The Trend of Combined Modality Treatment and its Outcomes in Elderly Patients With Primary CNS Lymphoma; A 12-Year Population-Based Analysis Using Propensity Score

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Research Article

Abstract

Background

The addition of radiation to chemotherapy in elderly patients with PCNSL remains controversial. Our objective was to assess the trend of combined modality treatment (CMT) and compare its survival with chemotherapy alone and radiation alone in non-HIV patients.

Methods

We identified 6,537 patients who received single treatment modality, combined modality treatment, or no treatment at all between 2004 and 2015 from the National Cancer Database. Factors affecting treatment selection were investigated using a logistic regression model. Annual percentage change (APC) was calculated to assess the trend of CMT use. A propensity score weighting methodology was used to compare survival outcomes.

Findings

Only 12.8% of patients received CMT, and this proportion steadily declined between 2004 (17.7%) and 2015 (8.7%), with APC of -6.0% (95% CI -8.0 to -4.0, p-value <0.001) during the 12 years. Apart from classical prognostic factors (age and comorbidities), treatment selection was significantly influenced by sex, facility type, degree of urbanization, and type of insurance. CMT had improved survival (median overall survival 19.5 months (95% CI 15.7-22.8)) compared with single-modality treatment. This effect was more prominent in the first year.

Conclusion

Socioeconomic factors affect the selection of treatment in elderly patients with PCNSL that can alter outcomes. CMT is falling out of favor in this patient population due to the risks of neurotoxicity. Further work should focus on developing strategies that minimize toxicity and access disparities without compromising survival

Introduction

Primary central nervous system lymphoma (PCNSL) is an aggressive form of extranodal non-Hodgkin lymphoma that involves the brain, spinal cord, meninges, or eyes without systemic involvement. Half of the patients with PCNSL are above 60 years (1). The incidence of PCNSL is four cases per million persons every year (2). However, this incidence fluctuated over the years with some decline that matched the improvement in human immunodeficiency virus (HIV) management. This decline did not apply to elderly patients above 65 years, where the incidence continues to rise (3, 4).

The introduction of high-dose methotrexate-based (HD-MTX) regimens has improved survival significantly compared with radiation alone. This observation was noticed for patients younger than 70

years old. Median survival in the elderly remains 6-7 months (5-7). The best treatment approach in older patients is unclear. A recent Dutch analysis showed that the use of chemotherapy alone in patients between 61-70 years increased from 6% in the period 1989-1995 to 36% in the period 2009-2015 (8). Among American patients, the use of chemotherapy has increased from 65.6% in 2004 to 78.8% in 2013 (p-value <0.001) (9). This increase makes chemotherapy the most common treatment modality used nowadays, compared with earlier reports where radiation was the most common therapeutic approach (10).

The addition of radiation to HD-MTX remains controversial. Radiation in PCNSL needs to involve the whole brain, given the microscopically diffuse and multifocal nature of PCNSL. Although not compared in randomized trials, there was a consensus in the late 1990s and early 2000s that adding radiation to chemotherapy would cause up to a four-fold increase in overall survival (OS), with 5-year survival reached 50% in some reports (11-13). The role of consolidation radiation after achieving complete remission with HD-MTX was studied in phase III non-inferiority trial. The study showed that the median OS was not different in patients who received consolidation radiation (32.4 months) compared to patients who did not receive radiation (37.1 months) (p-value 0.71) (14)

In the elderly, delayed neurotoxicity makes the combined modality approach less attractive. Neurotoxicity usually happens several months to years after treatment. Radiation was identified as an independent risk factor for neurotoxicity (15). The incidence was reported as high as 33%, with risk specifically higher in patients >60 years old (15). A long-term analysis of 80 patients found that patients who received radiation did worse on attention/executive function, motor skills, and neuropsychological composite score, which affect the quality of life (16). After the onset of neurotoxicity, median survival is 1-2 years (15, 17, 18).

Previous population-based analyses focused on incidence and treatment trends. However, there is a lack of studies comparing long-term survival outcomes of elderly patients diagnosed with PCNSL and treated by different modalities (8-10). This comprehensive National Cancer Database (NCDB) analysis aims to assess the trend of combined modality treatment and investigate predictors affecting treatment selection. We also sought to estimate the OS in elderly non-HIV patients diagnosed with PCNSL and treated with either chemotherapy, radiation, or combined modality as a first-line treatment from 2004-2015, using propensity score analysis.

Methods

Study design

We conducted a retrospective cohort analysis using de-identified data accessed from the NCDB. The NCDB is a joint program established in 1989 by the Commission on Cancer of the American College of Surgeons and the American Cancer Society (19). This comprehensive data set integrates registry records from more than 1500 accredited hospitals, capturing approximately 70% of all incident cancers in the United States (20). According to the agreements executed with each accredited facility, data from Veteran

Affairs, Department of Defense, Puerto Rican, and certain other programs are removed from research files. The accreditation requires an annual 90% follow-up rate for all eligible patients diagnosed within five years. Survival outcomes are released only after at least five years of follow-up to avoid censoring bias.

Data are coded using standardized algorithms, and duplicate records are eliminated. Variables include patient demographics, comorbidities, socioeconomic status, and the first course of therapy, defined as all treatment methods recorded in the treatment plan and administered to the patient before disease progression or recurrence. Treatments delivered or withheld because of progression, insufficient response, or other therapy modifications caused by restaging or intercurrent events are not recorded. Specific chemotherapy regimens, doses, or treatment durations are not recorded. Since this study used de-identified data, it was considered exempt from human protection oversight by the Allegheny Health Network institutional review board.

The NCDB provided records of 16,579 patients diagnosed with PCNSL between 2004 and 2015. Cases were identified using primary anatomical site codes C70.0, C70.1, C70.9-C72.1, C72.3-C72.5, C72.8, and C72.9, including the brain, spinal cord, cranial nerves, and meninges. We excluded patients younger than 65 and patients without histologic or cytologic confirmation of the diagnosis. We also excluded patients with HIV positive or unknown status, those with unknown status regarding chemotherapy or radiation administration. We excluded patients treated outside the reporting facility because, otherwise, the NCDB does not require documentation of their treatment and outcomes. We also excluded patients who started treatment with radiation or chemotherapy >120 days after diagnosis or started radiation > 365 days from diagnosis in the combined modality group to account for immortal time bias (Figure 1: Selection process, CONSORT diagram). Treatment was categorized into four groups: chemotherapy alone, radiation alone, combined modality treatment, and no treatment.

Variables and study outcomes

Race was recoded into four categories – non-Hispanic whites, non-Hispanic blacks, Hispanics, and others. Comorbidity was captured using the Charlson/Deyo comorbidity index (21). Socioeconomic data were provided as quintiles of median household income and number of persons with less than high school education in patients' census tract of residence. The type of facility was assigned according to the Commission on Cancer accreditation category based on annual case volume and available oncology services. Geographic locations corresponded to the U.S. Census Divisions. Insurance status is captured as it appears on the admission face sheet for the patient.

The primary outcome of the study is the overall survival (OS) in the four treatment groups. We estimated median OS as well as 12- and 24-month OS. Overall survival was defined from the time of diagnosis to the time of death. We determined predictors of receiving any treatment modality compared to no treatment and predictors of receiving CMT compared to chemotherapy alone among treated patients. We also calculated the annual percentage change (APC) for CMT to assess its trend over the study period.

Propensity score estimation

In this study, we obtained the average treatment effect (ATE) defined as an estimate of interest. Variables included in the propensity score model included age, sex, race, insurance status, median income, education, treatment facility type, type of area, comorbidity score, and distance from the treating facility.

Inverse probability of treatment weighting was used in estimating weight-adjusted OS in the four treatment groups. We used four different methods to estimate weights: multinomial regression propensity score, generalized boosted propensity score, covariate balancing propensity score, and entropy balancing method. The choice of weighting method was based on achieving small coefficients of variations, large effective sample sizes, and low covariate balance assessed using standardized bias. A standardized bias-cut off less than 0.25 was used (22). We used balance tables and love plots to assess for covariate balance before and after weighting (Figure 2). Generalized boosted modeling was used as a final method to estimate weights based on the above criteria. The absolute standardized mean difference among covariates was used as a balance criterion. We used the propensity score package "WeightIt" coded for R statistical program (23). We used a robust variance estimator to account for within-person homogeneity (24).

Statistical analysis

Descriptive statistics were used to compare baseline characteristics of the four treatment groups. Continuous variables were presented as mean with standard deviation or median with interquartile range (IQR). Categorical variables were presented as absolute numbers and percentages. The means of continuous variables were compared using t-test or ANOVA, and percentages were compared using Pearson chi-square or Fisher's exact test. Overall survival was compared using log-rank and GehanBreslow-Wilcoxon rank tests. A stratified log-rank test for every three years was used to account for possible variation in available and administered treatments. Univariable logistic regression was used to determine predictors of receiving any treatment versus no treatment and of receiving CMT versus single modality treatment. Those predictors were expressed as odds ratio (OR) and 95% confidence interval (CI). Statistically significant variables on univariable analysis were used to build multivariable logistic regression models.

To account for missing data, we created five multiply-imputed lists using the "mi" package. (25) All fives imputed data sets were analyzed, and the OS estimate was combined using the Rubin procedure (26). Regression diagnostics were used to evaluate model assumptions. All statistical tests were two-sided, and P-values <0.05 were considered statistically significant. We used R-statistical software (version 4.0.3) for statistical analysis (27).

Results

Cohort characteristics

We identified 6,537 patients diagnosed with PCNSL between 2004 and 2015. The weight-adjusted and unadjusted baseline characteristics of the four treatment groups are summarized in Table 1 and Table 2, respectively. The median age was 74 years (IQR 69-87). There were 3430 (52.5%) females. The majority of the patients were non-Hispanic whites (86.8%), had a comorbidity score of 0 (63.1%), belonged to metropolitan areas (83%), were treated at a comprehensive community cancer center or academic program (47.1%), and had Medicare insurance (84.7%). The median duration to start chemotherapy and radiation was 18 days (IQR 9-31) and 35 days (IQR 16-83), respectively. The median total radiation dose was 3600 cGy in the radiation alone and CMT groups. Median number fractions were 19 and 20 in the radiation alone and CMT groups, respectively.

Treatment Selection

Chemotherapy alone was received by 3389 (51.5%) patients, 1452 (22.2%) patients received no treatment, 856 (13.1%) patients received radiation alone, and 840 (12.8%) patients received CMT. On multivariable logistic regression analysis (Table 3), the odds of receiving any treatment decreased with increasing age and higher comorbidity score. Being at an academic/research institution and having insurance were associated with more treatment administration. Patients with private insurance and Medicare received more treatment compared with no insurance. Among treated patients (Table 4), the use of CMT was significantly lower in older patients, patients who received treatment at an academic/research center, those with higher income, and those who live in rural areas.

Survival analysis

Median follow-up for patients included in the survival analysis was 7.1 months (IQR 2.2-29.3). Adjusted median OS for the whole population was 7.0 months (95% confidence interval [CI] 6.3-7.5). Adjusted median OS for the four groups was: 19.5 months (95% CI 15.7-22.8) for CMT, 13.37 months (95% CI interval 12.1-15.3) for chemotherapy alone, 5.0 months (95% CI 4.4-6.1) for radiation alone, and 2.0 months (95% CI 1.7-2.1) for no treatment. Both adjusted log-rank and Wilcoxon-rank p-values were <0.001 (Figure 3). The adjusted median OS for patients who are 75 years or older was 5.2 months (95% CI 4.7-5.7). The adjusted median OS for the CMT group in this patient population was 14.0 months (95% 10.2-19.7), 7.0 months (95% CI 6.1-8.1) for chemotherapy alone group, 4.1 months (95% CI 3.6-4.8) for radiation alone group, and 1.7 months (95% CI 1.6-1.9) for patients who did not receive any treatment. Both adjusted log-rank and Wilcoxon-rank tests p-values were <0.001 (Figure 4).

Discussion

Combined modality therapy (CMT) was received by 12.8% of patients in the study cohort, with an annual percent change (APC) of -6.0 % (95% CI -8.0 to -4.0, p-value <0.001) over the 12 years. This percentage has almost decreased by half compared with the 1990s data (10). This is directly related to a better understanding of radiation-induced neurotoxicity in the elderly, which has reduced the acceptance of radiation as a treatment option. Neurotoxicity can render patients demented, ataxic, or incontinent and thus significantly affect the quality of life. Also, some reports showed decreased survival with the

addition of radiation, as opposed to our results. The fact that more patients will die from disease progression rather than neurotoxicity even with the use of vigorous treatment modalities argues against its use (15). All this led the most recent clinical trials to study HD-MTX in different combinations rather than add radiation (28-30). Several studies have addressed the use of reduced-dose radiation in an attempt to decrease neurotoxicity without affecting outcomes. Although using doses of 3600 cGy have been shown to delay neurotoxicity, it did not prevent it (31, 32). More promising results were evident when radiation was given at lower doses (23.4 cGy) (33, 34), which is the dose recommended by the National Comprehensive Cancer Network (NCCN) guidelines for consolidation radiation after achieving complete remission. (35)

Patients in our cohort who received CMT had improved median OS compared with single-modality treatment. The benefit of CMT was more prominent in the first year and decreased after that (table 5). Eventually, the curves cross over, indicating late toxicity and likely increased death in the combined modality group. Among treated patients, increased age, receiving treatment at an academic/research center, higher income, and living in rural areas decreased the odds of receiving CMT. The complexity of administering radiation that requires planning and frequent visits in addition to its toxicity probably led to this finding in older patients and those who live in rural areas. Being in academic/research programs increased the odds of receiving any treatment and receiving chemotherapy, two essential factors that can improve outcomes. This emphasizes the importance of referring patients to a center with experience in treating this deadly disease and implementing educational programs for smaller centers to optimize management.

Around 20% of our patients did not receive any treatment. This percentage seems to be stable over time (10). Our analysis identified important socioeconomic factors that affected treatment selection. The odds of receiving any treatment at all was decreased with age and comorbidity score. Having insurance was a predictor of receiving treatment as well, especially with Medicare or private insurance. This is important because not receiving treatment is associated with a dismal prognosis (median OS of 2 months in our analysis). More efforts are needed to expand the availability of treatment.

Our study is limited by its retrospective nature and the associated inherent bias. Observational studies are characterized by unequal and biased allocation of patients to different treatment arms. To address this problem, we used a propensity score weighting methodology in our analysis. All baseline variables were well balanced with standardized bias scores of ≤ 0.1 (Figure 2). Randomized clinical trials remain the gold standard to obtain causal inferences because of their ability to control for observed and non-observed confounders. However, the generalizability of randomized trials might be limited due to the strict inclusion criteria. Because population-based studies provide real-life data of a large number of patients from different parts of the U.S, they tend to be more generalizable. As a sensitivity analysis, we used various methods to estimate weights in the propensity score models. All methods resulted in similar OS estimates.

Another limitation is that NCDB lacks pertinent variables like the exact chemotherapy regimen used and dosing, toxicity information, progression, and salvage treatment details. Also, Memorial Sloan-Kettering Cancer Center and the International Extranodal Lymphoma Study Group have PCNSL prognostic scores that include variables such as performance status, serum lactate dehydrogenase, CSF total protein concentration, and involvement of deep brain structures (36, 37) that we could not account for in our survival model due to unavailability in the NCDB.

This analysis shows that adding radiation to chemotherapy is falling out of favor in the real world in the elderly population. Despite that, a considerable percentage of patients (~13%) still received CMT. Careful patient selection when choosing this treatment approach is vital to decrease neurotoxicity while preserving outcomes. Future work should investigate factors associated with increased toxicity and identify the best radiation dose and technique. Chronologic age alone should not be the only deciding criterion; a comprehensive geriatric assessment (GA), not limited to performance status, should guide treatment decisions to achieve the best outcome possible with the minimum toxicity (38, 39). The survival advantage of CMT over single modality treatment should be conformed in a randomized controlled fashion. Validation of PCNSL-specific GAs would be the ideal tool as many of the disease-related symptoms are present in these GAs and should be interpreted in the right context. Our analysis also showed important social and economic factors like gender, race, insurance status, and degree of urbanization that affect treatment decisions. Careful attention by the physicians to these factors is of utmost importance in daily clinical practice.

Declarations

Ethical approval: This study used de-identified data and was considered exempt from human protection oversight by the institutional review board

Data Sharing: Data was provided by the national cancer database (NCDB)

Transparency statement: Yazan Samhouri MD affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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Tables

Table 1: Adjusted baseline Characteristics of Patients Selected for Analysis

	Chemotherapy alone (%)	Radiation alone (%)	CMT (%)	No treatment (%)	P-value
Mean age (standard deviation)	73.9 (6.08)	74.5 (5.98)	73.8 (5.89)	74.3 (6.19)	0.08
Sex (Female)	1618 (52)	326 (54)	357 (52%)	618 (53)	0.93
Race					0.89
Non-Hispanic whites	2725 (88)	533 (88)	609 (89)	1044 (89)	
Blacks	81 (3)	17 (3)	15 (2)	26 (2)	
Hispanics	134 (4)	30 (5)	23 (3)	50 (4)	
Other	160 (5)	29 (5)	33 (5)	57 (5)	
Facility type					0.88
Community cancer program	95 (3)	20 (3)	18 (3)	39 (3)	
Comprehensive community cancer program	1078 (35)	226 (37)	236 (35)	417 (35)	
Academic/research program	1489 (48)	274 (45)	330 (48)	557 (47)	
Integrated network cancer program	437 (14)	89 (15)	97 (14)	163 (14)	
Median income					1.00
Less than $38,000	454 0.15	88 0.14	94 (14)	172 0.15	
$38,000-$47,999	689 (22)	134 (22)	156 (23)	261 (22)	
$48,000-$62,999	866 (28)	170 (28)	194 (28)	330 (28)	
More than $63,000	1090 (35)	217 (36)	237 (35)	414 (35)	
% of at least high school					1.00

education					
>= 29%	421 (14)	87 (14)	89 (13)	159 (14)	
20%-28.9%	746 (24)	148 (24)	167 (25)	290 (25)	
14%-19.9%	1095 (35)	215 (35)	242 (36)	413 (35)	
< 14%	838 (27)	159 (26)	183 (27)	314 (27)	
Insurance					0.95
Not insured	21 (1)	5 (1)	4 (1)	9 (1)	
Private insurance	369 (12)	71 (12)	85 (13)	141 (12)	
Medicaid	40 (1)	7 (1)	6 (1)	13 (1)	
Medicare	2641 (85)	521 (86)	583 (86)	1003 (85)	
Others	27 (1)	5 (1)	3 (0)	10 (1)	
Type of area					0.37
Metropolitan	2574 (83)	515 (85)	574 (84)	982 (83)	
Urban	465 (15)	89 (15)	98 (14)	171 (15)	
Rural	61 (2)	5 (1)	9 (1)	24 (2)	
Comorbidity Score					0.92
0	1866 (60)	368 (60)	419 (62)	696 (59)	
1	761 (25)	146 (24)	169 (25)	296 (25)	
2	323 (10)	65 (11)	67 (10)	125 (11)	
>=3	148 (5)	30 (5)	25 (4)	60 (5)	
Mean distance in miles (standard deviation)	140.9 (39.8)	26.93 (80.0)	86.5 (30.88)	106.1 (35.07)	<0.01

Table 2: Unadjusted baseline Characteristics of Patients Selected for Analysis

Characteristic	Chemotherapy alone (%)	Radiation alone (%)	CMT (%)	No treatment (%)	P-value
Mean age (standard deviation)	72.9 (5.63)	76.6 (6.26)	72.5 (5.69)	76.3 (6.66)	<0.01
Sex (Female)	1747 (52)	472 (55)	410 (49)	801 (55)	0.01
Race					
Non-Hispanic whites	2962 (87)	744 (87)	729 (87)	1239 (85)	0.29
Blacks	78 (2)	31 (4)	29 (3)	48 (3)	
Hispanics	147 (4)	30 (4)	35 (4)	73 (5)	
Other	173 (5)	42 (5)	43 (5)	75 (5)	
Unknown	29 (1)	9 (1)	4 (0)	17 (1)	
Facility type					<0.01
Community cancer program	86 (3)	47 (5)	31 (4)	64 (4)	
Comprehensive community cancer program	1038 (31)	356 (42)	312 (37)	586 (40)	
Academic/research program	1827 (54)	294 (34)	358 (43)	600 (41)	
Integrated Network cancer program	438 (13)	160 (19)	139 (17)	202 (14)	
Median Income					<0.01
Less than $38,000	451 (13)	129 (15)	128 (15)	237 (16)	
$38,000-$47,999	732 (22)	206 (24)	170 (20)	348 (24)	
$48,000-$62,999	921 (27)	254 (30)	255 (30)	395 (27)	
More than $63,000	1262 (37)	265 (31)	281 (33)	461 (32)	

Unknown	23 (1)	2 (0)	6 (1)	11 (1)	
% of at least with high school education					<0.01
≥ 29%	451 (13)	129 (15)	128 (15)	247 (17)	
20%-28.9%	732 (22)	206 (24)	170 (20)	348 (24)	
14%-19.9%	921 (27)	254 (30)	255 (30)	395 (27)	
< 14%	1262 (37)	265 (31)	281 (33)	461 (32)	
Unknown	23 (01)	2 (0)	6 (1)	11 (1)	
Insurance					
Not insured	20 (1)	4 (0)	8 (1)	15 (1)	0.51
Private insurance	405 (12)	93 (11)	123 (15)	163 (11)	
Medicaid	43 (1)	11 (1)	11 (1)	21 (1)	
Medicare	2822 (83)	725 (85)	680 (81)	1206 (83)	
Others	32 (1)	7 (1)	5.00 (1)	14 (1)	
Unknown	67 (2)	16 (2)	13 (2)	33 (2)	
Type of area					0.21
Metropolitan	2712 (80)	698 (82)	694 (83)	1139 (78)	
Urban	501 (15)	123 (14)	110 (13)	323 (22)	
Rural	73 (2)	8 (1)	12 (1)	31 (2)	
Unknown	103 (3)	27 (3)	24 (3)	50 (3)	
Comorbidity Score					<0.01
0	2102 (62)	502 (59)	534 (64)	780 (54)	
1	812 (24)	203 (24)	196 (23)	389 (27)	
2	322 (10)	99 (12)	83 (10)	184 (13)	
>=3	153 (5)	52 (6)	27 (3)	99 (7)	

| Distance in miles (standard deviation) | 165 (47.20) | 90.4 (24.70) | 114 (32.60) | 137 (42.00) | <0.01 |

Table 3: Multivariable logistic analysis for predictors of receiving any treatment versus no treatment

Covariate	OR (95% CI)	P Value
AGE	0.987 (0.986-0.989)	**<0.001**
Sex		
Male	reference	
Female	0.98 (0.97-1.00)	**0.07**
Facility type		
Community cancer program	reference	
Comprehensive community cancer program	1.02 (0.97-1.07)	0.53
Academic/research program	1.07 (1.02-1.13)	**0.001**
Integrated Network Cancer program	1.06 (1.01-1.12)	**0.03**
Median income		
Less than $38,000	reference	
$38,000-$47,999	1.01 (0.98-1.04)	0.61
$48,000-$62,999	1.03 (0.99-1.06)	0.11
More than $63,000	1.03 (0.99-1.07)	0.10
% of at least high school education		
>= 29%	Reference	
20%-28.9%	1.01 (0.98-1.04)	0.68
14%-19.9%	1.02 (0.98-1.05)	0.35
< 14%	1.03 (0.99-1.07)	0.15
Comorbidity score		
0	Reference:	
1	0.96 (0.94-0.98)	**0.001**
2	0.95 (0.92-0.98)	**0.001**
>=3	0.91 (0.87-0.95)	**<0.001**
Insurance		

Not insured	Reference	
Private insurance	1.11 (1.00-1.24)	**0.045**
Medicaid	1.10 (0.97-1.25)	0.16
Medicare	1.14 (1.02-1.26)	**0.02**
Others	1.10 (0.95-1.26)	0.20
Unknown	1.07 (0.95-1.21)	0.27

Table 4: multivariable logistic analysis for predictors of receiving CMT versus chemotherapy alone

Covariate	OR (95% CI)	P Value
AGE	0.99 (0.97-0.998)	**0.03**
Facility type		
Community cancer program	reference	
Comprehensive community cancer program	0.73 (0.49-1.10)	0.12
Academic/research program	0.48 (0.32-0.72)	**<0.001**
Integrated Network Cancer program	0.80 (0.52-1.22)	0.29
Median income		
Less than $38,000	reference	
$38,000-$47,999	0.81 (0.63-1.04)	0.09
$48,000-$62,999	0.89 (0.70-1.13)	0.35
More than $63,000	0.75 (0.59-0.96)	**0.02**
Type of area		
Metropolitan	reference	
Urban	0.81 (0.64-1.01)	0.06
Rural	0.49 (0.26-0.91)	**0.02**
Distance	0.999 (0.998-1.000)	0.06

Table 5: 12-month and 24-month survival

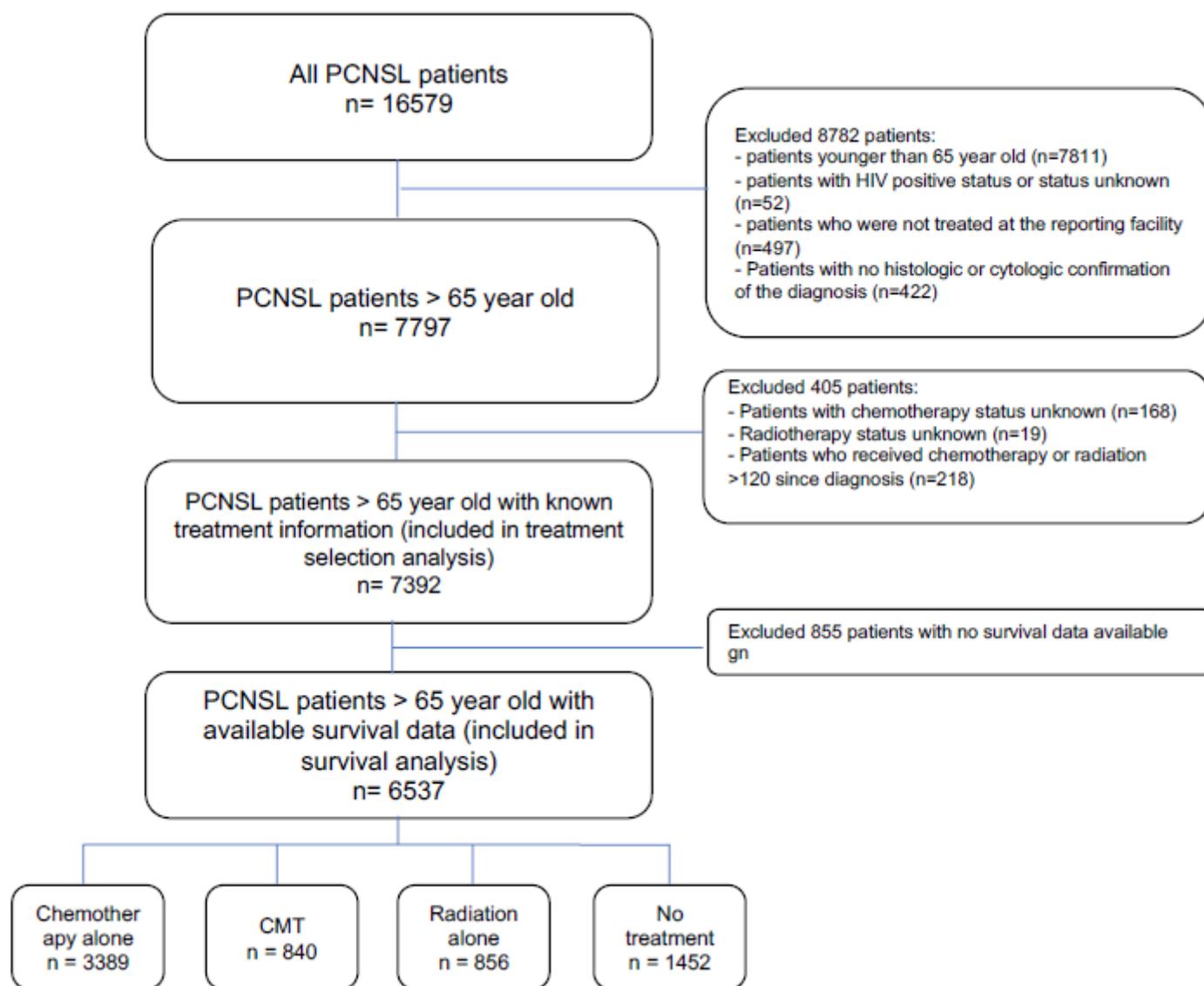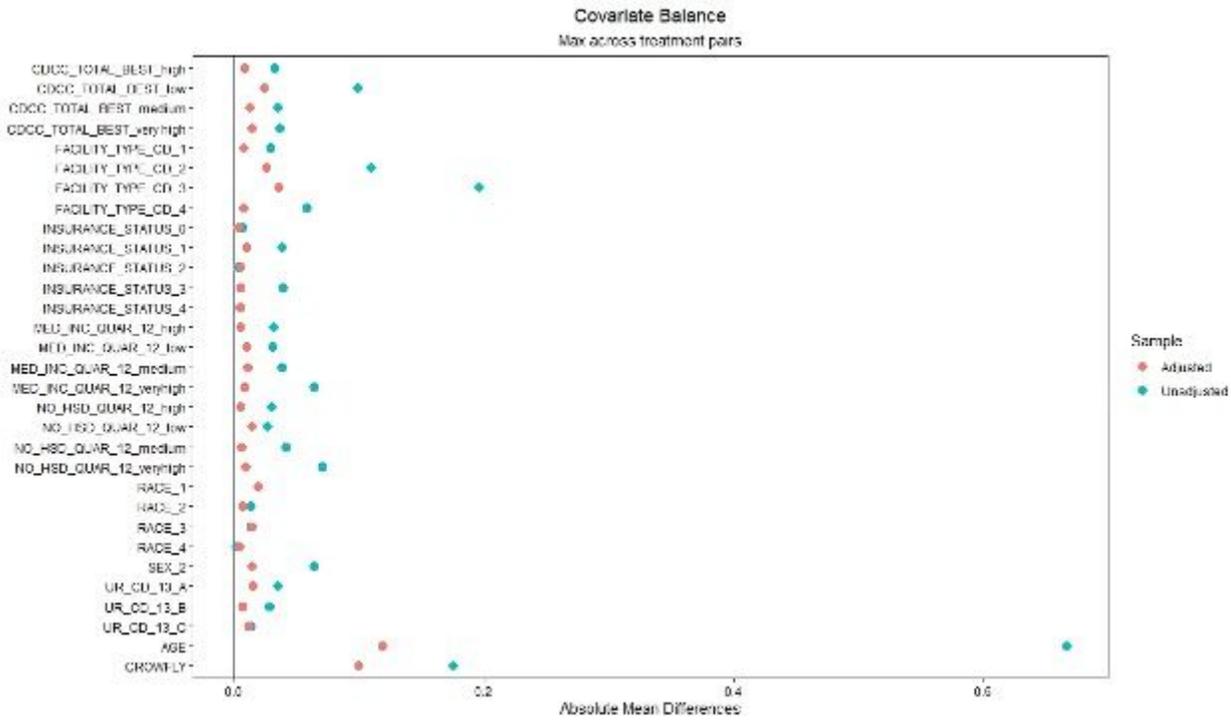|	Chemotherapy alone	CMT	Radiation alone	No treatment
12-month OS (95% CI)	40.6% (37.8-43.6)	53.2% (47.1-60.2)	25.2% (21.6-29.5)	14.3% (11.9-17.0)
24-month OS (95% CI)	31.3% (28.7-34.1)	38.5% (32.7-45.2)	14.3% (11.4-18.0)	10.1% (8.1-12.7)

Figures

Figure 1

selection process (CONSORT diagram)

Covariate Balance
Max across treatment pairs

Figure 2

We used balance tables and love plots to assess for covariate balance before and after weighting (Figure 2).

Figure 3
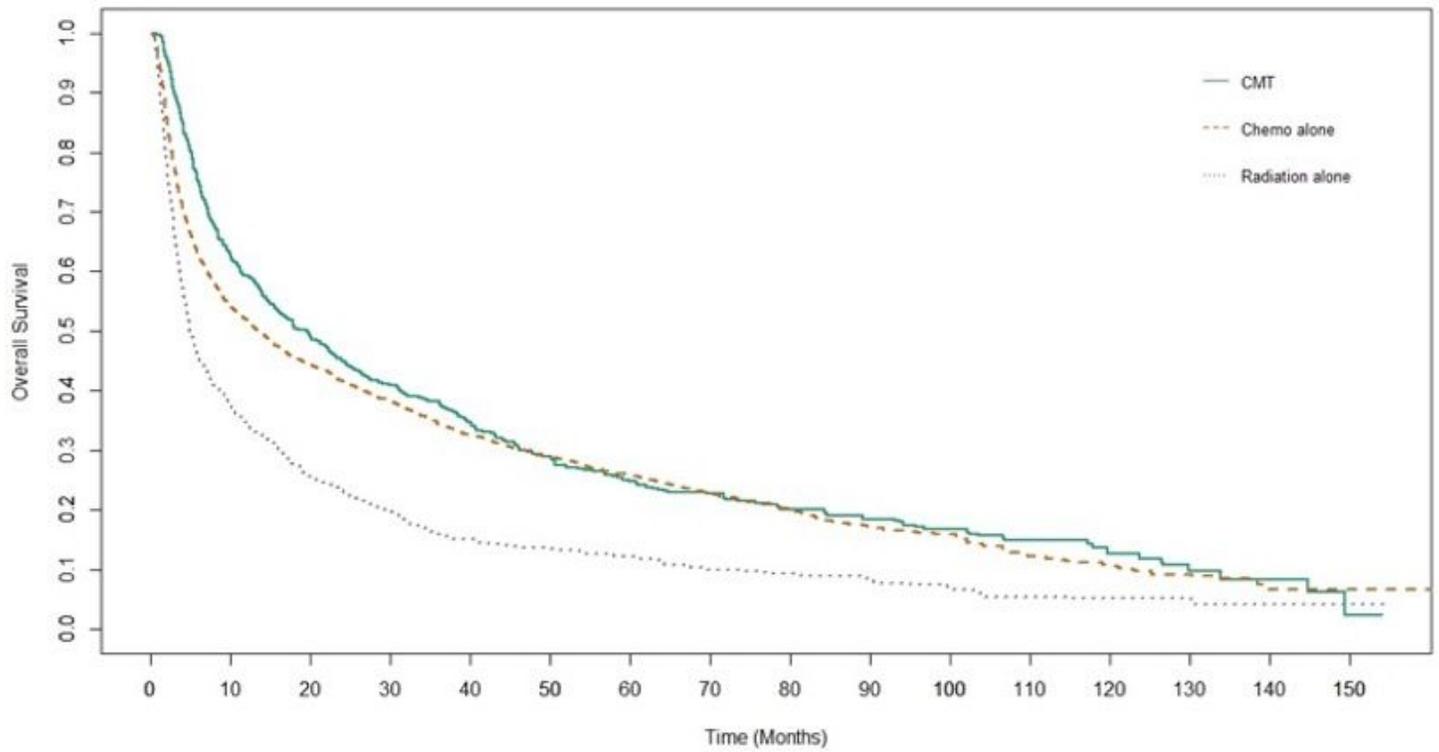
Both adjusted log-rank and Wilcoxon-rank p-values were <0.001 (Figure 3).
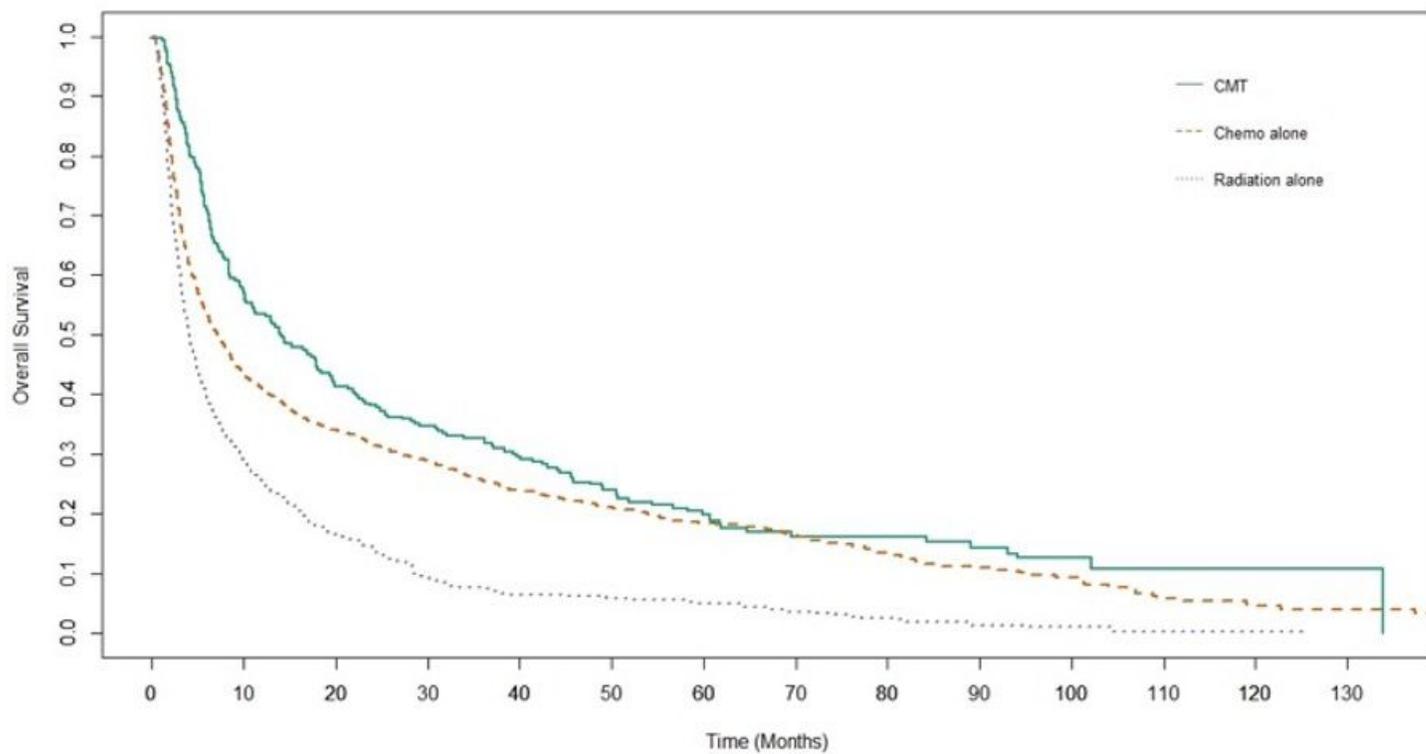
Figure 4

Both adjusted log-rank and Wilcoxon-rank tests p-values were <0.001 (Figure 4).