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Role of ^{131}I in the Treatment of Well Differentiated Thyroid Cancer

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^{131}I is an integral component in postsurgical management of well-differentiated thyroid cancer (WDTC), which includes papillary and follicular types. ^{131}I is used postsurgically to either destroy remaining thyroid tissue (thyroid ablation) or to treat recurrence and metastases (radioiodine therapy). ^{131}I is no longer a routine diagnostic modality, but it is widely used for remnant ablation after thyroidectomy for WDTC > 1 cm, under conditions of thyroxine withdrawal. It is generally—though not unanimously—accepted that postsurgical radioiodine is the most powerful method by which to lengthen disease-free survival. ^{131}I cannot be used if the residual thyroid remnant is large; many surgeons therefore perform near-total or total thyroidectomy for all WDTC > 1 cm. Since 1997, radioiodine treatment has been performed in outpatient settings, where side effects are common, but mild and transient. Secondary screening is by physical exam, thyroglobulin measurements, and ^{131}I diagnostic whole-body scans. This is performed under conditions of thyrotropin stimulation, which is accomplished either by thyroxine withdrawal or administration of recombinant human thyrotropin. While most cancers are well treated with radioiodine, some advanced cancers may no longer take up radioiodine, rendering them resistant to treatment. For these cancers, redifferentiation therapy and molecular target-specific medicines hold future promise for improved treatment.
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INTRODUCTION

On the surface, the basic treatment principles of well differentiated thyroid carcinoma (WDTC) seem clear and well-established: initial management is surgical removal of the thyroid gland and locoregional metastases, followed by postoperative ablation or therapy with radioiodine. The next phase in care is one of periodic secondary screening, and local or distant recurrences are generally treated with surgery or radioiodine as appropriate. Of course tumor biology is generally favorable, but this treatment strategy is a simple formula that appears to work. Patients with WDTC have survival estimates that exceed most other malignancies. In the National Cancer Data Base (NCDB) study of greater than 53,000 thyroid cancers reported between 1985 and 1995, the 10-year survival for WDTC was 85% (follicular cancers) and 93% (papillary cancers) [1]. Furthermore, it has been suggested that radioiodine therapy is very important in the treatment of WDTC. A large retrospective study of patients with WDTC showed that treatment with radioiodine (after surgery) was the most powerful prognostic indicator for increased disease-free survival [2]. Despite these findings, extensive practice pattern variations exist with regard to patient selection (i.e., threshold for treatment), radioiodine dose, follow-up intervals, method of TSH stimulation, and the treatment of recurrences. There are no randomized, prospective trials in this body of literature, and the clinical practice pattern guidelines that have evolved are largely based on data from retrospective

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case series. As such, most guidelines represent Level 2 evidence—that is, consensus among experts without major disagreement. Some areas of treatment (e.g., thyroxine withdrawal vs. recombinant human thyrotropin) generate major disagreement among experts and are regarded as Level 3 evidence.

In this chapter, we address the utility of ^{131}I in the diagnosis and management of both primary and recurrent well differentiated (papillary and follicular) thyroid carcinoma. The role of recombinant human thyroid-stimulating hormone (rhTSH; Thyrogen™) is discussed as well, and we include a proposed algorithm for secondary screening and follow-up after initial treatment for thyroid carcinoma.

BACKGROUND

Radioiodine is used in the post-surgical treatment of WDTC for either thyroid ablation or therapy. Thyroid ablation refers to the use of radioiodine to destroy the remaining normal thyroid tissue after less-than-total thyroidectomy (intended or otherwise), while therapy refers to the use of radioiodine to treat residual or recurrent thyroid cancer at the thyroid bed or more distant metastatic locations [3]. The terms can become confusing, however, especially when a total or near-total thyroidectomy is performed for WDTC. Although a dose of radioiodine may be given with the intent to clear the thyroid bed of remaining normal thyroid tissue (ablation), it cannot be assumed that the remaining tissue was free of cancer deposits (for which the treatment would be radioiodine therapy). Once accumulated within the cells, ^{131}I undergoes beta decay releasing high energy electrons for a short distance into the surrounding tissues. This cytotoxicity is quite focused and generally thought to effect tissues only within a 2 mm radius. Gamma rays are also released which allow for the radioisotope's use in scanning procedures. Of course, the cytotoxic decay only affects tissue which concentrates radioiodine. Problematically, dedifferentiated thyroid cancers can lose their ability to concentrate iodine, and therefore may receive substantial radiation only if closely neighbored by normal thyroid tissue. For similar reasons, large amounts of tissue (e.g., a large thyroid remnant) are difficult to destroy, which may influence the initial surgical approach.

PRIMARY CANCER

Diagnosis

Historically, thyroid scintigraphy using ^{131}I was used routinely in the workup of a thyroid nodule. Diagnostic and treatment algorithms were generated based on the various perturbations of history, physical exam, and whether the thyroid nodule had lost the ability to concentrate the radioactive isotope. The thyroid scan has been used far less over the past decade, commensurate with the widespread use and documented utility of fine needle aspiration for diagnosis. For diagnosis of a primary cancer, the thyroid scan is not routinely used.

Treatment

Radioiodine may be used in two ways after thyroidectomy: low doses are used to demonstrate remaining thyroid tissue or metastatic disease as part of a radioiodine thyroid scan, while higher doses are used for ablation or therapy. The timing of the initial postoperative scan is dictated by the physiology of T4. In order for remnant tissue to take up radioiodine, it must be stimulated by elevated levels of TSH. Although no precise threshold has been established, a general consensus is held that the TSH should be at least 30 μIU/ml. The TSH rise is generally achieved by thyroxine withdrawal, although recombinant human TSH is available (see below). Circulating T4 (either secreted from the thyroid gland or provided by exogenous supplementation) delays the rise in TSH. The half life of thyroxine is approximately 7 days, so TSH values are significantly elevated 4–5 weeks after total thyroidectomy or withdrawal from thyroxine treatment. In order to minimize the duration of hypothyroid symptoms, patients can be managed on T3 (Cytomel™) for the first 4 postoperative weeks. Due to the much shorter half-life of T3 (8–12 hr), it is held for 2 weeks prior to scanning [4–6].

Patient selection. Radioiodine therapy is well suited to WDTC because most tumor cells have the ability to concentrate radioiodine. Additionally, many studies have shown a decreased rate of recurrence and increased disease-specific and overall survival when ^{131}I is used. Mazzaferri [7] reported in 1997 a three-fold decrease in the incidence of distant metastatic disease and local tumor recurrence in tumors treated with radioiodine. In another study, the risk of cancer death was decreased by half (from 16% to 8%) when radioiodine was used after surgery compared to hormone replacement or external radiation alone [8]. Many treatment centers, retrospective studies, and individual clinicians agree that radioiodine is beneficial and well tolerated, but certainly this is not a unanimous conclusion. For instance, Hay et al. [9] reviewed the outcomes for nearly 2,500 patients with papillary thyroid carcinoma patients treated over six decades at a single institution. In this long-term retrospective review, the investigators show that the utilization of postoperative remnant ablation has greatly increased over the past several decades. Nevertheless, they report stable recurrence and cause-specific mortality rates even in the face of increased utilization of radioiodine therapy [9]. They conclude that routine radioiodine treatment for

all patients is unjustified, particularly for those with low-risk cancers.

As mentioned previously, there are no prospective, randomized trials with subgroup analysis to shed light on the dilemma of which patients should receive postoperative radioiodine. The argument is further complicated by the fact that more than five staging and prognostic systems are currently used, and comparisons across studies can be difficult. For instance, Cady and Rossi at the Lahey Clinic reported a reluctance to treat low risk patients (men under 41 and women under 51) without metastatic disease at original operation [10], but Samaan [2] has suggested a more universal approach to remnant ablation, as has Beierwaltes [11].

It is safe to summarize that postoperative radioiodine is commonly used, even for lower-risk cancers, and thyroid remnant ablation is generally accepted as part of the postoperative treatment of patients who have undergone total or near-total thyroid excision for WDTC. It is also widely recognized that this approach may not be the final answer, and it is not clear that using postoperative radioiodine to ''clear'' a whole-body scan will impact the patient's recurrence or survival. The future of WDTC treatment will likely involve an approach where patients are selected for postoperative radioiodine therapy based on individual risk assessment. Such assessment tools will need to be prospectively validated in a randomized fashion to offer the greatest help in selecting patients for radioiodine.

Several situations exist wherein it is generally agreed that ^{131}I is not necessary (or beneficial). If the cancer is non-differentiated and does not concentrate radioiodine, ablative or therapeutic efforts will be futile. Lesions smaller than 1 cm without evidence of metastatic disease are not treated with radioiodine because of their exceptionally low potential for local or distant recurrence. Finally, if only a lobectomy is performed, the radioiodine ablation is only possible 25% of the time (due to the volume of residual tissue) [12].

Relationship of surgical approach to postoperative radioiodine. The choice of thyroid operation for WDTC (i.e., total vs. subtotal vs. lobectomy) is not the focus of this chapter, but it is not always obvious that the extent of the resection actually affects the overall prognosis. However, thyroid surgery for WDTC is relatively unique among solid organ cancers in that the extent of resection (total vs. less-than-total thyroidectomy) directly affects the postoperative treatment options. As stated previously, radioiodine therapy is unlikely to be beneficial (or even possible) and is not used if a less-than-total thyroidectomy is performed. Surgery (typically total thyroidectomy) and postoperative radioiodine therapy [13] are generally agreed upon as standard treatment for those cancers 1 cm or greater. The theory behind this practice pattern is that residual microscopic disease (not removed by the original operation) would be eliminated with radioiodine treatment. As in the previous section on patient selection, this contention is generally accepted, but certainly not universal. For instance, the Mayo Clinic group has reported no difference in the frequency of local recurrence in those patients that underwent total thyroidectomy vs. bilateral subtotal thyroidectomy, suggesting the theory that postoperative ^{131}I treats ''residual microscopic disease'' may not be correct [14]. Additionally, the Mayo team showed that survival was not improved by total thyroidectomy (compared to bilateral subtotal thyroidectomy) in either minimal or higher risk patients with papillary carcinoma.

Indications and benefits of therapeutic radioiodine. Freitas has described the generally accepted indications for ^{131}I treatment: inoperable primary tumor, postoperative residual tumor in the neck, capsular invasion, local recurrence, and the presence of distant, cervical, or mediastinal metastatic disease [15]. Proponents of ^{131}I advocate that all patients who meet the indications for total thyroidectomy should undergo postoperative radioiodine therapy because it should not be assumed that residual thyroid tissue in the neck is tumor-free. Importantly, between 24% and 50% of well differentiated thyroid cancers will be multifocal, multicentric, or microscopic [8,16]. In these settings, postoperative remnant thyroid ablation after total thyroidectomy serves to destroy remaining thyroid tissue that may harbor occult microscopic carcinoma. There are additional compelling reasons to provide postoperative radioiodine ablation. In short, it is easier to manage and follow the patient without remaining thyroid tissue. Without competing normal tissue, visualization of local or distant recurrences on follow-up ^{131}I scanning is possible. If large amounts of thyroid tissue remained after the initial operation, the bright emission of ^{131}I from the residual thyroid will obscure any small areas of local recurrence. Additionally, remaining thyroid tissue will cause TSH suppression, which can decrease the uptake of ^{131}I during postoperative imaging [11]. Finally, thyroglobulin (TG) measurements are the most specific tests for recurrent cancer when no normal thyroid tissue is present, no TG antibodies (TG-Ab) are present, and when TG level is measured during a period of hypothyroidism—none of which are feasible when a remnant remains [17]. It follows, therefore, that only patients with a small cancer (<1 cm) carrying an exceptionally low risk of recurrence should be routinely excluded from consideration of treatment with postoperative radioiodine therapy.

Side effects of radioactive iodine. While radioiodine is generally well tolerated, a significant percentage of patients will experience side effects. While most of the side effects are mild and transient, some are more serious.

Local side effects are typically transient and occur with varying incidence: radiation thyroiditis/neck pain (up to 20% of patients), sialadenitis (12%), taste dysfunction (~50%), and nausea (67%) have all been reported [18–20]. These effects are generally more pronounced with higher or repeated doses of radioiodine. A potentially more serious side effect of decreased sperm count has been reported. While this side effect is common, and correlates to the dose of radioiodine [21], it is probably transient and does not result in an increased incidence of infertility [22]. Perhaps the greatest potential morbidity is the rare incidence of leukemia after radioiodine therapy. While this has been reported many times [23–27], the incidence does not appear to greater than that of the rest of the population [24,27,28], with the possible exception of very high-dose radioiodine treatment [23,29].

Outpatient radioiodine. Prior to 1997, an inpatient treatment setting was required for any patient receiving >30 mCi of radioiodine. This practice was cumbersome and required significant resource investment from both the patient and treating center. In May, 1997, however, the United States Nuclear Regulatory Committee revised the regulatory code which allowed patients to be treated with higher doses (up to 200 mCi) in an outpatient setting. Unique isolation precautions have arisen from the regulatory code revisions which protect a patient's family and community from excess radiation exposure. These precautions reduce external exposure to others (limit proximity to others, limit private travel, limit time at work, sleeping in a separate bed, avoidance of mouth-to-mouth contact, using separate dishes, utensils, linens, and thorough handwashing, etc.). The period of time for these precautions are short (from 2 to 6 days), and are relative to the dose administered [30,31].

Radioiodine dosing. Radioiodine dosing regimens for ablation or therapy are also subject to practice pattern variation. A typical ablation dose for very the small amount of remaining thyroid tissue in the thyroid bed (~5% uptake) after thyroidectomy is 30 mCi. Treatment regimens are more variable, however. Many centers use a standard fixed dose for all patients, with dose adjustments made only for site of radioiodine uptake [11,32,33]. In this method, not less than 100 mCi is given for uptake in the thyroid bed, not less than 150 mCi for uptake in the cervical nodes, and not less than 175 mCi for distant metastases. This is an attractive approach given its simplicity, but more specific alternate dosing regimens are utilized as well. One common method is a quantitated dosimetric approach based on the calculated radiation dose delivered to the cancer cells [34]. By this method, the calculated dose is given such that after delivery of 200 cGy to the bloodstream, no more than 120 mCi are retained by 48 hr. This approach can be modified with a peak-dose limit of 300 mCi per treatment [35]. Another approach that combines elements of the fixed and adjusted-dose methods is employed at the University of Michigan. In this method, the fractional retention of a diagnostic ^{131}I dose is measured at 2 days with a scintillation probe [36]. This simple safeguard allows for verification that the patient's fractional retention of ^{131}I is ~15%. If so, the patient receives a standard (adult) treatment dose of 150 mCi (allowing for a relatively low 30 mCi retention at 2 days). If significant differences in the fractional retention are noted, then dosage adjustments can be made.

Lithium and radioiodine. As mentioned above, some tumors are de-differentiated and concentrate radioiodine poorly, or not at all. In these cases, the use of lithium may be considered as an adjunct to radioiodine therapy, based on the fact that lithium reduces the release of iodine from thyroid tissue. Lithium carbonate is administered orally (10 mg/kg/day; 400–800 mg daily) for 7 days prior to radioiodine treatment. The serum levels should remain between 0.8 and 1.2 mmol/L. In several small, uncontrolled case series, lithium has been noted to increase the effective tissue half-life of radioiodine in metastatic lesions and in native thyroid tissue [37,38]. The effect of this phenomenon on recurrence or mortality has not been studied. It has not been studied on a larger scale, though, and the routine use of lithium as an adjunct to radioiodine treatment of WDTC is not common.

RECURRENT CANCER

Most recurrences of WDTC are within the first several years after thyroidectomy, and half of those who develop recurrences do so in the first 5 years [39]. Secondary screening is carried out every 6–12 months for the first several years to evaluate for recurrent or metastatic disease. Modern secondary screening is accomplished with a combination of physical exam, monitoring of thyroglobulin, and imaging (see Table II). Anti-thyroglobulin antibodies should be measured at the same time (and each time) as thyroglobulin. Although TG-Ab may decrease or disappear over time, if the antibodies are present, the thyroglobulin level is not valid and cannot be relied upon to detect recurrent disease. In the presence of TG-Ab, imaging becomes a more important secondary screening modality. Although ultrasound assessment of the neck has been utilized more over recent years, radioiodine whole-body scanning remains a common method by which to detect recurrent disease.

In Table I, we describe a practical approach to the secondary screening of WDTC patients. Of course, physical exam is necessary for all patients at regular intervals. The first postoperative thyroglobulin/thyroglobulin antibody (TG/TG-Ab) levels and ^{131}I scan are

TABLE I. Secondary Screening

Screening measure	Frequency
Physical exam	Every 3–6 months for 2 years, then annually
Thyroglobulin and TG-antibody measurement	At 6 weeks, 3 months, 12 months, then annually
^{131}I diagnostic scan	Yearly until negative

obtained at 6 weeks under conditions of thyroxine withdrawal. Subsequent TG/TG-Ab levels are unstimulated, and the trend over time is observed. If there is a concern over rising levels, a stimulated level can be obtained. This approach minimizes the duration of hypothyroidism over the first postoperative year. ^{131}I diagnostic scanning is performed yearly until negative except in those patients identified to be in a very-low risk prognostic category.

ALGORITHM FOR POSTOPERATIVE TREATMENT

Patients with WDTC should be evaluated 4–6 weeks after total thyroidectomy as described in Table II. These recommendations assume there is no gross residual disease in the neck. All patients will receive thyroxine for hormone replacement and TSH suppression after this point.

Recombinant Human Thyrotrophic (rhTSH; Thyrogen™)

The radioiodine whole body scan (WBS) detects tissue with ability to concentrate radioiodine. Some authors have advocated not obtaining a WBS if the patient has had an aggressive initial operation with no suggestion of recurrence by thyroglobulin levels [40]. Nevertheless, thyroglobulin levels are not 100% sensitive to recurrence and WBS continues to be widely utilized in early secondary screening. Recurrent cancer is best visualized when stimulated by TSH. Traditionally this has been accomplished in the same manner as for postoperative thyroid ablation—thyroxine withdrawal for 4–6 weeks, sometimes with the use of T3 to ameliorate hypothyroid symptoms in the first 4 weeks. The withdrawal period can be fairly morbid, however, and most patients experience significant side effects of hypothyroidism: lethargy, depression, irritability, weight gain, and limitation in ability to work [41]. Also, there has been concern in small reports that the prolonged TSH elevation of thyroxine withdrawal for total-body scanning could be associated with rapid growth of metastatic tumors, particularly those in neurologic locations [42]. As such, alternate methods for thyroid tissue stimulation have been sought. Historically, bovine and human thyrotropin were used, but more recently recombinant human TSH (rhTSH; Thyrogen™) has become available. Today, rhTSH is produced in the Chinese Hamster Ovary (CHO) cell line. Traditional bacterial drug production systems cannot be used as bacteria lack the cellular mechanisms to glycosylate the TSH protein [43,44].

Thyrogen™ is approved by the Food and Drug Administration for use as an adjunctive diagnostic tool for radionuclide imaging (and thyroglobulin testing) in the follow-up of patients with WDTC. The intended goal when using rhTSH is that residual or recurrent thyroid tissue cells would receive sufficient stimulation for effective imaging without having to remove the patient from their usual thyroxine therapy. Another potential way that rhTSH could be useful (though not currently approved by the FDA) is to stimulate recurrent cancer prior to radioiodine treatment while allowing the patient to remain on daily thyroxine.

Several studies have compared the rhTSH WBS to traditional thyroxine-withdrawal WBS. In general, peak TSH levels are higher in the rhTSH group, but this does not correlate with the level of uptake on WBS [45]. In one study, the level of neck radioiodine uptake was lower in the rhTSH scans when compared to withdrawal scans in 72% of patients. However, the scans were still read as

TABLE II. Evaluation and Treatment After Total Thyroidectomy at 4–6 Weeks

Scan and TG results	Action
Thyroid bed positive	Radioiodine ablation and post-treatment scan[a]
Metastatic site positive	Radioiodine therapy and post-treatment scan
Scan negative, TG low	None
Scan negative, TG elevated	Consider radioiodine treatment[b]

[a]Radioiodine in this setting is controversial. In a low-risk patient, some clinicians would follow if the image did not obscure the ability to image the surrounding neck.
[b]Radioiodine is also controversial in this setting (see text).

equivalent in 89% of cases (in the remaining cases, the withdrawal scans were superior) [46]. A second study by Ladenson [47] showed that the rhTSH scans are inferior 29% of the time, concordant to withdrawal scans 66% of the time, and better in 5% of patients. This study did not address, however, if the inferior scans were merely decreased uptake or if they showed a different stage of disease. Yet another study showed equivalent scans even in the setting of decreased radioiodine uptake in the rhTSH group [45].

Mazzaferri et al. [48] recently published a consensus statement on the use of serum thyroglobulin levels to monitor low-risk patients with WDTC. The consensus panel's statement represented the collective opinion of 15 senior endocrinologists from around the world. From a comprehensive literature review, it was determined that serum thyroglobulin levels were sensitive in the secondary screening of patients with WDTC when the serum levels were $\geq$2 μg/ml. The consensus panel additionally concluded that an rhTSH-stimulated thyroglobulin level carried an equivalent sensitivity to a traditional thyroglobulin level stimulated by thyroxine withdrawal.

Because of the avoidance of symptoms associated with thyroxine withdrawal, there has been much interest in using rhTSH for thyroid tissue stimulation prior to treatment—that is, not just for stimulation prior to a diagnostic scan or measurement of serum thyroglobulin levels. In a single-center uncontrolled case series of 12 patients with late-stage recurrent thyroid cancer, 0.9 mg daily of rhTSH was given subcutaneously for 2 days in order to stimulate uptake of radioiodine at both imaging and therapeutic doses. All 12 patients showed correlation between the initial WBS and the post-therapy WBS. In short-term follow-up, 10 patients had serial thyroglobulin (TG) levels measured. Four of 10 showed a decrease in TG, 4 had an increase, and 2 patients had a stable TG [49]. While rhTSH may have value in the stimulation of thyroid tissue for diagnostic scanning [50], caution must be utilized in the extension of this logic to the use of rhTSH for stimulation prior to radioiodine therapy. The authors are aware that rhTSH is being used while on thyroxine for the measurement of stimulated thyroglobulin levels. We also note that if rhTSH is used for diagnostic WBS and a lesion is found, it is tempting to proceed without delay and use rhTSH for stimulation of uptake prior to treatment (rather than making the patient withdraw from thyroxine for 6 weeks after the rhTSH diagnostic WBS). However, we advise caution in this regard as rhTSH has yet to be established as an efficacious alternative to traditional thyroxine withdrawal for radioiodine ablation or therapy. It is currently our practice to withdraw patients from thyroxine (unless medically contraindicated) prior to treatment with radioiodine.

Thyroglobulin-Positive, WBS-Negative Patients

Another important aspect of secondary screening for thyroid cancer is the serial measurement of serum thyroglobulin levels. Elevated TG levels may indicate recurrent or metastatic disease [51], particularly in the absence of thyroglobulin antibodies. Although the intricacies in this element of surveillance are out of the scope of this section, there does occasionally arise a clinical dilemma in which the thyroglobulin level is elevated (suggesting recurrence), but the radioiodine WBS is negative as well as all anatomic imaging studies such as ultrasound and CT scan. Clark et al. [52] have commented on several possible reasons behind this difficult situation. Of course, TG levels should always be rechecked in this scenario as lab error may occur. However, the elevated TG may represent a true recurrence, but of a tumor that is too diffuse and small for detection. Additionally, the recurrent cancer may be shielded from positive imaging by remaining normal thyroid tissue (not an issue if the original operation was a near-total or total thyroidectomy). Finally, the uptake of ^{131}I may be blocked by high levels of non-radioactive iodine from excess (or non-restricted) dietary intake. This can be excluded by checking a urinary iodine level, which should be less than 200 μg/day/g creatinine. Some tumors may also dedifferentiate in a manner such that they are able to secrete thyroglobulin but have lost the ability to trap iodine. If the non-diagnostic imaging is not due to any of the alterable causes above, the clinician is left not knowing if the patient may have a recurrence that would necessitate radioiodine therapy. Five studies have addressed this issue in a total of 79 patients who had normal diagnostic WBS and an elevated TG levels [3]. All were treated and in 66/79 patients the positive post-therapy scan was positive. That is, the smaller diagnostic dose of radioiodine did not visualize the recurrent or metastatic disease. Therapeutic doses of radioiodine have been advocated in the setting of scan-negative, TG positive patients [53], but this has yet to be established as a safe and efficacious practice. Even if some of the TG levels decrease, Fatourechi [54] has documented a lack of tumor response in these patients who do get treatment after negative WBS scans. It remains to be seen if there will be an impact on tumor recurrence or cause-specific survival. An alternative would be to use higher doses of radioiodine for imaging, but there are concerns that the initial diagnostic dose would stun the thyroid tissue and ultimately decrease the level of therapeutic radioiodine uptake.

REDIFFERENTIATION THERAPY

Adjunctive treatment of WDTC is dependent on the uptake and concentration of radioiodine by cancerous

thyroid tissue. Problematically, it has been reported that as many as 30% of advanced WDTC will eventually de-differentiate [55], and a portion of these cancers will lose the ability to concentrate radioiodine. This may be due to decreased expression of the human sodium iodide symporter (hNIS). Both in vivo and in vitro research has shown that follicular cancer cell lines have greater iodine uptake when stably transfected with hNIS [56]. Application of these gene therapy techniques to human subjects is not a current reality, but remains an exciting area of research [57]. Certain therapies have been used in humans in effort to ''redifferentiate'' thyroid cancer cells such that they would regain the ability to concentrate radioiodine. In early pilot studies, retinoic acid has been shown to increase radioiodine uptake and decrease thyroglobulin levels in advanced thyroid carcinomas [58], and further studies hold promise for the treatment of de-differentiated tumors.

NEW HORIZONS IN THE TREATMENT OF THYROID CANCER

There are no significantly effective medical therapies to offer patients with radioiodine-resistant thyroid cancers. In addition to the redifferentiation therapies mentioned above, the past two decades of research into the molecular biology and genetics of thyroid cancer have identified potential targets for alternate therapies. In a recent comprehensive review by Braga-Basaria and Ringel [59], the newest advances in thyroid cancer treatment were thoroughly summarized. Clinical trials have been established for a variety of drugs with wide-ranging targets and molecular mechanisms of actions, including drugs that target: intracellular signaling molecules (ras and raf inhibition), receptor tyrosine kinases (anti-VEGF, anti-EGFR, anti Her2/neu, and VEGF/EGF receptor inhibitors), angiogenesis (thalidomide, combretastatins), apoptotic pathways (TRAIL; TNF-related apoptosis-inducing ligand), and rapamycin's effect on the *mTOR* gene (mammalian target of rapamycin). These and multiple other new drug therapies are summarized in this review; and a re-emphasis is made that all patients with radioiodine-resistant tumors should be considered as candidates for clinical trials.

CONCLUSION

The lack of prospective, randomized data poses difficulty when deciding how to best manage WDTC. Nevertheless, extensive retrospective experience and rational use of treatment including ^{131}I has allowed for success in the treatment of papillary and follicular thyroid cancers. Disease-specific mortality remains exceptionally low for small cancers in low-risk patients, while larger tumors and recurrences can usually be effectively treated with surgery and radioiodine. The mainstay of treatment for WDTC greater than 1 cm remains near-total or total thyroidectomy with postoperative ^{131}I, then subsequent surveillance with thyroglobulin levels, physical exam, and selected imaging. Exciting new gene therapy and tumor redifferentiation research holds promise in discovering new methods to improve radioiodine therapy for patients with advanced disease.

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