Role of Radioactive Iodine for Adjuvant Therapy and Treatment of Metastases

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**Abstract**

Normal thyrocytes and thyroid cancer cells are characterized by possession of a sodium iodide symporter. Radioiodine administration is a unique and powerful means of treating differentiated thyroid cancer because of the ability of thyroid cancer cells to concentrate beta-emitting radiolabeled iodine. Several manipulations, such as iodine depletion and thyroid hormone-stimulating hormone elevation, are used to enhance uptake of radiolabeled iodine by tumor cells. Adjuvant radioiodine therapy, given to patients without evidence of residual disease, enhances the sensitivity of subsequent surveillance and may decrease recurrence rates and mortality. However, its exact role in the management of low-risk patients merits further investigation. In contrast, radioactive iodine therapy used in patients with residual or metastatic disease clearly improves outcomes. Several studies show decreased recurrence and mortality rates in patients treated with radioiodine compared with those not receiving radioactive iodine. Adverse events from radioiodine therapy include salivary gland dysfunction, bone marrow suppression, and reproductive disturbances. Side effects of radioiodine therapy are generally greater when higher activities of radioiodine are used and may be transient or permanent. Secondary malignancies also may occur after radioiodine therapy. These side effects must be weighed against potential benefits, especially when radioactive iodine is used as adjuvant therapy. Stimulation of the expression of the sodium iodide symporter, or its introduction *de novo* into nonthyroid cells, is promising in treating poorly differentiated thyroid cancer and nonthyroid malignancies, respectively. (JNCCN 2007;5:631–640)

**Thyrocytes and Iodine Transportation**

By virtue of the properties of the sodium-iodide symporter (NIS), thyrocytes have the ability to actively accumulate iodine.1,2 The physiologic role of this transporter is to provide the iodine required for thyroid hormone synthesis3,4 (Figure 1). Serendipitously, this feature is shared by malignant thyroid cells, although the expression of the symporter is reduced compared with benign thyroid cells.1,2 The trafficking of iodine into thyrocytes makes it possible to design a specific means of destroying thyroid cancer cells because administered radiolabeled iodine-131 (RAI) is concentrated within benign and malignant thyroid cells. Positive immunostaining for NIS seems to predict the ability of tumor to concentrate iodine.1,2 Once internalized and retained in thyrocytes, RAI emits both beta and gamma radiation. The short-wavelength emissions of beta radiation destroy thyroid cells, whereas gamma radiation allows sites of RAI uptake to be visualized using a gamma-scintillation camera.1,2 To harness this unique delivery system, NIS has been introduced, using various vectors, into undifferentiated thyroid cancer cells that can no longer concentrate iodine.1,2 Efforts also have been made to redifferentiate undifferentiated thyroid cancer cells by using compounds such as retinoids, DNA demethylation agents, or histone deacetylase inhibitors, with the goal of reactivating NIS expression.11 Toxicities of RAI administered as therapy for differentiated thyroid cancer are relatively limited compared with traditional chemotherapy for other malignancies or external-beam radiotherapy. The appeal of this relatively specific therapy has led to attempts to harness RAI therapy for noniodine transporting cells through novel expression of NIS in other cell types, such as breast,12 prostate,13 colon,13 and medullary thyroid cancer.14

**General Principles of Radioiodine Therapy**

RAI administration has become a mainstay of therapy for differentiated thyroid cancer. The efficacy of RAI therapy
Iodine Depletion

Iodine deficiency causes up-regulation of NIS expression in fetal thyroid and placental tissue, although this has not been demonstrated in thyroid cancer cells. Iodine administration is associated with NIS down-regulation in thyroid cell lines. An iodine-depleted state was shown to be associated with more delivery of RAI to remnant and tumor tissue in nude mice and patients with thyroid cancer. Usually, 1 to 2 weeks of a low-iodine diet is sufficient to render a patient iodine-depleted. A urinary iodine content of less than 50 µg/g creatinine is generally accepted as evidence of iodine depletion. Certainly, the longer 2-week period is necessary when patients remain on levothyroxine therapy, because under these circumstances 1 week is insufficient to achieve the target urinary iodine. Guidelines for low-iodine diets are available from the National Institutes of Health (NIH) and the Thyroid Cancer Survivor’s Association (http://www.cc.nih.gov/ccc/patient_education/pubs/index.html and http://www.thyca.org/rai.htm, respectively; accessed May 15, 2007).

TSH Elevation

An elevated serum TSH stimulates NIS and is necessary to ensure sufficient RAI delivery to tumor tissue. TSH elevation can be achieved using various protocols to withhold or withdraw levothyroxine therapy and raise the concentration of endogenous TSH. Using a withdrawal protocol, a serum TSH of more than 30 mIU/L seems adequate to allow uptake in iodine-concentrating metastases. Alternatively, recombinant human TSH (rTSH) can be administered to provide elevated exogenous TSH levels while a patient remains on levothyroxine. One advantage of using rTSH preparation is to avoid the deleterious effects of hypothyroidism, including decreased quality of life and potential exacerbation of cardiac and neuropsychiatric conditions. Currently, rTSH is not approved by the U.S. Food and Drug Administration for therapeutic purposes, although its use for diagnostic purposes has been sanctioned. The European Commission, however, has approved an indication for remnant ablation in the European Union. Considerable experience with the use of rTSH to treat thyroid remnants and metastases has now accumulated.
Radioactive Iodine Treatment

Adjuvant RAI Therapy
Definition and Potential Benefits
RAI can be administered to patients who seem free of thyroid cancer. This use is termed adjuvant therapy, and serves to ablate normal thyroid remnants. This is in contrast to its use in patients who are known to have residual disease after thyroidectomy, in which case the destruction of metastases may also be achieved. Diagnostic scanning may be performed with 2 to 5 mCi RAI before remnant ablation. However, these scans may not influence the activity selected for initial therapy. Additionally, controversy exists about the frequency with which the diagnostic dose may interfere with the subsequent uptake of the therapeutic dose,\(^{36-38}\) a phenomenon known as stunning. Some studies suggest that this is an occasional phenomenon,\(^{39}\) whereas others suggest it occurs more frequently.\(^ {40}\)

Adjuvant RAI that results in remnant ablation has several potential benefits. The destruction of normal thyroid tissue increases the sensitivity of subsequent follow-ups by rendering stimulated thyroglobulin levels low or undetectable.\(^ {41}\) It also reduces or eliminates the amount of RAI uptake seen in the thyroid bed in subsequent diagnostic scanning and may permit the diagnosis of disease within cervical lymph nodes or even distant sites.\(^ {42,46,47}\) Both maneuvers potentially allow residual or recurrent disease to be detected at the earliest opportunity. If undocumented occult disease is present, it should also be destroyed by remnant ablation. In addition, posttreatment scanning performed after initial RAI occasionally allows unsuspected metastatic disease to be documented,\(^ {48}\) thereby altering staging and subsequent management. The American Thyroid Association (ATA) and National Comprehensive Cancer Network (NCCN) guidelines discuss the data suggesting that the benefits of remnant ablation are restricted to patients with tumors larger than 1.5 cm.\(^ {49,50}\) The ATA recommends that remnant ablation be considered for stage I patients who have multifocal disease, nodal metastases, extrathyroidal extension, vascular invasion, or aggressive histologies.\(^ {51}\) However, this clearly remains a contentious issue.\(^ {52}\)

Activity of RAI for Adjuvant Therapy
RAI activities selected for adjuvant therapy, and for RAI therapy in general, are subject to considerable debate. Institutional and regional preferences certainly play a role. Typically, initial activities of 29 to 150 mCi are used (Table 1). When using criteria such as a stimulated thyroglobulin of less than 0.5 to 2 ng/mL and a thyroid bed uptake of less than 0.1% to 1% during subsequent diagnostic studies, reported success rates with 30 mCi vary between 10% and 80%.\(^ {60,61}\) Success rates with a higher activity of 100 mCi may be greater at 44% to 100%,\(^ {61,64-66}\) Some discrepant success rates may be caused by differences in diagnostic scanning doses, method of TSH stimulation, degree of iodine depletion, and the amount of thyroid remnant. Although a recent meta-analysis found no reliable difference between the effectiveness of the 2 activities,\(^ {66}\) an earlier meta-analysis concluded that an activity of 100 mCi was more effective than 30 mCi.\(^ {67}\) The NIH is currently enrolling patients in a clinical trial to determine whether lithium therapy enhances the effectiveness of remnant ablation using a 30-mCi activity (http://clinicaltrials.gov/ct/gui/show/NCT00251316; accessed May 15, 2007). Recent ATA guidelines recommend choosing the lowest effective activity for remnant ablation.\(^ {53}\)

Method of TSH Stimulation for Adjuvant Therapy
Both endogenous and exogenous TSH stimulation have been used to prepare patients for remnant ablation, although rTSH is labeled as indicated for this purpose only in Europe. Rates of effective remnant ablation seem to be similar with 30 to 100 mCi of RAI given either with hypothyroid or rTSH preparation.\(^ {68,69,70}\) One of these studies was an international, randomized, controlled trial of remnant ablation in patients whose TMN stage was T1 to T3. Patients received 100 mCi of RAI after either withdrawal of thyroid hormone or rTSH injection. Results showed similar success rates based on the combination of stimulated thyroglobulin levels and thyroid bed uptake documented 8 months after the initial ablation.\(^ {71}\)

Table 1 Empiric Dose Radioiodine Therapy for Thyroid Cancer

<table>
<thead>
<tr>
<th>Site of Disease</th>
<th>Range of Activities (mCi)</th>
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<tbody>
<tr>
<td>Thyroid remnant</td>
<td>29–150</td>
</tr>
<tr>
<td>Cervical or mediastinal lymph nodes</td>
<td>100–175*</td>
</tr>
<tr>
<td>Cancer penetrating capsule</td>
<td>150–200*</td>
</tr>
<tr>
<td>(incompletely resected)</td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>200*</td>
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</table>

*Discussed in the 2006 NCCN Thyroid Cancer Clinical Practice Guidelines in Oncology.
However, 30 mCi given after rTSH may not provide effective ablation when it is given 48 hours after the second rTSH injection.\textsuperscript{60} Iodide kinetics are certainly different in the hypothyroid state compared with the euthyroid state, which is maintained with protocols using rTSH. With euthyroidism, there is an increased clearance of activity from the blood, resulting in a lower absorbed dose than with hypothyroidism.\textsuperscript{26,48} With rTSH stimulation, remnant uptake tends to be less, but the effective half-time in the thyroid remnant is longer.\textsuperscript{39} The longer residence time within the remnant may be caused by reduced iodine efflux from the target tissue associated with the declining levels of rTSH after therapy.\textsuperscript{39} A committee of ATA members found the use of rTSH-stimulated remnant ablation to be acceptable.\textsuperscript{51}

**Effect of Adjuvant Therapy on Outcomes**

Whether RAI therapy improves outcomes in patients with low-risk thyroid cancer is controversial. Some studies suggest that RAI therapy improves survival\textsuperscript{15,20,21} and decreases recurrence rates.\textsuperscript{32,33,12–14} However, other studies suggest that this benefit is seen only in higher-risk patients who have evidence of residual disease.\textsuperscript{75–79} A recently published meta-analysis concluded that the evidence in support of remnant ablation decreasing recurrences or mortality in low-risk patients was unclear.\textsuperscript{80} One study actually showed a trend for increased recurrence rates in low-risk patients who underwent RAI treatment.\textsuperscript{13} A possible explanation for this unexpected finding is that RAI potentially allows for earlier detection of recurrence and a lead-time bias.

A recent analysis from the National Thyroid Cancer Treatment Cooperative Study Group showed that RAI therapy was associated with improved survival in patients with stage I disease.\textsuperscript{44} This study failed to show any benefit from adjuvant use of RAI in patients with stage I disease. Patients with stage I disease who underwent RAI therapy seemed to have decreased overall survival. However, detailed analysis of the cause of death in these patients did not support the premise that their deaths were caused by thyroid cancer or complications of its therapy. The median length of follow-up was 3 years, which may be a limitation of this study. However, unpublished analyses through 2006 with a longer median follow-up of 4.8 years confirm the original finding that there is no survival advantage of RAI in patients with stage I disease (Sherman SI, et al., unpublished data, 2006). Certainly, the role of RAI therapy in the management of low-risk patients must be further investigated.\textsuperscript{80,82} Although not causing harm in patients who already have excellent survival rates is important, it is also prudent to provide therapy that may allow earlier detection of recurrence and lessen disease progression.

**Side Effects of Adjuvant RAI Therapy**

RAI has proven efficacy in treating thyroid cancer but also can cause several serious side effects. The salivary glands, breast tissue during lactation, gastrointestinal tract, and the lacrimal glands all express NIS\textsuperscript{1,10,83,84} and are also able to actively concentrate radioiodine. Thus, despite its high specificity, RAI unfortunately also may damage nonthyroid tissue. Salivary gland dysfunction after RAI treatment occurs frequently, even with initial or low-dose therapy. Other side effects generally occur with higher activities of RAI than those used for adjuvant therapy or after repeated treatments.\textsuperscript{52}

**RAI Therapy for Metastatic Thyroid Cancer**

**Empiric Therapy**

Activities chosen to treat metastatic disease can be chosen on an empiric basis or using dosimetric calculations.\textsuperscript{7,17} Selection of activities on an empiric basis generally involves increasing the activity in proportion to the patient’s thyroid cancer stage, sites of RAI uptake, or known disease burden. However, the activities chosen for a particular site of involvement may differ substantially according to the individual physician or institution. For example, administered activities may be 100 to 150 mCi for cervical lymph nodes, 150 to 175 mCi for a tumor that has penetrated the thyroid capsule, and 150 to 200 mCi for distant metastases. Table 1 shows the range of empiric activities discussed in the 2006 NCCN Thyroid Cancer Clinical Practice Guidelines in Oncology.\textsuperscript{55} The main advantage of empiric therapy is its simplicity. The main disadvantage is that the dose delivered may be either inadequate and therefore ineffective, or excessive\textsuperscript{45} and therefore associated with unnecessary toxicities.\textsuperscript{16,17} Administration of excessive doses seems to be a particular problem in elderly patients.\textsuperscript{45} Use of an empiric activity of 200 mCi would exceed the maximum tolerated dose in 22% to 38% of patients older than 70 years in one study. The proportion of patients who would have received an excessive RAI dose with empiric therapy ranged from 1% to 17% in another study.\textsuperscript{86}
Dosimetry
Dosimetric selection of treatment activities is practiced in a relatively limited number of institutions. Dosimetric calculations can be performed to maximize the dose delivered to a tumor lesion. Alternatively, calculations can be performed to determine the maximum safe dose that does not cause excessive exposure of the red bone marrow or whole body. Bone marrow toxicity can be reduced by limiting the dose delivered to whole blood to 200 cGy. Whole-body retention should be limited to 120 mCi at 48 hours. Toxicity to the lungs can be minimized by limiting the whole-body retention of RAI at 48 hours to 80 mCi in the presence of pulmonary metastases.

Dosimetry designed to estimate the maximum safe RAI dose is achieved by determining the serial counts in blood samples approximately 96 hours after a diagnostic activity of RAI (either 131I or 123I). The dose delivered to blood can then be determined by scaling up to determine the counts that would be generated by the treatment activity. Similarly, counts determined by whole-body scanning with diagnostic RAI activity can be used to predict the dose that will be delivered to the whole body with administration of a therapeutic activity. Lesional dosimetry involves determining the calibrated counts within particular lesions for approximately 96 hours after administration of the diagnostic RAI activity. The percentage uptake within each lesion and the effective half-life of the activity within the lesions are calculated from these data. The volume of the lesions also must be estimated from imaging studies. A dosage formula then can be used to determine the activity required to deliver a therapeutic dose to individual metastatic lesions. Doses of more than 8000 cGy are generally effective, whereas those less than 3500 cGy are typically ineffective. Interestingly, remnant ablation requires a higher delivered dose of 30,000 cGy. Although particular institutions have considerable experience with dosimetry, no randomized controlled trials compare outcomes after empiric treatment versus dosimetric treatment, and comparison of outcomes from published studies is difficult.

Method of TSH Stimulation for Therapy of Metastatic Disease
Historically, RAI for treating metastatic disease has been administered under hypothyroid conditions. However, some experience has accumulated regarding dose delivery using rTSH stimulation. It seems that effective therapy can be delivered using both methods of preparation. Renal clearance of iodide is reduced during the hypothyroid state, leading to a prolonged whole-body half-life of RAI. Compared with a hypothyroid protocol, a rTSH protocol results in a shorter effective half-life and less whole-body radiation exposure. However, in a study of remnant ablation, despite the shorter whole-body and blood half-times, the effective half-time of RAI in the thyroid remnant was significantly longer. Retention of RAI within tumor metastases seemed adequate in one study but reduced in another. An ATA committee concluded that evidence is insufficient to routinely recommend rTSH-mediated therapy for patients with metastatic disease. Further studies are needed to determine if preparation for therapy with rTSH and preparation using thyroid hormone withdrawal produce comparable outcomes in patients with differentiated thyroid carcinoma.

Effect of RAI on Thyroid Cancer Outcomes
RAI treatment is associated with improved outcomes in high-risk patients with metastatic thyroid cancer. These improved outcomes include decreased recurrence and improved survival (Figure 2) and improved survival (Table 2). Posttherapy whole-body scans may also help show the full extent of a patient’s disease burden. In one retrospective study, patients with metastases whose follow-up whole-body scans were negative after RAI therapy had an improved 10-year survival rate of 92% compared with patients who had positive scans. The ATA committee concluded that evidence is insufficient to routinely recommend rTSH-mediated therapy for patients with metastatic disease. Further studies are needed to determine if preparation for therapy with rTSH and preparation using thyroid hormone withdrawal produce comparable outcomes in patients with differentiated thyroid carcinoma.

Figure 2 Tumor recurrence after total thyroidectomy and thyroid hormone therapy with RAI (radiolabeled iodine-131) therapy (circles) and without RAI therapy (squares) in a cohort of patients with thyroid cancer followed at Ohio State University. From Mazzaferri EL, Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86: 1447–1463. Reproduced with permission. Copyright 2001. The Endocrine Society. Figure modified with permission from the author.
Similarly, Other therapies are guided. RAI treatment of metastatic disease can be effective therapy for microscopic disease. Doses of at least 8000 to 10,000 cGy must be delivered to lesions for them to respond to RAI therapy. Similarly, pulmonary metastases respond best when the volume of disease is small or microscopic. Excellent outcomes are seen in patients with elevated thyroglobulin levels whose pulmonary metastases are only shown through posttreatment scanning. However, even micronodular disease is not always effectively treated with RAI therapy. Patients whose pulmonary metastases concentrate iodine have an improved survival rate of 60% compared with 30% in patients whose metastases do not concentrate iodine. The risk for pulmonary fibrosis can be minimized by limiting the whole-body retention at 48 hours to 80 mCi. Treatment may be repeated at intervals with additional response.

Surgical resection of bony metastases can be considered because it is associated with improved survival. RAI may slow the progression of bony metastases, decrease pain, and improve survival, but is almost never curative. Other treatment modalities, such as surgical resection, external-beam radiation, bisphosphonate use, or intra-arterial embolization may be necessary. Thyroid cancer that invades the upper aerodigestive tract should be resected as completely as possible. Subsequent RAI therapy or external-beam radiation is typically used. RAI has limited efficacy in treating brain and central nervous system metastases. TSH-mediated swelling of metastatic deposits is also a concern. RAI treatment of metastatic disease can be administered empirically or using dosimetry. Many experts advocate dosimetry for metastatic disease to safely provide a higher activity or to ensure that an adequate dose is delivered to metastatic lesions. In the absence of pulmonary metastases, the amount of RAI that limits whole-body retention to 120 mCi at 48 hours should be administered. Follow-Up RAI Treatment

After the initial RAI therapy, subsequent diagnostic radioiodine scanning, stimulated thyroglobulin values, cervical ultrasonography, and other imaging studies, such as computed tomography of the chest or 18F-fluorodeoxyglucose positron emission tomography, may permit detection of persistent or recurrent disease. For disease not amenable to surgical resection, additional RAI therapy can be given.

Table 2: National Thyroid Cancer Treatment Cooperative Study Group 2006: Analysis of Effects of Treatment on Overall Survival of High-Risk Thyroid Cancer Patients

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Treatment Modality</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III and IV patients (n = 1165, n of events 190)</td>
<td>No RAI vs. RAI</td>
<td>1.36</td>
<td>1.11–1.64</td>
<td>0.0005</td>
</tr>
<tr>
<td>Stage III and IV patients with adequate data regarding TSH</td>
<td>No RAI vs. RAI</td>
<td>1.42</td>
<td>1.06–1.85</td>
<td>0.0003</td>
</tr>
<tr>
<td>values (n = 743, n of events = 90)</td>
<td>NI-high vs. low TSH</td>
<td>3.06</td>
<td>1.56–5.54</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

*Source: Unpublished data courtesy of Sherman, S.I. et al. Analysis methods are discussed in reference 82.
†Risk ratio > 1 indicates a survival benefit of NTT, RAI, or low TSH.
‡P value for model with multivariate analysis of combined therapies.

Abbreviations: CI, confidence interval; NTT, near total thyroidectomy; <NTT, surgery less than a total thyroidectomy; NI-high TSH, normal to high TSH value; RAI, radiolabeled iodine-131; TSH, thyroid stimulating hormone; low TSH, low to undetectable TSH value.
in patients with known disease but negative diagnostic scans.

**Side Effects of RAI Therapy**

When given in the higher doses typically used to treat metastatic disease, RAI therapy can be associated with significant side effects. Salivary gland damage occurs in a dose-dependent manner, and reported incidence rates vary widely from 5% to 86%. The parotid glands seem to suffer damage more frequently than the submandibular glands. Salivary gland dysfunction can manifest as sialadenitis, xerostomia, taste alterations, hypoguesia, sialolithiasis, dental caries, stomatitis, salivary gland or oral infections, facial nerve damage, and even salivary gland neoplasia. Although side effects such as xerostomia may be transient, they also may persist for longer periods, have delayed onset, or even be permanent. These events can profoundly decrease patient quality of life.

Amifostine has excellent performance in reducing the incidence of salivary gland dysfunction caused by RAI. The protective effect of amifostine seems to be selective for normal tissue and to be due to its ability to scavenge the free radicals responsible for radiation-induced cellular damage. Although amifostine does not seem to protect tumor tissue, the fact that no long-term follow-up data prove that it does not also reduce the efficacy of the RAI treatment is a major concern. Hydration, lemon candy, salivary gland massage, and good oral hygiene are generally advocated to aid in salivary gland protection. Although a recent study suggested that using lemon drops may actually increase salivary gland damage, this study is difficult to interpret because it was not randomized and may have used differential application of protective measures in the 2 study groups.

RAI not trapped within thyrocytes also exposes the hematopoietic, gastrointestinal, and urologic systems to beta radiation during its clearance from the body. Thus, other tissues also potentially damaged by RAI include bone marrow, breast, nasolacrimal apparatus, bladder, colon, ovaries, and gonads. Iodide is primarily cleared through the renal route. Patients with renal failure who require RAI therapy should be treated with lower RAI activities or undergo dosimetric studies to avoid excessive whole-body exposure. The risk of bone marrow depression and secondary malignancies of the hematopoietic system are generally associated with repeated or high-dose RAI therapy. One study of a database of 6841 patients with thyroid cancer showed an increased risk of 27% for developing a second primary malignancy. The risk for both solid tumors and leukemia increased with increasing cumulative activity of RAI administered. The possible association between RAI therapy and breast cancer remains controversial. Increased incidence of colon cancer and bladder cancer has been reported, although the absolute risk remains low. Furthermore, not all studies confirm these findings. Other side effects, such as epistaxis and nasolacrimal duct obstruction, are infrequent. Reproductive problems in patients of either gender are rare and usually transient. However, a small increase in the rate of miscarriage and premature menopause may occur. All of the risks outlined earlier must be considered in relationship to the potential benefits for each individual patient.

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Radioactive Iodine Treatment


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