Management of Papillary Thyroid Cancer

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Papillary thyroid cancer is predominantly a sporadic disease that usually presents as an asymptomatic thyroid mass in a euthyroid patient. Irradiation to the neck during childhood significantly increases the subsequent risk of

Introduction

Thyroid cancer accounts for more than 90% of all endocrine malignancies and for more than 50% of all deaths from endocrine cancer. The incidence of thyroid cancer has been increasing since the 1930s, most likely because of the practice of therapeutic irradiation in childhood. The abrupt rise in incidence around 1974 was probably due to the institution at that time of vigorous examination of individuals who had had prior neck irradiation [1].

American Cancer Society statistics for the past 25 years suggest that the incidence of thyroid cancer has risen slowly since the mid 1970s. Disease incidence increased from 7,800 cases per year in 1974 to 12,500 cases per year in 1992, with more than two-thirds of new cases occurring in women. However, mortality from thyroid cancer has changed little during this period (Figure 1). Most patients have localized or regional disease at the time of diagnosis, and the 5-year survival rate has exceeded 80% since 1960 and 90% since 1970. Therefore, thyroid cancer remains a relatively modest oncologic concern, accounting for less than 2% of all cancers since 1974 and for less than 0.5% of all deaths from cancer (Figure 2).

Among patients with thyroid cancer, approximately 60% to 70% have differentiated, papillary thyroid cancer. This article presents a broad clinical overview of papillary thyroid cancer and emphasizes disease features that modify prognosis and affect clinical management.

Etiology

The risk of radiation-induced thyroid cancer has been well documented; data on other causes of thyroid cancer are sparse. Prolonged thyroid-stimulating hormone (TSH) elevation has been implicated as a potential risk factor, but patients with primary hypothyroidism do not appear to have an increased risk of papillary thyroid cancer. Thyroid-stimulatory immunoglobulins present in patients with Graves' disease have also been implicated. Associations with Hashimoto's thyroiditis, Graves' disease, and multinodular goiter have been reported. However, causative relationships between these diseases and papillary thyroid cancer remain poorly documented.

In a recent epidemiologic review of thyroid cancer in the United States [2], important differences in incidence emerged among ethnic groups. Thyroid cancer was less common in Puerto Rican Hispanics and blacks than in white persons, but New Mexican Hispanics and Asian-Americans had higher rates. Genetic susceptibility is unlikely to account for all the differences. For example, Asians living in the United States are at higher risk for thyroid cancer than Asians living in their native countries. Although papillary thyroid cancer is generally considered a sporadic disease, it is important to keep in mind that disease clusters have been reported in kindreds with familial polyposis and Gardner's syndrome [3]. Reports of familial disease in the absence of either a hereditary syndrome or neck irradiation increase the likelihood that genetic predisposition plays a role in pathogenesis. In support of this thesis, several recent studies have demonstrated complex structural chromosomal aberrations and cytogenetic abnormalities of chromosome 10q in association with papillary thyroid cancer [4].

Irradiation in Childhood

During the early decades of the 20th century, low-dose irradiation (usually < 2.0 Gy) to the head and neck was often used for the treatment of benign childhood conditions, such as thymic enlargement, tonsillitis, otitis, hemangiomas, ringworm, and acne. This medical practice has clearly emerged as an important risk factor for the development of papillary thyroid cancer and is considered by many to be responsible for increasing its incidence.
The excess relative risk of thyroid cancer appears to depend on total radiation dose, fractionation schedule, and patient age at the time of irradiation [5]. To date, medical use of radioactive iodine-131 has not been shown to confer a significant risk of papillary thyroid cancer (Table 1). A persistent concern has been the carcinogenic potential of radioactive fallout. However, careful review of available studies reveals methodologic inconsistencies that may have exaggerated risk estimates [5].

The time between the irradiation and diagnosis of the thyroid tumor averages 10 years but may be more than 30 years. In a recent study, Schneider et al [1] demonstrated that radiation-induced thyroid neoplasms are rare in the first 5 to 10 years after treatment and cluster between 20 and 40 years post-therapy. Women have a 40% higher rate of radiation-induced thyroid cancer than men, but the slopes of dose-response curves, which reach maximal rates 25 to 29 years after radiation exposure, appear similar for the two genders.

Increased awareness of thyroid radiosensitivity, especially in children, has resulted in the virtual elimination of irradiation for benign conditions and is generating a reassessment of medical radiation use. Thus, radiation-related thyroid cancer is expected to subside as a public health concern in the coming years.

**Radiotherapy for Hodgkin's and Non-Hodgkin's Lymphomas**

The efficacy of radiotherapy in controlling Hodgkin's and non-Hodgkin's lymphomas has been instrumental in achieving high cure rates. Consequently, radiotherapy is likely to continue as an important component of the therapeutic armamentarium for these cancers. Because many young cancer survivors can expect a near-normal lifespan after neck irradiation, it is important to define their particular risks of thyroid cancer and to design appropriate surveillance and therapeutic strategies.

Radiation doses to the thyroid of more than 200 cGy, especially when given at a young age, have been linked to an increased risk of both benign and malignant thyroid neoplasms [6]. Tucker et al found a 13-fold increase in the risk of thyroid cancer in this group [7], and Hancock et al noted that benign thyroid abnormalities are even more common [8]. Systematic evaluation of the irradiated thyroid gland reveals significant pathologic [9] as well as radiologic [10] abnormalities.

We also have found a heightened risk of thyroid cancer after therapeutic neck (mantle) irradiation for Hodgkin's disease during childhood (Table 2). Among 166 patients irradiated at or before age 16 years and for whom a minimum of 15 years of follow-up is available, 12 have been treated for thyroid cancer to date (unpublished data; patient population identified through a search of the database maintained by the Department of Patient Studies at M.D. Anderson). The presence of papillary thyroid carcinoma in 7% of irradiated Hodgkin's disease survivors exceeds the prevalence of thyroid cancer in the general population, and suggests that prior therapeutic irradiation represents an important risk factor for thyroid cancer.

In our patients, thyroid cancer was found 7 to 19 years after irradiation by investigation of either palpable thyroid nodules or ultrasound abnormalities; all have proven to be papillary thyroid cancers, and all patients remain alive. During the same period and using the same database, only two cases of thyroid cancer were diagnosed among 750 adults treated for Hodgkin's disease, emphasizing the importance of age as a cofactor for the carcinogenic potential of radiation. Fortunately, patients with radiation-related papillary thyroid cancer appear to have the same excellent prognosis as do patients with sporadic disease, even though the former may have more extensive disease at diagnosis [11]. Because hyperparathyroidism also may occur with increased frequency after neck irradiation [12], it is particularly important to investigate previously irradiated patients very carefully for parathyroid dysfunction before thyroid surgery, to avoid the potential need for reoperation.

**Clinical Presentation**

Papillary thyroid cancer is predominantly a sporadic disease. Patients typically present with a dominant thyroid mass or enlarged cervical lymph nodes [13]. Thyroid nodules are relatively common, but less than 15% of clinically detectable solitary thyroid nodules are malignant [14,15]. Histologically, many tumors have both papillary and follicular elements and are referred to as "follicular variants of papillary carcinoma;" such tumors are classified as papillary lesions because their clinical behavior resembles that of pure papillary cancers. In adults, the size of papillary thyroid cancer can vary considerably, from microscopic cancers to large tumors that may invade the thyroid capsule and even infiltrate adjacent structures.

Up to 40% of adults present with cervical lymph node metastases; the figure is much higher in persons younger than 20 years. At the time of presentation, affected lymph nodes are generally on
the same side as the primary tumor, but bilateral and mediastinal metastases are encountered in a few patients. Although regional lymph node invasion is fairly common, there is very little tendency toward systemic dissemination. Sites of distant metastases, in order of decreasing frequency, are the lung, bone, and, rarely, other soft tissues. Older patients are more likely to present with invasive tumors and have a higher risk for distant metastases [16,17].

**Prognosis**

The diagnosis of papillary thyroid cancer is consistent with a near-normal lifespan in most patients, especially women younger than 40 years whose disease is limited to the cervical region at the time of diagnosis [13,16-20]. Although large tumor size, older age, male gender, and presence of distant metastases are negative prognostic factors, survival still exceeds 5 years in most of these patients. Approximately 10% of patients develop pulmonary metastases. Although the life expectancy of these patients is shortened, most studies report an overall survival approaching 50% at both 5 and 10 years [21,22]. Tumor histology and the avidity with which metastases take up radioiodine, as well as patient age, influence outcome in such cases.

**Diagnostic Considerations**

In most cases of thyroid cancer, a neck mass is discovered during a routine physical examination by a physician or during incidental neck palpation by the patient. Although rapid enlargement of the mass and the development of hoarseness are significant factors in the patient's medical history, they occur rarely.

**Appropriate Sequence of Tests**

The appropriate sequence of diagnostic procedures and imaging techniques for proper identification of surgical candidates remains a subject of some discussion. Confirmation of the euthyroid state through measurement of serum hormone levels is often combined with ultrasonography or radionuclide thyroid scanning. Ultrasound examination of the neck is the best method for defining the parenchymal character of the dominant thyroid mass (purely cystic lesions have a lower malignant potential). It also can identify additional subclinical thyroid lesions (a multinodular appearance has a lower malignant potential) and can provide information about the presence of cervical lymphadenopathy (which has significance for both diagnosis and treatment planning). Thyroid scanning provides a functional definition of the thyroid mass and is especially helpful in the evaluation of solitary, solid thyroid masses (hypofunctioning or nonfunctioning nodules have a higher malignant potential).

**Emerging Role of Fine-Needle Aspiration**

At present, fine-needle aspiration of thyroid nodules is emerging as the single most effective diagnostic tool. Increased experience with the technique has helped clarify the cytologic characteristics of thyroid masses, and fine-needle aspiration now can provide reliable and prompt preoperative guidelines. With expert cytologic support, this procedure can correctly distinguish benign cysts and nodules from primary thyroid cancers or metastatic lesions in most patients. Some physicians believe that fine-needle aspiration is the only preoperative test needed. However, several inherent limitations of the technique make this approach insufficient in many cases. For example, cellular, follicular samples (follicular neoplasms), which may be obtained in up to half of cases, are considered inconclusive and require further evaluation.

**Incidental, Asymptomatic Thyroid Nodules**

The evolution of radiologic imaging techniques in recent years has resulted in the detection of subclinical thyroid inhomogeneities during studies performed for the evaluation of nonthyroid conditions. Such "incidental" thyroid nodules, which are increasingly common with advancing age, pose unresolved diagnostic and therapeutic dilemmas. At present, it is fair to say that no reliable algorithms for the evaluation of incidental, asymptomatic thyroid nodules are available and that management should be individualized.

**Management of Uncomplicated Cases**

Given the generally excellent prognosis of most patients with papillary thyroid cancer, it remains difficult to define the treatment of choice. Controversy persists over 1) the extent of thyroid excision and 2) the vigor of postoperative evaluation and treatment with radioiodine.

**Extent of Surgery**
Near-total thyroidectomy is currently advocated by most, but not all, groups[16,18,23,24]. Limited thyroid resection is often associated with an increased risk of recurrence (with the accompanying risks of reoperation), but is less likely to result in postsurgical hypoparathyroidism. On the other hand, near-total thyroidectomy is better suited to the elimination of subclinical, multifocal cancer (which is present in up to 78% of cases) [25,26], tends to minimize postoperative radioiodine requirements, optimizes postoperative tumor status surveillance with serial serum thyroglobulin measurements [27], and facilitates evaluation and treatment of metastatic deposits should they arise later.

The prognostic profile of each individual patient and the expertise of the available surgical team should be taken into consideration before a decision is reached about the extent of excision.

**Postoperative Radiation**

Postoperative radioiodine is used by most groups to ablate residual thyroid tissue and to treat radioiodine-incorporating metastases. Thyroxine replacement therapy is withdrawn for a period of time to induce hypothyroidism; the resulting TSH elevation stimulates tumor uptake of radioiodine and optimizes both the diagnostic and therapeutic efficacy of iodine-131. Ambulatory treatment with “low”-dose radioiodine (< 30 mCi) is advocated by several groups because of the ease of administration and the limited total exposure to radioiodine [28]. This approach can achieve thyroid bed remnant ablation in patients with limited disease who have had near-total thyroidectomy [29]. However, the average radioiodine dose required for postoperative thyroid ablation often exceeds 100 mCi [16]. Certainly, this modality is not appropriate for patients with extrathyroidal tumor extension.

The interest in limiting radioiodine exposure stems largely from the wish to avoid potential complications, especially when treating young people with an expected near normal lifespan. Radioiodine has been used to treat functioning metastases since the mid-1940s [30]. To date, serious complications remain extremely rare. The widely quoted study by Edmonds and Smith [31] analyzing the effect of high-dose therapy (exceeding 1,000 mCi in most cases) included two deaths from bladder cancer and a cluster of three deaths in middle-aged women that occurred within 3 years of radioiodine administration in the mid-1950s. Reviews of the impact of lower therapeutic doses have not confirmed these death rates.

Gonadal dysfunction, manifested as infertility, has been described more frequently, but appears transient in most cases [32,33]. The most common complications of radioiodine are sialadenitis and reduced salivary flow [34,35]. The resulting xerostomia, while not life-threatening, is a major contributor to dental caries and constitutes a significant health hazard.

Concerns over pulmonary fibrosis remain limited to individuals with extensive functioning lung metastases and are to date anecdotal. Nevertheless, due to significant environmental contamination from radioiodine therapy, all patients who receive such treatment should be isolated appropriately and undergo radiation measurements during each course [36].

**Treatment Recommendations**

Overall, for most patients with differentiated thyroid cancer, we recommend a near-total thyroidectomy with modified neck dissection as needed, followed by a postoperative iodine-131 whole-body scan and iodine-131 treatment if radioiodine-concentrating tissue is identified. Following this initial program, thyroxine replacement therapy should be prescribed, and patients should be carefully monitored with regular physical examination, chest radiographs, and measurement of serum thyroglobulin levels.

A relatively high thyroxine dose has generally been prescribed, with the aim of providing maximal suppression of pituitary TSH. However, current evidence that suppressive doses of thyroxine significantly reduce bone mineral density and thus may heighten the risk of osteoporosis has stimulated a reappraisal of this practice [37].

External-beam irradiation and systemic chemotherapy have an important but limited role in the management of rare patients with aggressive papillary thyroid cancer. A discussion of these modalities is beyond the scope of this review.

**Thyroid Cancer in Children**

Children and adolescents with thyroid masses are more likely than adults to harbor a thyroid malignancy, most commonly papillary thyroid cancer. Because these patients tend to present with extensive regional disease, and because pediatric thyroid malignancies have a high rate of recurrence, they should receive careful and fairly aggressive initial treatment [38]. Pulmonary metastases are reported to occur in 6% to 20% of children with papillary thyroid cancer [16,17,39,40]. These lesions create a diffuse micronodular pattern that may be misinterpreted as tuberculosis. Pulmonary metastases concentrate radioiodine and often respond to therapeutic
administration of the isotope, although large doses may be required [40-42].
Unlike adults with lung metastases, children with lung metastases enjoy very prolonged survival.
Among 209 evaluable patients younger than 25 years who were treated for differentiated thyroid cancer at M.D. Anderson Cancer Center between 1960 and 1990, 19 patients (9%) had pulmonary metastases [42]. All 19 patients also had regional lymphadenopathy in the neck at the time of diagnosis, and all but two had intense, diffuse radiiodine uptake in the lungs.
The chest radiograph was normal in 42% of the 17 cases with abnormal radioiodine scans. After therapy with radioiodine (100 to 499 mCi), lung uptake normalized in three of eight patients with initially normal radiographs, and in three of nine patients with initially abnormal radiographs. There have been no deaths in this group.

Management of Incidental Thyroid Cancer

In Patients With Coexisting Benign Thyroid Disease
Occult thyroid cancer limited to the thyroid gland is occasionally an incidental finding during surgery for other indications and is usually considered of minor clinical significance. For example, after thyroid excision for a clinically suspect or symptomatic but ultimately benign thyroid lesion, the final pathologic examination may reveal a microscopic malignancy. Clinically unsuspected thyroid cancer occurs in 1% to 10% of the population [43,44]. Although such lesions may occasionally become clinically significant [45], overall they are associated with excellent prognosis and do not cause significant morbidity.
Arguments can be made for different approaches to the management of such patients, who should be carefully assessed for additional risk factors (eg, radiation exposure, histologic features, multifocal disease). In general, these patients can be observed expectantly but conservatively. Thyroxine administration and regular clinical evaluation often suffice.

In Patients With Nasopharyngeal Carcinoma
Differentiated thyroid cancer metastatic to the cervical lymph nodes may be found incidentally during cervical neck dissection for another malignancy. Up to 3% of patients with cancer of the head and neck harbor clinically unsuspected papillary or follicular thyroid cancer.
In a review of patients with cervical lymph node metastases from thyroid cancer found incidentally during surgery for squamous cell carcinoma of the tongue [46], we found that patients' ultimate outcome was determined by the biology of the squamous cell carcinoma rather than by the treatment for the thyroid disease. Given the relative prognoses of the two diseases, it is reasonable to suggest that patients in whom metastatic papillary thyroid cancer is identified incidentally during surgery for squamous cell carcinoma of the tongue (or other head and neck sites) be followed conservatively if the thyroid gland demonstrates no anomaly on physical examination and noninvasive imaging.

Clinical Significance of Pulmonary Metastases
Pulmonary metastases may be classified radiographically as "micronodular" or "macronodular" disease [47]. The former type of metastases, which are more common in children, have a miliary, diffusely reticulate pattern predominating in the lower lung fields and are more likely to concentrate radiiodine diffusely. Macronodular lesions larger than 0.5 cm, with nodules of unequal size, are more frequent in older patients; radiiodine incorporation is heterogeneous and often absent.
Even in the presence of lung metastases, fewer than 20% of patients die of thyroid cancer. However, it remains difficult to anticipate who among these patients may develop aggressive disease with lethal complications.
In our experience, the appearance of malignant pleural effusion confers a marked prognostic disadvantage [48]. We recently found that metastases to cervical lymph nodes were present at initial surgery in all patients who developed malignant pleural effusion. All patients had radiologically apparent lung metastases at the time pleural effusion was found, and all died of thyroid cancer. Although overall survival was 7 to 170 months, these patients died within 20 months of the appearance of pleural effusion.

Long-Term Surveillance Strategies
Although most thyroid cancer patients do not die of the disease, it remains difficult to identify prospectively the few who may have an aggressive clinical course. Given the generally favorable prognosis of papillary thyroid cancer, therefore, it is important to correctly identify and treat the
minority of patients at risk for recurrence and death [22,49], while avoiding overzealous therapy in the majority of patients, who are expected to remain free of disease after initial therapy. Unlike more clinically aggressive malignancies, late recurrences are often described in patients with differentiated thyroid cancer, and the concept of 5-year survival is not clinically useful. Therefore, thyroid cancer patients require regular follow-up for a prolonged period regardless of the initial extent of disease. Physical examination and serum thyroglobulin measurements, with or without chest x-rays, are used to monitor disease activity. These components of follow-up care are fairly well accepted. However, the optimal strategy for subsequent radioiodine scanning and/or therapy remains controversial. Relevant issues include the burden of repeated hypothyroidism on the quality of life and productivity of patients, the potential for tumor stimulation by prolonged TSH elevation, the potential hazards of multiple low (scanning) doses of radioiodine, and the expected benefit in terms of disease control and survival. Recombinant TSH will likely prove useful in replacing thyroxine withdrawal in the future [50]. Because this approach will correct some of the problems associated with current methodology, periodic radioiodine body scans will become much easier to perform. It will, therefore, become especially important to critically assess and characterize the expected benefit of scanning so that optimal clinical practice guidelines can be developed. Individual patient risk profiles will retain an important role in reaching properly individualized management decisions.

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