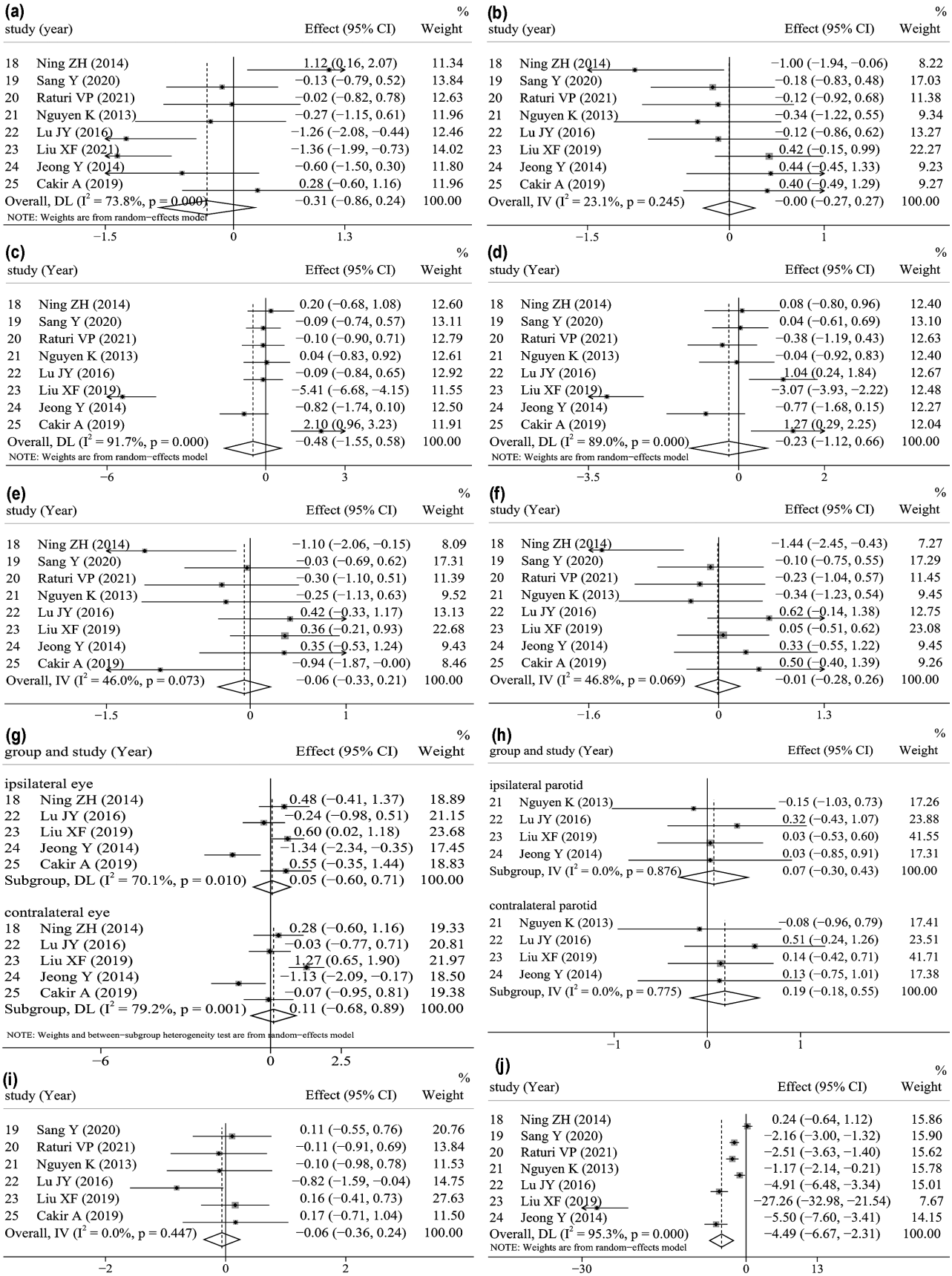

Figure 3. Forest plot of irradiational dose of OARs and forest plot of MUs between VMAT and IMRT plans. **(a)** brainstem, **(b)** chiasm, **(c)** Ispi len, **(d)** Cont len, **(e)** Ispi optic nerve, **(f)** Cont optic nerve, **(g)** eye, **(h)** parotid, **(i)** spinal cord, **(j)** MUs.

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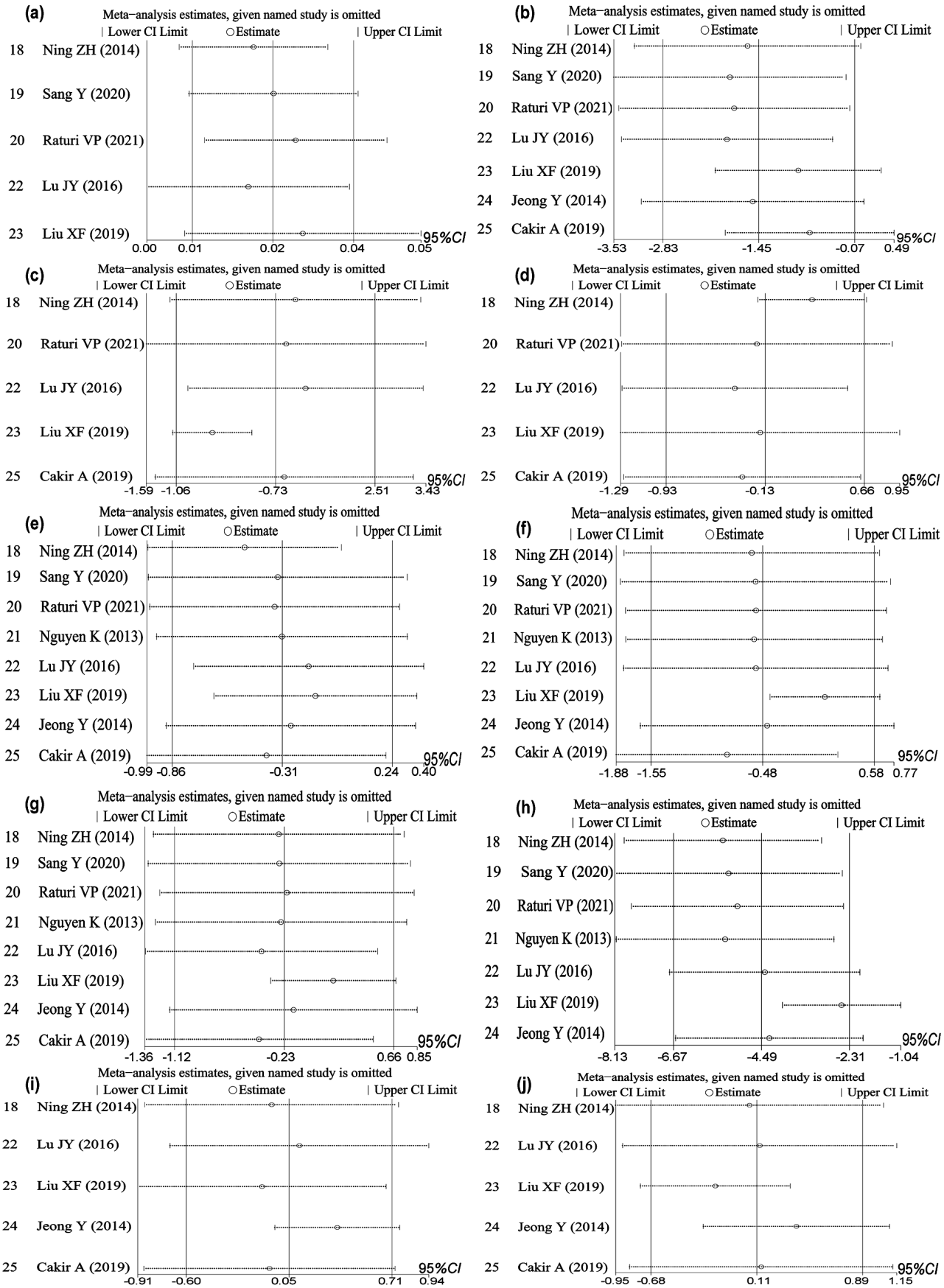

Figure 4. Sensitivity and stability analysis diagram. **(a)** CI<0, **(b)** HI, **(c)** 98%, **(d)** 2%, **(e)** brainstem, **(f)** Ipsi len, **(g)** Cont len, **(h)** MUs, **(i)** Ipsi eye, **(j)** Cont eye.

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DISCUSSION

VMAT was developed as an improved technique version of the fixed field IMRT. It can promote highly conformal therapy and reduce radiation damage to important structures around the target. In this meta-analysis, we investigated whether VMAT has a dosimetric advantage over IMRT in terms of target dose uniformity, conformal and dose to OARs during radiotherapy for nasal tumors. This is the first meta-analysis to compare in detail the dosimetric differences between VMAT techniques and IMRT techniques in the treatment of nasal neoplasm.

For clinical trials with small samples, meta-analysis can explore efficacy unlike traditional descriptive reviews [26-30]. Thus, we employed the meta-analysis approach to make an objective evaluation of the evidence, accurate and objective assessment of the effect indicators, and explain heterogeneity between the results of different studies. Several studies have compared the advantages and disadvantages of various radiation therapy technologies, but few of such studies were meta-analyses. In this study, we aimed to provide a better comparison of the original small-sample radiotherapy techniques and evaluate consistency among the results of multiple studies through meta-analysis.

The $D_{98\%}$ of PTV is used as the approximate minimum absorbed dose and $D_{2\%}$ of PTV is defined as the near-maximum absorbed dose [31]. In this meta-analysis, we found no significant difference in $D_{98\%}$ of target between VMAT plans and IMRT plans (P = 0.42). As can be seen from figure 2(c), only the study by Liu XF et al [23] reported that $D_{98\%}$ of PTV in VMAT plans was significantly higher than in IMRT plans. Analysis of literature 23 and literature 19 revealed that there were differences in collimator rotation angles and beam angles between coplanar radiation technology and non-coplanar radiation technology. Moreover, the $D_{2\%}$ of target was not significantly difference (P = 0.75) between VMAT and IMRT plans. Data shown in figure 2(d) showed that only the study by Ning *et al.* [18] found that $D_{2\%}$ of PTV in VMAT plan was lower than in IMRT. Notably, the setting models of the prescription dose in literature 18 differed from those of other studies.

The conformity index and homogeneity index are two complementary tools used to score treatment plans to allow comparisons of their effects on the same patient [32-35]. The closer the CI value is to 1, the better is the conformity of PTV. If the CI values of the studies were greater than 1, a smaller CI indicated better target conformity. If the CI values of the studies were less than 1, a greater CI indicated better target conformality. Figure 2(a) shows that the CI was higher in VMAT than IMRT for both CI<1 and CI>1. In the HI formula, the smaller the HI value is, the better the PTV uniformity will be. Figure 2(b) indicates that HI was significantly different between the two groups (P=0.04). Finally, this Meta-analysis found that the VMAT plan has significant advantages in improving the local tumor control rate.

In terms of the target dose distribution, there were no significant differences in $D_{98\%}$ and $D_{2\%}$ between VMAT to IMRT plans. However, the CI and HI values were markedly different between VMAT and IMRT plans. These results indicated that the coverage and homogeneity of the target dose was substantially different between VMAT and IMRT plans, and the target dose distribution may be affected by different radiation techniques.

The brainstem, lens, optic chiasm, and optic nerves are the foremost OARs in head and neck neoplasm. The maximum doses of these OARs were compared between VMAT plans and IMRT plans in the treatment of nasal tumor as shown in figure 3(a-f). The meta-analysis of the Dmax of these OARs showed comparable results between the two groups (P = 0.258, 0.981, 0.374, 0.611, 0.655, 0.933). The Dmax of the brainstem and the lens showed high heterogeneity among the included studies. These results suggested that the irradiation dose to different organs may not only affected by different technologies but is also influenced by a combination of multiple factors, including collimator rotation angles, algorithm, prescription dose, and beam angles. For instance, the results of literature 19 and 23 were significantly different due to the different collimator rotation angles used. The dosimetric parameter of other OARs (eyes, parotid glands, and spinal cord) are compared between VMAT plans and IMRT plans in figure 3(g-i). Notably, the results indicate that VMAT plans has no significant advantage over IMRT in protecting OARs.

Our meta-analysis showed that MUs were significantly lower in VMAT plans than in IMRT (P<0.0001), which is consistent to findings from previous studies [36, 37]. In this meta-analysis, we found high publication bias in MUs. Because VMAT plans had fewer MUs, we speculated that the VMAT treatment time was shorter than that for IMRT. The heterogeneity observed in MUs was due to plan optimization strategies, algorithms, as well as use of different linac, which is similar to the results reported previously [36-38].

Our meta-analysis has several limitations. First, the studies included in this meta-analysis are observational. The sample size of radiotherapy center studies in different regions is small, which provides limited suggestions for the comparison of VMAT and IMRT technologies. Secondly, due to the existence of different intervention measures in the two schemes, including the delineation of target areas and organs in crisis, optimization strategies for plans, different TPS, different optimization algorithms and different linear accelerator characteristics, some results between VMAT and

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IMRT schemes may inevitably be biased [39]. Third, there was heterogeneity in the results of this meta-analysis, including insufficient information on disease status, different stages of nasal tumors, and tumor size. However, sensitivity analysis in figure 4 was conducted which showed that the results were stable in all observational measures.

CONCLUSION

Our results demonstrate that in the treatment of nasal tumors, the VMAT does not reduce the assessment dose of OARs. However, the VMAT plan is superior to the fixed field IMRT plan in improving local tumor control rate, providing better treatment efficiency and reducing MUs. In conclusion, VMAT is a superior radiotherapy and can be used as an optional plan for nasal tumors.

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***Ethical consideration*:** *Not applicable.*

***Conflict of Interest*:** All authors declare no conflict of interest.

***Systematic review registration*:** PROSPERO CRD42022322318.

***Author's contributions*:** W.G. Feng: study conception, design, data acquisition, do the meta-analysis, wrote paper; W. Ma: study conception and drafted the manuscript and; Sh.P. Li: revised the manuscript; Y.X. Guo: drafted the manuscript; W. Du: data processed; H.Y. Cai: supervised the study; and all authors revised it critically for important intellectual content. All have given final approval.

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