

## **Thyroxine Hormone Suppression Treatment**

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One of the important modalities of treatment of Thyroid Cancer (TC) after surgery is the administration of thyroxin as an adjuvant treatment. Historically, the hormonal potential of TC was described in 1894 by Von Eiselberg (48) in a young woman who developed transient myxedema following total thyroidectomy for TC. Sometime later she became euthyroid when her sternal metastasis began to grow indicating the functioning nature of the metastasis. This observation was later corroborated by Sir Thomas Dunhill in 1937, (15). He reported two children first diagnosed at the ages of 5 and 8 years who developed recurrence 19 and 5 years later. Both patients were given large doses of thyroxin and the recurrent masses disappeared. Both these children had malignant masses and the reason for the regression of the masses was not known but Sir Thomas commented “There is much that we do not know about carcinoma of the thyroid and proliferation of thyroid epitheliums but I cannot help thinking that hyperplasia in response to demand or stimulation can closely approach the appearance which stimulates malignancy” (15). He later treated several patients with cervical and pulmonary metastases which responded well with treatment. Subsequently, almost 20 years later several reports (1, 10, 43) confirmed that some well differentiated cancers regressed with thyroid hormone therapy.

## **Stimulation Of Growth Of Thyroid Cancer**

Thyroid Stimulating hormone (TSH) is a potent stimulant for cancer cells. This observation was based on the fact that in association with clinical hypothyroidism and TSH stimulation some tumors grew more rapidly, pain intensified in the sites of metastases, and in a late stage “progressed” to an anaplastic variety (4, 32, 43). In our own experience, we have observed that metastases especially to the bone grew quite rapidly when the patient stopped thyroxin prior to radioiodine treatment. Although there are many described putative factors that stimulate the growth of TC cells there is a laboratory and clinical evidence that TSH plays a major role in activating both the function and growth of well differentiated cancer cells.

Thyroid stimulating hormone mediates its action by stimulating TSH receptors, which have been shown to be present on cancer cells (21). In fact, study in animals (36) reported in 1948 had shown that TSH played a major role in promoting the growth of TC. As in neoplasms of other endocrine glands, Differentiated Thyroid Cancers (DTC) retain properties of the normal thyroid. Growth and function, which may be affected by TSH are, however, often disparate. Autonomy of function may be relative with new set points for regulation of secretory activity. There is generally an inverse relation between functionality and degree of differentiation of endocrine tumors. Poorly differentiated tumors usually lose their hormone secretory function, while properties of invasion, autonomous growth and metastases become predominant. The two-stage theory of tumor carcinogenesis helps to understand the biology of TC (46). Malignant tumors arise as a result of a series of defects in stem cells, which are targets of transforming agent. Initiation and promotion are the primary changes in the process of carcinogenesis.

Clinical findings are in keeping with the concept that the genesis of well DTC is related to an initiating agent like radiation, effecting transitional changes in DNA into a dominant cancer cell. Most of the time the initiating factors are unknown.

Thyroid stimulating hormone is one factor, which serves as a promoting agent affecting cell growth (13). The growth and the function of the cancer cells are affected by the promoting factors. Other promoting factors described are thyroid stimulating immunoglobulin associated with Graves' disease (14,26,39). It is also now apparent that other promoting factors recently described include Epidermal Growth Factor (EGF), Insulin like Growth Factor (IGF), Thyroid Growth Immunoglobulin (TGIg), Vasoactive Intestinal Peptide (VIP), prostaglandins and growth hormone (7). Epidermal growth factor receptors have been demonstrated on TC cells and are increased by adenylate cyclase, which in turn is modulated by TSH (29).

Although these stimuli have been shown to be growth promoting in benign thyroid disease their exact influence on cancer cells is speculative. Thyroid stimulating hormone suppression is based on the feedback mechanism between thyroid and the pituitary. Definite biological basis was established with the demonstration of TSH receptors on TC cell (17,44). When TSH receptors are activated in normal thyroid epithelium, they combine with guanyl nucleotide, which stimulates the formation of adenosine cyclase, which catalyses the production of cAMP, acting as a second messenger to stimulate thyroid growth and function. Most thyroid tumors have differences in the degree of sensitivity of TSH receptors (40,47). Tumors which are more advanced may have fewer receptors. This may account for the variable responses of differentiated thyroid tumors to TSH (26).

### **Functionality of Thyroid Cancer**

Studies of <sup>131</sup>I uptake and secretion of Thyrogobulin (Tg) demonsrate that DTC is influenced by TSH. The enhanced uptake of <sup>131</sup>I by increasing levels of s-TSH as associated with hypothyroidism is well known and critical to treatment of these tumors with <sup>131</sup>I. A majority of tumors can be stimulated to concentrate more iodine by exogenous TSH given in sufficient quantities to be effective therapeutically (16, 28). The effect of TSH in TC cell as expressed by Tg secretion is reported by Schlumberger et al. (34) on the treatment of DTC metastatic to lungs and bone. Following total thyroidectomy the normal levels of s-Tg will become undetectable, if there is no residual thyroid present. When metastatic disease is present the levels of Tg are elevated especially in presence of lung and bone metastases (37). The s-Tg levels fall considerably when thyroxine is administered and rise again when thyroxine is discontinued. In most cancers, there is a concordance of <sup>131</sup>I uptake and the levels of s-Tg showing that there is correlation between the two important functions of the thyroid. At times elevated levels of s-Tg in metastasis may be associated with little or no iodine uptake. There are no positive identifiable factors in the metastasis to indicate the reason for this disassociation.

Our study of 136 patients of which 80 had metastases showed that 51 of them had elevated levels of s-Tg and 15 of them had functioning tissue, which synthesised enough thyroid hormone to keep the patients in a euthyroid state. All but one of these 15 cases as

follicular cancer with skeletal metastases. There is evidence to suggest that the hormone synthesis by tumor is less efficient than normal thyroid but when the tumor burden is large, there can be sufficient thyroid hormone secretion to keep the patient euthyroid (33).

### **Is Thyroid Stimulating Hormone suppression useful?**

At this point, it is important to understand the distinction between suppression and replacement. It is mandatory to give the patient thyroxin to maintain an euthyroid state. The dose required as replacement therapy is generally small and can be determined by monitoring s-TSH levels so as to maintain them in the normal range. However, when we treat TC patients the doses of thyroxin should be higher so that the TSH levels are maintained well below normal. This is required so that cancer tissue is not subjected to stimulation by elevated levels of s-TSH. Hence function of cancerous tissue will be suppressed and thereby its growth can be controlled and slowed.

There have been no controlled studies on the role of thyroxin in the management of DTC. The number of patients that may benefit from s-TSH suppression by the potential of prevention of tumor recurrence or metastasis and the prolongation of life is not well documented. There are conflicting reports. Reports have shown that there was a considerable improvement in the survival of both papillary and follicular cancer patients when thyroxin was given (41). In another study (5) the 25-years survival was 33% when thyroid hormone was administered and 54% when it not advised. This was more evident with follicular cancers. The best results were observed when a combination of thyroxin and 131I was given. The recurrence rate was reduced from 50% when neither was used to 10% when both were used (25). Papillary cancers more than 1.5 cm in diameter, multicentric, locally invasive, or metastatic to regional nodes recurred more often (17% vs.34%) when thyroid hormone was withheld post-operative (25). There is evidence to suggest that the effect of thyroid hormone is maximal in the first 10 years (41).

Some tumors, which are initially responsive to TSH suppression later lose their response (45). Some surgeons strongly advocate the use of thyroid hormones after surgery (9) especially for papillary cancer. Patients with cervical nodes when treated with thyroxin alone, showed that the nodes remained unchanged and patients were symptom free for 2-3 decades (35). Unusual responses were observed in showing regression in patients with medullary cancer and undifferentiated cancer (12,24).