Published in final edited form as:

Pediatr Hematol Oncol. 2012 August ; 29(5): 415–423. doi:10.3109/08880018.2012.684198.

Pediatric Hodgkin Lymphoma: Are We Over-Scanning Our Patients?

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Abstract

Despite the favorable outcome of most pediatric patients with Hodgkin lymphoma (HL), there is rising concern about risks of carcinogenesis from both diagnostic and therapeutic radiation exposure for patients treated on study protocols. Although previous studies have investigated radiation exposure during treatment, radiation from post-treatment surveillance imaging may also increase the likelihood of secondary malignancies. All diagnostic imaging examinations involving ionizing radiation exposure performed for surveillance following completion of therapy were recorded for 99 consecutive pediatric patients diagnosed with HL from 2000 to 2010. Cumulative radiation dosage from these examinations and the frequency of relapse detection by these examinations were recorded. In the first 2 years following completion of therapy, patients in remission received a median of 11 examinations (range 0–26). Only 13 of 99 patients relapsed, 11 within 5 months of treatment completion. No relapse was detected by 1- or 2-view chest radiographs ($n = 38$ and 296 , respectively), abdomen/pelvis computed tomography (CT) scans ($n = 211$), or positron emission tomography (PET) scans alone ($n = 11$). However, 10/391 (2.6%) of chest CT scans, 4/364 (1.1%) of neck CT scans, and 3/47 (6.4%) of PET/CT scans detected relapsed disease. Thus, only 17 scans (1.3%) detected relapse in a total of 1358 scans. Mean radiation dosages were 31.97 mSv for Stage 1, 37.76 mSv for Stage 2, 48.08 mSv for Stage 3, and 51.35 mSv for Stage 4 HL. Approximately 1% of surveillance imaging examinations identified relapsed disease. Given the very low rate of relapse detection by surveillance imaging stipulated by current protocols for pediatric HL patients, the financial burden of the tests themselves, the high cure rate, and risks of second malignancy from ionizing radiation exposure, modification of the surveillance strategy is recommended.

Keywords

Hodgkin disease; late effects; radiology

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Declaration of Interest

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

Hodgkin lymphoma (HL) accounts for 6% of pediatric cancers. A cure rate of 90% to 95% is achieved with contemporary treatment programs using a risk-adapted or response-adapted approach entailing multiagent chemotherapy with or without low-dose involved-field irradiation [1]. The high cure rate has prompted efforts to modify treatment protocols to minimize treatment-related toxicities and adverse late effects, which may include second malignancies.

For patients in first remission, upon completion of treatment, recent protocols from the pediatric cancer cooperative groups typically mandate follow-up surveillance imaging every 3 to 6 months for the first 1 to 2 years and then annually to year 4 or 5 with some combination of chest radiographs and CT scans, depending upon the patient's risk stratification. This intense schedule of surveillance scanning for disease recurrence comes at the cost of cumulative exposure to ionizing radiation. Given the largely successful outcomes for patients with HL, it is important to question whether this surveillance strategy is necessary or appropriate. Indeed, pediatric cancer patients in general are increasingly exposed to multiple CT scans raising concerns for radiation-induced second malignancies in cancer survivors [2].

It is possible to estimate the radiation dose absorbed by various organs and tissues from a radiologic study and calculate an effective dose based on a weighted sum of doses according to the variable sensitivity of different organs and tissues to stochastic effects such as carcinogenesis [3]. Due to assumptions, approximations, and interpolations in the methodology and deviations from an idealized "average" patient, these estimates are subject to substantial uncertainty in an individual patient. The cumulative amount of radiation a patient receives depends on the number and type of scans performed. Although studies have investigated radiation exposure during treatment, there is a paucity of information regarding the extent of radiation exposure to survivors during the course of post-therapy surveillance. Given that childhood Hodgkin lymphoma has a high expectation of cure and entails acquisition of numerous radiologic examinations during surveillance, it is imperative to define the yield of these surveillance examinations and to minimize adverse long-term effects of radiation [4]. To better determine the risk-benefit from surveillance imaging, we evaluated cumulative radiation dose and frequency of relapse detection in HL post-therapy survivors in a single institute experience.

METHODS AND MATERIALS

Definitions

Relapse was defined as occurring in any patient who received a second treatment protocol following failure to completely remit or stay in remission after primary therapy. This included patients who following initial therapy had progressive disease, partial remission, or complete remission with subsequent relapse. By Children's Oncology Group (COG) criteria, complete remission was considered to be 80% or more decrease of tumor size (defined as the product of the perpendicular diameters in the axial plane) or return to normal organ or lymph node size with no extranodal masses, partial response was greater than 50% but less than 80% decrease of tumor size, and disease progression was 50% or greater increase in tumor size or involved lymph nodes.

Stage 1 HL was defined as involvement of 1 lymph node region with possible direct extension; Stage 2: involvement of 2 or more lymph node regions on the same side of the diaphragm with possible extension of any one lymph node; Stage 3: involvement of 2 or more lymph node regions on both sides of the diaphragm with possible direct extension of any one lymph node or spleen involvement; and Stage 4: involvement of a nonlymphatic organ with or without lymph node involvement. Further staging with regard to A versus B

was based on the absence or presence, respectively, of at least 1 of the following “B symptoms”: greater than 10% weight loss in 6 months, fever over 38°C for at least 3 days, and/or excessive night sweats [5].

Radiation amounts for each type of scan were in part calculated based on values from the American Academy of Pediatrics, a study published in *Pediatric Radiology*, as well as estimates from our own institutional protocols [6, 7]. We estimated an effective dose of 3 mSv for neck computed tomography (CT), 3 mSv for chest CT, 5 mSv for abdomen/pelvis CT, 8 mSv for chest/abdomen/pelvis CT, and 11 mSv for neck/chest/abdomen/pelvis CT in a 10-year-old. The fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scans interpreted at Texas Children’s Hospital (TCH) are performed offsite and the radiation effective dose for each of these FDG-PET/CT scans from FDG alone (not considering the additional contribution of radiation from the concomitant CT scan) is in the range of 7 to 14 mSv, depending on the radiopharmaceutical dose of FDG administered at the offsite location. This compares to radiation effective doses of 6.4 mSv for a 10-year-old and 8.6 mSv for a 15-year-old, assuming radiopharmaceutical doses recently recommended for pediatric FDG-PET [8, 9].

Data Collection

Patient information was obtained through an electronic chart review of 99 consecutive patients diagnosed with HL at Texas Children’s Hospital between 2000 and 2010. This retrospective review was approved by the Baylor College of Medicine Institutional Review Board (IRB). Specifically, we documented disease status upon completion of chemotherapy and radiation therapy, if given. Disease status was tracked to the patients’ last clinic visit to insure validity of relapse results. Details of radiologic scans including x-rays (2-view and 1-view), CT (chest, abdomen/pelvis, and neck), PET, and PET/CT scans were derived from chart review. The total number of surveillance radiologic examinations was enumerated from completion of the treatment protocol until the date of last contact or relapse. Scan frequencies were grouped according to scan type and disease stage at diagnosis. Scans indicating relapse were separately identified and relapse was confirmed by chart review of pathology reports and clinical notes. Finally, cumulative radiation dose for each patient was calculated from the number of scans and the dose of each type of scan. All scans were mandated by the surveillance protocol and none were obtained for other indications such as suspected relapse. Mean, median, and range values were calculated for individual radiation totals grouped by stage.

RESULTS

Ninety-nine consecutive pediatric patients diagnosed with HL between the ages of 2 and 25 years and treated at Texas Children’s Hospital from 2000 to 2010 were included in this retrospective study (Table 1). Thirteen relapsed (range 2–17 months after completing therapy), 11 within the first year within a mean of 5 months. The 2 patients relapsing more than a year from completing therapy relapsed 16 and 17 months off therapy. In all but one case, the relapses were clinically occult and the surveillance scans were the sole means of detecting relapse.

After completion of primary treatment, a total of 1455 scans (mean of 15 scans per patient) were administered. A total of 296 2-view chest x-rays, 38 1-view chest x-rays, 391 chest CT scans, 211 abdomen/pelvis CT scans, 364 neck CT scans, 47 PET/CT scans, 11 PET scans, and 97 miscellaneous scans were performed. Miscellaneous scans consisted of x-rays and CTs of other body regions, DEXA (dual-emission x-ray absorptiometry) bone mineral density scans, and nuclear medicine bone scans. Excluding these miscellaneous scans, Stage 1 Hodgkin lymphoma patients ($n = 13$) received a total of 149 scans representing a mean

radiation exposure of 31.97 mSv. Stage 2 patients ($n = 54$) received a total of 719 scans with a mean exposure 37.76 mSv. Stage 3 patients ($n = 12$) received a total of 164 scans with a mean exposure of 48.08 mSv, and Stage 4 patients ($n = 20$) received a total of 326 scans with a mean exposure of 51.35 mSv (Tables 2–4).

No relapse was detected by 2-view or 1-view chest x-rays ($n = 296$ and 38, respectively), abdomen/pelvis CT scans ($n = 211$), or PET scans alone ($n = 11$). The scans that had the highest yield for detecting relapse were chest CT, neck CT, and PET/CT with 10/391 (2.6%), 4/364 (1.1%), and 3/47 (6.4%) detecting relapse, respectively. Thus, in a total of 1358 surveillance scans, only 17 (1.3%) detected relapse (Table 2).

For our pediatric HL patients in remission, the median number of surveillance scans received for 2 years following the termination of therapy was 11 (range 1–26). Surveillance scanning among high-risk patients typically consisted of CT scans every 3 to 6 months for the first 12 to 24 months following treatment completion. CT scans are required every 3 months for the first 18 months for patients treated according to the intermediate-risk protocol and every 4 to 6 months for the first 12 to 24 months according to the low-risk protocols. The body regions covered vary with the protocols, with some requiring coverage of the entire neck, chest, abdomen, and pelvis, whereas others specify only the sites involved at time of diagnosis. Although FDG-PET is increasingly used for response assessment during therapy and at completion of therapy, it has no current established role in surveillance.

DISCUSSION

Most pediatric patients with HL are treated on clinical trials that dictate the frequency of surveillance scans following completion of primary therapy. However, there is no standard surveillance schedule for patients not enrolled on a clinical trial [8]. Moreover, although the rationale for performing surveillance scans is to improve survival by early detection of relapse, there is little evidence to support this concept in HL [9]. Here, we reviewed the type and frequency of surveillance scans performed in patients with pediatric HL at the completion of primary therapy. Of 99 pediatric HL patients studied, only 1.3% of surveillance scans performed actually detected relapse.

This study is the first to specifically study radiation exposure from surveillance scans for pediatric HL patients and indicates that surveillance scanning rarely detects clinically occult relapses and results in substantial cumulative radiation dose. For a basis of comparison, the annual per capita effective radiation dose in the United States from natural background sources is 2.4 mSv [10]. Although care was taken to ensure accurate enumeration of radiologic scans during surveillance as well as precise determination of which scans detected relapse, our study is subject to interpretation bias given its retrospective design. Nevertheless, given that most scans were negative for relapse, our data suggest that typical surveillance scanning in pediatric HL is excessive and unnecessarily risks radiation-induced second malignancies in this patient group. Assuming a linear no-threshold risk model and no risk reduction from dose fractionation, and using current life tables and biologic effects of ionizing radiation (BEIR) VII preferred estimates of risk for radiation-induced leukemia and solid tumors, the lifetime attributable risk for a 10-year-old receiving an effective dose of 50 mSv is 0.72% for a male and 1.3% for a female for cancer incidence and 0.36% for a male and 0.55% for a female for cancer mortality [11]. Although these risks are small, they should not be regarded as negligible.

Many pediatric HL patients receive radiation therapy, and the cumulative radiation dose from surveillance scans is very small compared to the dose from radiation therapy. Although

the lifetime attributable risk of a radiation-induced second malignancy in these patients is dominated by the contribution of radiation dose from radiation therapy rather than surveillance scans, the radiation therapy dose is required for successful treatment, whereas the benefit of surveillance is subject to question. The assumption has been that the rationale for frequent surveillance scanning is to promptly detect relapse at a time of minimal disease burden to enable easier induction of a second remission and improved survival. However, this is probably more dependent on the availability of effective salvage therapy. Of the 13 patients in our study who relapsed, 11 relapsed within the first year, at a mean of 5 months after completing therapy. The majority of these relapses were detected by scans at a time when the patients were not symptomatic. Another study evaluating pediatric patients with solid tumors and leukemia/lymphoma showed that patient survival was not dependent on whether relapse was detected during surveillance scanning. In fact, half of the patient relapses were detected at unscheduled clinic visits when the patients presented with symptoms [12]. Additionally, another study identified that the greatest prognostic factor for patients who relapsed was the time that elapsed prior to relapse and not early relapse detection with scans [13]. Therefore, the inability to increase survival among cancer patients through frequent office visits and surveillance scans calls into question the high frequency of scanning and consequent radiation exposure after completion of therapy.

The possible risks of radiation exposure in the medical setting have come under increasing scrutiny. The concern in pediatric patients is much greater than in adults, as children tend to be more vulnerable to the carcinogenic effects of radiation. Pediatric HL patients are among the highest risk populations for secondary malignancy, particularly those subjected to radiation therapy [14, 15]. Moreover, children have a larger lifetime risk of radiation-induced malignancy because they are exposed at a young age and have more subsequent years for the malignancies to manifest [2]. Although the carcinogenic risks of relatively low dose radiation from individual scans is subject to considerable debate and uncertainty, it has been estimated that 2% of all future cancers in the United States may be attributable to radiation from CT examinations, and that 15% of the projected cancers will be due to CT scans performed on patients less than 18 years of age [16]. Pediatric HL patients are subjected to cumulative radiation doses from surveillance scans nearing or exceeding the threshold dose associated with an increased incidence of solid cancers in the Radiation Effects Research Foundation (RERF) Life Span Study (LSS) atomic bomb survivor cohort [17].

However, there still appears to be a lack of appreciation within the pediatric community regarding the potential harm of over-scanning. In a recent study conducted at a large children's hospital, 93% of surveyed pediatricians did not know or underestimated the lifetime excess cancer risk associated with radiation doses equivalent to those incurred by pediatric CT, and 87% of radiation dose estimates for pediatric radiologic examinations were underestimates [18]. This gap in medical knowledge is potentially hazardous to cancer patients who receive multiple scans during and after therapy. Attempts to reduce radiation exposure from individual scans, especially from CT scans of pediatric patients, has been a focal point of the Image Gently campaign of the Alliance for Radiation Safety in Pediatric Imaging [19]. Radiation dose reduction strategies for individual scans should be used in conjunction with reductions in scan frequency to reduce the cumulative radiation burden to pediatric cancer patients. Evaluation of alternative markers for relapsed disease would be valuable to reduce the reliance on imaging for detection of relapse. However, in our subjects, the erythrocyte sedimentation rate (ESR) did not prove sensitive for relapse detection. In 9 of the 13 patients at relapse, only 2 had an elevated ESR at the time relapse was detected by imaging.

Our study suggests that pediatric HL does not routinely warrant intensive prolonged radiologic surveillance, and modifications in surveillance protocols are indicated to reduce cumulative radiation exposure. Since relapse occurred most frequently within a year from completing treatment, we have halved our surveillance scanning at the end of treatment and every 3 months for 2 years, to performing scans at the end of treatment and then at 3, 6, 12, and a final scan between 18 and 24 months. Since relapse is highly unlikely 2 years or more from treatment and given the risk for increased malignancy risk from over-scanning, we have discontinued surveillance imaging beyond this time point. Finally, because chest x-rays failed to detect relapse in any patient, we have discontinued routine chest x-ray surveillance. Reductions in cumulative radiation exposure to pediatric HL patients could be further achieved by replacing surveillance CT examinations with magnetic resonance imaging (MRI). Whole-body MRI shows good agreement with FDG-PET/CT for delineating both nodal and extranodal lymphoma. Advances in MRI technology and availability have made routine MRI a viable alternative for evaluating pediatric lymphoma without ionizing radiation exposure [20, 21]. Additionally, detection of nodal masses during physical examinations as well as utilization of more basic imaging techniques such as ultrasound may provide less harmful ways of detecting relapse [13].

In conclusion, our data show the importance of limiting surveillance scans to minimize late effects from radiation and coincidentally reduce the cost of long-term follow-up of pediatric HL.

Acknowledgments

This work was supported by Cancer Center Support Grant P30CA125123.

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TABLE 1**Patient Characteristics**

Characteristics	All	Nonrelapsed	Relapsed
Median age at diagnosis	13 years		
Sex			
Male	57	49	8
Female	42	37	5
Hodgkin subtype			
Nodular sclerosis	64	52	12
Mixed-cellularity	16	15	1
Lymphocyte-rich	14	14	0
Lymphocyte-depleted	2	2	0
Other	3	3	0
Hodgkin stage			
1	13	12	1
2	54	48	6
3	12	8	4
4	20	18	2
Patients treated "on study"			
Yes	46	41	5
No	53	45	8
Radiation treatment			
Yes	81	72	9
No	18	14	4

TABLE 2

Total Number of Surveillance Scans Depending on Patient Stage at Diagnosis

Scan type	Stage 1	Stage 2	Stage 3	Stage 4
Chest XR 1V & 2V (total)	51	181	34	68
Nonrephase	51	181	34	68
Relapse	0	0	0	0
Chest CT (total)	32	225	43	91
Nonrephase	31	221	40	89
Relapse	1	4	3	2
Abdomen/Pelvis CT (total)	8	78	42	83
Nonrephase	8	78	42	83
Relapse	0	0	0	0
Neck CT (total)	48	206	35	75
Nonrephase	48	203	34	75
Relapse	0	3	1	0
PET/CT (total)	9	22	9	7
Nonrephase	8	21	8	7
Relapse	1	1	1	0
PET only (total)	1	7	1	2
Nonrephase	1	7	1	2
Relapse	0	0	0	0
Other [*]	19	56	7	15

^{*} Other scans included DEXA (dual-energy x-ray absorptiometry) bone density scan, x-rays of non-chest, CTs of non-chest/abdomen/pelvis/neck, nuclear glomerular filtration rate (GFR) scan, nuclear gastric emptying study, cardiac MUGA (multigated acquisition) scan, nuclear bone scan whole body, and outside hospital scans unable to be viewed through electronic charts.

TABLE 3

Individual Cumulative Radiation Dose During Surveillance Scanning

Stage 1	Stage 2	Stage 3	Stage 4
24.5	6	22.39	41.7
20.9	48.7	39	47.8
17.4	5.1	77.2	55.6
37.2	36.9	22	33.5
10.5	30.1	22.21	30
83.21	46	25	55
6	30.33	102	124.1
26.4	58.1	11.11	11
39.7	20.1	15.8	29
26.6	12	96	31.4
56	11	105.2	113.3
16.8	6	39.01	34.2
50.4	47.13		11.1
	24.5		74.5
	62.1		66.6
	21		11.2
	55.3		105.3
	24.1		88.3
	70.5		24.3
	36.7		39.01
	20.1		
	36.9		
	41.5		
	41.7		
	3.01		
	53.8		
	17		
	44.3		
	11.1		
	12		
	39.5		
	44.6		
	11.1		
	46.51		
	26.1		
	30.6		
	31.11		
	5.8		
	62.2		

Stage 1	Stage 2	Stage 3	Stage 4
	72.6		
	20.1		
	49.4		
	12.2		
	86.3		
	12.2		
	57.24		
	18.1		
	62.3		
	80.1		
	23.3		
	45.01		
	40.4		
	151.1		
	78.2		

TABLE 4

Mean Cumulative Radiation Dose During Surveillance Scanning Depending on Patient Stage at Diagnosis

	Stage 1	Stage 2	Stage 3	Stage 4
Mean	31.97	37.76185185	48.07666667	51.3455
Median	26.4	36.8	32	40.355
Min	6	3.01	11.11	11
Max	83.21	151.1	105.2	124.1