THYROID CANCER

I. Introduction

There are over 11,000 new cases of thyroid cancer each year in the US. Females are more likely to have thyroid cancer than men by a ratio of 3:1, and it is more common in people who have been treated with radiation to the head, neck, or chest, most often for benign conditions (although radiation treatment for benign conditions is no longer carried out). Thyroid cancer can occur in any age group, although it is most common after age 30 and its aggressiveness increases significantly in older patients. Rather than causing the whole thyroid gland to enlarge, a cancer usually causes small growths (nodules) within the thyroid. Although as many as 10% of the population will have thyroid nodules, the vast majority are benign. Only approximately 5% of all thyroid nodules are malignant. Nodules are more likely to be cancerous if only one nodule is found rather than several, if a thyroid scan shows that the nodule isn't functioning, if the nodule is solid rather than filled with fluid (cystic), if the nodule is hard, or if the nodule is growing quickly. Thus a nodule that is cold on scan is more likely to be malignant, but the majority of these are benign as well. Thyroid cancers often have a limited ability to take up iodine and produce thyroid hormone, but very rarely they produce enough hormone to cause hyperthyroidism. Symptoms that occur occasionally include hoarseness, neck pain, and enlarged lymph nodes, but it should be noted that the majority of patients present with a nodule on their thyroid that typically does not cause symptoms.

There are four types of thyroid cancer including papillary and mixed papillary/follicular (~ 75%), follicular and Hurthle cell (~ 15%), medullary (~ 7%) and anaplastic (~ 3%). Most thyroid cancers are very curable. In fact, the most common types of thyroid cancer (papillary and follicular) are the most curable. In younger patients, both papillary and follicular cancers can be expected to have better than 95% cure rate if treated appropriately. Both papillary and follicular cancers are typically treated with complete removal of the lobe of the thyroid that harbors the cancer, PLUS, removal of most or all of the other side.

When a nodule in the thyroid gland,is discovered, several tests are typically performed. A thyroid scan determines whether the nodule is functioning, since a nonfunctioning nodule is more likely to be cancerous than a functioning one. An ultrasound scan is less helpful but may be performed to determine whether the nodule is solid or filled with fluid. A sample of the nodule is usually taken by fine-needle aspiration (FNA) biopsy for pathology examination and this typically is the best way to determine whether the nodule is cancerous.

Thyroid cancer is unique among cancers, in fact, thyroid cells are unique among all cells of the human body. They are the only cells that have the ability to absorb Iodine. Iodine is required for thyroid cells to produce thyroid hormone, so they absorb it from the bloodstream and concentrate it inside the cell. Most thyroid cancer cells retain this ability to absorb and concentrate iodine. This provides a perfect "chemotherapy" strategy. Radioactive Iodine is given to the patient and the remaining thyroid cells (and any thyroid

cancer cells retaining this ability) will absorb and concentrate it. Since all other cells of our bodies cannot absorb the toxic iodine, they are unharmed. The thyroid cancer cells, however, will concentrate the iodine and the radioactivity destroys the cell from within with minial side effects. Not all patients with thyroid cancer need radioactive iodine treatments after their surgery. Others, however, should have it if a cure is to be expected. Which patients need it and which do not is a bit more detailed. Patients with medullary cancer of they thyroid usually do not need iodine therapy because medullary cancers almost never absorb the radioactive iodine. Some small papillary cancers treated with a total thyroidectomy may not need iodine therapy as well, because these cancers are often cured with simple (complete) surgical therapy alone. Ultimately, the decision to use radioactive iodine therapy varies from patient to patient and from cancer to cancer.

B. Papillary Cancer

Papillary cancer accounts for up to 75% of all thyroid cancers. Two to three times as many women as men have papillary cancer; however, since nodules are far more common in women, a nodule in a man is more suspicious for a cancer. Papillary cancer is more common in young people (peak onset is 30-50 years of age) but grows and spreads more quickly in the elderly. People who have received radiation treatment to the neck, usually for a benign condition in infancy or childhood or for some other cancer in adulthood, are at greater risk of developing papillary cancer. It is estimated that papillary cancer accounts for 85% of thyroid cancers due to radiation exposure.

Papillary carcinoma typically arises as an irregular, solid or cystic mass that arises from otherwise normal thyroid tissue. Prognosis is directly related to tumor size and a “good prognosis is associated with tumors less than 1.5 cm (1/2 inch) in size. This cancer has a high cure rate with ten year survival rates for all patients with papillary thyroid cancer estimated at 80-90%. Cervical metastasis (spread to lymph nodes in the neck) are present in 50% of small tumors and in over 75% of the larger thyroid cancers. The presence of lymph node metastasis in these cervical areas causes a higher recurrence rate but not a higher mortality rate. Distant metastasis (spread) is uncommon, but when it does occur the lung and bone are the most common sites. Tumors that invade or extend beyond the thyroid capsule have a worsened prognosis because of a high local recurrence rate.

Surgery is the treatment for papillary cancer, which sometimes spreads to nearby lymph nodes. Nodules smaller than three quarters of an inch across are removed along with the thyroid tissue immediately surrounding them, although some experts recommend removing the entire thyroid gland. Surgery almost always cures these small cancers.

Since papillary cancer may respond to thyroid-stimulating hormone, thyroid hormone is taken in doses large enough to suppress secretion of thyroid-stimulating hormone and help prevent a recurrence. If a nodule is larger, most or all of the thyroid gland is usually removed, and radioactive iodine is often given in expectation that any remaining thyroid tissue or cancer that has spread away from the thyroid will take it up and be destroyed. Another dose of radioactive iodine may be needed to make sure the entire cancer has been destroyed. Papillary cancer is almost always cured.

Considerable controversy exits when discussing the management of well differentiated thyroid carcinomas (papillary and even follicular as described below). Some experts contend than if these tumors are small and not invading other tissues (the usual case) then simply removing the lobe of the thyroid which harbors the tumor (and the small central portion called the isthmus) will provide as good a chance of cure as removing the entire thyroid. These proponents of conservative surgical therapy relate the low rate of clinical tumor recurrence (5-20%) despite the fact that small amounts of tumor cells can be found in up to 88% of the opposite lobe thyroid tissues. They also cite studies showing an increased risk of hypoparathyroidism and recurrent laryngeal nerve injury in patients undergoing total thyroidectomy (since there is an operation on both sides of the neck). Proponents of total thyroidectomy (more aggressive surgery) cite several large studies that show that in experienced hands the incidence of recurrent nerve injury and permanent hypoparathyroidism are quite low (about 2%). More importantly, these studies show that patients with total thyroidectomy followed by radioiodine therapy and thyroid suppression, have a significantly lower recurrence rate and lower mortality when tumors are greater than 1.5cm. One must remember that it is also desirable to reduce the amount of normal gland tissue that will take up radioiodine.

Based on the these studies and the above natural history and epidemiology of papillary carcinoma, the following is a typical plan: Papillary carcinomas that are well circumscribed, isolated, and less than 1cm in a young patient (20-40) without a history of radiation exposure may be treated with hemithyroidectomy and isthmusthectomy. All others should probably be treated with total thyroidectomy and removal of any enlarged lymph nodes in the central or lateral neck areas. The surgical options are covered in greater detail (with drawings) on another "surgical options" page.

Thyroid cells are unique in that they have the cellular mechanism to absorb iodine to synthesize thyroid hormone. No other cell in the body can absorb or concentrate iodine. This uptake is taken advantage of in radioactive iodine treatments for thyroid cancer. Papillary cancer cells absorb iodine and therefore they can be targeted for death by giving the toxic isotope (I-131). Once again, not everybody with papillary thyroid cancer needs this therapy, but those with larger tumors, spread to lymph nodes or other areas, tumors which appear aggressive microscopically, and older patients may benefit from this therapy. This is an extremely effective type of "chemotherapy" will little or no potential adverse reactions (no hair loss, nausea, weight loss, etc.). However, the decision to use RAI should be made on an individual patient basis.

Uptake is enhanced by high TSH levels; thus patients should be off of thyroid replacement and on a low iodine diet for at least one to two weeks prior to therapy. It is usually given 6 weeks post surgery (this is variable) can be repeated every 6 months if necessary (within certain dose limits).

Regardless of whether a patient has just one thyroid lobe and the isthmus removed, or the entire thyroid gland removed, most experts agree they should be placed on thyroid hormone for the rest of their lives. This is to replace the hormone in those who have no

thyroid left, and to suppress further growth of the gland in those with some tissue left in the neck. There is good evidence that papillary carcinoma responds to thyroid stimulating hormone (TSH) secreted by the pituitary, therefore, exogenous thyroid hormone is given which results in decreased TSH levels and a lower impetus for any remaining cancer cells to grow. Recurrence and mortality rates have been shown to be lower in patients receiving suppression.

In addition to the usual cancer follow up, patients should receive a yearly chest x-ray as well as thyroglobulin levels Thyroglobulin is not useful as a screen for initial diagnosis of thyroid cancer but is quite useful in follow up of well differentiated carcinoma (if a total thyroidectomy has been performed). A high serum thyroglobulin level that had previously been low following total thyroidectomy especially if gradually increased with TSH stimulation is virtually indicative of recurrence. A value of greater than 10 ng/ml is often associated with recurrence even if an iodine scan is negative.

C. Follicular Cancer

Follicular cancer accounts for about 15 percent of all thyroid cancers and is considered more malignant (aggressive) than papillary carcinoma. Vascular invasion is characteristic for follicular carcinoma and therefore distant metastasis is more common. Distant metastasis may occur in a small primary. Lung, bone, brain, liver, bladder, and skin are potential sites of distant spread. Lymph node involvement is far less common than in papillary carcinoma (8-13%). In contrast to papillary cancer, follicular cancer occurs only rarely after radiation therapy and occurs in a slightly older age group (peak onset at 40-60 years of age) than papillary and is also less common in children. Follicular cancer is also more common in women than in men (3:1), but as with papillary cancer, a nodule in a man is more likely to be cancerous. Mortality is related to the degree of vascular invasion. Treatment for follicular cancer requires surgically removing as much of the thyroid gland as possible and destroying any remaining thyroid tissue, including the metastases, with radioactive iodine. Age is a very important factor in terms of prognosis. Patients over 40 have a more aggressive disease and typically the tumor does not concentrate iodine as well as in younger patients. Prognosis also is directly related to tumor size with s good prognosis associated with tumors less than 1.0 cm (3/8 inch) in size. Overall cure rate high (near 95% for small lesions in young patients), decreases with advanced age

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thyroidectomy (since there is an operation on both sides of the neck). Proponents of total thyroidectomy (more aggressive surgery) site several large studies that show that in experienced hands the incidence of recurrent nerve injury and permanent hypoparathyroidism are quite low (about 2%). More importantly, these studies show that patients with total thyroidectomy followed by radioiodine therapy and thyroid suppression, have a significantly lower recurrence rate and lower mortality when tumors are greater than 1.0 cm. One must remember that it is also desirable to reduce the amount of normal gland tissue that will take up radioiodine.

It also must be kept in mind that frozen section (the rapid way that the tumor is examined under the microscope for characteristics of cancer) may be unreliable in making dfinitive diagnosis of follicular cancer at the time of surgery. This problem is not seen with other types of thyroid cancer.

Based on the these studies and the above natural history and epidemiology of follicular carcinoma, the following is a typical plan: Follicular carcinomas that are well circumscribed, isolated, minimally invasive, and less than 1cm in a young patient (< 40) may be treated with hemithyroidectomy and isthmusthectomy. All others should probably be treated with total thyroidectomy and removal of any enlarged lymph nodes in the central or lateral neck areas.

Thyroid cells are unique in that they have the cellular mechanism to absorb iodine. The iodine is used by thyroid cells to make thyroid hormone. No other cell in the body can absorb or concentrate iodine. Physicians can take advantage of this fact and give radioactive iodine to patients with thyroid cancer. There are several types of radioactive iodine, with one type being toxic to cells. Follicular cancer cells absorb iodine (although to a lesser degree in older patients) and therefore they can be targeted for death by giving the toxic isotope (I-131). Once again, not everybody with follicular thyroid cancer needs this therapy, but those with larger tumors, spread to lymph nodes or other areas, tumors which appear aggressive microscopically, tumors which invade blood vessels within the thyroid, and older patients may benefit from this therapy. This is extremely individualized and no recommendations are being made here or elsewhere on this web site...too many variables are involved. But, this is an extremely effective type of "chemotherapy" will few potential down-sides (no hair loss, nausea, weight loss, etc.).

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responds to thyroid stimulating hormone (TSH) secreted by the pituitary, therefore, exogenous thyroid hormone is given which results in decreased TSH levels and a lower impetus for any remaining cancer cells to grow. Recurrence and mortality rates have been shown to be lower in patients receiving suppression.
What Kind of Long-Term Follow Up is Necessary?

In addition to the usual cancer follow up, patients should receive a yearly chest x-ray as well as thyroglobulin levels. Thyroglobulin is not useful as a screen for initial diagnosis of thyroid cancer but is quite useful in follow up of well differentiated carcinoma (if a total thyroidectomy has been performed). A high serum thyroglobulin level that had previously been low following total thyroidectomy especially if gradually increased with TSH stimulation is virtually indicative of recurrence. A value of greater than 10 ng/ml is often associated with recurrence even if an iodine scan is negative.

D. Medullary Cancer

Medullary tumors are the third most common of all thyroid cancers (about 5-8%). Unlike papillary and follicular thyroid cancers which arise from thyroid hormone producing cells, medullary cancer of the thyroid originates from the parafollicular cells (also called C cells) of the thyroid. These C cells make a different hormone called calcitonin (thus their name) which regulates physiologic functions different than those controlled by thyroid hormone. In medullary cancer, the thyroid gland produces excessive amounts of calcitonin as well as other hormones, and thus it can cause unusual symptoms. This cancer tends to spread (metastasize) through the lymphatic system to the lymph nodes and through the blood to the liver, lungs, and bones. Medullary cancer can develop along with other types of endocrine cancers in what is called multiple endocrine neoplasia (MEN) syndrome as outlined below.

1. Sporadic- Accounts for 80% of all cases of medullary thyroid cancer. They are typically unilateral and there are no associated endocrinopathies (not associated with disease in other endocrine glands). The peak onset is 40 – 60 years of age and females outnumber males by a 3:2 ratio. One third will present with intractable diarrhea caused by increased gastrointestinal secretion and hypermotility due to the hormones secreted by the tumor (calcitonin, prostaglandins, serotonin, or VIP).

2. MEN II-A (Sipple Syndrome). Multiple Endocrine Neoplasia Syndromes (abbreviated as "MEN") are a group of endocrine disorders that occur in the same patient and typically are found in families because they are inherited. Sipple syndrome is characterized by [1] bilateral medullary carcinoma or C cell hyperplasia, [2] pheochromocytoma, and [3] hyperparathyroidism. This syndrome is inherited and is due to a defect of a gene (DNA) which helps control the normal growth of endocrine tissues. This syndrome is passed on to all children who get the gene (inherited in an autosomal dominant fashion), which theoretically, would be 50% of all offspring of a person with this defective gene. Because of this, males and females are equally affected. Peak incidence of medullary carcinoma in these patients is in the 30's.

3. MEN II-B. This syndrome also is characterized by [1] medullary carcinoma and [2] pheochromocytoma, but only rarely will have hyperparathyroidism. Instead these patients have [3] an unusual appearance which is characterized by mucosal ganglioneuromas (tumors in the mouth) and a Marfanoid habitus. Inheritance is autosomal dominant as in MEN II-a, or it can occur sporadically (without being inherited). MEN II-B patients usually get medullary carcinoma in their 30's, and males and females are equally effected. As with MEN II-A, pheochromocytomas must be detected prior to any operation. The idea here is to remove the pheochromocytoma first to remove the risk of severe hypertensive episodes while the thyroid or parathyroid is being operated on.

4. Inherited medullary carcinoma without associated endocrinopathies. This form of medullary carcinoma is the least aggressive. Like other types of thyroid cancers, the peak incidence is between the ages of 40 and 50.

Medullary cancer has a much lower cure rate than does the "well differentiated" thyroid cancers (papillary and follicular), but cure rates are higher than they are for anaplastic thyroid cancer (see below). Overall 10 year survival rates are 90% when all the disease is confined to the thyroid gland, 70% with spread to cervical lymph nodes, and 20% when spread to distant sites is present.

In contrast to papillary and follicular cancers, little controversy exits when discussing the management of medullary thyroid cancer. After assessment and treatment of associated endocrine conditions (such as pheochromocytomas if present), all patients should undergo a total thyroidectomy, a complete central neck dissection (removal of all lymph nodes and fatty tissues in the central area of the neck), and removal of all lymph nodes and surrounding fatty tissues within the side of the neck which harbored the tumor.

Because medullary thyroid cancer sometimes runs in families, close blood relatives of a person with this type of cancer should be screened for a genetic abnormality that can be easily detected in blood cells. If the screening test result is negative, the relative will almost certainly not develop medullary cancer. If the screening test result is positive, then the relative has or will develop medullary cancer, and thyroid surgery should be considered even before symptoms develop and the blood level of calcitonin rises. A high blood calcitonin level or an excessive rise in the level following stimulation is predictive of the potential to develop medullary cancer and indicates removing the thyroid gland, since early treatment provides the best chance of cure.

In addition to the usual cancer follow up, patients should receive a yearly chest x-ray as well as calcitonin levels Serum calcitonin is very useful in follow up of medullary thyroid cancer because no other cells of the body make this hormone. A high serum calcitonin level that had previously been low following total thyroidectomy is indicative of recurrence. Under the best circumstances, surgery will remove all of the thyroid and all lymph nodes in the neck which harbor metastatic spread. In this case, post operative calcitonin levels will go to zero. This is often not the case, and calcitonin levels remain elevated, but less than pre-operatively. These levels should still be checked every 6

months, and when they begin to rise, a more diligent examination is in order to find the source.

It is important to note that meduallry cancers do not arise thyroid cells that take up iodine. Thus radioactive iodine therapy is not useful for the treatment of medullary thyroid cancer. Similarly, if medullary cancer spreads to distant sites, it cannot be found by iodine scanning the way that distant spread from papillary or follicular cancer can.

E. Anaplastic Cancer

Anaplastic tumors are the least common (about 2-3%) and most deadly of all thyroid cancers. These tumors occur most commonly in elderly women (peak onset older than 65), and extremely rare in young patients. This cancer grows very quickly and usually causes a large growth in the neck. The most common way this cancer becomes evident is by the patient or his/her family member noticing a growing neck mass. About 80 percent of the people with anaplastic cancer die within 1 year. Treatment with radioactive iodine is useless because anaplastic cancers do not concentrate radioactive iodine. However, treatment with anticancer drugs and radiation therapy before and after surgery has resulted in some cures.

Anaplastic tumors often arise within a more differentiated thyroid cancer or even within a goiter. Like papillary cancer, anaplastic cancer may arise many years (~20) following radiation exposure. But once they emerge, they spread rapidly. Cervical metastasis (spread to lymph nodes in the neck) are present in the vast majority (over 90%) of cases at the time of diagnosis. The presence of lymph node metastasis in these cervical areas causes a higher recurrence rate and is predictive of a high mortality rate. Tracheal invasion is present in 25% at the time of presentation. Spread (metastasis) to the lung is present in 50% of patients at the time of diagnosis. Most of these cancers are so aggressively attached to vital neck structures that they are inoperable at the time of diagnosis. Even with aggressive therapy protocols such as hyperfractionated radiation therapy, chemotherapy, and surgery, survival at 3 years is less than 10%.

The major problem with anaplastic thyroid cancer, is that it is usually too aggressive and invasive when it is diagnosed. Therefore, only a small portion of patients can undergo surgical resection of the cancer in hopes of cure. For those patients that are diagnosed at an earlier stage, total thyroidectomy is necessary. Many patients, especially those who have advanced cancer and cannot undergo surgical resection, will benefit from external-beam radiation (this is different from radioactive iodine). Some chemotherapy treatments may also be beneficial to patients with anaplastic thyroid cancer.