Information for Physicians on Irradiation-Related Thyroid Cancer

The National Cancer Institute

The National Cancer Institute, in cooperation with the National Institute of Arthritis, Metabolism and Digestive Diseases and the Bureau of Radiological Health of the Food and Drug Administration, is making available to practicing physicians current information concerning a special population in the United States at increased risk of developing cancer, especially of the thyroid gland.

A workshop on the Late Effects of Irradiation to the Head and Neck in Infancy and Childhood was held in Bethesda, Maryland on September 24-25, 1975. Participants included experts on various aspects of thyroid disease under the chairmanship of Dr. Oliver H. Beahrs, Director, Department of Surgical Oncology, Mayo Clinic. Names of those participating are included in the accompanying listing.

The purpose of the workshop was to determine the present status of knowledge on this subject, and to develop guidelines for detection, diagnosis, treatment and follow-up of radiation-related thyroid cancers which might be of value to practicing physicians.

Background

It is now recognized that one of the groups in this country at increased risk of developing cancer includes those individuals who received therapeutic doses of X-radiation or radium applications to the head, neck or upper thorax for various non-malignant conditions during infancy or childhood. This population has shown a significant increase in the incidence of cancer of the thyroid gland and, to a lesser extent, of the salivary glands and other structures of the head and neck, developing five to 35 or more years after radiation.

Beginning in the early 1920’s radiation therapy was considered good medical practice in treating patients with such conditions as enlargement of the thymus, hypertrophy of tonsils and adenoids, deafness due to hypertrophy of lymphoid tissue around the Eustachian tubes, cervical adenitis, mastoiditis, sinusitis, hemangiomas and keloids of the head and neck, tinea capitis and acne. Unfortunately, the thyroid gland frequently received direct or scatter radiation during these treatments. Short term effects appeared to be excellent and radiation therapy was widely used for these purposes. Thousands of individuals received radiation for these conditions in the United States.

It was not until an increasing number of articles began to appear in the literature reporting the discovery of both benign and malignant tumors of the thyroid gland in individuals five or more years after such irradiation or after exposure to atomic bomb radiation or fallout that this form of treatment was
generally discontinued. Fortunately, by that time, other effective means of treatment had been developed for the conditions mentioned above.

As this irradiated population has grown older, it has become apparent that the increased cancer risk is continuing into adult life\textsuperscript{10,11} and additional efforts have been initiated to recall irradiated individuals for examination.\textsuperscript{12-15} The longest intervals reported to date between irradiation and discovery of a tumor have been over 35 years.\textsuperscript{13,16}

Fortunately, only a small percentage of irradiated individuals develop thyroid tumors. Most of the tumors found have been benign, and most of those that are malignant have been well differentiated papillary and/or follicular neoplasms which grow slowly, metastasize relatively late, and are curable by surgery if diagnosed while still localized.\textsuperscript{13-19}

Recent publicity on this problem through articles in scientific and lay journals and through newspapers, radio and television has alarmed individuals or their parents who are aware of a history of such irradiation. This had led to many requests for advice directed to the National Cancer Institute (NCI) and the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD) from both physicians and patients. Questions have been raised about the most effective methods for diagnosis, the optimum frequency for re-examination, and the best procedures for follow-up.

The Bureau of Radiological Health (BRH) of the Food and Drug Administration has also been asked for guidance on choice of isotopes for diagnosis, permissible frequency of scans, the reliability of scans in the absence of palpable abnormalities, and the availability of lower dose isotopes for scanning.

Because there seemed to be no uniformity of opinion on many of these questions, the NCI, with the assistance of the NIAMDD and the BRH, organized the workshop mentioned above. The following summary of that workshop has been prepared in consultation with members of the American Thyroid Association. It is hoped that this document will prove helpful to physicians in the decisions they must make when patients come to them with a history of irradiation to the head, neck or upper thorax in infancy or childhood.

Incidence and Mortality

Thyroid cancer is a relatively rare disease. It is estimated that it will account for approximately 1,150 deaths in the United States in 1976, and that 8,100 new cases will be diagnosed.\textsuperscript{20} It occurs approximately twice as frequently in females as in males and more frequently in whites than in blacks. The incidence increases with age.

There appears to have been a definite increase in the incidence of thyroid cancer between the Second National Cancer Survey in 1947\textsuperscript{21} and the Third National Cancer Survey in 1969-71.\textsuperscript{22} Thus, in those geographic locations represented in both surveys, the overall age-adjusted incidence for both sexes, all ages and races combined, increased from 2.4 to 3.9/100,000 population over that 23-year time period. The increase is particularly striking in the age-specific data for whites showing a two- to fourfold increase between the ages of 20 and 35.\textsuperscript{23} Smaller increases were recorded for blacks but the numbers were not sufficient for definitive analysis.

The age-adjusted rate of thyroid cancer in the United States as a whole in 1969-71 for all ages, races and sexes combined was 3.7/100,000.\textsuperscript{23} Thus, one might expect to encounter one case in 27,000 individuals in the general population. However, in one study of 100 asymptomatic individuals recalled for examination at the University of Chicago because of a history of radiation to the head or neck, palpable abnormalities of the thyroid were found in as many as
# NAMES OF PARTICIPANTS

**Workshop on Late Effects of Irradiation to the Head and Neck in Infancy and Childhood**

| Name                        | Institution                                                                                     |
|-----------------------------|-------------------------------------------------------------------------------------------------|
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| Dr. Reynold Brown           | Director, Radiological Health Sciences Educational Project, Department of Radiology, University of California, San Francisco, California |
| Dr. James M. Cerletty       | Director, Thyroid Screening Program, Department of Medicine, The Medical College of Wisconsin, Milwaukee, Wisconsin |
| Dr. Robert Conard           | Senior Scientist, Brookhaven National Laboratory, Upton, Long Island, N.Y.                    |
| Dr. Leslie J. DeGroot       | Professor of Medicine and Director of Thyroid Unit, University of Chicago, Pritzker School of Medicine, Chicago, Illinois |
| Dr. Brown M. Dobyns         | Associate Director and Professor, Reserve University, School of Medicine, Cleveland Metropolitan General Hospital, Cleveland, Ohio |
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| Dr. Lawrence Frohman        | Director, Division of Endocrinology and Metabolism, Michael Reese Medical Center, Chicago, Illinois |
| Dr. Alexander Gottschalk    | Director of Nuclear Medicine, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut |
| Dr. Alvin Hayles            | Professor of Pediatrics, Mayo Clinic, Rochester, Minnesota                                    |
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| Dr. Eugene L. Saenger       | Professor of Radiology and Director of Radiosotope Laboratory, University of Cincinnati College of Medicine, Cincinnati, Ohio |
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26 percent of those examined and malignant tumors in seven of 15 of that group who were explored surgically.\textsuperscript{11,12} In another larger series of 1,056 irradiated individuals recalled at Michael Reese Hospital, abnormalities of the thyroid by palpation and/or scan were found in 250 or 27 percent, and carcinomas were found in 33 percent of the 60 individuals in whom the results of surgical exploration were available.\textsuperscript{13,14}

The true incidence of thyroid cancer in irradiated individuals is not known, since not all patients found to have palpable thyroid abnormalities have been explored. Moreover, as in the case of prostate cancer, the careful histological examination of thyroid glands at autopsy in individuals dying with no known thyroid disease has revealed small foci of cells which appear to be malignant in up to 5.7 percent of the glands.\textsuperscript{24} The significance of these "occult" lesions is not understood. They appear to be more common in irradiated patients than in those who have no history of radiation.

**Identification of Patients**

Although it would be desirable to recall for examination every patient who received radiation therapy to the head or neck in infancy and childhood, it was concluded that, for the most part, this would be logistically impossible.

Records from more than 10 years ago are often not available and some have been destroyed. Many are inadequate or are not filed in a way to meet the present need. Hospital radiologists of that period have for the most part retired or died and many of their records have been destroyed or lost. Many patients were treated in the private offices of radiologists or dermatologists where their records were not entered into any continuing system. Many patients have moved and most females have changed their names. Their parents and physicians are often no longer available or are unable to recall such treatments. Moreover, to
search a large number of uncomputerized records extending over several
decades is very difficult and the actual tracing of individuals after such a long
interval is very expensive.

Therefore, although any hospital
department of radiology that still has
records from which such patients could
be traced is strongly encouraged to insti-
tute a recall program, in general, a pub-
lic education approach is considered
more appropriate.

The following recommendations were
made:

A. Practicing physicians who are not al-
ready acquainted with the problem
should be informed and provided
with expert advice as to the most ap-
propriate care for those patients who
present themselves with a history of,
or who can be identified as having
had, radiation therapy to the head or
neck. This educational effort should
be carried out by state and national
medical organizations, state and
local health departments, the Ameri-
can Cancer Society and the National
Cancer Institute.

B. After the practicing physicians have
been appropriately informed, a well-
planned, low-keyed program should
be launched to educate the public
about the problem, stressing the need
for medical examination, the low in-
cidence of cancer and the high proba-
bility of cure. Educators for the pub-
lic program should include the agen-
cies mentioned above and the pa-
tients' own physicians.

Detection and Diagnosis

History

The practicing physician should in-
clude a question about prior irradiation
as a routine part of any patient’s history.

When a patient gives a history of prior
irradiation to the head or neck in infancy
or childhood for anything other than
diagnostic purposes, the physician
should query the parents and former
physicians, if these can be contacted, as
to the reason for the radiation, the pa-

tient’s age at the time and the doses
given.

Most patients with radiation-related
thyroid tumors are asymptomatic. A
mass in the neck of increasing size adds
to the suspicion that a carcinoma may be
present. A history of persistent hoarse-
ness or difficulty in swallowing may in-
dicate relatively advanced disease.

Physical Examination

The findings on meticulous examination
of the thyroid gland are the most im-
portant part of the clinical evaluation.

- Inspection • Inspection, especially
  on swallowing, may reveal a mass or
  asymmetry in the neck that might be
  overlooked by palpation alone.

- Palpation • Palpation of the thyroid
gland, the cervical lymph nodes and
salivary glands should be done with
great care. The findings on palpation
should be recorded by a life-size
drawing and by a written description.
The drawing should show the actual
size of any masses and their relation-
ship to normal anatomic structures of
the neck.

- Laryngoscopy • Indirect laryn-
goscopic examination to observe the
functional state of the vocal cords is
essential if cancer is suspected, if
there is any question of hoarseness
and if the patient is being considered
for surgery.

Laboratory Examinations

Blood studies are not necessary in the
determination of a thyroid cancer. Most
patients with a thyroid neoplasm have
normal thyroid function.

Radioisotope Scans

The decision to perform a thyroid scan
is a matter of medical judgment. Some
physicians believe that radioisotope
scans contribute little useful information
regarding possible thyroid cancer and that most discrete nodules should be removed without consideration of a scan. Others prefer to obtain a scan on all patients with a history of irradiation or suspected thyroid disease whether or not palpable nodules are present.

Most malignant lesions are "cold" on scan (i.e., show decreased concentration of radioisotope), whereas as many as two-thirds of cold lesions may be benign.13,14 Most nodules which are "hot" on scan (i.e., show increased concentration of isotope) are not malignant.

If a scan is to be performed, the preferred scanning agent is 99mTc, Tc pertechnetate since it delivers a much lower radiation dose than 131I.25 However, 131I is still used because of its widespread availability and standardization and because it provides information on iodine uptake which 99mTc does not.*

When 123I has been satisfactorily purified and becomes readily available, it will represent a short-lived iodine isotope that will follow the normal iodine metabolic pathway and deliver a much lower radiation dose than 131I. For diagnostic purposes, it will probably supplant 131I and, to some extent, 99mTc pertechnetate.

The average doses of radiation to the thyroid given by these different agents in the course of a diagnostic scan are shown in the Table.

For pertechnetate scans, the gamma camera with a pinhole collimator is the preferred imaging instrument. Oblique views, in addition to the usual anterior view, are desirable.26 It is recommended that the scan be carried out under the direct supervision of a physician who is experienced in thyroid examination, so that it can be properly interpreted and all normal anatomical features, as well as pathological findings, can be identified on the scan at the time it is performed.

### Needle Biopsy

Needle biopsies are not recommended.

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**Table.**

| Radiopharmaceutical and Type of Examination | Estimated Dose to Adult Thyroid (Rad) |
|-------------------------------------------|--------------------------------------|
| 123I Thyroid Scan                          | 2.8                                  |
| 123I Thyroid Uptake                        | 6.0                                  |
| 131I Thyroid Uptake                        | 10.5                                 |
| 131I Thyroid Scan                          | 100 – 200                            |
| 99mTc Thyroid Scan                         | 0.1                                  |

The absorbed radiation dose to the thyroid depends on size of dose administered, type of radioisotope, percent uptake, size of thyroid gland, age of subject and route of administration. Thyroid absorbed doses vary greatly with age — they are lowest in adults (20 years of age and older), progressively higher in children, and in newborns may be over 20 times the adult dose. (From Silverman, C., and Hoffman, D.A.: Thyroid Tumor Risk from Radiation During Childhood. Preventive Medicine 4: 100 – 106, 1975.)

*It should be noted that the 99mTc scan may show hot nodules which sometimes may be either invisible or cold when one of the radioactive iodine isotopes is used.
except: (1) in patients with diffuse enlargement of the thyroid when it is important to rule out thyroiditis; (2) in some patients where there is a single palpable nodule; or (3) when the patient is a poor surgical risk.

Objections to needle biopsy are based on the following considerations. (1) If the lesion is small, the chance of missing the suspicious area is great. (2) The dominant mass may not be the one that is a carcinoma. (3) The sample of tissue is often too small to permit the pathologist to make a definitive diagnosis. (4) The sample often does not include the capsular area of the tumor where invasion may have taken place. (5) If the lesion proves to be cystic, it does not assure that the lesion is benign. (6) The possible complications include hematoma, damage to a recurrent laryngeal nerve, spreading of the disease by rupture of the tumor capsule and even puncture of the trachea.

For these reasons, the consensus was that for most patients in whom needle biopsy might be used, surgical exploration should be carried out instead. Exceptions should be limited to those institutions where special expertise in the use of this biopsy technique has been developed.

When needle biopsy is done, it is essential that the procedure be carried out by a physician who is well acquainted with the intrinsic anatomy of the neck and under circumstances where immediate surgical help is available if complications should occur.

The difficulties in pathological diagnosis make it necessary that the specimen be interpreted by a pathologist who is thoroughly experienced in the pathology of the thyroid gland and in the evaluation of needle biopsy material.

**Diagnostic Trial of Thyroid Hormone Administration**

It is well known that the administration of thyroid hormone, in doses sufficient to depress the secretion of thyroid stimulating hormone (TSH) by the pituitary, results in decreased secretion of thyroid hormone by the thyroid and in shrinkage of normal or hypertrophied thyroid tissue. Such suppressive therapy may be used in an attempt to reveal a small nodule(s) deep in the gland, which may have been difficult to palpate because of underlying normal tissue.

When a trial of thyroid suppression is elected, the physician has two clear obligations: (1) to give enough thyroid hormone to completely suppress secretion by the thyroid; and (2) to have the thyroid re-examined at the end of six months, if possible by the same examiner.

**Suggested Diagnostic Sequence**

All individuals with a history of head or neck irradiation should be considered at increased risk of developing thyroid cancer and should be examined periodically (at least every two years), indefinitely. There is no evidence that the natural history of irradiation-induced thyroid cancer differs from that of papillary or follicular thyroid cancer occurring "spontaneously" (i.e., without a known history of irradiation) except that the lesions, when they occur, are more likely to be multifocal. The tumors usually grow very slowly and, although adjacent lymph nodes may be involved, distant metastases usually occur late.

On the basis of physical examination, patients may be divided into three categories.

I. Those with no visible or palpable abnormalities.

II. Those with a discrete nodule or nodules on palpation.

III. Those with diffuse enlargement of the gland but without a palpable nodule.

**Category I. Normal to Palpation**

The majority of workshop participants
concluded that a thyroid scan is not mandatory if palpation of the gland by an experienced examiner reveals no abnormalities. Careful re-examination is recommended at least every two years.

Many physicians prefer to obtain a scan on every patient with a history of radiation and some patients request them. Although a scan may reveal an area of abnormal uptake that is not represented by a palpable nodule, the majority felt that these lesions are usually benign and that the patient's welfare will not be endangered if consideration of surgery is delayed until a nodule can be palpated.

Repeat scans are not recommended unless a change in the gland is detected on physical examination. Any scan involves a small, but significant radiation exposure and the risk/benefit ratio of repeated scans is not known at this time.

A. If a scan is performed and is considered normal, the patient should have his thyroid re-examined by palpation every two years.

B. If the scan is equivocal, or if it shows a hot area, the majority of consultants felt that no treatment is indicated, but that the patient should be re-examined by palpation in one year.

C. The most difficult situation is that in which a scan reveals a "cold" or nonfunctional area in a gland, which has no palpable abnormality. The first step is to have the patient examined again very carefully, preferably by more than one examiner experienced in examination of the thyroid.

1. In most cases, re-examination has revealed a small nodule which was missed on first palpation. These patients should be considered for surgical exploration.

2. If no nodule is felt, there are three options:
   a. The patient may be followed by careful palpation at yearly intervals.
   b. The patient may be placed on sup- pressive doses of thyroid hormone. Once the thyroid secretion is suppressed, the patient may be continued on maintenance levels indefinitely in the hope that this may prevent the development of thyroid nodules. If this treatment is elected, the patient should be re-examined annually to assess the state of the gland by palpation and the adequacy of the thyroid therapy, as well as to be sure that the dosage is not producing chronic hyperthyroidism.

C. Since up to 27 percent of cold lesions without a palpable nodule have been found malignant, surgical exploration can be considered, although the majority of the workshop participants would prefer to keep the patient under annual observation until or unless a nodule becomes palpable.

**Category II. Discrete Nodule(s) on Palpation**

When palpation of the thyroid reveals one or more firm, discrete nodules, the majority of consultants felt that these should be removed regardless of the findings on a scan. However, a scan may be useful in assessing the functional status of a nodule.

If the scan shows a cold area, which corresponds with the palpable mass, the patient should be considered for prompt surgical exploration. If the scan shows a hot nodule, it is usually not malignant. However, the majority of workshop participants recommended surgical removal. If the nodules are small (<1.5 cm.), soft and poorly demarcated and the scan is normal, the patient may be given a trial of thyroid hormone administration for six months. If no regression is noted, surgical exploration should be considered.

**Category III. Diffuse Enlargement Without Nodules**

The third category consists of individ-
uals who have diffuse enlargement of the thyroid without any palpable, discrete nodules. If the patient has normal thyroid function, the enlargement is usually due either to benign hypertrophy or to lymphocytic thyroiditis.

Appropriate studies include determination of levels of TSH, thyroid hormones, antithyroid antibodies and possibly a needle biopsy to differentiate between benign hypertrophy and lymphocytic thyroiditis (Hashimoto’s disease). The patient should also have a thyroid scan.

A. If the scan shows no areas of abnormal isotope concentration, the patient may be placed on suppressive therapy to shrink the hypertrophied tissue since this may conceal a nodule buried deep in the gland. The patient should be re-examined in six months. If a nodule(s) is then palpable, surgical exploration is indicated. If no nodule is felt, the patient may be continued on thyroid therapy indefinitely and re-examined annually.

B. If the scan shows a definite cold area but no nodule is palpable, the patient should be placed on thyroid hormone administration and be re-examined in six months. Surgical exploration is not indicated until or unless a nodule becomes palpable.

Treatment
Surgery

Any individual with a history of radiation to the head or neck in whom palpation reveals a firm, discrete nodule or nodules in the thyroid gland, or firm, discrete nodes in the lower anterior neck, should be considered a candidate for surgical exploration.\(^{18,27}\)

Thyroidectomy is associated with significant risk to the recurrent laryngeal nerves and parathyroid glands and should be undertaken only by surgeons who are well trained in thyroid surgery.

The surgical procedure should be as extensive as necessary to remove all possible abnormal tissue without excessive morbidity or mortality. The extent will depend on the findings from careful inspection and palpation of the exposed thyroid and regional lymph nodes at the time of operation and on the results of frozen section of the tissue from the nodule(s) and/or from any enlarged regional nodes as interpreted by an experienced pathologist.

Most patients after partial thyroidectomy and all patients after total thyroidectomy will require replacement thyroid therapy. Such patients should continue to be seen by their physicians at least annually in order to detect possible recurrence and to assess the adequacy of replacement therapy.

Hormonal Therapy

Animal studies have led to the theory that suppression of secretion of TSH by administration of thyroid hormone might prevent the development of thyroid neoplasms.\(^{28-30}\) This conclusion is valid in irradiated rats, but has not been clearly demonstrated in man. Nevertheless, it may be worth trying as a prophylactic measure, especially in a patient with a cold area on scan but no palpable abnormalities, or with a diffusely enlarged gland.

If suppressive therapy is to be used in the hope of preventing the development of cancer, the patient should be continued on that treatment indefinitely or until a nodule develops and surgery becomes necessary. Such a program should not be started unless the patient is willing to take the medication faithfully. In any case, he should be re-examined annually. Care should be taken to ensure that the patient is not rendered chronically hyperthyroid with possible damage to the cardiovascular system.

\(^{31}\) Therapy, Chemotherapy, Radiation

If unresectable cancer remains in the neck or distant metastases are detected, the patient should be referred to special-
ists in thyroid disease for consideration of treatment with \(^{131}\)I, chemotherapy or radiation therapy.

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