Effect of Fragmented Care for Pediatric Neuroblastoma Patients: A Single Institution Analysis

By

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Abstract

Background/Purpose: Children with high-risk neuroblastoma (NBL) have high-mortality rates and undergo complex, multi-modal therapy. They may be subject to fragmented care among different providers and institutions, which has been associated with worse outcomes for various adult cancers. These patients may also experience significant travel burden in accessing appropriately equipped facilities. We hypothesize that fragmented care for pediatric NBL patients is associated with inferior outcomes compared to treatment consolidated at one location.

Methods: Paper and electronic records for pediatric NBL patients having received ≥1 bone marrow transplant at our institution from 1990-2018 were manually reviewed. Variables collected include demographics, diagnostic and treatment characteristics, complications, and relapse and survival outcomes. Fragmented care is defined by treatment occurring at >1 institution and grouped according to 2 institutions vs. >2 institutions. Distances are calculated using Google Maps. Fisher's exact and Kruskal-Wallis tests were used to compare patients receiving fragmented versus consolidated care. Unadjusted overall survival (OS) was estimated using the Kaplan-Meier method, and differences in OS between groups were tested using the log-rank test.

Results: We extracted data from 128/148 patients. The most common reasons for exclusion included incomplete medical records (n=9) and BMT for relapse/recurrence only (n=8). 103 patients experienced fragmented care, with 18 of them being treated at 3+ facilities. More patients with consolidated care were above the 75th percentile for distance traveled to chemotherapy and surgery, while more patients with 3+ facilities were above the 75th percentile for distance traveled to BMT and immunotherapy (all $p<0.01$). On univariate analysis, neither fragmented care group was associated with mortality ($p>0.05$). Diagnosis in earlier decades, particular chemotherapy protocols, enrollment on a clinical trial (compared to being treated according to its guidelines), and increased distance to BMT were all significantly associated with increased mortality ($p<0.05$). Only diagnostic year and distance to BMT remained significantly associated with OS on multivariate analysis.

Conclusion: In the largest institutional analysis of fragmented care for pediatric NBL patients, we demonstrate no association between degree of fragmented care or travel distance and OS or relapse rates. These findings may be critical to those living far removed from appropriate treatment. Further research and interventions should explore lower-risk disease and aim to improve supportive processes for patients undergoing complicated and burdensome care.

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Introduction

Treatment of pediatric cancer is frequently complex and multimodal, often delivered through enrollment on or according to clinical trial protocols.[1,2] Accordingly, the American Academy of Pediatrics (AAP) recommends that pediatric cancer patients receive care at specialized pediatric cancer centers that have the expertise and resources necessary to deliver trial-based therapy safely and effectively.[3] For many pediatric cancer patients, consistent evidence demonstrates improved clinical and survival outcomes associated with receipt of care at these specialized centers.[4-8] Many of these centers are members of the Children's Oncology Group (COG), a National Cancer Institute-sponsored clinical trials group organized in 2000 to ensure regionalized, multidisciplinary treatment.[9] Recommendations to deliver care at COG institutions, in addition to advanced therapeutic innovations, have led to survival rates now exceeding 80% for pediatric cancer patients.[10]

Over 90% of pediatric cancer patients in the US are treated at COG-member institutions, but many may receive care from more than one facility.[11] In these circumstances, there is concern for a lack of effective communication and coordination among providers. Such fragmented care for adult oncology patients, following major cancer surgery or otherwise, has been associated with increased healthcare costs, more complications, and decreased survival.[12-17] Numerous studies have also demonstrated improved outcomes for several malignancies associated with use of multidisciplinary tumor conferences (MDCs), which allow multiple providers to convene in one setting to discuss the treatment plan for a given patient.[18-21] Together, these results create an argument for centralizing and coordinating pediatric cancer care within single, specialized institutions. In addition to improved clinical outcomes, such

coordinated oncologic care has the benefit of reducing anxiety and unnecessary responsibility for family members.[22]

Despite certain advantages of consolidated care, reducing fragmented oncologic care for pediatric cancer patients constitutes a significant challenge. The 194 COG-member institutions in the US remain concentrated in major urban environments.[11] This is problematic given that approximately 20% of American families live in rural communities far removed from COG-member institutions.[23] Additionally, as pediatric cancer treatment grows in complexity with such treatments as immunotherapy, not every specialized facility is equipped to offer all facets of treatment. As such, pediatric cancer patients and their families must frequently travel significant distances in the hopes of receiving appropriately consolidated treatment. For adult cancer patients, some studies have shown that those who live and travel further to treatment may present with later stage disease, receive different treatments than their closer counterparts, and experience worsened survival outcomes.[24] However, comparably sparse literature exists examining the effect of fragmented care and travel burden for pediatric cancer patients.

Populations with specific cancers may be at higher risk for adverse outcomes associated with fragmented care delivery. Neuroblastoma (NBL) is the most common solid extracranial pediatric malignancy and presently accounts for nearly 15% of childhood cancer deaths.[25] It is a tumor derived from neural crest sympthoadrenal lineage progenitor cells and has a highly heterogeneous clinical course.[21] While it can develop anywhere within the sympathetic nervous system, the adrenal gland is the most common primary site, followed by other retroperitoneal and thoracic locations.[25] Beginning in 2009, NBL patients are classified as either low, intermediate, or high-risk based on numerous pathological and clinical factors, as outlined in the International Neuroblastoma Risk Group Staging System (INRGSS).[26] High-risk patients typically receive

complex treatment regimens consisting of chemotherapy, surgical resection, radiation, high-dose autologous peripheral blood stem cell (PBSC) transplantation, and immunotherapy.[21] Because effective PBSC transplantation and immunotherapy is only offered at few COG-member institutions, high-risk NBL patients may be particularly susceptible to fragmented care.

In this study, we sought to use an institutional series of neuroblastoma patients whose treatment course has involved at least one bone marrow transplantation at Duke University to elucidate and better understand the effects of fragmented care and travel distance on clinical and survival outcomes. We hypothesize that patients whose care is split between more institutions and who have had to travel further will experience increased rates of relapse and mortality.

Methods

Data Sources

We conducted a retrospective analysis of pediatric NBL patients diagnosed from 1990-2017 who received multimodality therapy and at least one bone marrow transplantation (BMT) at Duke University. Paper and electronic medical records were reviewed by AT and MA to extract relevant variables into a standardized Excel spreadsheet. Specifically, we examined all relevant discharge summaries, outpatient notes, flowsheets, correspondences, operation notes, and pathology and radiology reports. Ethical approval for this study was granted by the Duke University and University of North Carolina – Chapel Hill Institutional Review Boards. Informed consent was not required. All collected patient data and protected health information (PHI) was stored on secure server provided by the IRB team.

Study Population and Case Selection

The study population included any patients aged 0-18 with histologically confirmed NBL treated with at least one BMT at Duke from 1990-2017. This patient population was selected because the pediatric BMT team at Duke has maintained detailed clinical records of all patients seen on their service, including NBL patients. Patients were excluded if they had BMT only subsequent to relapsed NBL or had incomplete or unavailable medical records. Additional exclusion criteria included incorrect diagnoses, low-risk disease at diagnosis, and any international treatment prior to referral to Duke.

Study Variables

A comprehensive database of all information related to patient demographics, diagnosis, treatment, and outcomes was compiled. The variables utilized for analysis in this study are reported here.

Diagnosis date was defined as the date of histologically confirmed NBL. Demographic variables collected included age at diagnosis, sex, race/ethnicity, insurance status (defined as public payer, private, or both), and home address.

Disease-related variables included the primary anatomic site of the tumor, size of the largest dimension, histologic grade (defined as favorable or unfavorable histology), amplification status of the N-MYC gene, DNA ploidy as a continuous variable, and the presence of any image-defined risk factors (IDRFs). The INRG task force has identified 20 IDRFs based on anatomic location of the primary tumor and extent of involvement into adjacent vasculature, organs, and/or body cavities.[26] Importantly, IDRFs were not incorporated into the INRGSS until 2009, meaning many patient records did not mention presence or absence of IDRFs. In these instances, available

radiologic reports were reviewed by AT and MA and classified according to the task force report.[26] Because of the changes in NBL staging in recent decades, both INRG risk groups and traditional INSS staging was reported. Additionally, the diagnostic method of confirmation or biopsy type was also recorded.

Variables related to BMT, surgery, chemotherapy, radiation, and immunotherapy were also collected. For BMT, we recorded the number of BMTs received and the presence or absence of any major complications, defined as any complication requiring invasive intervention or resulting in serious disability or death. For surgery, we recorded whether patients received surgical resection, days to surgery from diagnosis, complete or incomplete resection, tumor margin status, length of stay (days) for the surgical admission, the presence of any major surgical complications and/or unplanned readmissions, and the total number of surgeries conducted for the primary tumor (including the initial surgical biopsy if performed). For chemotherapy, we recorded the days to the first cycle from diagnosis, whether patients were enrolled on or treated only according to a given clinical trial protocol, the number of cycles received, and the presence of any major complications. For radiation, we recorded the days to radiation from diagnosis, the modality of radiation received (involved field, proton beam, MIBG, TBI), dose, and total days of radiation received. We also reported whether patients received immunotherapy, whether any thrombotic complications resulted during treatment, how many central lines were placed, and the number of line infections per patient.

The facility location of each treatment modality was reported and used to stratify patients into either consolidated or fragmented care cohorts. Consolidated care was defined as all cancer-specific treatments occurring at Duke University. The fragmented cohort was further stratified into 2 facilities or >2 facilities involved in cancer-specific treatments. Importantly, we were not

able to assess all other clinical visits, such as PCP or acute care visits. These were therefore not factored into the definitions of consolidated or fragmented care. We also reported whether each facility involved in cancer-specific treatment was a COG-member institution, and a variable was created to determine whether each patient had all treatment or some treatment at COG-member institutions. Distances to each treatment facility were calculated as the driving distance between each patient's home postal code and the postal code of the treatment facility using Google Maps.

Data Analysis

The consolidated and two fragmented care groups were first compared by demographic, disease-related, and treatment-related characteristics using descriptive statistics (means and standard deviations, median and IQR, or counts and percentages where appropriate). The presence of any major and minor complications were also analyzed and stratified by consolidated or fragmented groups. Fisher's exact test was used for categorical variables, and Kruskall-Wallis tests were used for continuous variables.

The primary outcome was overall survival (OS), defined as death due to any cause. The time to event was defined as the time from date of diagnosis to the date of death or last follow-up. Secondary outcomes included the presence of relapse occurring after documented completion of the initial treatment course. Time to event distributions for OS and relapse were estimated with the Kaplan-Meier method and compared across the 3 study groups. The univariate significance of fragmented care and other patient, disease, and treatment characteristics on both OS and relapse was assessed using Cox proportional hazards modeling. The year of diagnosis was divided into 3 decades to approximate the timing and availability of various well-known clinical trials for neuroblastoma treatment. The mean for days from diagnosis to surgery was

skewed as a result of some patients receiving surgical resection as a part of the diagnostic work-up, as compared to those receiving surgery later in the treatment course. As such, a variable dividing patients into those receiving surgery before or after initiation of chemotherapy was used. In analyzing the effect of particular clinical trial protocols, we used the most well-known and common among this dataset. Finally, the distance to chemotherapy was chosen to approximate the shorter distance many patients traveled in receiving local therapy, and the distance to BMT was chosen to estimate the effect of long-distance travel for some patients during their treatment course. Variables that were significant in univariate analysis and with clinical relevance were included in a multivariate regression model for both OS and relapse. Not all variables were included due to overall small sample size and number of events.

Results

We identified 148 children with NBL treated at Duke University for BMT diagnosed from 1990 – 2017. Of these, 128 were deemed eligible and included in the final analysis. The most common reasons for exclusion included BMT for relapse/recurrence only (n=8), incomplete medical records (n=9), one patient with an incorrect diagnosis, one patient with low-risk disease, and one patient who received all initial treatment outside the United States. Patients hailed from and were treated at facilities in eight different states (Figure 1).

As seen in Table 1, 103/128 (80.4%) of patients experienced fragmented care. Of these, 85/103 (82.5%) were treated at 2 separate facilities, while 18/103 (17.5%) were treated at 3+ facilities. Mean patient age was 3.5 years at diagnosis, and those with 2 treatment facilities were older on average (3.9 ± 2.52 years, p=0.01). No significant differences were identified between consolidated and fragmented groups based on sex, race, or insurance. Those with 3+ treatment

facilities were more likely to receive only some of their care at COG-member institutions (22.2% for 3+ facilities, 4.7% for 2 facilities, p=0.02). Regarding disease-level characteristics, no significant differences were identified based on primary tumor site, histology, N-MYC status, presence of IDRFs, or INSS stage.

Patients treated at 3+ facilities were more likely to have an increased length of stay for the surgical admission compared to those with 2 facilities or consolidated care (mean 7.2 days for 3+ facilities, 6.2 days for 2 facilities, 5.4 days for consolidated care, p=0.04). A significant difference was also noted between groups for the mean number of central lines a patient had placed (mean 4.1 lines for 3+ facilities, 3.2 lines for 2 facilities, 4.4 lines for consolidated care, p=0.002). Patients receiving care at 3+ facilities were more likely to receive immunotherapy (55.6% for 3+ facilities, 25.9% for 2 facilities, 44.0% for consolidated care, p=0.03). Significant differences were noted for distance traveled to each therapy between groups. More patients with consolidated care were above the 75th percentile for distance traveled to chemotherapy and surgery, while more patients with 3+ facilities were above the 75th percentile for distance traveled to BMT and immunotherapy (all p<0.01). Finally, those with consolidated care were more likely to have a major complication during treatment, specifically a major BMT-related complication (p=0.01, p=0.02, respectively) (Table 2).

Kaplan-Meier analysis demonstrated significant differences between the three study groups for relapse-free survival (log-rank p=0.0251) but no significant difference for OS (log-rank p=0.025) (Figure 2). On univariate analysis, neither fragmented care group was associated with mortality (p>0.05 for both groups). Diagnosis in earlier decades, particular chemotherapy protocols, enrollment on a clinical trial (compared to being treated according to its guidelines), and increased distance to BMT were all significantly associated with increased mortality

($p<0.05$) (Table 3). Being treated at 3+ facilities was associated with worsened relapse-free survival (HR 2.583, 95% CI: 1.113 - 5.990, $p=0.027$). Additionally, diagnosis in earlier decades, enrollment on a clinical trial (compared to being treated according to its guidelines), and increased distance to BMT were all significantly associated with increased rates of relapse ($p<0.05$) (Table 4). On multivariate analysis, only diagnosis in earlier decades and increased travel distance to BMT remained significantly associated with worsened mortality ($p=0.024$ and $p=0.043$, respectively). For relapse, only diagnosis in earlier decades remained significantly associated with higher mortality rates ($p=0.05$).

Discussion

In this institutional study of NBL patients treated with at least one BMT, we hypothesized that those patients whose care is fragmented between multiple institutions and who have had to travel further for each treatment would experience increased rates of relapse and mortality. Our results demonstrate that consolidated care does not necessarily confer long-term survival advantage for high-risk NBL patients, but that traveling further to receive BMT is associated with increased relapse and mortality. Increasingly, guidelines recommend consolidating and centralizing care for oncology patients.[27-31] However, our findings constitute an important consideration for pediatric cancer patients and their families who must overcome significant travel burdens to receive such highly specialized, consolidated care.[27-31]

With no apparent survival advantage based on consolidated care, many families may elect to receive as much treatment as possible closer to home and avoid a significant travel burden. As such, it is critical to ensure that rural facilities are adequately equipped to handle the

complexity associated with high-risk NBL, regardless of their COG membership status. There is a well-established relationship between better surgical outcomes and higher hospital volume for adult cancers of the colon and rectum, esophagus, adrenal glands, and thyroid gland.[32-37] However, many such high-volume hospitals are located in metropolitan settings, leaving certain rural facilities without the necessary volume and expertise for effective oncologic surgery. Markin et al. demonstrated that complex oncologic surgical resections have higher mortality in rural hospitals as compared to specialty centers.[38] Similarly, Lidsky et al. demonstrated that patients undergoing pancreaticoduodenectomy for pancreatic cancer experience improved outcomes in urban high-volume hospitals despite an increased travel burden.[39] Yet, similar volume-outcome relationships for pediatric surgery have been challenged, as Gutierrez et al. found no correlation between hospital volume and survival outcomes for pediatric patients with Wilms tumor or neuroblastoma.[40] Ultimately, our study supports the findings by Gutierrez et al. and may indicate that pediatric cancer patients and their families may achieve equitable outcomes by opting for care closer to home.

Interestingly, our results showed that increased travel distance to BMT was associated with poorer relapse and survival outcomes. However, the distance traveled to chemotherapy, used as a proxy for the shorter distance many patients travel to receive most of their care, was not significant. Several studies have shown worsened outcomes for adult cancer patients based on increased travel distance.[24,41,42] There has been comparably little research in pediatric cancer, but some studies have demonstrated no survival detriment from increased travel distance.[43-46] Those patients that traveled furthest to BMT in our dataset were predominately from Alabama, Georgia, and Florida and were diagnosed in the 1990s prior to the institution of more local specialized BMT options. As such, our results may be more indicative of the poorer survival in

the 1990s as compared to recent years, even though diagnostic time-period was adjusted for in the multivariate model. Additionally, it may be that the sickest patients were referred to Duke for BMT instead of local facilities because of perceived expertise in complex pediatric cancer management, thus skewing mortality outcomes.

Fragmentation in our study was largely driven by patients traveling to Duke for BMT or to other highly specialized facilities for complex immunotherapy or unique radiation modalities, such as proton beam therapy or MIBG therapy. These reasons likely explain the significant differences in distance between each group. Such treatments are generally able to be delivered safely and effectively only at select large institutions in the US, and avoiding fragmented care for patients who require them may be impossible. Several studies have demonstrated that providing autologous BMT and proton beam therapy to pediatric patients may be cost-effective, prompting consideration for establishing more facilities capable of delivering such treatments to rural patients.[47,48] Despite supposed cost-effectiveness, however, the total costs for such therapies are exorbitant and typically too prohibitive for smaller, rural centers to consider funding, particularly given the small volume of requisite patients they might see.[47,48] As these therapies grow to become treatment mainstays for many malignancies, the high price of expansion and consolidation must be considered for families seeking to avoid increased travel and fragmented care.

Importantly, most patients in this study received all of their treatment at COG-member institutions, regardless of fragmented versus consolidated care. Because of the extensive resources and expertise available at such institutions, all patients likely received high-quality care and any potential effects of fragmentation may have been mitigated. The COG has significantly expanded its reach since its inception in 2000, meaning even those families living in

rural settings may still access high-quality, standardized care.[11] Our results do not demonstrate any disparity among patients receiving care at COG-member institutions based on residence, age, or other socioeconomic factors. Other studies have similarly noted that children are equally treated at COG facilities regardless of race, place of residence, or insurance status.[49,50] However, these studies also note that increasing age is associated with a decreased likelihood of treatment at appropriate pediatric cancer centers, particularly for adolescents aged 15-19.[49,50] Because neuroblastoma is typically seen in younger children, these findings are less concerning but merit important consideration for older NBL patients.

Improvements in survival for higher-risk NBL patients, despite the low rates compared to other pediatric cancers, can also be attributed to clinical trial-directed therapy. Most patients in our study were either enrolled on or treated according to risk-appropriate clinical trials. Several studies have noted widely variable enrollment on clinical trials for pediatric cancer patients, and myriad reasons exist for why patients may not be treated according to trial guidelines.[51-53] The most common reasons for non-trial enrollment were lack of trial availability, physician decision, Hispanic race, and increased distance to the treating center.[51-53] Our study did not assess the effect of distance on trial enrollment, but there was no significant difference between fragmented and consolidated groups based on trial enrollment status. With univariate analysis, those enrolled on a trial experienced higher rates of mortality than those simply treated according to trial guidelines. This was not assessed in multivariate analysis due to excess amount of missing data. However, it may be that those enrolled on a trial would not experience as much individualized treatment when it may be necessary. Additionally, physicians may seek out more experimentally-rigorous trials on which to enroll the sickest patients.

For rare childhood cancers such as NBL, large national databases provide the strength of increased sample sizes for analysis. However, such databases often lack the requisite data granularity, here defined as the level of detail and comprehensiveness of available patient and tumor-related variables, to conduct more in-depth analyses.[54] Our study is strengthened by the granular detail achieved with manual chart review as compared to utilization of large national databases. We were able to collect and create a comprehensive database of relevant demographic, clinical, treatment-related, and outcome information for our institutional series of higher-risk NBL patients.

However, our findings must interpreted in light of several limitations. The first is the small sample size inherent to single-institution analyses. However, high-risk NBL is a rare disease and even national databases may lack sufficient sample sizes and statistical power. Secondly, we were limited by the incompleteness of portions of available medical records. Frequently, adequate information about treatments offered at other institutions was lacking from discharge summaries, outpatient notes, and correspondences. However, this challenge is also indicative of the potential harms of fragmented care when providers and institutions communicate incompletely. We also chose to examine where each treatment was offered but could not track each hospitalization or if additional outpatient or ER visits occurred at additional institutions. With more complete records, a more comprehensive picture of the degree of fragmentation might be gleaned. Finally, while our study suggests that fragmented care and travel distance do not significantly affect survival for high-risk NBL patients, survival rates were poor among the entire cohort. Any potentially significant survival effects may have been undermined by the generally poor prognosis faced by high-risk NBL patients.

Conclusion

Our retrospective, single-institution study examining high-risk NBL patients suggests that oncologic care fragmented among multiple institutions is not associated with increased rates of relapse or mortality, which runs counter to increasing recommendations to consolidate and centralize cancer care. These results are critical for pediatric cancer patients and their families, who may live far removed from specialized pediatric cancer centers and would otherwise face significant financial and psychosocial stress associated with travel. It remains important to ensure that patients are treated at institutions, COG-members or otherwise, that are capable of delivering trial-directed therapy and are equipped with the necessary resources and oncologic expertise.

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Figure 1: Heat Map Showing Locations of Referred Patients and Treating Facilities

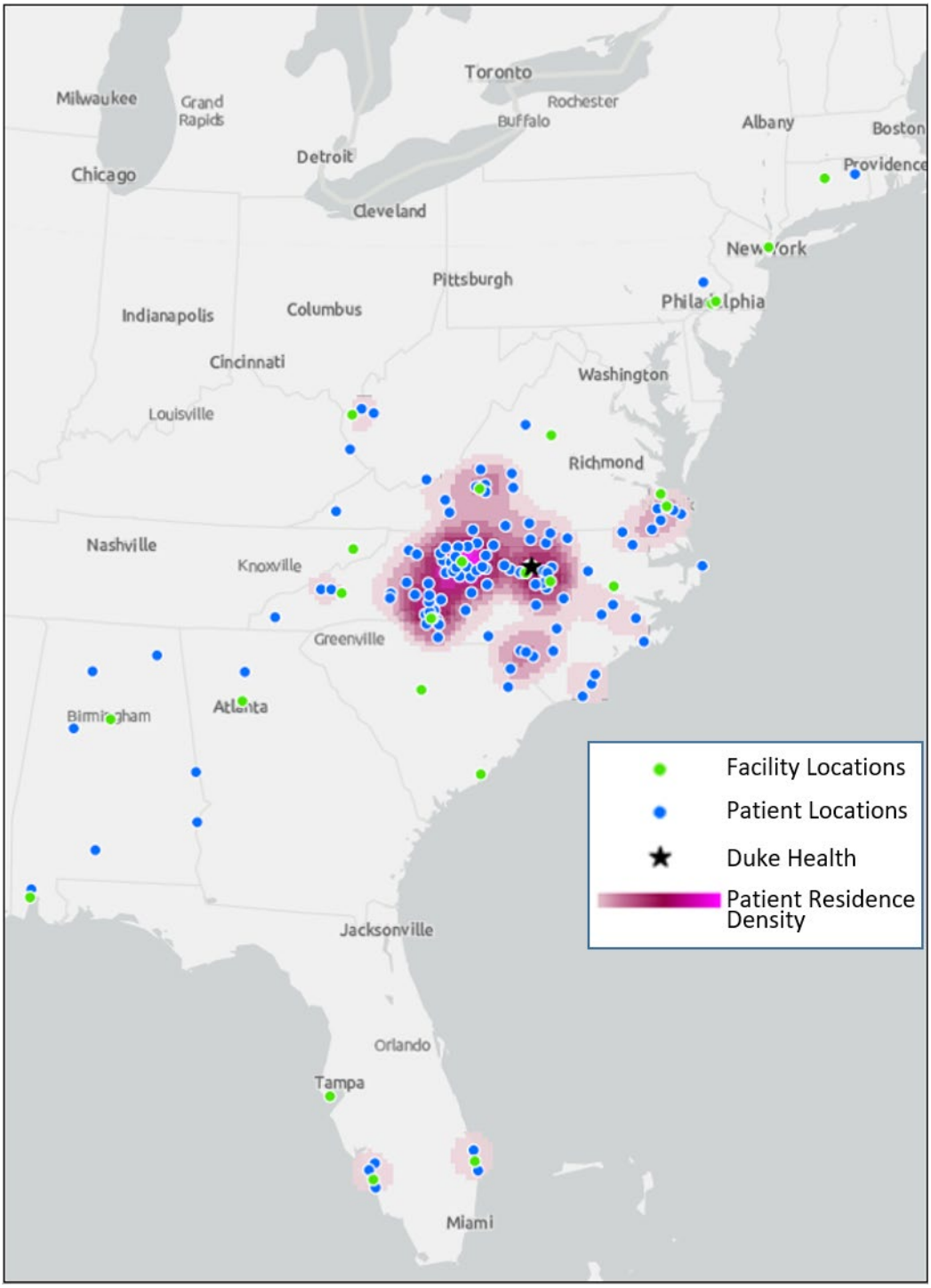


Table 1: Patient Characteristics between Consolidated and Fragmented Care Groups

	All Patients (N=128)	Consolidated Care (N=25)	Fragmented Care 2 Facilities (N=85)	Fragmented Care >2 Facilities (N=18)	P-Value
Year of Diagnosis					0.19
1990-1999	41 (32.0%)	6 (24.0%)	30 (35.3%)	5 (27.8%)	
2000-2009	51 (39.8%)	7 (28.0%)	36 (42.4%)	8 (44.4%)	
2010-2017	36 (28.1%)	12 (48.0%)	19 (22.4%)	5 (27.8%)	
Age*	3.5 (2.41)	2.5 (1.58)	3.9 (2.52)	3.1 (2.45)	0.01
Sex					0.82
Male	83 (64.8%)	16 (64.0%)	54 (63.5%)	13 (72.2%)	
Female	45 (35.2%)	9 (36.0%)	31 (36.5%)	5 (27.8%)	
Race					0.17
White	97 (75.8%)	16 (64.0%)	65 (76.5%)	16 (88.9%)	
African-American	24 (18.8%)	8 (32.0%)	15 (17.6%)	1 (5.6%)	
Other	4 (3.1%)	0 (0.0%)	3 (3.5%)	1 (5.6%)	
Insurance					0.12
Public	41 (32.0%)	11 (44.0%)	27 (31.8%)	3 (16.7%)	
Private	74 (57.8%)	11 (44.0%)	51 (60.0%)	12 (66.7%)	
Both	7 (5.5%)	1 (4.0%)	4 (4.7%)	2 (11.1%)	
COG Facility Status					0.02
Some treatment	8 (6.3%)	0 (0.0%)	4 (4.7%)	4 (22.2%)	
All treatment	120 (93.8%)	25 (100.0%)	81 (95.3%)	14 (77.8%)	
Primary Tumor Site					0.69
Adrenal	92 (71.9%)	18 (72.0%)	61 (71.8%)	13 (72.2%)	
Retroperitoneal	20 (15.6%)	4 (16.0%)	13 (15.3%)	3 (16.7%)	
Mediastinum	7 (5.5%)	2 (8.0%)	5 (5.9%)	0 (0.0%)	
Paraspinal	4 (3.1%)	0 (0.0%)	3 (3.5%)	1 (5.6%)	
Other	2 (1.6%)	0 (0%)	1 (1.2%)	1 (5.6%)	
Histological Favorability					1.00
Favorable	2 (1.6%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	
Unfavorable	71 (55.5%)	16 (64.0%)	45 (52.9%)	10 (55.6%)	
Unknown	55 (43.0%)	9 (36.0%)	38 (44.7%)	8 (44.4%)	
N-Myc Status					0.82
Non-Amplified	43 (33.6%)	10 (40.0%)	27 (31.8%)	6 (33.3%)	
Amplified	45 (35.2%)	8 (32.0%)	30 (35.3%)	7 (38.9%)	
Unknown	40 (31.3%)	7 (28.0%)	28 (32.9%)	5 (27.8%)	
IDRFs					0.30
No	28 (21.9%)	6 (24.0%)	20 (23.5%)	2 (11.1%)	
Yes	75 (58.6%)	15 (60.0%)	45 (52.9%)	15 (83.3%)	
Unknown	25 (19.5%)	4 (16.0%)	20 (23.5%)	1 (5.6%)	
Tumor Diagnostic Confirmation Method					0.01
Surgical Resection	22 (17.2%)	0 (0.0%)	20 (23.5%)	2 (11.1%)	
Open Biopsy Only	39 (30.5%)	10 (40.0%)	21 (24.7%)	8 (44.4%)	
Percutaneous/Needle Biopsy	9 (7.0%)	2 (8.0%)	7 (8.2%)	0 (0.0%)	
Bone Marrow Biopspy					0.31
No	2 (1.6%)	0 (0.0%)	1 (1.2%)	1 (5.6%)	
Yes	116 (90.6%)	25 (100.0%)	75 (88.2%)	16 (88.9%)	
Unknown	10 (7.8%)	0 (0.0%)	9 (10.6%)	1 (5.6%)	

Table 1 (cont.) Patient Characteristics between Consolidated and Fragmented Care Groups

INSS Stage					0.31
Stage 2B	1 (0.8%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	
Stage 3	17 (13.3%)	4 (16.0%)	13 (15.3%)	0 (0.0%)	
Stage 4	97 (75.8%)	19 (76.0%)	61 (71.8%)	17 (94.4%)	
Stage 4S	2 (1.6%)	0 (0.0%)	1 (1.2%)	1 (5.6%)	
Stage D	11 (8.6%)	2 (8.0%)	9 (10.6%)	0 (0.0%)	
Surgery Performed	121 (94.5%)	23 (92.0%)	81 (95.3%)	17 (94.4%)	0.84
Days to Surgery from Diagnosis*	113.6 (65.85)	130.0 (24.03)	105.3 (64.80)	129.4 (98.60)	0.26
Complete Resection					0.06
No	36 (28.1%)	10 (40.0%)	19 (22.4%)	7 (38.9%)	
Yes	32 (25.0%)	2 (8.0%)	24 (28.2%)	6 (33.3%)	
Unknown	60 (46.9%)	13 (52.0%)	42 (49.4%)	5 (27.8%)	
Surgical Margins					0.26
No	28 (21.9%)	8 (32.0%)	17 (20.0%)	3 (16.7%)	
Yes	29 (22.7%)	5 (20.0%)	16 (18.8%)	8 (44.4%)	
Unknown	71 (55.5%)	12 (48.0%)	52 (61.2%)	7 (38.9%)	
Surgery Length of Stay (Days)*	6.0 (4.40)	5.4 (5.75)	6.2 (3.75)	7.2 (3.19)	0.04
Readmission Following Surgery	6 (4.7%)	1 (4.0%)	4 (4.7%)	1 (5.6%)	0.81
Number of Central Lines Placed*	3.5 (1.40)	4.4 (1.73)	3.2 (1.16)	4.1 (1.31)	0.002
Central Line Infection	87 (68.0%)	21 (84.0%)	55 (64.7%)	11 (61.1%)	0.34
Number of Line Infections*	1.2 (1.09)	1.5 (0.98)	1.1 (1.12)	1.2 (1.09)	0.11
Days to Chemotherapy from Diagnosis*	6.6 (6.97)	5.2 (4.80)	7.3 (7.88)	5.0 (4.34)	0.44
Treatment Protocol					0.19
ANBL0532	28 (21.9%)	6 (24.0%)	18 (21.2%)	4 (22.2%)	
ANBL12P1	7 (5.5%)	5 (20.0%)	2 (2.4%)	0 (0.0%)	
CCG 3891	10 (7.8%)	1 (4.0%)	6 (7.1%)	3 (16.7%)	
COG A3961	2 (1.6%)	1 (4.0%)	1 (1.2%)	0 (0.0%)	
COG A3973	31 (24.2%)	5 (20.0%)	22 (25.9%)	4 (22.2%)	
N7	12 (9.4%)	0 (0.0%)	9 (10.6%)	3 (16.7%)	
POG 9640	8 (6.3%)	2 (8.0%)	5 (5.9%)	1 (5.6%)	
POG 9340/41/42	6 (4.7%)	0 (0.0%)	6 (7.1%)	0 (0.0%)	
POG 9341/42	6 (4.7%)	1 (4.0%)	5 (5.9%)	0 (0.0%)	
Other	12 (9.4%)	2 (8.0%)	7 (8.2%)	3 (16.7%)	
Unknown	6 (4.7%)	2 (8.0%)	4 (4.7%)	0 (0.0%)	
Treatment Protocol Status					0.66
Enrolled On	42 (32.8%)	8 (32.0%)	30 (35.3%)	4 (22.2%)	
According To	69 (54.0%)	15 (60.0%)	42 (49.4%)	12 (66.7%)	
Unknown	17 (13.3%)	2 (8.0%)	13 (15.3%)	2 (22.2%)	
Number of Chemo Cycles*	6.8 (2.58)	6.5 (1.81)	6.8 (2.86)	7.1 (2.14)	0.49
Radiation Received	124 (96.9%)	25 (100.0%)	81 (95.3%)	18 (100.0%)	0.77
Days to Radiation from Diagnosis*	270.1 (101.64)	268.8 (76.20)	273.0 (108.49)	259.9 (108.53)	0.78
Radiation Modality					0.07
XRT Involved Field	92 (71.9%)	21 (84.0%)	61 (71.8%)	10 (55.6%)	
Proton Beam Therapy	5 (3.9%)	0 (0.0%)	1 (1.2%)	4 (22.2%)	
MIBG Therapy	2 (1.6%)	1 (4.0%)	1 (1.2%)	0 (0.0%)	
TBI	5 (3.9%)	1 (4.0%)	4 (4.7%)	0 (0.0%)	
XRT/TBI	9 (7.0%)	2 (8.0%)	6 (7.1%)	1 (5.6%)	
MIBG + XRT	2 (1.6%)	0 (0.0%)	1 (1.2%)	1 (5.6%)	
MIBG + TBI	1 (0.8%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	
Unknown	12 (9.4%)	0 (0.0%)	10 (11.8%)	2 (11.1%)	

Table 1 (cont.) Patient Characteristics between Consolidated and Fragmented Care Groups

Days of Radiation*	13.7 (6.29)	14.7 (6.61)	12.5 (5.40)	17.4 (8.33)	0.09
Receipt of Immunotherapy	43 (33.6%)	11 (44.0%)	22 (25.9%)	10 (55.6%)	0.03
Distance to Diagnostic Facility					
Median (IQR)	36.2 (21.1-77.5)	78.1 (34.8-123.0)	30.8 (17.4-67.6)	35.6 (28.9-95.0)	0.002
<25th Percentile	31 (24.2%)	1 (4.0%)	27 (31.8%)	3 (16.7%)	0.002
25th – 75th Percentile	65 (50.8%)	11 (44.0%)	44 (51.8%)	10 (55.6%)	
>75th Percentile	32 (25.0%)	13 (52.0%)	14 (16.5%)	5 (27.8%)	
Distance to Chemo Facility					
Median (IQR)	38.5 (21.7-82.5)	78.1 (34.8-123.0)	30.8 (19.1-69.5)	35.6 (28.9-112.0)	0.004
<25th Percentile	32 (25.0%)	1 (4.0%)	28 (32.9%)	3 (16.7%)	0.003
25th – 75th Percentile	64 (50.0%)	12 (48.0%)	43 (50.6%)	9 (50.0%)	
>75th Percentile	32 (25.0%)	12 (48.0%)	14 (16.5%)	6 (33.3%)	
Distance to Surgical Facility					
Median (IQR)	42.0 (21.1-111.0)	78.1 (34.8-150.0)	31.1 (18.3-70.5)	68.8 (33.6-123.0)	0.002
<25th Percentile	29 (22.7%)	1 (4.0%)	25 (29.4%)	3 (16.7%)	0.006
25th – 75th Percentile	61 (47.7%)	12 (48.0%)	42 (49.4%)	7 (38.9%)	
>75th Percentile	30 (23.4%)	10 (40.0%)	13 (15.3%)	7 (38.9%)	
Distance to Radiation Facility					
Median (IQR)	96.8 (33.1-156.0)	78.1 (34.8-123.0)	108.5 (35.0-162.0)	78.5 (32.2-317.0)	0.73
<25th Percentile	30 (23.4%)	6 (24.0%)	19 (22.4%)	5 (27.8%)	0.42
25th – 75th Percentile	61 (47.7%)	16 (64.0%)	38 (44.7%)	7 (38.9%)	
>75th Percentile	30 (23.4%)	3 (12.0%)	21 (24.7%)	6 (33.3%)	
Distance to Duke (BMT Facility)					
Median (IQR)	126.0 (78.2-176.0)	78.1 (34.8-123.0)	134.0 (92.7-178.0)	136.0 (64.0-317.0)	0.006
<25th Percentile	32 (25.0%)	13 (52.0%)	14 (16.5%)	5 (27.8%)	0.001
25th – 75th Percentile	64 (50.0%)	10 (40.0%)	49 (57.6%)	5 (27.8%)	
>75th Percentile	32 (25.0%)	2 (8.0%)	22 (25.9%)	8 (44.4%)	
Distance to Immunotherapy Facility					
Median (IQR)	86.3 (32.7-155.0)	57.8 (28.5-121.0)	68.6 (26.9-125.0)	529.0 (121.0-567.0)	0.003
<25th Percentile	10 (7.8%)	3 (12.0%)	7 (8.2%)	0 (0.0%)	0.008
25th – 75th Percentile	22 (17.2%)	8 (32.0%)	11 (12.9%)	3 (16.7%)	
>75th Percentile	10 (7.8%)	0 (0.0%)	4 (4.7%)	6 (33.3%)	
Furthest Distance Traveled (Excluding BMT)**	113.0 (40.8-224.5)	78.1 (34.8-123.0)	96.8 (32.3-174.0)	492.0 (193.0-567.0)	0.001

ǂ Percentages are out of total population counts unless otherwise indicated and may not add up to 100% due to rounding or missing values
* Values presented are Mean (SD)
** Values presented are Median (IQR)

Table 2: Complications between Consolidated and Fragmented Care Groups

	All Patients (N=128)	Consolidated Care (N=25)	Fragmented Care 2 Facilities (N=85)	Fragmented Care >2 Facilities (N=18)	P-Value
Minor Chemo Complications	117 (91.4%)	24 (96.0%)	77 (90.6%)	16 (88.9%)	1.00
Major Chemo Complications	10 (7.8%)	4 (16.0%)	4 (4.7%)	2 (11.1%)	0.13
Minor Surgical Complications	24 (18.8%)	6 (24.0%)	14 (16.5%)	4 (22.2%)	1.00
Major Surgical Complications	12 (9.4%)	4 (16.0%)	6 (7.1%)	2 (11.1%)	1.00
Minor Central Line Complications	98 (76.6%)	21 (84.0%)	64 (75.3%)	13 (72.2%)	0.86
Major Central Line Complications	71 (55.5%)	20 (80.0%)	42 (49.4%)	9 (50.0%)	0.09
Minor BMT Complications	128 (100%)	25 (100.0%)	85 (100%)	18 (100.0%)	----
Major BMT Complications	15 (11.7%)	7 (28.0%)	6 (7.1%)	2 (11.1%)	0.02
Minor Radiation Complications	14 (10.9%)	4 (16.0%)	5 (5.9%)	5 (27.8%)	0.28
Major Radiation Complications	2 (1.6%)	1 (4.0%)	0 (0.0%)	1 (5.6%)	0.22
Minor Immunotherapy Complications	26 (20.3%)	8 (32.0%)	15 (17.6%)	3 (16.7%)	1.00
Major Immunotherapy Complications	2 (1.6%)	0 (0.0%)	2 (2.4%)	0 (0.0%)	1.00
Thrombotic Complications	32 (25.0%)	4 (16.0%)	24 (28.2%)	4 (22.2%)	0.56
Any Major Complication	81 (63.3%)	22 (88.0%)	49 (57.6%)	10 (55.6%)	0.01
Any Major Complication (Excluding Central Lines)	31 (24.2%)	11 (44.0%)	17 (20.0%)	3 (16.7%)	0.04

* Major complications defined as those requiring invasive intervention or resulting in serious disability or death
** Complications requiring removal/replacement of a central line were considered major

Table 3: Univariate and Multivariate Models for Overall Survival (OS)

			Univariate			Multivariate**		
	N	Deaths*	HR (95% CI)	P-Value	Overall P-Value	HR (95% CI)	P-Value	Overall P-Value
Age at diagnosis (years)	127	3.0 (1.0 - 4.0)	1.048 (0.953 - 1.153)	0.33	0.33			
Number of central line infections	103	1.0 (1.0 - 2.0)	1.207 (0.954 - 1.529)	0.12	0.12			
Number of central lines	115	3.0 (2.0 - 5.0)	1.052 (0.860 - 1.289)	0.62	0.62			
Care Fragmentation					0.10			0.21
Coordinated Care	25	9 (36.0%)	Reference			Reference		
Fragmented Care (2 Locations)	84	40 (47.6%)	1.116 (0.539 - 2.312)	0.77		0.855 (0.389 - 1.879)	0.70	
Fragmented Care (>2 Locations)	18	12 (66.7%)	2.173 (0.912 - 5.179)	0.08		1.539 (0.607 - 3.901)	0.36	
Year of Diagnosis					0.002			0.024
1990-1999	41	32 (78.0%)	Reference			Reference		
2000-2009	50	20 (40.0%)	0.409 (0.231 - 0.723)	0.002		0.472 (0.263 - 0.847)	0.012	
2010-2017	36	9 (25.0%)	0.378 (0.178 - 0.799)	0.011		0.480 (0.220 - 1.045)	0.06	
Histological Favorability					0.17			
Favorable	2	2 (100.0%)	Reference					
Unfavorable	71	24 (33.8%)	0.362 (0.085 - 1.538)	0.17				
Surgery before Chemotherapy					0.51			
No	97	41 (42.3%)	Reference					
Yes	21	11 (52.4%)	1.250 (0.639 - 2.448)	0.51				
Chemotherapy Protocol					0.014			
Other	35	17 (48.6%)	Reference					
ANBL0532	28	11 (39.3%)	1.090 (0.502 - 2.366)	0.83				
COG A3973	30	9 (30.0%)	0.474 (0.208 - 1.079)	0.08				
CCG 3891	10	8 (80.0%)	2.098 (0.893 - 4.929)	0.09				
N7	12	6 (50.0%)	0.816 (0.317 - 2.096)	0.67				
POG 9341/2	12	10 (83.3%)	2.089 (0.944 - 4.624)	0.07				
Chemotherapy On/Off Protocol					0.043			
No	67	24 (35.8%)	Reference					
Yes	41	23 (56.1%)	1.810 (1.019 – 3.218)	0.043				
Home Distance to Chemotherapy Facility					0.96			
25-75th percentile	63	30 (47.6%)	Reference					
<25th percentile	32	15 (46.9%)	1.007 (0.536 - 1.891)	0.98				
>75th percentile	32	16 (50.0%)	1.085 (0.587 - 2.007)	0.79				
Home Distance to Duke (BMT Facility)					0.002			0.043
25-75th percentile	63	24 (38.1%)	Reference			Reference		
<25th percentile	32	13 (40.6%)	1.026 (0.509 - 2.067)	0.94		1.005 (0.481 - 2.098)	0.99	
>75th percentile	32	24 (75.0%)	2.612 (1.477 - 4.618)	<0.001		2.060 (1.135 - 3.741)	0.018	
Immunotherapy					0.09			
No	82	48 (58.5%)	Reference					
Yes	43	12 (27.9%)	0.573 (0.303 - 1.085)	0.09				

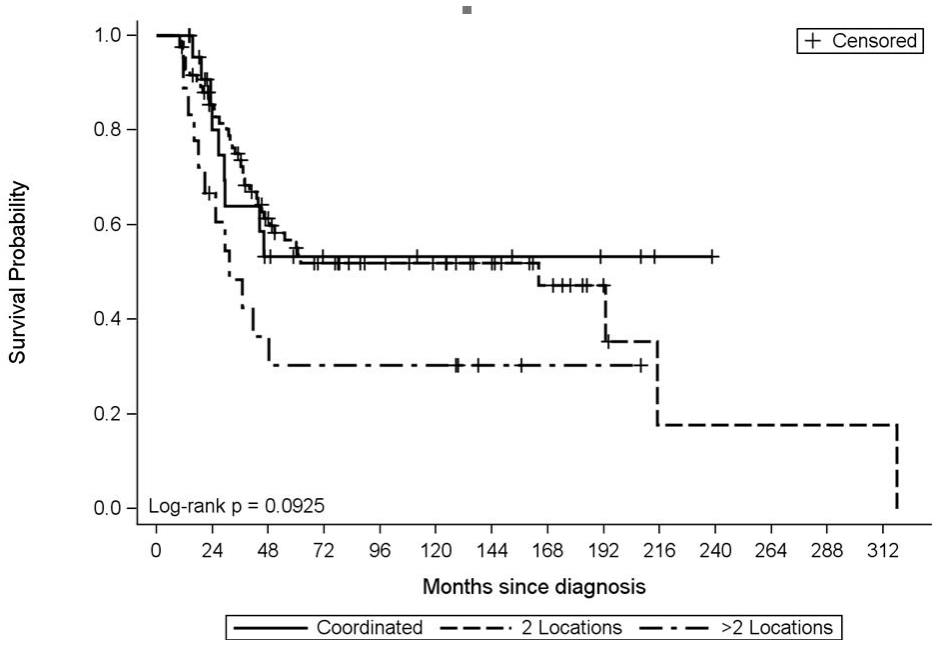
*N (%) of patients who died in each category. For continuous variables, median (Q1 – Q3) are presented of patients who died.
**Values may not align exactly with Table 1 due to missing survival or covariate information for some patients.

Table 4: Univariate and Multivariate Models for Relapse

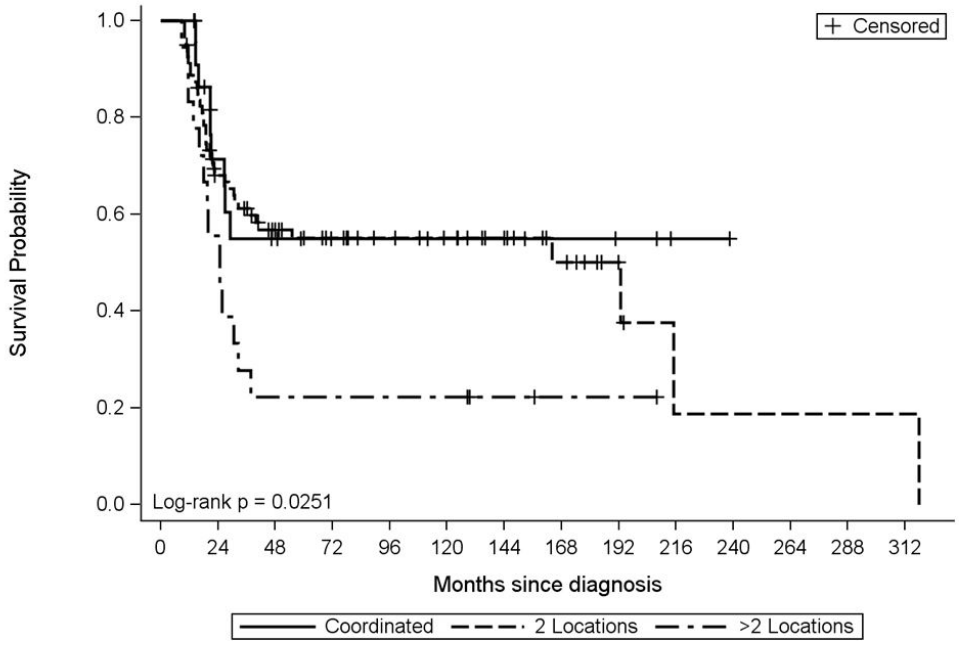
			Univariate			Multivariate**		
	N	Deaths*	HR (95% CI)	P-Value	Overall P-Value	HR (95% CI)	P-Value	Overall P-Value
Age at diagnosis (years)	123	3.0 (1.0 - 4.0)	1.032 (0.939 - 1.134)	0.51	0.51			
Number of central line infections	100	1.0 (1.0 - 2.0)	1.158 (0.911 - 1.472)	0.23	0.23			
Number of central lines	112	3.0 (2.0 - 5.0)	1.073 (0.883 - 1.304)	0.48	0.48			
Care Fragmentation					0.031			0.10
Coordinated Care	25	9 (36.0%)	Reference			Reference		
Fragmented Care (2 Locations)	80	38 (47.5%)	1.209 (0.582 - 2.511)	0.61		0.939 (0.434 - 2.029)	0.87	
Fragmented Care (>2 Locations)	18	14 (77.8%)	2.583 (1.113 - 5.990)	0.027		1.847 (0.758 - 4.497)	0.18	
Year of Diagnosis					0.007			0.05
1990-1999	39	30 (76.9%)	Reference			Reference		
2000-2009	48	20 (41.7%)	0.466 (0.262 - 0.830)	0.010		0.524 (0.289 - 0.949)	0.033	
2010-2017	36	11 (30.6%)	0.395 (0.196 - 0.798)	0.010		0.493 (0.238 - 1.024)	0.06	
Histological Favorability					0.003			
Favorable	2	2 (100.0%)	Reference					
Unfavorable	68	23 (33.8%)	0.090 (0.018 - 0.437)	0.003				
Surgery before Chemotherapy					0.48			
No	94	42 (44.7%)	Reference					
Yes	21	11 (52.4%)	1.274 (0.652 - 2.489)	0.48				
Chemotherapy Protocol					0.06			
Other	35	18 (51.4%)	Reference					
ANBL0532	28	12 (42.9%)	1.006 (0.478 - 2.119)	0.99				
COG A3973	28	9 (32.1%)	0.536 (0.238 - 1.209)	0.13				
CCG 3891	9	7 (77.8%)	2.152 (0.887 - 5.222)	0.09				
N7	12	6 (50.0%)	0.805 (0.316 - 2.051)	0.65				
POG 9341/2	11	9 (81.8%)	1.847 (0.820 - 4.158)	0.14				
Chemotherapy On/Off Protocol					0.05			
No	65	25 (38.5%)	Reference					
Yes	39	22 (56.4%)	1.774 (0.997 – 3.158)	0.05				
Home Distance to Chemotherapy Facility					0.83			
<25th percentile	30	14 (46.7%)	Reference					
25-75th percentile	61	30 (49.2%)	0.948 (0.498 - 1.806)	0.87				
>75th percentile	32	17 (53.1%)	1.142 (0.561 - 2.324)	0.71				
Home Distance to Duke (BMT Facility)					0.003			0.09
<25th percentile	32	13 (40.6%)	Reference			Reference		
25-75th percentile	62	27 (43.5%)	1.226 (0.618 - 2.434)	0.56		0.845 (0.414 - 1.722)	0.64	
>75th percentile	29	21 (72.4%)	2.876 (1.397 - 5.922)	0.004		1.798 (0.983 - 3.289)	0.06	
Immunotherapy					0.10			
No	78	45 (57.7%)	Reference					
Yes	43	15 (34.9%)	0.612 (0.339 - 1.104)	0.10				

*N (%) of patients who died in each category. For continuous variables, median (Q1 – Q3) are presented of patients who died.
**Values may not align exactly with Table 1 due to missing relapse or covariate information for some patients.

Figure 2. Kaplan-Meier Analysis for Overall Survival (OS) and Relapse



(A) Kaplan-Meier Curve for OS



(B) Kaplan-Meier for Relapse-Free Survival

Appendix A: Living Remotely from Pediatric Cancer Treatment and the Effect on Survival and Treatment-Related Outcomes: A Systematic Review

Introduction

Delivering safe and effective pediatric cancer treatment requires multiple, complex therapeutic modalities and collaboration between many providers across myriad clinical specialties. To ensure best practice, the American Academy of Pediatrics (AAP) has established guidelines for pediatric cancer centers in an effort to centralize and coordinate care for both patients and providers. These recommendations include that pediatric cancer centers must be equipped with a board-certified pediatric oncologist; appropriately qualified medical and surgical pediatric subspecialists; access to a pediatric ICU, hemodialysis, and up-to-date imaging and radiotherapy; and the capability to deliver multidisciplinary care.[1] Additionally, the Children's Oncology Group (COG) has enrolled many such specialized institutions in an effort to more effectively enroll and treat pediatric cancer patients on appropriate clinical trials.[2] Presently, over 90% of pediatric cancer patients are treated at COG-member institutions.[2] These coordinated efforts and therapeutic innovations have led to survival rates over 80% for many pediatric cancer patients.[3]

However, accessing treatment at COG-member institutions or similarly-equipped centers may prove challenging for many patients and their families. While the COG has significantly expanded its reach since its inception, the 194 US institutions are located predominately in urban and metropolitan areas.[2] However, approximately 20% of the US population lives in rural areas often far removed such population centers.[4] As a result, many families may face a significant travel burden associated with treatment at COG-member institutions.

The financial and psychosocial burden associated with increased travel for pediatric cancer patients has been well documented. Families who live far removed from appropriate treatment frequently pay more in travel costs and accommodations, often must take excessive time off work, and may utilize savings to afford treatment.[5-10] The excess financial burden associated with travel also poses detriment to many families' ability to cope with their situation. Additionally, receiving treatment far away means that patients and their immediate families are often separated from home support, feel a lack of coordination and trust in local providers, must take on increased responsibility during the treatment process, and face feelings of isolation.[11-13]

Regarding survival and treatment-related outcomes, there have been myriad studies examining the association of distance to survival and/or treatment-related outcomes in adult healthcare. A recent systematic review by Kelly et al. demonstrated that increased travel distance to health services may be associated with poorer outcomes for adults.[14] Additionally, for adult cancer patients, some studies have shown that those who live further from major treatment centers may present with later stage disease, receive different treatments than their closer counterparts, and experience worsened survival outcomes.[15-17] However, comparably sparse literature has examined the association between travel burden and similar outcomes for pediatric cancer patients.

Accordingly, the aim of this systematic review is to synthesize the published literature describing the effect of travel burden on survival and treatment-related outcomes for pediatric cancer patients and families living far removed from appropriate treatment. We hypothesized that increased distance would be associated with decreased survival, access to appropriate care, and enrollment on clinical trials.

Methods

Search Strategy

We searched PubMed, EMBASE, and Scopus electronic databases through March 22, 2019. Basic search criteria included English-language studies with terms relevant to pediatric cancer care and distance/travel to treatment. We reviewed all available citations published after 1986, which is the aforementioned date of the first AAP published guidelines for pediatric cancer centers and treatment. A full search strategy is detailed in Figure A-1.

Selection Criteria

To be eligible for inclusion, studies needed to be (1) full-text, peer-reviewed articles, (2) focus on pediatric cancer patients, and (3) describe a relationship between distance/travel to treatment and overall survival or treatment-related outcomes such as treatments received, place of care, disease stage, and clinical trial participation. Studies examining urban vs rural residence as a proxy for distance were also included. Studies were excluded if they did not examine geographic relation to treatment as an exposure or if comparisons between geographic regions (i.e. Northeast vs. Southeast) was the measure of comparison. Additionally, studies examining the experiences of families traveling to other countries for advanced treatment were excluded. An age of 21 years was chosen as a cutoff for pediatric patients as many of these patients may still be treated at children's cancer facilities. Studies examining patients aged >21 years were included if appropriate subset analysis for children aged <21 years was conducted. Importantly, however, any studies that self-identified as focusing on a teen and young adult (TYA) population were excluded due to wide variation in care and practice patterns for young adults (such as variable treatment at adult vs pediatric centers), unless appropriate subset analysis was conducted. Finally, those studies focusing only on financial or psychosocial outcomes were

excluded because of the influence of myriad factors aside from travel distance. A full, detailed table of inclusion and exclusion criteria can be found in Table A-1.

Data Collection Process

Following the deletion of duplicate articles, all articles derived from the three databases were independently screened by two reviewers (AT and LO) using Covidence™ software using criteria summarized in Table A-1. The full-text articles of titles and abstracts marked as potentially relevant were reviewed again to confirm eligibility using the same criteria. Any disagreement was resolved by consensus-based decision.

Data Extraction

Data extraction was performed using a standardized form to ensure collection of each variable of interest. Each study had relevant information extracted independently by two reviewers (AT and LO) with any discrepancies resolved by consensus in order to ensure quality of extraction. Variables of interest included the study location, year of publication, population studied, study design, type of cancer (if stratified), measurement of distance, potential socioeconomic and clinical confounders, outcomes measured, statistical methods used, and results with regard to measured outcomes.

Summary Measures and Results Synthesis

Overall study characteristics were first reported by study design, study population, type of cancer analyzed, and by distance measure utilized. Results were then reported and summarized by their relationship of distance/travel to either survival outcomes or treatment

related outcomes. Due to the heterogeneity in study design and measured outcomes, meta-analysis was not performed. Descriptive statistics and univariate results were not presented when multivariate analysis with adjustment was conducted, and results were presented with reporting of overall conclusions and effect.

Analysis of Quality and Potential Bias

Each study was individually assessed for risk of bias using the Newcastle-Ottawa Quality Assessment Scale (NOQAS), modified slightly to fit different study designs. Two authors (AT and LO) reviewed each study and results were compared. All discrepancies were resolved by consensus-based decision. Risk of bias across similar studies was analyzed from the perspective of potential publication bias, consistency of findings, and overall strength of association.

Results

Study Selection and Characteristics

Following the removal of duplicates, the literature search identified 7,607 articles eligible for title and abstract screening. Of these, 106 studies were assessed during full-text review. Ultimately, 24 studies were included in the final analysis.[18-41] The most common reasons for exclusion included a focus primarily on young adults, no analysis based on distance, or an incorrect outcome or study design. Of the included studies, 20 were retrospective cohort studies[18-22,24,25,28,29,31-41], two were prospective cohort studies[23,30], one was cross-sectional[26], and one was a case-control study[27].

In terms of population, most focused on pediatric cancers overall. However, specific cancers analyzed included any CNS tumors[20,26,39], any non-CNS solid tumors[21,26,36], leukemias[23,26,28,35], medulloblastoma[31,33], retinoblastoma24, and melanoma[29]. Tools and methods

used to measure distance varied significantly, including use of the Great Circles Algorithm[18,32,36], distance between midpoints of home address and treating facility[19,22,38], and road driving distance using either ArcGIS or Google Maps.[19,20,29,35,39] The distance traveled was categorized variably and ranged from 0-5 miles[19] to 300+ miles.[38] Rurality of residence was used as a proxy for geographic access (either in place of or in addition to mileage) in 9 studies.[24,25,26,28,31,33,35,36,41] Three studies included analysis of adults or young adults but also included appropriate subset analysis for children.[18,25,39] Most studies were rated as good, with those receiving fair or poor ratings due largely to lack of appropriate multivariate adjustment. These characteristics, outcomes, and quality assessments can be seen in Tables A2 – A4.

Survival Outcomes

Of the 24 included studies, 12 included survival as an outcome measurement.[20,21,23,28,29,31,33,35,37,39,41] All but 2 used a measure of overall survival (OS) as the outcome. Those other two focused on retinoblastoma-specific mortality and event-free survival, respectively.[24.28] In 5 of 12 studies, distance was not included in a multivariate survival analysis.[28,29,31,37,39] Ultimately, no studies found an association between travel distance and survival, in either univariate or multivariate analysis. Covariates commonly controlled for included age, sex, race, and disease stage when available. However, three studies demonstrated worsened survival outcomes for those living in rural counties as compared to urban counties closer to treatment centers.[24,31,41] Tai et al. conducted a population-based study only examining cancer-specific mortality rates for adolescents and did not analyze factors associated with survival. However, they found worsened cancer-specific mortality closest to COG centers.

Treatment-Related Outcomes

Of the 24 included studies, 19 examined outcomes related to treatment or place of care.[18-22,25-27,30-32,34,36,38,39] Specific outcomes measured included the likelihood of receiving care at specialized pediatric cancer centers[18,19,22,39,40], likelihood of advanced stage presentation at diagnosis[20,21,29,41], clinical trial participation[25,34], likelihood of receiving proton beam therapy or hematopoietic stem cell transplantation (HSCT)[31,32,36,38], length of stay for febrile neutropenia patients[19], use of emergency transportation[26], likelihood of same-day cancellation[27], and waiting times.[30] Travel distance >40 miles was associated with a decreased likelihood of receiving care at specialized pediatric cancer centers, but living 6-20 miles away was associated with an increased likelihood compared to 0-5 miles away.[19] Increasing travel distance was also associated with more care received at local facilities than specialized ones located further away.[40] There was no demonstrated association between travel distance and disease stage at first presentation or diagnosis. One of the two studies examining clinical trial enrollment found that enrollment decreased with every 100km away from specialized treatment[34], but the other found no association.[25] Results regarding the effect of distance on receipt of particular therapies were inconsistent, with 2 of 4 studies demonstrating increased odds of receiving proton beam therapy (HSCT)[36,38], one showing decreased follow-up after proton therapy for those living >300km away[32], and the fourth demonstrating that distance had no significant effect on treatment.[31] Finally, increasing travel distance/time was associated with greater need for emergency transportation and shorter length of stay[26,19] but not with same-day cancellations or waiting times.[27,30]

Discussion

To our knowledge, this is the first systematic review synthesizing and compiling studies that examined the potential effect of travel distance and/or rurality on both survival and treatment-related outcomes for pediatric cancer patients. Across all 24 included studies, there was no consistent association between travel distance/rurality and measured clinical outcomes. Some studies demonstrated that those from rural settings had decreased survival compared to their urban or metropolitan counterparts[24,31,41], but these results were tenuous at best given minimal multivariate analysis or adjustment for relevant covariates. More studies demonstrated an association between travel distance/rurality and select outcomes such as place of care, clinical trial participation, and receipt of particular complex treatment modalities. However, the direction of effect was inconsistent, with several studies unexpectedly demonstrating increased likelihood of receiving proton therapy, HSCT, or shorter hospital stays when diagnosed with febrile neutropenia for those living further away.[19,36,38] Together, these studies suggest that those living furthest away from treatment are not at increased risk for poor outcomes and that other socioeconomic and patient characteristics are more significant for ensuring best treatment practices and improving survival.

Effectively treating pediatric cancer frequently requires utilization of multiple, complex therapeutic modalities, including surgery and HSCT for select cancers. For adult cancer patients, an abundance of literature demonstrates that survival outcomes are improved at high-volume centers in major metropolitan areas.[42-47] Additionally, Lidsky et al. found that pancreatic patients undergoing pancreaticoduodenectomy at high-volume centers, even after accounting for the increased travel burden to get there, had superior survival outcomes relative to those traveling a shorter distance to low-volume centers.[48] Similarly, it is well-established that high survival rates for pediatric cancer patients can largely be attributed to receipt of care at specialized institutions.

These results and the findings of this review suggest that seeking care at such places is likely to result in improved survival outcomes for pediatric cancer patients, even if it means overcoming a significant travel burden.

Studies examining the effect of travel on treatment-related outcomes had more variable results. Those that had to travel further were not at increased likelihood of having advanced stage disease or experiencing increased waiting times at specialized facilities, indicating that disease progression is likely a more protracted process and that rural patients need not worry about receiving delayed or inferior care. These results run counter to findings for adult oncology patients that rural patients are more likely to experience delays throughout the treatment process.[49] While encouraging for pediatric cancer patients, Klein-Getlink et al. conducted their study in Canada, where treatment times and processes may be different than in the US due to a national health system. Moreover, Fluchel et al. demonstrated that patients with increased travel times or from rural areas utilized emergency transportation at higher rates.[26] This may result from a need for rapid and effective transportation in the event of complications or emergencies occurring at home. Families living far removed from specialized centers must often take on increased responsibility for home care and management of factors such as central lines, creating a nidus for increased complications.[50]

Only one of two studies demonstrated decreased clinical trial enrollment with increased travel burden, and that studied was conducted in Canada.[34] Much of pediatric cancer treatment in the US occurs through clinical trial-directed therapy, despite variable reported outcomes.[2,51] As such, it is essential to ensure that pediatric cancer patients have equitable access to clinical trials. That same study found that physician preference was a major reason for trial non-enrollment.[34] Physicians may be more reluctant to enroll patients on clinical trials with strict guidelines when

regular travel to treatment may pose a significant barrier. Paradoxically, 2 studies also found that living further away from centers equipped to deliver proton therapy or HSCT was associated with increased likelihood of receiving those treatments.[36,38] However, in the study by Shen et al., that effect was only present when further stratifying by income. Several other studies have shown either no effect of distance or place of residence or have demonstrated decreased likelihood of receiving HSCT for those living further away.[52-54] Truong et al. suggest that patients living closer to specialized treatment facilities may be offered more experimental and investigative therapies than HSCT.[38] However, the overall lack of association between distance and clinical trial enrollment, which are often experimental in nature, would suggest the opposite.

Due to the rarity and complexity of pediatric cancer, traversing large distances to specialized institutions for treatment may be unavoidable for many patients and families. As such, the results of this review are encouraging in demonstrating no effect of travel distance on various outcomes overall. Given the well-documented financial and psychosocial burden associated with increased travel for pediatric cancer patients and families, patients may choose to receive some elements of care at local facilities and avoid unnecessary travel where possible. In these circumstances, it is essential to ensure that local, unspecialized facilities and providers are adequately equipped to provide high-quality treatment. This might be accomplished through increased investment in pediatric cancer care and potentially by use of telemedicine modalities to share with rural facilities expertise that is otherwise concentrated at select, specialized centers.[55]

While somewhat minimal and inconsistent, the results that were significant in this study were primarily found with comparisons of rurality rather than actual travel distance. We elected to include rurality comparisons as a distance proxy because of the urban locations of many specialized pediatric cancer centers. However, rurality status is an imperfect proxy because that

status does not truly incorporate the distance that patients might travel to treatment. Moreover, the methods used to determine or classify rurality was inconsistent across studies, with some using census continuums and others self-stratifying based on populations of individual areas. The discrepancy between significant results by rurality but not by travel distance may be reflective of additional socioeconomic factors relevant to those from rural areas. Some studies adjusted for such socioeconomic factors well, but not all did so or utilized multivariate analysis. Therefore, any conclusions for those from rural areas must be taken lightly with regard to evaluations of the effects of travel distance to treatment.

Importantly, we chose to restrict our review to studies examining pediatric and adolescent patients aged <21 and excluded any studies examining older young adults. Increasingly, the adolescent and young adult population (AYA), sometimes defined as ages 15-29 and others as ages 15-39, is recognized as a separate patient population for cancer treatment. Recommendations and practice guidelines for this group differ significantly from those for pediatric cancer patients. While excluded from our review because of these differences, a growing body of literature has recognized disparities in access to and treatment at pediatric cancer centers associated with increasing age and travel distance for AYA patients.[56-63] These discrepancies may result from older adolescents increasingly being treated at adult centers closer to home. Comprehensively reviewing the literature for AYA patients is outside the scope of this review, but a similar systematic review of the effects of distance and geographic relation to treatment for this patient population may be warranted.

This review has several important limitations. First, our search strategy and inclusion criteria may have missed relevant articles. However, the searches of multiple databases and independent review by 2 authors using the same criteria minimized this risk. Second, we elected

to include studies from all countries in which the COG operates as treatment for pediatric cancers is likely to be more uniform and standardized. We also chose a cutoff date of 1986 following the first AAP pediatric cancer center recommendations, even though those recommendations may not be relevant in other countries. The inclusion of studies outside the US may minimize generalizability due to differences in health systems and transportation, but our focus on survival and treatment-related outcomes rather than financial burden or psychosocial outcomes minimized this potential discrepancy. Third, the included body of literature had limitations. While most studies were retrospective cohort studies, there was significant heterogeneity in study design, distance measurement, and confounder adjustment, limiting direct comparison or possible meta-analysis. Third, no studies tracked the cumulative distance traveled by patients during the entire course of treatment. This may be more indicative of potential travel burden but is challenging to impossible to measure with retrospective studies.

Conclusion

This review has synthesized findings about the effects of travel distance to treatment and/or rural residence for pediatric cancer patients with regard to survival and treatment-related outcomes. Several studies demonstrated worsened survival outcomes for those living in more rural areas and decreased clinical trial enrollment, greater likelihood of receiving proton therapy and HSCT, and shorter hospital stays for febrile neutropenia patients associated with increased travel distance. However, results were inconsistent and varied overall, leading to a final conclusion that living further away from treatment centers does not confer poorer outcomes. These findings are valuable for rural patients and families who must overcome a significant travel burden in order to access and receive high-quality care.

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Table A1: Study Inclusion and Exclusion Criteria

Criteria	Include	Exclude
Population(s)	• Children (<21 years) • Cancer diagnosis	• Adults • TYA-specific population • Other non-cancer diagnoses
Exposure	• Distance/travel to treatment or hospitals	• Survivorship care • Between-country travel
Comparison(s)	•	•
Outcome(s)	• Survival • Clinical or treatment-related outcomes (i.e. treatment adherence, place of care, disease stage, complications, etc)	• Incidence/prevalence of cancer • Financial outcomes • Psychosocial outcomes
Timing	• 1986 - Present	• Prior to 1986
Setting(s)	• Clinical/hospital settings • US, Canada, Europe, New Zealand, Australia	• Community Settings • Other Countries
Study Design(s)	• Prospective and retrospective cohort, case-control, cross-sectional	• Editorials, position/opinion pieces, news articles, case reports/series, pilot studies
Language	• English	•

Figure A1: Pubmed, EMBASE, and Scopus Search Strategy

Database (including vendor/platform): PubMed

Set #		Results
1	**"Pediatrics"[Major] OR pediatric[tiab] OR pediatrics[tiab] OR paediatric[tiab] OR paediatrics[tiab] OR juvenile[tiab] OR "Child"[Major] OR child[tiab] OR children[tiab] OR childhood[tiab] OR teenage[tiab] OR adolescent[tiab] OR adolescents[tiab]**	1,615,336
2	**"Neoplasms"[Mesh] OR neoplasms[tiab] OR neoplasm[tiab] OR cancer[tiab] OR cancers[tiab] OR malignant[tiab] OR malignancy[tiab] OR malignancies[tiab] OR oncology[tiab] OR oncologic[tiab] OR tumor[tiab] OR tumors[tiab] OR tumours[tiab] OR tumour[tiab]**	3,977,881
3	**Travel[mesh] OR travel[tiab] OR traveling[tiab] OR travelling[tiab] OR traveled[tiab] OR travelled[tiab] OR distance[tiab] OR distances[tiab] OR distantly[tiab] OR location[tiab] OR locations[tiab] OR located[tiab] OR remote[tiab] OR remotely[tiab] OR rural[tiab] OR geography[tiab] OR geographic[tiab] OR geographical[tiab] OR geographically[tiab]**	1,253,170
4	**treatment[tiab] OR treatments[tiab] OR cancer care[tiab] OR hospital[tiab] OR hospitals[tiab] OR center[tiab] OR centers[tiab] OR facility[tiab] OR facilities[tiab] OR site[tiab] OR sites[tiab] OR clinic[tiab] OR clinics[tiab]**	6,553,853
5	1 AND 2 AND 3 AND 4	5,286
6	NOT (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	5,272

Database (including vendor/platform): Embase (Elsevier)

Set #		Results
1	'pediatrics'/mj **OR pediatric:ti,ab OR pediatrics:ti,ab OR paediatric:ti,ab OR paediatrics:ti,ab OR juvenile:ti,ab OR** 'child'/mj **OR child:ti,ab OR children:ti,ab OR childhood:ti,ab OR teenage:ti,ab OR adolescent:ti,ab OR adolescents:ti,ab**	2,219,992
2	**'neoplasm'/exp OR neoplasms:ti,ab OR neoplasm:ti,ab OR cancer:ti,ab OR cancers:ti,ab OR malignant:ti,ab OR malignancy:ti,ab OR malignancies:ti,ab OR oncology:ti,ab OR oncologic:ti,ab OR tumor:ti,ab OR tumors:ti,ab OR tumours:ti,ab OR tumour:ti,ab**	5,523,734
3	**'travel'/exp OR travel:ti,ab OR traveling:ti,ab OR travelling:ti,ab OR traveled:ti,ab OR travelled:ti,ab OR distance:ti,ab OR distances:ti,ab OR distantly:ti,ab OR location:ti,ab OR locations:ti,ab OR located:ti,ab OR remote:ti,ab OR remotely:ti,ab OR rural:ti,ab OR geography:ti,ab OR geographic:ti,ab OR geographical:ti,ab OR geographically:ti,ab**	1,537,214
4	**treatment:ti,ab OR treatments:ti,ab OR 'cancer care':ti,ab OR hospital:ti,ab OR hospitals:ti,ab OR center:ti,ab OR centers:ti,ab OR facility:ti,ab OR facilities:ti,ab OR site:ti,ab OR sites:ti,ab OR clinic:ti,ab OR clinics:ti,ab**	9,149,450
5	1 AND 2 AND 3 AND 4	10,462
6	AND ([article]/lim OR [article in press]/lim OR [erratum]/lim OR [review]/lim OR [short survey]/lim)	5,893

Database (including vendor/platform): Scopus (Elsevier)

Set #		Results
1	**TITLE-ABS (pediatric OR pediatrics OR paediatric OR paediatrics OR juvenile OR child OR children OR childhood OR teenage OR adolescent OR adolescents)**	2,316,228
2	**TITLE-ABS (neoplasms OR neoplasm OR cancer OR cancers OR malignant OR malignancy OR malignancies OR oncology OR oncologic OR tumor OR tumors OR tumours OR tumour)**	3,350,005
3	**TITLE-ABS (travel OR traveling OR travelling OR traveled OR travelled OR distance OR distances OR distantly OR location OR locations OR located OR remote OR remotely OR rural OR geography OR geographic OR geographical OR geographically)**	1,537,214
4	**TITLE-ABS(treatment OR treatments OR "cancer care" OR hospital OR hospitals OR center OR centers OR facility OR facilities OR site OR sites OR clinic OR clinics)**	11,152,836
5	1 AND 2 AND 3 AND 4	10,462
6	AND (EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "ed"))	5,318

Figure A2: PRISMA Flow Diagram

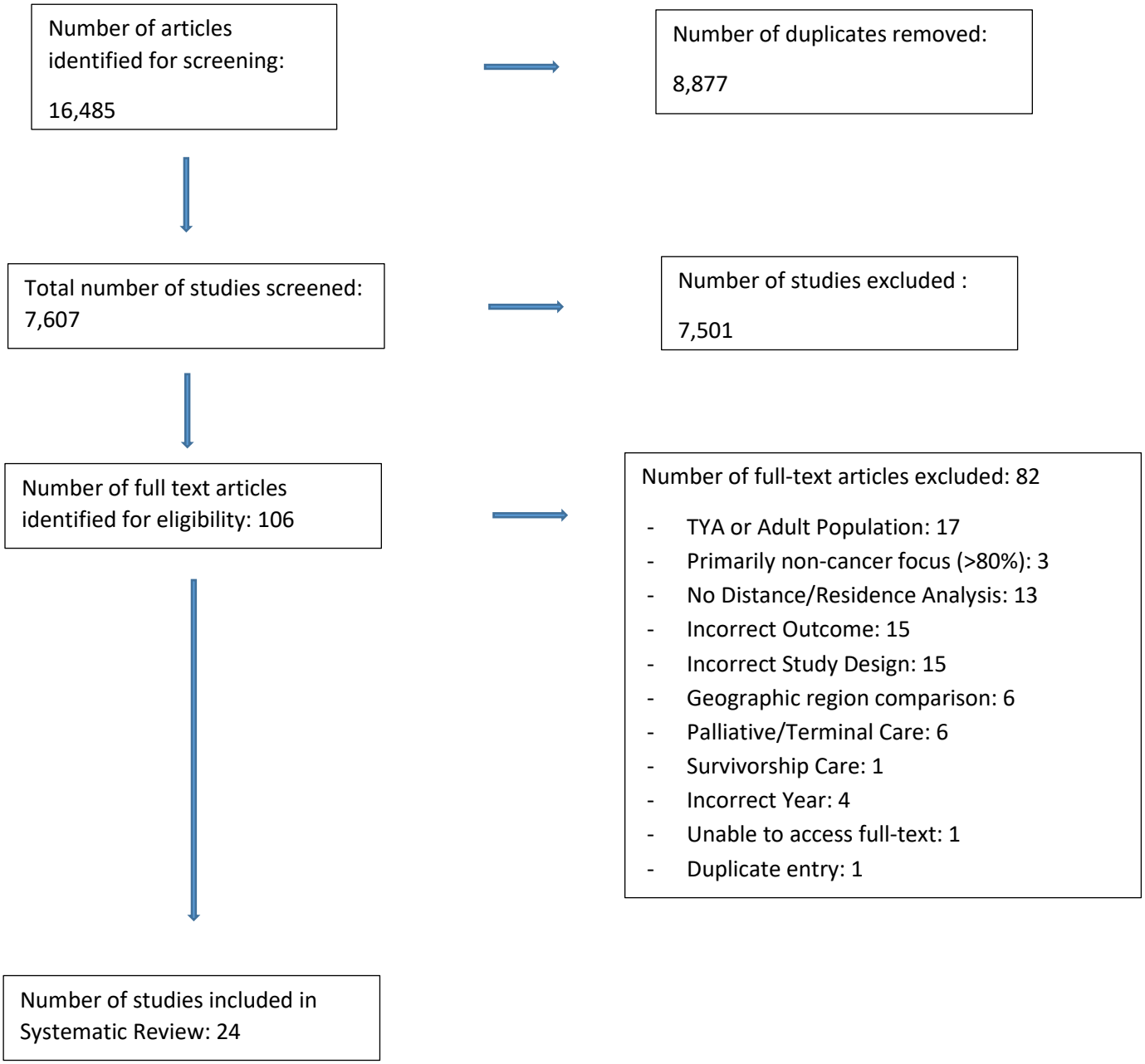

Table A2: Survival Studies Characteristics and Results

Study	Study Time	Location	Study Type	Case-Control Details	Data Sources	Pop.	Age Range	Overall Sample Size	Cancer Type	Sub-Group Analysis For Age	Sub-Group Age Range	Sub-Group Sample Size
Austin et al. (2016)	1995 - 2009	Texas	Retrospective Cohort	N/A	State Clinical Database	Pts	0-18	2,421	CNS Solid Tumors	N	*n/a*	*n/a*
Austin et al. (2015)	1995 - 2009	Texas	Retrospective Cohort	N/A	State Clinical Database	Pts	0-18	4,630	Non-CNS Solid Tumors	N	*n/a*	*n/a*
Charalampopoulou et al. (2004)	1996-2002	Greece	Prospective Cohort	N/A	Hospital records from 4/6 heme/onc units in Greece	Pts	Not Specified	293	ALL	N	*n/a*	*n/a*
Cheung (2013)	Not Stated	USA	Retrospective Cohort	N/A	National Clinical Database	Pts	Not Specified	1,456	Retinoblastoma (Rb)	N	*n/a*	*n/a*
Gupta et al. (2014)	1995 - 2011	Ontario	Retrospective Cohort	N/A	Multiple databases; hospital records	Pts	0-18	1541	Primary ALL	N	*n/a*	*n/a*
Hamilton et al. (2016)	1995 - 2009	Texas	Retrospective Cohort	N/A	State Clinical Database	Pts	0-18	235	Melanoma	N	*n/a*	*n/a*
Kopecky et al. (2017)	2004 - 2009	USA	Retrospective Cohort	N/A	National Clinical Database	Pts	0-19	783	Medulloblastoma (Mb)	N	*n/a*	*n/a*

Table A2 (cont.): Survival Studies Characteristics and Results

Study	Distance Measurement Method	Outcomes Measured	Distance Categories	Results	Covariates	Interpretation
Austin et al. (2016)	ArcGIS driving distance to nearest center	Overall Survival (OS)	0-25 miles 25-50 miles >50 miles	Adjusted OR (95% CI) Reference 0.97 (0.78 – 1.20) 0.91 (0.76 – 1.11)	Age, sex, race, SES quintile, behavior of tumor, disease stage	No effect of distance
Austin et al. (2015)	ArcGIS driving distance to nearest center	Overall Survival (OS)	0-25 miles 25-50 miles >50 miles	Adjusted OR (95% CI) Reference 1.1 (1.0 - 1.3) 1.1 (1.0 - 1.3)	Age, sex, race, SES quintile, year of diagnosis, disease stage	No effect of distance
Charalampopoulou et al. (2004)	Not Specified	Overall Survival (OS)	<50 km 50+ km	Adjusted Death Rate Ratio (95% CI) Reference 1.77 (0.93 - 3.37)	Age, gender, maternal schooling, marital status, number of children, day care, WBC count, ALL type	No effect of distance
Cheung (2013)	Rural vs Urban Rural-urban continuum measured by area under ROC curve	Rb-Specific Mortality	Rural (Pop<25,000) Urban	Cox-Proportional Hazard Estimate Reference β = 0.9337, p=0.0198	SEER stage, race/ethnicity, county % college graduates, county household income	Rural residents had higher mortality
Gupta et al. (2014)	Rural vs Urban Rurality defined by Ontario Index based on zip code Short vs Long Distance Based on 75th %tile	Event Free Survival (EFS)	Urban Rural Short Long	Hazard Ratio (95% CI)* Reference 1.15 (0.80 – 1.64) Reference 1.05 (0.79 – 1.38)	No Multivariate Analysis	No effect of distance
Hamilton et al. (2016)	ArcGIS driving distance to nearest center	Overall Survival (OS)	0-25 miles 26-50 miles >50 miles	Hazard Ratio (95% CI)* Reference 0.6 (0.2 - 1.9) 0.7 (0.2 - 2.0)	No Multivariate Analysis	No effect of distance
Kopecky et al. (2017)	Not Specified	Overall Survival (OS)	<12.5 miles 12.5-50 miles >50 miles Metropolitan Urban Rural	Adjusted Hazard Ratio (95% CI) Reference* 0.96 (0.69-1.37) 1.16 (0.80-1.67) Reference 0.75 (0.47-1.19) 2.73 (1.44-5.20)	No Multivariate Analysis for Distance Histology	Decreased survival in rural counties

*Only Univariate Analysis Conducted

Table A2 (cont.): Survival Studies Characteristics and Results

Study	Study Time	Location	Study Type	Case-Control Details	Data Sources	Pop.	Age Range	Overall Sample Size	Cancer Type	Sub-Group Analysis For Age	Sub-Group Age Range	Sub-Group Sample Size
Moschovi et al. (2007)	1973 - 2003	Greece	Retrospective Cohort	N/A	Hospital records	Pts	0-14	50	Medulloblastoma (Mb)	N	*n/a*	*n/a*
Sergentanis et al. (2013)	1996 - 2011	Greece	Retrospective Cohort	N/A	National Clinical Database; Survey Responses	Pts	0-14	994 (ALL = 883) (AML = 111)	ALL AML	N	*n/a*	*n/a*
Tai et al. (2018)	1999 - 2011	USA	Retrospective Cohort	N/A	Census Data; Adolescent Cancer Mortality Data from NCHS	Pts	15-19	N/A	Any	N	*n/a*	*n/a*
Wolfson et al. (2014)	1998 - 2008	Los Angeles	Retrospective Cohort	N/A	County Clinical Database	Pts	0-40	1344	Primary CNS Tumors	Y	Children 0-14 Adolescents 15-21	560 139
Youlden et al. (2011)	1996 - 2006	Australia	Retrospective Cohort	N/A	National Clinical Database	Pts	0-14	6756	Any	N	*n/a*	*n/a*

Table A2 (cont.): Survival Studies Characteristics and Results

Study	Distance Measurement Method	Outcomes Measured	Distance Categories	Results	Covariates	Interpretation
Moschovi et al. (2007)	Not Specified	Overall Survival (OS)	Urban Rural	Adjusted Death Rate Ratio (95% CI) Reference 3.43 (0.91 - 12.07)	Chemotherapy, sex, age, maternal education	No effect of distance
Sergentanis et al. (2013)	Distance to Treating Hospital Google Maps	Overall Survival (OS)	Urban Semiurban Rural <50 miles 50-249 miles 250+ miles Urban Semiurban Rural <50 miles 50-249 miles 250+ miles	Adjusted Death Rate Ratio (95% CI) **ALL** Reference 1.16 (0.74 - 1.81) 1.08 (0.69 - 1.70) Reference 1.29 (0.80 - 2.10) 1.24 (0.82 - 1.87) **AML** Reference 0.52 (0.22 - 1.24) 1.08 (0.48 - 2.46) Reference 0.84 (0.34 - 2.07) 1.06 (0.48 - 2.31)	Age, sex, marital status, socioprofessional category, maternal age at birth, maternal education, # of children, ALL subtype	No effect of distance
Tai et al. (2018)	Straight-line distance surrounding COG centers	Mortality	Zone A (0-10 miles) Zone B (10-25 miles) Zone C (25-50 miles) Zone D (> 50 miles)	Total Deaths Rate per 100,000/year 2645 3.21 1949 3.05 (p<0.05 compared to Zone A) 1396 2.94 (p<0.05 compared to Zone A) 1697 2.88 (p<0.05 compared to Zone A)	N/A	Highest mortality closest to COG centers

Table A2 (cont.): Survival Studies Characteristics and Results

Study	Distance Measurement Method	Outcomes Measured	Distance Categories	Results	Covariates	Interpretation
Wolfson et al. (2014)	ArcGIS straight-line distance to nearest treating center	Mortality Risk for WHO Grade II CNS Tumors	Not Specified	Results not reported	N/A	No effect of distance
Youlden et al. (2011)	Remoteness classification based on road distance to closest service centers	5-year Relative Survival	Major Cities Inner Regional Outer Regional Remote	5-year Survival Adjusted HR (95% CI) **All Cancers** Reference 1.12 (0.94–1.34) 1.15 (0.92–1.44) 1.55 (1.08–2.23) $P_{gradient}$ = 0.017	Sex, age group, stage	Worse survival for those living further removed for leukemia, but only remote for all cancers
			Major Cities Inner Regional Outer Regional Remote	**Leukemias** Reference 1.52 (1.11–2.08) 1.53 (1.03–2.28) 1.57 (0.76–3.24) $P_{gradient}$ = 0.009		

Table A3: Treatment-Related Studies Characteristics and Results

Study	Study Time	Location	Study Type	Case-Control Details	Data Sources	Pop.	Age Range	Overall Sample Size	Cancer Type	Sub-Group Analysis For Age	Sub-Group Age Range	Sub-Group Sample Size
Albritton et al. (2007)	1994 - 2000	Utah	Retrospective Cohort	N/A	State Clinical Database	Pts	0-24	1,355	Any	Y	15-19	321
Alvarez et al. (2017)	1983 - 2011	California	Retrospective Cohort	N/A	State Clinical Database	FN Pts‡	0-18	24,599 Hospital Discharges	Any	N	*n/a*	*n/a*
Alvarez et al. (2017)	1983 - 2011	California	Retrospective Cohort	N/A	State Clinical Database	FN Pts‡	0-18	24,599 Hospital Discharges	Any	N	*n/a*	*n/a*
Austin et al. (2016)	1995 - 2009	Texas	Retrospective Cohort	N/A	State Clinical Database	Pts	0-18	2,421	CNS Solid Tumors	N	*n/a*	*n/a*
Austin et al. (2015)	1995 - 2009	Texas	Retrospective Cohort	N/A	State Clinical Database	Pts	0-18	4,630	Non-CNS Solid Tumors	N	*n/a*	*n/a*
Chamberlain et al. (2014)	1999 - 2010	California	Retrospective Cohort	N/A	State Clinical Database	Pts	0-18	103,961 Hospital Discharges	Any	Y	15-18	24,009 discharges
Donnelly et al. (2017)	2007 - 2012	Northern Ireland (NI)	Retrospective Cohort	N/A	National Clinical Database	Pts	Any	51,024	Any	Y	Children (<15)	317

‡ Febrile Neutropenia

Table A3 (cont.): Treatment-Related Studies Characteristics and Results

Study	Distance Measurement Method	Outcomes Measured	Distance Categories	Results	Covariates	Interpretation
Albritton et al. (2007)	Great Circles Algorithm (Shortest spherical distance between home & hospital zip codes)	Likelihood of Receipt of Care at Children's Center	<25 miles 25-49.9 miles 50-99.9 miles 100+ miles	Only 15-19 Subgroup Analysis Square Root of Distance from Center Adjusted OR (95% CI) 0.93 (0.86 - 1.02)	Cancer Type, Age (for 15-19)	No effect of distance by any age group
Alvarez et al. (2017)	Distance between midpoints of home and hospital zip	Likelihood of Receipt of Care at Children's Center	0-5 miles 6-10 miles 11-20 miles 21-40 miles >40 miles	Adjusted OR (95% CI) Reference 1.52 (1.15 - 2.00) 1.43 (1.07 - 1.92) 0.91 (0.71 - 1.17) 0.77 (0.63 - 0.94)	Age, Sex, Insurance Payer, Race, Zip-code level household income, diagnosis	Slightly increased likelihood with living 6-10 and 11-20 and slightly decreased with living >40
Alvarez et al. (2017)	Distance between midpoints of home and hospital zip	Length of Stay >8 days for Febrile Neutropenia Patients	0-5 miles 6-10 miles 11-20 miles 21-40 miles >40 miles	Adjusted OR (95% CI) Reference 0.98 (0.92 - 1.05) 0.85 (0.78 - 0.92) 0.87 (0.81 - 0.95) 0.87 (0.80 - 0.94)	Institution Type, Age, Sex, Insurance Payer, Race, Zip-code level household income, Diagnosis, Complications	Slightly less likelihood with increasing distance
Austin et al. (2016)	ArcGIS driving distance to nearest center	Likelihood of Advanced-Stage Presentation	0-25 miles 25-50 miles >50 miles	Adjusted OR (95% CI) Reference 1.15 (0.85 – 1.56) 0.91 (0.69 – 1.21)	Age, sex, race, SES quintile, behavior of tumor, disease stage	No effect of distance
Austin et al. (2015)	ArcGIS driving distance to nearest center	Likelihood of Advanced-Stage Presentation	0-25 miles 25-50 miles >50 miles	Adjusted OR (95% CI) Reference 1.1 (0.9 - 1.3) 1.0 (0.9 - 1.2)	Age, sex, race, SES quintile, year of diagnosis, disease stage	No effect of distance
Chamberlain et al. (2014)	Distance between midpoints of home and hospital zip	Likelihood of Receipt of Care at Children's Center	0-5 miles 6-10 miles 11-20 miles 21-40 miles >40 miles	Adjusted OR (95% CI) Reference 0.70 (0.66 - 0.75) 1.21 (1.12 - 1.32) 1.49 (1.36 - 1.63) 1.11 (1.02 - 1.20)	Age, gender, insurance payer, race, income, distance, yearly trends	No effect of distance Same conclusion for adolescent subset
Donnelly et al. (2017)	Not Specified	Clinical Trial Participation	<7.22 miles 7.22 - 22.63 miles 22.64 - 44.26 miles >44.26 miles Urban Rural	Adjusted HR (95% CI) Reference 0.70 (0.31 - 1.61) 0.64 (0.27 - 1.52) 1.22 (0.52 - 2.88) Reference 1.06 (0.57 - 1.96)	Age, sex, deprivation, urban/rural residence, cancer site	No effect of distance or rurality

Table A3 (cont.): Treatment-Related Studies Characteristics and Results

Study	Study Time	Location	Study Type	Case-Control Details	Data Sources	Pop.	Age Range	Overall Sample Size	Cancer Type	Sub-Group Analysis For Age	Sub-Group Age Range	Sub-Group Sample Size
Fluchel et al. (2014)	2010 - 2012	Salt Lake City, Utah	Cross-Sectional Cohort	N/A	Survey Responses	Parents	0-18	354 (79% response rate)	ALL; AML; Brain Tumors; Solid Tumors	N	*n/a*	*n/a*
Grunwell et al. (2018)	2012 - 2017	Atlanta, Georgia	Case Control	Cases: PS same-day cancellation (SDC); Control: pts undergoing PS	Hospital Records	PS Pts^	Not Stated	606; SDC (n=100), Control (n=506)	Any	N	*n/a*	*n/a*
Hamilton et al. (2016)	1995 - 2009	Texas	Retrospective Cohort	N/A	State Clinical Database	Pts	0-18	235	Melanoma	N	*n/a*	*n/a*
Klein-Geltink et al. (2005)	1995 - 2000	Canada	Prospective Cohort	N/A	Clinical Database; Hospital Records	Pts	0-14	2316	Any	N	*n/a*	*n/a*
Kopecky et al. (2017)	2004 – 2009	USA	Retrospective Cohort	N/A	National Clinical Database	Pts	0-19	783	Medulloblastoma (Mb)	N	*n/a*	*n/a*
Lawell et al. (2019)	2012 – 2017	Mass. (MGH)	Retrospective Cohort	N/A	National Clinical Database; External/ Hospital Records	Pts	0-21	333	Any	N	*n/a*	*n/a*

^ Procedural Sedation

Table A3 (cont.): Treatment-Related Studies Characteristics and Results

Study	Distance Measurement Method	Outcomes Measured	Distance Categories	Results	Covariates	Interpretation
Fluchel et al. (2014)	Rural vs Urban; Classified by commuting area codes based on zip MapQuest calculated travel times; 1hr based on neutropenic fever referral 2hr based on surrounding metro	**Emergency Transportation** Any Ambulance Required Air Transport Required	Rural vs Urban Travel time >1hr vs < 1hr Travel time >2hr vs <2hr Rural vs Urban Travel time >1hr vs < 1hr Travel time >2hr vs <2hr	Rate Ratio (95% CI) 1.6 (0.9 - 2.8) 1.6 (1.1 - 2.6) 1.6 (1.0 - 2.5) 5.9 (2.7 - 13.1) 3.8 (1.7 - 8.5) 7.2 (3.5 - 14.5)	Poisson Regression Model Other Dichotomous Outcomes Relocated residence, quit work, patient held back in school	Increasing distance/travel time increases need for emergency travel
Grunwell et al. (2018)	Not Specified	Same-Day Cancellations (SDC)	Median Distance SDC No Cancellation	Only Descriptive Presented Chi-Square 29.0 miles 32.3 miles p=0.8711	No Multivariate Analysis	No effect of distance
Hamilton et al. (2016)	ArcGIS driving distance to nearest center	Likelihood of Advanced-Stage Presentation	0-25 miles 26-50 miles >50 miles	Adjusted HR (95% CI) Reference 1.4 (0.6 - 3.0) 1.8 (0.8 - 4.1)	Sex, age, race, dx year, SES quartile	No effect of distance
Klein-Geltink et al. (2005)	Postal codes converted to latitude and longitude Aerial distances between residence and treating location	**Waiting Times (Days)** Symptom Onset to First Contact First Contact to Oncologist Assessment First Assessment to Treatment	0-24 km 25-99 km >100 km 0-24 km 25-99 km >100 km 0-24 km 25-99 km >100 km	Adjusted OR for Waiting Longest Quartile Vs Three Shortest OR (99% CI) Reference 0.88 (0.63–1.25) 0.92 (0.66–1.27) Reference 0.92 (0.65–1.30) 0.92 (0.67–1.27) Reference 1.20 (0.83–1.74) 1.23 (0.88–1.72)	Age, sex, diagnosis, region of residence, type of initial healthcare consultation	No effect of distance
Kopecky et al. (2017)	Not Specified	Likelihood of Receipt of Proton Beam Therapy	Metropolitan Urban Rural	OR* Reference 0.58, p=0.098 0.38, p=0.35	No Multivariate Analysis	No effect of distance
Lawell et al. (2019)	Great Circles Algorithm (Shortest spherical distance between home zip and hospital zip)	Duration of Follow-Up after Proton Therapy (years)	Within 75 mile radius Outside 75 mile radius	Linear Regression Parameter Estimate (95% CI) Reference β = -0.53 (-0.81 - -0.26)	Trial co-enrollment, treatment delay, Medicaid status, Race, Follow-up method	Further distance associated with decreased follow-up

*Only Univariate Analysis Conducted

Table A3 (cont.): Treatment-Related Studies Characteristics and Results

Study	Study Time	Location	Study Type	Case-Control Details	Data Sources	Pop.	Age Range	Overall Sample Size	Cancer Type	Sub-Group Analysis For Age	Sub-Group Age Range	Sub-Group Sample Size
Pole et al. (2017)	2001 – 2012	Canada	Retrospective Cohort	N/A	National Clinical Database	Pts	0-14	9204	Any	N	*n/a*	*n/a*
Shen et al. (2017)	2004 – 2013	USA	Retrospective Cohort	N/A	National Clinical Database	Pts	0-21	12,101	Solid Tumors	N	*n/a*	*n/a*
Truong et al. (2019)	2001 – 2018	Canada	Retrospective Cohort	N/A	National Clinical Database	Pts	0-14	3992	ALL	N	*n/a*	*n/a*
Wolfson et al. (2014)	1998 – 2008	Los Angeles, California	Retrospective Cohort	N/A	County Clinical Database	Pts	0-40	1344	Primary CNS Tumors	Y	Children: 0-14 Adolescents: 15-21	560 139
Yeager et al. (2006)	1996 - 1999	Ohio	Retrospective Cohort	N/A	State Clinical Database	Pts	15-19	169	Any	N	*n/a*	*n/a*
Youlden et al. (2011)	1996 - 2006	Australia	Retrospective Cohort	N/A	National Clinical Database	Pts	0-14	6756	Any	N	*n/a*	*n/a*

Table A3 (cont.): Treatment-Related Studies Characteristics and Results

Study	Distance Measurement Method	Outcomes Measured	Distance Categories	Results	Covariates	Interpretation
Pole et al. (2017)	Not Specified	Clinical Trial Participation	Per 100 Km	Adjusted OR (95% CI) 0.96 (0.94 - 0.98)	Age, sex, race, diagnostic era, diagnosis, income quintile	Less enrollment with increasing distance
Shen et al. (2017)	Great Circles Algorithm (Shortest spherical distance between home zip and hospital zip); Rurality defined by population size, degree of urbanization, and adjacency to metro area	Likelihood of Receipt of Proton Beam Therapy	Metropolitan Urban/Rural <100 miles >100 miles, median income <$63,000 >100 miles, median income >$63,000	Adjusted OR (95% CI) Reference 0.47 (0.36-0.61) Reference 2.04 (1.62-2.58) 4.01 (2.89-5.82)	Age, primary tumor site, histology, stage, primary insurance, median income, education, location of facility (all treatment or some elsewhere)	Effect of distance only when factoring in income; Effect no longer present with subset analysis of treatment at the reporting facility vs elsewhere
Truong et al. (2019)	Distance between midpoints of home and hospital zip	Likelihood of Receipt of HSCT	0-100 km 100-200 km 200 - 300 km >300 km	Adjusted OR (95% CI) Reference 0.79 (0.47 -1.32) 0.76 (0.35 - 1.65) 1.84 (1.17 - 2.91)	Age, sex, race, initial WBC count, region, immunophenotype, cytogenetics, diagnostic eriod, relapse before HSCT, HSCT center diagnosis, distance from treating center, neighborhood income quintile	>300km associated with increased odds of HSCT
Wolfson et al. (2014)	ArcGIS straight-line distance to nearest treating center	Likelihood of Receipt of Care at Childrens Center	0-5 miles >5 miles	Adjusted OR (95% CI) Reference 0.90 (0.38 to 2.09)	Age group (0-14, 15-21), race, SES, Insurance status	No effect of distance
Yeager et al. (2006)	45 of Ohio counties grouped by increasing distance from Franklin county, where the academic childrens and adult center is located	Likelihood of Receipt of Care at Local Facility vs Peds/Adult Facility	Group 1 Group 2 Group 3 Group 4 Group 5	Cochran-Armitage Test for % Treated at Each Facility Type p-value Local vs Peds/AA 1 (4.2%) vs 23 (85.8%) 10 (32.3%) vs 21 (67.7%) 12 (32.4%) vs 25 (67.6%) 11 (30.6%) vs 25 (69.4%) 5 (41.7%) vs 7 (58.3%) p=0.0272	N/A	Increasing distance associated with more care at local facilities
Youlden et al. (2011)	Remoteness classification based on road distance to closest service centers	Likelihood of Advanced-Stage Presentation	Major Cities Inner Regional Outer Regional	Stage 1/2 vs Stage 3/4** 41.0% vs 44.3% 38.3% vs 48.5% 44.3% vs 45.2% p=0.323	N/A	No effect of remoteness

**Only Descriptive Analysis Conducted

Table A4: Quality Assessment – Cohort Studies

		Selection				Comparability
Study	Study Type	Representativeness	Control Selection	Ascertainment of Exposure	Outcome of Interest Not Present at Start	Comparability of Cohorts by Design/Analysis
Albritton et al. (2007)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for diagnosis or stage ★
Alvarez et al. (2017)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for diagnosis or stage ★ Study controls for sex, age, insurance, race, income ★
Austin et al. (2016)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for sex, age, race, SES, year, and malignant behavior ★
Austin et al. (2015)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for sex, age, race, SES, year ★
Chamberlain et al. (2014)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for sex, age, race, insurance, income ★
Charalampopoulou et al. (2004)	Prospective Cohort	Somewhat Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for WBC count ★ Study controls for sex, age, ALL type ★
Cheung (2013)	Retrospective Cohort	No Description	No Description	Secure Records ★	Yes ★	Study controls for diagnosis or stage ★ Study controls for race, % college graduates, income ★
Donnelly et al. (2017)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for age, sex, deprivation, cancer site ★
Gupta et al. (2014)	Retrospective Cohort	Somewhat Representative ★	Same Community ★	Secure Records ★	Yes ★	Only univariate analysis for exposure of interest
Hamilton et al. (2016)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for diagnosis or stage ★ Study controls for sex, age, race, diagnosis year, SES ★
Klein-Geltink et al. (2005)	Prospective Cohort	Somewhat Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for diagnosis or stage ★ Study controls for sex and age ★
Kopecky et al. (2017)	Retrospective Cohort	Somewhat Representative ★	Same Community ★	Secure Records ★	Yes ★	Only univariate analysis for exposure of interest
Lawell et al. (2019)	Retrospective Cohort	Select Group	Same Community ★	Secure Records ★	Yes ★	Study controls for follow-up method ★ Study controls for trial enrollment, delays, insurance ★
Moschovi et al. (2007)	Retrospective Cohort	Somewhat Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for sex, age, chemotherapy, and maternal education ★
Pole et al. (2017)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for diagnosis or stage ★ Study controls for sex, age, race, time period, income ★
Sergentanis et al. (2013)	Retrospective Cohort	Somewhat Representative ★	Same Community ★	Structured Interview ★	Yes ★	Study controls for age sex, SES, marital status, number of children ★

Table A4 (cont.): Quality Assessment – Cohort Studies

Study	Study Type	Outcome			Number of Stars	Grade
		Assessment	Follow-Up Timing	Adequacy of Follow-Up		
Albritton et al. (2007)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	7	Good
Alvarez et al. (2017)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	8	Good
Austin et al. (2016)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	7	Good
Austin et al. (2015)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	7	Good
Chamberlain et al. (2014)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	7	Good
Charalampopoulou et al. (2004)	Prospective Cohort	Independent Assessment ★	Yes ★	Complete ★	9	Good
Cheung (2013)	Retrospective Cohort	Record Linkage ★	No	No Description	5	Poor
Donnelly et al. (2017)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	7	Good
Gupta et al. (2014)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	6	Poor
Hamilton et al. (2016)	Retrospective Cohort	Record Linkage ★	Yes ★	<20% loss ★	9	Good
Klein-Geltink et al. (2005)	Prospective Cohort	Record Linkage ★	Yes ★	No Description	8	Good
Kopecky et al. (2017)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	6	Poor
Lawell et al. (2019)	Retrospective Cohort	Record Linkage ★	Yes ★	Complete ★	8	Good
Moschovi et al. (2007)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	7	Good
Pole et al. (2017)	Retrospective Cohort	Record Linkage ★	Yes ★	Complete ★	9	Good
Sergentanis et al. (2013)	Retrospective Cohort	Independent Assessment ★	Yes ★	Complete ★	8	Good

Table A4 (cont.): Quality Assessment – Cohort Studies

		Selection				Comparability	
Study	Study Type	Representativeness	Sample Selection	Ascertainment of Exposure	Outcome of Interest Not Present at Start	Comparability of Cohorts by Design/Analysis	
Shen et al. (2017)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for diagnosis or stage Study controls for age, site, insurance, income, facility location	★ ★
Tai et al. (2018)	Retrospective Cohort	Truly Representative ★	Same Community ★	Other	No	Study controls for diagnosis or stage Study controls for sex, race	★ ★
Truong et al. (2019)	Retrospective Cohort	Somewhat Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for diagnosis or stage Study controls for WBC count, sex, age, race, income, relapse, diagnosis year	★ ★
Wolfson et al. (2014)	Retrospective Cohort	Somewhat Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for age, race, SES, insurance	★
Yeager et al. (2006)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	No adjustment	
Youlden et al. (2011)	Retrospective Cohort	Truly Representative ★	Same Community ★	Secure Records ★	Yes ★	Study controls for sex and age	★

Table A4 (cont.): Quality Assessment – Cohort Studies

		Outcome			Number of Stars	Grade
Study	Study Type	Assessment	Follow-Up Timing	Adequacy of Follow-Up		
Shen et al. (2017)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	8	Good
Tai et al. (2018)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	6	Fair
Truong et al. (2019)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	8	Good
Wolfson et al. (2014)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	7	Good
Yeager et al. (2006)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	6	Poor
Youlden et al. (2011)	Retrospective Cohort	Record Linkage ★	Yes ★	No Description	7	Good

Table A5: Quality Assessment – Case Control Studies

Study	Study Type	Selection				Comparability	Exposure			Number of Stars (Max = 8)
		Representativeness	Case Definition	Control Definition	Control Selection	Comparability of Cohorts by Design/Analysis	Ascertainment of Exposure	Same Method of Ascertainment	Non-Response Rate	
Grunwell et al. (2018)	Case-Control	Yes ★	Yes ★	Yes ★	Same Population ★	No adjustment	Medical Record ★	Yes ★	N/A	6

Table A6: Quality Assessment – Cross Sectional Studies

Study	Study Type	Selection				Comparability	Outcome		Number of Stars (Max=10)
		Representativeness	Ascertainment of Exposure	Sample Size	Non-Respondents	Comparability of Cohorts by Design/Analysis	Assessment	Statistical Test	
Fluchel et al. (2014)	Cross-Sectional	Somewhat Representative ★	Tool is Described ★	Justified & Satisfactory ★	No Description of Non-Responders	Study controls for stage ★ Study controls for age, race, education ★	Self-Report ★	Appropriate★	7