Additional file 3. Supplementary data for focused Clinical Questions

CQ 1. Which is the preferred approach to obtain the pathology specimen in patients with PCNSL, stereotactic brain biopsy or resection?

- Population: Patients with PCNSL who need to obtain the pathology specimen
- Intervention: Stereotactic brain biopsy
- Comparison: Resection

1.1. Inclusion and exclusion criteria

- Inclusion criteria: we included published RCT, cohort studies and case control studies, which compared stereotactic brain biopsy with resection in patients with PCNSL who need to obtain the pathology specimen. Studies published in English and Chinese are included.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

1.2. Characteristic information of included studies

Supplementary Table S2.1.1. characteristic information of included studies (recent five years)

Year	Country	Journal	Study type	Age	Sample size	Group 1	Group 2	Outcomes	Conclusion
2021[1]	Tongji Hospital, China	BMC Neurology	retrospecti ve study	Media n 53.3 ± 14.3y	70 patients	Resectio n 28 patients	Biopsy 42 patients	Complication : Resection 10.7% vs biopsy 7.1% ; OS : Resection mean 23.4m vs biopsy 11.2m ; PFS : Resection mean 8.6m vs biopsy 4.6m	Compared to stereotactic biopsy, surgical resection may play a role in significantly improving OS and PFS in a subset of patients. Type of surgery and tumor location are prognostic factors for PCNSL.
2021[2]	Tiantan Hospital, China	Chinese Journal of Surgery	retrospecti ve study	<60y count 50%	2125 patients	Resectio n 115 patients	Biopsy 2010 patients	Median Survival Time : Biopsy : 2m (95%Cl 1.76-2.24) ; STR : 2m (95%Cl 1.4-2.6) ;	Surgical resection may improve the prognosis of some patients with PCNSL. Chemothera

							GTR:19m (95 % 0-39)	py May Prolong Tumor- Specific Survival in Patients with Complete or Selected Tumor Resection.
2021[Israel 3]	J Neurosurg	retrospecti ve database study	≥18y	113 patients	Resectio n 36 patients	Biopsy 77 patients	Patients with superficial tumors who underwent resection had significantly longer survival than those who underwent biopsy (median survival 34.3 months vs. 8.9 months, P= 0.014). Patients younger than 70 years with superficial tumors who underwent	Compared to undergoing diagnostic biopsy only, a specific subgroup of patients with a single PCNSL lesion may have a survival benefit from resection.

2020[4]	Wenzhou Medical University, China	Frontiers in Oncology	retrospecti ve database study	60-80y count 50%	3543 patients	Resectio n 851 patients	Biopsy or nonsurgery 2692 patients	resection had a significantly longer survival with a median survival of 35.0 months compared to 8.9 months for the same group of patients who underwent needle biopsy (P = 0.007). 1 year OS : Resection 59.2% vs Biopsy or nonsurgery 46.8% ; 3-year OS : Resection 44.7% vs Biopsy or nonsurgery 32.5% 5-year OS : Resection 36.0% vs Biopsy or	Total excision is superior to subtotal excision. Studies support the favorable impact of surgery on the clinical outcomes of patients with PCNSL. Although further randomized
-------------	--------------------------------------------	--------------------------	----------------------------------------	------------------------	------------------	-------------------------------	------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

								nonsurgery 26.3% Resection vs nonsurgery HR=0.81	controlled trials are needed, the currently available evidence should be considered in the clinical manageme nt of this disease.
2020[5]	The First Affiliated Hospital of Nanchang University, China	World Neurosurge ry	retrospecti ve study	2-72y	89 patients (intracrania I)	Cranioto my 71 patients , GTR : 57 patients STR : 14 patients	Biopsy 18 patients,multi ple or isolated lesions invading deep structures	Midian PFS: Resection 22±1.454m vs Biopsy 14±2.863m, P<0.05 ; Midian OS : Resection 33±2.998m vs Biopsy 26±2.308m, P>0.05	For intracranial PCNSL, surgical resection improves PFS but not OS. invasion of deep structures is the only independent risk factor for intracranial PCNSL.
2019[6]	US, Northwest ern University,	Neurosurge ry	Case- control study	IS ∶67y vs 63y	132 PCNSL	Cranioto my 60 patients	Biopsy 72 patients	Median Survival Time : Craniotomy	In 3 retrospectiv e datasets, craniotomy

NCDB ∶ 65y vs 65y	8936 patients , NHL with CNS	Cranioto my 3423 patients	Biopsy 5513 patients	46.0 m (95% Cl [35.7, 133.4]) vs Biopsy 24.7 m(95% Cl [13.8, 54.9]) ,HR 0.68; Median Survival Time : Craniotomy 19.5m (95%Cl,16 .8-22.0) vs Biopsy 11.0m (95%Cl,10 .1-12.3), HR=0.83 ;	associated with improved survival compared
SEER∶ 62y vs 63y vs 65y	4636 patients NHL with CNS	Cranioto my STR : 216 patients GTR : 1070 patients		Median Survival Time : Craniotomy 29m for GTR (95% CI [24, 34]), 24m for STR (95% CI [13, 40]) vs Biopsy 10m (95% CI [10, 12])	

2018[7]	Oslo University Hospital	Neurosurgic al Review	retrospecti ve database study	Media n 65.3 y [range 18.9– 80.7]	79 patients	Cranioto my 32 patients	Biopsy patients	47	Median OS : Craniotomy 28.6m (0.7- 157.5) vs Biopsy 11.7m (0.2-136.5) Median PFS : Craniotomy 12.6m (0- 157.7) vs Biopsy 7.7m (0-117)	In patients with PCNSL, resective surgery plays no role in significantly improving OS or PFS, so we do not advocate total resection as a treatment. However, cytoreductiv e surgery may be useful in patients with
2018[8]	Argentina	Arq Neuropsiqui atr	retrospecti ve study	Media n 59 y (range: 25–84 y)	47 patients	Resectio n 18 patients	Biopsy patients	29	Median Survival Time : Resection 31m (4-194) vs Biopsy 14.5 (2- 218) ,P=0.0 16	potential brain herniation. Patients who had their tumors surgically removed had a median survival of 16.5 months longer than

										those who underwent biopsy alone.
2017[9]	Columbia University Irving Medical Center	Journal of Neuro- Oncology	retrospecti ve study	Media n 65 (range 21–88)	129 patients	Resectio n 58 patients	Biopsy patients	71	Complication rate : Resection 17.2% vs Biopsy 28.2% , P>0.05 ;	Surgical resection of PCNSL is

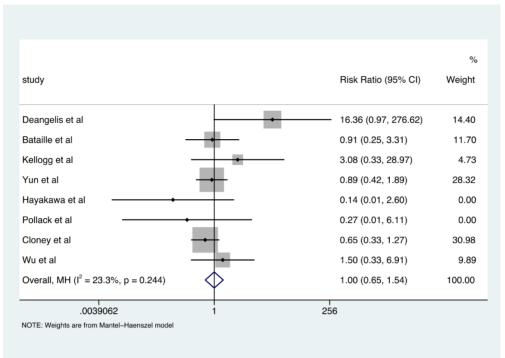
NHL: non-Hodgkin's lymphoma; PCNSL: primary central nervous system lymphoma; CNS: central nervous system; OS: overall survival; PFS: progression-free survival; SEER: Surveil- lance, Epidemiology, and End Results Program; NCDB: National Cancer Database-Participant User File; GTR: gross total resection; STR: subtotal resection.

1.3. Risk of bias

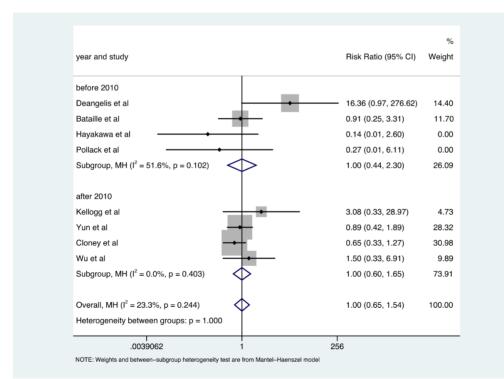
Supplementary Table S2.1.2. Risk of bias of included studies using Newcastle-Ottawa Scale

		Selection o	of exposure	9	Co	omparabilit	у	Outc	ome	
Study ID	Represe ntativene ss of the exposed cohort	Selection of the non- exposed cohort	Ascertai nment of exposur e to implant s	Demonstr ation that outcome of interest was not present at start of study	Study controls the most importan t factor	Study controls for any addition al factor	Assess ment of outcom e	Was follow up long enough for outcomes to occur	Adequac y of follow up of cohorts	Total score
Wu et al, 2021 [1]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	7
Yang et al, 2021[2]	Yes	Yes	Yes	No	No	No	No	Yes	Yes	5
Schellekes et al, 2021[3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Deng et al, 2020[4]	Yes	Yes	No	No	No	Yes	No	Yes	Yes	5
Ouyang et al, 2020[5]	Yes	Yes	Yes	No	No	No	No	Yes	No	4
Rae et al, 2019[6]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	7
Jahr et al, 2018[7]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Villalonga et al, 2018[8]	Yes	Yes	Yes	No	No	No	No	Yes	Yes	5
Cloney et al, 2017[9]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	7

1.4. Meta-analysis results



Supplementary Figure S2.1.1. Pooled results of complication incidence in patients with PCNSL who received the stereotactic brain biopsy or resection



Supplementary Figure S2.1.2. Pooled results of complication incidence in patients with PCNSL who received the stereotactic brain biopsy or resection (studies published before 2010 on top, studies published after 2010 at bottom)

1.5. Summary of finding (SoF) table

Patient or population: PCNSL Setting: Intervention: resection Comparison: stereotactic brain biopsy

Outcom es	Anticipate effects*	d absolute (95% Cl)	Relati ve effect	№ of participa nts	Certai nty of the	Comme nts
	Risk with [comparis on]	Risk with [interventi on]	(95% CI)	(studies)	eviden ce (GRAD E)	
complicat ion incidence	121 per 1,000	121 per 1,000 (79 to 187)	RR 1.00 (0.65 to 1.54)	781 (8 observati onal studies)	⊕⊖⊖ VERY LOW ª	
complicat ion incidence before 2010	42 per 1,000	42 per 1,000 (19 to 97)	RR 1.00 (0.44 to 2.30)	406 (4 observati onal studies)	€⊖⊖ VERY LOW	
complicat ion incidence after 2010	189 per 1,000	189 per 1,000 (123 to 291)	RR 1.00 (0.65 to 1.54)	375 (4 observati onal studies)	⊕⊖⊖ VERY LOW ⁵	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval: RR: Risk ratio

 GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that
of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate:
The true effect is likely to be close to the estimate of the effect, but there is
a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true
effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate:
The true effect is likely to be substantially different from the estimate of
the effect is likely to be substantially different from the estimate of
the effect is likely to be substantially different from the estimate of
the effect is likely to be substantially different from the estimate of
the effect is likely to be substantially different from the estimate of
the effect is likely to be substantially different from the estimate of
the effect is likely to be substantially different from the estimate of
the effect is likely to be substantially different from the estimate of
the effect is likely to be substantially
different from the estimate of
the effect is likely to be substantially
different from the estimate of
the effect is likely
the effect is likely
the effect is
likely
the effect is
likely
the effect is
likely
the effect is
likely
the effect is
likely
the effect is
likely
the effect is
likely
the effect is
likely
the effect is
likely
the effect is
likely
li The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The risk of bias was high in eight included studies; b. The risk of bias was high in four included studies; c. I^2 =51.6%

1.6. References

- [1] Wu S, Wang J, Liu W, et al. The role of surgical resection in primary central nervous system lymphoma: a single-center retrospective analysis of 70 patients. BMC Neurol. 2021;21(1):190. doi:10.1186/s12883-021-02227-3
- [2] Yang C, Ren X, Jiang H, et al. Different treatment regimens for primary

central nervous system lymphoma: based on SEER database. Chin J Surg, 2021,59(01):52-58.

- [3] Schellekes N, Barbotti A, Abramov Y, et al. Resection of primary central nervous system lymphoma: impact of patient selection on overall survival. J Neurosurg. 2021;1-10. doi:10.3171/2020.9.JNS201980
- [4] Deng X, Xu X, Lin D, et al. Real-World Impact of Surgical Excision on Overall Survival in Primary Central Nervous System Lymphoma. Front Oncol. 2020;10:131. Published 2020 Feb 26. doi:10.3389/fonc.2020.00131
- [5] Ouyang T, Wang L, Zhang N, et al. Clinical Characteristics, Surgical Outcomes, and Prognostic Factors of Intracranial Primary Central Nervous System Lymphoma. World Neurosurg. 2020;139:e508-e516. doi:10.1016/j.wneu.2020.04.049
- [6] Rae AI, Mehta A, Cloney M, et al. Craniotomy and Survival for Primary Central Nervous System Lymphoma. Neurosurgery. 2019;84(4):935-944. doi:10.1093/neuros/nyy096
- [7] Jahr G, Da Broi M, Holte H Jr, Beiske K, Meling TR. The role of surgery in intracranial PCNSL. Neurosurg Rev. 2018;41(4):1037-1044. doi:10.1007/s10143-018-0946-0
- [8] Villalonga JF, Alessandro L, Farez MF, et al. The role of surgery in primary central nervous system lymphomas. Arq Neuropsiquiatr. 2018;76(3):139-144. doi:10.1590/0004-282x20180002
- [9] Cloney MB, Sonabend AM, Yun J, et al. The safety of resection for primary central nervous system lymphoma: a single institution retrospective analysis. J Neurooncol. 2017;132(1):189-197. doi:10.1007/s11060-016-2358-8

CQ 2. Should corticosteroids be withdrawn from patients with suspected PCNSL/PVRL before biopsy?

- Population: suspected PCNSL/PVRL patients
- Intervention: withdrawn corticosteroids
- Comparison: not withdrawn corticosteroids

2.1. Inclusion and exclusion criteria

- Inclusion criteria: we included published studies, which compared the diagnosis true positive rate or false negative rate for suspected PCNSL/PVRL patients between withdrawn corticosteroids and not withdrawn corticosteroids.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

2.2. Characteristic information of included studies

Supplementary Table S2.2.1. characteristic information of included studies

Study	Publicati	Countr		Study	oortioostoroi	PCNSL/PVRL ¹ Case group					Control groups			
Study ID	Publicati on year	Countr y	Ν	Study type	corticosteroi ds dose	Duration	n	not withdra wn	withdraw n	n	not withdra wn	withdra wn		
Bullis CL et al[1]	2020	Americ a	54	Case series	Cumulative Dexamethaso ne 4mg- 120mg	1-27d	5 4	18	36	-	-	-		
Binnah il M et al[2]	2016	Canada	15 5	Case Contr ol	mean dose of 4 mg every 6 hours	2-45d	2 0	15	5	13 5	120	15		
Onder E et al[3]	2015	Turkey	25	Case series	4 mg dexamethaso ne with 6 hours intervals	2-30d	2 5	22	-	-	-	-		
Manoj N et al[4]	2014	India	76	Case series	-	-	7 2	26	46	-	-	-		
Zhao H et al[5]	2011	China	73	Case series	340mg(10- 6000mg)	5.5d(1`60 d)	7 3	39	34					
Porter AB et al[6]	2008	Americ a	10 9	Case Contr ol	25mg- 6325mg	1-90d	1 3	8	5	94	60	34		
Choi YL et al[7]	2006	South Korea	4	Case Repor	-	2~18d	4	4	0		-			
Geppe rt M et	1990	Germa ny	2	Case Repor	8 or 20 mg dexamethaso	2w	2	2	0		-			

al[8]	t	ne				
		Daily				
¹ PCNSL: primary central nervous system lymphoma; PVRL: primary vitreoretinal lymphoma						

"-": not applicable

2.3. Risk of bias

Supplementary Table S2.2.2. Risk of bias of included case control studies assessed by the Newcastle-Ottawa Scale

		Selecti	on		Comparabili	I				
Study ID	definiti veness of Col		Select ion of Contr ols	Demonstr ation that outcome of interest was not present at start of study	Study controls the most important factor	Study contro Is for any additi onal factor	Ascertain ment of exposure	Same method of ascertain ment for cases and controls	Non- Respo nse rate	Tot al sco re
Binnahil M et al[2]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Porter AB et al[6]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6

Supplementary Table S2.2.3. Risk of bias of included case series assessed by the Institute of Health Economics checklist

	Study objective			Intervention and co- intervention				
Study ID	Is the hypothesis, aim, objective of the study clearly stated?	Are the characterist ics of the participants included in the study described?	Were the cases collect ed in more than one centre ?	Are the eligibili ty criteria for entry into the study clearly stated?	Were participants recruited consecutively?	Did participa nts enter the study at a similar point in the disease?	Was the interventi on of interest clearly described ?	Were additional interventio ns (co- interventio ns) reported in the study?

Bullis CL et al[1]	Yes	Yes	No	Yes	Unclear	No	Yes	No
Önder E et al[3]	Yes	Yes	No	Yes	Unclear	No	Yes	No
Manoj N et al[4]	Yes	Yes	No	Yes	Unclear	No	No	No
Zhao H et al[5]	Yes	Yes	No	Yes	Unclear	No	Yes	No

Continued Supplementary Table S2.2.3

		Outcome measu	re	Statistical analysis	Results and con	clusions
Study ID Bullis CL et al[1]	Are the outcome measures established a priori?	Were the relevant outcomes measured with appropriate objective and/or subjective methods?	Were the relevant outcomes measured before and after the intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?
Bullis CL et al[1]	Yes	Yes	No	No	No	Yes
Önder E et al[3]	Yes Yes		No	No	No	Yes
Manoj N et al[4]	Yes Yes		No	No	No	Yes
Zhao H et al[5]	Yes Yes		No	No	No	Yes

Continued Supplementary Table 2.2.3

Cturdue ID	Resul	ts and concl	usions	Competing interest and source of support	New it	Tota I	
Study ID	Does the study	Are the adverse	Are the conclusio	Are both competing interests and sources	Was the study	Were the relevant	scor e

	provide estimate s of the random variabilit y in the data analysis of relevant outcome s?	events related with the interventi on reported?	ns of the study supported by results?	of support for the study reported?	conducted prospectivel y?	outcomes assessed blinded to interventi on status?	
Bullis CL et al[1]	No	No	Yes	Yes	No	No	9
Onder E et al[3]	No	No	Yes	Yes	No	No	9
Manoj N et al[4]	No	No	Yes	Yes	No	No	8
Zhao H et al[5]	No	No	Yes	No	No	No	8

Supplementary Table S2.2.4. JBI Critical Appraisal Checklist for Case Reports

Study ID	patient's demographic characteristic s			diagnosti c tests	intervention(s)	post- interventio n clinical condition	advers e events	takeawa y lessons	Total scor e
Choi YL et al[7]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7
Geppert M et al[8]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7

2.4 Reference

- Bullis CL, Maldonado-Perez A, Bowden SG, et al. Diagnostic impact of preoperative corticosteroids in primary central nervous system lymphoma. J Clin Neurosci. 2020;72:287-291.
- [2] Binnahil M, Au K, Lu JQ, Wheatley BM, Sankar T. The Influence of Corticosteroids on Diagnostic Accuracy of Biopsy for Primary Central Nervous System Lymphoma. Can J Neurol Sci. 2016;43(5):721-725.
- [3] Önder E, Arıkök AT, Önder S, et al. Corticosteroid pre-treated primary CNS lymphoma: a detailed analysis of stereotactic biopsy findings and consideration of interobserver variability. Int J Clin Exp Pathol. 2015;8(7):7798-7808.
- [4] Manoj N, Arivazhagan A, Mahadevan A, et al. Central nervous system lymphoma: patterns of incidence in Indian population and effect of steroids on stereotactic biopsy yield. Neurol India. 2014;62(1):19-25.
- [5] Zhao, H., Tian, Z., Liu, R., et al., Effect of corticosteroid administration before biopsy on histopathological diagnosis of primary central nervous system lymphoma. Chin J Lab Diagn. 2011;15(5):828-829.
- [6] Porter AB, Giannini C, Kaufmann T, et al. Primary central nervous system lymphoma can be histologically diagnosed after previous corticosteroid use: a pilot study to determine whether corticosteroids prevent the diagnosis of primary central nervous system lymphoma. Ann Neurol. 2008;63(5):662-667.
- [7] Choi YL, Suh YL, Kim D, Ko YH, Sung CO, Lee JI. Malignant lymphoma of the central nervous system: difficult histologic diagnosis after glucocorticoid therapy prior to biopsy. Clin Neuropathol. 2006;25(1):29-36.
- [8] Geppert M, Ostertag CB, Seitz G, Kiessling M. Glucocorticoid therapy obscures the diagnosis of cerebral lymphoma. Acta Neuropathol. 1990;80(6):629-634.

CQ 3. Which is the preferred imaging examination for PCNSL patients, MRI or whole-body PET-CT?

- Population: Patients with PCNSL
- **O** Intervention: Imaging examination by MRI
- **©** Comparison: Imaging examination by whole-body PET-CT

3.1. Inclusion and exclusion criteria

- inclusion criteria: we included published studies, which compared the sensitivity and specificity for a PCNSL patient MRI and whole-body.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

3.2. Characteristic information of included studies

We didn't identify any study met the inclusion criteria.

CQ 4. Should cognitive function assessment be used for PCNSL patients?

- Population: Patients with PCNSL
- Intervention: cognitive function assessment
- Comparison: no treatment

4.1. Inclusion and exclusion criteria

- inclusion criteria: we only included published RCTs, the benefits of cognitive function evaluation for patients were studied. Studies published in English and Chinese are included.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

4.2. Characteristic information of included studies

Supplementary Table 2.4.1 characteristic information of included studies

Study ID	Years	Country	Research type	Disease Stage	Ν	Intervention	Comparation
Meulen [1]	2018	Netherlands	Systematic review	newly diagnosed	/	cognitive functioning and HRQOL	/
Correa [2]	2007	America	Systematic review	/	/	cognitive functioning	/
Houillier [3]	2019	French	RCT	/	140	WBRT	ASCT
Meulen [4]	2021	Netherlands	RCT	/	199	standard chemotherapy+ rituximab	standard chemotherapy
Aaronson [5]	1993	England	Cross- sectional study	1	305	/	/

/: none

4.3. Risk of bias

Supplementary Table 2.4.2. Risk of bias of included systematic reviews assessed by the AMSTAR

Study ID	Was an 'a priori' design provid ed?	Was there duplica te study selecti on and data extracti on?	Was a comprehe nsive literature search performed ?	Was the status of publica tion (i.e. grey literatu re) used as an inclusi on criterio n?	Was a list of studie s (includ ed and exclud ed) provid ed?	Were the characteri stics of the included studies provided?	Was the scientific quality of the included studies assesse d and documen ted?	Was the scientific quality of the included studies used appropri ately in formulati ng conclusi ons?	Were the methods used to combine the findings of studies appropri ate?	Was the likeliho od of publica tion bias assess ed?	Was the likeliho od of publica tion bias assess ed?
Meule n [1]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Corre a [2]	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Aaron son [5]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes

Supplementary Table S2.4.3. Risk of bias of included RCTs assessed by the Cochrane Risk of Bias tool

Study ID	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
----------	---------------------------------------------------------	--------------------------------------------------	---------------------------------------------------	-------------------------------------------------------------	------------------------------------------------	-----------------------------------------------	---------------

			(performance bias)				
Meulen 2021 [4]	Low ROB	Low ROB	Unclear ROB	Unclear ROB	Low ROB	Low ROB	Low ROB
Meulen [4]	Low ROB	Low ROB	Unclear ROB	Unclear ROB	Low ROB	Low ROB	Low ROB

Note: ROB: risk of bias.

Supplementary Table S2.4.4. Risk of bias of included Cross-sectional study assessed by the JBI Critical Appraisal Tools

Study ID	Were the criteria for inclusio n in the sample clearly defined ?	Were the study subjects and the setting describe d in detail?	Was the exposur e measure d in a valid and reliable way?	Were objective, standard criteria used for measureme nt of the condition?	Were confounding factors identified?	Were strategies to deal with confoundi ng factors stated?	Were the outcom es measure d in a valid and reliable way?	Was appropria te statistical analysis used?	Adequa cy of follow up of cohorts
Aaronson [5]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

4.4. Reference

- van der Meulen, M., Dirven, L., Habets, E.J.J., et al., Cognitive functioning and health-related quality of life in patients with newly diagnosed primary CNS lymphoma: a systematic review. The Lancet Oncology, 2018. 19(8): p. e407-e418 DOI: 10.1016/s1470-2045(18)30356-5.
- [2] Correa, D.D., Maron, L., Harder, H., et al., Cognitive functions in primary central nervous system lymphoma: literature review and assessment guidelines. Ann Oncol, 2007. 18(7): p. 1145-51 DOI: 10.1093/annonc/mdl464.
- [3] Houillier, C., Taillandier, L., Dureau, S., et al., Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. J Clin Oncol, 2019. 37(10): p. 823-833 DOI: 10.1200/JCO.18.00306.
- [4] van der Meulen, M., Dirven, L., Habets, E.J.J., et al., Neurocognitive functioning and radiologic changes in primary CNS lymphoma patients: results from the HOVON 105/ALLG NHL 24 randomized controlled trial. Neuro Oncol, 2021. 23(8): p. 1315-1326 DOI: 10.1093/neuonc/noab021.
- [5] Aaronson, N.K., Ahmedzai, S., Bergman, B., et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a qualityof-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst, 1993. 85(5): p. 365-76 DOI: 10.1093/jnci/85.5.365.

CQ 5. What needs to be recommended as the combined regimen with HD-MTX backbone in induction therapy?

- Population: Patients with PCNSL
- **•** Intervention: Combined regimen with HD-MTX
- **©** Comparison: Other combined regimens with or without HD-MTX

5.1. Inclusion and exclusion criteria

- inclusion criteria: we only included published RCTs, which compared combined regimen with HD-MTX vs other combined regimens. Studies published in English and Chinese are included.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

5.2. Characteristic information of included studies

Supplementary Table S2.5.1 characteristic information of included studies

					int	tervention 1			intervention 2			Interven tion 3
Study ID	Publica tion year	Country	Ν	n	Interventio n name	Treatment (dose, duration)	n	Interventi on name	Treatment (dose, duration)	n	Interven tion name	Treatme nt (dose, duration)
Bromb erg et al[1]	2019	Netherla nds, Australia , New Zealand	20 0	99	R-MBVP ¹	-d1+d15: MTX: 3g/m ² ; d2+d3: teniposide: 100mg/m ² ; d4: carmustine: 100mg/m ² ; d1-5: prednisone: 60mg/m ² ; c1: d0+d7+d14+d 21/c2: d0+d14: rituximab: 375mg/m ² -28d/cycle, 2 cycles	10 0	MBVP	-d1+d15: MTX: 3g/m ² ; d2+d3: teniposide: 100mg/m ² ; d4: carmustine: 100mg/m ² ; d1-5: prednisone: 60mg/m ² -28d/cycle, 2 cycles	_	-	_
Ferreri et al[2]	2009	Argentin a, Greece, Italy, Peru, Portugal,	79	39	MTX ² + cytarabine	-d1: MTX: 3.5g/m ² ; d2-3: cytarabine: 2g/m ² , twice a day -3w/course, 4	40	MTX	-d1: MTX:3.5g/m ² -3w/course, 4 courses	-	-	-

	and Switzerla				courses							
Omuro et al[3] 2015	nd	95	47	MTX + procarbazi ne + vincristine + cytarabine	-d1+d15: MTX: 3.5g/m ² ; d1-d7: procarbazine: 100 mg/m ² /d; d1+d15: vincristine: 1.4mg/m ² ; d1- d5: Methylprednis olone; d8- 13+d16-27: filgrastim: 5µg/kg/d. After the end of cycle 3: cytarabine: 3g/m ² : two consecutive days -28d/cycle, 3 cycles -d1:	48	MTX + temozolo mide	-d1+d15: MTX: 3.5g/m ² ; d1-d5: temozolomide : 150mg/m ² Methylprednis olone: 60mg/d; Filgrastim: 5µg/kg/d -28d/cycle, 3 cycles	_	-	-	
Thiel 2010 et al[4]	German y	31 8	15 4	MTX + ifosfamide + WRBT ³	MTX:4g/m ² ; d3-5: MTX+ifosfami de: 1.5g/m ² ; WBRT: 45Gy in total, 1.5Gy/d, 30 days	16 4	MTX + ifosfamide	-d1: MTX: 4g/m ² ; d3-5: MTX + ifosfamide: 1.5g/m ² -14d/cycle, 6 cycles	-	-	-	

					-14d/cycle, 6 cycles						d1:
Ferreri et al[5]	2016	Italy	21 75 9 75	MTX + cytarabine	-d1: MTX: 3.5g/m ² ; d2-3: cytarabine: 2g/m ² , twice a day -3w/cycle, 4 cycles	69	MTX + Rituximab + cytarabine	-d1: MTX:3.5g/m ² d2-3: cytarabine: 2g/m ² , twice a day; d-5-+0: Rituximab: 375mg/m ² -3w/cycle, 4 cycles	75	MTX + cytarabin e + Rituxima b + thiotepa	MTX: 3.5g/m2; d2-3: cytarabin $e: 2g/m^2,$ twice a day; d-5- +0: Rituxima b: 375mg/ $m^2; d4:$ thiotepa:
He et al[6]	2016	China	28 14	MTX + Rituximab	-Rituximab: 375mg/m ² ; MTX: 3g/m ² -4w/cycle, 4 cycles	14	MTX + WBRT ³	-MTX:3g/m²; WBRT -4w/cycle. 4 cycles	-	-	30mg/m ² -
Li et al[7]	2019	China	58 28	MTX + Rituximab + cytarabine	-d1: Rituximab: 375mg/m ² ; d2:MTX: 3.0g/m ² ; d3: cytarabine: 0.5-1.0g/m ² -21d/cycle	29	MTX + WBRT + 3- dimensio nal conforma I radiation therapy	- WBRT:1.8~2. 0Gy a time, 5 times/w, 20 times, 40~45Gy in total; 3- dimensional conformal radiation therapy 8~16Gy in	-	-	-

Luo et al[8]	2016	China	58	29	MTX + Rituximab	-Rituximab: 375mg/m ² ; MTX: 3g/m ² -4w/cycle, 2-6 cycles	29	MTX + WBRT	total; MTX: d1:3.0g/m ² -28d/cycle MTX: 3g/m ² ; WBRT: 1.8- 2.0Gy a time, 5 times/w -4w/cycle, 2-6 cycles WBRT: 40- 45Gy in total,	-	-	-
Sun et al[9]	2017	China	52	26	MTX + Rituximab + cytarabine	-d1: Rituximab: 375mg/m ² ; d2: MTX: 3g/m ² ; d3: cytarabine: 0.5-1.0g/m ² -21d	26	MTX + WBRT + 3- dimensio nal conforma I radiation therapy	1.8-2.0Gy a time, 5 times/w, 20 times; 3- dimensional conformal radiation therapy: 8- 16Gy in total, 4Gy a time; MTX: 3.0g/m ²	-	-	-
Song et al[10]	2018	China	91	31	MTX + Rituximab + cytarabine+ Dexametha sone	-d1: Rituximab: 375mg/m ² ; d2:HD-MTX: 3.5g/m ² ; d3: cytarabine: 0.5-1.0g/m ² ; d2-4: dexamethaso ne: 10mg -4-6 courses	30	MTX + Rituximab	-28d/cycle Rituximab: 375mg/m ² /w; MTX:3.5g/m ² / w -4w/course, 4 courses	3 0	MTX + WBRT	MTX: 3.5mg/m 2

Shan et al[11]	2019	China	12 0	60	MTX + Rituximab	-MTX: 3g/m ² ; Rituximab: 375mg/m ² -4w/course, 4- 6 courses	60	MTX + WBRT	MTX: 3g/m ² ; WBRT: 1.8- 2.0Gy a time, 5 times/w -4w/course, 4- 6 courses	-	-	-
Wang et al[12]	2016	China	60	30	MTX + Rituximab	-MTX: 3g/m ² ; Rituximab: 375mg/m ² -4 cycles -MTX: 3g/m ² ;	30	MTX + WBRT	MTX:3g/m ² ; WBRT -1m/cycle, 4 cycles	-	-	-
Zhang et al[13]	2018	China	54	27	MTX + Rituximab + WBRT	WBRT: 2.0Gy a time, 5 times/w, <36Gy in total; Rituximab: 375mg/m ² -1m/cycle, 4 cycles -d1:	27	MTX + WBRT	-MTX:3g/m ² ; WBRT:2.0Gy a time, 5 times/w, <36Gy in total -1m/cycle, 4 cycles	-	-	-
Wu et al[14]	2018	China	49	24	Fotemustin e + teniposide + dexametha sone	Fotemustine: 100mg/m ² , 1h; d2-4: teniposide: 60mg/m ² , >0. 5h; d1-5: dexamethaso ne: 40mg, 1h -21d/cycle, 4	25	HD-MA ⁴	-d1: MTX:3.5g/m ² ; d2-3: cytarabine: 1.0g/m ² -21d/cycle, 4 cycles	-	-	-
Huang et al[15]	2017	China	48	24	MTX + temozolomi de	cycles -d1:MTX: 3g/m ² ; d2-6: temozolomide	24	MTX + WBRT	-d1: MTX:3.0g/m²; WBRT: 36Gy	-	-	-

					: 150mg/m ² -21d/cycle, 6- 8 cycles			in total, 2Gy a time, 5 times/w -21d/cycle, 6-	
Yi et al[16]	2014	China	42 21	MTX + WBRT	-MTX: 1g/m ² ; WBRT: 2Gy a time, 5 times/w -3w/cycle, 8 cycles	21	MTX + WBRT	8 cycles -MTX: 3g/m ² ; WBRT:2Gy a time, 5 times/w -3w/cycle, 8 cycles	

¹R-MBVP: methotrexate, carmustine, teniposide, and prednisone (MBVP) plus rituximab

²MTX: methotrexate

³WBRT: whole brain radiation therapy

⁴HD-MA: high-dose methotrexate plus cytarabine

"-": not applicable

5.3. Risk of bias

Zhang 2018	Yi 2014	Wu 2018	Wang 2016	Thiel 2010	Sun 2017	Song2018	Shan2019	Omuro 2015	LUO 2016	Li 2019	Huang 2017	He 2016	Ferreri 2021	Ferreri 2016	Bromberg 2019	
•	6	•	<mark>。</mark>	•	••	•	•	•	•	••	••	•	•	•	•	Random sequence generation (selection bias)
?	<mark>?</mark>		?		••	••	~		~	~	~	~		•	•	Allocation concealment (selection bias)
?	<mark>。</mark>		?		->	->	~		~	~>	~>	~>				Blinding of participants and personnel (performance bias)
•	•	Ŧ	+	Ŧ	Ŧ	•	•	•	•	•	•	Ŧ	•	•	•	Blinding of outcome assessment (detection bias)
?	<mark>。</mark>	<mark>6</mark>	?	•	••	•	->	•	->	->	->	••	•	•	•	Incomplete outcome data (attrition bias)
•	•	•	•	•	•	•	•	•	•	•	•	+	•	•	•	Selective reporting (reporting bias)
•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Other bias

Supplementary Figure S2.5.1. Risk of bias of included studies assessed by the Cochrane Risk of Bias tool

5.4. Meta-analysis results

			%			
Study		ES (95% CI)	Weight	Study	E8 (96% CI)	Weight
He 2016		0.86 (0.57, 0.98)	7.51	He 2016	0.59 (0.23, 0.77)	9.99
Luo 2016		0.83 (0.64, 0.94)	15.28	Luo 2016	0.31 (0.15, 0.51)	16.45
Song 2018		0.67 (0.47, 0.83)	15.80	Sung 2018	0.27 (0.12, 0.46)	16.80
Shan 2019		0.72 (0.59, 0.83)	31.35	Shan 2019	0.23 (0.13, 0.36)	24.22
Wang 2016		0.73 (0.54, 0.88)	15.80	Warg 2016	0.40 (0.23, 0.59)	16.80
Zhang 2018		0.70 (0.50, 0.86)	14.25	25varg 2018	0.15 (0.04, 0.34)	15.74
Overall (1*2 = 0.00%, $p = 0.68$)	\diamond	0.74 (0.67, 0.80)	100.00	Overal (172 = 38,58%, p = 0.15)	0.29 (0.20, 0.38)	100.00
0	.5	1		0 .5	1	

Supplementary Figure S2.5.2. Pooled results of MTX + rituximab (ORR on the left, CR on the right)

ORR				CR			
			Weight				Weight
Dudy		E8 (M% C)	(flandsm)	1.4		88 (Mrs. 0)	Persons
Farrest 2016		0.53 (0.41, 0.65)	97.61	Faran 2018	- _	0.01 (0.14, 0.24)	-
Ferreri 2021		0.69 (0.52, 0.63)	33.19	Faren 2021		0.00.000	10.08
Vev. 2014		0.84 (0.64, 0.95)	29.30	We 214		0.00.001	28.55
Random Overall: (*2 = 76.07%, μ = 0.01)		0.68 (0.50, 0.84)	100.00	Render-Densit (*2 + 72.00%, p = 5.03)		0.00.00.000	
Fixed Querali	\sim	0.64 (0.66, 0.72)		Prest Quest	\diamond	0.32 (6.24, 6.45)	
1 .25	A 212	;	_		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	!	

Supplementary Figure S2.5.3. Pooled results of MTX + cytarabine (ORR on the left, CR on the right)



Supplementary Figure S2.5.4. Pooled results of MTX + temozolomide (ORR on the left, CR on the right)

ORR			54	CR			
			Weight				Weight
Study		ES (95% CI)	(Random)	Dudy		ES (H5% CI)	(Randum)
Ferrori 2016		0.74 (0.62, 0.84)	29.64	Farmi 2016		0.30 (0.20, 0.43)	51.02
LI 2019	•	0.66 (0.46, 0.82)	18.26	U-2019		0.38 (0.21, 0.58)	17.95
Sun 2017		0.88 (0.70, 0.98)	16.97	Sun 2017	· · · · · · · · · · · · · · · · · · ·	0.31 (0.14, 6.52)	16.58
Song 2018		0.84 (0.66, 0.95)	19.06	Song 2018	•	0.55 (0.34, 6.78)	18.40
Wu 2018		0.88 (0.68, 0.97)	16.07	Wu 2018		0.33 (0.14, 0.56)	15.42
Random Overall (I*2 = 36.74%, p = 0.18)	$\langle \rangle$	0.80 (0.71, 0.87)	100.00	Pandom Overall (172 + 29.89%, p + 0.22)		0.37 (0.26, 0.46)	100.00
Fixed Overall	\diamond	0.79 (0.72, 0.85)		Fired Overall	$\langle \rangle$	0.36 (0.29, 0.43)	
25 .5	.757	1			I I I 43 3 3	!	

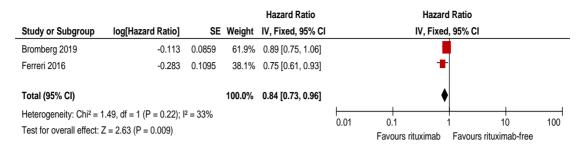
Supplementary Figure S2.5.5. Pooled results of triple therapy with HD-MTX (ORR on the left, CR on the right)



Supplementary Figure S2.5.6. Pooled results of four regimen with HD-MTX (ORR on the left, CR on the right)

	HD-MTX+ritu	ıximab	rituxumal	o-free		Risk Ratio	Risk Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
.1.1 MTX+RTX vs I	MTX+WBRT						
le 2016	12	14	7	14	2.6%	1.71 [0.97, 3.02]	
uo 2016.	24	29	17	29	6.4%	1.41 [1.00, 2.00]	
han 2019	43	60	28	60	10.6%	1.54 [1.12, 2.10]	
ong 2018	20	30	16	30	6.1%	1.25 [0.82, 1.90]	
Vang 2016	22	30	20	30	7.6%	1.10 [0.79, 1.53]	
hang 2018	19	27	10	27	3.8%	1.90 [1.10, 3.29]	
ubtotal (95% CI)		190		190	37.1%	1.43 [1.22, 1.68]	◆
otal events	140		98				
leterogeneity: Chi ² =	= 4.40, df = 5 (P	= 0.49);	$I^2 = 0\%$				
est for overall effec	t: Z = 4.33 (P <	0.0001)					
.1.2 MTX+RTX+Ar	a-C vs MTX+WE	BRT/Ara-	с				
erreri 2016	51	69	40	75	14.5%	1.39 [1.08, 1.79]	
i 2019	19	29	10	29	3.8%	1.90 [1.08, 3.35]	
ong 2018	26	31	16	30	6.2%	1.57 [1.09, 2.27]	
un 2017	23	26	16	26	6.1%	1.44 [1.03, 2.01]	
ubtotal (95% CI)		155		160	30.5%	1.50 [1.26, 1.78]	◆
otal events	119		82				
leterogeneity: Chi ² =	= 1.16, df = 3 (P	= 0.76);	$I^2 = 0\%$				
est for overall effec	t: Z = 4.58 (P <	0.00001)					
.1.3 MBVP+RTX vs	MBVP						
Bromberg 2019	85	99	86	100	32.4%	1.00 [0.89, 1.12]	+
ubtotal (95% CI)		99		100	32.4%	1.00 [0.89, 1.12]	♦
otal events	85		86				
leterogeneity: Not a	pplicable						
est for overall effec	t: Z = 0.03 (P =	0.98)					
otal (95% CI)		444		450	100.0%	1.31 [1.20, 1.43]	•
otal events	344		266				
leterogeneity: Chi ² :	= 30.43, df = 10	(P = 0.00)	$(007); I^2 = 6$	7%			0.01 0.1 1 10 10
	t: Z = 5.89 (P <						0.01 0.1 1 10 10 Favours [RTX-free] Favours [HD-MTX+RTX]

Supplementary Figure S2.5.7. Pooled ORR of HD-MTX based regimen with or without rituximab



Supplementary Figure S2.5.8. Pooled PFS of HD-MTX based combined regimen with or without rituximab

				Hazard Ratio			Hazard Ratio		
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI		I	V, Fixed, 95% (
Bromberg 2019	-0.0315	0.0988	49.7%	0.97 [0.80, 1.18]			+		
Ferreri 2016	-0.2006	0.0983	50.3%	0.82 [0.67, 0.99]			-		
Total (95% CI)			100.0%	0.89 [0.78, 1.02]			•		
Heterogeneity: Chi ² = Test for overall effect:	1.47, df = 1 (P = 0.23); I	² = 32%			0.01	0.1	1	10	100
rest for overall effect.	L = 1.07 (F = 0.09)					Favours ritu	ıximab Favol	ırs rituximab-fre	e

Supplementary Figure S2.5.9. Pooled OS of HD-MTX based combined regimen with or without rituximab

	HD-MTX+cytar	abine	cytarabine	-free		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Ferreri 2021	18	39	7	40	20.4%	2.64 [1.24, 5.60]	- -
Omuro 2015	28	47	19	48	55.5%	1.51 [0.99, 2.29]	⊢ ∎-
Wu 2018	10	25	8	24	24.1%	1.20 [0.57, 2.52]	
Total (95% CI)		111		112	100.0%	1.66 [1.19, 2.32]	•
Total events	56		34				
Heterogeneity: Chi ² = 2	2.40, df = 2 (P = 0.3	30); l² = 17	%				
Test for overall effect:	Z = 3.00 (P = 0.003	3)					0.01 0.1 1 10 100 cvtarabine-free cvtarabine

Supplementary Figure S2.5.10 Pooled ORR of HD-MTX based combined regimen with or without Cytarabine

			Hazard Ratio		Hazard Ratio				
Study or Subgroup	log[Hazard Ratio]	SE Weight		IV, Fixed, 95% CI	IV, Fixed, 95% C			CI	
Ferreri 2021	-0.18708664	0.12073848	55.6%	0.83 [0.65, 1.05]			-		
Omuro 2015	-0.07058107	0.16077913	31.4%	0.93 [0.68, 1.28]			-		
Wu 2018	0.02530586	0.25010317	13.0%	1.03 [0.63, 1.67]					
Total (95% CI)			100.0%	0.88 [0.74, 1.06]			•		
Heterogeneity: Chi ² = 0.74, df = 2 (P = 0.69); l ² = 0% Test for overall effect: Z = 1.37 (P = 0.17)					0.01	0.1 Favours cyta	1 arabine Favo	10 urs cytarabine-fre	100 ee

Supplementary Figure S2.5.11 Pooled OS of HD-MTX based combined regimen with or without Cytarabine

				Hazard Ratio			Hazard Ratio		
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI			IV, Fixed, 95% C	I	
Ferreri 2021	-0.26760624	0.12051687	42.8%	0.77 [0.60, 0.97]			-#-		
Omuro 2015	-0.09151498	0.12092607	42.5%	0.91 [0.72, 1.16]			-		
Wu 2018	0.04921802	0.20502688	14.8%	1.05 [0.70, 1.57]			-		
Total (95% CI)			100.0%	0.86 [0.74, 1.01]			•		
0,	2.13, df = 2 (P = 0.35); I	² = 6%			0.01	0.1	1	10	100
Test for overall effect: 2	Z = 1.85 (P = 0.06)					Favours cyt	arabine Favou	rs cytarabine-fre	e

Supplementary Figure S2.5.12 Pooled PFS of HD-MTX based combined regimen with or without Cytarabine

5.5. Summary of finding (SoF) tables

Outcomes		d absolute (95% CI)	Relative effect	Nº of participants	Certainty of the evidence	Comments
Outcomes	Risk with [comparison]	Risk with [intervention]	(95% CI)	(studies)	(GRADE)	Comments
MTX + rituximab vs MTX + WBRT ORR	586 per 1,000	0 per 1,000 (0 to 0)	not estimable	526 (8 studies)	⊕⊕⊕⊖ Moderate ª	
MTX + rituximab vs MTX ORR	609 per 1,000	0 per 1,000 (0 to 0)	not estimable	1094 (14 studies)	⊕⊕⊖⊖ Low ^{a,b}	
MTX + cytarabine vs MTX ORR	304 per 1,000	0 per 1,000 (0 to 0)	not estimable	223 (3 studies)	⊕⊕⊕⊖ Moderate °	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanation

a. the risk of bias in many items is unclear; b. $I^2=65$; c. the simple size is under 300

5.6. Reference

- [1] Bromberg JEC, Issa S, Bakunina K, et al. Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study. Lancet Oncology. 2019;20:216-228.
- [2] Ferreri AJ, Reni M, Foppoli M, et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet (london, england). 2009;374:1512 - 1520.
- [3] Omuro A, Chinot O, Taillandier L, et al. Methotrexate and temozolomide versus methotrexate, procarbazine, vincristine, and cytarabine for primary CNS lymphoma in an elderly population: an intergroup ANOCEF-GOELAMS randomised phase 2 trial. The lancet Haematology. 2015;2:e251 - 9.
- [4] Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncology. 2010;11:1036-1047.
- [5] Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3:e217-27.
- [6] He Z. Efficacy of high-dose methotrexate in combination with rituximab in the treatment of primary central nervous system lymphoma. Chinese Journal of Clinical Rational Drug Use. 2016;9:51-52.
- [7] Li J. Efficacy of rituximab in combination with chemotherapy in the treatment of primary central nervous system lymphoma. The Journal of Medical Theory and Practice. 2019;32:3823-3824.
- [8] Luo W, Ji L, Geng H, et al. Clinical Therapeutic Efficacy of Rituximab Combined with Methotrexate on Primary Central Nervous System Lymphoma. Journal Of Experimental Hematology. 2016;24:444-447.
- [9] Sun H, Liu H, Yan J. Therapeutic effect of rituximab combined chemotherapy on primary central nervous system lymphoma. Journal of Chinese Practical Diagnosis and Therapy. 2017;31:914-916.
- [10] Song C, Fang B, Cai X. Efficacy of Rituximab Combined with Chemotherapy Regimen in Treatment of Elderly Patients with Primary Central Nervous System Lymphomas. Journal of Chinese Oncology. 2018;24.
- [11] Shan X. [Clinical efficacy of high-dose methotrexate in combination with rituximab in the treatment of patients with PCNSL]. Heilongjiang Medicine Journal. 2019;32:1364-1366.
- [12] Wang B, Mu P. [Effect of high-dose methotrexate combined with rituximab

in the treatment of primary CNS lymphoma]. CHINA PRACTICAL MEDICINE. 2016;11:155-156.

- [13] Zhang N. [Clinical effect of rituximab monoclonal antibody plus methotrexate on primary CNS lymphoma]. Laboratory Medicine and Clinic. 2018;15:768-771.
- [14] Wu J, Duan L, Zhang L, et al. Fotemustine, teniposide and dexamethasone versus high-dose methotrexate plus cytarabine in newly diagnosed primary CNS lymphoma: a randomised phase 2 trial. Journal of neuro-oncology. 2018;140:427 - 434.
- [15] Huang X, Wang Y. [Effects of Methotrexate Combined with Temozolomide in Treatment of Primary Central Nervous System Lymphoma]. Neural Injury and Functional Reconstruction. 2017;12:132-134.
- [16] Yi Z. [Efficacy of different doses of methotrexate combined with radiotherapy in the treatment of primary central nervous system lymphoma]. Chinese Journal of Practical Nervous Diseases. 2014;17:120-121.

CQ 6. Should rituximab be used to treat newly-diagnosed PCNS-DLBCL patients in induction therapy?

- Population: Patients with PCNS-DLBCL
- Intervention: Rituximab or rituximab combined standard care
- Comparison: Placebo or standard care

6.1. Inclusion and exclusion criteria

- inclusion criteria: we only included published RCTs and observational studies in patient with PCNS-DLBCL, which compared rituximab (rituximab combined standard care) vs placebo (standard care). Studies published in English and Chinese are included.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

6.2. Characteristic information of included studies

Supplementary Table S2.6.1. characteristic information of included studies

Study		Study			Interve	ention group			Co	ontrol group	
ID	Country	design	Ν	n	Interventio n	Medication regimen	Course	n	Control	Medication regimen	Course
Brombe rg JEC et al, 2019 [1]	Netherlan ds, Australia, New Zealand	RCT	199	99	R-MBVP	-Intravenous rituximab 375 mg per m ² on days 0, 7, 14, and 21 in cycle one and days 0 and 14 in cycle two. - Methotrexate 3 g per m ² on days 1 and 15 of 28-day cycles, intravenous teniposide 100 mg per m ² on days 2 and 3, intravenous carmustine 100 mg per m ² on day 4, and oral prednisolone 60 mg per m ² on days 1-5.	28d/cycl e, 2 cycles	100	MBVP	Methotrexate 3 g per m2 on days 1 and 15 of 28-day cycles, intravenous teniposide 100 mg per m ² on days 2 and 3, intravenous carmustine 100 mg per m ² on day 4, and oral prednisolone 60 mg per m ² on days 1-5.	28d/cycle, 2 cycles

Ferreri AJM et al, 2016 [2]	Denmark, Germany, Italy, Switzerlan d, United Kingdom	RCT	144	69	R-MA	-Two doses of rituximab 375 mg/m^2 on days -5 and 0. - Methotrexate $3.5g/m^2$ (0.5 g/m ² in 15 min, followed by 3 g/m ² in a 3-h infusion) on day 1 and cytarabine 2 g/m ² (1-h infusion, twice daily, every 12 h) on days 2	3w/cycl e, 4 cycles	75	MA	Methotrexate $3.5g/m^2$ (0.5 g/m ² in 15 min, followed by 3 g/m ² in a 3-h infusion) on day 1 and cytarabine 2 g/m ² (1-h infusion, twice daily, every 12 h) on days 2 and 3.	3w/cycle, 4 cycles
Patekar M et al, 2019 [3]	India	Retrosp ective cohort study	73	27	R-MVP	and 3. -Rituximab 375 mg/m ² on day1. - Methotrexate 3.5g/m ² IV day 1 with hydration, alkalinisation and leucovorin rescue (25 mg IV every 6 h day 2–4),	2w/cycl e, 5 cycles	46	MVP	Methotrexate 3.5g/m ² IV day 1 with hydration, alkalinisation and leucovorin rescue (25 mg IV every 6 h day 2–4), vincristine 1.4 mg/m ² (capped at 2 mg) IV day 1,	2w/cycle, 5 cycles

						vincristine 1.4 mg/m ² (capped at 2 mg) IV day 1, procarbazine 100 mg/m ² P.O. days1-7 in odd number cycles. -Rituximab				procarbazine 100 mg/m ² P.O. days1-7 in odd number cycles.	
Chen C et al, 2019 [4]	China	Retrosp ective cohort study	62	32	R-MT	375 mg/m ² on day 0. - Methotrexate (3.5g/m ²) was intravenously administered on day 1, and temozolomid e (150mg/m ²) was orally administered on days 1 -	3w/cycl e, 6-8 cycles	30	MT	Methotrexate (3.5g/m ²) was intravenously administered on day 1, and temozolomid e (150mg/m ²) was orally administered on days 1 - 5.	3w/cycle, 6-8 cycles
Da Broi M et al, 2018 [5]	Norway	Retrosp ective cohort study	43	18	R-MVP	5. - Rituximab 375 mg/m ² on day1. - Methotrexate 3.5g/m ² IV day 1 with	2w/cycl e, 5 cycles	25	MVP	- Methotrexate 3.5g/m ² IV day 1 with hydration, alkalinisation and	2w/cycle, 5 cycles

		hydration, alkalinisation and leucovorin rescue (25 mg IV every 6 h day 2–4), vincristine 1.4 mg/m ² (capped at 2 mg) IV day 1, procarbazine 100 mg/m ² P.O. days1-7 in odd number	leucovorin rescue (25 mg IV every 6 h day 2–4), vincristine 1.4 mg/m ² (capped at 2 mg) IV day 1, procarbazine 100 mg/m ² P.O. days1-7 in odd number cycles.
Sun X et al, China 2017 [6]	Retrosp ective 60 36 R cohort study	cycles. -Rituximab 375 mg/m ² on day 0. -High dose methotrexate was administered intravenously 3w/cycl R-MAD at a dose of e, 24 3.5 g/m ² over 6 cycles 3 hours on day 1; Ara-C was administered intravenously at (0.5–1) g/m ² on day	High dose methotrexate was administered intravenously at a dose of 3.5 g/m ² over 3 hours on day 1; Ara-C 3w/cycle, 6 cycles was administered intravenously at (0.5–1) g/m ² on day 2; dexamethas one was

Houillier C et al, France 2017 [7]	Retrosp ective 90 39 cohort 90 39 study	R-MPV- AAA	2; dexamethas one was administered at 5-10 mg on days 1-3. -Rituximab 375 mg/m ² on day 0. - Methotrexate was administered intravenously at a dose of 3.5 g/m ² on day 1 and -MPV: day 15; 4w/cycl procarbazine e, was 3 51 administered e, was 3 51 administered cycles; 51 at a dose of 100 -AAA: 3 mg/m ² /day cycles from day 1 to day 7; vincristine was administered at a dose of 1.4 g/m ² on day 1 and day 15; cytarabine	Administered at 5-10 mg on days 1-3. Methotrexate was administered intravenously at a dose of 3.5 g/m ² on day 1 and day 15; procarbazine was administered at a dose of -MPV: 100 - 4w/cycle, 3 cycles; from day 1 to day 7; -AAA: 3 vincristine was administered at a dose of 1.4 g/m ² on day 1 and day 15; cytarabine consolidation was administered at a dose of 3
------------------------------------------	--------------------------------------------------	---------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

						consolidation was administered at a dose of 3 g/m ² on day 1 and day 2. -Rituximab 375 mg/m ² on day 1.				g/m ² on day 1 and day 2. Methotrexate , 1-3.5g/m ²	
Mocikov a H et al, 2016 [8]	Czech	Retrosp ective cohort study	164	49	R-MVP	Methotrexate , 1-3.5g/m ² intravenously day 1 in 4 h infusion, vincristine, 2 mg intravenously day 1, and procarbazine 100mg/m2 orally day 1-7 in odd courses.	2w/cycl e, 5-7 cycles	115	MVP	intravenously day 1 in 4 h infusion, vincristine, 2 mg intravenously day 1, and procarbazine 100mg/m2 orally day 1-7 in odd courses.	2w/cycle, 5-7 cycles
Madle M et al, 2015 [9]	Germany	Retrosp ective cohort study	79	27	R+ Combinatio n chemothera py	-Rituximab -Multiple combination chemotherap y (with or without high- dose methotrexate)	NA	52	Combinati on chemother apy	Multiple combination chemotherap y (with or without high- dose methotrexate)	NA
Kansar	Canada	Retrosp	74	25	R+HDMTX	Rituximab	2w/cycl	49	HDMTX	High-dose	2w/cycle,

a R et al, 2015 [10]		ective cohort study				375 mg/m ² on day 1 or day 2. -High-dose methotrexate 8g/m ²	e, 4 cycles			methotrexate 8g/m ²	4 cycles
Holdhof f M et al, 2014 [11]	America	Retrosp ective cohort study	81	27	R+HDMTX	-Rituximab 375 mg/m ² on day 3 -High-dose methotrexate 8g/m ² -Rituximab	2w/cycl e, 5 cycles	54	HDMTX	High-dose methotrexate 8g/m ²	2w/cycle, 5 cycles
Gregory G et al, 2013 [12]	Australia	Retrosp ective cohort study	117	18	R+ Combinatio n chemothera py	375 mg/m ² - Methotrexate dose of 8 g/m ² per cycle vs 2– 3.5 g/m ² , cytarabine, rituximab, radiotherapy, and intrathecal	2-7 cycles	99	Combinati on chemother apy	Methotrexate dose of 8 g/m ² per cycle vs 2- 3.5g/m ² , cytarabine, rituximab, radiotherapy, and intrathecal methotrexate	NA
Birnbau m T et al, 2012 [13]	Germany	Retrosp ective cohort study	36	17	R-MI	methotrexate -Rituximab 375 mg/m ² on day 0. - Methotrexate 4 g/m ² on day 1 and ifosfamide	2w/cycl e, 6 cycles	19	MI	Methotrexate 4 g/m ² on day 1 and ifosfamide 1.5 g/m ² on days 3-5; dexamethas one was	2w/cycle, 6 cycles

1.5 g/m ² on	given for 10
days 3-5;	days during
dexamethas	the first cycle
one was	only.
given for 10	
days during	
the first cycle	
only.	

Note: R-MBVP: methotrexate, carmustine, teniposide, and prednisone (MBVP) plus rituximab; HDMTX: High dose methotrexate; R: Rituximab; HD-MA: high-dose methotrexate plus cytarabine; MVP: Methotrexate, vincristine, and procarbazine; MA: Methotrexate and Ara-C; MT: Methotrexate and temozolomide; MAD: Methotrexate, Ara-C and dexamethasone; MI: Methotrexate and ifosfamide; "NA ": not applicable.

6.3. Risk of bias

Supplementary Table S2.6.2. Risk of bias of included RCTs assessed by the Cochrane Risk of Bias tool

Study ID	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Ot her bia s
Bromberg JEC et al, 2019 [1]	Low ROB	Low ROB	High ROB	Unclear ROB	Low ROB	Low ROB	Lo w RO B
Ferreri AJM et al, 2016 [2]	Low ROB	Low ROB	High ROB	Unclear ROB	Low ROB	Low ROB	Lo w RO B

Supplementary Table S2.6.3. Risk of bias of included cohort studies assessed by the Newcastle-Ottawa Scale

		Selection of	of exposure	9	C	omparabilit	y	Outc		
Study ID	Represe ntativene ss of the exposed cohort	Selection of the non- exposed cohort	Ascertai nment of exposur e to implant s	Demonstr ation that outcome of interest was not present at start of study	Study controls the most importan t factor	Study controls for any addition al factor	Assess ment of outcom e	Was follow up long enough for outcomes to occur	Adequac y of follow up of cohorts	Total score
Patekar M et al, 2019 [3]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Chen C et al, 2019 [4]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8

Da Broi M et al, 2018 [5]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Sun X et al, 2017 [6]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Houillier C et al, 2017 [7]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	6
Mocikova H et al, 2016 [8]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Madle M et al, 2015 [9]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Kansara R et al, 2015 [10]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Holdhoff M et al, 2014 [11]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Gregory G et al, 2013 [12]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Birnbaum T et al, 2012 [13]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8

Note: "*" equals "low risk of bias"; "-" equals "high risk of bias".

6.4. Meta-analysis results

	rituxin	nab	non-ritux	imab		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Birnbaum 2012	17	17	17	19	5.8%	1.11 [0.93, 1.33]	
Bromberg 2019	80	99	75	100	26.2%	1.08 [0.93, 1.25]	- +
Chen 2019	30	32	20	29	7.4%	1.36 [1.05, 1.76]	
Da Broi 2018	17	18	14	25	4.1%	1.69 [1.17, 2.43]	
Ferreri 2016	51	69	40	75	13.5%	1.39 [1.08, 1.79]	
Houillier 2017	30	39	27	51	8.2%	1.45 [1.07, 1.98]	
Kansara 2015	12	25	25	49	5.9%	0.94 [0.58, 1.54]	
Mocikova 2016	32	49	61	115	12.8%	1.23 [0.94, 1.61]	
Patekar 2019	24	27	34	46	8.8%	1.20 [0.97, 1.49]	+
Sun 2017	26	36	17	24	7.2%	1.02 [0.74, 1.41]	
Total (95% CI)		411		533	100.0%	1.22 [1.12, 1.32]	•
Total events	319		330				
Heterogeneity: Chi ² =	= 11.74. df	= 9 (P =	= 0.23); ² =	= 23%		-	
Test for overall effect		`					0.5 0.7 1 1.5 2 Favours (non-rituximab) Favours (rituximab)

Supplementary Figure S2.6.1. Meta-analysis for OR in patient with PCNSL (rituximab vs. non-rituximab)

	rituxin	nab	non-ritux	cimab		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Birnbaum 2012	17	17	13	19	6.7%	1.44 [1.05, 1.97]	-
Bromberg 2019	67	99	66	100	34.4%	1.03 [0.84, 1.25]	- -
Chen 2019	17	32	8	29	4.4%	1.93 [0.98, 3.78]	
Da Broi 2018	17	18	14	25	6.1%	1.69 [1.17, 2.43]	
Ferreri 2016	21	69	17	75	8.5%	1.34 [0.78, 2.33]	
Holdhoff 2014	19	27	19	54	6.6%	2.00 [1.29, 3.10]	
Kansara 2015	9	25	17	49	6.0%	1.04 [0.54, 1.98]	
Mocikova 2016	20	49	39	115	12.2%	1.20 [0.79, 1.84]	
Patekar 2019	22	27	26	46	10.1%	1.44 [1.06, 1.97]	
Sun 2017	24	36	8	24	5.0%	2.00 [1.09, 3.69]	
Total (95% CI)		399		536	100.0%	1.34 [1.18, 1.51]	•
Total events	233		227				
Heterogeneity: Chi ² =	15.94. df	= 9 (P :	= 0.07); l ² :	= 44%			<u></u>
Test for overall effect:	•						0.2 0.5 1 2 5 Favours (non-rituximab) Favours (rituximab)

Supplementary Figure S2.6.2. Meta-analysis for CR in patient with PCNSL (rituximab vs. non- rituximab)

	rituxin	nab	non-ritux	dimab				Hazard Ratio		Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI		Exp[(O-E) / V], Fixed, 95% Cl
Birnbaum 2012	0	0	0	0	0.77	5.91	5.3%	1.14 [0.51, 2.55]		
Bromberg 2019	0	0	0	0	-6.88	26.32	23.5%	0.77 [0.53, 1.13]		
Chen 2019	0	0	0	0	-1.74	2.85	2.5%	0.54 [0.17, 1.73]		
Da Broi 2018	0	0	0	0	-0.6	2.67	2.4%	0.80 [0.24, 2.65]		
Ferreri 2016	0	0	0	0	-5.82	8.91	8.0%	0.52 [0.27, 1.00]		
Holdhoff 2014	0	0	0	0	-5.77	7.3	6.5%	0.45 [0.22, 0.94]		_
Houillier 2017	0	0	0	0	-0.22	16.14	14.4%	0.99 [0.61, 1.61]		_
Kansara 2015	0	0	0	0	-3.3	11.47	10.2%	0.75 [0.42, 1.34]		
Mocikova 2016	0	0	0	0	-6.4	26.09	23.3%	0.78 [0.53, 1.15]		
Sun 2017	0	0	0	0	-4.55	4.29	3.8%	0.35 [0.13, 0.89]	-	
Total (95% CI)		0		0			100.0 %	0.73 [0.61, 0.88]		•
Total events	0		0					- / -		
Heterogeneity: Chi ² =	8.17, df =	9 (P =	0.52); $l^2 =$	0%						
Test for overall effect:	Z = 3.26 ((P = 0.0	001)						0.1	0.2 0.5 1 2 5 10 Favours (rituximab) Favours (non-rituximab)

Supplementary Figure S2.6.3. Meta-analysis for PFS in patient with PCNSL (rituximab vs. non- rituximab)

Study or Subgroup								Hazard Ratio	Hazard Ratio
	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% Cl	Exp[(O-E) / V], Fixed, 95% Cl
Birnbaum 2012	0	0	0	0	1.5	2.38	2.6%	1.88 [0.53, 6.69]	
Bromberg 2019	0	0	0	0	-1.52	20.91	22.6%	0.93 [0.61, 1.43]	
Chen 2019	0	0	0	0	-1.75	1.8	1.9%	0.38 [0.09, 1.63]	
Da Broi 2018	0	0	0	0	-0.88	2.05	2.2%	0.65 [0.17, 2.56]	
Ferreri 2016	0	0	0	0	-6.03	13.06	14.1%	0.63 [0.37, 1.08]	
Gregory 2013	0	0	0	0	-0.33	1.69	1.8%	0.82 [0.18, 3.72]	
Holdhoff 2014	0	0	0	0	-3.62	6.4	6.9%	0.57 [0.26, 1.23]	
Houillier 2017	0	0	0	0	1.18	8.57	9.3%	1.15 [0.59, 2.24]	
<ansara 2015<="" td=""><td>0</td><td>0</td><td>0</td><td>0</td><td>-2.35</td><td>7.46</td><td>8.1%</td><td>0.73 [0.36, 1.50]</td><td></td></ansara>	0	0	0	0	-2.35	7.46	8.1%	0.73 [0.36, 1.50]	
Madle 2015	0	0	0	0	-2.26	4.2	4.5%	0.58 [0.22, 1.52]	
Mocikova 2016	0	0	0	0	-1.53	21.53	23.3%	0.93 [0.61, 1.42]	
3un 2017	0	0	0	0	-0.3	2.29	2.5%	0.88 [0.24, 3.20]	
fotal (95% CI)		0		0			100.0%	0.82 [0.67, 1.01]	•
Fotal events	0		0						
Heterogeneity: Chi ² = I	6.83, df=	11 (P :	= 0.81); l ² =	= 0%				-	
Fest for overall effect: .								t	D.1 D.2 D.5 1 2 5 11 Favours (rituximab) Favours (non-rituximab)

Supplementary Figure S2.6.4. Meta-analysis for OS in patient with PCNSL (rituximab vs. non- rituximab)

A 中性粒细胞减少症	B血小板湯	沙症	
rituximab non-rituximab Risk Ratio	Risk Ratio	rituximab non-rituximab	Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl Study or Subgroup	Events Total Events Total Weight M-I	I. Fixed, 95% Cl M-H. Fixed, 95% Cl
Bromberg 2019 8 99 9 100 12.2% 0.90 (0.36, 2.23)	Bromberg 2019	7 99 9 100 10.6% (0.79 [0.30, 2.03]
Chen 2019 9 32 8 30 11.2% 1.05 [0.47, 2.37]	Chen 2019		.25 [0.30, 5.13]
Ferreri 2016 39 69 39 75 50.7% 1.09 [0.81, 1.47]	Ferreri 2016		1.05 [0.85, 1.28]
Houillier 2017 25 39 22 51 25.9% 1.49 [1.00, 2.20]	Houillier 2017		1.10 [0.73, 1.64]
Total (95% Cl) 239 256 100.0% 1.16 [0.93, 1.46]	Total (95% CI)		.04 [0.86, 1.26]
Total events 81 78	Total events	83 90	.04 [0.00, 1.20]
Hotorogonoity Chill = 2 05 df = 2 /D = 0.551; Il = 004		= 0.48, df = 3 (P = 0.92); P = 0%	
Test for supral effect 7 = 1.20 /D = 0.10	1 Z 5 Test fax suprell offer	t Z = 0.39 (P = 0.69)	0.2 0.5 1 2 5
Favours	rituximab] Favours (non-rituximab)	2 - 0.05 ((- 0.05)	Favours (rituximab) Favours (non-rituximab)
C 贫血	D肝毒性		
rituximab non-rituximab Risk Ratio	Risk Ratio	rituximab non-rituximab F	Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl Study or Subgroup	Events Total Events Total Weight M-H	, Fixed, 95% CI M-H, Fixed, 95% CI
Bromberg 2019 5 99 5 100 16.0% 1.01 (0.30, 3.38)	Bromberg 2019		.59 [0.64, 3.93]
Chen 2019 7 32 3 30 10.0% 2.19 [0.62, 7.69]	Chen 2019		34 (0.06, 14.33)
Ferreri 2016 24 69 24 75 74.0% 1.09 (0.68, 1.72)	-Ferreri 2016		.97 [0.39, 2.36]
	Houillier 2017	16 39 25 51 56.6% 0	.84 [0.52, 1.34]
Total (95% CI) 200 205 100.0% 1.18 [0.79, 1.78]	Total (95% CI)	239 256 100.0% 1	01 [0.69, 1.47]
Total events 36 32	. Total events	36 42	
Heterogeneity: Chi ² = 1.11, df = 2 (P = 0.57); I ² = 0%		1.57, df = 3 (P = 0.67); I ² = 0%	0.02 0.1 1 10 50
	ituximab] Favours (non-rituximab) Test for overall effec	Z = 0.03 (P = 0.98)	Favours (rituximab) Favours (non-rituximab)
1.010010	maninary - around from meanined		r and a presented in an and from memory
E肾毒性			
rituximab non-rituximab Risk Ratio	Risk Ratio		
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl		
Bromberg 2019 6 99 2 100 24.4% 3.03 [0.63, 14.65]	+•		
Ferreri 2016 1 69 1 75 11.8% 1.09 [0.07, 17.04]			
Houillier 2017 4 39 6 51 63.8% 0.87 [0.26, 2.88]	- - -		
Total (95% CI) 207 226 100.0% 1.42 [0.60, 3.39]	—		
Total events 11 9			
Heterogeneity: Chi ² = 1.57, df = 2 (P = 0.46); P = 0%	1 10 100		
	rituximab) Favours (non-rituximab)		

Supplementary Figure S2.6.5. Grade 3 or higher adverse events: A Neutropenia; B Thrombocytopenia; C Anemia; D Hepatotoxicity; E Nephrotoxicity.

6.5. Summary of finding (SoF) tables

Outcomes	Anticipate effects*	d absolute (95% CI)	Relative effect	Nº of participants	Certainty of the evidence	Comments	
Outcomes	Risk with [comparison]	Risk with [intervention]	(95% CI)	(studies)	(GRADE)		
OR	619 per 1,000	755 per 1,000 (693 to 817)	RR 1.22 (1.12 to 1.32)	944 (10 studies)	⊕⊕⊖⊖ Low ^a	None	
CR	424 per 1,000	568 per 1,000 (500 to 639)	RR 1.34 (1.18 to 1.51)	935 (10 studies)	⊕⊕⊖⊖ Low ^a	None	
PFS	NA	NA	HR 0.73 (0.61 to 0.88)	953 (10 studies)	⊕⊕⊖⊖ Low ^a	None	
OS	OS NA		HR 0.82 (0.67 to 1.01)	1149 (12 studies)	⊕⊕⊖⊖ Low ^a	None	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio; NA: Not applicable.

Explanation

^a The initial quality of evidence for the results of meta-analyses of observational studies was low.

6.6. References

- [1] Bromberg JEC, Issa S, Bakunina K, et al. Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study. The Lancet Oncology. 2019;20(2):216 - 28.
- [2] Ferreri AJM, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. The lancet haematology. 2016;3(5):e217 - e27.
- [3] Patekar M, Adhikari N, Biswas A, et al. Primary CNS Lymphoma in India: A 17-Year Experience From the All India Institute of Medical Sciences. Journal of global oncology. 2019;5:1-9.
- [4] Chen C, Sun P, Cui J, et al. High-dose Methotrexate plus temozolomide with or without rituximab in patients with untreated primary central nervous system lymphoma: A retrospective study from China. Cancer medicine. 2019;8(4):1359-67.
- [5] Da Broi M, Jahr G, Beiske K, et al. Efficacy of the Nordic and the MSKCC chemotherapy protocols on the overall and progression-free survival in intracranial PCNSL. Blood cells, molecules & diseases. 2018;73:25-32.
- [6] Sun X, Liu J, Wang Y, et al. Methotrexate-cytarabine-dexamethasone combination chemotherapy with or without rituximab in patients with primary central nervous system lymphoma. Oncotarget. 2017;8(30):49156-64.
- [7] Houillier C, Ghesquières H, Chabrot C, et al. Rituximab, methotrexate, procarbazine, vincristine and intensified cytarabine consolidation for primary central nervous system lymphoma (PCNSL) in the elderly: a LOC network study. Journal of neuro-oncology. 2017;133(2):315-20.
- [8] Mocikova H, Pytlik R, Sykorova A, et al. Role of rituximab in treatment of patients with primary central nervous system lymphoma: a retrospective analysis of the Czech lymphoma study group registry. Leukemia & lymphoma. 2016;57(12):2777-83.
- [9] Madle M, Krämer I, Lehners N, et al. The influence of rituximab, high-dose therapy followed by autologous stem cell transplantation, and age in patients with primary CNS lymphoma. Annals of hematology. 2015;94(11):1853-7.
- [10]Kansara R, Shenkier TN, Connors JM, et al. Rituximab with high-dose methotrexate in primary central nervous system lymphoma. American journal of hematology. 2015;90(12):1149-54.
- [11]Holdhoff M, Ambady P, Abdelaziz A, et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. Neurology. 2014;83(3):235-9.

- [12]Gregory G, Arumugaswamy A, Leung T, et al. Rituximab is associated with improved survival for aggressive B cell CNS lymphoma. Neuro-oncology. 2013;15(8):1068-73.
- [13]Birnbaum T, Stadler EA, von Baumgarten L, et al. Rituximab significantly improves complete response rate in patients with primary CNS lymphoma. Journal of neuro-oncology. 2012;109(2):285-91.

CQ 7. Which is the preferred approach to treat patients with PCNSL at consolidation therapy, whole-brain radiotherapy (WBRT) or autologous hematopoietic stem cell transplantation (ASCT)?

- Population: Patients with PCNSL
- Intervention: Autologous hematopoietic stem cell transplantation (ASCT)
- Comparison: Whole-brain radiotherapy (WBRT)

7.1. Inclusion and exclusion criteria

- Inclusion criteria: we only included published RCTs and observational studies in patient with PCNS, which compared whole-brain radiotherapy vs autologous hematopoietic stem cell transplantation. Studies published in English and Chinese are included.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

7.2. Characteristic information of included studies

Supplementary Table S2.7.1. Characteristic information of included studies

Study		Study			Intervent	ion group		Control	group
ID	Country	design	Ν	n	Intervention	Medication regimen	n	Control	Medication regimen
Ferreri AJM et al, 2017 [1]	Italy	RCT	118	58	HDC-ASCT	D-6: carmustine (400 mg/m ²); D-5,-4: thiotepa (5 mg/kg q12h) D0: re-infusion of autologous peripheral blood stem cells	55	WBRT	36 Gy, with the addition of a 9 Gy tumour-bed boost in patients in partial response: photons of 4-10 MeV; 180 cGy/fraction; 5 d/wk
Houillier C et al, 2019 [2]	France	RCT	140	44	HDC-ASCT	D-9,-8,-7: thiotepa (250 mg/m2/d); D-6,-5,-4: busulfan (8 mg/kg); D-3,-2: Cyclophosphamide (60 mg/kg/day); D-3: polyethylene glycol filgrastim; D0: re-infusion of autologous peripheral blood	53	WBRT	40 Gy: photons of 6-10 MeV; 2 Gy/fraction; 5 d/wk
Correa DD et al, 2019 [3]	America	Observational study	29	15	HDC-ASCT	stem cells Thiotepa, busulfan, cyclophosphamide, and autohematopoietic stem cell transplantation	14	rdWBRT + Ara- C	23.4 Gy: 1.8 Gy/fraction; 13 day; two cycles of Ara-C

Ferreri AJM et al, 2020 [4] Houillier C et al, 2020 [5]	Italy France	Observational study Observational study	28	5	HDC-ASCT	Carmustine, thiotepa, and autohematopoietic stem cell transplantation Thiotepa-based HDC-ASCT: 86%; BEAM-ASCT (carmustine, etoposide, cytarabine, melphalan + autologous hematopoietic stem cell transplantation):	7	WBRT	30-36 Gy 18-56 Gy: >30 Gy: 58%; ≤30 Gy: 32%; NA: 10%
						14%			
Kim JE et al, 2012 [6]	Korea	Observational study	65	18	Chemotherapy- ASCT	NA	13	Chemotherapy- WBRT	NA
HDC: high	-dose chei	motherapy; WBF	RT: who	le-br	ain radiotherapy; /	ASCT: autologous her	natopo	pietic stem cell trai	nsplantation; NA: not

applicable.

7.3. Risk of bias

Table S2.7.2 Risk of bias of included RCTs assessed by the Cochrane Risk of Bias tool

Study ID	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ferreri AJM et al, 2017 [1]	Low ROB	Low ROB	High ROB	Unclear ROB	Low ROB	Low ROB	Low ROB
Houillier C et al, 2019 [2]	Low ROB	Low	High	Unclear ROB	Low ROB	Low ROB	Low ROB

Note: ROB: risk of bias.

		Selection of	of exposure	9	Co	omparabilit	y	Outc	ome	
Study ID	Represe ntativene ss of the exposed cohort	Selection of the non- exposed cohort	Ascertai nment of exposur e to implant s	Demonstr ation that outcome of interest was not present at start of study	Study controls the most importan t factor	Study controls for any addition al factor	Assess ment of outcom e	Was follow up long enough for outcomes to occur	Adequac y of follow up of cohorts	Total score
Rorrea DD et al, 2019 [3]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	6
Ferreri AJM et al, 2020 [4]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	6

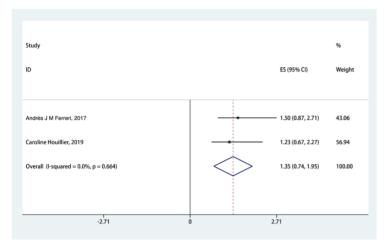
Houillier C et al, 2020 [5]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Kim JE et al, 2012 [6]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7

Note: "*" equals "low risk of bias"; "-" equals "high risk of bias".

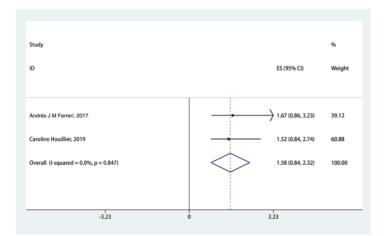
7.4. Meta-analysis results

	Intervention	ASCT	Comparator	WBRT		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
Ferreri 2017	24	28	24	27	46.5%	0.75 [0.15, 3.72]			
Houillier 2020	54	56	133	149	34.6%	3.25 [0.72, 14.61]			
Kim 2012	16	18	11	13	18.9%	1.45 [0.18, 11.94]			
Total (95% CI)		102		189	100.0%	1.75 [0.70, 4.35]		-	
Total events	94		168						
Heterogeneity: Chi ² =	= 1.76, df = 2 (P	= 0.42);	I² = 0%				L		100
Test for overall effect	: Z = 1.20 (P = 0	0.23)					0.01	0.1 1 10 Favours (ASCT) Favours (WBRT)	100

Supplementary Figure S2.7.1. Meta-analysis for OR in patient with PCNSL (ASCT vs. WBRT)



Supplementary Figure S2.7.2 Meta-analysis for 2-year PFS in patient with PCNSL (ASCT vs. WBRT).



Supplementary Figure S2.7.3. Meta-analysis for 2-year OS in patient with PCNSL (ASCT vs. WBRT)

7.5. Summary of finding (SoF) tables

Outcomes		d absolute (95% CI)	Relative effect	№ of participants	Certainty of the evidence	Comments	
Outcomes	Risk with [comparison]	Risk with [intervention]	(95% CI)	(studies)	(GRADE)	Comments	
OR	889 per 1,000	933 per 1,000 (848 to 972)	RR 1.75 (0.70 to 4.35)	291 (1RCT, 2 observational studies)	⊕⊖⊖⊖ Lowª	None	
2-year PFS	NA	NA	HR 1.35 (0.61 to 0.88)	250 (2 RCTs)	⊕⊕⊖⊖ Low ^{a,b}	None	
2-year OS	NA	NA	HR 1.58 (0.84 to 2.32)	250 (2 RCTs)	⊕⊕⊖⊖ Low ^{a,b}	None	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio; NA: Not applicable.

Explanation

a. The sample size is lower than the optimal information sample size. b. None of the RCTs were blinded.

7.6. References

- [1] Ferreri AJM, Cwynarski K, Pulczynski E, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after highdose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. The lancet Haematology. 2017;4(11):e510 - e23.
- [2] Houillier C, Taillandier L, Dureau S, et al. Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results o the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. Journal of Clinical Oncology. 2019;37(10): 823-833.
- [3] Correa DD, Braun E, Kryza-Lacombe M, et al. Longitudinal cognitive assessment in patients with primary CNS lymphoma treated with induction chemotherapy followed by reduced-dose whole-brain radiotherapy or autologous stem cell transplantation. Journal of Neuro-Oncology. 2019;144(3):553-62.
- [4] Ferreri AJM, Calimeri T, Ponzoni M, et al. Improving the antitumor activity of R-CHOP with NGR-hTNF in primary CNS lymphoma: final results of a phase 2 trial. Blood Adv. 2020;4(15):3648-58.
- [5] Houillier C, Soussain C, Ghesquières H, et al. Management and outcome of primary CNS lymphoma in the modern era: An LOC network study. Neurology. 2020;94(10):e1027-e39.
- [6] Kim JE, Yoon DH, Kim S, et al. Relapse pattern and prognostic factors for patients with primary central nervous system lymphoma. The Korean journal of hematology. 2012;47(1):60-6.

CQ 8: Should BTK inhibitors be used to treat patients with PCNSL?

- Population: Patients with PCNSL
- Intervention: BTK inhibitors
- Comparison: Other treatment, placebo

8.1. Inclusion and exclusion criteria

- inclusion criteria: we included published studies, which treated the localized recurrent refractory PCNSL with BTK inhibitors. Studies published in English and Chinese are included.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

8.2. Characteristic information of included studies

Supplementary Table S2.8.1. Characteristic information of included studies

Study ID	Count ry	Research type	Disease Stage	•	N	Interven tion	Dosing method	ORR	CR	PR	PFS	os
Yu 2021 [1]	China	Case report	newly diagnose relapsed refractory	ed / or	3	ibrutinib	single/combination	100% (3/3)	67%	33%	7m	9.3 m
Lewis 2021 [2]	Austral ia	Case series	relapsed refractory	or	9	ibrutinib	single/combination	44% (4/9)	44%	/	31m	31m
Chen 2020 [3]	China	Case series	newly diagnose	ed	11	ibrutinib	ibrutinib+HD-MTX	82% (9/11)	64%	18%	7.4m	1
Grommes 2017 [4]	Americ a	Case series	relapsed refractory	or	13	ibrutinib	single/combination	77% (10/13)	38.5 %	38.5 %	4.6m	15m
Grommes 2019 [5]	Americ a	Cohort study	relapsed refractory	or	9	ibrutinib	combination	89% (8/9)	67%	22%	/	1
Chamoun 2017 [6]	French	Case series	relapsed refractory	or	14	ibrutinib	single/combination	50% (7/14)	21%	28.5 %	/	1

Lionakis 2017 [7]	French	Case series	newly diagnosed / relapsed or refractory		ibrutinib	single/combination	94% (17/18)	88%	6%	11.2 m	/
Soussain 2019 [8]	French	Single-arm study	relapsed or refractory CNSL / PVRL	52	ibrutinib	single	52% (27/52)	19%	33%	4.8m	19.2 m
LAUER EM 2020 [9]	Germa ny	Single centre case series	relapsed or refractory	9	ibrutinib	single/combination	66% (6/9)	66% (6/9)	/	/	/
Grommes 2018 [10]	Americ a	Single-arm study	relapsed or refractory	27	ibrutinib	single	81% (31/40)	/	/	/	/
Grommes 2019 [11]	Americ a	Single-arm study	relapsed or refractory	6	ibrutinib	Ibrutinib + copanlisib	67% (4/6)	17%	50%	1	/
Dunleavy 2015 [12]	Americ a	Cohort study	newly diagnosed / relapsed or refractory		ibrutinib	single/combination (ibrutinib + DA- TEDDI-R)	73% (8/11)	/	64%	/	/
Bairey 2019 [13]	Israel	Single-arm study	newly diagnosed / the elder	12	ibrutinib	Ibrutinib + HD- MTX	/	25%	/	22.5 m	/
Roschew ski 2020 [14]	Americ a	Single-arm study	relapsed or refractory	13	ibrutinib	combination	85% (11/13)	61.5 %	/	/	/

Lewis 2019 [15]	Austral ia	Case series	newly diagnose relapsed refractory	~ ~	8	ibrutinib	combination	50% (4/8)	/	/	/	/
Roschew ski 2018 [16]	Americ a	Cohort study	newly diagnose relapsed refractory	~ ~	18	ibrutinib	ibrutinib + TEDD-R	/	50%	/	15.2 m	/
Christian G 2015 [17]	Americ a	Case series	relapsed refractory	or	4	ibrutinib	single	50%(2/ 4)	/	/	/	/
Yuedan C 2020 [18]	China	Single-arm study	relapsed refractory	or	18	ibrutinib	ibrutinib + I-MIDD regimen	83.3% (5/18)	55.5 %	27.8 %	6m	/
Narita 2021 [19]	Japan	non- randomized controlled study	relapsed refractory	or	44	tirabrutin ib	single	64% (28/44)	9.1% (4/44)	29.5 % (13/ 44)	4.9m	/
Hou K 2021 [20]	China	Systematic review	non-GCB DLB and relapsed/refract y CNSL		11 45	ibrutinib	Single/combinatio n (ibrutinib + RTX)	57.9 % (663/1 145)	35.0 %	20.1 %	4.45 m	11.5 m

/: none

8.3. Risk of bias

Supplementary Table S2.8.2. Risk of bias of included non-randomized controlled studies assessed by the Newcastle-Ottawa Scale

	Se	election o	of exposure		Cor	nparabilit	У	Outo	ome	
Study ID	Representativ eness of the exposed cohort	Select ion of the non- expos ed cohort	Ascertain ment of exposure to implants	Demonstr ation that outcome of interest was not present at start of study	Study controls the most important factor	Study contro Is for any additio nal factor	Assess ment of outcom e	Was follow up long enoug h for outco mes to occur	Adequ acy of follow up of cohort s	Tot al sco re
Grommes 2019 [5]	С	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Dunleavy 2015 [12]	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	6
Roschewski 2018 [16]	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	6
Soussain [8]	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	6
LAUER EM [9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	4
Grommes [10]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Grommes [11]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Bairey [13]	Yes	No	Yes	No	No	Yes	Yes	No	Yes	5
Roschewski [14]	Yes	Yes	Yes	No	No	Yes	No	No	No	4
Yuedan C [18]	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	6
Narita[19]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7

Supplementary Table S2.8.3. Risk of bias of included case report and case series studies assessed by the Institute of Health Economics checklist

	Study objective	Study population	on				Intervention intervention	
Study ID	Is the hypothesis , aim, objective of the study clearly stated?	Are the characteristic s of the participants included in the study described?	Were the cases collecte d in more than one centre?	Are the eligibility criteria for entry into the study clearly stated?	Were participants recruited consecutively ?	Did participant s enter the study at a similar point in the disease?	Was the interventio n of interest clearly described ?	Were additional intervention s (co- intervention s) reported in the study?
Yu [1]	Yes	No	No	Unclear	Unclear	Unclear	No	Yes
Lewis [2]	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Chen [3]	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Grommes [4]	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Chamoun [6]	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Lionakis [7]	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Lewis [15]	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes

Continued Supplementary Table S2.8.3.

		Outcome measure		Statistical analysis	Results and cond	clusions
Study ID	Are the outcome measures established a priori?	Were the relevant outcomes measured with appropriate objective and/or	Were the relevant outcomes measured before and after	Were the statistical tests used to assess the relevant outcomes	Was the length of follow-up reported?	Was the loss to follow-up reported?

		subjective methods?	the intervention?	appropriate?		
Yu [1]	Yes	Yes	No	Yes	No	No
Lewis [2]	Partial reported	Unclear	No	Unclear	No	No
Chen [3]	Yes	Yes	No	No	No	No
Grommes [4]	Yes	Yes	No	Yes	Unclear	No
Chamoun [6]	No	Yes	Yes	No	Unclear	Unclear
Lionakis [7]	No	Partial reported	Yes	No	Unclear	Unclear
Lewis [15]	No	Yes	Yes	No	No	Unclear

Continued Supplementary Table S2.8.3.

	Results	s and conclu	sions	Competing interest and source of support	New it	ems	
Yu [1] N Lewis [2] N Chen [3] N	Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	study provide estimates of the random variability n the data nalysis of relevant		Are both competing interests and sources of support for the study reported?	Was the study conducted prospectivel y?	Were the relevant outcomes assessed blinded to interventi on status?	Tota I scor e
Yu [1]	No	No	Yes	Yes	Unclear	Unclear	10
Lewis [2]	No	No	Yes	Partial reported	No	Unclear	5
Chen [3]	No	No	Yes	Partial reported	Yes	Unclear	8
Grommes [4]	No	No	Yes	No	Yes	Unclear	9
Chamoun [6]	No	No	Unclear	Yes	Unclear	No	8

Lionakis [7]	Partial reported	Unclear	Unclear	Unclear	Yes	No	6
Lewis [15]	Yes	Yes	Unclear	Yes	No	No	8

Supplementary Table S2.8.4 Risk of bias of included systematic reviews assessed by the AMSTAR

Stu dy ID	Was an 'a priori' design provid ed?	Was there duplica te study selecti on and data extracti on?	Was a compreh ensive literature search performe d?	Was the status of publicatio n (i.e., grey literature) used as an inclusion criterion?	Was a list of studies (includ ed and exclud ed) provide d?	Were the charac teristic s of the includ ed studie s provid ed?	Was the scientific quality of the included studies assesse d and docume nted?	Was the scientific quality of the included studies used appropriate ly in formulating conclusion s?	Were the methods used to combine the findings of studies appropri ate?	Was the likeliho od of publica tion bias assess ed?	Was the likeliho od of publica tion bias assess ed?
Hou K [20]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes

8.4 Meta-analysis results

				Risk Difference	Risk Difference
Study or Subgroup	Risk Difference	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Chamoun 2017	0.5	0.134	6.0%	0.50 [0.24, 0.76]	
Chen(ca) 2020	0.833	0.088	9.0%	0.83 [0.66, 1.01]	
Chen 2020	0.82	0.116	7.0%	0.82 [0.59, 1.05]	
Dunleavy(ca) 2015	0.73	0.134	6.0%	0.73 [0.47, 0.99]	
Grommes(ca) 2015	0.67	0.271	2.1%	0.67 [0.14, 1.20]	
Grommes(ca) 2018	0.81	0.075	10.0%	0.81 [0.66, 0.96]	
Grommes(ca) 2019	0.67	0.192	3.7%	0.67 [0.29, 1.05]	
Grommes 2017	0.77	0.117	6.9%	0.77 [0.54, 1.00]	
Grommes 2019	0.89	0.104	7.8%	0.89 [0.69, 1.09]	
Lauer 2020	0.6	0.22	3.0%	0.60 [0.17, 1.03]	
Lewis(ca) 2019	0.5	0.177	4.1%	0.50 [0.15, 0.85]	
Lewis 2021	0.44	0.165	4.6%	0.44 [0.12, 0.76]	
Lionakis 2017	0.94	0.056	11.6%	0.94 [0.83, 1.05]	+
Roschewski(ca) 2020	0.85	0.099	8.1%	0.85 [0.66, 1.04]	
Soussain 2019	0.59	0.074	10.1%	0.59 [0.44, 0.74]	
Yu 2021	1	0		Not estimable	
Total (95% CI)			100.0%	0.74 [0.66, 0.83]	◆
Heterogeneity: Tau ² = 0	.01; Chi ² = 29.44, d	f = 14 (F	e = 0.009)); I² = 52%	-1 -0.5 0 0.5 1
Test for overall effect: Z	= 17.46 (P < 0.000)	01)			
					Favours [experimental] Favours [control]

Supplementary Figure S2.8.1. Forest plot of overall efficiency of ibrutinib

				Risk Difference	Risk Difference
Study or Subgroup	Risk Difference	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Bairey(ca) 2019	0.25	0.125	6.9%	0.25 [0.01, 0.49]	
Chamoun 2017	0.21	0.109	7.4%	0.21 [-0.00, 0.42]	
Chen(ca) 2020	0.555	0.117	7.1%	0.56 [0.33, 0.78]	
Chen 2020	0.64	0.145	6.3%	0.64 [0.36, 0.92]	
Dunleavy(ca) 2015	0.45	0.15	6.2%	0.45 [0.16, 0.74]	
Grommes(ca) 2015	0.33	0.271	3.5%	0.33 [-0.20, 0.86]	
Grommes(ca) 2019	0.17	0.153	6.1%	0.17 [-0.13, 0.47]	
Grommes 2017	0.385	0.135	6.6%	0.39 [0.12, 0.65]	· · · · · · · · · · · · · · · · · · ·
Grommes 2019	0.67	0.157	6.0%	0.67 [0.36, 0.98]	
Lauer 2020	0.6	0.22	4.4%	0.60 [0.17, 1.03]	
Lewis 2021	0.44	0.165	5.7%	0.44 [0.12, 0.76]	
Lionakis 2017	0.86	0.082	8.1%	0.86 [0.70, 1.02]	
Roschewski(ca) 2018	0.5	0.118	7.1%	0.50 [0.27, 0.73]	
Roschewski(ca) 2020	0.615	0.135	6.6%	0.61 [0.35, 0.88]	
Soussain 2019	0.23	0.063	8.6%	0.23 [0.11, 0.35]	
Yu 2021	0.67	0.271	3.5%	0.67 [0.14, 1.20]	
Total (95% CI)			100.0%	0.47 [0.34, 0.59]	•
Heterogeneity: Tau ² = 0.	04; Chi ² = 55.67, d	f = 15 (F	, < 0.000i	D1); I² = 73%	
Test for overall effect: Z:					-1 -0.5 0 0.5 1 Favours (experimental) Favours (control)

Supplementary Figure S2.8.2. Forest plot of complete remission rate of ibrutinib

				Risk Difference	Risk Difference
Study or Subgroup	Risk Difference	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Chamoun 2017	0.285	0.121	10.1%	0.28 [0.05, 0.52]	
Chen(ca) 2020	0.278	0.106	12.2%	0.28 [0.07, 0.49]	
Chen 2020	0.18	0.116	10.7%	0.18 [-0.05, 0.41]	+
Grommes(ca) 2015	0.33	0.271	2.6%	0.33 [-0.20, 0.86]	
Grommes(ca) 2019	0.5	0.204	4.3%	0.50 [0.10, 0.90]	· · · · · · · · · · · · · · · · · · ·
Grommes 2017	0.385	0.135	8.6%	0.39 [0.12, 0.65]	
Grommes 2019	0.22	0.138	8.3%	0.22 [-0.05, 0.49]	+
Lionakis 2017	0.08	0.064	21.5%	0.08 [-0.05, 0.21]	+
Soussain 2019	0.36	0.072	19.2%	0.36 [0.22, 0.50]	
Yu 2021	0.33	0.271	2.6%	0.33 [-0.20, 0.86]	
Total (95% CI)			100.0%	0.26 [0.17, 0.35]	•
Heterogeneity: Tau ² =	0.01; Chi ² = 12.58,	df = 9 (P = 0.18)	l² = 28%	
Test for overall effect: .			. ,		-1 -0.5 0 0.5 1 Favours [experimental] Favours [control]

Supplementary Figure S2.8.3. Forest plot of partial response rate of ibrutinib

A Single

n onigie				Risk Difference	Risk Difference
Study or Subgroup	Risk Difference	SE	Weight	IV, Random, 95% CI	CI IV, Random, 95% CI
Chamoun 2017	0.5	0.134	15.4%	0.50 [0.24, 0.76]	3]
Grommes(ca) 2015	0.67	0.271	5.1%	0.67 [0.14, 1.20]	(c
Grommes(ca) 2018	0.81	0.075	28.0%	0.81 [0.66, 0.96]	3]
Grommes 2017	0.77	0.117	18.2%	0.77 [0.54, 1.00]	(c
Lauer 2020	1	0		Not estimable	e
Lewis 2021	0.33	0.271	5.1%	0.33 [-0.20, 0.86]	3]
Soussain 2019	0.59	0.074	28.2%	0.59 [0.44, 0.74]	4]
Yu 2021	1	0		Not estimable	e
Total (95% CI)			100.0%	0.66 [0.53, 0.79]	a 🔶
Heterogeneity: Tau ² =	0.01; Chi ² = 8.54,	df = 5 (F	e = 0.13);	I ² = 41%	
Test for overall effect.	Z=10.17 (P < 0.00	0001)			-1 -0.5 0 0.5 Favours [experimental] Favours [control]

B Combination

				Risk Difference	Risk Difference
Study or Subgroup	Risk Difference	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Chen(ca) 2020	0.833	0.088	15.6%	0.83 [0.66, 1.01]	
Chen 2020	0.82	0.116	9.0%	0.82 [0.59, 1.05]	
Dunleavy(ca) 2015	0.73	0.134	6.7%	0.73 [0.47, 0.99]	· · · · · ·
Grommes(ca) 2019	0.67	0.192	3.3%	0.67 [0.29, 1.05]	
Grommes 2019	0.89	0.104	11.1%	0.89 [0.69, 1.09]	
Lauer 2020	0.5	0.25	1.9%	0.50 [0.01, 0.99]	
Lewis 2021	0.67	0.271	1.6%	0.67 [0.14, 1.20]	
Lionakis 2017	0.94	0.056	38.5%	0.94 [0.83, 1.05]	
Roschewski(ca) 2020	0.85	0.099	12.3%	0.85 [0.66, 1.04]	· · · · · · · · · · · · · · · · · · ·
Yu 2021	1	0		Not estimable	
Total (95% CI)			100.0%	0.86 [0.79, 0.93]	•
Heterogeneity: Tau ² = 0	.00; Chi ² = 6.83, df	= 8 (P =	0.55); P=	= 0%	
Test for overall effect: Z	= 24.77 (P < 0.000)	01)	- 100 - 1 11 (10)		-1 -0.5 0 0.5 1 Favours [experimental] Favours [control]

Supplementary Figure S2.8.4. Forest plot of overall efficiency of ibrutinib for PCNSL (A) alone (B) in combination

A Single

Study or Subgroup	Risk Difference	SE	Weight	Risk Difference IV, Random, 95% Cl	Risk Difference I IV, Random, 95% Cl
Chamoun 2017	0.21	0.109	19.7%	0.21 [-0.00, 0.42]	1
Grommes(ca) 2015	0.33	0.271	3.2%	0.33 [-0.20, 0.86]	i
Grommes 2017	0.385	0.135	12.9%	0.39 [0.12, 0.65]	i
Lauer 2020	1	0		Not estimable	a
Lewis 2021	0.33	0.271	3.2%	0.33 [-0.20, 0.86]	1
Soussain 2019	0.23	0.063	59.1%	0.23 [0.11, 0.35]	i
Yu 2021	0.5	0.354	1.9%	0.50 [-0.19, 1.19]	i
Total (95% CI)			100.0%	0.26 [0.16, 0.35]	1 🔶
Heterogeneity: Tau ² =	0.00; Chi ² = 1.88,	df = 5 (F	= 0.86);	l ² = 0%	
Test for overall effect:	Z = 5.31 (P < 0.000	001)	22		-1 -0.5 0 0.5 Favours [experimental] Favours [control]

B Combination

				Risk Difference	Risk Difference
Study or Subgroup	Risk Difference	SE	Weight	IV, Random, 95% CI	I IV, Random, 95% CI
Bairey(ca) 2019	0.25	0.125	10.3%	0.25 [0.01, 0.49]	1
Chen(ca) 2020	0.555	0.117	10.7%	0.56 [0.33, 0.78]	· · · · ·
Chen 2020	0.64	0.145	9.3%	0.64 [0.36, 0.92]	· · · · ·
Dunleaw(ca) 2015	0.45	0.15	9.0%	0.45 [0.16, 0.74]]
Grommes(ca) 2019	0.17	0.153	8.9%	0.17 [-0.13, 0.47]	1
Grommes 2019	0.67	0.157	8.7%	0.67 [0.36, 0.98]	1
Lauer 2020	0.5	0.25	5.3%	0.50 [0.01, 0.99]	i
Lewis 2021	0.67	0.271	4.7%	0.67 [0.14, 1.20]	1
Lionakis 2017	0.86	0.082	12.6%	0.86 [0.70, 1.02]	j —••
Roschewski(ca) 2018	0.5	0.118	10.7%	0.50 [0.27, 0.73]	· · · ·
Roschewski(ca) 2020	0.615	0.135	9.8%	0.61 [0.35, 0.88]	1
Yu 2021	1	0		Not estimable	9
Total (95% CI)			100.0%	0.54 [0.40, 0.68]	•
Heterogeneity: Tau ² = 0.	.03; Chi ² = 27.84, d	f = 10 (8	= 0.002); I ² = 64%	
Test for overall effect: Z	= 7.61 (P < 0.0000	1)			-1 -0.5 0 0.5 1 Favours [experimental] Favours [control]

Supplementary Figure S2.8.5. Forest plot of complete remission rate of PCNSL treated with ibrutinib (A) alone (B) in combination

A Single

Study or Subgroup	Risk Difference	SE	Weight	Risk Difference IV, Random, 95% Cl	Risk Difference IV, Random, 95% Cl
Chamoun 2017	0.285	0.121	20.2%	0.28 [0.05, 0.52]	· · · · ·
Grommes(ca) 2015	0.33	0.271	4.0%	0.33 [-0.20, 0.86]	
Grommes 2017	0.385	0.135	16.2%	0.39 [0.12, 0.65]	
Soussain 2019	0.36	0.072	57.1%	0.36 [0.22, 0.50]	
Yu 2021	0.5	0.354	2.4%	0.50 [-0.19, 1.19]	
Total (95% CI)			100.0%	0.35 [0.24, 0.46]	•
Heterogeneity: Tau ² =	0.00; Chi ² = 0.56,	df = 4 (F	= 0.97);	l² = 0%	
Test for overall effect:					-1 -0.5 0 0.5 Favours [experimental] Favours [control]

B Combination

Study or Subgroup	Risk Difference	SE	Weight	Risk Difference IV, Random, 95% CI			ifference lom, 95% Cl	
Chen(ca) 2020	0.278	0.106	21.4%	0.28 [0.07, 0.49]				
Chen 2020	0.18	0.116	18.9%	0.18 [-0.05, 0.41]				
Grommes(ca) 2019	0.5	0.204	7.6%	0.50 [0.10, 0.90]				2
Grommes 2019	0.22	0.138	14.6%	0.22 [-0.05, 0.49]				
Lionakis 2017	0.08	0.064	37.5%	0.08 [-0.05, 0.21]			+-	
Total (95% CI)			100.0%	0.19 [0.08, 0.31]			•	
Heterogeneity: Tau ² =	0.01; Chi ² = 5.77,	df = 4 (P	= 0.22);	l² = 31%	5	1	1	1
Test for overall effect:					-1	-0.5 Favours lexperimental	0 0.5 1 Favours (control)	1

Supplementary Figure S2.8.6. Forest plot of partial remission rate of PCNSL treated with ibrutinib (A) alone (B) in combination

8.5. Summary of finding (SoF) tables

Outcomes	Anticipate effects*	d absolute (95% CI)	Relative effect	Nº of participants	Certainty of the evidence	Comments
Outcomes	Risk with [comparison]	Risk with [intervention]	(95% CI)	(studies)	(GRADE)	Comments
overall efficiency	-	-	-	215 (15 observational studies)	⊕⊕⊖⊖ LOW	
complete remission rate	-	-	-	199 (14 observational studies)	⊕⊕⊖⊖ LOW	
partial response rate	-	-	-	158 (11 observational studies)	⊕⊕⊖⊖ LOW	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanation

a. the risk of bias in many items is unclear; b. $I^2=65$; c. the simple size is under 300

8.6. Reference

- [1] YU H, KONG H, LI C, et al. Bruton's tyrosine kinase inhibitors in primary central nervous system lymphoma-evaluation of anti-tumor efficacy and brain distribution [J]. TRANSLATIONAL CANCER RESEARCH, 2021, 10(5): 1975-83.
- [2] Lewis K L, CHIN C K, MANOS K, et al. Ibrutinib for central nervous system lymphoma: the Australasian Lymphoma Alliance/MD Anderson Cancer Center experience [J]. Br J Haematol, 2021, 192(6): 1049-53.
- [3] Chen F, Pang D, Guo H, et al. Clinical outcomes of newly diagnosed primary CNS lymphoma treated with ibrutinib - based combination therapy: A real - world experience of off - label ibrutinib use[J]. Cancer medicine, 2020, 9(22): 8676-8684.
- [4] GROMMES C, PASTORE A, PALASKAS N, et al. Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma [J]. Cancer discovery, 2017, 7(9): 1018-1029.
- [5] Grommes C, Tang S S, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma[J]. Blood, The Journal of the American Society of Hematology, 2019, 133(5): 436-445.
- [6] CHAMOUN K, CHOQUET S, BOYLE E, et al. Ibrutinib monotherapy in relapsed/refractory CNS lymphoma: A retrospective case series [J]. Neurology, 2017, 88(1): 101-2.
- [7] LIONAKIS M S, DUNLEAVY K, ROSCHEWSKI M, et al. Inhibition of B Cell Receptor Signaling by Ibrutinib in Primary CNS Lymphoma [J]. Cancer cell, 2017, 31(6): 833-43.e5.
- [8] Soussain C, Choquet S, Blonski M, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: final analysis of the phase II 'proof-of-concept'iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network[J]. European journal of cancer, 2019, 117: 121-130.
- [9] LAUER EM, WATERHOUSE M, BRAIG M, et al. Ibrutinib in patients with relapsed/refractory central nervous system lymphoma: A retrospective single-centre analysis [J]. Br J Haematol, 2020, 190(2): e110-e4.
- [10]Grommes C, Wolfe J, Gavrilovic I, et al. Phase II of single-agent ibrutinib in recurrent/refractory primary (PCNSL) and secondary CNS lymphoma (SCNSL)[J]. Blood, 2018, 132: 2965.
- [11]Grommes C, Gavrilovic I, Miller A M, et al. Phase Ib of copanlisib in combination with ibrutinib in recurrent/refractory primary CNS lymphoma (PCNSL)[J]. Blood, 2019, 134: 1598.
- [12] Dunleavy K, Lai C E, Roschewski M, et al. Phase I study of doseadjusted-Teddi-R with ibrutinib in untreated and relapsed/refractory primary CNS lymphoma[J]. Blood, 2015, 126(23): 472.

- [13] Bairey O, Amiel A, Yust-Katz S, et al. P05. 04 Phase 2 open-label study of maintenance treatment with ibrutinib following first line methotrexatebased immuno-chemotherapy in elderly patients with primary CNS lymphoma (PCNSL)[J]. Neuro-Oncology, 2019, 21(Suppl 3): iii34.
- [14]Roschewski M, Melani C, Lakhotia R, et al. Phase 1 study of escalating doses of ibrutinib and temozolomide, etoposide, liposomal doxorubicin, dexamethasone, rituximab (TEDDI-R) with isavuconazole for relapsed and refractory primary CNS lymphoma[J]. Blood, 2020, 136: 12-13.
- [15]Lewis K L, Manos K, Casey J, et al. Outcomes for Patients with Primary or Secondary Central System Lymphoma Treated with Ibrutinib: A Multicentre Retrospective Analysis[J]. Blood, 2019, 134: 1620.
- [16]Roschewski M, Lionakis M S, Melani C, et al. Dose-adjusted teddi-R induces durable complete remissions in relapsed and refractory primary CNS lymphoma[J]. Blood, 2018, 132: 4195.
- [17] Christian G, Thomas K, Abdel-Wahab O, et al. Phase I Study of Single Agent Ibrutinib in Recurrent/Refractory Primary and Secondary CNS Lymphoma[J]. Blood, 2015, 126(23): 3960.
- [18]Yuedan C, Sun X, Bai X, et al. Preliminary Exploration of Ibrutinib Combined with Methotrexate, Ifosfamide, Liposomal Doxorubicin and Methylprednisolone in the Treatment of Relapsed/Refractory Primary CNS Lymphoma[J]. Blood, 2020, 136: 13-14.
- [19]Narita, Y., Nagane, M., Mishima, K., et al., Phase I/II study of tirabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, in relapsed/refractory primary central nervous system lymphoma[J]. Neuro Oncol, 2021. 23(1): p. 122-133.
- [20] Hou K, Yu Z, Jia, Y, et al., Efficacy and safety of ibrutinib in diffuse large Bcell lymphoma: A single-arm meta-analysis[J]. Crit Rev Oncol Hematol, 2020. 152: p. 103010.

CQ 9: Should stereotactic radiosurgery be used to treat localized recurrent PCNSL patients who were refractory to chemotherapy and previously received WBRT?

- Population: Patients with localized recurrent PCNSL who were refractory to chemotherapy and previously received WBRT
- Intervention: Treat with stereotactic radiosurgery (SRS)
- Comparison: Other treatment

9.1. Inclusion and exclusion criteria

- final inclusion criteria: we included published studies, which treated the localized recurrent refractory PCNSL with SRS. Studies published in English and Chinese are included.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

9.2. Characteristic information of included studies

Supplementary Table S2.9.1. Characteristic information of included studies

Study ID	Public ation year	Coun try	N	Popul ation	Stu dy typ e	Lesio n	Volume of tumors	Dosa ge	Other treat ment	C R	P R	SD+ PD	mP FS	mO S	Neurovir ulence
Matsu moto et al [1]	2007	Japa nese	2	recurre nt PCNS L	cas e rep ort	Patie nt 1: Singl e lesion (38.4 *39.1 *30.0 mm with a volu me of 24.6 mL) Patie	NR	Cente r dose 30Gy Edge dose 15Gy	NR	N R	N R	NR	3m	13 m	NR
						nt 2: Multi ple lesion s	NR	NR	NR	N R	N R	NR	13 m	15 m	NR
Kenai et al [2]	2006	Swed en	22 (4 initial, 18 recurr ent)	PCNS L	cas e seri es	16.2 mm (3.24 mm- 42.4 mm)	4.14cm ³ (0.02cm ³ 39.9cm ³)	Maxi mum dose 38.5 Gy Edge dose	NR	N R	N R	NR	32. 1m (6m - 67 m)	NR	0 (0%)

Saka moto et al [3]	2006	Japa nese	9	recurre nt PCNS L	cas e rep ort	NR	3.5mL(0. 4- 24.5mL)	16.5 Gy Minim um dose 9.1Gy Maxi mum dose 15.2 Gy	NR	8(88.9 %)	1(11. 1%)	NR	7.7 m	0 (0%)
Shin et al [4]	2017	Ameri ca	23 (7 initial, 16 recurr ent)	PCNS L	cas e seri es	NR	4cm3(0.1 cm3- 26cm3)	NR	NR	N N R R	NR	NR	11 m (5.7 - 33. 2m)	0 (0%)
Kumar et al [5]	2015	Ameri ca	14 (7 initial, 7 recurr ent)	Intracr anial recurre nt lymph oma	cas e seri es	NR	6.7cm3(0. 5cm3- 37.7cm3)	Edge dose 15.5 Gy Maxi mum dose 32Gy	NR	11 (78.6 %)	NR	3.3 m	9.5 m (0.4 m- 94 m)	0 (0%)

NR: Not report; CR: Complete Response; PR: Partial Response; SD+PD: Stable Disease + Progressive Disease; mPFS: median Progression-Free Survival; mOS: median Overall Survival.

9.3. Risk of bias

Supplementary Table 2.9.2. Risk of bias of included case series assessed by the Institute of Health Economics checklist

	Study objective			Study pop	ulation		Intervention and co- intervention		
Study ID	Is the hypothesis, aim, objective of the study clearly stated?	Are the characteris tics of the participant s included in the study described?	Were the cases collect ed in more than one centre ?	Are the eligibility criteria for entry into the study clearly stated?	Were participants recruited consecutively?	Did participa nts enter the study at a similar point in the disease?	Was the interventi on of interest clearly describe d?	Were additional interventio ns (co- interventio ns) reported in the study?	
Matsumoto et al,	Yes	Yes	No	Yes	Unclear	No	Yes	Yes	
Kenai et al.	Yes	Yes	No	No	Yes	No	Yes	Unclear	
Sakamoto et al.	No	Yes	No	No	Yes	No	Yes	No	
Shin et al.	Yes	Yes	Yes	Partial reported	Yes	No	Yes	Unclear	
Kumar et al.	Yes	Yes	No	Partial reported	Unclear	Unclear	Yes	Unclear	

Continued Supplementary Table S2.9.2.

	Ou	tcome measu	ire	Statistical analysis	Results and conclusions	
Study ID	Are the outcome measures established a priori?	Were the relevant outcomes measured with	Were the relevant outcomes measured before and	Were the statistical tests used to assess the relevant	Was the length of follow-up reported?	Was the loss to follow- up

		appropriat e objective and/or subjective methods?	after the intervention ?	outcomes appropriate ?		reported ?
Matsumoto et al,	No	No	Unclear	Yes	Unclear	No
Kenai et al.	Partial reported	Unclear	Unclear	Unclear	Yes	No
Sakamoto et al.	Yes	Yes	Unclear	Yes	No	No
Shin et al.	Yes	Yes	Unclear	Yes	Yes	No
Kumar et al.	Partial reported	Unclear	Unclear	Yes	Yes	No

Continued Supplementary Table S2.9.2

	Result	s and conclus	sions	Competing interest and source of support	New it	ems	
Study ID	Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Are the adverse events related with the interventio n reported?	Are the conclusio ns of the study supporte d by results?	Are both competing interests and sources of support for the study reported?	Was the study conducted prospective ly?	Were the relevant outcome s assessed blinded to interventi on status?	Tota I scor e
Matsumoto et al,	No	Yes	Yes	No	Unclear	Unclear	8
Kenai et al.	No	Partial reported	Yes	No	Unclear	Unclear	6

Sakamoto et al.	No	Yes	Yes	No	No	Unclear	8
Shin et al.	Partial reported	Yes	Yes	Yes	Unclear	Unclear	12
Kumar et al.	Yes	Yes	Yes	Partial reported	No	Unclear	8

9.4. Reference

- Matsumoto Y, Horiike S, Fujimoto Y, et al. Effectiveness and limitation of gamma knife radiosurgery for relapsed central nervous system lymphoma: a retrospective analysis in one institution. International Journal of Hematology. 2007;85(4):333-337.
- [2] Kenai H, Yamashita M, Nakamura T, et al. Gamma Knife surgery for primary central nervous system lymphoma: usefulness as palliative local tumor control. Journal of Neurosurgery. 2006;105 Suppl:133-138.
- [3] Sakamoto M, Oya N, Mizowaki T, et al. Initial experiences of palliative stereotactic radiosurgery for recurrent brain lymphomas. Journal of Neuro-Oncology. 2006;77(1):53-58.
- [4] Shin SM, Silverman JS, Bowden G, et al. Relapsed or refractory primary central nervous system lymphoma radiosurgery: Report of the International Gamma Knife Research Foundation. Journal of Radiosurgery and SBRT. 2017;4(4):247-253.
- [5] Kumar R, Laack N, Pollock BE, et al. Stereotactic Radiosurgery in the Treatment of Recurrent CNS Lymphoma. World Neurosurgery. 2015;84(2):390-397.

CQ 10. Which is the preferred approach to make the diagnosis of a suspected PVRL, vitreous biopsy or aqueous humor/vitreous puncture?

- Population: Patients with PVRL
- Intervention: Diagnosis with vitreous biopsy
- Comparison: Diagnosis with aqueous humor/vitreous puncture

10.1. Inclusion and exclusion criteria

- inclusion criteria: we included published studies, which compared the diagnosis sensitivity and specificity for a suspected PVRL patient between vitreous biopsy or aqueous humor/vitreous puncture.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

10.2. Characteristic information of included studies

Supplementary Table S2.10.1. Characteristic information of included studies

					Stu	Paired	Aqueous I pu	numor/vit Incture	reous	Vitreo	us biops	ÿ
Study ID	Publicat ion year	Countr y	Ν	Populati on	dy type	- sampl es	Diagnosis methods	Sampl e numb ers	Positi ve numb ers	Diagnosis methods	Sampl e numb ers	Positi ve numb ers
Oahalo u A et al [1]	2014	Netherl and	75 (84 eye s)	suspect ed patients with uveitis	case seri es	Yes	cytologic- testing	53 eyes	0	cytologic- testing plus flow cytometry	53 eyes	1 eye
Hiemck e-Jiwa	2018	Netherl	23 (28	patients with	coh ort	Yes	polymerase chain reaction (MYD88 L265P)	11 (12 eyes)	8 (8 eyes)	cytologic- testing plus flow cytometry	11 (12 eyes)	7 (8 eyes)
LS et al [2]	2010	and	eye s)	VRL	stud y	No	polymerase chain reaction (MYD88 L265P)	10 (15 eyes)	2 (3 eyes)	cytologic- testing plus flow cytometry	8 (9 eyes)	4 (4 eyes)
Dalal M et al [3]	2014	America	27	patients with VRL	case seri es	No	cytology, microdissec tion plus molecular analysis	3	2	cytology, microdissec tion plus molecular analysis	19	15
Miseroc chi E et al [4]	2019	Italy	8 (16 eye s)	patients with VRL	case seri es	No	polymerase chain reaction (MYD88 L265P)	8 (15 eyes)	6 (8 eyes)	cytologic- testing	8 (10 eyes)	7 (8 eyes)

Cassou x N et al 2007 France 167 [5]	suspect ed case patients seri No with es uveitis	molecular 45 40 analysis	cytologic- testing plus flow cytometry	51	47
--------------------------------------------	--------------------------------------------------------------	-----------------------------	-------------------------------------------------	----	----

10.3. Risk of bias

Supplementary Table S2.10.2. Risk of bias of included cohort studies assessed by the Newcastle-Ottawa Scale

		Selection of	f exposure	9	Co	omparabilit	у	Outco	ome	
Study ID	Represe ntativene ss of the exposed cohort	Selection of the non- exposed cohort	Ascertai nment of exposur e to implant s	Demonstr ation that outcome of interest was not present at start of study	Study controls the most importan t factor	Study controls for any addition al factor	Assess ment of outcom e	Was follow up long enough for outcomes to occur	Adequac y of follow up of cohorts	Total score
Hiemcke- Jiwa LS et al	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7

Supplementary Table S2.10.3. Risk of bias of included case series assessed by the Institute of Health Economics checklist

	Study objective			Intervention and co- intervention				
Study ID	Is the hypothesis, aim, objective of the study clearly stated?	characteriscasesetics of the participantcollectered ines includedmorethin the studythanthdescribed?centre?		Are the eligibility criteria for entry into the study clearly stated?	Were participants recruited consecutively?	Did participa nts enter the study at a similar point in the disease?	Was the intervent ion of interest clearly describe d?	Were additional interventio ns (co- interventio ns) reported in the study?
Oahalou A et al	Yes	Yes	No	Yes	Yes	Unclear	Yes	Unclear
Dalal M et al	Yes	Yes	No	Partial reported	Yes	Unclear	Yes	Unclear

Miserocchi E et al	Yes	Yes	Unclea r	Partial reported	Yes	Unclear	Yes	Unclear
Cassoux N et al	Yes	Yes	No	Partial reported	Yes	Unclear	Yes	Unclear

Continued Supplementary Table 2.10.3.

	(Dutcome measure)	Statistical analysis	Results and cond	lusions
Study ID	Are the outcome measures established a priori?		Were the relevant outcomes measured before and after the intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?
Oahalou A et al	Yes	Yes	No	Yes	No	No
Dalal M et al	Partial reported	Unclear	No	Unclear	No	No
Miserocchi E et al	Yes	Yes	No	No	No	No
Cassoux N et al	Yes	Yes	No	Yes	Unclear	No

Continued Supplementary Table S2.10.3.

	Resul	ts and concl	lusions	Competing interest and source of support	New it	ems	
Study ID	Does the study provide estimate s of the random variabilit	Are the adverse events related with the interventi	Are the conclusio ns of the study supported by results?	Are both competing interests and sources of support for the study reported?	Was the study conducted prospectivel y?	Were the relevant outcomes assessed blinded to interventi	Tota I scor e

	y in the data analysis of relevant outcome s?	on reported?				on status?	
Oahalou A et al	No	No	Yes	Yes	Unclear	Unclear	10
Dalal M et al	No	No	Yes	Partial reported	No	Unclear	5
Miserocchi E et al	No	No	Yes	Partial reported	Yes	Unclear	8
Cassoux N et al	No	No	Yes	No	Yes	Unclear	9

10.4. Reference

- [1] Oahalou A, Schellekens PA, de Groot-Mijnes JD, et al. Diagnostic pars plana vitrectomy and aqueous analyses in patients with uveitis of unknown cause. Retina. 2014;34(1):108-114.
- [2] Hiemcke-Jiwa LS, Ten DN, Leguit RJ, et al. Potential Diagnosis of Vitreoretinal Lymphoma by Detection of MYD88 Mutation in Aqueous Humor with Ultrasensitive Droplet Digital Polymerase Chain Reaction. JAMA Ophthalmology. 2018;136(10):1098-1104.
- [3] Dalal M, Casady M, Moriarty E, et al. Diagnostic procedures in vitreoretinal lymphoma. Ocular Immunology and Inflammation. 2014;22(4):270-276.
- [4] Miserocchi E, Ferreri A, Giuffrè C, et al. MYD88 L265P MUTATION DETECTION IN THE AQUEOUS HUMOR OF PATIENTS WITH VITREORETINAL LYMPHOMA. Retina. 2019;39(4):679-684. Cassoux N, Giron A, Bodaghi B, et al. IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. Investigative Ophthalmology & Visual Science. 2007;48(7):3253-3259.

CQ 11: Which is the preferred approach to treat PVRL patients and PCNSL patients with concurrent VRL, systemic therapy, local therapy, or combined systemic and local therapy?

- Population: PVRL patients and PCNSL patients with concurrent VRL
- Intervention: systemic treatment
- Comparison: local treatment, or combined systemic and local treatment

11.1. Inclusion and exclusion criteria

- inclusion criteria: we included published studies, which compared the systemic treatment, local treatment, or combined systemic and local treatment for PVRL patients and PCNSL patients with concurrent VRL.
- exclusion criteria: we excluded studies where we failed to access full text, or studies without sufficient data.

11.2. Characteristic information of included studies

Supplementary Table S2.11.1. Characteristic information of included studies

Study ID	Country	N	Age	Systemic treatment	Local treatment	Combined systemic and local treatment	Follow time
Castellino, et al 2019[1]	United States	69	65 (36- 85)	34	19	15	33.6(95% CI: 1.2- 175.2)
Klimova, et al 2018[2]	Czech Republic	20	61(48- 77)	1	3	16	66 (14-166)
Akiyama, et al 2016[3]	Japan	10	68.5 (46– 78)	-	8	10	29.5
Grimm, et al 2008[4]	16 centers in 7 countries	221	60	74	-	106	36
Jahnke, et al 2006[5]	Germany	22	64 (38- 83)	13	9	-	10.25
Grimm, et al 2007[6]	16centersin7countries	83	63 (24- 85)	-	23	53	32
Riemens, et al 2015[7]	17 centers in Europe	78	58 (39- 86)	40	30	17	49

"-": not applicable

11.3 Risk of bias

Supplementary Table S2.11.2. Risk of bias of included cohort studies assessed by the Newcastle-Ottawa Scale

	Se	election o	of exposure		Compara	ability	C	Dutcome		
Study ID	Representativ eness of the exposed cohort	Select ion of the non- expos ed cohort	Ascertain ment of exposure to implants	Demonstr ation that outcome of interest was not present at start of study	Study controls the most important factor	Study contro Is for any additio nal factor	Assess ment of outcom e	Was follow up long enoug h for outco mes to occur	Adequ acy of follow up of cohort s	Tot al sco re
Castellino, et al 2019[1]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	6
Klimova, et al 2018[2]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	6
Grimm, et al 2008[4]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	6
Jahnke, et al 2006[5]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	6
Grimm, et al 2007[6]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	6
Riemens, et al 2015[7]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	6

Supplementary Table S2.11.3. National Institutes of Health (NIH) Study Quality Assessment Tools for Before-After (Pre-Post) Studies with No Control Group

Item	Akiyama, et al 2016[3]
1. Was the study question or objective clearly stated?	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes
3. Were the participants in the study representative of those who would be eligible for the	Yes
test/service/intervention in the general or clinical population of interest?	
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	Not reported
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Not reported
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the	Yes

	level?	
--	--------	--

11.4. Reference

- [1] Castellino A, Pulido JS, Johnston PB, et al. Role of systemic high-dose methotrexate and combined approaches in the management of vitreoretinal lymphoma: A single center experience 1990-2018. Am J Hematol. 2019;94(3):291-298. doi:10.1002/ajh.25350.
- [2] Klimova A, Heissigerova J, Rihova E, et al. Combined treatment of primary vitreoretinal lymphomas significantly prolongs the time to first relapse. Br J 2018;102(11):1579-1585. doi:10.1136/bjophthalmol-2017-Ophthalmol. 311574.
- [3] Akiyama H, Takase H, Kubo F, et al. High-dose methotrexate following intravitreal methotrexate administration in preventing central nervous system involvement of primary intraocular lymphoma. Cancer Sci. 2016;107(10):1458-1464. doi:10.1111/cas.13012.
- [4] Grimm SA, McCannel CA, Omuro AM, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. Neurology. 2008;71(17):1355-1360. doi:10.1212/01.wnl.0000327672.04729.8c.
- [5] Jahnke K, Korfel A, Komm J, et al. Intraocular lymphoma 2000-2005: results of a retrospective multicentre trial. Graefes Arch Clin Exp Ophthalmol. 2006;244(6):663-669. doi:10.1007/s00417-005-0138-9.
- [6] Grimm SA, Pulido JS, Jahnke K, et al. Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. Ann Oncol. 2007;18(11):1851-1855. doi:10.1093/annonc/mdm340.
- [7] Riemens A, Bromberg J, Touitou V, et al. Treatment strategies in primary vitreoretinal lymphoma: a 17-center European collaborative study. JAMA Ophthalmol. 2015;133(2):191-197.

doi:10.1001/jamaophthalmol.2014.4755.