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Medulloblastoma: Identifying High Risk Time Points during Treatment for Development of Nutrition Deficits

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MEDULLOBLASTOMA: IDENTIFYING HIGH RISK TIME POINTS DURING TREATMENT FOR DEVELOPMENT OF NUTRITION DEFICITS

by

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ABSTRACT

Background: Medulloblastoma is the most common type of pediatric brain cancer and accounts for 20% of all diagnosed brain tumors. The aims of this research were to describe the nutrition status patterns and nutrition related complications occurring during treatment of children diagnosed with medulloblastoma and to identify specific time points in treatment for the initiation of proactive nutrition therapy.

Design: A retrospective study of 60 patients who were treated on a one treatment protocol, Clinical and Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma (SJMB12). Nutrition assessments, nutrition-related adverse events and nutrition intervention strategies were recorded at the beginning and end of each cycle of treatment.

Results: The majority of participants (in all strata) had at least mild malnutrition (80% among W1 patients, 75% for S1/S2 patients, 91% for N1 patients and 94% for N2/N3 patients). Nearly 75% of patients received an appetite stimulant and 62% required EN or PN. Grade 3 and higher anorexia was observed in approximately 20% of the patients.

Conclusion: This current study demonstrates that children with medulloblastoma have significant malnutrition exacerbated by disease state, treatment and chemotherapy-related adverse events. A pattern of declining nutrition status emerged in all stratums of medulloblastoma early on in treatment.

TABLE OF CONTENTS

List of Tables

List of Figures

CHAPTER 1

INTRODUCTION

Medulloblastoma is the most common type of pediatric brain cancer and accounts for 20% of all diagnosed brain tumors [1]. The prognosis for medulloblastoma is fairly good with a 70-75% cure rate if "average risk" and diagnosed above the age of three. Medulloblastoma can spread easily in the cerebrospinal fluid and therefore has the capability of metastasizing beyond the central nervous system making the disease more difficult to irradiate. Patients with metastatic disease are classified as "high risk" and have a 40-60% cure rate [2-5]. Frontline treatment for medulloblastoma comprises a multi modal treatment approach including surgery, craniospinal irradiation, and chemotherapy. Patients are assigned treatment based on the stage of disease, with higher risk diagnoses requiring the most intensive treatments [3,6-7]. Nutrition related complications occur throughout the continuum of treatment and are often more severe in highest risk patients. Malnutrition is an unfortunate side-effect of cancer itself, but is also a consequence of treatment. The prevalence of malnutrition in pediatric oncology patients ranges from 8-60%. This wide range is due to differences between cancer types, therapy given, and methods used for measuring malnutrition [8-12]. Few studies have documented nutritional problems specific to medulloblastoma patients [13]. Although the incidence of malnutrition in those diagnosed with medulloblastoma is not known, retrospective studies show that patients with advanced disease are at a particularly high risk of developing malnutrition [14].

Malnutrition is associated with increased therapy complications, including mucositis, nausea, vomiting anorexia, lower quality of life and higher rates of mortality [15-22]. In addition to the lack of evidence regarding the incidence of malnutrition, there are no standards for nutrition intervention strategies, including criteria for implementation, timing, or duration [23].

However, several studies demonstrated the need for proactive nutrition intervention strategies in order to combat nutritional decline and long-term complications of anticancer treatments [13,24]. Therefore, the aims of this quality improvement project were to describe the nutrition status patterns and nutrition related complications occurring during treatment of children diagnosed with medulloblastoma and to identify specific time points in treatment for the initiation of proactive nutrition therapy.

CHAPTER 2

METHODS

Participant Selection

Participants included patients diagnosed with medulloblastoma who were treated on a one treatment protocol, Clinical and Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma (SJMB12), at St. Jude Children's Research Hospital (St Jude) (Table 1). Although SJMB12 is a multi-center protocol, only patients at St Jude were included in the quality improvement project.

Nutrition Assessment

The nutrition diagnoses were recorded at each time point as per the Academy of Nutrition and Dietetics' Electronic Nutrition Care Process Terminology Reference Manual [22]. The sub-classification of malnutrition was diagnosed using the Academy of Nutrition and Dietetics' and the American Society for Parenteral and Enteral Nutrition's guidelines (Table 2) at each time point [16]. If there was a lack of height or weight measurements, the previously recorded height or weight measurement was extracted. Differences in height measurements by >2 cm were adjusted to the previously recorded height. Other height inconsistencies were smoothed by the rule that no child shrinks over time [13]. Patient information was obtained at the start of treatment and again at each cycle of treatment (Table 3). Any patients taken off protocol were included in the analysis until the end of the latest completed treatment cycle.

Nutrition-Related Adverse Events

Nutrition- related adverse events ≥3 from the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) were evaluated [23]. These nutrition-related adverse events specifically included mucositis, nausea, vomiting, malabsorption, diarrhea, and anorexia (Table 4). The

number of days within each cycle that a patient experienced these specific adverse effects was recorded.

Nutrition Intervention

Patients receiving parenteral nutrition, enteral nutrition or appetite stimulants were noted. The number of days within each cycle that a patient was undergoing parental nutrition and/or enteral nutrition was recorded. The type of enteral nutrition was recorded (e.g. G-tube) as well as whether or not the patients were prescribed appetite stimulates during the cycle.

Treatment Risk Stratification

All patients on SJMB12 were classified as being subjected to Level 3: Very Intensive Treatments. This categorization was made based on the Intensity of Treatment Rating Scale [24].

Data Collection

All data was collected at the beginning and end of each treatment cycle (Table 3). Patients were assessed for nutrition status at the beginning and end of each cycle. Nutrition data was collected by the Principal Investigator via retrospective chart review. Nutrition data was recorded based on the dietitian assessment, notes and growth charts. Adverse events and other non-nutrition data was collected by the Research Nurse and all data was entered into an excel spread cheat by the Principal Investigator.

CHAPTER 3

RESULTS

Data was frozen in the research data base on August 9, 2016. One hundred and sixty three eligible patients had been enrolled on SJMB12, 78 of whom were enrolled at St. Jude Children's Research Hospital. At the time of data abstraction for this research project, 60 St. Jude patients had received at least one cycle of treatment and were included in this assessment of nutrition status. As seen in Table 5, the participants were mostly male, Caucasian with a mean age of 8.3 (range 3.3-18.9).

Participants were assigned to treatment strata based first on molecular subgroup assignment (WNT, SHH, or Non-WNT Non- SHH) and then by clinical risk stratification (extent of resection, M stage, histologic subtype, and cytogenetic features). The SJMB12 treatment schema is shown in the Appendix A. All patients receive radiation therapy initially. After radiation WNT patients (stratum W) receive only 4 cycles of cyclophosphamide, cisplatin and vincristine. Stratum S patients receive radiation therapy followed by 4 cycles of cyclophosphamide, cisplatin and vincristine, but then receive maintenance therapy with vismodegib. Stratum N1 patients receive only 4 cycles of cyclophosphamide, cisplatin and vincristine after radiation, while strata N2 and N3 patients receive 7 cycles of therapy with cyclophosphamide, cisplatin and vincristine (cycles 1, 2, 4 and 5) or pemetrexed and gemcitabine (cycles 3, 6 and 7). Table 6 summarizes nutrition outcomes by stratum. The majority of participants (in all strata) had at least mild malnutrition (80% among W1 patients, 75% for S1/S2 patients, 91% for N1 patients and 94% for N2/N3 patients). Thirty- one percent of N2/N3 patients had severe malnutrition at some time point, compared to 27% of N1 patients, 20% of W1 patients and 13% of S1/S2 patients. Nearly 75% of patients received an appetite stimulant

and 62% required EN or PN. Grade 3 and higher anorexia was observed in approximately 20% of the patients.

Figure 1 shows Z-scores for BMI for age for W1 patients. The patient with the largest decrease in BMI for age Z-score (39813) had severe malnutrition at the end of cycle A1. This same patient had moderate malnutrition at the end of the rest period following radiation. One other W1 patient had moderate malnutrition (42050); this patient had moderate malnutrition at the beginning of radiation therapy and all the way through the end of cycle A4. Figure 2 shows Z-scores for BMI for age for S1 and S2 patients. The one patient with severe malnutrition (40459) had severe malnutrition at the beginning of radiation therapy. This patient had severe malnutrition at his/her last assessment as well. Figure 3 shows Z-scores for BMI for age for N1 patients. Three patients had severe malnutrition. One of these had severe malnutrition at the beginning of radiation therapy (42276). Another (43037) had mild malnutrition at the beginning of radiation which became moderate at the end of radiation therapy assessment. By the end of cycle A3, this patient had severe malnutrition which did not improve during cycle A4. The third patient (43828) did not have severe malnutrition until the end of cycle A4; this patient did not have malnutrition at the beginning of radiation but had mild malnutrition after radiation which progressed to moderate malnutrition after the radiation rest period and also at the completion of cycles A2 and A3. Figure 4 shows Z-scores for BMI for age for N2 and N3 patients. Approximately a third of these patients had severe malnutrition. Six of these had severe malnutrition before radiation, 2 at the end of radiation, 2 and the completion of cycle A1, and 1 at the completion of cycle A4.

CHAPTER 4

DISCUSSION

Although medulloblastoma has been studied in the past in terms of survival and long-term consequences of treatment, there have been few studies looking directly at nutrition status, adverse effects and nutritional interventions [13, 32-35].

According to The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), pediatric malnutrition can now be defined as "an imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development and other relevant outcomes." Hospitalized pediatric patients experiencing malnutrition are at greater risk for complications due to their disease state, poor wound healing, and delayed energy levels. Previous studies suggest that as many as 25% of pediatric patients in a hospital setting experience acute protein-energy malnutrition [14]. In the past, malnutrition was measured in various ways: ideal body weight, decreases in two centile channels, deceleration of weight in time, etc. However, the use of the *z* score is what is now recommended for proper malnutrition classification. Weight gain velocity is an important indicator for identifying malnutrition in pediatrics. When a child is well nourished, the rate of weight gain will remain stable on growth charts [20]. Very low weight gain velocity measured via *z* score has been distinguished to be an accurate indicator of mortality, more so than other such measurements i.e., BMI for age [19]. This study supports that children with decreased z scores were malnourished.

Pediatric oncology patients experiencing poor nutrition status also have higher risks for complications during treatment and survivorship such as decreased quality of life, increased rates

of relapse, and mortality. Children diagnosed with cancer have the duel problem of maintaining oral intake which is sufficient to maintain nutritional status and promote growth [28-29]. In addition to insufficient nutrient intake and absorption, medulloblastoma patients are at greater risk for adverse growth effects due to the combination of craniospinal radiation and chemotherapy treatments [30-31]. Craniospinal irradiation can result in loss of appetite, anorexia, mucositis and chewing/swallowing difficulties. Adequate nutrition is also necessary to prevent infection, wasting and treatment delays [18, 21].

Presently, there are no standardized criteria for nutrition intervention in the pediatric cancer population regarding strategies for implementation, timing, or duration of interventions [23]. Longitudinal studies involving brain malignancies are rare and little is known about the exact timing or causation of malnutrition onset during treatment. More studies need to be done in order to identify the optimum nutrition strategies [29]. In a retrospective cohort study of 327 patients done to determine the point prevalence of malnutrition in pediatric cancer patients, it was shown that the incidence of malnutrition rose during anticancer therapy. Twenty-two percent of patients experiencing malnutrition at 30 days, 36% at 60 days and the incidence peaked at 47% later in treatment. Medulloblastoma patience experienced the highest rate and longest occurrence of malnutrition. At 311 days into treatment, 94% of medulloblastoma patients were considered malnourished using BMI SDS <−2.0 and weight loss of >10% as criteria for malnutrition. Medulloblastoma patients also had the highest risk of becoming malnourished using univariable logistic regression. During therapy, there were several characteristics that resulted in higher rates of malnutrition: age >10 years, female gender, emotegenic drugs, and lower BMI at diagnoses [14]. In the current study, the majority of participants declined in nutrition status following treatment initiation. Eighty-five percent in all strata had at least mild

malnutrition while 23% were classified as being severely malnourished at some point during therapy.

A decrease in nutritional intake leading to weight loss can be caused by many factors: anorexia, damage to the mucous membranes, taste perception, and etcetera [13]. This current study demonstrated that the treatment modality determined which weight loss factors affected the participants. When comparing the type of nutrition adverse outcome by stratum, it is of note, that for W1, mucositis (20%) and vomiting (20%) were more of a problem than with the other treatment stratums in the current study. In the S1 and S2 stratums, participants were more likely to experience nausea and anorexia while in the N1 stratum, there were less recorded nutrition adverse events. In the N2 and N3 stratums, patients were more likely to suffer from anorexia (28%). Adverse effects were only captured in this study if grade 3 or above. Due to the retrospective nature of the study, it is possible that some effects did not get recorded and thus were not included in this study. Adverse effects, such as weight loss, vomiting, and constipation, can be commonly seen as a result of both radiation and chemotherapy. Cisplatin is a cytostatic agent with documented emetic effects [14]. Emetic reactions have been documented in medulloblastoma related to irradiation and vincristine in previous studies [13]. In a multicenter retrospective study of 41 children treated for medulloblastoma, it was noted that 49% of patients had significant adverse effects (grade 1 or above CTC score) of vomiting and constipation after radiation therapy. A peak significant weight loss (mean of -8.2% since diagnoses) and weight/height loss ratio (mean of 91.3%) was observed during course 2 of chemotherapy. However, neither age nor toxicity were found to be statistically significant with the occurrence of weight loss [13]. In another retrospective study of 103 medulloblastoma patients, it was noticed that weight loss after surgery and radiation therapy was not significant; however, weight loss

from the start and 3 months into chemotherapy was significant at 4.35% (P 0.001). Significant weight loss was determined using a loss >5% of their body weight [36].

There are various nutrition intervention strategies used to combat malnutrition. The use of a Registered Dietitian's assessment and care plan improve nutrition status and quality of life outcomes in adult and pediatric patient populations [37]. Oral appetite stimulates, specifically cyproheptadine hydrochloride and/or megestrol acetates, use in pediatrics have been found to result in weight gain in clinical trials [38]. In the current study, 70% of participants used an appetite stimulant at some point during therapy. The oral route of feeding administration is ideal; however, because of adverse effects seen during treatment, the enteral feeding route may be necessary to achieve adequate nutrition [39]. In a study done by Bakish et al., differences between nutrition strategy interventions on weight status in newly diagnosed medulloblastoma patients were noted. It was found that oral nutrition resulted in a significant weight loss after 1 month of implementation. Parenteral nutrition resulted in weight gain only after 1 month of implementation, while enteral nutrition (gastrostomy/nasogastric tube insertion) brought about a significant weight gain after both 1 month (4.78%) and 3 months (11.73%) of implementation [36]. In a retrospective study of 56 patients aged 10–20 years who received adjuvant treatment for medulloblastoma, 73% had a weight loss greater than 10% and 48% required either enteral or parenteral feeding [40]. In the current study, 23% had a weight loss of over 10% (severe malnutrition) and 62% required either enteral or parental feeding strategies.

Several studies demonstrate the need for proactive nutrition intervention strategies in order to combat nutritional decline during anticancer treatment [13, 24]. In past studies, proactive enteral feeding resulted in improved nutrition status outcomes, while the placement of PEG tubes at diagnoses have brought about fewer surgical complications, relapses, and deaths [18]. In the

study done by Ward et al., there were significant differences between centers that treated malnutrition proactively and reactively by use of enteral feeding. At course 2 of chemotherapy, the mean % weight loss in the proactive center peaked at around 7 % compared to around 9% in the reactive center. Although both centers saw an increase in mean % weight loss, nutrition status in the proactive center began to improve after course 2 of chemotherapy, while nutrition status continued to decline in the reactive center. By course 7 of chemotherapy, the reactive center had a mean % weight loss of 11.6% compared to only 2.4% in the proactive center [13]. Limitations to the current study include time plotted by months instead of specific time points (i.e., radiation, rest, chemotherapy) during biostatistical analysis and small sample size (n=60).

CHAPTER 5

CONCLUSION

This current study demonstrates that children with medulloblastoma have significant malnutrition exacerbated by disease state, treatment and chemotherapy-related adverse events. A pattern of declining nutrition status emerged in all stratums of medulloblastoma early on in treatment. The majority of participants in all stratums required nutrition support in the form of enteral or parenteral nutrition as well as appetite stimulants. While these modes of nutrition support are necessary at times, if nutrition intervention strategies (placement of PEG tube) were begun earlier in treatment, patients may be able to avoid a decrease in nutrition status. Proactive nutrition strategies are recommended in order to negate nutrition decline in future studies.

TABLE 1 SJMB12 Protocol Flow Sheet

	Strata W1, W2, W3, N1	Strata S1, S2	Strata N2, N3
Weeks 1- 6	RT	RT	RT
Weeks 7-12	Rest	Rest	Rest
Weeks 13-16	Cycle A1 Adjuvant Chemo	Cycle A1 Adjuvant Chemo	Cycle A1 Adjuvant Chemo
Weeks 17-20	Cycle A2 Adjuvant Chemo	Cycle A2 Adjuvant Chemo	Cycle A2 Adjuvant Chemo
Weeks 21-24	Cycle A3 Adjuvant Chemo	Cycle A3 Adjuvant Chemo	Cycle B1 Adjuvant Chemo
Weeks 25-28	Cycle A4 Adjuvant Chemo	Cycle A4 Adjuvant Chemo	Cycle A3 Adjuvant Chemo
Weeks 29-32		Vismodegib Maintenance Chemo	Cycle A4 Adjuvant Chemo
Weeks 33-36		Vismodegib Maintenance Chemo	Cycle B2 Adjuvant Chemo
Weeks 37-40		Vismodegib Maintenance Chemo	Cycle B3 Adjuvant Chemo
Weeks 40-80		Vismodegib Maintenance Chemo	

Table 2 Criteria for Defining Malnutrition

	Mild Malnutrition	**Moderate Malnutrition**	**Severe Malnutrition**
Weight-for-height *z* score	-1 to -1.9 *z* score	-2 to -2.9 *z* score	-3 or greater *z* score
BMI-for-age *z* score	-1 to -1.9 *z* score	-2 to -2.9 *z* score	-3 or greater *z* score
Length/height-for-age *z* score	No data	No data	-3 *z* score
Weight loss	5% usual body weight	7.5% usual body weight	10% usual body weight
Deceleration in weight for length/height z score	Decline of 1 *z* score	Decline of 2 *z* score	Decline of 3 *z* score

Table 3 Time Points and Data Collected

Time Point	Data to Be Collected
Start of Week 1	Age Gender Race Treatment Strata Risk Stratification Nutrition Diagnoses
Completion of Week 6/Start of Week 7	Age Nutrition Diagnosis Nutrition-Related Adverse Events≥3 Nutrition Intervention
Completion of Week 12/Start of Week 13	
Completion of Week 16/Start of Week 17	
Completion of Week 20/Stark of Week 21	
Completion of Week 24/Start of Week 25	
Completion of Week 28/Start of Week 29	
Completion of Week 32/Start of Week 33	
Completion of Week 36/Start of Week 37	
Completion of Week 40/Start of Week 41	
Completion of Week 80	

Table 4 Nutrition-related Adverse Events Examined

	Grade		
Adverse Event	**3**	**4**	**5**
Nausea	Inadequate oral caloric or fluid intake; IV[a] fluids, tube feedings, or TPN[b] indicated ≥24 hrs	Life-threatening consequences	Death
Diarrhea	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL[c]	Life-threatening consequences	Death
Malabsorption	Inability to aliment adequately via GI[d] tract (i.e., TPN indicated)	Life-threatening consequences	Death
Anorexia	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
Mucositis	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death

[a] Intravenous

[b] Total Parenteral Nutrition

[c] Activities of Daily Living

[d] Gastrointestinal

Table 5 Participants Characteristics by Treatment Stratum

	Stratum								All Patients
	N1		N2/N3		S1/S2		W1		
	n	%	n	%	n	%	n	%	n
Sex									
Female	4	36.4	9	25.0	2	25.0	3	60.0	18
Male	7	63.6	27	75.0	6	75.0	2	40.0	42
Race									
Asian	0	0	1	2.8	0	0	0	0	1
Black	0	0	4	11.1	2	25.0	0	0	6
Multiple Race (NOS)[s]	0	0	0	0	1	12.5	0	0	1
Other	0	0	1	2.8	0	0	0	0	1
White	11	100.0	30	83.3	5	62.5	5	100.0	51
Age at Enrollment									
Median	8.5		8.2		8.4		9.5		8.3
Range	4.9-17.9		3.3-18.9		5.0-14.0		5.3-16.8		3.3-18.9
All Patients	11	100.0	36	100.0	8	100.0	5	100.0	60

[a] Not Otherwise Specified

Table 6 Summary of Nutrition Outcomes by Stratum

	W1[a] (n=5)		S1/S2[b] (n=8)		N1[a] (n=11)		N2/N3[c] (n=36)	
	n	%	n	%	n	%	n	%
# of assessments	60	-	120	-	120		553	
# of patients with mild, moderate or severe malnutrition	4/5	80%	6/8	75%	10/11	91%	34/36	94%
# of patients with moderate or severe malnutrition	2/5	40%	4/8	50%	6/11	55%	25/36	69%
# of patients with severe malnutrition	1/5	20%	1/8	13%	3/11	27%	11/36	31%
# of patients who received an appetite stimulant	3/5	60%	6/8	75%	8/11	73%	26/36	72%
# of cycles during which as appetite stimulant was used*	9/30	30%	27/59	46%	30/60	50%	129/274	47%
# of patients with grade 3+ nausea	0/5	0%	2/8	25%	0/11	0%	1/36	3%
# of patients with grade 3+ vomiting	1/5	20%	1/8	13%	1/11	9%	2/36	6%
# of patients with grade 3+ diarrhea	0/5	0%	0/8	0%	0/11	0%	2/36	6%
# of patients with grade 3+ malabsorption	0/5	0%	0/8	0%	0/11	0%	1/36	3%
# of patients with grade 3+ anorexia	0/5	0%	2/8	25%	1/11	9%	10/36	28%
# of patients with grade 3+ mucositis	1/5	20%	0/8	0%	0/11	0%	0/36	0%
# of patients who required enteral and/or parenteral nutrition	3/5	60%	3/8	38%	6/11	55%	25/36	69%

Table 6 Summary of Nutrition Outcomes by Stratum, Continued

# of patients who required enteral nutrition	2/5	40%	2/8	25%	2/11	18%	22/36	61%
# of patients who required parenteral nutrition	1/5	20%	3/8	38%	5/11	45%	12/36	33%

[a] W1 and N1 patients were assessed before and after radiation, rest, and cycles A1-A4.

[b] S1/S2 patients were assessed before and after radiation, rest, cycles A1-A4, and before and after vismodegib for weeks 29-32, weeks 33-36, weeks 37-40 and weeks 40-80 (4 time points during vismodegib). The total number of assessments for S1/S2 patients was 120, as some patients did not receive all cycles.

[c] N2 and N3 patients were assessed before and after radiation, rest, cycles A1, A2, B1, A3, A4, B2 and B3.

* Appetite stimulant use was only assessed at the completion of cycles. Some patients did not have assessments at cycle completion for some cycles.

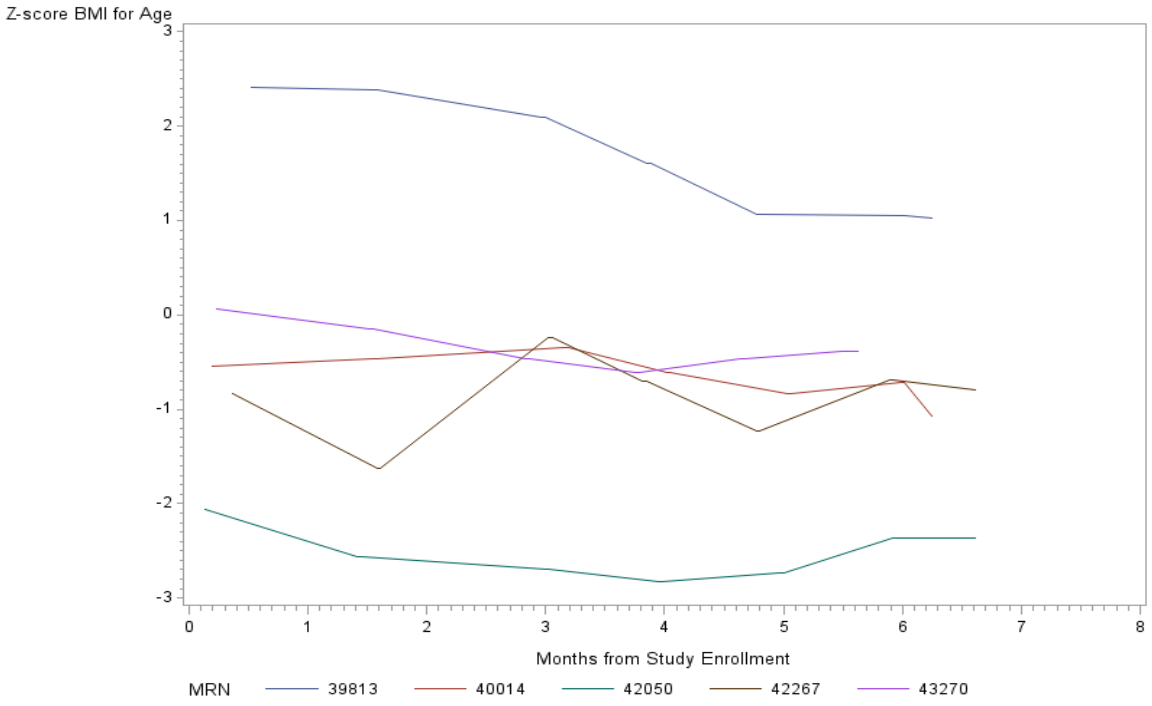

Figure 1. Z-scores for BMI for Age for Stratum W1 Patients (n=5). This figure shows the change in BMI-for-age z score throughout the months of treatment on the SJMB12 protocol. Each line represents a specific patient's MRN (medical record number). Mild malnutrition is classified by having a z score between -1 to -1.9. Moderate malnutrition is classified by having a z score of -2 to -2.9 z score while severe malnutrition is classified has having a z score of -3 or greater.

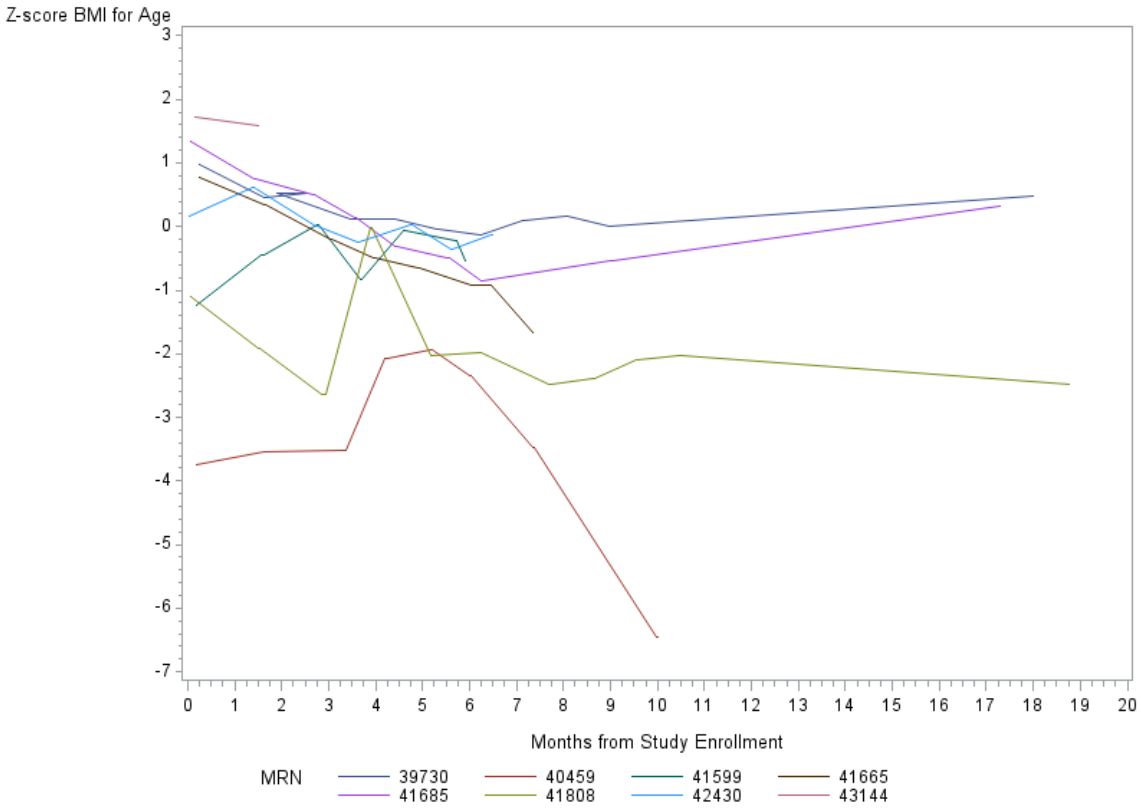

Figure 2. **Z-scores for BMI for Age for Stratum S1 and S2 Patients (n=8).** This figure shows the change in BMI-for-age z score throughout the months of treatment on the SJMB12 protocol. Each line represents a specific patient's MRN (medical record number). Mild malnutrition is classified by having a z score between -1 to -1.9. Moderate malnutrition is classified by having a z score of -2 to -2.9 z score while severe malnutrition is classified has having a z score of -3 or greater.

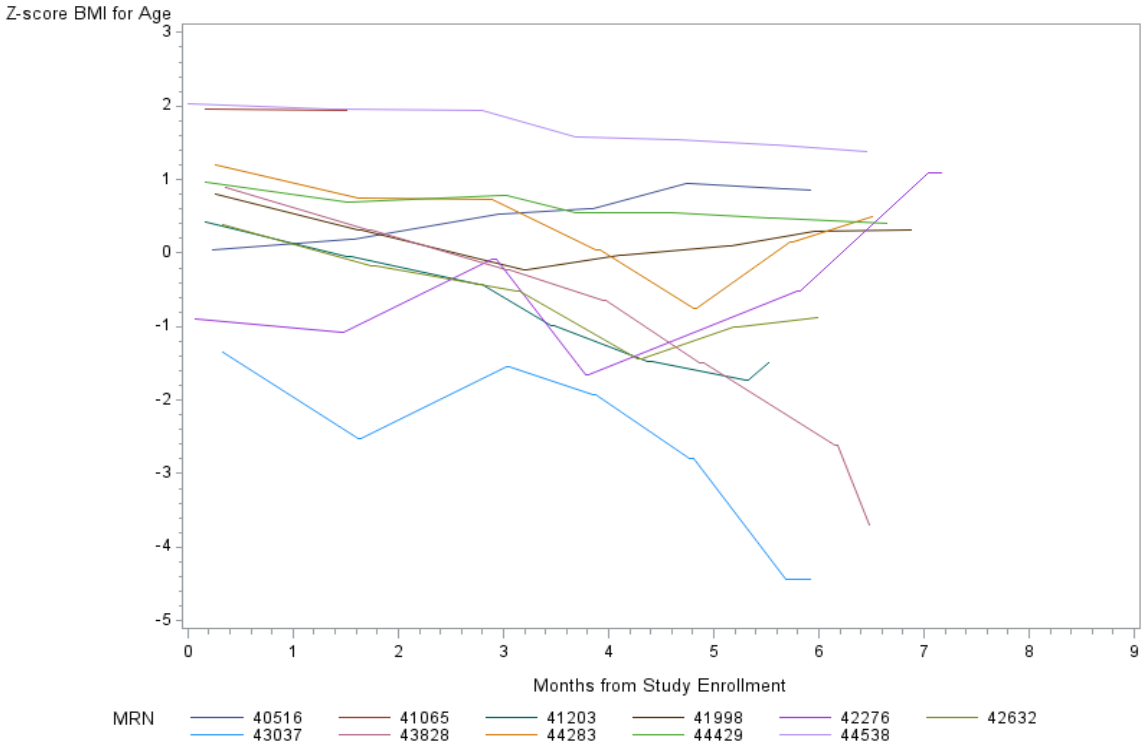

Figure 3. Z-scores for BMI for Age for Stratum N1 Patients (n=11). This figure shows the change in BMI-for-age z score throughout the months of treatment on the SJMB12 protocol. Each line represents a specific patient's MRN (medical record number). Mild malnutrition is classified by having a z score between -1 to -1.9. Moderate malnutrition is classified by having a z score of -2 to -2.9 z score while severe malnutrition is classified has having a z score of -3 or greater.

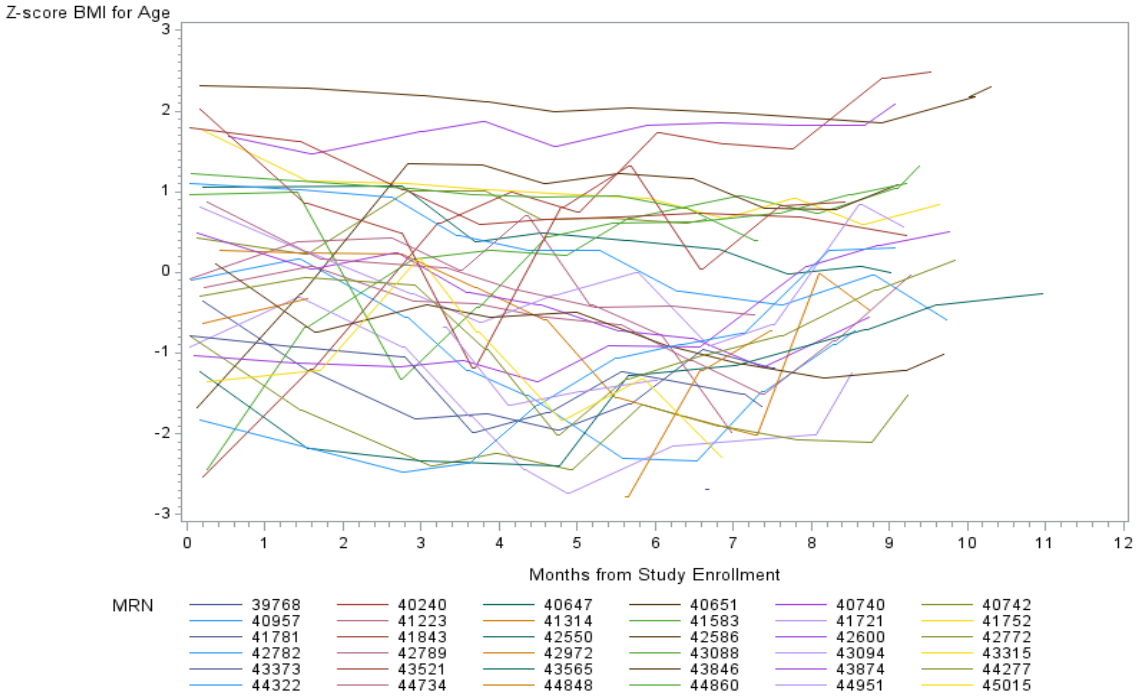

Figure 4. Z-scores for BMI for Age for Stratum N2 and N3 Patients (n=36). This figure shows the change in BMI-for-age z score throughout the months of treatment on the SJMB12 protocol. Each line represents a specific patient's MRN (medical record number). Mild malnutrition is classified by having a z score between -1 to -1.9. Moderate malnutrition is classified by having a z score of -2 to -2.9 z score while severe malnutrition is classified has having a z score of -3 or greater.

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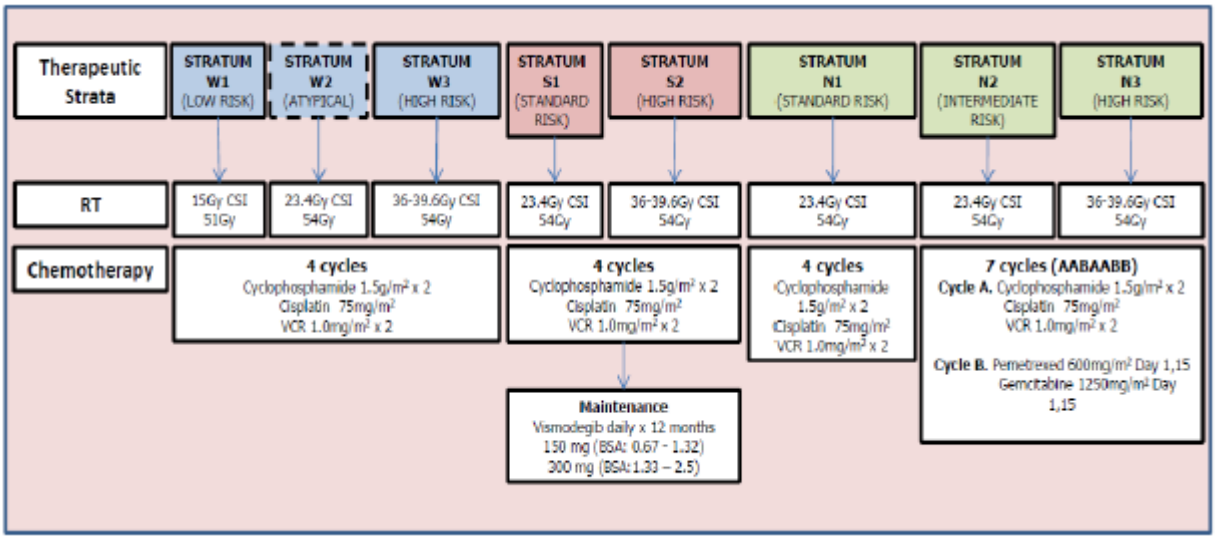
APPENDIX A



SJMB12 treatment schema

APPENDIX B

Abbreviations	
SJMB12	Clinical and Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma
CTCAE	Common Terminology Criteria for Adverse Events
WNT	Literally "wingless" + "int-1" – describes a cellular signaling pathway that is disrupted in certain cancers
SHH	Sonic Hedgehog
M stage	Level of Metastasis
EN	Enteral Nutrition
PN	Parenteral Nutrition
BMI	Body Mass Index
A.S.P.E.N	The American Society for Parenteral and Enteral Nutrition
SDS	Standard Deviation Score
CTC	Common Terminology Criteria
PEG	Percutaneous Endoscopic Gastrostomy

APPENDIX C

LITERATURE REVIEW

Nutrition Status: Optimal nutrition status is related to an improved prognosis within the pediatric cancer population. An ideal nutrition status benefits the patients to be able to better handle the cancer-related burdens to the body. Additionally, growth, a necessity in the pediatric population, is achieved in patients who adequately meet their nutrition needs.1 Pediatric oncology patients experiencing poor nutrition status, both under- and overnutrition, have higher risks for complications during treatment and survivorship, such as the development of endocrine and cardiovascular problems, decreased quality of life, increased rates of relapse, and mortality.1-2

Malnutrition: Although malnutrition is most commonly associated with undernourishment, overnourishment is also a form of malnutrition. A classification of undernourishment involves a patient whose diet does not meet their energy and protein needs for growth and healing, whereas overnourishment exceeds those needs. Undernourishment can also be classified when the patient is not capable of full utilization of the incoming nutrients due to the advancement of the disease state.3 The prevalence of malnutrition in the pediatric oncology population ranges from 6-50%; however, the differences observed are dependent upon the several factors: cancer type, stage, and criteria used to determine nutritional status.4 According to The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), pediatric malnutrition can now be defined as “an imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development and other relevant outcomes.” In the past, malnutrition was measured in various ways: ideal body weight, decreases in two centile channels, deceleration of weight in time, etc. However, the use of the z score is what is now recommended for proper malnutrition classification. Weight gain velocity is an important

indicator for identifying malnutrition in pediatrics. When a child is well nourished, the rate of weight gain will remain stable on growth charts.5 Very low weight gain velocity measured via z score has been distinguished to be an accurate indicator of mortality, more so than other such measurements i.e., BMI for age.6 A decrease in nutritional intake leading to weight loss can be caused by many factors: anorexia, damage to the mucous membranes, taste perception, and etcetera.7 Hospitalized pediatric patients experiencing malnutrition are at greater risk for complications due to their disease state, poor wound healing, and delayed energy levels. Some studies suggest that as high as 25% of pediatric patients in a hospital setting experience acute protein-energy malnutrition. These factors can lead to higher healthcare costs and prolonger hospitalization stays.5 Evidence shows that patients with advance disease, such as medulloblastoma, are at a high risk of developing malnutrition.3 Because infancy and adolescence require increased needs for growth, these specific populations are at an even greater risk for developing this condition. Cancer cachexia (a state of severe malnutrition) is commonly seen in pediatric patients. Cancer cachexia is characterized by anorexia, weight loss, muscle wasting, and anemia.8

Quality of Life: Malnutrition is associated with lower quality of life in pediatric oncology patients. In a study done by Brinksma et al., patients who were undernourished had lower PedsQL scores in physical and social functioning, nausea and overall cancer summary scale. Weight loss was linked with lower scores in physical functioning, emotional and social functioning, pain, and nausea. Overnourished children were associated with lower scores in emotional and cognitive functioning, social functioning, and cancer summary scale, while weight gain accompanied worse social functioning and more pain.2

Point Prevalence and Ideology of Malnutrition: Presently, there are no agreed upon standards for nutrition intervention strategies in the pediatric cancer population regarding criteria for implementation, timing, or duration.9 Longitudinal studies involving brain malignancies are rare and little is known about the exact timing or causation of malnutrition onset during treatment in this specific population. As such, more studies need to be done in order to identify the timing of optimum nutrition strategies.2 In a retrospective cohort study of 327 patients done to determine the point prevalence of malnutrition in pediatric cancer patients, it was shown that the incidence of malnutrition rose during anticancer therapy. Twenty-two percent of patients experiencing malnutrition at 30 days, 36% at 60 days and the incidence peaked at 47% later in treatment. Medulloblastoma patience experienced the highest rate and longest occurrence of malnutrition. At 311 days into treatment, 94% of medulloblastoma patients were considered malnourished using BMI SDS <−2.0 and weight loss of >10% as criteria for malnutrition. Medulloblastoma patients also had the highest odds of becoming malnourished using univariable logistic regression. During therapy, there were several qualities that resulted in higher rates of malnutrition: age >10 years, female gender, emotegenic drugs, and lower BMI at diagnoses.3 Adverse effects, such as weight loss, vomiting, and constipation, can be commonly seen as a result of both radiation and chemotherapy. In a study documenting nutritional problems in medulloblastoma patients during treatment, it was noted that 49% of patients had significant adverse effects (grade 1 or above CTC score) of vomiting and constipation after radiation therapy. A peak significant weight loss (mean of -8.2% since diagnoses) and weight/height loss ratio (mean of 91.3%) was observed during course 2 of chemotherapy. However, neither age nor toxicity were found to be statistically significant with the occurrence of weight loss in this study.7 In another study dealing with medulloblastoma patients performed by Bakish et al., it

was noticed that there are both significant and insignificant weight loss changes reliant upon the timing during the course of treatment. In that study, weight loss after surgery and radiation therapy was not significant; however, weight loss from the start and 3 months into chemotherapy was significant at 4.35% (P 0.001). Significant weight loss was determined using a loss >5% of their body weight.10

Body Composition: The ideology of body composition change during cancer treatment is largely unknown. However, it is hypothesized to be related to a myriad of issues related to cancer and treatment, such as altered energy intake and expenditure, inflammation, malabsorption, and loss of nutrients. In a study of childhood cancer survivors, it was determined that the survivors had significantly different body compositions than controls with survivors showing increased fat mass (FM) and decreased body cell mass index (BCMI).1 This was also seen in a study stratifying body composition differences between cancer types. In that study, brain cancer patients had increased FM and the lowest fat-free mass (FFM) compared with other cancer malignancies. The loss of fat-free mass is associated with poorer prognosis and increased protein needs.2 According to Ballal et al., the loss of fat-free mass is a documented side-effect of chemotherapy.8

Nutrition Intervention: There are various nutrition intervention strategies in order to combat malnutrition. The use of a Registered Dietitian, for example, has been seen to improve nutrition status and improve quality of life outcomes in adult pediatric patient populations.11-12 Oral appetite stimulates, specifically cyproheptadine hydrochloride and/or megestrol acetates, use in pediatrics have been found to result in weight gain in clinical trials; however, megestrol acetate treatment has also been found to be associated with a multitude of negative side-effects in pediatric patients.13-15 When it comes to preventing malnutrition, the oral route of feeding

administration is ideal; however, because of adverse effects seen during treatment, the enteral feeding route may be necessary to achieve adequate nutrition.16 Enteral nutrition is preferred over parental nutrition since those on enteral nutrition experience less incidences of infection and are maintaining and promoting gut function.17-18 Enteral nutrition has been determined to be a safe and effective strategy to promote combat undernutrition in the pediatric cancer population.16 Nevertheless, parental nutrition may be a necessity to ensure nutrition status in some patients. In a study done by Bakish et al., differences between nutrition strategy interventions on weight status in newly diagnosed medulloblastoma patients were noted. It was found that oral nutrition resulted in a significant weight loss after 1 month of implementation. Parenteral nutrition resulted in weight gain only after 1 month of implementation, while enteral nutrition (gastrostomy/nasogastric tube insertion) brought about a significant weight gain after both 1 month (4.78%) and 3 months (11.73%) of implementation.10 In a study of proactive verses reactive feeding strategy differences in newly diagnosed cancer patients, it was shown that one third of subjects with brain tumors were underweight at diagnosis. Although the proactive participant group experienced more incidence of infection i.e., localized infection, the control group experienced episodes of polymicrobial sepsis, Streptococcus mitis infection and fungal infection, while the proactive group did not. Those not in the proactive group also were also twice as likely to receive parenteral nutrition. Overall, the proactive participant group experienced less weight loss and was the only group that improved in nutrition status at the end of the study.19

Timing of Nutrition Intervention: Several studies demonstrate the need for proactive nutrition intervention strategies in order to combat nutritional decline during anticancer treatment.7, 20 In past studies, proactive enteral feeding resulted in improved nutrition status outcomes, while the

placement of PEG tubes at diagnoses have brought about fewer surgical complications, relapses, and deaths.21 In the study done by Ward et al., there were significant differences between centers that treated malnutrition proactively and reactively by use of enteral feeding. At course 2 of chemotherapy, the mean % weight loss in the proactive center peaked at around 7 % compared to around 9% in the reactive center. Although both centers saw an increase in mean % weight loss, nutrition status in the proactive center began to improve after course 2 of chemotherapy, while nutrition status continued to decline in the reactive center. By course 7 of chemotherapy, the reactive center had a mean % weight loss of 11.6% compared to only 2.4% in the proactive center.7

Infection Risk: Pediatric oncology patients are at high risk for developing infections, particularly during chemotherapy-induced neutropenia. These infections are related to high morbidity and mortality rates. Infections can postpone therapy and lead to a reduction of chemotherapy dose. Malnourished children are at even greater risk for developing infections. This has been attributed to possible changes in hormones and cytokine response. Moreover, malnutrition may decrease the efficiency of treatment by reducing dose toleration and absorption of chemotherapy drugs. In a study done by Loeffen et al., it was found that patients who were malnourished at diagnoses and 3 months into treatment had higher rates of mortality. Patients who lost more than 5% of their body weight 3 months into treatment were found to also have higher rates of bacteremia related febrile occurrences. The study concluded that the monitoring of nutrition status and proactive nutrition intervention could increase survival rates in the future.22

Obesity: Obesity in cancer survivors is related to a combination of factors during treatment: glucocorticoids, chemotherapy, cranial irradiation and psychosocial stressors.23 Obesity and weight gain are common issues specifically linked with various brain cancers.24 Hypothalamic

damage from tumor location, surgery, or irradiation is the primary cause of obesity in survivors. Tumors located within the hypothalamus, removal of the hypothalamus as a result of surgery, and irradiation above 51 Gy, are all considered to be risk factors for increased BMI post-therapy. The age of diagnoses can also have an effect on weight gain risk. Those diagnosed at or before the age of six tend to increase BMI at a faster and more significant rate than those diagnosed later.23 Additionally, irradiation to the cranium can lead to decreased sensitivity to leptin, the satiety hormone.8 The Childhood Cancer Survivor Study found that females at or below the age of four exposed to cranial irradiation above 20 Gy were at an even greater risk for developing obesity.25 Exposure to dexamethasone (used in chemotherapy) is also associated with obesity, while the use of glucocorticoids leads to increased fat mass.8, 26

Metabolic Syndrome: Metabolic syndrome includes visceral adiposity, insulin resistance, dyslipidemia, and hypertension. According to studies, the risk for developing metabolic syndrome increases in survivors of pediatric cancer compared to the general population.27 In an additional study, it was found that survivors had a greater risk of hyperinsulinemia and reduced HDL concentrations.28 Similarly, those that had undergone transplantation were found to have had the highest prevalence of metabolic syndrome in a separate study.29 Risk factors for the development of metabolic syndrome include an older age at diagnoses and cranial radiation exposure.30

Cardiovascular Disorders: The St. Jude Lifetime Cohort study, in combination with other studies, found that pediatric cancer survivors have an increased prevalence of cardiovascular disease.31 In one cohort, individuals were 5 times more likely to die from cardiovascular disease and 5.8 times more likely to die from vascular disease. The risk increased in those that had been exposed to radiation and alkylating agents.32 Alkylating agents, such as cisplatin and cyclophosphamide,

include dyslipidemia as an established late effect.31 Obesity, hypertension, dyslipidemia and impaired fasting glucose put survivors at increased risk for cardiovascular disorders.33 Because survivors are at increased risk for the development of metabolic disease, they may also be at increased risk for the development of heart disease.8

Diabetes Mellitus: Survivors of childhood cancers have an increased risk of developing diabetes. A report from the Childhood Cancer Survivor Study concluded that cancer survivors have a higher prevalence of diabetes mellitus when compared to their siblings. Cranial irradiation, the use of alkylating agents, and younger age at diagnoses (less than 4 years), were associated with increased risks. Black and Hispanic/Latino cancer survivor populations were also observed to be at higher risk for the development of this disease later in life.34

Growth Effects: Growth is used as a measure of nutritional status, whereas stunting develops as a result of chronic malnutrition.5 Cranial irradiation causes detrimental effects on growth.35 Subnormal GH secretion combined with decreased GH levels after irradiation contributes to the fact that 40-70% of patients treated for brain tumors will have decreased growth and short stature.36-41 The effects on GH are more severe in patients exposed to 18 to 20 Gy.42 GH deficiencies are dependent upon several factors: fraction size of radiation, age of diagnosis, and the time interval between treatments.24 Hypothalamic damage, due to the focused area of radiation, is thought to be the primary cause of the observed GH deficiency.36, 39, 43-44 Medulloblasoma patients are also exposed to spinal irradiation, which can lead to a decrease in total height as demonstrated by a decrease in sitting height.35, 41 Moreover, chemotherapy is known to have several negative effects on growth, such as growth arrest, bone age retardation, and catch-up growth delays.35 Medulloblastoma patients are at even greater risk for adverse growth effects due to the combination of craniospinal radiation and chemotherapy treatments.45

Additionally, the use of glucocorticoids can result in growth inhibition and bone metabolism alteration. Glucocorticoids are also known to compete for GH action; consequently, growth inhibition and deceleration are observed after treatments involving glucocorticoid use.35

APPENDIX D

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