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Kelly Ann Hoth

Date _____

INTRODUCTION

Hodgkin's disease is a malignant lymphoma arising in the lymphatic tissues. It is characterized by the presence of Reed-Sternberg cells and can present in the lymph nodes, spleen, liver, bone marrow, lungs, thymus, and lymph vessels. Hodgkin's lymphoma accounts for approximately 6% of childhood cancers, and the survival rate for the disease is 70% to 90% (1). Pediatric musculoskeletal tumors are soft-tissue and bone tumors, including rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft-tissue sarcoma (STS), and Ewing's sarcoma family of tumors (ESFT). RMS is a highly malignant soft-tissue sarcoma originating from primitive muscle cells termed rhadomyoblasts. It accounts for approximately 40% of pediatric soft-tissue sarcomas and can arise wherever striated muscle is found in the body (2,3). Approximately 60% of diagnosed pediatric soft-tissue sarcomas are classified as non-rhabdomyosarcoma. These tumors originate in mesenchymal cells and can present anywhere in the body, except bone. It has recently been shown that germline mutations of the *p53*, *RB*, and *NF-1* genes put individuals at high risk for developing STSs (4). ESFT has a neuroectodermal origin and account for approximately 40% of bone cancers in children. These tumors primarily involve the pelvis, ribs, and shaft of long bones (5).

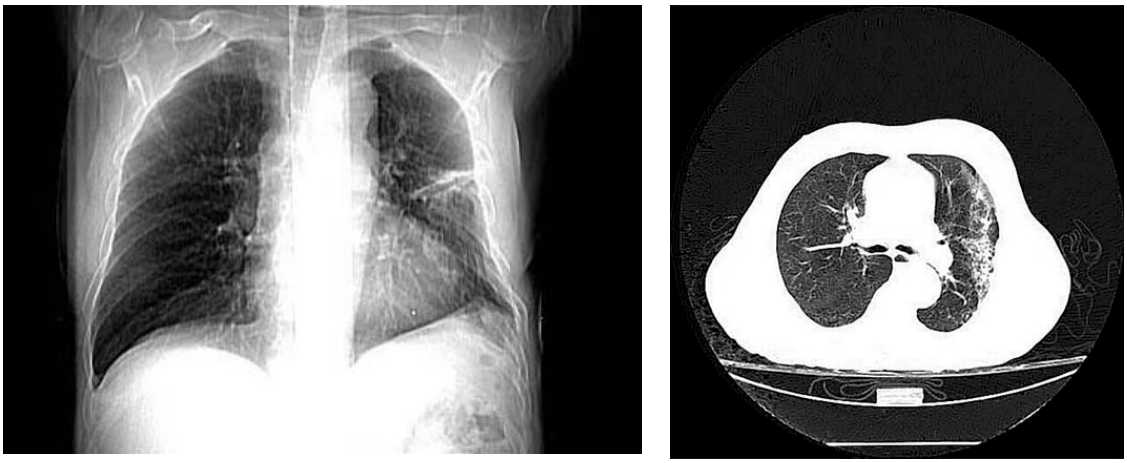
The treatment of Hodgkin's lymphoma and musculoskeletal tumors often includes radiation therapy for local tumor control. Radiation can be delivered externally using linear accelerators or internally using brachytherapy seed implants (6). External-beam radiation therapy utilizes either x-ray or electron fields delivered through a rotational gantry. Both field types release electrons into the cell through an ionization process. These electrons directly interact with cellular components, damaging DNA, and

disrupting normal cell activity. Death of cells occur after they attempt mitotic division and is therefore proportional to the proliferative activity of its components. Damage of DNA can also occur through electrons' production of hydroxyl radicals (7). Even though both fields act the same, x-ray fields allow for deeper dose penetration than electron fields. The dose relates to the energy released in the ionization process (6,7), and the SI unit for absorbed dose is the gray (Gy). Radiation doses are determined by protocol and vary depending on tumor type, staging, size, and location (8).

Initially, external-beam radiation was delivered using a 2D conventional method. Therapy was planned using x-ray images, and as a result of these 2D images, the tumor and surrounding healthy tissues and critical structures could not be well defined (9). Correction of this limitation led to the development of 3D conformal and intensity modulated radiation therapy (IMRT). To plan treatment, these delivery methods require 3D images from computed tomography (CT) and/or magnetic resonance imaging (MRI) scans. With these images, the volume of the tumor can be accurately determined, and the location of surrounding structures can be described (7,10,11). These advancements enable delivery of the appropriate dose to the tumor with increased sparing of surrounding healthy tissues and critical structures.

Despite the improvements associated with 3D conformal and IMRT, acute and chronic effects on normal tissues are still observed (12). One such treatment-related acute effect is radiation pneumonitis (Figure 1), which presents within 6 months of radiation treatment. Characterized by a cough, fever, and shortness of breath, radiation pneumonitis or inflammation of the lung develops in 5% to 15% of patients receiving thoracic irradiation, and it has a morality rate up to 10% (13,14,15). Radiation-induced

pneumonitis predominately develops within the irradiated volume of the lung, although it can spread to non-irradiated volumes (14). Fibrosis or chronic inflammation accompanies pneumonitis in most cases. Currently, two mechanism of development exist for pneumonitis – classic and sporadic. In classic radiation pneumonitis, therapy results in direct toxic injury of endothelial and epithelial cells producing acute alveolitis. This leads to an accumulation of inflammatory and immune effectors cells which distorts the normal alveolar structures and results in the release of lymphokines and monokines. In sporadic radiation pneumonitis, bilateral lymphocytic alveolitis results from an immunologically mediated process (16). Researchers also believe that increased expression of CD95 and CD95L, resulting from radiation therapy and acute lung injury, induces the inflammatory response (14,17). The National Cancer Institute's Common Toxicity Criteria (CTC) for pneumonitis is shown in Table 1 (18).



X-Ray Transverse CT

Figure 1.
Radiographic images of radiation pneumonitis.
Inflammation is located in the left upper lobe.

Table 1. NCI Common Toxicity Criteria v2.0 for Radiation Pneumonitis

Grade				
0	1	2	3	4
None	Radiographic changes but asymptomatic or symptoms not requiring steroids	Radiographic changes and requiring steroids or diuretics	Radiographic changes and requiring oxygen	Radiographic changes and requiring assisted ventilation

As the pediatric cancer cure rate continues to rise, clinical researchers have turned their attention to treatment-related side effects. Currently, only limited data about these effects is available. Therefore, the objective of this study is to analyze acute lung toxicity in pediatric Hodgkin's lymphoma and sarcoma patients receiving 3D conformal or IMRT. The ultimate goal is to identify a pediatric patient population at risk for pneumonitis with the hope of intervening in their treatment to minimize the severity of reaction. In addition, evaluation of the applicability of lung dose-volume constraints and pneumonitis risk models derived from irradiated adult cancer patients will occur.

Yorke and colleagues released a clinical review of radiation pneumonitis in 2005 identifying dosimetric factors that correlate with the toxicity. It concluded that the degree of inflammation in the lung is influenced by the mean lung dose (19). Additionally, a Washington University study found that lung volume treated above 20 Gy predicted for radiation pneumonitis (20). Therefore, I hypothesize that the grade of radiation pneumonitis increases with mean lung radiation dose. Some chemotherapy drugs cause DNA damage and inhibit cell replication and repair (7). These are termed radiosensitizers since they alter the cell's response to radiation therapy. Previous research found that the use of radiosensitizers before, during, and immediately after radiation therapy has no effect on the development of radiation pneumonitis (16,19). In

spite of this, I hypothesize that the use of prior chemotherapy increases the grade of toxicity since chemotherapy and radiation damaged lung cells cannot quickly and effectively repair themselves. In particular, I believe that bleomycin and methotrexate will increase toxicity since these two chemotherapy agents have previously been linked to lung damage (21). I also predict that gender influences the development of radiation pneumonitis. Most women have smaller lung volumes and given a similar field size as men, a greater portion of their lung is irradiated. Therefore, I hypothesize that females will develop radiation pneumonitis more often than males. Finally, I hypothesize that age influences the development of radiation pneumonitis since older individuals have been exposed to more detrimental environmental factors.

In the adult lung cancer population, the Radiation Therapy Oncology Group's (RTOG) adopted dose-volume constraints are mean lung dose (MLD) < 20Gy and $V_{20} \leq 37\%$ (22). These differ slightly from the Princess Margaret Group's constraints for adult Hodgkin's lymphoma that defines MLD < 14Gy and $V_{20} < 36\%$ (23). I hypothesize that pediatric patients require tighter dose-volume constraints since they have smaller total lung volumes compared to adults.

Radiation pneumonitis risk models have been developed for the adult lung cancer population. The first model, radiation pneumonitis risk (RP risk) model, was developed for sarcoma patients from a combined analysis of RTOG9311 and Washington University data for adult lung cancer. The two-parameter model utilizes MLD and superior-to-inferior gross tumor volume position (GTV S-I) to predict pneumonitis (20):

$$\text{RP risk} = \text{logistic function}[-1.5 + 0.11 \times \text{MLD} - 2.8 \times \text{GTV S-I}]$$

The second model, Lyman normal tissue complication probability (NTCP), was developed from the Netherlands Cancer Institute and University of Michigan's lymphoma and lung cancer pneumonitis incidence data. The probability integral is:

$$NTCP(D) = \frac{1}{\sqrt{2\pi}} \int^{(deff - TD50)/(mTD50)} \exp(-t^2/2)dt$$

where d_{eff} is the effective uniform dose, TD50 is the dose at which 50% of complications occur, and m determines the slope of the dose-response curve at D50 (24). I hypothesize that these models will underestimate a pediatric patient's risk of pneumonitis since a child will have a smaller GTV S-I, d_{eff}, and TD50.

In summary, I speculate that a correlation exists between radiation pneumonitis and mean lung dose, as well as between radiation pneumonitis, gender, age, and prior chemotherapy regime. Finally, I hypothesize that adult constraint guidelines and pneumonitis risk models will not be applicable in pediatric Hodgkin's lymphoma and sarcoma patients.

PATIENTS AND METHODS

Patients

40 patients treated for Hodgkin's lymphoma on a St. Jude prospective, risk-adapted therapy protocol titled *Risk-Adapted Therapy for Pediatric Hodgkin's Disease* (HOD99) were examined. Eligibility criteria included informed consent, age less than 21 years, and confirmed diagnosis of previously untreated Hodgkin's lymphoma. 23 patients enrolled on a St. Jude phase II protocol titled *Image Guided Radiotherapy for the Treatment of Musculoskeletal Tumors* (RT-SARC) were also evaluated. Eligibility criteria for this protocol included informed consent, age less than 25 years, histological confirmation of a musculoskeletal tumor, and no prior irradiation to the primary site.

Table 2 contains the patient statistics for the two patient populations included in this study. 34 of the 63 patients (54.0%) were male with RT-SARC contributing the larger portion of male patients. The majority of patients were greater than 10 years of age at diagnosis (54 cases, 85.7%). All patients on HOD99 were administered chemotherapy prior to radiotherapy, and overall, 57 of the 63 patients (90.5%) received prior chemotherapy; chemotherapy regimes were determined by protocol and varied depending on tumor type and staging.

Table 2. Patient Characteristics

		HOD99 No (%)	RT-SARC No (%)	Total No (%)
Sex	Male	18 (45)	16 (69.6)	34 (54.0)
	Female	22 (55)	7 (30.4)	29 (46.0)
Gender	< 10 years	1 (2.5)	8 (34.8)	9 (14.3)
	> 10 years	39 (97.5)	15 (65.2)	54 (85.7)
Prior	Yes	40 (100)	17 (73.9)	57 (90.5)
Chemotherapy	No	0 (0)	6 (26.1)	6 (9.5)

Chemotherapy

Chemotherapy was delivered prior to irradiation, with a minimum two-week resting period between the treatments. Favorable Hodgkin's lymphoma patients received 4 cycles of vinblastine, adriamycin, prednisone, and methotrexate (VAMP). Hodgkin's lymphoma patients classified as intermediate received cyclophosphamide, vincristine, and procarbazine (COP) in addition to VAMP. Unfavorable Hodgkin's lymphoma patients received 12 weeks of Stanford V (adriamycin, vinblastine, nitrogen mustard, vincristine, bleomycin, etposide, and prednisone). The chemotherapy regimes for sarcoma patients varied with type and extent of disease.

Radiation Therapy

Each patient received an initial CT simulation during which positioning was determined; positioning was disease site and patient specific. A variety of immobilization devices, including AlphaCradles and VacLock bags, were utilized to ensure daily realignment and restrict patient motion. The isocenter was also marked on patients for repositioning purposes.

External-beam radiation therapy was used on all patients. It was delivered using two Siemens linear accelerators, PRIMUS and PRIMART. Treatment planning was performed using the PLanUNC (PLUNC) software developed at University of North Carolina and modified at St. Jude Children's Research Hospital. Diagnostic images provided by CT, MRI, and positron emission tomography (PET) scans enabled definition of target volumes. Delivery methods included 3D-conformal and IMRT. Prescribed doses were 25.5 Gy (1.5 Gy/fraction) for Hodgkin's lymphoma, and 41.4 to 70.2 Gy (1.8

Gy/fraction) for sarcoma. For advanced-stage Hodgkin's lymphoma, 8 Gy was concurrently delivered to the entire lung.

Patient Follow-Up

Patients were evaluated weekly during the deliverance of radiation therapy. After the completion of therapy, patients were evaluated every 6 weeks until 90 days post-treatment and then every 2 months until 6 months post-treatment. At these visits, the treating physician utilized a physical exam and chest radiograph to diagnose radiation pneumonitis. Lung injury was graded according to the National Cancer Institute's CTC v2.0 (Table 1).

Dose-Volume Data

Using the CT planning scans input into the PLUNC software, the total lung was contoured. Dose-volume histograms (DVHs) were created for the contoured structures; this enabled determination of the MLD and the percent volume receiving dose greater than 10, 20, 25, and 30 Gy.

RESULTS

The distribution of radiation pneumonitis is shown in Table 3. In the 40 patients treated for Hodgkin's lymphoma, 37 patients (92.5%) had a maximum grade 0 reaction, 2 (5.0%) had a maximum grade 1 reaction, and 1 (2.5%) had a maximum grade 2 reaction. 22 sarcoma patients (95.7%) had a maximum grade 0 reaction and 1 (4.3%) had a maximum grade 2 reaction. No patients on either protocol required interruption of radiation therapy as a result of their toxicity, and all patients completed their treatment as planned.

Table 3. Distribution of Pneumonitis

Maximal Grade of Pneumonitis	HOD99 No (%)	RT-SARC No (%)
0	37 (92.5)	22 (95.7)
1	2 (5.0)	0
2	1 (2.5)	1 (4.3)
3	0	0
4	0	0

Figure 2 shows the maximal pneumonitis with respect to the mean lung dose (MLD) delivered. MLD varied from 169 to 1945 cGy for Hodgkin's patients and from 70 to 2794 cGy for sarcoma patients. Generally, as the MLD increased, grade of pneumonitis also increased, indicating a positive relationship between the variables. Patients developing grade 2 radiation pneumonitis had a MLD > 16 Gy. The red horizontal lines depict RTOG and Princess Margaret Group's adult MLD constraints (MLD <20 Gy and MLD <14 Gy, respectively). All of the CTC grade 1 and 2 patients fell around or above the 14 Gy constraint.

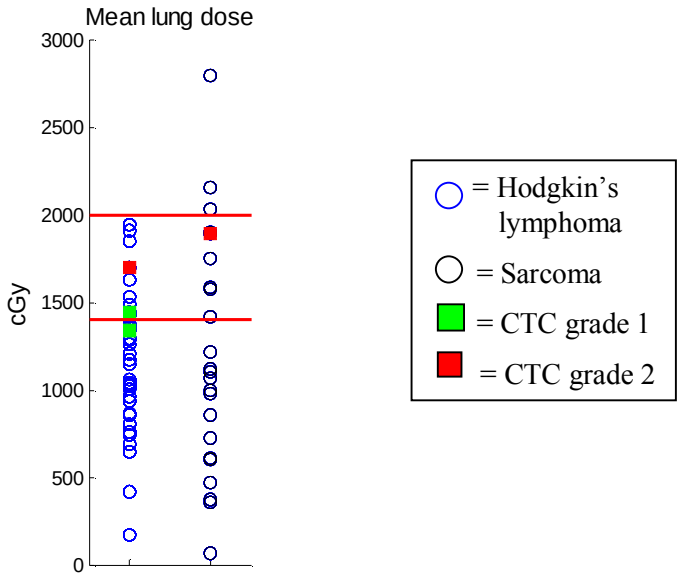


Figure 2.
Maximum pneumonitis grades with respect to MLD

Figures 3 and 4 show the overlays of total lung DVHs for the 40 Hodgkin's lymphoma patients and 23 sarcoma patients, respectively; these overlays report what volume of the lung received what dose. Prescribed doses were 25.5 Gy (1.5 Gy/fraction) for Hodgkin's lymphoma, and 41.4 to 70.2 Gy (1.8 Gy/fraction) for sarcoma. For advanced-stage Hodgkin's lymphoma, 8 Gy was concurrently delivered to the entire lung. The green curves are the DVHs for grade 1 patients not requiring clinical intervention, and the red curves are the DVHs for grade 2 patients requiring steroids for clinically significant symptoms. Pediatric patients who developed radiation pneumonitis (CTC grade 1 or 2) appear to have higher total lung DVHs.

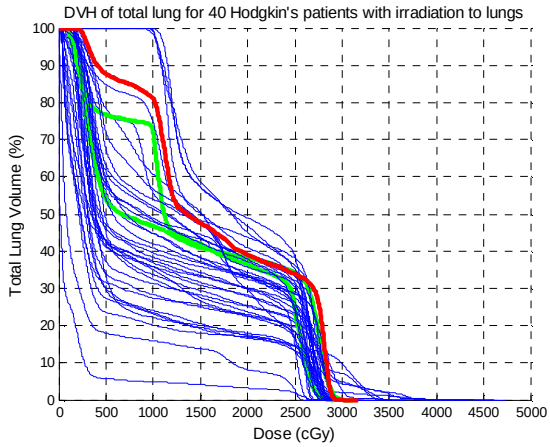


Figure 3.
DVHs of total lung for Hodgkin's patients

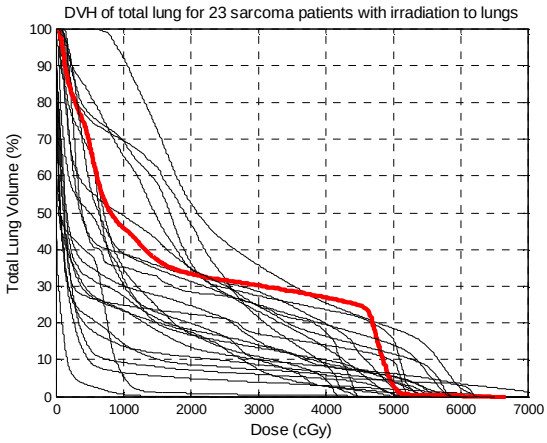


Figure 4.
DVHs of total lung for sarcoma patients

Figure 5 shows the volume of the total lung receiving 20 Gy. In general, as the treated volume of lung increased, the grade of toxicity also increased. Patients developing grade 2 pneumonitis had a $V_{20} > 35\%$. The red horizontal line depicts the RTOG and Princess Margaret Group's adult V_{20} constraint ($V_{20} < 36\%$). Hodgkin's lymphoma and sarcoma patients who developed radiation pneumonitis (CTC grade 1 or 2) had their V_{20} around or above this threshold.

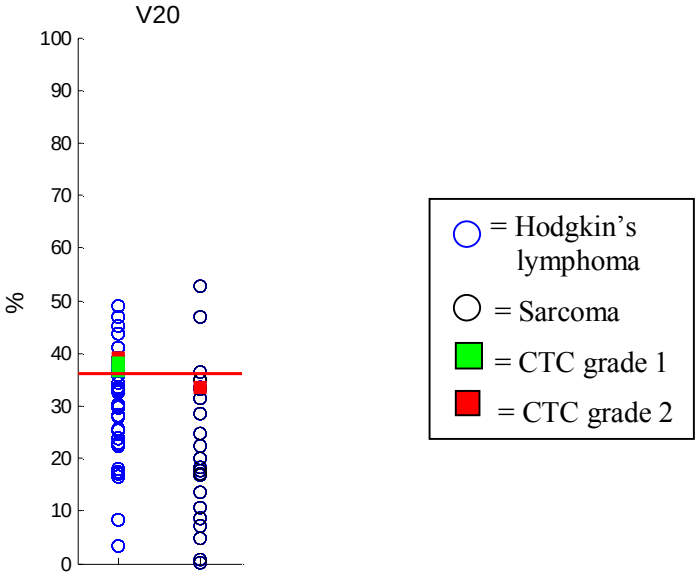


Figure 5.
Maximum pneumonitis grades with respect to V_{20}

Since 57 of the 63 patients (90.5%) received prior chemotherapy, the patients' maximal degree of pneumonitis was compared to chemotherapy regimes. Per HOD99 protocol, all patients with the same predicted outcome (favorable, intermediate, or unfavorable) received the same regime of chemotherapy. Of the 3 Hodgkin's lymphoma patients who developed radiation pneumonitis, none of them received a different dosage than their outcome counterparts. This suggests that chemotherapy does not influence the development of radiation pneumonitis. In addition, only one patient within the sarcoma population developed radiation pneumonitis; his data was omitted since no clinical conclusion could be drawn from delivered chemotherapy regime and developed lung reaction.

The patient's gender was statically compared to the maximum pneumonitis grade. Overall, 34 of the patients (54.0%) were males and 29 (46.0%) were females. Of the patients developing pneumonitis, both grade 1 patients were female and both grade 2 patients were male. A one-way ANOVA indicated that the grade of pneumonitis did not differ as a function of gender ($p=0.91$).

The patient's maximal pneumonitis grade was also compared to their age (Figure 6). Patients ranged in age from 2 to 22 years. Two of the patients developing pneumonitis were 14 years old and the other two were 17 years old. The graph shows no difference in grade based on age, and this lack of statistical difference was confirmed by the high p-value of association ($p=0.78$).

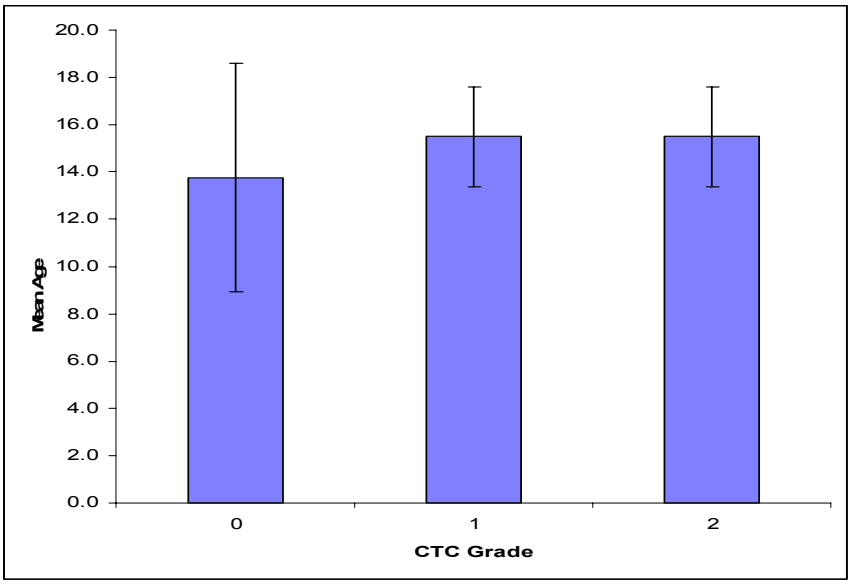


Figure 6.
Maximum pneumonitis grades by mean age.
Vertical bars represent one standard deviation.

RP risk for sarcoma patients was calculated using MLD and GTV S-I. Probability results are reported in figure 7. A low risk (0.2) was predicted for the lone sarcoma patient developing radiation pneumonitis.

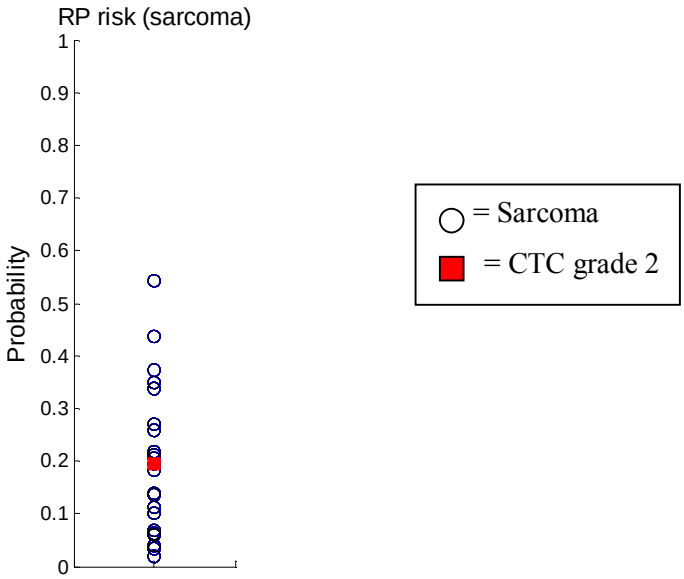


Figure 7.
RP risk plotted against maximal grade of toxicity

Figure 8 shows the maximal lung toxicity with respect to the Lyman NTCP. Compared with the RP risk model, a slightly higher risk (0.25) was predicted for the grade 2 sarcoma patient. NTCP also predicted low probability (0.15-0.25) for the Hodgkin's lymphoma patients who actually developed radiation pneumonitis.

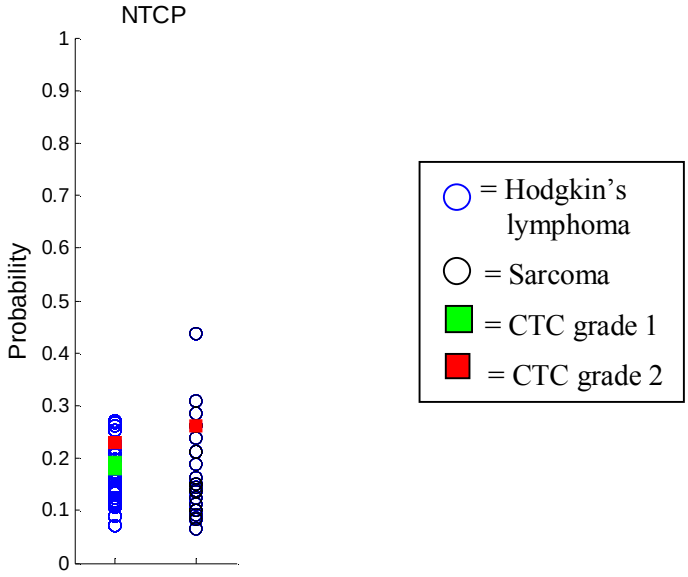


Figure 8.
Maximal lung toxicity cross NTCP

DISCUSSION

In the data, a direct relationship was observed between radiation pneumonitis, MLD, DVHs, and V_{20} (Figures 2, 3, 4, and 5). This suggests that patients requiring higher radiation doses to larger lung volumes for effective local control will be at an increased risk for radiation pneumonitis. Several options are available for radiation oncologists to intervene in the planning and treatment of these patients. First, medical physicists could generate additional radiation therapy plans with the goal of maintaining maximum tumor volume coverage while reducing dose delivered to the lung. In particular, physicists should attempt to spare the lower lung since an earlier study by Yorke and colleagues determined it to be more radiosensitive than the upper lung (24). Upper and lower lung subvolumes are determined by defining the plane halfway between the most superior and most inferior imaging slices to contain lung. These different radiation tolerances arise because the lower lung has a greater density of radiation target cells, and irradiated cells in the lower lung can induce lesion formation in the upper lung (25,26). Second, since fraction size also plays a role in the degree of pneumonitis, high dose/large volume patients could receive less dose in each daily fraction (27); this would increase the overall time of treatment, but could potentially decrease lung injury. Lastly, experimental preventive methods could be looked into for these at-risk patients. Gene therapists are currently exploring whether the administration of a recombinant human adenoviral vector carrying the TGFβ1 Type II receptor gene can protect the lung from radiation-induced injury (28).

Study data showed no difference in grade of radiation pneumonitis based on treatment and demographic factors. First, prior chemotherapy regime had no effect on

the development of pneumonitis in Hodgkin's lymphoma patients and did not support the hypothesis that bleomycin and methotrexate increase lung toxicity. This analysis of prior chemotherapy regime needs to be carried out for sarcoma patients as more data becomes available. On the RT-SARC protocol, chemotherapy is not prescribed for all patients, so future research should first explore whether the use of prior chemotherapy increases the grade of toxicity; if this hypothesis is supported, regime analysis can then be conducted. The data also showed no relationship between gender and grade of lung inflammation. This suggests that, for the pediatric population, females are not more susceptible to radiation pneumonitis. Finally, study data refuted the hypothesis that age influences the development of radiation pneumonitis (Figure 6). It must be stated that a narrow age range was represented in the study with the majority (85.7%) of the patients being greater than 10 years of age. Therefore, I propose repeating this arm of the study with a new age diverse patient population to again explore the hypothesis.

Two of the eight Hodgkin's lymphoma patients receiving the prescribed 25.5 Gy to the planning target volume with an additional 8 Gy to the entire lung developed grade 2 radiation pneumonitis. In contrast, only one of 32 patients receiving 25.5 Gy without whole lung irradiation developed grade 1 pneumonitis. This suggests that the lung may be sensitive to a low-dose bath effect where large volumes exposed to low doses in the proximity of other high-dose regions are more susceptible. In light of these findings, whole lung irradiation should be avoided whenever possible to minimize increasing mean lung dose and the chance of lung injury.

In addition, the MLD and V_{20} constraints developed for adult lung cancer appear to be appropriate for the pediatric population; these guidelines successfully identified

children at a higher risk for radiation lung toxicity. For mean lung dose, all of the patients developing radiation pneumonitis had MLDs below the RTOG's 20 Gy constraint and around or above the Princess Margaret Group's 14 Gy constraint (Figure 2). Similarly, with V_{20}, all the CTC grade 1 and 2 patients had 20 Gy irradiated volumes around or above the 36% threshold (Figure 5). This suggests that MLD < 14 Gy and V_{20} < 36% should serve as a starting point when developing a set of pediatric dose-volume constraints.

Finally, both adult radiation pneumonitis risk models emerge as poor predictors of lung toxicity in the pediatric cancer population. The RP risk model predicted a low probability (0.2) for the sarcoma patient who actually developed pneumonitis, and NTCP predicted equally low probabilities (0.15-0.25) for both sarcoma and Hodgkin's lymphoma patients developing lung inflammation (Figures 7 and 8). Based on these findings, new models need to be developed from analysis of pediatric pneumonitis incidence data or the two existing models need to be adapted for accurate prediction in children.

CONCLUSION

MLD, V_{20}, and boosts to the entire lung influence the degree of radiation pneumonitis, whereas chemotherapy regime, gender, and age have no effect. These findings can be used in a clinical setting to predict patients at risk for lung toxicity. Early intervention in these patients may help reduce or eliminate radiation-induced lung side effects. In addition, adult lung dose-volume constraints can be applied to the pediatric population to minimize development of radiation pneumonitis; in particular, MLD < 14 Gy and V_{20} < 36% should be observed until pediatric constraints are published. Finally, adult radiation pneumonitis risk models are not capable of producing accurate pneumonitis probabilities in the pediatric Hodgkin's lymphoma and sarcoma population without improvements.

ABBREVIATIONS

CT	Computed tomography
CTC	Common Toxicity Criteria
COP	Cyclophosphamide, Vincristine, and Procarbazine
d_{eff}	Effective uniform dose
DVH	Dose-volume histogram
ESFT	Ewing's sarcoma family of tumors
Gy	Gray
GTV S-I	Superior-to-inferior gross tumor volume position
HOD99	*Risk-Adapted Therapy for Pediatric Hodgkin's Disease*
IMRT	Intensity modulated radiation therapy
MLD	Mean lung dose
MRI	Magnetic resonance imaging
NTCP	Normal tissue complication probability
PLUNC	PLanUNC software
RMS	Rhabdomyosarcoma
RP risk	Radiation pneumonitis risk
RTOG	Radiation Therapy Oncology Group
RT-SARC	*Image Guided Radiotherapy for the Treatment of Musculoskeletal Tumors*
Stanford V	Adriamycin, Vinblastine, Nitrogen mustard, Vincristine, Bleomycin, Etopside, and Prednisone
STS	Non-rhabdomyosarcoma soft-tissue sarcoma
t	time
TD50	Dose of 50% complications
V_{20}	Volume of the lung receiving 20 Gy
VAMP	Vinblastine, Adriamycin, Methotrexate, and Prednisone

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