Is It Time to Remove Radiotherapy in the Management of Primary Central Nervous System Lymphoma? Population-based Study, Pool-Analysis and Retrospective Study of Recurrence Pattern.

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Title page

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Abstract

Background Before the introduction of the chemotherapeutic agent methotrexate, radiotherapy (RT) and steroids have been the sole, first-line treatment of primary central nervous system lymphoma (PCNSL). With the application of methotrexate, the role of RT in the treatment of PCNSL has been challenged.

Methods We performed observation analysis on 2,486 PCNSL patients between 1988 and 2016 from the Surveillance, Epidemiology and End Results (SEER) database. Propensity score matching (PSM) was employed to ensure well-balanced characteristics of two groups of patients who received RT and those who did not receive it. Two randomized controlled trials (RCTs) were pooled to further evaluate the role of consolidation whole-brain radiotherapy (WBRT) in PCNSL. To clarify whether WBRT is necessary for PCNSL, 27 relapsed patients who attained complete response (CR), partial response (PR) or stable disease (SD) during or after first-line treatment without WBRT for newly diagnosed PCNSL in our institution was retrospectively analyzed; the pattern and location of relapse was identified.

Results After matching, there was no statistical difference on survival between the two groups. In patients did not received chemotherapy, RT significantly improved the survival of patients who undergone biopsy (All $P < .0001$) or subtotal resection (All $P < .0001$). In particular, RT helped improve survival for patients with other infectious and parasitic diseases including HIV (OIPDH). Pool-analysis shown the better progression free survival (PFS) of patients with WBRT arm compared with no WBRT arm in per-protocol (PP) population (HR 0.71, 95% CI 0.52 to 0.98). In the 27 relapse patients, 17 (63%) had new measurable enhancing lesions at relapse at a spatially distinct site, the remote recurrence after CR was 9/11 (82%), and after PR was 8/15 (53%). Single lesion occurred remote recurrence was 11/13 (85%), while multiple lesions were 7/14 (50%). We also established a

novel prediction model with excellent performance to estimate the potential benefit from RT with respect to the end point of overall survival.

Conclusions RT is still an important method in the treatment of PCNSL, which cannot be removed. More precise studies should be carried out to perfect the treatment strategies of the disease.

Key words

central nervous system neoplasm; lymphoma, non-Hodgkin; radiotherapy; propensity score; retrospective study.

Background

PCNSL is a rare and aggressive extra-nodal non-Hodgkin lymphoma that manifests exclusively in the central nervous system (CNS) or eyes, accounting for approximately 4% of all intracranial tumors[1]. The incidence of this disease has been increasing over the last decade, especially in elderly patients (≥ 70 years), which represent the majority of immunocompetent PCNSL[2]. It is estimated that overall PCNSL after immunosuppression, e.g. post-transplant lymphoproliferative disorders (PTLD) or HIV (AIDS-related PCNSL), accounts for <10% of PCNSL cases (<0.1% of NHL)[3-6]but no accurate incidence figures exist. Radiotherapy (RT), historically, has been an integral part of PCNSL treatment[7,8], and HD-MTX chemotherapy is considered to be the backbone of the treatment strategy for PCNSL with high response rates and improved survival[9,10].Despite high initial response rates with the above treatment, over 50% of patients relapse within 2 years of diagnosis[11-14].

Some retrospective analyses and prospective trials suggest that regimens using WBRT result in prolonged progression-free survival (PFS) but not in overall survival (OS) [12,15,16], which could be attributed to the high risk for late-delayed neurotoxicity in patients who treated with WBRT[12,17-19]. In an attempt to minimize the neurotoxicity, some investigators defer radiotherapy until tumor progression, which may lead to disease control compromised[14,20-22]; some other sopted to reduced-dose WBRT(rdWBRT) instead, although the efficacy remain to be demonstrated[23,24].In the era of precision radiotherapy with advanced technology, further evaluation of the role of radiotherapy for PCNSL is needed.

To investigate the association of RT with PCNSL prognosis to assess its efficacy, we performed the study on one large cancer registry program data, two randomized controlled trials pooled analysis and retrospective study of relapse PCNSL patients in our institution. Propensity score matching (PSM)

analysis, which is widely applied in case-control studies from rare disease[25], to estimate the average treatment effect with the aim of minimizing selection bias, was additionally employed to test our findings. We also validated our finding by two randomized controlled trials[26,27]dataand revealed the recurrence pattern of PCNSL with the information of patients in our hospital. Finally, we developed a practical clinical tool for individualized risk prediction[28,29]based on the population-based data for PCNSL patients.

Methods

Study Cohort Definition and Data Sources

Surveillance, Epidemiology, and End Results (SEER)is an ongoing population-based surveillance program, which documents the demographics, disease, and survival information of cancer patients using selected US state cancer registries[30].PCNSL patients were identified in SEER 18 registries custom data (with additional treatment fields) (1975–2016) by filtering the databases based on histology codes (9590-9599，9670-9699，9700-0719，9720-9729) and primary anatomic location (C72.0- C72.9). Ocular lymphomas were not included. Eligible patients had histologically or cytologically confirmed primary central nervous system lymphoma, which were the first or only cancer. Patients were ineligible if they were diagnosed only through autopsy or death certificate, or had Ann Arbor stage II-IV, or had metastasis to bone, liver, lung, nodes and other site except brain. For the survival analysis, patients who recommended but unknown whether to receive radiotherapy as well as with an unknown surgical information or survival information or follow-up were removed, leaving 2,486 patients (24.84% of the initial cohort) diagnosed in 1988-2016 remaining for analysis.

Definition of Variables

Available patient demographics in the SEER files included sex (male or female), age at diagnosis(0-19, 20-34, 35-44, 45-54, 55-64, 65-74, 75-84, or 85+ years), race(white, black, American Indian/Alaska Native (AIAN), Asian Pacific Islander (API), or unknown), marital status(married, unmarried, or unknown), and year of diagnosis (1988-1999, 2000-2016).Data for selected cancer variables such as tumor histological type (diffuse large B-cell lymphoma (DLBCL), non-diffuse large B-cell lymphoma (non-DLBCL)), anatomic site of disease (supratentorial, infratentorial, overlapping, or other), laterality (one side or not one side), tumor size (0-19, 20-39, 40-59, 60-79, 80+mm, or

unknown), tumor number (1, 2, 3, 4, 5, or unknown), treatment information (surgery, radiotherapy and chemotherapy), survival time (month, m) and vital status at last follow-up were also available. Surgery treatment was categorized as biopsy, subtotal resection (STR), and gross total resection (GTR), according to SEER site-specific coding guidelines.

Pool-analysis

The pool-analysis[31]focused on the role of consolidation therapy with or without radiotherapy in PCNSL. The results of 524 intent-to-treat (ITT) patients and 437 per protocol (PP) patients from 2 randomized control trials (G-PCNSL-SG-1, IELSG32) were analyzed. The characteristics of the ITT patients, including sex, age are summarized in Supplementary Table 2.

Data extraction was performed independently by 2 independent investigators(RPL and YQ) from the eligible studies using a predefined information sheet, which including clinical baseline characteristics (name of clinical trial or the first author, study design, phase, country, recruitment time, number of included patients with PCNSL and outcome), progression-free survival(PFS) and overall survival (OS) or HR and 95% CI from each eligible study. All the relevant data were proofread by the third investigator (SSD) who re-read the fulltext. Study design, search strategy, and selection criteria of pool-analyses are given in Supplementary Methods.

Retrospective study and radiologic assessment

Our institutional review board approves the analysis of these patient-derived samples. This retrospective review identified all newly diagnosed immunocompetent PCNSL patients from January 2009 to December 2020 at our institution. Patients were eligible for inclusion in the study if they met the following criteria: PCNSL confirmed by histology; Recurrence after attained complete response (CR), partial response (PR) or stable disease (SD) during or after first-line treatment without WBRT.

Patients with evidence of lymphoma outside the CNS at initial presentation, and patients with no measurable radiologic lesions (diagnosis only by CSF analysis) were excluded. Imaging data of tumor (magnetic resonance imaging (MRI))was collected from the medical charts in this study.

Imaging and response assessment was in line with current international consensus-based guidelines[32].At initial diagnosis and relapse, contrast enhanced T1-weighted MR images with anatomical location of Axial and Coronal T1 was determined. Local relapse (LR) was considered to be enhancing lesions inside or within a 2 cm margin of theT1-weighted hyperintensity at initial presentation, while distant relapse (DR) was considered to be enhancing lesions outside this margin[11,33].All MRI examinations were re-evaluated by an experienced radiotherapist.

Statistics

The clinical primary outcome for study cohort based on SEER analysis was PCNSL cancer–specific survival(CSS), defined as the time in months from diagnosis to death specific to PCNSL, and overall survival (OS)defined as the length of time in months from diagnosis to death from any cause or last follow-up. First, data were summarized using standard descriptive statistics and frequency tabulation. Between with radiotherapy and without radiotherapy groups, categorical variables were compared using chi-square or Fishers exact tests and continuous variables compared using Wilcoxon rank-sum tests. Survival curves were depicted via Kaplan–Meier method and assessed by log-rank tests. Survival curves were generated using the Kaplan–Meier method, and two-sided log-rank tests were performed on survival curves.

To reduce potential treatment selection bias, we applied propensity score matching(PSM) to adjust for baseline characteristics, included age, sex, race, marital status, insurance record, other infectious

and parasitic diseases including HIV(OIPDH),year of diagnosis, histology, site of lesion, laterality of lesion, number of tumor(s), tumor size, symptoms, international prognostic index (IPI).

Multivariate analysis was performed using the Cox proportional hazards model and identify independent prognostic factors on outcome. A nomogram model was established to predict the1-, 3-, and 5-years OS for PCNSL patients based on the related risk factors. Calibration curves were constructed between nomogram-predicted survival and observed outcome. Concordance index (C-index) and time dependent receiver operating characteristic curve (ROC) with the area under the curve (AUC) value were utilized to measure the predictive accuracy of the established model.

$\chi 2$ heterogeneity test and inconsistency index (I^2) statistic were used to assess statistical heterogeneity in the pool-analyses; values were considered significant when $\chi 2$ p-value < 0.1 or I^2> 50%. When analyses had statistically significant heterogeneity, the random-effect model was used. Otherwise, the fixed-effect model was selected.

Statistical analyses were performed using R version 3.6.3 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics Based on SEER

We identified 2,486 eligible patients with PCNSL on the basis of our inclusion and exclusion criteria (Figure 1).Of this initial cohort, 1,265 patients (50.88%) were stratified into with radiotherapy group, and 1,221 patients (49.12%) were stratified into without radiotherapy group. Patient demographics, tumor characteristics and treatment information according to receipt of radiotherapy are summarized in Table 1. In this cohort,24.22% of patients were aged 65-74 years and 1.21% were 0-19 years at the time of the initial diagnosis. More than half of the patients were male (57.04%) and 79.85% were of White. PCNSL were more likely to occur in the supratentorial (49.52%) with not a one side (67.98%)single(94.97%) lesion, more likely to be diffuse large B-cell lymphoma(DLBCL, 67.30%).The proportion of deaths due to other infections or parasitic diseases, including HIV is 14.32%.More than half of the population received partial surgical resection (54.10%) and chemotherapy (54.59%). There was a decrease in the proportion of patients who received radiotherapy from 1988 to 2016 (Supplementaryfigure1).

Association of Radiotherapy with Survival Based on SEER

The Kaplan–Meier CSS (Figure 2A)and OS (Figure 2B)plots for unadjusted study cohort showed significantly improved CSS and OS in without RT arm. (Log-rank test P= .00021 and P = .00011).After propensity score matching (PSM) adjustment, there was no longer a significant difference between the two groups in CSS (Figure 2C) and OS (Figure 2D).The histograms after PSM (Supplementary figure2, Matched Treated vs. Matched Control) were much more similar than without PSM (Supplementary figure2, Raw Treated vs. Raw Control), indicating good balance in patient characteristics was achieved for estimating average treatment effect (Supplementary table1).To further evaluate the role of RT in

patients receiving different treatment modalities, the cohort were divided into three groups based on biopsy, STR, GTR. Then these groups further divided into without chemotherapy and RT, with chemotherapy, with RT, both chemotherapy and RT, respectively. In the three different surgical groups, surgery with chemotherapy showed a better survival benefit than any surgery alone, both before(Figure 3，biopsy vs. biopsy + chemo CSS P < .0001, OSP < .0001; STR vs. STR + chemo P < .0001；GTR vs. GTR + chemo P < .0001).Interestingly, patients received biopsy (Figure 3 A,B) and STR (Figure 3 C,D) with radiotherapy signatures showed significantly better CSS and OS outcomes compared who underwent biopsy and STR only, but in patients received GTR(Figure 3 E,F),a similar trend has not been seen and did not reach statistical significance. Compared with surgery combined with chemotherapy with or without RT, none of the comparisons reached statistical significance.

Stratification Analyses Based on SEER

To determine the role of radiotherapy in different subgroups, stratification analyses as well as PSM were carried out and showed that radiotherapy achieved better survival both in OS and CSS in OIPDH group whether to matched or not(Figure4A-D;all P < .001).There was no significant difference in OS and CSS was observed in patients in not-OIPDH group between with or without RT groups before matching, but they showed better CSS with RT after matching (Supplementary figure 3A-D, unadjusted CSS P = .24, unadjusted OS P = .072; adjusted CSS P = .022; adjusted OS P = .063). Before matching, PCNSL patients diagnosed at 20-44 years old (Supplementary figure 3E-H), with DLBCL(Supplementary figure 3I-L), or with supratentorial tumor (Supplementary figure 3M-P) who did not receive radiotherapy had better OS and CSS than those treated with radiotherapy. However, this benefit no longer exists in the matched study cohort (Supplemental figure 3). PCNSL patients were diagnosed in 1988 to 1999 (Supplementary figure 3Q-T) who received radiotherapy showed better CSS

and OS before matching while null of the differences was statistically significant after matching.PCNSL patients over 85 years old with radiotherapy (Supplementary figure 3U-X) have better CSS before matching, but this trend is no longer statistically different after matching.

Pool-Analysis

To investigate the consolidation role of WBRT in PCNSL patients who received first-line high-dose methotrexate-based chemotherapy, we included two RCT studies for systematic pool-analysis. Results of 524 intent-to-treat (ITT) patients and 437 per-protocol (PP) patients were analysed. The PFS of the patients with WBRT arm compared with without WBRT arm slightly improved in the PP population (Figure 5A, HR 0.71, 95% CI 0.52 to 0.98), but not in the ITT population (Figure 5C, HR0.85, 95% CI 0.53 to 1.35).A difference in OS between the with WBRT arm and without WBRT arm could not be demonstrated, either in the PP population (Figure 5B, HR 0.89, 95% CI 0.69 to 1.14) or the ITT population (Figure 5D, HR 1.07, 95% CI 0.77 to 1.48).

Retrospective study

We screened out 32 immuncompetent patients with relapse of a histologically proven primary CNS lymphoma. 5 patients were excluded because they received WBRT before achieving CR,PR or SD. In the remaining 27 patients, 11 (41%) had achieved CR, 15 (55%) achieved PR, and 1 (4%) patients achieved SD (Table 2).Median age at diagnosis was 53 years (range, 23,72 years), and the median time to relapse was 10 months (95%CI 7-13M).In the observational cohort, 2 patients received GTR only. Among the 24 patients who received HD-MTX based chemotherapy with or without Rituximab(R), 11 patients received with only HD-MTX, 8 patients additionally received stereotactic radiosurgery (SRS), 6 patients additionally received GTR, 1 patients additionally received GTR and immunotherapy(Supplementary table3).

At recurrence, new enhancement was noted in spatially distinct sites in 17 of 27 (63%) patients, which 3 (11%) patients relapsed both in initial and distant, 14 (51%) patients in distant (Table 3).Nine patients (82%)had remote recurrence in the eleven CR patients, including 1 patient occurred both with DR and LR, one patient relapsed in spinal cord. In 15 PR patients, there are 8 (53%) patients had enhancing lesions outside the 2 cm margin of T2 hyperintensity of the initial presentation (Table 4A). Among the 13 patients with single lesion, ten (85%) patients relapsed in spatially distant sites, including two patients relapsed both in local and distant. 7 of 14 (50%) patients with multiple lesions had DR, within 2 patients had both DR and LR (Table 4B). Representative two cases are described in Figure 6.

Nomogram Development and Internal Validation

Furthermore, we constructed a nomogram (Figure 8B) to predict OS at 1, 3 and 5 years for PCNSL in the total cohort based on the results of multivariate Cox analysis (Figure 8A). The calibration plot (Figure 8C), which runs very close to the diagonal, exhibited excellent concordance between the nomogram-predicted survival and actual outcome. The favorable prognostic accuracy of OS in the nomogram model was also confirmed by ROC analysis, which tests how well a final model predicts its covariates(Figure8D, 1-year AUC, 0.828; 3-years AUC, 0.823; 5-years AUC,0.813).

Discussion

PCNSL is a rare extra-nodal lymphoma with aggressive clinical behavior, which by definition arises only in the central nervous system（CNS）or eyes and should be confirmed with evidence of histology or cytology[34]. Therefore, patients who had systemic lymphoma with CNS involvement, patients with PCNSL as a second or concomitant cancer, patients with Ann Arbor stage II to IV and metastases to bone, liver lung, LN and other parts were ineligible in this study.

With the application of HD-MTX-based chemotherapy in PCNSL patients, the role of radiotherapy (RT) is controversial, especially for patients who have received HD-MTX. In order to explore the role of RT in PCNSL patients, we first extracted patients with PCNSL from the SEER program, which was a population-based cancer database, to process a retrospective analysis. In our study, we used the PSM method to balance the related demographic and clinic-pathologic covariates of PCNSL patients between received RT and not received RT groups. In the unadjusted results, compared with the PCNSL patients who received RT, the patients who did not receive RT had better survival. However, this statistical significance did not persist after PSM. Combining the three main therapy strategies for PCNSL patients, further research on the role of RT in different treatment modalities was managed. In the patients who did who received biopsy and partial resection without chemotherapy, the survival of patients who received RT was still better than patients who did not. Such trend was not shown in patients who have undergone gross total resection and those who have received chemotherapy. Subgroup analysis of infection status of RT revealed significant effect on CSS or OS for PCNSL patients with OIPDH.

The above results can be explained as follows. Firstly, there were apparent imbalances in baseline characteristics between the two groups in raw data, suggesting that the two groups of patients included

were not comparable. After PSM, there was no statistical difference in sex, age and other covariates between the two groups, suggesting that the two groups of patients included in this study were comparable. Therefore, for the matched population, the result is more credible because of its better comparability. Secondly, WBRT and steroids used to be the mainstay of treatment of PCNSL, with good remission rates and survival rates to some extents[22,35].Since Canellos et al.[10,36]demonstrated the remarkable efficacy of systemic high-dose methotrexate (HD-MTX) plus leukovorin rescue in the treatment of CNS lymphomas in 1970s, the cornerstone of treatment now is HD-MTX-based systemic chemotherapy. RT, as a local regional therapy for newly diagnosed patients, is generally applied for who cannot or unwilling to receive chemotherapy. It is reasonable to assume that RT may be especially recommended to patients with poor performance status or with the larger tumor burden[37]. Moreover, patients resistant to the previous chemotherapy or the need for emergency due to neurological symptoms caused by the tumor, tend to followed by RT[38].And for the analysis of subgroups, it is reasonable to assume that most patients with OIPDH represent HIV- and immunocompromised cases, as immune deficiency is the most significant risk factor for PCNSL[39,40], and AIDS-related primary central nervous system lymphoma (AR-PCNSL) has long been regarded as an end-stage manifestation of HIV infection[41]. Whole brain radiotherapy (WBRT) is considered a standard first-line intervention for patients with AR-PCNSL[42-44].

It should be noted that our retrospective analysis based on SEER database has some limitations. Due to lack of detailed treatment information, the study on the role of RT in PCNSL patients can only as a general analysis. To begin with, it is difficult to determine what proportions of patients actually received whole brain radiotherapy (WBRT) and the response to that treatment in the lack of specific treatment regimen information and the treatment time course. In addition, this study is unable to

capture status of patient who underwent RT. For example, WBRT can be used as an alternative to second-line chemotherapy for younger patients who have not achieved complete remission (CR) with first-line systemic chemotherapy alone. It can also be used as a salvage treatment option for patients with chemotherapy contraindications or relapsed and refractory diseases[37,38].Last but not least, the SEER database does not include the type, volume and dosing information of RT. We were not able to determine what proportions of PCNSL patients who received radiation dose greater than 45Gy or less than 45Gy, which may have a nonnegligible impact on the survival results. Nelson et al.[45] pointed out that radiation dose escalation at doses higher than 50Gy increased toxicity without any survival benefit. By contrast, Shah et al.[24]reported that the 23.4Gy reduced-dose radiotherapy should be recommended, which showed excellent survival benefit and without neurotoxicity. Another phase I/II study of 66 PCNSL patients used methotrexate, temozolomide, and rituximab plus hyperfractionated WBRT (36 Gy, divided dose 1.2 Gy/time, twice a day), which showed the remission rate was 86%, no progress in 2 years, and overall survival rate are 81%[46,47].

Therefore, due to the problems mentioned above, we pooled two randomized control trails in PCNSL for further analysis.G-PCNSL-SG-1 is the largest and the only published randomized phase III study on this rare disease to investigate whether first-line chemotherapy based on high-dose methotrexate was non-inferior to the same chemotherapy regimen followed by WBRT for overall survival[12,27], and the hypothesis was not be proven. While, IELSG32 is another international randomized trial addressing different consolidation strategies in patients with newly diagnosed PCNSL treated with high-dose methotrexate-based induction chemoimmunotherapy, which demonstrates that both WBRT and autologous stem-cell transplantation (ASCT) are feasible and effective consolidation[26,48].When putting the two studies together, we found that PCNSL in PP population who

received RT had better PFS than those who did not. There is no significant difference in OS between the ITT population and the PP population. Still, limitations should be noted. Because of lacking the information of the treatment response on the patients after induction therapy in the IELSG32, we cannot subdivide the response before RT. In G-PCNSL-SG-1 trial, the large number of dropouts or patients lost to follow-up, inconsistencies between PP and ITT analyses, and an underpowered design are the methodological limitations [49]. Although 45Gy achieved good local control, the dose still too high in the two studies, combined with HD-MTX-based chemotherapy increased the toxicity, which results with no-improved OS.

Regardless of the treatment type used for PCNSL patients, the rate of recurrence within 2 years is more than 50%[11-14]even if patients achieve complete remission. To better understand the pattern and mechanism of relapse, we reviewed 27 relapsed patients who attained complete response (CR), partial response (PR) or stable disease (SD) during or after first-line treatment without WBRT for newly diagnosed PCNSL in our institution. We found more than half of the patients had distant recurrence and among those reached CR patients, 9/11(82%)had distant recurrence as well, which are comparable to those described with intravenous HD-MTX (12/16, 75%)[33] and those with intra-arterial HD-MTX in conjunction with blood–brain barrier disruption (BBBD)[50] (30/37, 80%).Recently, a number of studies[51-55] have shown that surgery may be beneficial for PCNSL patients. It is worth noting that 8 of the 11patients who achieved CR by receiving GTR, eventually relapsed with DR, which reminds us that there may be subclinical CNS lymphomas which contrast enhanced MRI cannot to detect. However, the underlying mechanism of this phenomenon is unclear. Ambady et al[11]. point out that this may suggest either (1) reactivation of occult reservoirs behind an intact neurovascular unit (NVU) in the CNS (or ocular) or (2) seeding from bone marrow or other extra CNS sites, which need

to be considered when developing strategies and approaches for new therapies in PCNSL. WBRT after CR may one of the strategies can delay relapses including those that address seeding from occult reservoir lesions within the CNS (including the CSF and eye), and should be further evaluated. Finally, our study established the survival prediction model in PCNSL, which can be well-controlled in the prediction sensitivity or specificity. But our findings should be externally validated.

Conclusion

Our study is the first to apply PSM analysis for evaluating the role of RT in PCNSL and evaluate the relationship of receiving GTR with tumor recurrence. These associations suggest that studying the process of relapse can provide insight into the mechanism of relapse for this rare disease. Further randomized testing is warranted to identify the true underlying response rates for RT therapies.

List of abbreviations

PCNSL	primary central nervous system
CNS	central nervous system
PTLD	post-transplant lymphoproliferative disorders
AR-PCNSL	AIDS-related primary central nervous system lymphoma
RT	radiotherapy
SEER	Surveillance, Epidemiology and End Results
PSM	propensity score matching
AIAN	American Indian/Alaska Native
API	Asian Pacific Islander
DLBCL	diffuse large B-cell lymphoma
non-DLBCL	non-diffuse large B-cell lymphoma
STR	subtotal resection
GTR	gross total resection
RCTs	randomized controlled trials
WBRT	whole-brain radiotherapy
CR	complete response
PR	partial response
SD	stable disease
OIPDH	other infectious and parasitic diseases including HIV
CSS	cancer–specific survival

PFS	progression free survival
OS	overall survival
PPP	per-protocol population
ITT	intent-to-treat
MRI	magnetic resonance imaging
LR	local relapse
DR	distant relapse
ROC	receiver operating characteristic
AUC	area under the curve
ASCT	autologous stem-cell transplantation

Declarations

Ethics approval and consent to participate

Institutional review board approval with waiver of consent was obtained for this retrospective study.

Consent for publication

All images and personal information are de-identified in this manuscript.

Availability of data and materials

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/data/. The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

None

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Authors' contributions

CR and RL designed the study. XL, LG, YC, LX and NT collected the data. RL, SD and YQ contributed to data analysis. RL and YQ interpreted the imaging findings and the patient data. RL wrote the initial draft of the manuscript. CR, SD, DW, WZ, and XL reviewed and edited the manuscript. All authors read and approved the manuscript.

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Figure 1

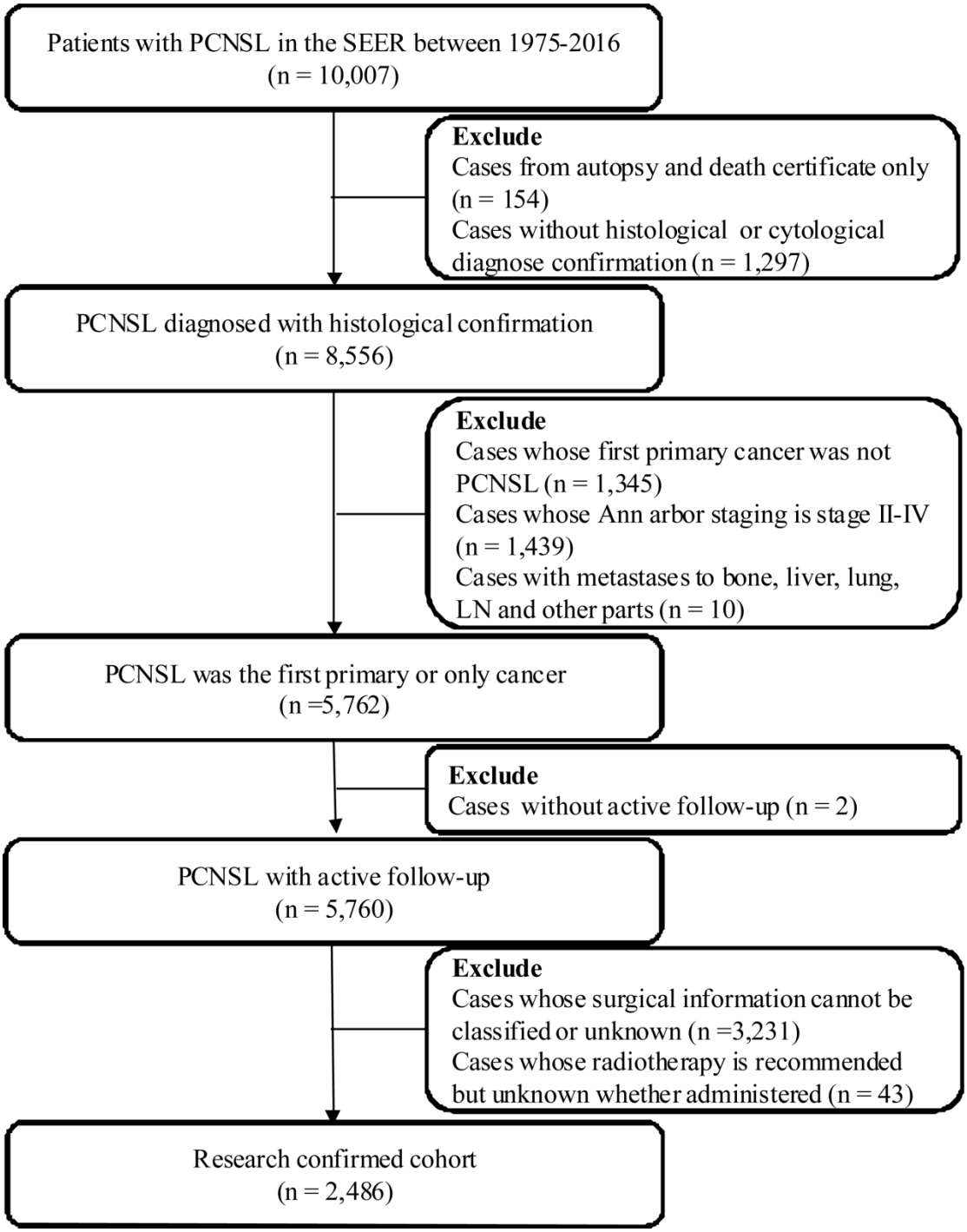
Patients with PCNSL in the SEER between 1975-2016
(n = 10,007)
Exclude
Cases from autopsy and death certificate only (n = 154)
Cases without histological or cytological diagnose confirmation (n = 1,297)
PCNSL diagnosed with histological confirmation
(n = 8,556)
Exclude
Cases whose first primary cancer was not PCNSL (n = 1,345)
Cases whose Ann arbor staging is stage II-IV (n = 1,439)
Cases with metastases to bone, liver, lung, LN and other parts (n = 10)
PCNSL was the first primary or only cancer
(n =5,762)
Exclude
Cases without active follow-up (n = 2)
PCNSL with active follow-up
(n = 5,760)
Exclude
Cases whose surgical information cannot be classified or unknown (n =3,231)
Cases whose radiotherapy is recommended but unknown whether administered (n = 43)
Research confirmed cohort
(n = 2,486)

Figure 2

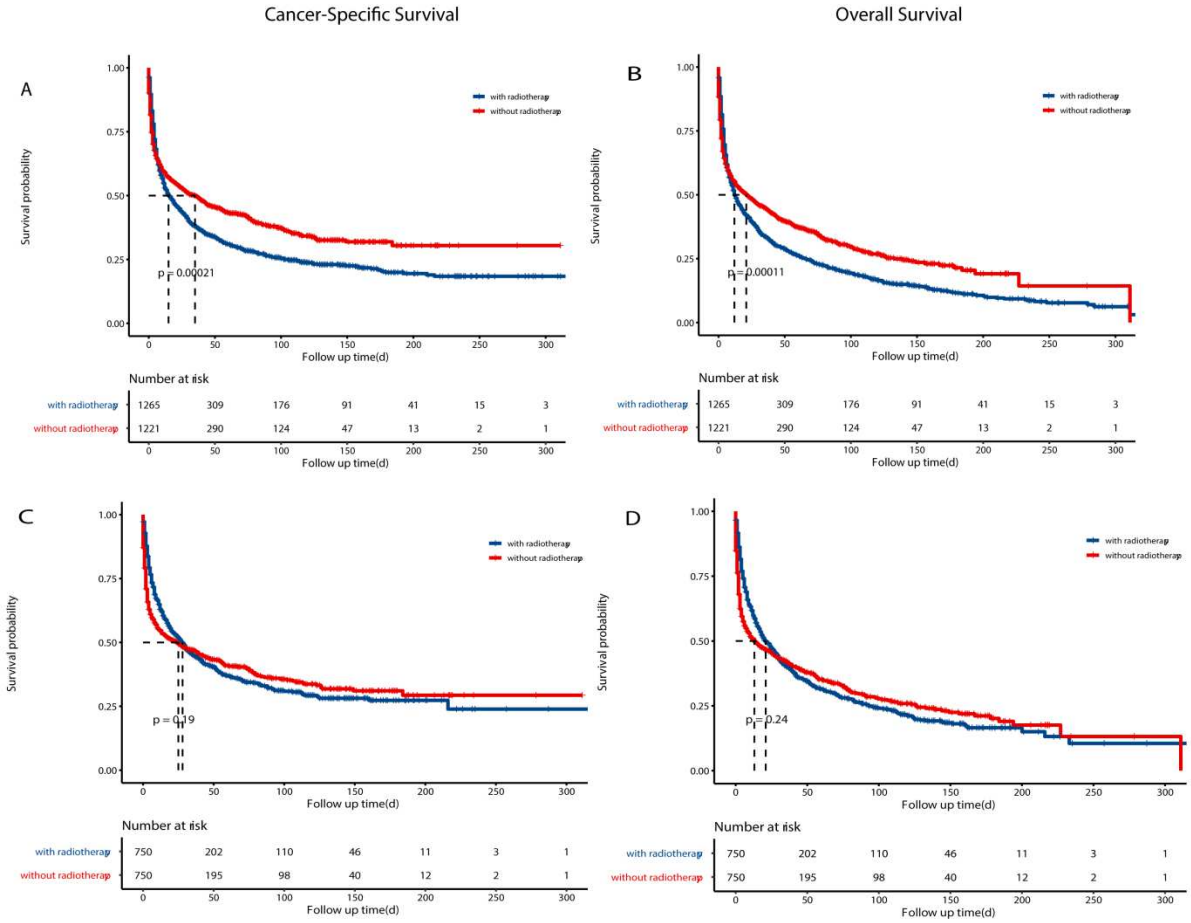
Cancer-Specific Survival
Overall Survival
A
B
C
D
Survival probability
Follow up time(d)
with radiotherap
without radiotherap
p = 0.00021
p = 0.00011
p = 0.19
p = 0.24
Number at risk
with radiotherap 1265 309 176 91 41 15 3
without radiotherap 1221 290 124 47 13 2 1
with radiotherap 750 202 110 46 11 3 1
without radiotherap 750 195 98 40 12 2 1

Figure 3

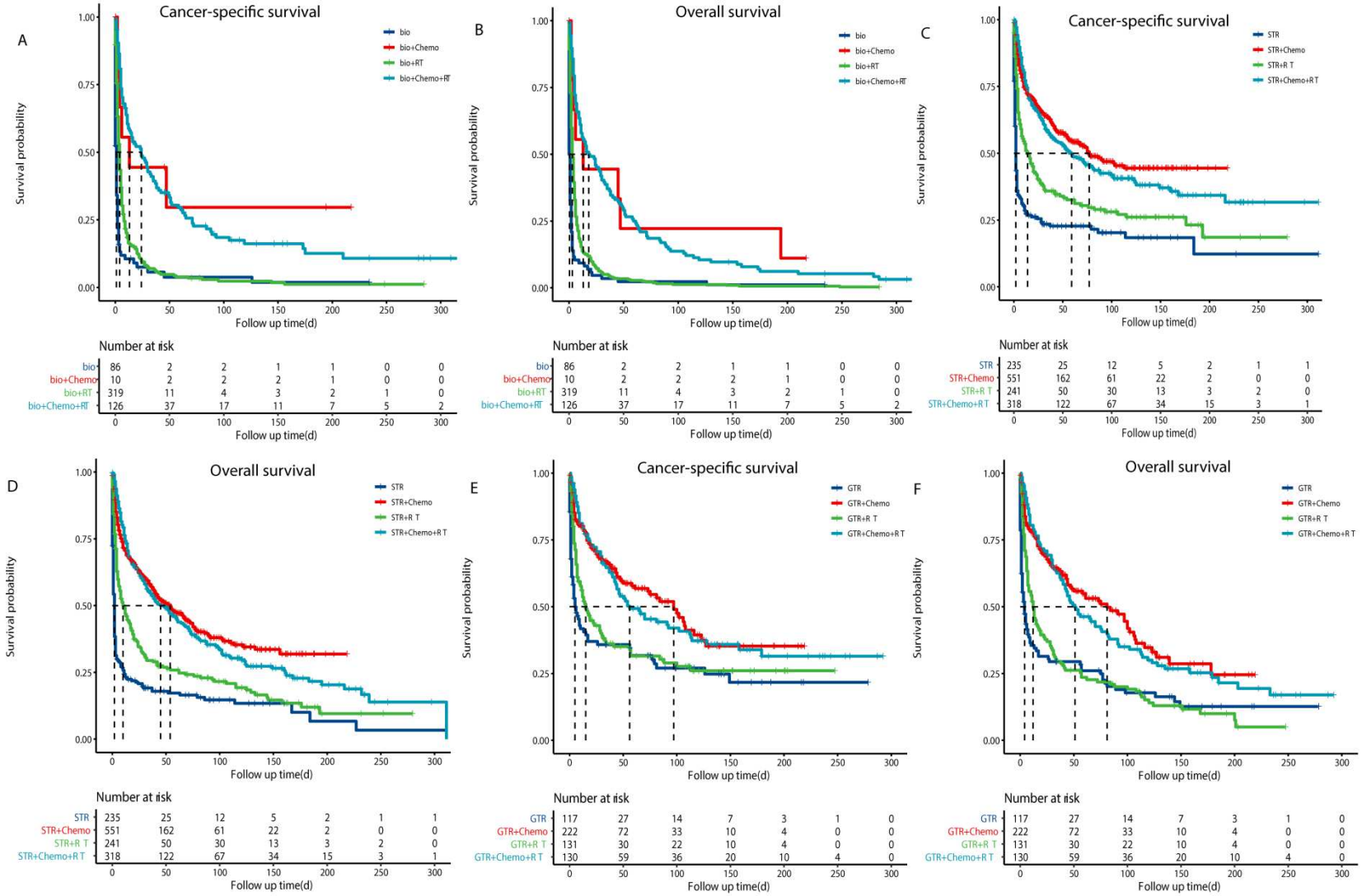
A
Cancer-specific survival
Survival probability
Follow up time(d)
bio
bio+Chemo
bio+RT
bio+Chemo+RT
Number at risk
B
Overall survival
C
Cancer-specific survival
STR
STR+Chemo
STR+R T
STR+Chemo+R T
D
Overall survival
E
Cancer-specific survival
GTR
GTR+Chemo
GTR+R T
GTR+Chemo+R T
F
Overall survival

Figure 4

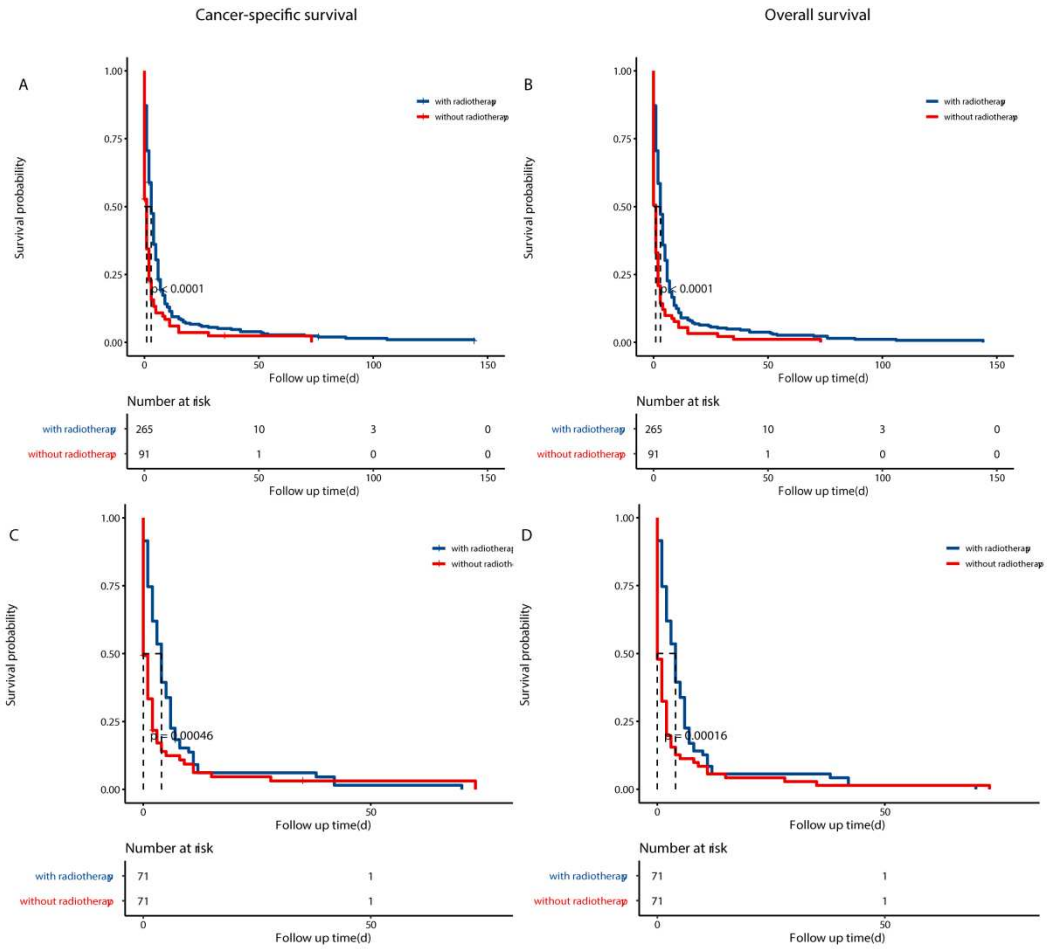
Cancer-specific survival
Overall survival
A
B
C
D
Survival probability
Follow up time(d)
Number at risk
with radiotherap
without radiotherap
p < 0.0001
p = 0.00046
p = 0.00016
265
10
3
0
91
1
0
0
71
1

Figure5

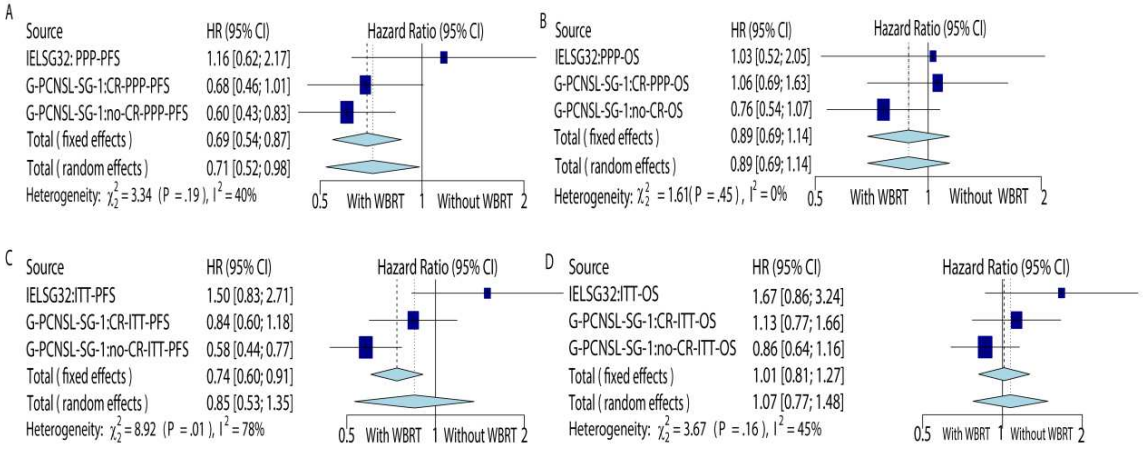
A
Source
HR (95% CI)
IELSG32: PPP-PFS
1.16 [0.62; 2.17]
G-PCNSL-SG-1:CR-PPP-PFS
0.68 [0.46; 1.01]
G-PCNSL-SG-1:no-CR-PPP-PFS
0.60 [0.43; 0.83]
Total (fixed effects)
0.69 [0.54; 0.87]
Total (random effects)
0.71 [0.52; 0.98]
Heterogeneity: $\chi^2_2 = 3.34$ (P = .19), $I^2 = 40\%$
Hazard Ratio (95% CI)
0.5
With WBRT
1
Without WBRT
2
B
Source
HR (95% CI)
IELSG32:PPP-OS
1.03 [0.52; 2.05]
G-PCNSL-SG-1:CR-PPP-OS
1.06 [0.69; 1.63]
G-PCNSL-SG-1:no-CR-OS
0.76 [0.54; 1.07]
Total (fixed effects)
0.89 [0.69; 1.14]
Total (random effects)
0.89 [0.69; 1.14]
Heterogeneity: $\chi^2_2 = 1.61$ (P = .45), $I^2 = 0\%$
Hazard Ratio (95% CI)
0.5
With WBRT
1
Without WBRT
2
C
Source
HR (95% CI)
IELSG32:ITT-PFS
1.50 [0.83; 2.71]
G-PCNSL-SG-1:CR-ITT-PFS
0.84 [0.60; 1.18]
G-PCNSL-SG-1:no-CR-ITT-PFS
0.58 [0.44; 0.77]
Total (fixed effects)
0.74 [0.60; 0.91]
Total (random effects)
0.85 [0.53; 1.35]
Heterogeneity: $\chi^2_2 = 8.92$ (P = .01), $I^2 = 78\%$
Hazard Ratio (95% CI)
0.5
With WBRT
1
Without WBRT
2
D
Source
HR (95% CI)
IELSG32:ITT-OS
1.67 [0.86; 3.24]
G-PCNSL-SG-1:CR-ITT-OS
1.13 [0.77; 1.66]
G-PCNSL-SG-1:no-CR-ITT-OS
0.86 [0.64; 1.16]
Total (fixed effects)
1.01 [0.81; 1.27]
Total (random effects)
1.07 [0.77; 1.48]
Heterogeneity: $\chi^2_2 = 3.67$ (P = .16), $I^2 = 45\%$
Hazard Ratio (95% CI)
0.5
With WBRT
1
Without WBRT
2

Figure 6

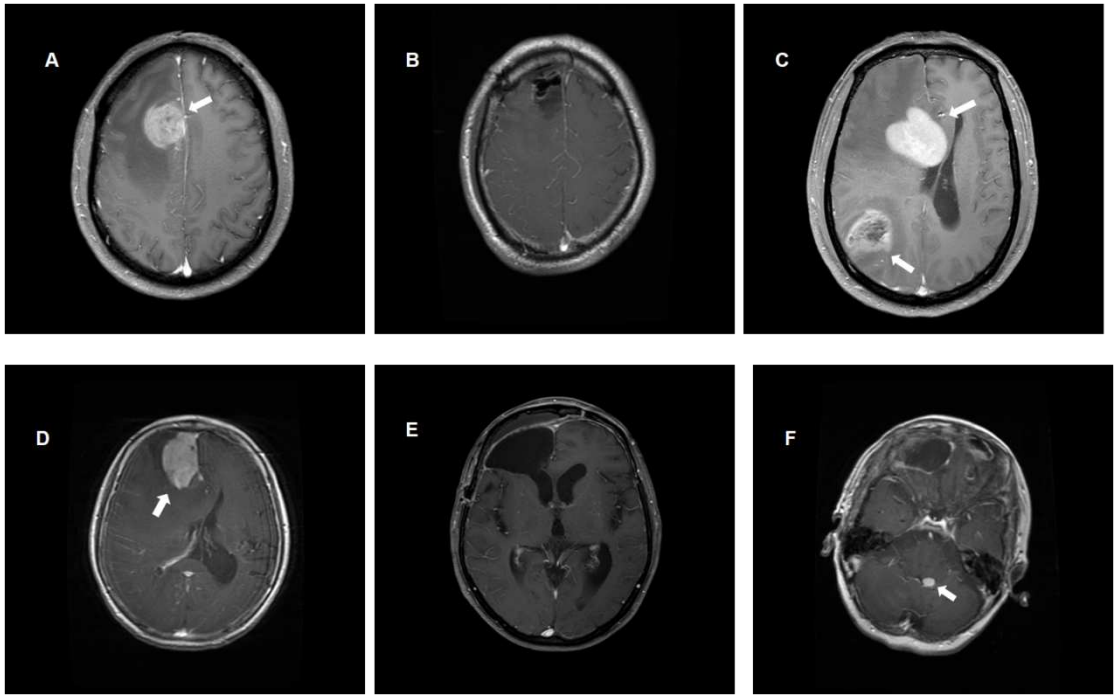

Figure 7

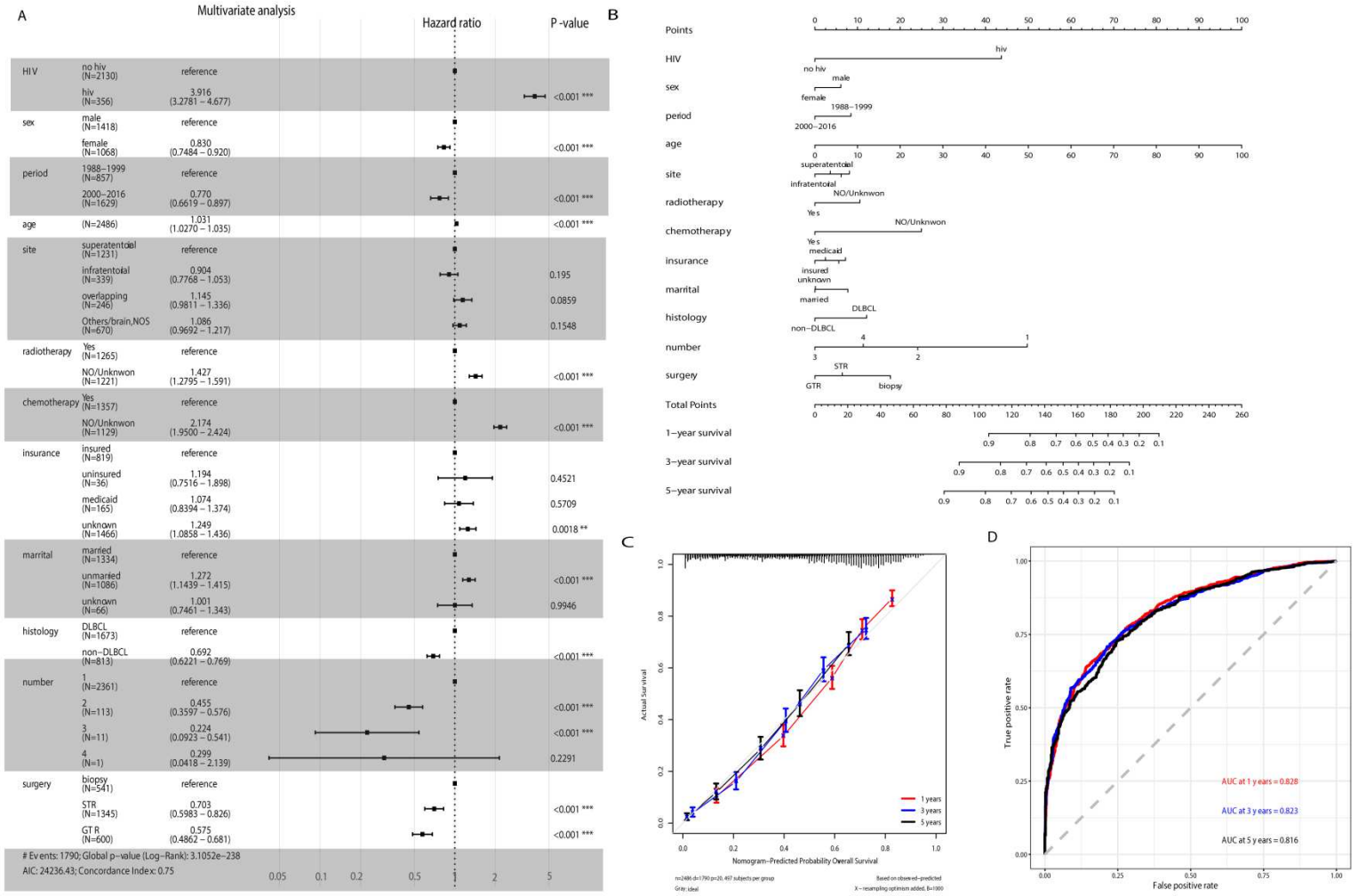
A
Multivariate analysis
Hazard ratio
P -value
HIV
no hiv (N=2130) reference
hiv (N=356) 3.916 (3.2781 – 4.677) <0.001 ***
sex
male (N=1418) reference
female (N=1068) 0.830 (0.7484 – 0.920) <0.001 ***
period
1988–1999 (N=857) reference
2000–2016 (N=1629) 0.770 (0.6619 – 0.897) <0.001 ***
age
(N=2486) 1.031 (1.0270 – 1.035) <0.001 ***
site
superatentorial (N=1231) reference
infratentorial (N=339) 0.904 (0.7768 – 1.053) 0.195
overlapping (N=246) 1.145 (0.9811 – 1.336) 0.0859
Others/brain,NOS (N=670) 1.086 (0.9692 – 1.217) 0.1548
radiotherapy
Yes (N=1265) reference
NO/Unknwon (N=1221) 1.427 (1.2795 – 1.591) <0.001 ***
chemotherapy
Yes (N=1357) reference
NO/Unknwon (N=1129) 2.174 (1.9500 – 2.424) <0.001 ***
insurance
insured (N=819) reference
uninsured (N=36) 1.194 (0.7516 – 1.898) 0.4521
medicaid (N=165) 1.074 (0.8394 – 1.374) 0.5709
unknown (N=1466) 1.249 (1.0858 – 1.436) 0.0018 **
marrital
married (N=1334) reference
unmarried (N=1086) 1.272 (1.1439 – 1.415) <0.001 ***
unknown (N=66) 1.001 (0.7461 – 1.343) 0.9946
histology
DLBCL (N=1673) reference
non–DLBCL (N=813) 0.692 (0.6221 – 0.769) <0.001 ***
number
1 (N=2361) reference
2 (N=113) 0.455 (0.3597 – 0.576) <0.001 ***
3 (N=11) 0.224 (0.0923 – 0.541) <0.001 ***
4 (N=1) 0.299 (0.0418 – 2.139) 0.2291
surgery
biopsy (N=541) reference
STR (N=1345) 0.703 (0.5983 – 0.826) <0.001 ***
GTR (N=600) 0.575 (0.4862 – 0.681) <0.001 ***
Events: 1790; Global p–value (Log–Rank): 3.1052e–238
AIC: 24236.43; Concordance Index: 0.75
0.05 0.1 0.2 0.5 1 2 5
B
Points
HIV
sex
period
age
site
radiotherapy
chemotherapy
insurance
marrital
histology
number
surgery
Total Points
1–year survival
3–year survival
5–year survival
C
Actual Survival
Nomogram–Predicted Probability Overall Survival
1 years
3 years
5 years
Gray: ideal
X – resampling optimism added, B=1000
D
True positive rate
False positive rate
AUC at 1 years = 0.828
AUC at 3 years = 0.823
AUC at 5 years = 0.816

Figure Legends

Figure 1. The flowchart of the inclusion and exclusion process of studycohort based on SEER.

Figure 2. The histogram of raw data and propensity score–matched data with or without radiotherapy. (A) PCNSL without radiotherapy before matching (upper plot) and with radiotherapy before matching (lower plot). (B) PCNSL without radiotherapy after matching (upper plot) and with radiotherapy after matching (lower plot).

Figure 3. Kaplan-Meier survival comparison of combined effect of surgery, chemotherapy, or radiotherapy in patients with primary central nervous system lymphoma. Biopsy only vs. Biopsy + chemotherapy vs. Biopsy + RT vs. Biopsy + chemotherapy +RT (A) cancer-specific survival in PCNSL unmatched, (B) overall survival unmatched. STR only vs. STR + chemotherapy vs. STR + RT vs. STR + chemotherapy +RT (C) cancer-specific survival in PCNSL unmatched, (D) overall survival unmatched. GTR only vs. GTR + chemotherapy vs. GTR + RT vs. GTR + chemotherapy +RT (E) cancer-specific survival in PCNSL unmatched, (F) overall survival unmatched.

Figure 4. Unadjusted and propensity score–matched Kaplan-Meier survival comparison of with or without radiotherapy in PCNSL patients with OIPDH. (A) cancer-specific survival unmatched, (B) overall survival unmatched, (C) cancer-specific survival matched, (D)overall survival matched.

Figure 5. Forest plots of survival comparison betweenindividuals with WBRT or without WBRT after received first-line high-dose methotrexate-based chemotherapy. (A) PFS in PPP, (B) OS in PPP, (C) PFS in ITT, (D) OS in ITT. CR: complete response; OS, overall survival; PFS, progression-freesurvival; ITT, intent-to-treat population; PPP, per protocol population.

Figure 6. A 54-year-old male PCNSL patient (A-C). (A) At the initial presentation.T1-weighted image shows an isolated lesion in the right medial frontal lobe (arrow).（B）At CR after accepting

GTR.(C) At recurrence, 23 months after achieving CR.Image shows LR in the operation region and DR in the right parietal/temporal/occipital junction (arrows). A 63-year-old female PCNSL patient (D-F). (D) At the initial presentation.T1-weighted image shows a isolated lesion in theright medial frontal lobe (arrow).（E）At CR after accepting GTR.(F) At recurrence, 6 months after achieving CR. Image shows DR in the medulla oblongata dorsal (arrow). PCNSL, primary central nervous system lymphoma; CR, Complete response; GTR, Gross total resection; DR, Distant recurrence; LR, Local recurrence.

Figure 7.(A)Multivariate analysis of factors associated with OS of PCNSL.(B) Construction of the nomogram for estimating the probability of 1-, 3-, and 5-years overall survival for PCNSL. (C)Calibration plot of the nomogram for predicting the probability of overall survival at 1, 3, and 5 years. (D)The time-dependent receiver operating characteristiccurve (ROC) analysis showed that the nomogram had the best performance. AUC, area under the curve.

Figures

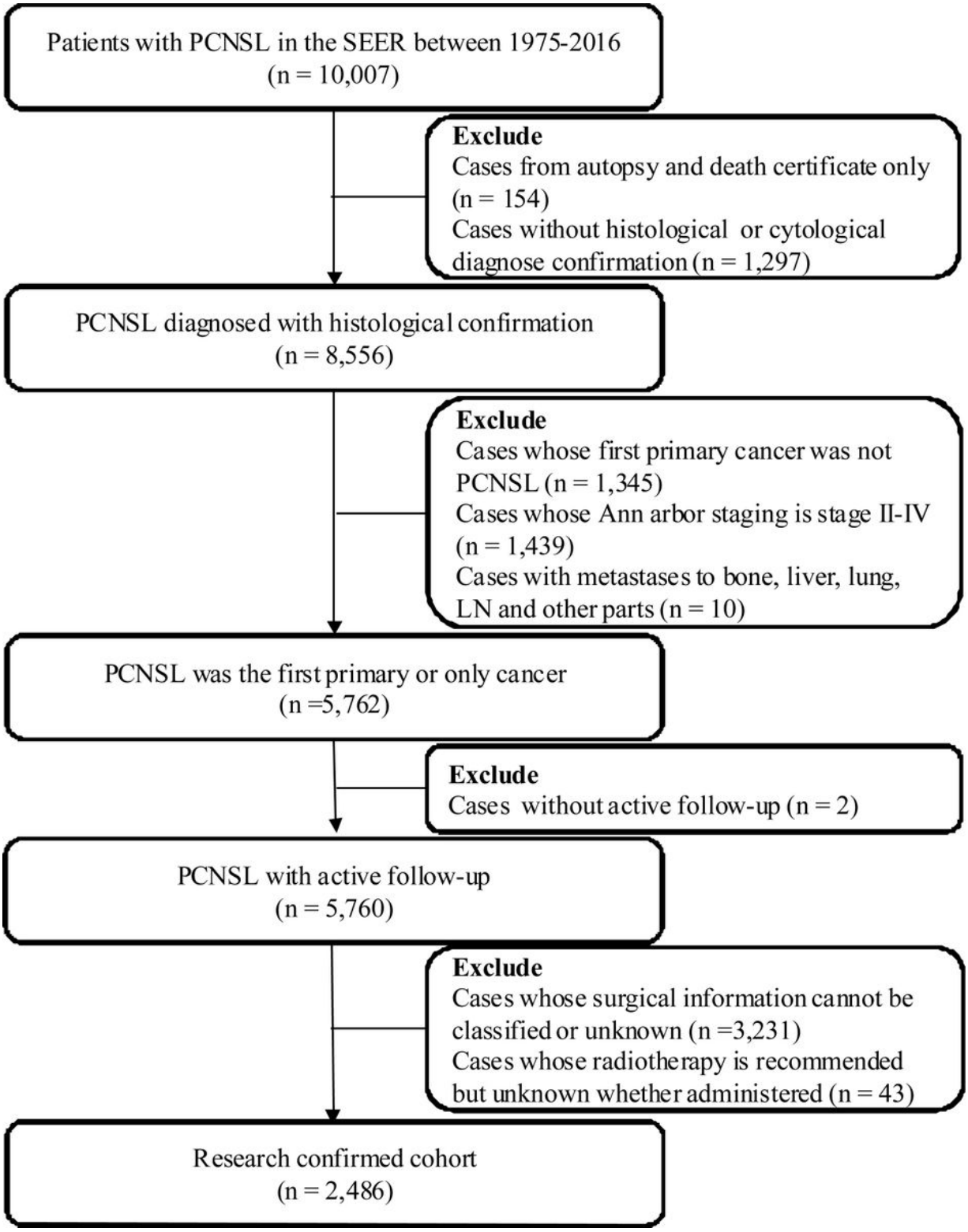

Figure 1

The flowchart of the inclusion and exclusion process of studycohort based on SEER.

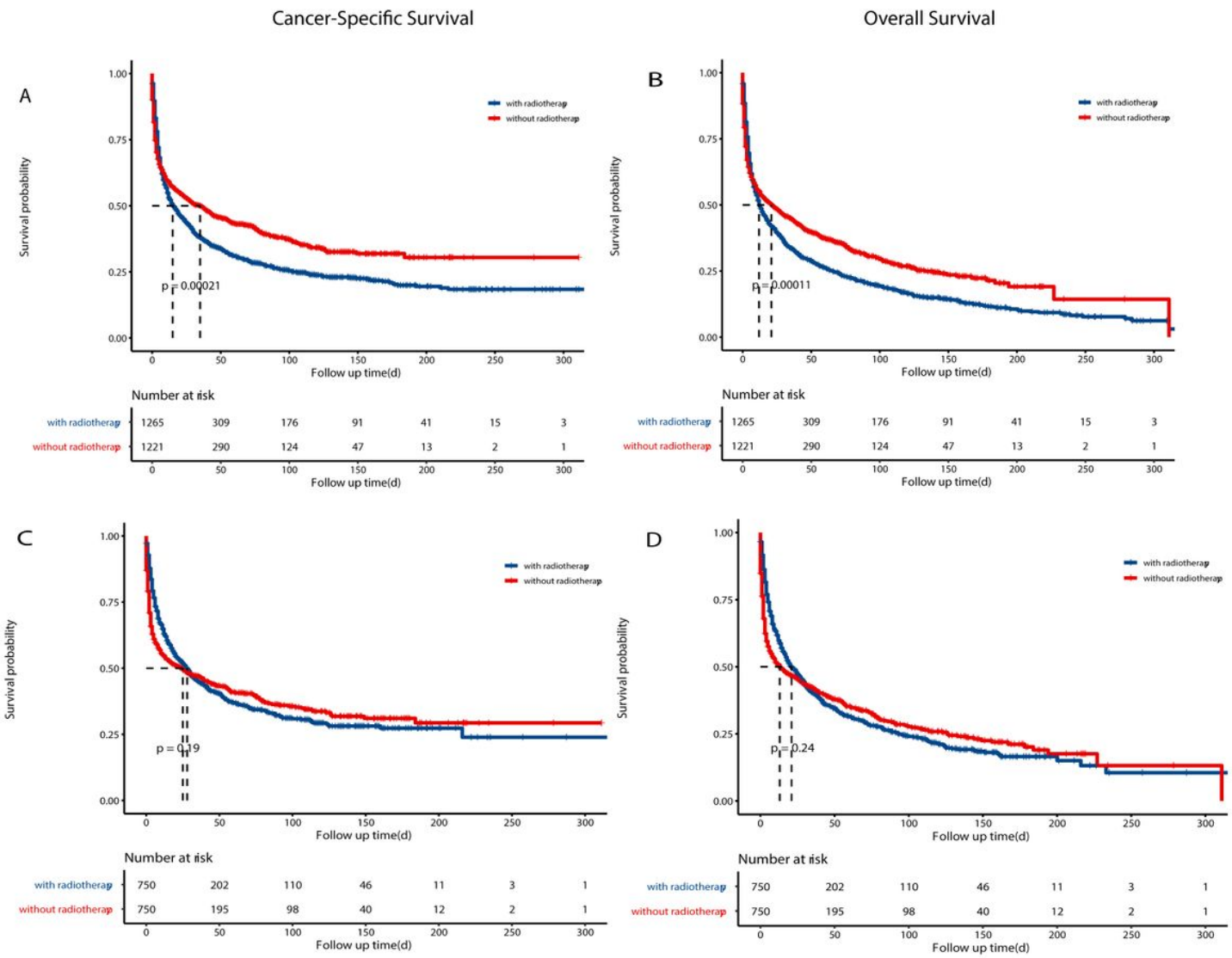

Figure 2

The histogram of raw data and propensity score–matched data with or without radiotherapy. (A) PCNSL without radiotherapy before matching (upper plot) and with radiotherapy before matching (lower plot). (B) PCNSL without radiotherapy after matching (upper plot) and with radiotherapy after matching (lower plot).

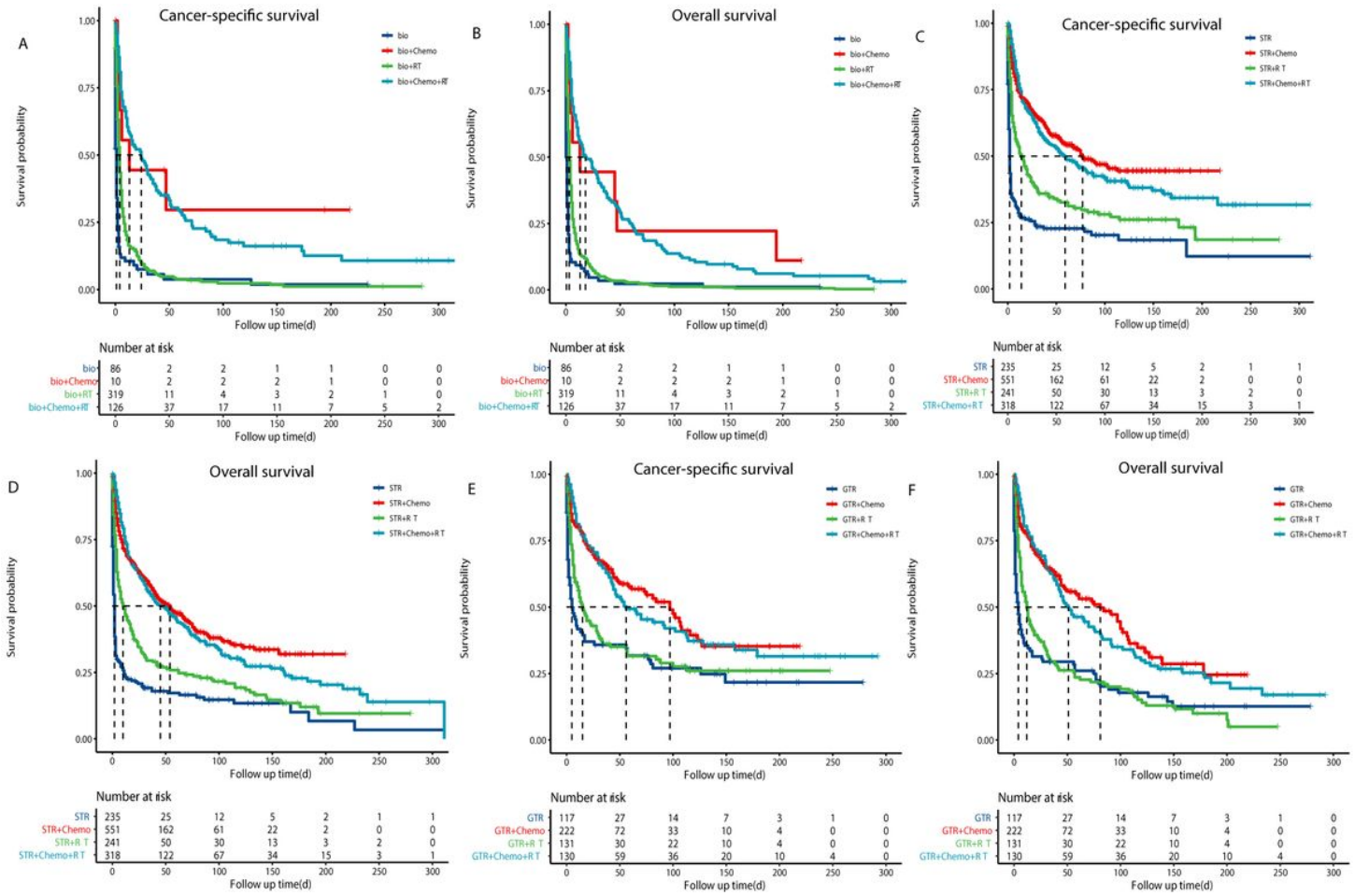

Figure 3

Kaplan-Meier survival comparison of combined effect of surgery, chemotherapy, or radiotherapy in patients with primary central nervous system lymphoma. Biopsy only vs. Biopsy + chemotherapy vs. Biopsy + RT vs. Biopsy + chemotherapy +RT (A) cancer-specific survival in PCNSL unmatched, (B) overall survival unmatched. STR only vs. STR + chemotherapy vs. STR + RT vs. STR + chemotherapy +RT (C) cancer-specific survival in PCNSL unmatched, (D) overall survival unmatched. GTR only vs. GTR + chemotherapy vs. GTR + RT vs. GTR + chemotherapy +RT (E) cancer-specific survival in PCNSL unmatched, (F) overall survival unmatched.

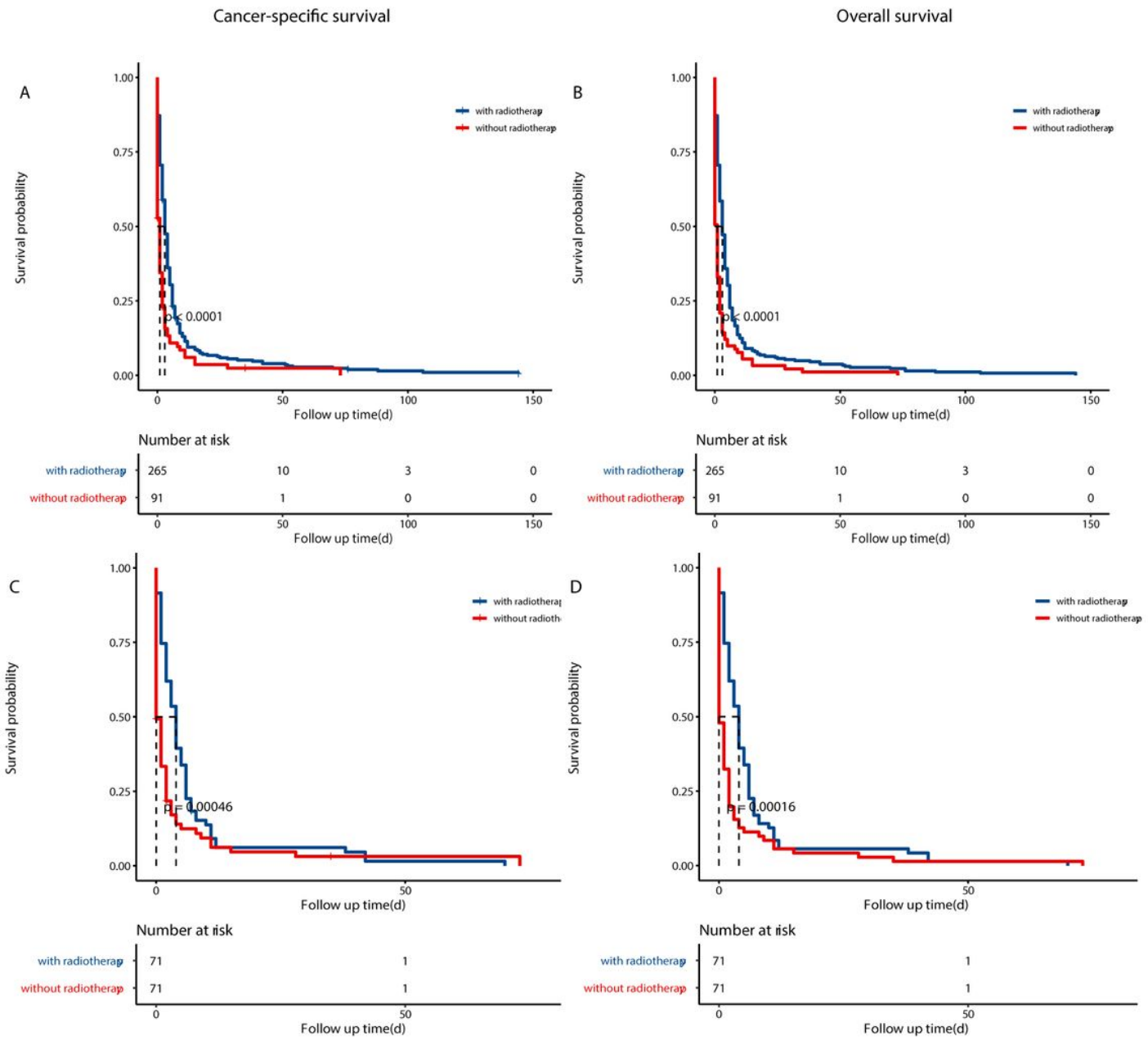

Figure 4

Unadjusted and propensity score–matched Kaplan-Meier survival comparison of with or without radiotherapy in PCNSL patients with OIPDH. (A) cancer-specific survival unmatched, (B) overall survival unmatched, (C) cancer-specific survival matched, (D)overall survival matched.

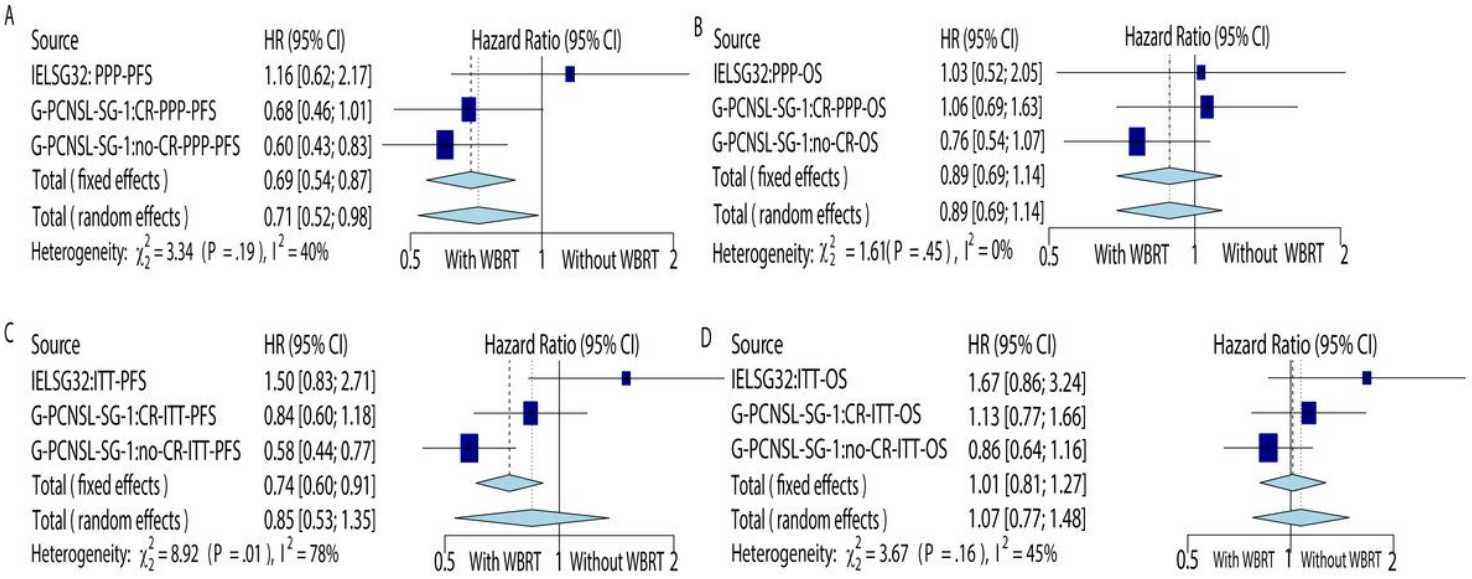

Figure 5

Forest plots of survival comparison betweenindividuals with WBRT or without WBRT after received first-line high-dose methotrexate-based chemotherapy. (A) PFS in PPP, (B) OS in PPP, (C) PFS in ITT, (D) OS in ITT. CR: complete response; OS, overall survival; PFS, progression-freesurvival; ITT, intent-to-treat population; PPP, per protocol population.

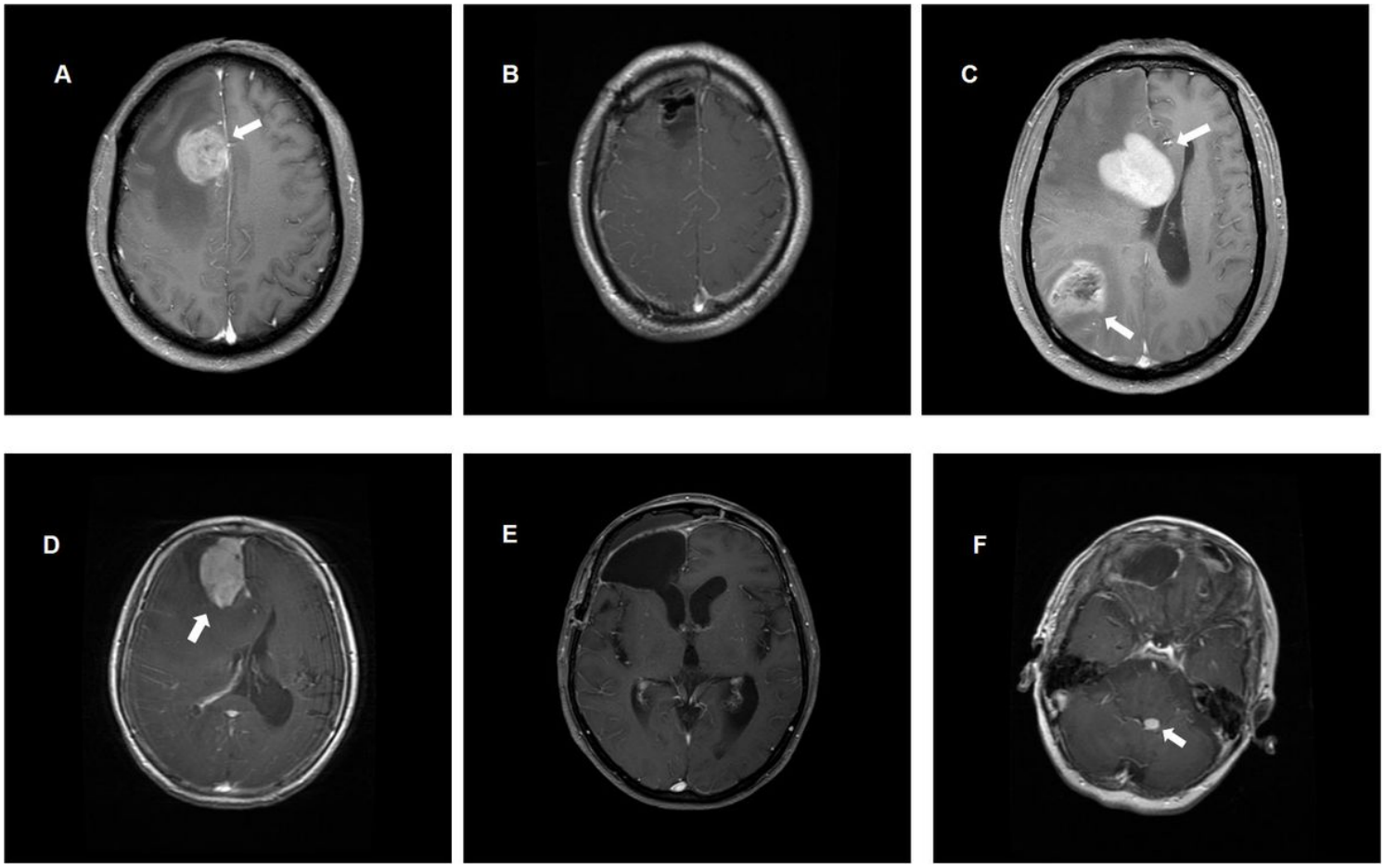

Figure 6

A 54-year-old male PCNSL patient (A-C). (A) At the initial presentation.T1-weighted image shows an isolated lesion in the right medial frontal lobe (arrow).□B□At CR after accepting GTR.(C) At recurrence, 23 months after achieving CR.Image shows LR in the operation region and DR in the right parietal/temporal/occipital junction (arrows). A 63-year-old female PCNSL patient (D-F). (D) At the initial presentation.T1-weighted image shows a isolated lesion in theright medial frontal lobe (arrow).□E□At CR after accepting GTR.(F) At recurrence, 6 months after achieving CR. Image shows DR in the medulla oblongata dorsal (arrow). PCNSL, primary central nervous system lymphoma; CR, Complete response; GTR, Gross total resection; DR, Distant recurrence; LR, Local recurrence.

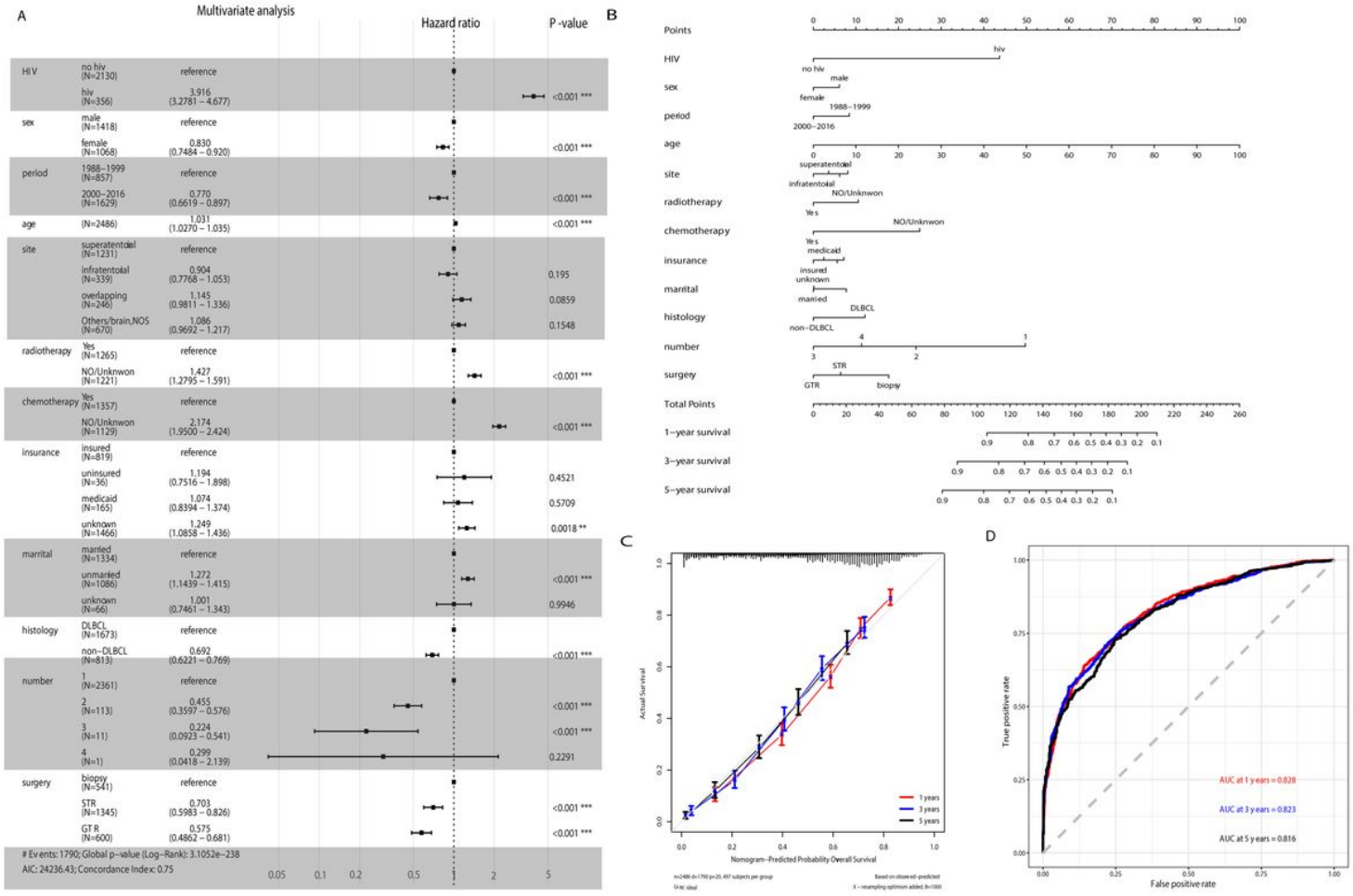

Figure 7

(A)Multivariate analysis of factors associated with OS of PCNSL.(B) Construction of the nomogram for estimating the probability of 1-, 3-, and 5-years overall survival for PCNSL. (C)Calibration plot of the nomogram for predicting the probability of overall survival at 1, 3, and 5 years. (D)The time-dependent receiver operating characteristiccurve (ROC) analysis showed that the nomogram had the best performance. AUC, area under the curve.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigures.pdf
- Supplementarymethod.pdf
- Supplementarytable1.pdf
- Supplementarytable2.pdf
- Supplementarytable3.pdf
- Table1.pdf
- Table2.pdf
- Table3.pdf
- Table4.pdf