

Behavior of Small Thyroid Cancers Found by Screening Radiation-Exposed Individuals

ANGELA BUCCI, EILEEN SHORE-FREEDMAN, THERESA GIERLOWSKI, DAN MIHAILESCU, ELAINE RON, AND ARTHUR B. SCHNEIDER

Section of Endocrinology and Metabolism, University of Illinois College of Medicine (A.B., E.S.-F., T.G., D.M., A.B.S.), Chicago, Illinois 60612; Michael Reese Hospital (E.S.-F., T.G., A.B.S.), Chicago, Illinois 60616; and Radiation Epidemiology Branch, National Cancer Institute (E.R.), Bethesda, Maryland 20892

Thyroid cancers detected by screening irradiated individuals are often small and of uncertain clinical significance. We retrospectively analyzed the effect of screening in a cohort of 4296 individuals exposed to radiation as children in the 1940s and 1950s and followed by us from 1974 until the present. We compared the thyroid cancers diagnosed before 1974 (122 cases, routine care) with the cancers found in subjects screened by us after 1974 (172 cases, screened), using cancer recurrence as the end point. Screening included a thyroid scan or, more recently, thyroid ultrasound. As expected, many of the cancers found by screening were very small (52% were <10 mm), but the range of tumor sizes overlapped those found by routine care. The recurrence rate was significantly lower in the cases found by screening, but when the comparison was limited to cancers 10 mm or larger, no difference in the recurrence rates was seen. This would suggest that the lower

recurrence rate observed for small thyroid cancers detected at screening was due to earlier diagnosis rather than more effective treatment. By univariate analysis, four factors were associated with an increased risk of recurrence of small (<10 mm) thyroid cancers: short latency (*i.e.* a shorter time interval between the radiation exposure and the first thyroid surgery), lymph node metastases present at diagnosis, multifocal cancers, and higher radiation dose. In a multivariate analysis combining the four risk factors, only short latency was significant. As thyroid cancers that escape detection by routine means should be diagnosed at screening, and both large and small thyroid cancers have the potential to recur, screening may be of value, but only if groups with a sufficiently high prevalence of thyroid cancer can be identified to offset the adverse effects of unnecessary treatment due to false positive results. (*J Clin Endocrinol Metab* 86: 3711–3716, 2001)

IT IS WELL known that exposure to external radiation for therapeutic purposes, particularly during childhood for benign head and neck conditions, is associated with an enhanced risk of thyroid cancer (1–4). It has been estimated that in the U.S. there are over 1 million individuals who received such exposure. The association with internal ¹³¹I exposure is less clear; however, studies conducted after the Chernobyl accident indicate that childhood exposure increases the incidence of thyroid cancer (5–7). As a result of the accident, an entire population in a large geographic area was placed at risk. These findings have increased concern among other people who have lived in the vicinity of nuclear facilities or atomic weapons testing grounds because iodine isotopes were released into the atmosphere. Radiation doses to the thyroid resulting from the U.S. atomic weapons tests were high for milk-drinking young children who lived near the Nevada test site in the early 1950s (8).

These exposures have raised an important public health issue regarding the medical value of screening for thyroid disease, particularly nodular disease (9). The goal of the work described here is to evaluate thyroid screening in an irradiated cohort and the clinical behavior of small cancers detected by screening.

Subjects and Methods

Radiation-exposed cohort

Between the years 1939 and 1962, 4296 patients, less than 16 yr of age, received radiation treatments for benign conditions in the head and neck area at Michael Reese Hospital (Chicago, IL). Prior publications describe

this cohort and the clinical observations that have been made (3, 10). The medical records of these patients were located, and a screening or follow-up program was initiated in 1974. At that time, an effort was made to contact all irradiated patients. When contacted, the individuals were notified of the radiation exposure, and a detailed medical history with emphasis on thyroid diseases was obtained. They were invited to Michael Reese Hospital for clinical evaluation, which included a physical examination of the head and neck area and thyroid imaging. The imaging was, until recently, a thyroid scan using ^{99m}Tc-pertechnetate and a pinhole collimator; since 1993 ultrasound has been used. When abnormalities were detected, the subjects were referred to their own physicians. Follow-up information was obtained by subsequent correspondence and/or visits to the program. If thyroid surgery was performed, surgical and pathology reports as well as histological slides were reviewed when possible. During the course of this follow-up, the histological classification of well differentiated thyroid cancer changed (11). As the slides for most of the cases had been returned to the original institutions, cancers were reclassified based on medical records. Mixed papillary-follicular cancers were reclassified as papillary cancer. Follicular cancers were reclassified as follicular variant of papillary carcinoma when the original pathologist or our reviewing pathologist mentioned the presence of nuclear inclusions. Other follicular cancers were not reclassified because insufficient information was available from the reports, and pathology slides could not be reviewed. There were no medullary or anaplastic carcinomas or thyroid lymphomas.

Study groups and comparisons

To date, 382 individuals in the exposed cohort have been diagnosed with thyroid cancer. Two groups of thyroid cancer patients are compared in this report. The first had thyroid cancers detected before the beginning of the screening program, *i.e.* before 1974 and is referred to as the routine group (*n* = 122). The second had thyroid cancers diagnosed after 1974 as part of a Michael Reese Hospital screening program and is referred to as the screened group (*n* = 172). Another 88 cases of thyroid cancer, diagnosed after 1974 outside of Michael Reese Hospital,

are not included in the comparison of the routine with screened group, but are included in the analysis of the behavior of small thyroid cancers (see below).

Each case of thyroid cancer was characterized by sex (female = 1, male = 2), age at radiation treatment (years), radiation dose to the thyroid (Gy, gray), age at time of thyroid cancer surgery (years), and latency (time from radiation treatment to first surgery) as well as the pathological findings at the time of the initial surgery [tumor size (millimeters), lymph node involvement (absent = 0, present = 1), bilaterality (unilateral = 1, bilateral = 2), invasiveness (none = 0, into capsule = 1, into soft tissues = 2), multifocality (unifocal = 1, multifocal = 2)], the initial treatment [extent of surgery ($\leq 50\%$ removed = 1, $>50\%$ removed = 2), use of radioactive iodine for completion (not used = 0, used = 1)], and subsequent evidence of recurrence (yes/no). The size of the thyroid cancer was taken as the largest dimension of the largest intrathyroidal focus of the cancer. Cancers less than 10 mm were classified as small.

Recurrences of thyroid cancer that were confirmed by surgery were reviewed as described above. Other recurrences were detected by ^{131}I scans. Focal uptake outside the thyroid bed and/or uptake in the thyroid bed after ablative (>75 mCi) treatment was considered confirmation of recurrence.

Statistical analysis

Statistical analyses of between-group comparisons for discrete variables were carried out by χ^2 analysis, and those for continuous variables were performed using *t* test. Recurrences were analyzed by Kaplan-Meier plots and were compared using the log-rank test (12). A difference at the level of $P < 0.05$ was considered significant. Univariate and multivariate comparisons of recurrences between groups were carried out by the proportional hazards method of Cox (13). For each covariate the estimate of the relative risk and its 95% confidence interval were determined. When the confidence interval excluded 1.0, the risk was considered significant. The analyses were implemented using NCSS 6.0 (Kaysville, UT), SigmaPlot 4.0 (SPSS, Inc., Chicago, IL) for the Kaplan Meier plots and Epicure (14) for univariate and multivariate proportional hazards analyses.

Results

Effects of screening

The characteristics of the 122 thyroid cancers in the routine group and the 172 in the screened group are summarized in Table 1. Before the initiation of screening more of the cancers occurred in women (54.1%); afterward more occurred in men (60.5%). This represented a shift toward the gender composition of the total cohort ($\sim 55\%$ of the cohort are men). The ages at first radiation treatment and the thyroid doses were very similar in the two groups. Age at cancer surgery and latency were greater in the screened group, because, by design, all of their cancers were diagnosed in 1974 and later.

The thyroid cancers in the routine group were larger, involved lymph nodes, and were bilateral, invasive, and multifocal more often than in the screened group. However, only the difference in lymph node involvement was statistically significant. The extent of surgery and the use of radioactive iodine for completion were significantly greater in the screened group than in the routine group. Presumably, the history of radiation exposure, which was not appreciated at the time of surgery for most of patients in the routine group, influenced the treatment decisions in the screened group.

A frequency histogram of the sizes of the thyroid cancers in the routine and screened groups and the sizes of the thyroid cancers that subsequently recurred are shown in Fig. 1. Over 50% of the screened patients had small cancers (<10 mm), and almost all of these did not recur. Recurrences were more frequent in the routine group compared with the

TABLE 1. Characteristics of thyroid cancers detected by routine care (<1974) and by screening (≥ 1974)

	Routine	Screened
Demographic characteristics		
No. of subjects	122	172
Male (%) ^a	45.9	60.5
Age at radiation treatment (yr)	3.8 \pm 2.5	3.7 \pm 2.6
Thyroid dose (Gy)	0.74 \pm 0.55	0.62 \pm 0.33
Age at cancer surgery (yr)	22.9 \pm 7.4	34.4 \pm 7.2
Latency (yr)	19.1 \pm 6.8	30.7 \pm 6.2
Pathological characteristics		
Size (mm)	18.9 \pm 12.5	9.3 \pm 8.0
Lymph node involvement (%) ^a	55.0	24.3
Bilateral (%)	29.2	26.3
Invasion (capsule and soft tissue; %)	32.4	24.3
Multifocal (%)	62.3	51.2
Histology (% papillary)	93.0	93.5
Treatment characteristics		
Extent of surgery ($>50\%$ removed; %) ^a	66.1	81.8
Radioactive iodine for completion (%) ^a	20.5	37.2

For each continuous variable, ± 1 SD is shown. The following data were unavailable: thyroid dose in 8 of the routine and 17 of the screened patients, size in 15 of the routine and 6 of the screened patients, lymph node involvement in 11 of the routine and 3 of the screened patients; bilaterality in 16 of the routine and 5 of the screened patients, invasiveness in 11 of the routine and 3 of the screened patients, multicentricity in 16 of the routine and 4 of the screened patients, histology in 8 of the routine and 3 of the screened patients, and extent of surgery in 4 of the routine and 2 of the screened patients.

^a $P < 0.05$, by χ^2 analysis.

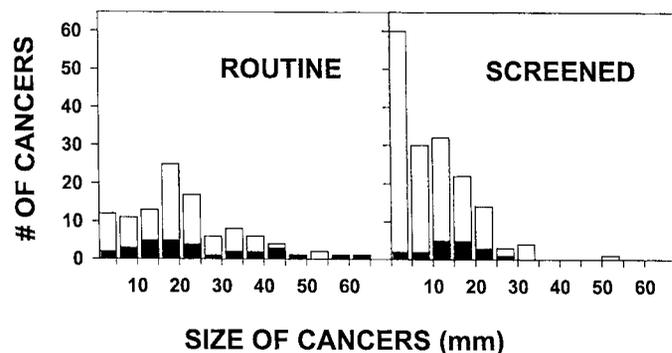


FIG. 1. Frequency histogram of the sizes of the thyroid cancers initially detected by routine care (left) and screening (right). The black portion of each bar represents the cancers that recurred.

screened group (Fig. 2, upper panel). The plots separated at about 3 yr after surgery and continued to diverge so that 24 yr after surgery, slightly over 85% of the patients diagnosed at screening had not developed a recurrence, whereas only 72% of the routine group remained recurrence free.

To determine to what extent the small cancers account for the apparently more favorable outcome in screened cases, the recurrence-free survival was analyzed for cancers 10 mm or larger (Fig. 2, lower panel). When only these larger cancers were considered, very little difference between the screened and routine groups was observed.

Behavior of small (<10 mm) thyroid cancers

Among the 382 thyroid cancers, tumor size of the original cancer was not available for 31 cases. Among the remaining

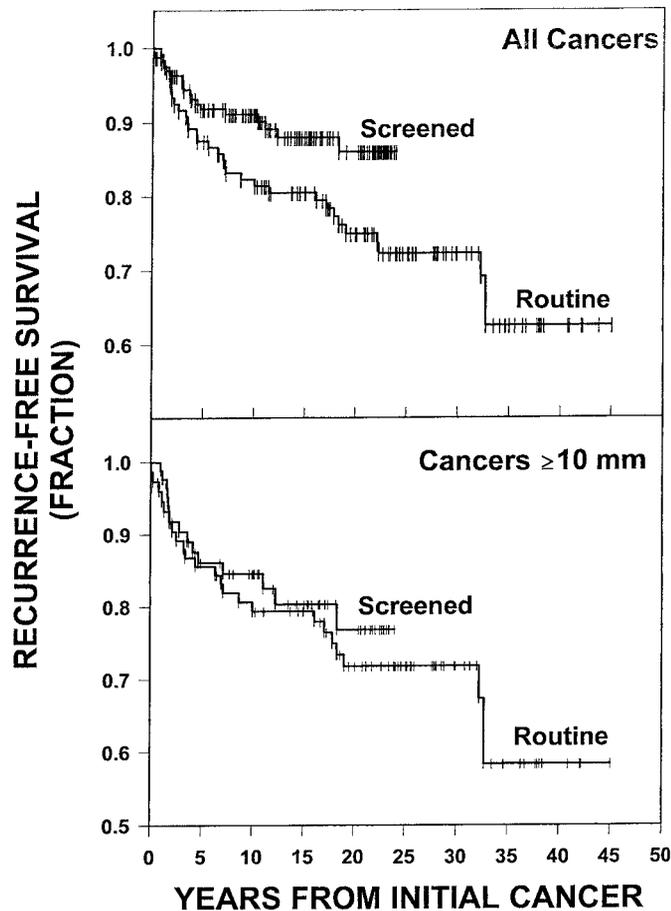


FIG. 2. Recurrence-free survival in patients whose thyroid cancers were originally detected by routine care compared with those detected by screening (as defined in *Subjects and Methods*). The top panel shows recurrence-free survival, by Kaplan-Meier plots, for thyroid cancers regardless of their original size. The lower panel shows recurrence-free survival for the larger thyroid cancers (original size, ≥ 10 mm). The difference between the two groups in the upper panel was significant ($P = 0.02$).

351 cases, 151 of the original cancers were less than 10 mm in greatest dimension. One cancer was found at autopsy, and no follow-up information was available for another, leaving 149 small cancers available for analysis.

The frequency of recurrence among the 149 subjects with small thyroid cancers was significantly less ($P = 0.0005$) than that in the subjects with larger thyroid cancers (Fig. 3). In total, only 11 of the 149 cases recurred, all in patients with papillary thyroid cancer. A comparison of the characteristics of the patients with and without recurrences revealed several potentially explanatory factors, although due to the small number of recurrences, few were statistically significant (Table 2). The individuals with recurrence had received a larger dose of radiation to the thyroid, and their cancers occurred at an earlier age and after a shorter latency (the latter reaching statistical significance). Recurrences were more frequent in cases with lymph node involvement, bilateral involvement, multifocal involvement, and invasion (with lymph node involvement reaching statistical significance). Recurrences were not associated with the extent of surgery or the use of radioactive iodine for completion. Table 3 shows the clinical

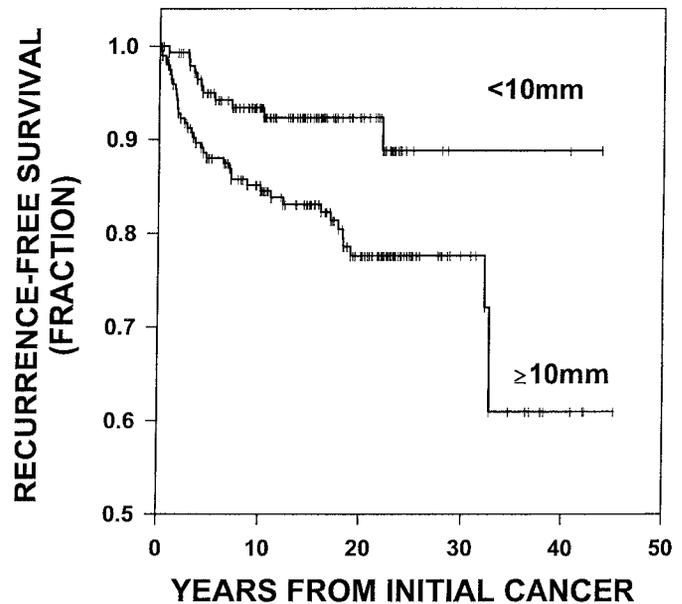


FIG. 3. Recurrences of thyroid cancer according to the size of the original cancer. The difference between the less than 10-mm and the 10-mm or larger cancers was significant ($P = 0.0005$).

TABLE 2. Comparison of the characteristics of the subjects with small (<10 mm) thyroid cancers at initial diagnosis with and without recurrence

	No recurrence	Recurrence
General characteristics		
No. of subjects	138	11
Male (%)	55.1	45.5
Age at radiation treatment (yr)	3.9 \pm 2.8	3.8 \pm 2.0
Thyroid dose (Gy)	0.63 \pm 0.29	1.05 \pm 1.06
Age at cancer surgery (yr)	34.5 \pm 7.7	27.7 \pm 8.1
Latency (yr) ^a	30.6 \pm 7.0	23.9 \pm 8.2
Pathological characteristics		
Size (mm)	3.6 \pm 2.8	4.3 \pm 3.3
Lymph node involvement (%) ^a	19.6	50.0
Bilateral (%)	13.6	30.0
Invasion (capsule and soft tissue) (%)	7.3	18.2
Multifocal (%)	41.0	70.0
Histology (% papillary)	96.6	100
Treatment characteristics		
Extent of surgery (>50% removed) (%)	70.3	72.7
RAI for completion (%)	25.7	36.4

The following data were unavailable: thyroid dose in 13 patients without and 1 patient with recurrence, lymph node involvement in 1 patient with recurrence, bilaterality in 6 patients without and 1 patient with recurrence, invasiveness in 1 patient without recurrence, and multicentricity in 4 patients without and 1 patient with recurrence.

^a $P < 0.05$, by *t* test or χ^2 analysis.

findings in the 11 recurrent cases. At last follow-up (mean, 16.2 yr; range, 2.4–42.1 yr), none had known residual thyroid cancer or had died of thyroid cancer.

To determine the magnitude of the risk factors for recurrence taking into account individual lengths of follow-up, univariate proportional hazards analyses were performed (Table 4). Among the cancers larger than 10 mm, size was the only significant factor, whereas several factors were signif-

TABLE 3. Individual descriptions of the 11 recurrent small (<10 mm on initial diagnosis) thyroid cancers

Yr to recurrence	Extent of surgery	Post-op RAI (mCi)	Presentation of recurrence	Confirmation	Findings
0.9	R lobectomy L subtotal	45	Follow-up ¹³¹ I scan	RAI	Two areas of uptake, one in neck outside thyroid bed, one in L perihilar mediastinum
2.9	R lobectomy L lobectomy	100	Follow-up ¹³¹ I scan	RAI	Residual uptake in thyroid bed 30 months after 100 mCi ¹³¹ I treatment
3.0	R lobectomy L lobectomy	75	Follow-up ¹³¹ I scan	RAI	Uptake and 0.5-cm palpable nodule in submental region
3.5	L nodulectomy	None	Patient noticed swelling in anterior lower neck	Surgery	Cancer in right lobe, metastatic to carotid sheath and infrathyroidal LNs, largest 0.5 cm
3.7	R lobectomy L lobectomy	None	Follow-up ¹³¹ I scans	RAI	Uptake in lateral left upper neck outside thyroid bed
4.1	L lobectomy	None	Follow-up ¹³¹ I scan	Surgery	Focal papillary carcinoma
4.3	R lobectomy	None	Follow-up physical examination	Surgery	Eight lymph nodes with metastatic thyroid cancer, largest 2.5 cm
5.5	R lobectomy	None	Patient noticed swelling in neck	Surgery	Metastatic 4-cm right cystic mass, lateral to thyroid
7.2	R lobectomy	30	Patient noticed mass in right neck	Surgery	Metastatic 0.8- and 1.2-cm lymph nodes on right
10.3	R subtotal	None	Hypercalcemia	Surgery	A 0.5-cm cancer in the thyroid remnant and a 2-cm metastatic mediastinal lymph node
22.1	R lobectomy L subtotal	None	Hypercalcemia	Surgery	A nonencapsulated 2.5-mm thyroid cancer in the residual thyroid gland

icantly related to recurrences in the small cancers. Among the general characteristics of the population, higher dose, younger age at cancer surgery, shorter latency, and detection by routine care were significant predictors of recurrence. When the latter three highly correlated time-dependent variables (latency, age at cancer surgery, and detection by routine care *vs.* screening) were analyzed together, latency was the dominant factor and was used in the multivariate analyses. Among the pathological characteristics, lymph node involvement and multifocal involvement were significant predictors of recurrence. In a multivariate analysis (Table 5) of the general characteristics, dose and latency remained significant factors. In a multivariate analysis of the two pathological characteristics, neither was significant. When the four characteristics were analyzed, only latency was a significant risk factor for the recurrence of small thyroid cancers. The estimated relative risk for latency was very similar in the univariate and multivariate analyses. The final multivariate analysis indicates that the risk of recurrence falls by about 14% for each year separating the radiation exposure from the first thyroid cancer surgery.

Discussion

In this paper we examined the behavior of small thyroid cancers and whether the clinical outcomes for thyroid cancer are improved by screening. The findings demonstrate again that many radiation-related thyroid cancers are not diagnosed during routine medical care, but are discovered by screening (10). Early detection by screening appeared to improve the outcome by reducing the frequency of recurrence

TABLE 4. Relative risks for recurrence of thyroid cancers by cancer size at initial diagnosis

	Cancer size	
	<10 mm (n = 149)	≥10 mm (n = 200)
General characteristics		
Sex (female)	0.87 (0.31;2.49) ^a	1.35 (0.72;2.54)
Age at radiation treatment (yr)	1.07 (0.91;1.26)	0.91 (0.78;1.04)
Thyroid dose (Gy)	2.50 (1.18;5.30)	1.10 (0.55;2.17)
Age at cancer surgery (yr)	0.88 (0.82;0.94)	0.97 (0.93;1.01)
Latency (yr)	0.88 (0.83;0.94)	0.98 (0.94;1.02)
Group (screened <i>vs.</i> routine) ^b	0.26 (0.08;0.87)	0.81 (0.41;1.59)
Pathological characteristics		
Tumor size (mm, ±SD)	1.08 (0.88;1.32)	1.03 (1.01;1.06)
Lymph node involvement	3.98 (1.22;13.1)	1.61 (0.86;3.00)
Bilateral	1.97 (0.52;7.44)	1.35 (0.71;2.56)
Invasion (capsule)	2.45 (0.31;19.3)	1.28 (0.64;2.54)
Invasion (soft tissue)	2.33 (0.50;10.8)	0.84 (0.29;2.45)
Multifocal	3.82 (1.01;14.4)	1.16 (0.60;2.22)
Histology (% papillary)	ND ^c	0.91 (0.32;2.56)
Treatment characteristics		
Extent of surgery (>50% removed; %)	0.87 (0.26;2.85)	1.50 (0.67;3.35)
RAI for completion (%)	1.22 (0.38;3.90)	1.35 (0.71;2.56)

^a Relative risk (95% confidence interval) estimated using univariate proportional hazards model.

^b Analysis confined to the 122 individuals in the routine group and the 172 in the screened group.

^c In this category there were no recurrences after a follicular cancer.

TABLE 5. Relative risks for recurrence of small thyroid cancers

General characteristics	
Latency (yr)	0.88 (0.83;0.94)
Thyroid dose (Gy)	2.12 (1.04;4.33)
Pathological characteristics	
Lymph node involvement	2.81 (0.79;9.99)
Multifocal	4.39 (0.90;21.5)
Combined characteristics	
Thyroid dose (Gy)	0.29 (0.00;13.9)
Latency (yr)	0.86 (0.76;0.97)
Lymph node involvement	1.56 (0.31;8.00)
Multifocal	2.68 (0.48;14.9)

Relative risks (95% confidence interval) estimated using multivariate proportional hazards model; small tumors are less than 10 mm.

in the screened group. However, another likely interpretation is that the clinical course of the thyroid cancers was not altered by screening, but, rather, because the cancers were diagnosed earlier, there appeared to be a longer time interval before recurrences occurred (lead bias). As the clinical outcomes for the screened and routine cases of the larger (≥ 10 mm) thyroid cancers did not differ, the apparent benefit of screening appears to be due in large part to the detection of small thyroid cancers.

There are two observations, however, that indicate that thyroid cancer screening may be of benefit. First, some large cancers that escaped detection among persons receiving routine care were diagnosed at screening. We recently showed that about half of ultrasound-detected thyroid nodules larger than 15 mm were not palpable in this cohort (15). Similar to the higher recurrence rate seen for large thyroid cancers in nonradiation-exposed patients, in this irradiated cohort thyroid cancer size was the predominant risk factor for recurrence among the cancers that were 10 mm or larger. In addition, screening detected a large number of smaller thyroid cancers as discussed below. They also can recur and require further therapy.

Although many reports describe thyroid cancers found as a result of screening, including recent reports from the Chernobyl area (7), there has been very little attention to documenting the potential benefits of screening compared with routine care. The most direct attempt to evaluate thyroid screening was carried out in Japan; Ishida *et al.* (16) screened 152,651 women for thyroid cancer, followed them for 7 yr, and then screened 3,557 of them again. At the initial screening thyroid cancers were detected. When the cancers found by screening were compared with those diagnosed in their out-patient clinic (unscreened group), the cancers found by screening were smaller in size and less likely to have lymph node metastases. The cumulative 7-yr survival rate was 97.6% in the screened group compared with 90.3% in the out-patient group. However, as reviewed by Eden *et al.* (17), potential biases in the selection of the groups make it difficult to interpret these data.

Observations by Mazzaferri and Jhiang (18) suggest that delayed treatment of thyroid cancer is associated with increased mortality. In their 30-yr follow-up study of 1355 thyroid cancer patients, they found that the likelihood of cancer death increased as the time interval between when the cancer became clinically evident and when it was finally

removed increased. If screening leads to prompt evaluation and, when necessary, surgery, it is likely to have a beneficial effect on outcome. The observations of Mazzaferri and Jhiang, however, are limited by the fact that their analyses were retrospective, and the reasons for the delayed surgeries were not determined.

The value of screening can only be established definitively by a randomized prospective study. Retrospective analyses, such as the ones presented here, cannot be interpreted unambiguously. The potential biases are especially relevant when analyzing thyroid cancer, because most cases progress very slowly, and some may not progress at all.

The behavior of small thyroid cancers in radiation-exposed patients is not as well described as it is in other patients. The data presented here highlight the similarities as well as some differences. The frequency of recurrences was lower among the patients with small cancers, but it was not negligible. In some instances the recurrences of the small cancers required further surgery.

Although it is evident that screening will detect small thyroid cancers, it is less clear whether there is a benefit to detecting these microcarcinomas. Microcarcinomas have a favorable prognosis, but there have been reports of patients who have died of their cancer. Two large studies of thyroid microcarcinomas show that not all microcarcinomas are cured at the time of first surgery (19, 20). Hay *et al.* (19) reported follow-up of as long as 48 yr (median, 16 yr) for 400 cases of papillary thyroid microcarcinoma. There were 2 deaths due to thyroid cancer as a result of the incident cancers. There were a total of 27 recurrences, with a 6% cumulative rate at 20 yr after the initial surgery. Most of the recurrences were observed within 10 yr of the initial surgery. Recurrences were associated with lymph node metastases at the initial surgery and lobectomy as the initial procedure. Yamashita and Noguchi (20) followed 1734 patients with microcarcinomas for a mean interval of 11.2 yr. There were 31 recurrences (1.8%, not corrected for varying length of follow-up), and 4 patients died of recurrent thyroid carcinoma. They observed that invasion of metastatic thyroid cancer through the lymph node capsule found at the time of initial surgery was the only significant risk factor for recurrence.

This is the first report analyzing the risk factors for recurrence of small thyroid cancers in irradiated patients. For the small thyroid cancers in our cohort, four factors were found to be associated with recurrences. 1) The increased risk of recurrence associated with short latency may be a marker of younger age at diagnosis, a well known risk factor for thyroid cancer recurrence (18, 21). Because of our study design, younger age at diagnosis, shorter latency, and discovery by routine care were highly correlated. Short latency may also be an indicator of inherently faster growth and earlier metastasis, possibly as a result of radiation-related somatic mutations. Despite this risk, mortality from thyroid cancer arising at a young age is rare. 2) The presence of metastases in lymph nodes was a risk factor. It is included in most, but not all, prognostic staging systems for recurrence of thyroid cancer (22). 3) The observation that multifocal involvement is a risk factor for recurrence has not been made previously. Multifocal cancers are seen frequently in radiation-related

cases (10), and it would be expected that the possibility of incomplete surgical removal would be increased in these cases. Also, multicentricity may be a sign of increased susceptibility to the effects of radiation, making new primaries more likely. 4) Why radiation dose is associated with increased risk of recurrence of small thyroid cancers, an observation that has not been made previously, is not clear. It seems likely that higher radiation exposure would increase the possibility of new primary cancers, especially small ones. It is possible that future work using the molecular characteristics of the cancers will be able to differentiate between cancer recurrences and new primary cancers.

In summary, the current study shows that thyroid screening of irradiated individuals identifies many small thyroid cancers associated with a very good prognosis. Some small cancers recur, especially those occurring with a short latency. To the extent that small cancers are included in the evaluation of a screening program, its benefits may be overestimated. However, screening also detects larger cancers, where a clinical benefit is more likely. Only a controlled prospective study will be able to prove clinical benefit, but the logistics of such a study make it unlikely that one will ever be performed.

Acknowledgments

Received February 7, 2001. Accepted April 18, 2001.

Address all correspondence and requests for reprints to: Arthur B. Schneider, M.D., Ph.D., Section of Endocrinology and Metabolism, University of Illinois, 1819 West Polk Street, MC 640, Chicago, Illinois 60612. E-mail: abschnei@uic.edu.

This work was supported in part by NCI Grant RO1-CA-21518.

References

1. Degroot LJ, Paloyan E 1973 Thyroid carcinoma and radiation: a Chicago endemic. *JAMA* 225:487–491
2. Shore RE, Hildreth N, Dvoretzky PM, Andresen E, Moseson M, Pasternack B 1993 Thyroid cancer among persons given X-ray treatment in infancy for an enlarged thymus gland. *Am J Epidemiol* 137:1068–1080
3. Favus M, Schneider A, Stachura M, et al. 1976 Thyroid cancer occurring as a late consequence of head-and-neck irradiation. *N Engl J Med* 294:1019–1025
4. United Nations Scientific Committee on the Effects of Radiation 1994 Sources and effects of ionizing radiation. New York: United Nations
5. Astakhova LN, Anspaugh LR, Beebe GW, et al. 1998 Chernobyl-related thyroid cancer in children of Belarus: a case-control study. *Radiat Res* 150: 349–356
6. Jacob P, Kenigsberg Y, Goulko G, et al. 2000 Thyroid cancer risk in Belarus after the Chernobyl accident: comparison with external exposures. *Radiat Environ Biophys* 39:25–31
7. Robbins J, Schneider AB 1998 Radioiodine-induced thyroid cancer: studies in the aftermath of the accident at Chernobyl. *Trends Endocrinol Metab* 9:87–94
8. NCI 1997 Estimated exposures and thyroid doses received by the American people from I-131 in fallout following Nevada atmospheric nuclear bomb tests. Bethesda: NIH
9. National Research Council and Institute of Medicine 1999 Exposure of the American people to Iodine-131 from Nevada nuclear-bomb tests: review of the National Cancer Institute Report and Public Health Implications. Washington DC: National Academy Press
10. Schneider AB, Recant W, Pinsky S, Ryo UY, Bekerman C, Shore-Freedman E 1986 Radiation-induced thyroid carcinoma: clinical course and results of therapy in 296 patients. *Ann Intern Med* 105:405–412
11. Hedinger C, Williams ED, Sobin LH 1989 The WHO histological classification of thyroid tumors: a commentary on ed. 2. *Cancer* 63:908–911
12. Kaplan EL, Meier P 1958 Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–481
13. Cox DR 1972 Regression models and life tables. *J R Stat Soc* 34:187–220
14. Preston DL, Lubin JH, Pierce, DA 1991 *Epicure users guide*. Seattle: Hirosoft International
15. Schneider AB, Bekerman C, Leland J, et al. 1997 Thyroid nodules in the follow-up of irradiated individuals: comparison of thyroid ultrasound with scanning and palpation. *J Clin Endocrinol Metab* 82:4020–4027
16. Ishida T, Izuo M, Ogawa T, Kurebayashi J, Satoh K 1988 Evaluation of mass screening for thyroid cancer. *Jpn J Clin Oncol* 18:289–295
17. Eden K, Helfand M, Mahon S 1999 Screening for thyroid cancer: background paper. National Research Council and Institute of Medicine. Exposure of the American people to iodine-131 from Nevada nuclear-bomb tests: review of the National Cancer Institute Report and Public Health Implications. Washington DC: National Academy Press; 221–263
18. Mazzaferrri EL, Jhiang SM 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 97: 418–428
19. Hay ID, Grant CS, Vanheerden JA, Goellner JR, Ebersold JR, Bergstralh EJ 1992 Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. *Surgery* 112:1139–1147
20. Yamashita H, Noguchi S, Murakami N, et al. 1999 Extracapsular invasion of lymph node metastasis. A good indicator of disease recurrence and poor prognosis in patients with thyroid microcarcinoma. *Cancer* 86:842–849
21. Viswanathan K, Gierlowski TC, Schneider AB 1994 Childhood thyroid cancer: characteristics and long-term outcome in children irradiated for benign conditions of the head and neck. *Arch Pediatr Adolesc Med* 148:260–265
22. Mazzaferrri EL 2000 Thyroid diseases: tumors: radioiodine and other treatment and outcomes. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's the thyroid*, 8th Ed. Philadelphia: Lippincott, Williams & Wilkins; 904–929