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Screening for Thyroid Cancer in Survivors of Childhood and Young Adult Cancer Treated with Neck Radiation

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Abstract

Background—The optimal method of screening for thyroid cancer in survivors of childhood and young adult cancer exposed to neck radiation remains controversial. Outcome data for a physical exam-based screening approach are lacking.

Methods—We conducted a retrospective review of adult survivors of childhood and young adult cancer with a history of neck radiation followed in the Adult Long-Term Follow-Up Clinic at Memorial Sloan Kettering between November 2005 and August 2014. Eligible patients underwent physical exam of the thyroid and were followed for at least one year afterwards. Ineligible patients were those with prior diagnosis of benign or malignant thyroid nodules.

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COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As a retrospective analysis, MSK IRB approval was obtained and the need for informed consent was waived.

Conflict of interest statement: Emily S. Tonorezos, MD MPH has no conflict of interest; Dana Barnea, MD has no conflict of interest; Chaya S. Moskowitz, PhD has no conflict of interest; Joanne F. Chou, MPH has no conflict of interest; Charles A. Sklar, MD has no conflict of interest; Elena B. Elkin, PhD has no conflict of interest; Richard J. Wong, MD has no conflict of interest; Duan Li, MD has no conflict of interest; R. Michael Tuttle, MD has no conflict of interest; Deborah Korenstein, MD has no conflict of interest; Suzanne L. Wolden, MD has no conflict of interest; Kevin C. Oeffinger, MD has no conflict of interest.

Results—During a median follow-up of 3.1 years (range 0–9.4 years), 106 ultrasounds and 2,277 physical exams were performed among 585 patients. Forty survivors had an abnormal thyroid physical exam a median of 21 years from radiotherapy; fifty percent of those with an abnormal exam were survivors of Hodgkin lymphoma, 60% had radiation at ages 10–19 and 53% were female. Ultimately, 24 underwent fine needle aspiration (FNA). Surgery revealed papillary carcinoma in 7 survivors; 6 are currently free of disease and one with active disease is undergoing watchful waiting. Among those with one or more annual visits, representing 1,732 person-years of follow-up, no cases of thyroid cancer were diagnosed within a year of normal physical exam.

Conclusions—These findings support the application of annual physical exam without routine ultrasound for thyroid cancer screening among survivors with a history of neck radiation.

Implications for cancer survivors—Survivors with a history of neck radiation may not require routine thyroid ultrasound for thyroid cancer screening.

Keywords

radiation therapy; screening; survivorship; thyroid cancer; ultrasound

INTRODUCTION

With advances in treatment and supportive care, the population of childhood and young adult cancer survivors has risen steadily in the last decades [1, 2]. Numerous publications have demonstrated that these survivors suffer from multiple morbidities and early mortality [3–9]. Unfortunately, those with a history of radiation therapy (RT) may be at highest risk for late effects of therapy, including cardiovascular morbidity and second malignant neoplasms [5, 3, 4, 6–9]. When compared with their siblings, childhood cancer survivors exposed to RT are 8 times more likely to suffer from a serious or life-threatening chronic health condition [3] and are at elevated risk of death from second malignant neoplasms [4].

Among second malignant neoplasms in this population, thyroid cancer is one of the most common [10], especially among those with a history of RT [11]; cumulative incidence of developing secondary thyroid cancer is approximately 0.5% by age 45, representing an 18-fold increase in risk compared to the general population [12]. In spite of this increased incidence, RT-associated thyroid cancer does not appear to be more aggressive than the sporadic form; the most common histologic types of thyroid cancer following RT are papillary (69–87%) and follicular carcinoma (5–23%) [13, 14], which have 5-year survival rates approaching 98%. [15] At the same time, benign thyroid nodules are ubiquitous, with incidence among those with a history of RT ranging from 27% to 81% [16–20]. Hence, thyroid cancer following RT does not appear to be more aggressive, benign thyroid ultrasound findings are common, and decisions regarding screening have implications for a substantial number of survivors.

Recommendations regarding screening for thyroid cancer among individuals exposed to RT must carefully consider the balance of benefits and harms [21]. The Children's Oncology Group (COG) guidelines recommend a yearly thyroid physical exam [22], while other professional societies have recommended periodic thyroid ultrasound [23]. Targeted thyroid cancer screening in other populations has not been shown to reduce mortality, while potential harms of screening include false positive tests, overdiagnosis and overtreatment, increased cost, and patient anxiety [24–26]. Unnecessary thyroidectomies could result in lifelong thyroid replacement therapy and potential complications of surgery such as permanent hypoparathyroidism or injury to the recurrent laryngeal nerve [27]. In the general population, overdiagnosis of thyroid cancer has been implicated as the major cause of the steep rise in thyroid cancer incidence worldwide [24, 25, 28, 29], which has occurred in the setting of stable mortality [30].

Despite numerous reports on ultrasound-based thyroid cancer screening [31, 19, 16, 18, 20], and growing concern regarding overdiagnosis of thyroid cancer [29], reports of clinical outcomes of physical exam-based screening are lacking. Therefore, we report the outcomes of real-world thyroid cancer screening using physical exam among survivors of childhood, adolescent and young adult cancer at the Memorial Sloan Kettering (MSK) Adult Long-Term Follow-Up (LTFU) clinic.

METHODS

The Adult LTFU clinic at MSK in New York, NY delivers longitudinal risk-based health care [32], including management of late effects, for adults who had their first primary malignancy prior to age 40 and who are at high risk for serious late effects or have multiorgan complications following their cancer therapy. Survivors must be over 18 and finished with therapy to be followed in the clinic. Screening and surveillance for late effects occurs during an annual visit. In accordance with the COG guidelines, palpation of the thyroid is performed as a screening method for thyroid cancer in high-risk individuals, including survivors with a history of RT to the neck or surrounding structures (Figure 1). For survivors found to have abnormalities on thyroid physical exam a thyroid ultrasound is obtained. Benign-appearing nodules are followed sequentially with ultrasound, while nodules with suspicious features such as microcalcifications, hypoechogenicity, or central vascularity are referred for fine needle aspiration (FNA) and cytology evaluation. A survivor with a suspicious or malignant FNA is referred for evaluation by surgery and endocrinology. Inconclusive cytologic results are followed by an additional biopsy or referred for surgical evaluation.

After Institutional Review Board approval, a retrospective chart review was conducted on all patients seen in the Adult LTFU clinic between November 1, 2005 and August 31, 2014 (n=1069) by author DB and confirmed where needed by ET and KO. Notably, every Adult LTFU chart includes a detailed cancer treatment summary with treatment exposures. Survivors with a history of RT to the neck or surrounding structures and at least one visit in the Adult LTFU clinic were included. Those with a diagnosis of a thyroid nodule or thyroid cancer prior to their first visit to the Adult LTFU clinic were excluded. Ultimately, five hundred and eighty five survivors were eligible for the analysis. All data were obtained from review of the MSK medical record, which includes internal documentation as well as outside correspondence with survivors' local physicians.

In order to better understand the utility of thyroid exam, a subset of patients with more than one annual exam was evaluated. False referral probability and negative predictive value for thyroid exam were calculated using the reference standard of incident thyroid cancer (not detected on exam) within one year of an Adult LTFU thyroid exam. The false referral probability represents the percentage of visits during which there was an abnormal thyroid physical exam, yet thyroid cancer was not diagnosed within one year. Because exam is repeated annually, a longer follow-up window was not applicable. To account for the multiple exams per patient, confidence intervals were calculated using a logit transformation with a standard error estimated with linearization methods.

RESULTS

Patient characteristics

Clinical characteristics of the 585 Adult LFTU patients with a history of RT exposure are detailed in Table 1. Forty survivors had an abnormal thyroid physical exam. For these 40 survivors, the median time from RT to the abnormal thyroid physical exam was 21.0 years (range, 4.5–44.4 years). Not unexpectedly, fifty percent of survivors with an abnormal thyroid physical exam were Hodgkin lymphoma survivors, treated at a median age of 15.3 years.

Clinical outcome of survivors with an abnormal thyroid physical exam

Of the 40 survivors with abnormal thyroid physical exam, thyroid ultrasound was performed in 39 (Figure 2). One patient with an abnormal exam had widely disseminated bladder cancer at the time of evaluation; thyroid nodule workup was not pursued. The remaining 39 patients underwent a total of 106 ultrasound exams during a median of 6.1 years of follow-up in the Adult LTFU clinic. The median number of ultrasound exams per patient was 2 (range, 1–10).

Three survivors with an abnormal physical exam did not have a thyroid nodule detected on ultrasound (false referrals). Five survivors were found to have a single thyroid nodule and 31 survivors had more than one nodule on ultrasound. Among nodules for which size was reported (N=139), median size was 7mm (range, 1–39 mm). After sonographic evaluation, 24 patients were referred for FNA; cytology was benign in 15 of 24 cases. One patient with inconclusive cytology and 8 patients with suspicious cytology were referred to surgery (7 total thyroidectomies and 2 lobectomies); surgical pathology revealed papillary thyroid carcinoma in seven patients. In addition, one patient had a Hurthle cell adenoma and one a follicular adenoma.

Patients with papillary thyroid carcinoma

Of the seven patients with papillary thyroid carcinoma, three had prior CNS tumor, three had prior lymphoma, and one had prior chronic myeloid leukemia diagnoses. Prior cancer diagnoses were CNS tumor (N = 3), lymphoma (N = 3), and chronic myeloid leukemia (N = 1). The median time period from RT to thyroid cancer diagnosis was 18.6 years (range, 12.7–22.8).

All seven patients with thyroid cancer had papillary carcinoma; two had classical papillary carcinoma, one had solid variant of papillary carcinoma, 3 had follicular variant of papillary carcinoma and one survivor had one noninvasive follicular variant papillary carcinoma focus and one classical papillary carcinoma focus. Four patients had a microcarcinoma (i.e. <10 mm); two of which had multiple foci. Six patients had nodular hyperplasia in the non-malignant thyroid tissue. All patients were stage I and all underwent total thyroidectomy. Four underwent excision of at least one lymph node and one patient had radioiodine (I-131) ablation after surgery. One patient was found to have lymph node involvement, which did not change the stage (I). None had distant metastases.

Six patients have not recurred and were doing well at most recent follow-up (2016). One patient had a regional recurrence in a cervical lymph node. After this recurrence, he underwent radioiodine (I-131) ablation. He was being actively monitored and his disease has not progressed since then.

Assessment of thyroid physical exam as screening method

We estimated the clinical utility thyroid physical exam as a screening method using diagnosis of thyroid cancer within one year of follow-up as a reference standard. Among 468 survivors representing 1,732 person-years of follow-up, no incident clinically significant or advanced thyroid cancer was diagnosed among those with a normal thyroid physical exam, corresponding to a negative predictive value of 100% and a false referral probability of 2.0% (95% CI 1.3 – 2.6%).

DISCUSSION

Among 585 survivors of childhood, adolescent and young adult cancer who were exposed to neck RT and followed for a median of 3.1 years, annual thyroid physical exam detected seven early-stage papillary thyroid carcinomas. While thyroid carcinoma may have gone undetected during this follow-up time, it is not clear that undetected thyroid cancer is clinically significant. Importantly, no thyroid cancer has presented with symptoms or was detected incidentally during these years of follow-up. In addition, the substantial cost of annual screening thyroid ultrasound was avoided. To our knowledge, this is the first description of outcomes of thyroid cancer screening in RT-exposed cancer survivors using thyroid physical exam.

This report supports the safety of the Children's Oncology Group (COG) long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancer, which do not recommend routine ultrasound screening for thyroid cancer in RT-exposed survivors [22]. The American Thyroid Association guidelines on thyroid nodules and cancer conclude that there is insufficient evidence to endorse ultrasound screening in cancer survivors previously exposed to neck RT [33]. However, some professional society guidelines, such as those issued jointly by the American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association [23], advocate thyroid ultrasound for screening this population. In light of this controversy, our findings support an opportunity for shared decision-making regarding the method of thyroid cancer screening that takes into account clinical evidence as well as the perceptions and concerns of the individual patient regarding potential benefit and potential harms.

Ultrasound screening is highly sensitive for thyroid carcinoma, particularly microcarcinoma, but has the potential to cause significant harm [20, 16, 34, 19]. Eden et al estimated that ultrasound screening of 10,000 irradiated survivors would detect 150 more cases of thyroid cancer, compared to screening with physical exam. However, this strategy would also result in an estimated 1,689 surgeries for nonmalignant nodules [35]. Surgery for a suspicious thyroid nodule may cause harm whether a total or partial thyroidectomy is performed; potential complications include recurrent laryngeal nerve injury and hypoparathyroidism with hypocalcemia [27]. Additionally, an unavoidable consequence of total thyroidectomy is hypothyroidism and the need for lifelong thyroid replacement therapy. Other potential ultrasound screening-related harms include anxiety, which can be especially difficult for cancer survivors, and the cost of annual thyroid ultrasound [36]. Therefore, thyroid cancer screening with annual ultrasound is costly to the health system and to individual patients; the burden of these costs may be substantial and should be taken into consideration [37–39]. In contrast, our false referral probability was low (2.0%, 95% CI 1.3–2.6), and most survivors did not undergo unnecessary evaluations.

The key question is whether ultrasound screening would affect clinical outcomes, such as mortality or quality of life. A highly sensitive screening test may be reasonable if detection of smaller tumors improves survival, yet data from thyroid cancer in the general population does not support this concept. In the past four decades, thyroid cancer incidence in the U.S. has tripled, while thyroid cancer-related mortality has remained stable and very low [24, 29]. One explanation for the steep increase in thyroid cancer incidence is overdiagnosis due to the increased use of imaging and the detection of incidental tumors; between 2008 and 2009, 39% of the tumors were <1 cm as opposed to 25% between 1988 and 1989 [24]. Smaller tumors are more likely to be detected using imaging since nodules are usually palpable when larger than 1.5 cm [40]. Autopsy studies have detected occult thyroid cancer in 1.8 – 35.6% of thyroid glands dissected, suggesting a silent reservoir [41–46].

A recent systematic review by Clement et al examined the associations between stage of detection of differentiated thyroid cancer with mortality and morbidity [26]. Their findings suggest that in adults, detection of thyroid cancer at an earlier stage is associated with lower mortality; however none of the reviewed studies performed prospective comparison of screening approaches. Therefore, whether ultrasound-based screening is necessary to control thyroid cancer mortality, or whether annual thyroid physical exam would be sufficient to detect early stage thyroid cancer, remains unknown. One opportunity for future research could be a case- control study among adult survivors of childhood or young adult cancer with new thyroid cancer diagnoses; manner of cancer detection among the newly diagnosed patients could be explored in this way, although this approach also has limitations.

Notably, RT-induced thyroid cancer appears to be primarily of the papillary subtype, which has an excellent prognosis [14]. In our series, seven of nine detected malignancies (and all of the thyroid cancer cases) were papillary thyroid carcinoma. Rubino et al conducted a single institution nested case-control study comparing 91 RT-induced thyroid cancer cases and 273 spontaneous thyroid cancer cases [47]. They found no difference in recurrence or thyroid-related death between the two groups. A study from the Rhône-Aples Thyroid Cancer Registry reported similar findings; despite a more aggressive initial presentation at time of thyroid cancer diagnosis, the risk of recurrence between RT-associated cancers and control cases was comparable [48]. Smaller cohorts of childhood and young adult cancer survivors have also noted excellent prognosis [49–52]. Therefore, RT-related thyroid cancer does not appear to be more aggressive than non-RT-related cases.

Our report has several limitations. First, this analysis represents a single institution-based retrospective study. Yet, while the data for this study was collected retrospectively, the patients in the clinic were followed prospectively with a clinical algorithm and continue to be observed for adverse outcomes. An additional limitation of this study is the relatively short follow-up. It is possible that with longer follow-up advanced thyroid cancers will become apparent. However, given the excellent prognosis of thyroid cancer in the general population and the similarities of thyroid cancer characteristics between the general population and cancer survivors, the likelihood of missing a life-threatening thyroid cancer with this physical exam-based approach appears remote.

In conclusion, this study supports the use of annual physical exam to screen for thyroid cancer in at-risk cancer survivors. Although RT-exposed childhood and young adult cancer survivors are at high risk for thyroid cancer, a strategy of annual thyroid physical exam rather than ultrasound screening missed no cases of advanced thyroid cancer. These findings suggest that harms of screening, such as expense, invasive procedures, and anxiety, could be safely reduced if practitioners caring for RT-exposed survivors focus on physical exam of the neck, rather than costly imaging.

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Condensed abstract

Among adult survivors of childhood and young adult cancer with a history of radiation therapy to the neck, annual physical exam is an acceptable thyroid cancer screening strategy.

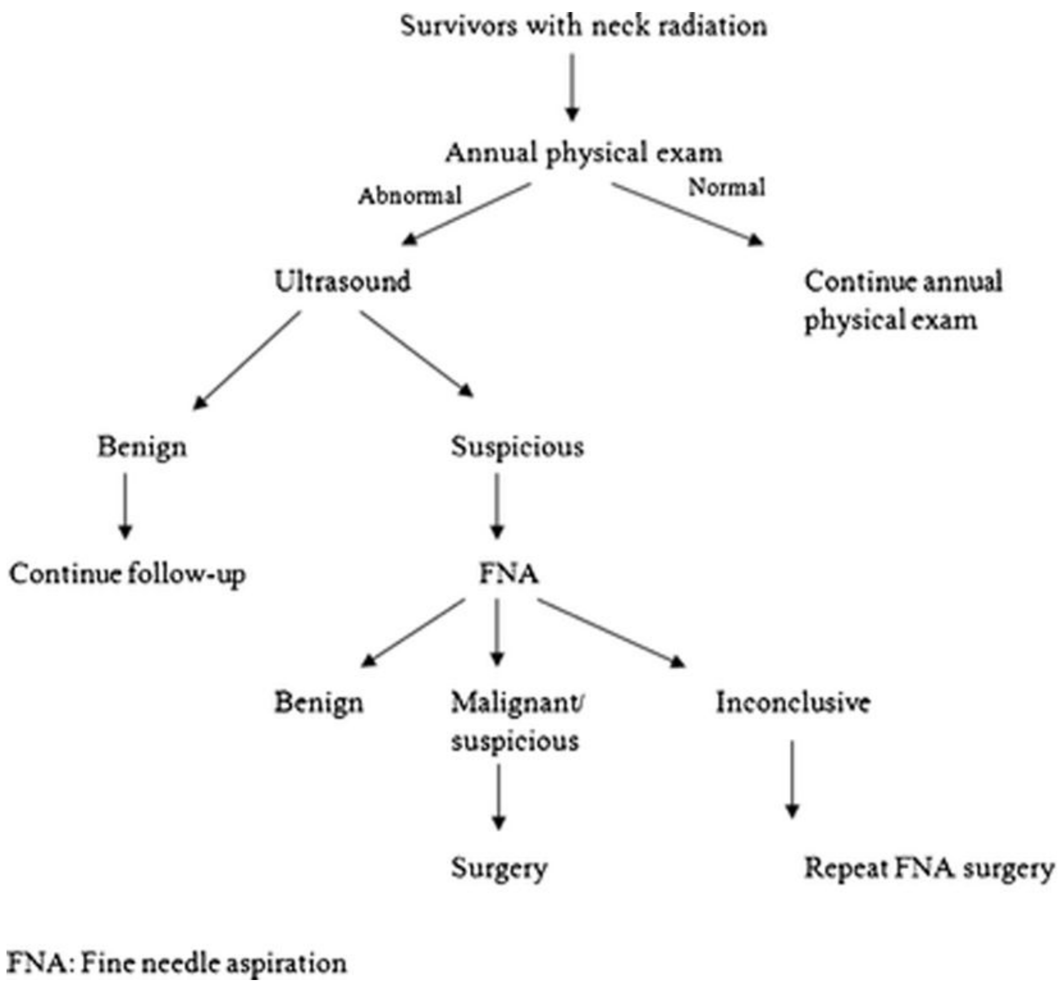
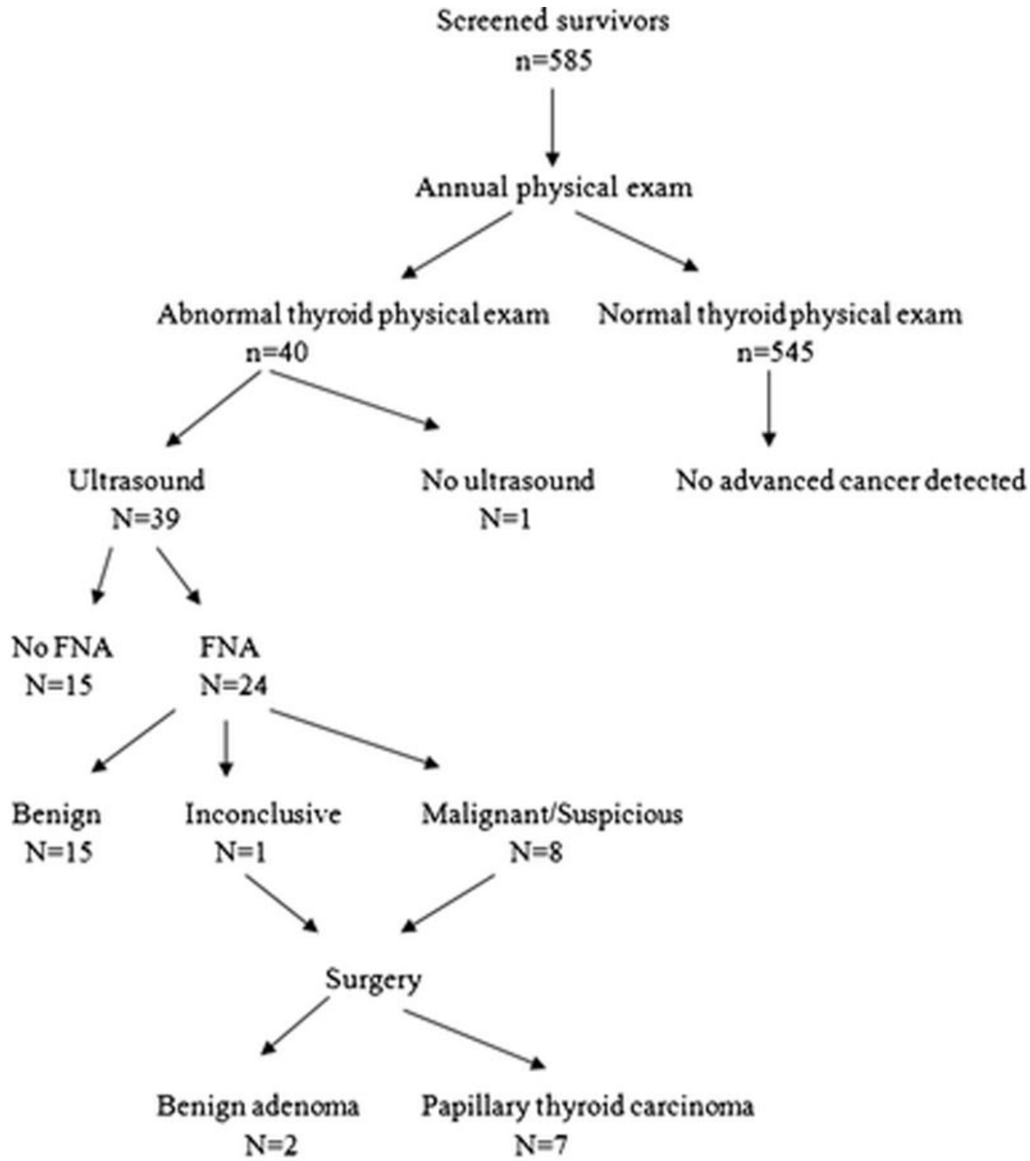


Figure 1.
Algorithm for thyroid cancer screening at Memorial Sloan Kettering Adult Long-Term Follow-Up Program.



FNA: Fine needle aspiration

Figure 2.
Physical exam findings and clinical course among 585 survivors of childhood and young adult cancer with a history of radiation therapy to the neck or surrounding structures.

Table 1

Patient characteristics of 585 survivors of childhood and young adult cancer with a history of radiation therapy to the neck or surrounding structures.

	Abnormal thyroid exam N=40	**Normal thyroid exam N=545**
Primary diagnosis – N (%)	20 (50)	180 (33)
Hodgkin Lymphoma	6 (15)	38 (7)
Non-Hodgkin Lymphoma	7 (18)	115 (21)
Leukemia	6 (15)	72 (13)
CNS Cancer	0 (0)	92 (17)
Sarcoma	1 (2)	48 (9)
Other		
Radiation field – N (%)	3 (7)	70 (13)
Cranial	0 (0)	29 (5)
Face	5 (13)	58 (11)
Cervical spine *	23 (58)	209 (38)
Neck *	1 (2)	28 (5)
Mediastinum	0 (0)	41 (8)
Other thorax	8 (20)	110 (20)
Total body irradiation *		
Age at radiation – N (%)	8 (20)	104 (19)
0–9	24 (60)	235 (43)
10–19	7 (18)	138 (25)
20–29	1 (2)	69 (13)
≥30		
Chemotherapy – N (%)	34 (85)	457 (84)
Alkylating agents	19 (48)	372 (68)
Anthracyclines	10 (25)	126 (23)
Bleomycin		
Gender – N (%)	21 (53)	261 (48)
Female	19 (47)	284 (52)
Male		
Hypothyroidism ** – N (%)	19 (47)	244 (45)
Yes	21 (53)	301 (55)
No		
Median interval from radiation to nodule detection or last clinic visit (range, yrs)	21.0 (4.5–44.4)	16.7 (0.4–57.7)
Median years of follow-up in Adult LTFU (range, yrs)	6.1 (0–9.1)	3.0 (0–9.4)
Alive at time of review – N (%)	36 (90)	507 (93)

* Thyroid included in radiation field.

** For survivors with abnormal physical exam – hypothyroidism diagnosis at or before nodule detection. For survivors with normal physical exam – hypothyroidism diagnosed any time.