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Patterns of Radiation-Associated Lymphopenia in Children with Cancer

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Abstract

Adults with cancer commonly develop severe lymphopenia two months following chemoradiation therapy, which is an independent predictor of survival. In this retrospective study of 53 children with central nervous system tumors and sarcomas, the frequency, severity, and duration of radiation-associated lymphopenia was similar to that seen in adults. Pretreatment lymphocyte counts were 1,000 cells/mm³ or greater in all patients, with 66% experiencing grade III-IV lymphopenia two months after chemoradiation. Lymphocyte counts remained significantly lower than baseline 12 months later. Further studies are needed to determine if this is also associated with poorer survival, as seen in adults.

Keywords

Brain tumors; Sarcomas; Radiation therapy; Lymphopenia

Introduction

Lymphocytes are essential effector cells in the immune response to cancer (1). Intratumoral T-cell infiltration is a favorable prognostic factor in many solid tumors, including nonsmall cell lung cancer (NSCLC), breast, colorectal and ovarian cancers, and glioblastoma (2–5). Conversely, pretreatment lymphopenia is an independent predictor of worse overall survival in adults with sarcomas, lymphomas, and metastatic solid tumors (6, 7). More significantly, radiation-associated lymphopenia is an independent predictor of survival in adults with brain (8), pancreatic (9, 10), and lung cancer (11).

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

T-cells, which play a central role in the immune system's response to cancer (1), originate from hematopoietic stem cells in the bone marrow as double-negative thymocytes, and undergo maturation through positive and negative selection in the thymic true epithelial space (TES). Only two percent of all T lymphocytes successfully migrate into peripheral circulation and secondary lymphatic organs as naïve T-cells (12). This process is most active just after birth and slows down at one year of age, when the TES is at its maximum size, comprising 95% of the total thymic volume (13). The proportion of the thymus occupied by the TES decreases to approximately 60% at age 10, 40% at age 20, and is less than 10% at age 50 (14). Accordingly, the capacity of the thymus to regenerate following severe depletion decreases with age, as shown in several experimental models that used sublethal doses of radiation (12).

In children with hematologic malignancies, the absolute lymphocyte count (ALC) at the end of induction therapy is a strong predictor of outcome (15, 16). In addition, early lymphocyte recovery, considered to be ALC 500–800 cells/mm³ 14 days following the first cycle of chemotherapy, is thought to be an independent predictor of survival in patients with Ewing sarcoma (17), and children with osteosarcoma (18). The extent and duration of posttreatment lymphopenia in pediatric patients who received radiation for the treatment of solid tumors has not been reported till date.

Children with newly diagnosed solid tumors—unlike those with hematologic malignancies—typically have normal immune parameters, including T-cell, B-cell, and NK-cell distribution, T-cell receptor repertoire, and T-cell receptor excision circle values (19) at the time of diagnosis. It is, therefore, unknown if children have a greater capacity to recover from radiation-associated lymphopenia than do adults, who frequently have demonstrable abnormalities in circulating lymphocyte populations as long as 10 years after radiation exposure (20). With the developing immune system and thymic capacity for regeneration in mind, this hypothesis-generating study was conducted to determine if children treated with chemoradiation experience the same frequency, severity, and duration of lymphopenia as adults.

Methods and materials

The study was reviewed and approved by our institution's internal institutional review board. Informed consent for radiation treatment had been provided before therapy in all cases. The medical records of 65 pediatric patients with sarcomas and 103 with brain tumors were identified in a database of 168 children, who underwent concurrent chemotherapy and radiation at the authors' home institution, which is a large tertiary care center with a dedicated pediatric oncology service, from 1997–2011. Eligibility criteria for inclusion in this study were: (1) 21 years of age; (2) at least one complete blood count performed before chemotherapy and/or radiation therapy (RT) that was accessible through the electronic patient record; and (3) monthly or bimonthly complete blood counts available from initiation of therapy until at least 12 months afterwards. Patients were excluded if they had received any prior chemotherapy or radiation treatment, or if they had any part of their treatment done elsewhere. Fifty-three children, 28 with brain tumors and 25 with sarcomas, met the criteria and comprised the study population.

In addition to demographic data and monthly ALCs, the following information was obtained from the medical record of each patient: tumor grade, primary location, size, clinical stage, dose and duration of RT, and chemotherapy regimens. In children with sarcomas, time between initiation of neoadjuvant chemotherapy and radiation was recorded, as well as prechemotherapy and preradiation ALCs. Baseline ALCs were classified as normal ($> 1,000$ cells/mm³) or abnormal ($< 1,000$ cells/mm³). Following the initiation of antineoplastic treatment, the National Cancer Institute's common terminology criteria for adverse events (CTCAE) (version 4.0) were used to classify the severity of lymphopenia. The ALCs at two months after the initiation of radiation and chemotherapy were dichotomized to CTCAE grade I-II vs. grade III-IV for the relevant analyses. For patients with missing counts at two months, the ALCs at one month were used instead. In all cases, only those ALCs taken at least 28 days following administration of chemotherapy were considered.

Patient baseline characteristics were summarized using descriptive statistics. Chi-square test statistics were used to compare the number of children with CTCAE grade III-IV lymphopenia (ALC < 500 cells/mm³) before and after therapy. Mean ALCs at different time points were compared using paired *t* test. The two sample *t* test were used for between group comparisons. All *p* values are reported as two-sided, and all analyses were conducted using SAS software (version 9.1, SAS Institute).

Results

Baseline patient characteristics

A total of 53 patients, 28 with central nervous system (CNS) tumors and 25 with sarcomas, were studied. Baseline demographic information is provided in Table 1. All children had received some form of chemotherapy along with radiation. Sixty-four percent of patients with sarcomas received neoadjuvant chemotherapy, consisting of vincristine, doxorubicin, and cyclophosphamide (50%); vincristine, actinomycin D, and cyclophosphamide/ ifosfamide (43%); or vincristine and irinotecan (7%). All went on to receive cyclophosphamide or ifosfamide-containing adjuvant chemotherapy for a median duration of 24 weeks (range 6–39). Patients with CNS tumors did not receive neoadjuvant therapy. Adjuvant chemotherapy for patients with CNS tumors consisted of vincristine, cisplatin/ carboplatin, and lomustine (28% of patients); temozolomide (25%); vincristine, cisplatin, and cyclophosphamide (21%); cetuximab and irinotecan (11%); or arsenic trioxide (11%). The median duration of chemotherapy was 28 (range 3–52) weeks. Overall, 70% of patients received a chemotherapy regimen containing a potentially lymphotoxic drug (cyclophosphamide, ifosfamide, or temozolomide).

The median duration of RT was 36 days (26 fractions, range 5–40) in children with sarcomas and 42 days (30 fractions, range 13–45) in those with CNS tumors. Fifty percent of children with CNS tumors received craniospinal radiation. At the time of this analysis, death had been reported in 32% of patients, including 28% of children with sarcomas and 35% of those with brain tumors.

Absolute lymphocyte counts over time

Pretreatment ALCs were 1,000 cells/mm³ in all but one patient, with a median of 2,430 cells/mm³ (range 1,200–5,490) in the sarcoma group and 2,175 cells/mm³ (range 700–4,502) in the CNS tumor group. All children with sarcomas had received neoadjuvant chemotherapy and had preradiation ALCs that were significantly lower than baseline (median 550 cells/mm³, range 50–3,213, $p < .01$), with 48% having grade III-IV lymphopenia. Two months after beginning RT, they experienced a further, significant decrease compared to preradiation ALCs [median 480 cells/mm³, range 5–890, $p < .03$; Figure 1(A)]. ALCs remained significantly lower than baseline 12 months later (median 1,145 cells/mm³, range 240–2,239, $p < .05$).

In children with CNS tumors, median ALCs two months after the start of chemoradiation were 300 cells/mm³ (range 45–2,450, $p < .0001$ compared to baseline) and remained significantly lower than baseline 12 months later [median 415 cells/mm³, range 50–1,180, $p < .02$; Figure 1(B)]. Patients with medulloblastoma, the only in our data set to have received craniospinal radiation, were significantly more lymphopenic at two months than those with other brain tumors (93% vs. 39% with grade III-IV lymphopenia, $p = 0.0019$, Figure 2).

The combined data from all 53 patients show that two months after initiation of chemoradiation, 66% of all patients experienced grade III-IV lymphopenia. As noted in Table 1, there was no significant difference in the baseline demographic characteristics, including age of patients whose ALCs remained above 500 cells/mm³ or fell significantly at two months after chemoradiation treatment. Both children who received lymphotoxic agents as part of their chemotherapy regimen and those who did not, experienced a similar decrease in ALCs two months after RT. In patients who received potentially lymphotoxic chemotherapy, the median ALC two months after treatment was 300 cells/mm³ (range 100–1,960); and in patients who did not, median ALC two months after treatment was 470 cells/mm³ (range 10–2,450) ($p = 0.17$). Twelve months after radiation, median ALC = remained significantly lower than baseline both in patients who had, and had not received lymphotoxic induction chemotherapy (198 cells/mm³, range 50–420, $p < .0001$ and 850 cells/mm³, range 240–2,239, $p < .0001$, respectively).

Discussion

We performed this study to describe the incidence, severity, and duration of radiation-associated lymphopenia in a group of children receiving therapy for CNS tumors and sarcomas. Radiation-associated lymphopenia has been correlated with inferior overall survival in adults with a number of treatment-refractory solid tumors, including glioblastoma (8), pancreatic cancer (9, 10), and NSCLC (11). It is unknown if children are as susceptible to the development of radiation-associated lymphopenia as adults, given the differences in pediatric vs. adult immune physiology, particularly with respect to the age-related involution of the thymus gland.

Our results demonstrate that despite the presence of presumably functional thymic tissue (19), and normal baseline lymphocyte counts in a group of children receiving chemotherapy and radiation treatment for sarcomas and CNS tumors, the development of prolonged and

severe lymphopenia was common, with 66% of children developing grade III-IV lymphopenia two months after beginning chemoradiation. Interestingly, in this group of patients, no relationship was observed between age and the severity of lymphopenia, as might be expected if the thymus—which progressively involutes with age—were involved in the response to the lymphopenia that we observed. Although lymphopenia was observed in children treated with lymphotoxic chemotherapy regimens (including cyclophosphamide, ifofamide, and temozolomide), children who received lymphotoxic induction chemotherapy regimens experienced a further worsening of lymphocyte counts with the initiation of RT. Additionally, lymphopenia persisted during an entire year of follow-up, even after the completion of maintenance chemotherapy. In contrast, lymphocyte recovery following cytotoxic chemotherapy alone is more rapid, with ALCs generally return to normal within three months of completing treatment (21). This confirms a similar finding in 67 children who received craniospinal radiation for posterior fossa tumors, and had decreased ALCs for up to six years of follow-up. While in our study lymphopenia was indeed more common in children with medulloblastomas who received craniospinal radiation (Figure 2), it was present across all tumor types and sizes. Furthermore, in children with sarcomas decreased ALCs did not vary by tumor location, even though the amount of bone marrow involved by the radiation field was variable.

Studies in adults have documented severe, long-lasting lymphopenia following radiation regardless of concurrent chemotherapy and corticosteroid use (8–11, 22). The same studies have demonstrated a correlation between the development of radiation-associated lymphopenia and inferior overall survival. In addition, two prospective studies of adults with glioblastoma demonstrated significant drops in ALCs following RT, regardless of whether temozolomide was used or not (8, 22).

Similar findings have also been observed in adults with visceral solid tumors. In 53 patients with resected pancreatic adenocarcinoma, 45% had grade III-IV lymphopenia two months after receiving adjuvant RT with either 5-FU or gemcitabine-based regimens that are not typically considered to be lymphotoxic (9). Adults who developed radiation-associated lymphopenia had a significantly increased risk of death (HR for death 2.20, 95% CI 1.17–4.12, $p = 0.01$). Likewise, adults with unresectable pancreatic cancer who were treated with definitive chemoradiation had a high rate of grade III-IV radiation-associated lymphopenia—46% (10). Adults with radiation-associated lymphopenia also had poorer survival (HR for death 2.88, 95% CI 1.53–5.41, $p = 0.001$). A 50% rate of grade III-IV lymphopenia was observed in a group of 47 adults with NSCLC. Patients in this group who developed radiation-associated lymphopenia also were found to have a trend towards decreased overall survival (HR 1.70, 95% CI 0.80–3.61, $p = 0.17$) (11).

Radiation-associated lymphopenia was first described in the early 20th century, within 20 years of the initial discovery of X-rays, and is likely due to the irradiation of circulating lymphocytes as they flow through the radiation treatment field (23, 24). In the mid-20th century, as radiation treatment became a common cancer treatment modality, decreased lymphocyte counts following focal RT were documented after external beam irradiation of many different sites (including the brain, breast, lung, genitourinary tract, and rectum), regardless of whether bone marrow or lymphatic tissue was included in the field (25). Even

extracorporeal irradiation of blood in adults undergoing hemodialysis causes severe and durable lymphopenia (26).

A recent study that calculated the dose received by circulating blood during a typical course of RT for a brain tumor (2 Gy $\times$ 30 fractions) showed that all of the circulating blood had received at least 0.5 Gy by the end of treatment (24). The mean dose to circulating lymphocytes was 2 Gy, enough to decrease the number of lymphocytes by half (27). The most important factor modifying the dose to circulating blood was thought to be the number of fractions. Field size, dose rate, and delivery techniques also contributed, but were much more difficult to change appropriately without decreasing the dose delivered to the target volume (24). The more profound lymphopenia seen in our patients receiving craniospinal irradiation (CSI) for medulloblastoma seems to corroborate this, as craniospinal radiation treats a large field that includes the bone marrow, but that also includes major blood vessels, such as the aorta. Monitoring ALCs in patients undergoing proton-beam CSI, which includes bone marrow but not structures anterior to the vertebral bodies (28), could further elucidate how much irradiation of the vasculature contributes to radiation-associated lymphopenia.

This study was limited by its retrospective design and small sample size. Due to the low number of deaths observed and a heterogeneous population that received several different treatment regimens, we were unable to analyze any correlations between radiation-associated lymphopenia and survival. Nevertheless, we demonstrated that children with solid tumors experience severe radiation-associated lymphopenia that starts soon after initiation of therapy and is long-lasting, following a similar pattern to that of adults. Although children who received lymphotoxic chemotherapy with radiation had the lowest lymphocyte counts one year after treatment, lymphocyte counts one year after RT were abnormally low in all patients, regardless of what type of chemotherapy was given. Radiation-associated lymphopenia appears to be strongly correlated with inferior overall survival in adult cancer patients. Pediatric patients with solid tumors have an overall better prognosis than adults, limiting extrapolation. However, in children with hematologic malignancies ALC at the end of induction therapy is a strong predictor of outcome (15, 16). Further research is needed to determine to what extent posttreatment lymphopenia in pediatric patients with solid tumors is associated with radiation, and whether there is a correlation with inferior overall survival. If such a correlation is demonstrated, preservation of the immune system during treatment may become of major importance in pediatric oncology.

References

1. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011; 480:480–489. [PubMed: 22193102]
2. Hiraoka K, Miyamoto M, Cho Y, et al. Concurrent infiltration by CD8+ T-cells and CD4+ T-cells is a favorable prognostic factor in nonsmall-cell lung carcinoma. *Br J Cancer*. 2006; 94:275–280. [PubMed: 16421594]
3. Lohr J, Ratliff T, Huppertz A, Ge Y, Dictus C, Ahmadi R, et al. Effector T-cell infiltration positively impacts survival of glioblastoma patients and is impaired by tumor-derived TGF- β . *Clin Cancer Res off J Am Assoc Cancer Res*. 2011; 17:4296–4308.

4. Gooden M, Lampen M, Jordanova ES, Leffers N, Trimpos JB, van der Burg SH, et al. HLA-E expression by gynecological cancers restrains tumor-infiltrating CD8+ T lymphocytes. *Proc Natl Acad Sci USA*. 2011; 108:10656–10661. [PubMed: 21670276]
5. Gu-Trantien C, Loi S, Garaud S, Equeter C, Libin M, de Wind A, et al. CD4+ follicular helper T-cell infiltration predicts breast cancer survival. *J Clin Invest*. 2013; 123:2873–2892. [PubMed: 23778140]
6. Ray-Coquard I, Dussart S, Goillot C, Mayeur D, Debourdeau P, Ghesquieres H, et al. A risk model for severe anemia to select cancer patients for primary prophylaxis with epoetin alpha: A prospective randomized controlled trial of the ELYPSE study group. *Ann Oncol off J Eur Soc Med Oncol ESMO*. 2009; 20:1105–1112.
7. Lissoni P, Brivio F, Fumagalli L, Messina G, Ghezzi V, Frontini L, et al. Efficacy of cancer chemotherapy in relation to the pretreatment number of lymphocytes in patients with metastatic solid tumors. *Int J Biol Markers*. 2004; 19:135–140. [PubMed: 15255546]
8. Grossman SA, Ye X, Lesser G, Sloan A, Carraway H, Desideri S, et al. Immunosuppression in patients with high-grade gliomas treated with radiation and temozolomide. *Clin Cancer Res off J Am Assoc Cancer Res*. 2011; 17:5473–5480.
9. Balmanoukian A, Ye X, Herman J, Laheru D, Grossman SA. The association between treatment-related lymphopenia and survival in newly diagnosed patients with resected adenocarcinoma of the pancreas. *Cancer Invest*. 2012; 30:571–576. [PubMed: 22812722]
10. Wild AT, Ye X, Ellsworth SG, Smith JA, Narang AK, Garg T, et al. The association between chemoradiation-related lymphopenia and clinical outcomes in patients with locally advanced pancreatic adenocarcinoma. *Am J Clin Oncol*. 2013; 0:1–7.
11. Campian JL, Ye X, Brock M, Grossman SA. Treatment-related lymphopenia in patients with stage III nonsmall-cell lung cancer. *Cancer Invest*. 2013; 31:183–188. [PubMed: 23432821]
12. Globerson A. Developmental aspects of the thymus in aging. *Adv Cell Aging Gerontol*. 2003; 13:47–78.
13. George AJ, Ritter MA. Thymic involution with ageing: Obsolescence or good housekeeping? *Immunol Today*. 1996; 17:267–272. [PubMed: 8962629]
14. Steinmann GG, Klaus B, Müller-Hermelink HK. The involution of the ageing human thymic epithelium is independent of puberty: A morphometric study. *Scand J Immunol*. 1985; 22:563–575. [PubMed: 4081647]
15. De Angulo G, Yuen C, Palla SL, Anderson PM, Zweidler-McKay PA. Absolute lymphocyte count is a novel prognostic indicator in ALL and AML. *Cancer*. 2008; 112:407–415. [PubMed: 18058809]
16. Rubnitz JE, Campbell P, Zhou Y, Sandlund JT, Jeha S, Ribeiro RC, et al. Prognostic impact of absolute lymphocyte counts at the end of remission induction in childhood acute lymphoblastic leukemia. *Cancer*. 2013; 119:2061–2066. [PubMed: 23456849]
17. De Angulo G, Hernandez M, Morales-Arias J, Herzog CE, Anderson P, Wolff J, et al. Early lymphocyte recovery as a prognostic indicator for high-risk Ewing sarcoma. *J Pediatr Hematol Oncol*. 2007; 29:48–52. [PubMed: 17230066]
18. Moore C, Eslin D, Levy A, Roberson J, Giusti V, Sutphin R. Prognostic significance of early lymphocyte recovery in pediatric osteosarcoma. *Pediatr Blood Cancer*. 2010; 55:1096–1102. [PubMed: 20734401]
19. Wiegering V, Schlegel P-G, Winkler B. Immune function in newly diagnosed children with malignancy. *J Pediatr Hematol*. 2012; 34:559–564.
20. Raben M, Walach N, Galili U, Schlesinger M. The effect of radiation therapy on lymphocyte subpopulations in cancer patients. *Cancer*. 1976; 37:1417–1421. [PubMed: 1083285]
21. Mackall CL. T-Cell immunodeficiency following cytotoxic antineoplastic therapy: A review. *The Oncologist*. 1999; 4:370–378. [PubMed: 10551553]
22. Hughes MA, Parisi M, Grossman S, Kleinberg L. Primary brain tumors treated with steroids and radiotherapy: Low CD4 counts and risk of infection. *Int J Radiat Oncol Biol Phys*. 2005; 62:1423–1426. [PubMed: 16029802]
23. Shohan J. Some theoretical considerations on the present status of roentgen therapy. *Boston Med Surg J*. 1916; 175:321–327.

24. Yovino S, Kleinberg L, Grossman SA, Narayanan M, Ford E. The etiology of treatment-related lymphopenia in patients with malignant gliomas: Modeling radiation dose to circulating lymphocytes explains clinical observations and suggests methods of modifying the impact of radiation on immune cells. *Cancer Invest.* 2013; 31:140–144. [PubMed: 23362951]
25. Campbell AC, Hersey P, MacLennan IC, Kay HE, Pike MC. Immunosuppressive consequences of radiotherapy and chemotherapy in patients with acute lymphoblastic leukaemia. *Br Med J.* 1973; 2:385–388. [PubMed: 4574043]
26. Weeke E. The development of lymphopenia in uremic patients undergoing extracorporeal irradiation of the blood with portable beta units. *Radiat Res.* 1973; 56:554–559. [PubMed: 4767134]
27. Nakamura N, Kusunoki Y, Akiyama M. Radiosensitivity of CD4 or CD8 positive human T-lymphocytes by an *in vitro* colony formation assay. *Radiat Res.* 1990; 123:224–227. [PubMed: 2117766]
28. Yuh GE, Lored LN, Yonemoto LT, Bush DA, Shahnazi K, Preston W. Reducing toxicity from craniospinal irradiation: Using proton beams to treat medulloblastoma in young children. *Cancer J Sudbury Mass.* 2004; 10:386–390.

Figure 1.

Total lymphocyte counts of (A) children with sarcomas before and after neoadjuvant chemotherapy and chemoradiation and (B) children with CNS tumors before and after chemoradiation therapy (grade III-IV lymphopenia below the dotted line; * $p < .01$ compared to baseline, † $p < .05$ compared to after neoadjuvant chemotherapy).

Figure 2. Percentage of children with medulloblastomas and other tumors of the CNS who developed grade III-IV lymphopenia after treatment.

Table 1

Baseline characteristics of all patients and those with lymphocyte counts above and below 500 cells/mm³ at two months

	All patients (N = 53)	Patients with TLCs ≥ 500 at two months (N = 18)	Patients with TLCs < 500 at two months (N = 35)
Demographic data			
Age: median (range)	11 (2-20)	10.5 (3-19)	11 (2-20)
Male: no. (%)	28 (53)	6(33)	22 (62)
Caucasian: no. (%)	37(70)	13 (72)	24 (68)
Baseline laboratory data			
TLC: median (range)	2,320 (700-5,490)	2345 (1,170-5,490)	2,280 (700-4,300)
WBC: median (range)	7870 (3,640-32,160)	8,105 (3,640-32,160)	7,240 (3,940-27,570)
Hematocrit: median (range)	38.3 (28.2-48.6)	39.5 (28.5-45.2)	37.5 (28.2-48.6)
Platelets: median (range)	292 (29-532)	287.5 (136-532)	303 (29-501)
Tumor type			
CNS tumor: no. (%)	28 (53)	9 (50)	19 (54)
Medulloblastoma: no. (%)	15 (28)	1 (5)	14 (40)
Astrocytoma: no. (%)	6 (11)	4 (22)	2 (6)
High-grade glioma: no. (%)	6 (11)	4 (22)	2 (6)
Oligodendroglioma: no. (%)	1 (2)	-	1 (3)
Sarcoma: no. (%)	25 (47)	9 (50)	16 (46)
Rhabdomyosarcoma: no. (%)	14 (26)	6 (33)	8 (22)
Ewing's sarcoma: no. (%)	6 (11)	1 (5)	5 (14)
Synovial sarcoma: no. (%)	3 (6)	2 (11)	1 (3)
Chondrosarcoma: no. (%)	2 (4)	-	2 (6)
Tumor characteristics			
Size: mean (range)	5.20 (0.7-16)	5.99 (1.3-11)	4.79 (0.7-16)
Surgically resected: no. (%)	31 (58)	8 (44)	23 (66)
Location, CNS tumors			
Posterior fossa: no. (%)	12 (23)	1 (5)	11 (31)
Supratentorial: no. (%)	8 (15)	4 (22)	4 (11)
Brainstem: no. (%)	7 (13)	3 (17)	4 (11)
Spinal cord: no. (%)	1 (2)	1 (5)	-
Location, sarcomas			
Head and neck: no. (%)	10 (19)	4 (22)	6 (17)
Pelvis: no. (%)	7 (13)	2 (11)	5 (14)
Extremities: no. (%)	4 (7)	2 (11)	2 (6)
Chest: no. (%)	3 (6)	1 (5)	2 (6)
Abdomen: no. (%)	1 (2)	-	1 (3)
Treatment data			
Radiation dose (Gy): median (range)	50.4 (18.0-79.2)	50.7 (23.4-59.4)	50.4 (18.0-79.2)
Neoadjuvant chemotherapy: no. (%)	25 (47)	9 (50)	16 (46)
Concurrent chemotherapy			

	All patients (<i>N</i> = 53)	Patients with TLCs $\geq$ 500 at two months (<i>N</i> = 18)	Patients with TLCs < 500 at two months (<i>N</i> = 35)
Cyclophosphamide/ifosfamide: no. (%)	31 (58)	10 (56)	21 (60)
Temozolomide: no. (%)	7 (13)	2 (11)	5 (14)
Other: no. (%)	15 (28)	6 (33)	9 (26)