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Treatment Selection and Survival in Patients with Gray Zone Lymphoma; A Comprehensive Population-Based Analysis

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ORIGINAL RESEARCH REPORT

Treatment Selection and Survival in Patients with Gray Zone Lymphoma: A Comprehensive Population-Based Analysis

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Abstract

Background and objectives: **There are no treatment guidelines for gray-zone lymphoma (GZL), given the disease's rarity and being a relatively new entity. Our objective was to assess factors affecting treatment selection in GZL and its effect on survival, focusing on combined modality treatment (CMT) versus chemotherapy alone.**

Patients and methods: **We identified 1047 patients with GZL treated with CMT or chemotherapy alone between 2004 and 2016 from the National Cancer Database (NCDB). We excluded patients without histologic confirmation of the diagnosis, those who did not receive chemotherapy, and those who started chemotherapy >120 days or radiation >365 days from diagnosis to account for immortal time bias. Factors affecting treatment selection were investigated using a logistic regression model. A propensity score-matched methodology was used to compare survival outcomes.**

Results: **Only 164 patients (15.7%) received CMT, while 883 (84.3%) received chemotherapy alone. Treatment selection was affected by clinical factors (age, odds ratio [OR] 0.99, 95% confidence interval [CI] 0.98−0.997, p-value 0.01 and advanced stage, OR for stage 4: 0.21, 95% CI 0.13−0.34, p-value < 0.001) but not socioeconomic factors. Higher median income was associated with better survival, while increased age, higher comorbidity score, and B symptoms were associated with worse survival. The use of CMT had a survival advantage over chemotherapy alone (hazard ratio [HR] 0.54, 95% CI 0.351−0.833, p-value 0.005).**

Conclusion: **CMT is associated with survival advantage in our analysis. Careful selection of patients is essential to achieve the best outcomes with minimal toxicity. Socioeconomic factors affect treatment selection in patients with GZL that can alter outcomes. Future work should focus on strategies that access disparities without compromising survival.**

1. Introduction

Gray-zone lymphoma (GZL) is a rare lymphoid neoplasm initially described in 2005 by Traverse-Glehen et al. [1] Twenty-one cases were reported with features similar to primary mediastinal B-cell lymphoma (PMBCL) and classic Hodgkin lymphoma (cHL). The World Health Organization (WHO) first recognized GZL as a separate entity in 2008, as B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and cHL [2]. Despite being recognized as a mediastinal-only disease in early reports, GZL can present as a systemic disease [3]. Diagnosis is usually challenging and requires a review by an expert hematopathologist. These tumors have transitional or intermediate morphologic and phenotypic features between DLBCL and cHL. The

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most common phenotypes are: CD20+, CD30+, CD79a+, PAX5+, OCT2+, and MUM1+. CD15, CD45, CD10, and EBV staining are more variable [4]. Being a separate entity was confirmed at the epigenetic level as well [5].

In a multicenter retrospective analysis, Evans et al. evaluated treatment patterns and outcomes in 112 GZL patients. The most common regimens used were cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) ± rituximab (R), followed by doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) +/− (R); subsequently, dose-adjusted etoposide, prednisone, oncovin, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) were added. With a median follow-up of 31 months, the two-year progression-free survival (PFS) and overall survival (OS) were 40% and 88%, respectively. Patients treated with ABVD had significantly inferior outcomes, and patients with mediastinal disease had similar outcomes compared with non-mediastinal presentation.

The role of consolidative radiation is even less clear, although it is considered primarily in bulky and localized diseases. We know from early studies of PMBCL that the addition of radiation to systemic chemotherapy can improve curative chances [6]. Although radiation use has become less common with the use of more intensive regimens like DA-EPOCH-R [7,8]. Further, in a prospective phase II trial, mediastinal GZL had inferior event-free survival (62% vs. 93%; P = .0005) and OS (74% vs. 97%; P = .0012) compared with PMBCL, even when treated with DA-EPOCH-R [9].

The rarity of the disease, being relatively a new entity, and paucity of high-quality evidence have led to uncertainty regarding treatment approaches. Moreover, more data regarding disease characteristics and prognosis is needed to guide future research and establish treatment strategies. In this context, we hypothesize that combined modality treatment (CMT) will have better outcomes than chemotherapy alone. We sought to examine this theory and investigate the predictors of treatment selection and survival using the National Cancer Database (NCDB). To our knowledge, this is the first population-based analysis of GZL.

2. Patients and methods

2.1. Study design and participants

We conducted a retrospective cohort analysis using de-identified data accessed from the NCDB. NCDB is a joint program established in 1989 by the Commission on Cancer of the American College of Surgeons and the American Cancer Society [10]. This comprehensive data set integrates registry records from more than 1500 accredited hospitals, capturing around 70% of all incident cancers in the United States [11]. According to the agreements executed with each accredited facility, data from Veteran Affairs, Department of Defense, and Puerto Rico are removed from research files. The accreditation requires an annual 90% follow-up rate for eligible patients diagnosed within five years. Censoring bias is avoided by releasing survival outcomes (calculated from the date of diagnosis) only after at least five years of follow-up. Data are coded using standardized algorithms, and duplicate records are eliminated. Variables include patient demographics, comorbidities, socioeconomic status, stage, 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. NCDB does not record specific chemotherapy regimens, doses, or treatment durations. Since this study used de-identified data, it was considered exempt from human protection oversight by the institutional review board of Allegheny Health Network.

The NCDB provided records of 2176 patients diagnosed between 2004 and 2016 with GZL, defined in the NCDB as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma, ICD-0-3 morphology code: 9596. We excluded patients without histologic or cytologic confirmation of the diagnosis or patients with unrecorded stage information, those who did not receive chemotherapy, and those with a database flag that radiation was contra-indicated or unrecorded. We also excluded patients treated outside the reporting facility because otherwise, the NCDB does not require documentation of their treatment and outcomes. We excluded patients who started chemotherapy >120 days or radiation >365 days since diagnosis to account for immortal time bias (Fig. 1: selection process, CONSORT diagram).

2.2. Variables

Race was recoded into four categories − non-Hispanic White, non-Hispanic Black, Hispanic, and other. Comorbidity was captured using the Charlson/Deyo comorbidity index [12]. Stage was based on American Joint Committee on Cancer/Union for International Cancer Control TNM staging.

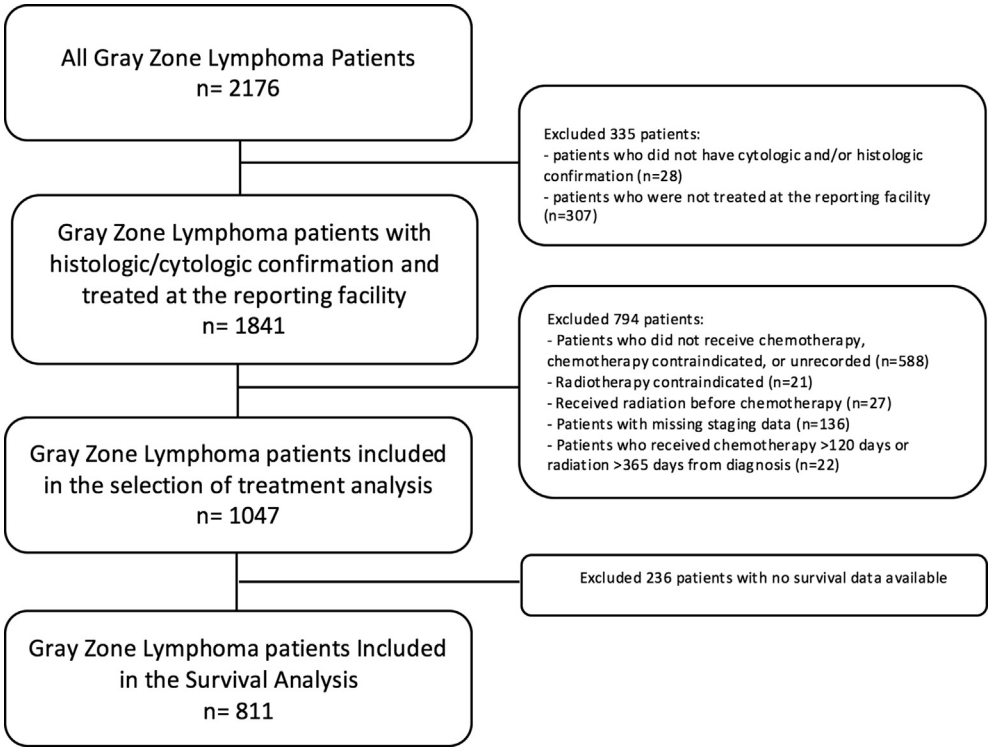

Fig. 1. Patient selection process.

Socioeconomic data were provided as quintiles of median household income and percentage of people with less than high school education in patients' census tract of residence. According to the Commission on Cancer accreditation category, the facility type was assigned based on annual case volume and oncology services that are available. Geographic locations corresponded to the US Census Divisions. Insurance status is captured as it appears on the patient's admission face sheet and was recoded as insured or uninsured.

Missing data on symptoms (7.9%), education (0.2%), income (0.3%), facility type (17.6%), and location (2.4%) were managed by multiple imputation, using chained equations [13]. This method is superior to existing alternatives as far as analytic bias is concerned [14].

2.3. Outcomes and statistical analyses

Treatment was categorized as CMT (chemotherapy + radiation) or chemotherapy alone. Exploratory analysis of the patient groups was performed. Summary statistics are presented as percentages for categorical data and median with interquartile range (IQR) for quantitative data.

A multivariable logistic regression model was used to analyze the predictors of selecting CMT versus chemotherapy alone. It was represented as odds ratio (OR) and 95% confidence interval (CI), averaged among the imputed data sets and incorporated variables associated with treatment selection. Survival was measured in terms of months (m) from the day of diagnosis to the day of censoring (last follow-up or day of death). Cox-regression hazard model was used to analyze survival predictors, represented as hazard ratio (HR) and 95% CI, averaged among all imputed data sets, and incorporated all variables associated with survival [15]. Variables with a P-value less than 0.10 in univariate analyses were entered into the multivariate Cox proportional hazards model in a stepwise manner [16].

We used a 1:1 propensity score matching methodology for the comparative survival analysis. Variables included in the propensity score model were age, sex, race, insurance status, median income, education, facility type, type of area, comorbidity score, distance from the treating facility, stage, and year of diagnosis. A standardized mean difference was used to assess covariate balance before and after propensity score matching [17]. Survival

estimates were performed using the Kaplan–Meier method, and survival differences were assessed using the log-rank test [18,19]. Adjusted effect size estimates and 95% CIs are reported using an alpha level of 0.05 to indicate statistical significance. All statistical analyses were conducted with IBM SPSS Statistics Version 23.

3. Results

3.1. Cohort characteristics

We identified 1047 patients with GZL who were treated with CMT or chemotherapy alone between 2004 and 2016. The baseline characteristics of the cohort are summarized in Table 1. The median age

Table 1. Baseline characteristics of patients selected for analysis.

Characteristic	All patients n = 1047 N (%)	SMT N (%) 883 (84.3)	CMT N (%) 164 (15.7)
Median Age in years (IQR)	63 (47–74)	64 (51–74)	57 (38–72)
Sex			
Male	694 (56.7)	505 (57.2%)	89 (54.3)
Female	453 (43.3)	378 (42.8%)	75 (45.7)
Race			
Non-Hispanic White	863 (80.7)	711 (80.5)	136 (82.9)
Non-Hispanic Black	78 (7.3)	64 (7.2)	11 (6.7)
Hispanic	59 (5.5)	50 (5.7)	7 (4.3)
Others	69 (6.5)	58 (6.6)	10 (6.1)
Insurance			
Uninsured	29 (2.8)	22 (2.5)	7 (4.3)
Insured	1006 (96.1)	850 (96.3)	156 (95.1)
Median Income			
<$38,000	171 (16.3)	148 (16.8)	23 (14.0)
$38,000–$47,999	245 (23.4)	216 (24.5)	29 (17.7)
$48,000–$62,999	288 (27.5)	242 (27.4)	46 (28.0)
≥$63,000	340 (32.5)	275 (31.1)	65 (39.6)
% of at least high school education			
≥21%	156 (14.9)	136 (15.4)	20 (12.2)
13.0–20.9%	252 (24.1)	222 (25.1)	30 (18.3)
7.0–12.9%	357 (34.1)	392 (33.1)	65 (39.6)
<7.0%	280 (26.7)	231 (26.2)	49 (29.9)
Comorbidity Score			
0	889 (75.4)	657 (74.4)	132 (80.5)
1	170 (16.2)	146 (16.5)	24 (14.6)
2	54 (5.2)	48 (5.4)	6 (3.7)
≥3	34 (3.2)	32 (3.6)	2 (1.2)
Type of area			
Metropolitan	873 (83.4)	735 (83.2)	138 (84.1)
Urban	139 (13.3)	119 (13.5)	20 (12.2)
Rural	10 (1.0)	9 (1.0)	1 (0.6)
Facility Type			
Community Cancer Center	57 (5.4)	49 (5.5)	8 (4.9)
Comprehensive Community Cancer Center	338 (32.3)	280 (31.7)	58 (35.4)
Academic/Research Program	349 (33.3)	319 (36.1)	30 (18.3)
Other	119 (11.4)	97 (11.0)	22 (13.4)
Year Group			
2004–2006	49 (4.7)	39 (4.4)	10 (6.1)
2007–2008	52 (5.0)	42 (4.8)	10 (6.1)
2009–2010	85 (8.1)	67 (7.6)	18 (11.0)
2011–2012	112 (10.7)	101 (11.4)	11 (6.7)
2013–2014	291 (27.8)	243 (27.5)	48 (29.3)
2015–2016	458 (43.7)	391 (44.3)	67 (40.9)
Stage			
Stage I	185 (17.7)	129 (14.6)	56 (34.1)
Stage II	230 (22.0)	167 (18.9)	63 (38.4)
Stage III	213 (20.3)	200 (22.7)	13 (7.9)
Stage IV	419 (40.0)	387 (43.68)	32 (19.5)
Distance (median)	215 (91–329)	218 (94–329)	198 (88–329)

SMT, single modality treatment; CMT, combined modality treatment; IQR, inter-quartile range.

was 63 (IQR: 47–74), and there were 56.7% males. Most of the patients were non-Hispanic White (80.7%), had insurance (96.1%), had a comorbidity score of 0 (75.4%), belonged to metropolitan areas (83.4%), and were treated at comprehensive community cancer centers or academic programs (65.5%). The median duration to start chemotherapy was 24 days (IQR: 13–41), and radiation was started at a median of 164 days (IQR: 134–199).

Table 2. Multivariable logistic analysis for predictors of receiving CMT versus chemotherapy alone.

Characteristic	Odds ratio	p-value
Age	0.987 (0.978–0.997)	**0.012**
Sex		
Male	Reference	
Female	1.014 (0.703–1.464)	0.940
Race		
Non-Hispanic White	Reference	
Non-Hispanic Black	1.061 (0.492–2.288)	0.881
Hispanic	0.816 (0.339–1.966)	0.622
Others	0.838 (0.394–1.782)	0.646
Insurance		
Uninsured	Reference	
Insured	0.400 (0.148–1.086)	0.072
Median Income		
<$38,000	Reference	
$38,000-$47,999	0.819 (0.414–1.618)	0.565
$48,000-$62,999	0.928 (0.479–1.957)	0.928
≥$63,000	1.341 (0.619–2.903)	0.457
% of at least high school education		
≥21%	Reference	
13.0–20.9%	0.770 (0.384–1.546)	0.462
7.0–12.9%	1.325 (0.645–2.718)	0.443
<7.0%	1.128 (0.497–2.564)	0.773
Location		
Metropolitan	Reference	
Urban	1.240 (0.683–2.252)	0.479
Rural	1.141 (0.273–4.768)	0.856
Stage		
Stage 1	reference	
Stage 2	0.817 (0.518–1.288)	0.385
Stage 3	0.142 (0.073–0.277)	**<0.001**
Stage 4	0.207 (0.125–0.341)	**<0.001**
Facility Type		
Community Cancer Center	reference	
Comprehensive Community Cancer Center	1.199 (0.497–2.889)	0.684
Academic/Research Program	0.583 (0.225–1.511)	0.261
Others	1.326 (0.508–3.463)	0.562
Comorbidity Score		
0	Reference	
1	0.913 (0.546–1.528)	0.730
2	0.843 (0.333–2.133)	0.718
≥3	0.368 (0.081–1.675)	0.196
Distance	1.000 (0.998–1.001)	0.500
Symptoms		
No B symptoms	Reference	
B symptoms	0.857 (0.560–1.311)	0.475

Table 3. Multivariable Cox-regression analysis for predictors of survival.

Characteristic	Covariate	p-value
Age	1.040 (0.1.031–1.048)	**<0.001**
Median Income		
<$38,000	Reference	
$38,000–$47,999	0.906 (0.634–1.296)	0.590
$48,000–$62,999	0.664 (0.463–0.954)	**0.027**
≥$63,000	0.663 (0.468–0.939)	**0.020**
Comorbidity Score		
0	Reference	
1	1.512 (1.121–2.041)	**0.007**
2	1.653 (1.056–2.587)	**0.028**
≥3	3.381 (1.918–5.960)	**<0.001**
Treatment modality		
Chemotherapy alone	Reference	
Chemotherapy + radiation (CMT)	0.541 (0.351–0.833)	**0.005**
Symptoms		
No B symptoms	Reference	
B symptoms	1.599 (1.246–2.051)	**<0.001**

3.2. Treatment selection and survival analyses

Only 164 patients (15.7%) received CMT, while 883 (84.3%) received chemotherapy alone. Treatment selection was affected by clinical factors but not socioeconomic factors. The odds of receiving CMT decreased with increasing age (OR 0.99, 95% CI 0.98–0.997, p-value = 0.01) and advanced stage (OR for stage 3: 0.14, 95% CI 0.07–0.28, p-value <0.001, OR for stage 4: 0.21, 95% CI 0.13–0.34, p-value <0.001) (Table 2).

Median follow-up for the 811 patients with available survival data was 28.8 months (IQR: 12.4–50.3). CMT and higher median income were associated with better survival, while increased age, higher comorbidity score, and B symptoms were associated with worse survival (Table 3). Table 4 shows the covariate balance before and after propensity score matching. The standardized mean difference was <0.1 in all covariates after matching [17]. Median OS was significantly higher in the CMT group compared with the chemotherapy alone group (not reached vs. 39.1 months, respectively, log-rank p-value <0.01) (Fig. 2). The aggregate 2-year survival was 79% and 54% in the CMT and chemotherapy alone groups, respectively.

4. Discussion

In this comprehensive NCDB analysis of GZL, we focused on the choice of CMT and chemotherapy alone as a primary treatment strategy. The number of patients with GZL increased gradually over the years, from 49 patients in the year 2004–2006 group to 458 patients in the year 2015–2016 group, reflecting the increased recognition of this disease entity since its inclusion in the WHO classification in 2008. The use of

Table 4. Covariate balance before and after propensity score (PS) matching (categorical variables are presented as n [%]).

	Before PS matching		After PS matching
Characteristic	**Chemo alone** 681 (%)	**CMT** n = 130	**Chemo alone** N = 130
Median Age in years (IQR)	64 (51–74)	53 (35–72)	54 (36–73)
Sex			
Female	293 (43.0)	56 (43.1)	56 (43.1)
Race			
Non-Hispanic White	554 (81.4)	111 (85.4)	112 (86.0)
Non-Hispanic Black	47 (6.9)	6 (4.6)	5 (4.0)
Hispanic	35 (5.1)	4 (3.1)	4 (3.1)
Others	45 (6.6)	9 (6.9)	9 (6.9)
Insurance			
Uninsured	15 (2.2)	5 (3.9)	5 (3.9)
Insured	656 (97.8)	124 (96.1)	124 (96.1)
Median Income			
<$38,000	116 (17.1)	20 (15.5)	20 (15.5)
$38,000–$47,999	164 (24.2)	19 (14.7)	21 (16.3)
$48,000–$62,999	180 (26.5)	33 (25.6)	34 (26.5)
≥$63,000	219 (32.3)	57 (44.2)	54 (41.7)
% of at least high school education			
≥21%	108 (15.9)	14 (10.8)	14 (10.8)
13.0–20.9%	165 (24.3)	21 (16.2)	21 (16.0)
7.0–12.9%	227 (33.4)	55 (42.3)	55 (42.3)
<7.0%	179 (26.4)	40 (30.8)	40 (30.8)
Comorbidity Score			
0	503 (73.9)	111 (85.4)	111 (85.4)
1	114 (16.7)	16 (12.3)	16 (12.3)
2	40 (5.9)	3 (2.3)	3 (2.3)
≥3	24 (3.5)	0 (0)	0 (0)
Type of area			
Metropolitan	578 (86.8)	110 (86.6)	110 (86.6)
Urban	82 (12.3)	17 (13.4)	17 (13.4)
Rural	6 (0.9)	0 (0)	0 (0)
Facility Type			
Community Cancer Center	39 (6.7)	5 (5.7)	5 (5.7)
Comprehensive Community Cancer Center	219 (37.8)	47 (54.0)	47 (54.0)
Academic/Research Program	244 (42.1)	20 (23.0)	20 (23.0)
Other	77 (13.3)	15 (17.2)	15 (17.2)
Year Group			
2004–2006	39 (5.7)	10 (7.7)	10 (7.7)
2007–2008	42 (6.2)	10 (7.7)	10 (7.7)
2009–2010	67 (9.8)	18 (13.8)	18 (13.8)
2011–2012	101 (14.8)	11 (8.5)	11 (8.5)
2013–2014	243 (35.7)	48 (36.9)	48 (36.9)
2015–2016	189 (27.8)	33 (25.4)	33 (25.4)
Stage			
Stage I	100 (14.7)	44 (33.8)	44 (33.8)
Stage II	126 (18.5)	50 (38.5)	50 (38.5)
Stage III	160 (23.5)	11 (8.5)	11 (8.5)
Stage IV	295 (43.3)	25 (19.2)	25 (19.2)
Median distance (IQR)	191 (82–284)	176 (61–284)	176 (61–284)

CMT, combined modality treatment; IQR, inter-quartile range.

CMT has increased over the study period from 4.7% of the patients in the year 2004–2006 group to 43.0% in the year 2015–2016 group.

We also identified clinical and socioeconomic factors associated with the selection of treatment and survival. Increased age and advanced stage of the disease led to less radiation use. Radiation is associated with increased cost, requires complex planning, and creates a significant psychosocial burden [20,21], in addition to toxicity which could have contributed to its lesser use in older patients identified in this analysis. Historically, socioeconomic factors were associated with treatment selection in solid tumors and hematologic malignancies [22–26]. Age, median income, comorbidity score, and having B symptoms significantly affected survival, contrary to the analysis mentioned above by Evans et al. [4], where

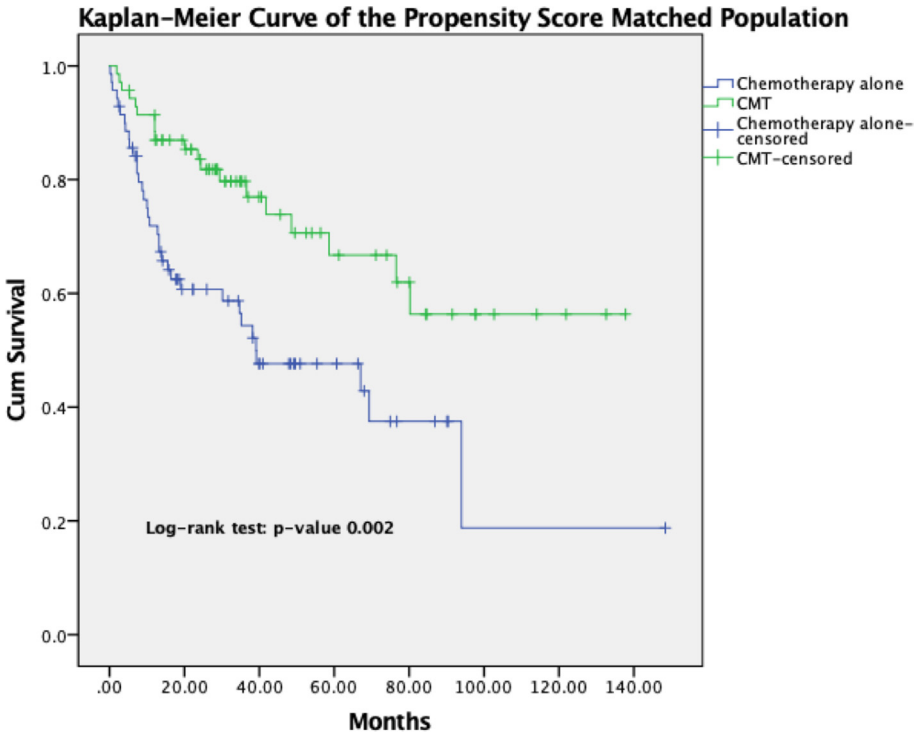

Fig. 2. Kaplan–Meier curve of the propensity score matched population.

advanced stage was the only significant predictor of survival in GZL. Higher median income was a predictor of better survival, although it did not affect treatment selection. This unparallel improvement in survival is probably related to other external factors not identified in this analysis. Median income remained a significant factor even when we adjusted for age, comorbidity score, and B symptoms.

Receiving CMT had a survival advantage over chemotherapy alone (HR 0.54, 95% CI 0.35–0.83, p-value <0.01). Evans and colleagues reported no effect on survival using consolidative radiation in 37 patients in their series (HR 0.56, 95% CI 0.16–2.05, p-value 0.39) [4]. Authors attribute these different results to the larger sample size for patients who received radiation in our cohort (n = 130), in addition to adjustment to baseline characteristics using propensity score. The present study was based on data available from the NCDB and did suffer from limitations resulting from its retrospective nature and the inherent selection bias. The use of propensity score matching methodology strengthens our results. 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 many patients from different parts of the U.S, they tend to be more generalizable. NCDB lacks certain pertinent variables, like the exact chemotherapy regimen used and dosing, toxicity information, progression, and salvage treatment details; we could not adjust to these variables in our survival model.

In conclusion, further prospective research is needed to assess the role of consolidative radiation in patients with GZL, even with more intensive chemotherapy regimens like DA-EPOCH-R. However, with the advent of newer radiation techniques like intensity-modulated radiotherapy (IMRT), it is possible to achieve the best outcome with minimum toxicity. Clinical and socioeconomic factors affected treatment selection and survival in American patients with GZL. Identifying and eliminating social and economic disparities that affect treatment selection and outcomes in future research is of utmost importance, and our study aimed to increase insight into these disparities. Further studies are warranted to validate our findings in this regard.

Contributors

Dr. Samhouri had full access to all the data and analysis in the study and takes responsibility for the integrity of data and the accuracy of the data analysis. **Concept and design**: Samhouri. **Acquisition, data analysis, and result interpretation**: All authors. **Drafting of the manuscript**: All authors. **Critical**

revision of the manuscript: All authors. **Statistical analysis**: Samhouri. **Administrative and** technical support: Lister, Fazal, Khan, Samhouri. **Supervision**: Lister, Samhouri.

Data sharing

Data was provided by 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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Conflict of interest

All authors have no conflict of interest.

Ethical approval

This study used de-identified data and was considered exempt from human protection oversight by institutional review board.

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