Second Malignancy After Treatment of Pediatric Hodgkin Disease

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Summary: Although treatment of pediatric Hodgkin disease has become highly effective over the past 40 years, a number of patients have developed concerning late effects, such as secondary malignancies. These cancers may occur years to decades after remission and arise in the breast, thyroid, gastrointestinal tract, lung, skin, urogenital tract, and brain. There is also an increased risk of leukemia and non-Hodgkin lymphoma. Etiology and risk factors for each cancer type vary but often include certain chemotherapy agents and radiation dosages. Survivorship also varies but is often poor. The authors examined retrospective analyses of these secondary malignancies and present a summary of these findings. The information may allow clinicians to better monitor childhood Hodgkin disease survivors and reduce mortality.

Key Words: second malignancy, pediatric Hodgkin disease, childhood cancer, late effects

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In 1974–1976, the 5-year survival rate for all pediatric cancers in the United States was 55.7%. In 1992–1997, that figure was 77.1%. For Hodgkin lymphoma, the 5-year survival rate for those under 20 years of age increased from 87% in 1975–1984 to 91% in 1985–1994. This increase in remission rates coincides with a general decrease in the incidence of Hodgkin disease (HD) among children in recent years.[1] As the prospects for treating HD improve, new challenges are becoming increasingly apparent as these children grow into adulthood: specifically, survivors are at increased risk for developing secondary malignancies, years after going into remission. Follow-up of HD survivors in the United States and Europe over the past 25 years has revealed these malignant sequelae. Here, we summarize these findings.

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METHODS

We searched PubMed using the following search terms: SMN or secondary malignancy with childhood cancer survivors, secondary malignancy and Hodgkin disease survivors, second cancer, secondary malignancy or second malignancy with childhood Hodgkin disease, secondary malignancy, second malignancy or second cancer with pediatric Hodgkin disease, and second malignancy or second cancer with Hodgkin disease. Limits included English language, and all years of the database were searched.

RESULTS

We identified 435 unique citations, of which 48 were relevant to this review. Sixteen of these papers were retrospective studies focusing on pediatric patients.[2–17] Analyses ranged from institutional to regional, national and international levels and incorporated different variables when assessing risk, making a meta-analysis difficult.

Secondary Malignancies

Despite relatively few pediatric studies compared with adults, there appears to be a significantly elevated risk of secondary cancer following HD treatment. The cumulative incidence, relative risk (RR = standard incidence ratio [SIR] = observed/expected cases) and absolute excess risk (AER = [observed – expected]/person years at risk) are elevated yet highly variable among studies (Table 1). Although study design, patient demographics, cohort size, and predominant treatment modalities contribute to these differences, additional statistical considerations are factors. Cumulative incidence fails to account for the natural increase in cancer risk as patients make the transition between age groups, and while RR incorporates this trend in determining how much more likely a survivor is to develop a second malignancy, RR assessments require external, age-matched controls from the general population.[18] As such, control databases vary, especially among studies from different countries. The same is true for AER, which assesses risk during the time available to develop cancer. Nevertheless, 95% confidence intervals generally overlap, suggesting a probable tumor type-specific increased risk (Table 1).

Leukemia

Secondary leukemia is one of the most common and well-documented malignant late effects in the pediatric and adult literature.[19] Acute forms represent more than 95% of cases, with subtypes including nonlymphocytic, lymphoblastic, myeloid, and type not otherwise specified.[7,13] Survivors

TABLE 1. Summary of Secondary Malignancies Following Pediatric HD Treatment

Study	Cumulative	Incidence*	RR (95% CI)	AER
Bhatia et al, 2003[3]	0–4 yrs	3.8	18.5 (15.6, 21.7)	6.5 per 1,000 person-yrs
	4–9 yrs	3.2		
	10–14 yrs	6.1		
	15–19 yrs	11.6		
Neglia et al, 2001[6]	N/A		9.7 (8.05, 11.59)	5.13 per 1,000 person-yrs
Metayer et al, 2000[7]	N/A		7.7 (60.6, 8.8)	27–36 per 10,000 person-yrs
Green et al, 2000[8]	N/A		9.39 (4.05, 18.49)†	N/A
			10.16 (5.56, 17.05)‡	
van Leeuwen et al, 2000[2]	1–4 yrs	2.2	7.0 (5.9, 8.3)	72.3 per 10,000 person-yrs
	4–9 yrs	3.7		
	10–14 yrs	10.6		
	15–19 yrs	19.3		
Wolden et al, 1998[10]	1–5 yrs	2.9† 5.5‡	10.6 (6.6, 16.0)†	43.8 per 10,000 person-yrs†
	5.1–10 yrs	3.0† 2.7‡	15.4 (10.6, 21.5)‡	86.8 per 10,000 person-yrs‡
	10.1–15 yrs	5.4† 13.1‡		
	15.1–20 yrs	8.8† 15.0‡		

*Cumulative incidence was calculated from those studies that reported absolute number of events and person years during a specified time frame using the formula, cumulative incidence = (number of cancers/person years examined) × 1,000 person-years.
†Men.
‡Women.

have a 3.99 to 174.8 times greater risk of developing leukemia compared with the general pediatric population.[2,3,6–8,10,12,13] Most studies report a significant decrease in incidence 10 to 15 years after therapy,[2,7,13,20] though some consider this trend a statistical artifact[21] (Table 2).

Although the details of pathogenesis are unclear, secondary leukemia is strongly associated with chemotherapy. The greatest reported risk factor is alkylating agent use, especially as single modality treatment, with one study noting a three times greater risk when regimens contained two agents compared with one.[13] Increased risk was also associated with primary disease recurrence, late disease stage at presentation, and older age (10–16 years old) at presentation. The first two factors, however, were associated with greater alkylating agent use, such that chemotherapy may be the true risk factor. Supporting a role for alkylating agent use, Schellong et al[22] reported a decline in incidence in secondary leukemia that was associated with limiting cumulative doses of alkylating agent therapy while substituting less leukemogenic alkylators. Epipodophyllotoxins, such as the topoisomerase II inhibitor etoposide, were also associated with acute leukemia, occurring a median of 2 years after initial therapy and thought to result from chromosomal recombination producing a neo-oncogene.[23] One study found that of all chemotherapy agents, only epipodophyllotoxins had an independent, dose-dependent, statistically significant effect on leukemia risk.[6]

Myelodysplastic syndrome (MDS) was another risk factor, occurring 0.5 to 3 years after combined treatment with at least two alkylating agents in four out of five patients who developed acute nonlymphocytic leukemia.[17] In these patients, bone marrow stem cells became dysplastic, with an arrest of maturation and accumulation of blast cells that resulted in varying degrees of anemia, neutropenia, and thrombocytopenia. Although alkylating agents are thought to be primarily responsible for causing MDS, topoisomerase II inhibitors have also been associated.[24,25] The mechanism may involve neo-oncogene formation, although recombination may also produce mutant enzymes that are active outside of normal regulation, becoming dominant and promoting dysplasia.

The prognosis of secondary leukemia is generally poor, with one study reporting 23 of 26 patients dying and a median survival of 2.5 months after diagnosis.[13] Similar findings have been observed in other studies.[10,17] The explanation for this trend may lie in the rapidly proliferative nature of pluripotent white blood cells, which are more susceptible and likely to propagate the oncogenic effects of alkylating agents and topoisomerase II inhibitors. As genetic insults accumulate, rapid cell turnover may make it difficult for repair mechanisms to correct damage, leading to preneoplastic states such as MDS. These agents also appear to inhibit drug-metabolizing enzymes (glutathione S-transferase, cytochrome P450, NADPH), allowing carcinogens to accumulate.[26] With a greater mutagenic burden, the likelihood of early, aggressive secondary malignancy increases. Conversely, since pluripotent cells can have rapid turnover, any mutation that does not provide a survival advantage could be lost over time, which may help to explain the decreased RR after 10 years. Treatment may begin with a standard approach that includes intensive combination chemotherapy and allogeneic hematopoietic stem cell transplantation. Additional, less conventional therapies may include interferon-b, monoclonal antibodies to the proliferating cell phenotype, or antiviral agents, such as acyclovir or ganciclovir, with variable results.[23]

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is another commonly occurring malignancy following HD treatment, with an RR

TABLE 2. Cumulative Incidence of Secondary Malignancies

Follow-Up Interval	Cumulative Incidence (Per 1,000 Person-years of Follow-Up)* All Neoplasms		Leukemia	Lymphoma	Solid Tumor	Breast Cancer†	Significant Associations
Bhatia et al, 2003[3]							
0–4 yrs	3.8		2.6	0.3	1.0	0.2	Breast: >26 Gy of radiation exposure; female gender
4–9 yrs	3.2		1.3	0.4	1.5	0.0	
10–14 yrs	6.1		1.0	0.2	4.8	1.2	
15–19 yrs	11.6		0.0	0.4	11.2	5.2	
Metayer et al, 2000[7]							
1–4 yrs	N/A		N/A	N/A	0.4	0.0	Solid: Initial Tx with RT Breast: Tx at age 10 yrs or older
4–9 yrs	N/A		N/A	N/A	1.4	0.7	
10–14 yrs	N/A		N/A	N/A	4.5	1.7	
15–19 yrs	N/A		N/A	N/A	6.8	3.2	
van Leeuwen et al, 2000[2]							
1–4 yrs	2.2		0.9	0.0	1.3	0.0	Solid: Tx at young ages, CT for relapse Breast: mantle field irradiation before age 30 yrs old
4–9 yrs	3.7		1.9	0.0	1.9	0.2	
10–14 yrs	10.6		1.2	2.3	7.2	3.7	
15–19 yrs	19.3		0.0	1.9	17.3	6.3	
Wolden et al, 1998[10]	†	‡					
1–5 yrs	2.9	5.5	2.0	0.0	N/A	0.0	All: HD relapse, female gender Leukemia: HD relapse, CT as initial Tx, alkylating agents
5.1–10 yrs	3.0	2.7	0.8	0.0	N/A	0.9	
10.1–15 yrs	5.4	13.1	0.6	1.2	N/A	5.1	
15.1–20 yrs	8.8	15.0	0.0	0.9	N/A	12.3	

*Cumulative incidence was calculated from those studies that reported absolute number of events and person years during a specified time frame using the formula, cumulative incidence = (number of cancers/person years examined) × 1000 person years.
†Men.
‡Women.

of 5 to 20 compared with the general pediatric population.[3,7,10,13,19,27] This risk increases 5 to 10 years after remission and steadily decreases with time. Unlike secondary leukemia, however, there are no strong risk factors. Bhatia et al[13] noted a significant risk associated with alkylating agent use, but Abrahamsen et al[28] found no correlation. Age at diagnosis was also unclear, with some authors reporting no correlation[28] and others finding anything from a nonsignificant higher RR with older age[2] to an increased AER in late adolescence.[14] According to one author, patients may have an immune deficiency associated with their lymphoproliferative disorder.[29] This underlying defect may be partially causative, as true with NHL that develops in other immunodeficient states, such as AIDS.

The mortality of NHL is severe, with one study noting four of six patients dying from the disease and a median survival of 2.5 months after diagnosis.[13] As with leukemia, the early occurrence and rapid progression of disease may be due to the inherent rapidly proliferative nature of the stem cells in a carcinogenic environment. Although definitive risk factors have yet to be defined, the occurrence of NHL in immunodeficient states suggests that there is either some infectious etiology (eg, Epstein-Barr virus) or that immune surveillance has become ineffective. This disability would allow premalignant cells that are normally detected and eliminated to progress and proliferate into lymphoma.

Solid Tumors

Unlike leukemia and NHL, solid tumors generally occur much later in life and present an equal if not greater threat to pediatric HD survivors (see Table 2). As a group, cumulative incidence increases with greater follow-up but is variable and most likely due to study differences. Even so, risk is greater among patients who receive salvage treatment with multiple courses of chemotherapy and radiation.[2] Commonly observed tumors are found in the breast, thyroid, gastrointestinal tract, lung, bone, connective tissue, skin, urogenital tract, and brain.

Breast

Breast cancer following pediatric HD treatment is well established and has been relatively well studied. Despite notable variability, the RR is significantly elevated at 5.2 to 136[2–4,6–8,10,12,13,30] and cumulative incidence consistently increases with greater follow-up (Table 2). One reason for this may be that some studies better approximate patients receiving therapy during puberty, which has been associated

with a higher incidence of malignancy.[2,5,13,30] However, a growing number of authors disagree over the statistical significance of this association, citing the previous use of inappropriate analysis techniques.[3,4,6,7,10] Specifically, Cox regression was used without accounting for the natural rise of breast cancer with age, an oversight corrected in latter studies by using age as a time scale or switching to Poisson regression models.[18] Nevertheless, investigators do agree that breast cancer incidence increases 10 to 20 years following remission,[3,7,10,30] among women in their 30s and 40s, more than 20 years before the general population.[5,7,8,12,13] With continuing age, RR decreases but AER remains consistently elevated.[7] This pattern suggests that patients continue to be at a greater risk for breast cancer, even as their age-associated risk increases.

Radiation therapy is strongly linked to secondary breast cancer.[4,5] When examined by Tinger et al,[31] patients had a 6.2 RR with more than 40 Gy, compared with 2.6 in those receiving less. In another study, no tumors developed with less than 26 Gy (current recommended exposure limit), and all were within or at the margin of the radiation field.[3] These malignancies were often bilateral (or subsequently developed contralaterally), predominantly infiltrating ductal carcinomas (10–65% of all cancers)[3,10,30] and were located in either the medial breast[13] or the upper outer quadrant.[10] Irradiation during puberty and young adulthood was another risk factor, with the breast more likely to be in an ovarian hormone-sensitive, proliferative state that is more sensitive to carcinogenic effects.[32] Consistent with this idea, Travis et al[4] reported a reduced breast cancer risk from ovarian damage caused by radiation or alkylating agents in young women treated for HD, while van Leeuwen et al[33] suggested that ovarian hormonal stimulation provides an increased breast cancer risk following initiating events caused by radiation therapy. A number of long-term retrospective studies of all ages support this idea by showing a marked increase in risk among children compared with adults.[19,27,34,35]

An increased risk of breast cancer has also been associated with chemotherapy. Some investigators have found an increased RR when alkylating agents, such as in MOPP, are combined with radiation.[10,30] Others, however, report either a decrease or no change in risk.[36,37] A higher incidence of ovarian failure has been observed in patients who receive combination therapy. It may be that certain chemotherapies reduce the carcinogenic effects of radiation by suppressing the proliferative environment of the breast, leading to the observed reduced risk.[2,38] At the same time, however, lower doses or alternative chemotherapies may be insufficient to suppress ovarian function yet be adequate to exert their own carcinogenic effects that result in the reported increased risk.

Although infrequent since the 1960s and 1970s, when staging laparotomy was routine, splenectomy may be another risk factor for breast cancer. Some authors have reported an associated increased RR, which may be due to reduced immune surveillance that allows tumor cells to proliferate and metastasize.[39,40] Others, however, found no change in risk.[10,31] This is more likely, since any surveillance would occur late in disease progression, when cells had already become cancerous and encountered the spleen as metastases.

Unlike secondary leukemia and NHL, the breast cancer survival rate varies depending on diagnosis stage. Following a greater awareness of increased risk and a significant shift toward early disease detection after 1990, the 5-year survival rate is 88% for stage I, 55% for state II, 60% for stage III, and 0% for stage IV.[41] This distribution may correlate with the degree of genetic mutation in breast cells. As in familial cases involving BRCA 1 and 2 mutations, patients develop cancer more than 20 years before the general population, suggesting a therapy-associated premalignant state early in life, which is more conducive to spontaneous and additional carcinogen-induced mutations. Loss of cell cycle regulation and DNA proofreading functions in youth may be particularly devastating, since there will be more time to accumulate carcinogen exposure while the breast is proliferating. If true, then ovarian failure might be protective by suppressing the proliferative stimulus, which appears to be the case.

Treatment, then, consists primarily of modified radical mastectomy, hormones, and chemotherapy, not only to remove the tumor but also to suppress and eliminate any occult premalignant lesions. Breast-conserving surgery has recently been examined in certain cases,[42] though with such a risk for tumors, great care must be taken in follow-up. Yet since patients are given some choice regarding bilateral mastectomies when appropriate screening is available,[32] such an approach may not be unreasonable. Screening would include annual breast examinations until age 25, then every 6 months and yearly mammography beginning at age 25, or 8 years after radiation.[3] Low-dose involved field radiation therapy is also theoretically possible in early cases, though in practice only patients with metastases receive it.

Thyroid

Secondary thyroid carcinoma occurred with a 1.74 to 36.4 times greater risk than the general pediatric population.[3,6,10,12] Although the number of reported cases was small at first,[2,7–10,12–14] suggesting RR inflation due to low population incidence, follow-up has revealed additional cases, making it the second most common solid secondary malignancy.[3] Cancer risk increased 10 years following remission and remained elevated after 40 years.[7,13] Children under 5 to 10 years old at treatment had a significantly elevated RR and AER compared with adults,[3,7,27] and although follicular carcinomas did occur, 63% to 90% of observed cancers were papillary thyroid carcinomas.[3,9]

The greatest risk factor appears to be radiation therapy. Tucker et al[43] found a higher incidence of carcinoma in patients who received more than 2 Gy of incidental thyroid irradiation, while Bhatia et al[3] found that 95% of tumors occurred within the radiation field. Similar associations have been found in other studies.[7,9,12] Additional possibilities include genetic predisposition to multiple malignancies, common environmental risk factors, and immunosuppression.[9] The role of chemotherapy, however, is unclear: some investigators have found it a risk factor, while others found it protective.[43] In reality, it may act as both, with prominent carcinogenic side effects when certain regimens are added to low-dose radiation but overwhelming cytotoxic effects when others are used.

The sensitivity of the thyroid to radiation damage has been well established, both in patients who survived nuclear fallout and in those irradiated for other diseases.[44–49] Since there is a significant increased risk in younger exposed children, the pediatric thyroid may have greater activity and growth that allows radiation-induced mutations to form and propagate more easily. However, the latency of more than 10 years suggests that additional genetic mutations are needed and/or that a long period of persistent, mutated TSH receptor stimulation is required for tumorigenesis. Papillary thyroid carcinoma (prevalent in adults >40 years old) predominates in these patients (who are in an age group where follicular carcinoma is most prevalent), while follicular carcinoma is also seen. This may suggest that although children are more susceptible to thyroid cancer, the specific mutations may be similar in adults. Prognosis is currently very good, with approximately 80% of patients surviving long term.[9] Although metastases are found in up to 50% of patients, complete or partial thyroidectomy with or without radioiodine and appropriate lymph node dissection appears very effective at inducing remission.[9]

Gastrointestinal Tract

Gastrointestinal tumors after HD treatment have a 7.2 to 22 times greater chance of occurring than in the general population[35,50] and occur more frequently in children than in adults.[2,3,27,51] Although grouped together in the literature and this discussion, the cancer subtypes have often been analyzed separately, revealing dramatic variation among anatomic locations and studies.[2] With RR ranging from 2.8 for colon cancer in one study[2] to 169 for esophageal cancer in another,[12] it is important to remember that some of these malignancies have a low population incidence, such that even a small number of observed cases dramatically increases risk. Despite statistical inflation, the greater risk is reinforced by an AER of 14.1 in one study[2] and the consistent occurrence of GI tumors in this population.[7,10,12,13] In particular, colorectal and gastric cancers have recently been found to carry significantly elevated risk.[3] Latency appears to be 10 to 20 years following treatment,[50] and increased risk may persist, although there are currently insufficient data to clarify this issue.

The role of combined modality therapy as a risk factor appears relatively well established. Likewise, radiation therapy by itself increases the GI cancer risk, although some have reported only borderline significance,[27,28] while others found it highly notable.[2,35,50] Chemotherapy, however, was by itself a significant risk factor in only one study,[2] suggesting that its role, if any, is additive. As for cancer subtypes, Metayer et al[7] reported esophageal adenocarcinoma, commonly associated with Barrett's esophagus, and suggested that environmental factors or other conditions, such as gastroesophageal reflux disease (GERD), may play a role in pathogenesis. Although GERD may be idiopathic in these patients, its association with steroids may suggest that chemotherapy is a greater factor in this cancer. Gastric cancer risk increased with extended field and large doses of radiation, as well as with younger age at HD diagnosis.[51]

The greater risk in children and the strong association with irradiation suggests that the pediatric GI tract may be in a rapidly proliferative state, which becomes premalignant as the gut responds to accumulated genomic and stromal damage. This propensity for GI cancers has been observed following radiation therapy for other diseases,[7] and the absence of chemotherapy-associated increased risk in most studies may suggest that radiation therapy-induced stromal damage is necessary for tumorigenesis. The role of environmental factors, such as carcinogens in the diet, has not been examined in depth but may provide the additional insults needed to produce cancer. Regardless, tumorigenesis generally occurs without symptoms until advanced stages, when cancers are particularly aggressive. Although there are no exclusively pediatric statistics, one study of all ages reported that 19 of 25 patients died of the secondary malignancy,[50] compared with a 44% survival rate in adult primary GI cancer.[52] Despite reports of GI malignancies in cohorts of long-term survivors linking radiation to an increased risk of GI cancers,[50] the median age of onset is not as well established as that of secondary breast cancer following chest radiation. Hence, as with most of the screening guidelines in childhood cancer survivors, there are no studies indicating that implementation of early surveillance will enhance early detection or reduce morbidity or mortality. The Children's Oncology Group modified their recommendation for colorectal cancer screening after abdominal radiation following the recommendations published by Bhatia et al in 2003.[3] The current recommendation is that "monitoring begins 15 years after radiation or at age 35 years (whichever occurs last), with more frequent monitoring if clinically indicated."

Lung

The increased RR of lung cancer ranges from 5.1 to 27.3,[2,3,10] which is similar to adults,[21,28,34,53] although the elevation in AER is less in children.[35] The risk decreased slightly with time according to Metayer et al,[7] but the number of observed cases was limited, and in other studies[2,3] the risk increased after 10 to 15 years, as in other solid malignancies. Although RR increased with treatment at younger ages,[21] the AER was low, making the association with age uncertain. In one pediatric study, all lung cancers were non-small cell carcinomas,[10] whereas with all ages, ratios were similar to primary malignancies (38% were squamous cell carcinoma, 24% were adenocarcinoma, 16% were small cell carcinomas, 20% were unspecified, and 2% were other).[35]

Pulmonary tumorigenesis in these patients remains unclear. Swerdlow et al[21] found that the risk increased uniformly by three- to four-fold in all treatment groups, while Bhatia et al[3] found that all tumors occurred in the mantle irradiation field. However, with all ages, radiation and chemotherapy effects were additive, and drug-associated cancers occurred approximately 5 years before those from radiation.[54,55] As in the general population, tobacco smoking was a significant risk factor, although its effect was more pronounced in treated adult patients. The relationship with radiation was almost multiplicative, and tobacco use after treatment increased the risk of lung cancer by more than 20-fold.[55,56]

Although primary lung cancer is the most frequent and deadly tumor in the general adult population, it generally occurs much later and with greater histologic diversity than in

pediatric survivors, suggesting the modifying role of treatment or the cancer state. As in primary tumorigenesis, smoking appears to provide the necessary carcinogen exposure and tissue damage to form tumors, with chemotherapy and radiation therapy producing a level of genomic and regulatory damage that facilitates the process. This may explain the greater risk in adult treated patients, since children have had less time and opportunity to accumulate mutations prior to initiating therapy. Previous damage may also help explain differences in risk with treatment modality, such that all modalities may have similar mutagenic effects with no prior insults, but chemotherapy may have a greater impact after previous damage. Without prior insults, secondary pediatric tumors would depend more on the carcinogenic effects of therapy and smoking, which may explain why only non-small cell carcinomas were observed. Poor immunosurveillance of tumors may also have a role, but this has yet to be examined. Although the 5-year survival rate in adults is 14.9%,[57] mortality in pediatric survivors has not been reported, highlighting the need for greater investigation.

Sarcomas

Sarcomas are 10 to 14.9 times more common after HD treatment,[10,13] with bone (RR 1.31–37.1)[3,6,7,13] and connective tissue (RR 10.32–15.1)[2,6,7] being the most common forms. Other histologic subtypes include malignant fibrous histiocytoma, osteosarcoma, chondrosarcoma, nerve sheath sarcoma, spindle cell sarcoma, and undifferentiated soft tissue sarcoma.[10] Latency is unclear, with an early study[17] reporting it at 10 to 15 years following remission, while more recent ones[3,7] noted an increased risk in the first decade, which dramatically increased in the second and persisted beyond 20 years.[3,10] With few cases, statistical artifact from a low population incidence rate may help explain the differences in latency. As for age at treatment, Metayer et al[7] noted a greater bone sarcoma risk among those age 10 to 16 years old, while the connective tissue sarcoma risk appeared greatest among children treated before 9 and between 17 and 20 years old. Compared with adults treated for HD, sarcomas were much more frequent in children.[58]

Alkylating agents[7] and radiation have been reported as independent risk factors, especially in bones.[10] This tissue may be particularly sensitive to radiation, with studies showing a dose–response gradient for developing malignancy[3,10,59,60] that may be due to greater absorption of radiation by bone.[17] Reports of sarcomas in the radiation fields, involving the T12 vertebral body, clavicle, and scapula, support this association.[10] Increased risk for soft tissue sarcomas was also associated with anthracycline use.[6]

Since the greatest sarcoma risk occurs during the period of rapid puberty-associated growth, it may be that the highly proliferative state of these tissues makes them more susceptible to carcinogenic effects. The greater risk among pediatric-treated patients versus adults supports this idea, as does the close association between radiation dose and cancer risk. It may be that as the level of radiation- and chemotherapy-induced damage increases, so too does the proliferative response, such that the combination of rapid mitosis and genomic instability allows dysplasia to occur. As proliferation continues and insults accumulate, these dysregulated cells may gain additional knockout mutations that allow them to outcompete normal cells. The timing of these insults may also help explain the differences in latency, since a greater overlap with puberty, which varies individually, may translate to a longer period of effective carcinogenesis and earlier tumor occurrence. The mortality of these secondary sarcomas is unknown, although the primary osteosarcoma survival rate is 63% at 5 years for children and 70% for adults with chemotherapy and surgical intervention.[51,57]

Melanoma

The RR of melanoma ranges from 1.9 to 8.7.[7,10] Although one group questioned the statistical significance,[7] two other studies[2,12] found significantly elevated RR with overlapping confidence intervals, suggesting that the greater risk is real. As for latency, risk increased slightly beyond the first decade of remission.[7] No particular pediatric age group was at greater risk for melanoma, and risk was similar in adults.[34,35]

As in the general population, ultraviolet radiation was a significant risk factor. Chemotherapy also increased the risk and as in other hematologic malignancies was associated with developing significant numbers of melanocytic nevi,[61,62] of which the dysplastic forms may be melanoma precursors. Although ionizing radiation was not identified as a risk factor,[7] melanomas often occurred in the mantle field distribution,[8,10] suggesting a possible carcinogenic effect. But since melanomas often appear on the trunk, this may be coincidence.

The strong correlation with UV exposure and similar risk in adults and children suggest that the tumorigenesis of secondary melanoma may not differ significantly among groups. Additional risk after HD treatment likely stems from the carcinogenic and immunosuppressive effects of chemotherapy, which provides the genetic insult and prevents the removal of premalignant cells. The greater incidence of dysplastic melanocytic nevi supports this idea, although there may also be an inherent HD-associated immunosurveillance defect, as theorized in other secondary malignancies. The greater risk with UV over ionizing radiation may be due to greater repetition of exposure, which although of lower dose intensity may provide the necessary additional insults over time to produce cancer. Melanoma formation has also traditionally been much more sensitive to UV irradiation, which in the setting of a premalignant lesion may explain its prevalence over other skin cancer subtypes. Although there are no reported survival rates in this population, both pediatric and adult primary melanomas have an approximately 90% survival rate at 5 years.[52,57] If at an early stage, local excision would presumably provide adequate treatment and cure, as in the case of a primary lesion.

Urogenital Tract

Secondary urogenital tract tumors have a combined RR of 3.5 and an AER of 4.8,[2] with a urinary tract RR of 2.4 to 4.3.[2,7,12] Among males, genital cancer risk ranges from 1.4 to 3.0; in females, it ranges from 4.1 to 7.3.[2,7,12] Along with a greater risk for ovarian cancer, women had a 6.1 RR of cervical cancer,[7] which became significant 10 to 14 years after remission and persisted beyond 20 years. Despite an association

of cyclophosphamide and pelvic radiation therapy with bladder carcinoma in adults, the AER for children in a 25-year HD survivorship study was only 0.8.[35] Although children may not have the same risk as adults for cyclophosphamide-induced bladder cancer, the true risk may not be estimable, since children receive milder dosing of shorter duration in general.[63,64] There are no data correlating age at diagnosis or latency for the other urogenital malignancies.

The etiology of these tumors remains unclear, except for possibly cervical cancer. Metayer et al[7] suggested that when adolescents become sexually active and are infected with the human papillomavirus, they may have defective cellular immunity due to HD and its treatment. This lack of surveillance may allow the virus to exert its carcinogenic effect unhindered. The role of radiation is considered small since the cervix is relatively radioresistant.[65] Chemotherapy, however, may amplify this process, since certain agents have both immunosuppressive and carcinogenic properties. The inability of most of these drugs to penetrate the blood–testes barrier may also explain the lower risk of male genital cancer compared with female genital and urinary tract cancer. With greater exposure to chemotherapy, these tumors are more likely to develop activating mutations that allow for additional insults or, in the case of ovarian cancer, persistent stimulation. The survival rates in these patients are also unknown, but for primary pediatric germ cell tumors the survival rate is 94% at 5 years.[57] Among adults, the 5-year statistics are 74.4% for urinary tract cancers, 71.4% for female genital cancers, and 97.2% for male genital cancers.[52]

Brain and Central Nervous System

Neurologic tumors are infrequent but have an RR as high as 10.5, although it may actually be closer to 2.0.[6,7,12,13] Although often labeled as brain tumors, two cases were observed in the spine[12] and one was a meningioma that developed in the posterior fossa 27 years after remission.[66] The spinal tumors occurred in irradiated fields, suggesting that radiation is a risk factor. Although past delivery regimens involved the mantle area, patients may have been exposed to high-dose scatter radiation that contributed to brain lesion formation. Since the blood–brain barrier protects the CNS, systemic chemotherapy is unlikely to be tumorigenic here, although the effect of intrathecally delivered regimens is unclear. The survival rate is unknown but likely to be as poor as the 32.8% 5-year survival rate in adults.[52]

DISCUSSION

Retrospective studies of pediatric HD survivors from the past 50 years have revealed that these patients are at greater risk for a spectrum of second cancers following therapy, some of which are highly curable (eg, basal cell and thyroid carcinoma) while others are routinely fatal (eg, secondary leukemia and NHL) and still others have intermediate outcomes (eg, breast carcinoma and sarcoma). Fatal leukemia and NHL appear in the first decade after remission, numerous types of solid tumors beyond 10 years. Chemotherapy and/or radiation therapy appears to be instrumental in establishing a premalignant state in most cancer subtypes, with environmental factors, poor immunosurveillance and other factors participating in tumorigenesis to varying degrees. Unfortunately, second cancer treatment options and outcome may also be compromised if prior HD therapy precludes the optimal use of certain chemotherapeutic agents (anthracyclines) or radiation therapy (eg, secondary breast cancer in young women treated with ABVD and chest radiation). With a growing awareness of late effects, investigators have adjusted treatment regimens in the hopes of reducing these consequences while continuing to maximize efficacy.

While the medical community awaits these trial results, it is important to keep the potential for secondary malignancies in perspective. Although dramatic increases in risk have been observed, these often occur as cancers that have a low incidence, such that the resulting risk may still be relatively low. Also, for specific histologies, the relationship of host and treatment factors have been well established, whereas the contribution of genetic and behavioral factors has not been well studied and will require further evaluation to obtain a more complete understanding and management of increased risk. It is also important to remember that without treatment, HD has a very high mortality rate, and that many more people would die from the primary malignancy than from the secondary. Although perhaps of little comfort to those who do develop these late effects, the cancer occurs after time that they would otherwise not have had without treatment.

With a greater risk for developing cancer, screening and education in this population become extremely important, as does awareness in those who treat them. Unfortunately, survivors face obstacles in obtaining proper health care, with one retrospective study reporting a lack of insurance as the greatest factor for failure to follow-up.[67] For those who do have insurance, coverage for pre-existing conditions or conditions that incur significant expense are often precluded. This practice makes optimal patient care a great challenge and underscores the need for changes in both the health care system and in how we treat HD patients.

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