

Management of Aggressive Thyroid Tumors

Of all thyroid tumors biopsied, about 97% have been reported as benign hyperplastic adenomas. When treated with I-131, the vast majority of hyperthyroid cats are cured, and resume good health with no further thyroid therapy.

However, this “97%” value may not entirely reflect what we’re seeing today. Most thyroid tumors aren’t biopsied, and they change character as they grow. Given that thyroid carcinomas in cats are relatively well differentiated, with low metastatic potential, and often respond well to I-131, it’s likely that malignancy isn’t always recognized since tissue from hyperthyroid cats is rarely submitted for histopathology.

For whatever reason, we’ve been seeing a surge of cats with more aggressive thyroid tumors over the last year or so. We see at least 6-8 cats every week with T4’s over 12 $\mu\text{g}/\text{dl}$, and 2-3 of these have T4’s of 25-45 $\mu\text{g}/\text{dl}$. I don’t think it’s a testing phenomenon as these cats have big tumors and exhibit clinical evidence of severe, long-term hyperthyroidism; they look as ill as their numbers are high. These are complex, often fragile, cases requiring more attendance, and yielding less predictable outcomes post I-131, than expected from more routine cases with milder hyperthyroidism.

With this in mind, we identify and loosely categorize cats with aggressive thyroid disease in order to help establish candidacy for I-131 and expectations for outcomes afterwards. We set up more proactive plans for travel, treatment, hospitalization and recovery from chronic thyroid disease.

Owners and primary veterinarians should be prepared to flex with each individual’s response to I-131, rather than assuming a complete cure after a single injection of I-131 with nothing further to do. As many as 10 % of the cases we treat, must be considered ‘works in progress.’ Even so, most recover well after I-131, with conscientious management of any other illnesses by the primary veterinarian and good communication with their client.

Shades of Gray

Every hyperthyroid cat has at least one, and 80% have bilateral, thyroid tumor(s), surrounded by normal tissue. The hyperactive thyroid tissue begins as a benign hyperplastic adenoma, which gradually becomes more aggressive and may eventually transform into an adenocarcinoma. In other

words, the pathology increases with time, and the pathogenesis of adenoma and carcinoma may be identical, one a darker shade of gray, rather than representing two separate disease processes. In addition, studies have shown that the prevalence of thyroid carcinomas in hyperthyroid cats receiving long-term methimazole treatment increases considerably over time, rising to approximately 20 % in cats treated over 4 years.

By the time the tumor(s) are about three years old, they’ve typically become much more aggressive. Hormone control with methimazole becomes erratic.

From a clinical standpoint, it may not matter much whether the tumor has been biopsied and proven to be malignant vs. a ‘benign’ adenoma. If either exhibits aggressive behavior, the tumor(s) must be eliminated and the side-effects of long-term thyroid hormone toxicity addressed.

Ideally, the hyperthyroidism should be in the earliest stages rather than allowing it to progress toward the aggressive state. Owners pursuing I-131 for cats with aggressive thyroid tumors often express regret that they didn’t know about or perceive the value of a permanent cure sooner. They’ve often treated their cat twice daily with methimazole for years, with repeated visits to their veterinarians for exams and lab work to monitor hormone control, only to ultimately lose regulation of growing tumors and need to resort to I-131 after all, against greater odds of complete recovery.

Aggressive Thyroid Tumor Behavior

Regardless of how they’re defined histopathologically, aggressive thyroid tumors share similar features:

They’re usually large, present more than 3 years (regardless of when hyperthyroidism was diagnosed), produce extremely high levels of thyroid hormones (5, 10, 20 times normal), and respond less and less to increasing doses of methimazole. Some cats show erratic responses to even minor methimazole dose adjustments.

If surgically explored, these tumors may be locally invasive or highly vascular. Some are cystic, others solid, and some may include more than one stage of pathology in the same thyroid lobe.

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Technetium scans reveal large, bright, and often irregular, areas of radionuclide uptake, and occasionally distant metastases.

Treatment Objectives

Aggressive thyroid tumors must be destroyed. Hormone production may have been controlled in early stages with methimazole, like tapping the brakes of a slow-moving train. However, once the hyperplastic tissue progresses into the more pathologic ‘run-away’ stages, the only solution is to blow the train off the tracks with radioiodine.

Killing the thyroid tumor(s) with I-131, and thereby eliminating the need for methimazole or y/d® diet, is considered treatment success.

Veterinarians should prepare owners for the fact that destruction of the tumor(s) does not mean that the patient will not require other care, e.g., providing hormone support in those unable to produce adequate amounts of thyroxine, or treating concurrent, non-thyroidal illnesses. Old cats often have multiple factors affecting their health that need ongoing management.

Outcomes Post I-131

Although the majority of cats with aggressive thyroid tumors do become euthyroid after one dose of I-131, this outcome isn’t the ‘slam-dunk’ cure seen in about 95% of routine cases. The larger and more aggressive, older tumors may be more ‘stubborn’, requiring more than one dose to obliterate all abnormal tissue. Conversely, a greater number will need l-thyroxine support indefinitely if the thyroid hormone drops and remains low after the abnormal tissue has been eliminated. The reasons vary, but have more to do with the nature of the thyroid cells than an “under” or “over” dose of I-131. Some explanations for differing outcomes follow.

Euthyroidism

As long as the tumor cells are ‘hyperactively’ producing thyroid hormones, they typically uptake iodine ‘greedily’, as it’s a necessary constituent of l-thyroxine. Therefore, most aggressive tumors are destroyed with a single dose of radioiodine.

Treatment “Failure” (Requiring Retreatment)

On the other hand, thyrocytes in tumors may have poor radioiodine uptake (RIU) ability. This is more likely in older, more aggressive tumors than it is in younger adenomas. We are not able to discern which cats will ‘fail’ to respond before we treat them. If the T4 doesn’t steadily fall to $\leq 2.5 \mu\text{g/dl}$

within weeks (or, rarely, months) after I-131, we will advise **retreatment** with a second, more assertive dose, which we’ve traditionally provided at no cost to the client. The exception would be for particularly ‘stubborn’ tumors, in which case we’ll recapture at least some of our cost for a very high dose of I-131, purchased from a nuclear pharmacist. We still ‘carry’ basic hospitalization costs associated with prolonged stays, but do charge for intensive care needed by some debilitated cats.

Iatrogenic Hypothyroidism

Cats with longstanding thyroid disease are more likely to become **hypothyroid** after the hyperactive tissue is destroyed. Normal thyroid tissue sometimes dies if it has been suppressed for a long time, in the presence of hyperactive tissue which has assumed almost all hormone production. This is referred to as ‘**disuse atrophy**’, and explains why some cats generate insufficient thyroxine after I-131.

Another cause of iatrogenic hypothyroidism (IH) is that the amount of radiation necessary to destroy the abnormal thyroid tissue might impact normal tissue to some degree as well, especially if some normal tissue is still taking up iodine for hormone production.

Lastly, some cats have concurrent illness, such as CKD, or inflammation, causing thyroid hormone suppression, a condition called ‘sick euthyroid syndrome.’

Regardless of etiology, if the thyroid hormone levels remain low after sufficient time for residual tissue to reactivate, l-thyroxine should be supplemented indefinitely. In humans, this is most often the case after I-131 therapy for Grave’s Disease or thyroid adenocarcinomas. Hormone support, although not always easy to administer to cats, is a small price to pay for elimination of the aggressive thyroid tumor(s) that would not only require lifelong treatment, but continue to grow and become more life-threatening.

Bad and Worse

I loosely categorize highly-productive thyroid tumors into two groups: ‘**semi-aggressive**’ and ‘**aggressive**’. This helps me establish an individual’s candidacy for I-131, more accurately predict outcomes, and define a course of action. Non-productive thyroid cancers in cats are rare, and don’t respond well, if at all, to I-131.

Note: These categories and percentages are approximations only, based upon my clinical impressions (of thousands of cases), and are not intended to be interpreted literally.

Cats with higher doses of radiation are required by the State of Washington to remain in the hospital longer than the average

2-3 days. We are not legally allowed to release patients from our facility until the radiation discharge rate of each falls below 2 mr/hr.

SEMI-AGGRESSIVE Thyroid Tumors:

T4's = 12 to 20-ish $\mu\text{g}/\text{dl}$

The majority may still be adenomas, but are starting to behave more aggressively. Normal hormone levels in those on methimazole may be more difficult to control.

Moderate dose of radioiodine: 3.75 to 6 mCi

Charge: \$0-300 more than base (\$1100) + \$95 exam

Estimated hospital stay: 3-6 days.

Potential Outcomes: about 80-90% are cured after one dose of I-131 with no further anti-thyroid therapy needed. With that said, about 10-20% of these need retreatment and/or thyroxine support for life.

AGGRESSIVE Thyroid Tumors:

T4's = 20-45+ $\mu\text{g}/\text{dl}$

These are very aggressive, often malignant (carcinomas), and may be 'stubborn' (poor RIU ability.) Disuse atrophy of normal thyroid tissue is more likely. We must assume thyrotoxic heart disease.

High dose of radioiodine: 6-15 mCi

Charge: \$550-750 + base cost (\$1100) + \$95 exam.

Estimated stay: 6-14 days.

Potential Outcomes:

Euthyroid: There is about a **70-80% chance** the hyperactive tissue will be obliterated and the T4 will return to normal after just one injection of I-131. The tumor(s) will generally shrink, but may remain palpable even after hyperactive tissue is destroyed. Cysts often remain, but don't need to be excised, or even drained, as long as they are not compressing vital structures in the neck. Some large, old masses gravitate into the thoracic cavity (prior to I-131), in which case we won't palpate them, but they'll still usually uptake the radioiodine and be obliterated.

Treatment Failure/Retreatment: There is roughly a **20-30% chance** that the hormones may remain above normal after one dose of I-131. 'Stubborn' tumors may require 2, or rarely 3, treatments over months to completely cure the thyroid disease. Occasionally surgical debulking of very large masses is necessary, in addition to I-131. I see only a case

among thousands that fails to respond to I-131 at all. These are typically huge, irregular carcinomas, which would need to be surgically removed to procure even a guarded prognosis.

Iatrogenic Hypothyroidism: 20-30% will need thyroid hormone support for life after obliteration of all diseased thyroid tissue. Disuse atrophy is common in these cats; normal tissue may be long dead.

Other Considerations

Cats with long-standing hyperthyroidism often have **thyrotoxic heart disease**.

Decompensation (congestive heart failure and/or thyroid storm) is more likely when they go off hormonal control via methimazole, and when they are stressed during travel, hospitalization, and/or are sick from other disease.

It's never a bad idea to **engage a cardiologist** who may perform (and properly interpret!) an echocardiogram in order to assess how much heart damage has occurred prior to the referral to us. Occasionally there's just too much 'burnt-out' cardiomyopathy to warrant going further. More often, a cardiologist will prescribe an informed course of therapy to reduce the risk of a cardiovascular event during this more difficult time, and will already be on board in case heart failure occurs while we're attempting to treat and stabilize these fragile cats.

Minimally, the blood pressure should be checked, and **hypertension** controlled with amlodipine or benazepril. I've seen a number of cats with acutely detached retinas upon arrival, especially after long trips, which sometimes include a flight.

If the HR is greater than 240-260 bpm, the primary veterinarian may consider a B-blocker (atenolol or propranolol) for **HR control**.

B-type natriuretic peptide (BNP) test: This hormone, produced by stressed heart muscle, is increased during CHF, so may be useful to help differentiate CHF-related signs, such as dyspnea, from other conditions.

Agitation and anxiety may escalate in traveling, hospitalized cats with high thyroid hormones off methimazole. I suggest starting alprazolam, 0.0625-0.125 mg (1/4-1/2 of a 0.25 mg tab), or gabapentin, 50-100 mg p.o., Q 12-24 hours, before travel, during hospitalization, and for the trip home.

Cachexia is extreme in most cats with severe thyroid disease. Proper diet is crucial for recovery. Carnivores are best fed meat-based, ideally plant-free, diets, which are usually canned, raw, wild (prey) or freeze-dried. Nausea should be controlled with Cerenia® (maropitant) and appetites stimulated, as needed,

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with Entyce® (capromorelin) or mirtazapine. Clients should be encouraged to feed their cats as much as they can possibly eat.

Occasionally, if the cat has had no adverse reactions to **methimazole**, we restart it 2-3 days after the I-131, and have the owners continue it 3 weeks post I-131 to help lessen weight loss and reduce the risk of CHF. If the cat hasn't ever had methimazole and/or the thyroid hormone isn't that high, I do not always suggest this; it's case-by-case.

If I've advised methimazole, the owners should discontinue it 1 week prior to the 1-month post I-131 recheck.

Naturally, if the cat has had toxic or allergic responses to methimazole, or I haven't specifically advised it, do not resume methimazole post-I-131. After the 1 month post-I-131 recheck, simply recheck the T4/chem screen every 2 months until the T4 plateaus. The majority of cats, even those with aggressive tumors, have T4's that normalize within the first month. On the other hand, I've seen an occasional cat take several months for the T4 to normalize. In early stages after resolution of the thyroid disease the T4 could even be subnormal until the normal residual thyroid tissue fully reactivates, if it is capable of doing so.

I will review lab work from each recheck and help fine-tune the treatment direction as needed. I also rely upon the owner's observations at home and the primary DVM's exam findings and clinical impressions to form my advice for each step in the recovery process.

Despite the more complex nature of treatment and management for cats with more significant thyroid disease, a cure with I-131 gives them the best medical chance, by far. More often than not, thyrotoxic hearts may repair with time, and these cats generally rebuild muscle mass and recover their health if they don't have too much other illness.

Dr. Dennis Wackerbarth Retires

After creating the Feline Hyperthyroid Treatment Center in 1992, and devoting many years to treating thousands of hyperthyroid cats, Dr. Dennis Wackerbarth has retired. He continues to travel internationally with his wife, Cheryl, and takes time to catch up with their sons, Joel and Jesse, both of whom are physicians for 'human animals.' I'm grateful to Dr. Wackerbarth for inviting me to join him in feline practice over thirty years ago. We've enjoyed a good work relationship, ripe with opportunities to learn, grow, and share our lives.

Thank you Dennis,

Faythe Vaughan, DVM

We're available for consultation any time – please contact us if you have any questions.

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