

Advances in Systemic Therapy of Differentiated Thyroid Cancer Across Lines of Therapy



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In this **CancerNetwork® OncView™** program, Lori Wirth, MD, discusses the unmet needs and ongoing trials in development for patients with radioiodine-refractory differentiated thyroid cancer.



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Lori Wirth, MD, associate professor of medicine at Harvard Medical School and medical director of the Center for Head and Neck Cancers at Massachusetts General Hospital in Boston, recently shared expert perspectives and updates in the treatment of second-line radioiodine-refractory differentiated thyroid cancers (DTCs) in an installment of the *OncView™* program, presented by CancerNetwork®.

Wirth began the discussion by describing the typical presentation and treatment of DTCs, explaining that although DTCs are often described in the singular form, they are in fact a “spectrum” of several different cancers.

“The most common is papillary thyroid cancer,” Wirth said. “We also see follicular thyroid cancers, Hurthle cell carcinomas, and poorly differentiated thyroid cancers that all fall under that DTC umbrella.”

These thyroid cancer subtypes, Wirth continued, are similar in that they all come from the follicular cells of the thyroid gland, but “they have different molecular drivers and different natural histories. So, when it’s convenient, we lump them together; when we need to get into specifics, we divvy them up.”

Often, patients with DTCs present with a mass on the thyroid gland. The mass may be found incidentally when the patient is undergoing imaging for an unrelated problem.

“Say somebody was in a car crash and has a neck CT, or [undergoes a] PET/CT

scan for another problem,” said Wirth. “Sometimes there will be a [fluorodeoxyglucose]-avid mass in the thyroid gland that leads to a diagnosis. That accounts for a fairly large number of differentiated thyroid cancers that we find.”

More often, however, a patient or their clinician will discover a lump on the neck.

“Generally, patients will then have an ultrasound, and if [we see] characteristics there that warrant a fine-needle aspiration, that’s typically the next step in the diagnostic workup of a thyroid mass,” described Wirth.

Prognosis and Treatment Selection

Most patients who present with DTCs have a good prognosis, according to Wirth. Usually, patients will begin treatment with surgery, although the surgical approach depends on the individual patient’s cancer type and on the extent of the disease.

“A patient who has a small 2-cm papillary thyroid cancer primary tumor, based on fine-needle aspiration and no suspicious lymph nodes in the neck, might be able to get away with just a hemithyroidectomy,” Wirth said. “But in general, most patients will have surgery first. And then if patients have, from a surgical point of view, intermediate- or high-risk disease, there’s a risk that the cancer could come back, either locally, regionally, or distantly.”

As such, after surgery, patients will typically receive a course of radioactive iodine.

The challenges of treating DTCs, Wirth said, include the possibility of overtreating relatively minor disease. A significant number of patients present with disease that is in such an early stage it does not need immediate treatment. This is particularly true in the case of patients who have thyroid nodules measuring less than 1.5 cm.

“Not all of those patients need to have surgery. By not overtreating patients with very early-stage disease that’s indolent, we can avoid complications from surgical management of these cases,” said Wirth.

What’s more, clinicians have learned that DTCs are frequently overtreated with radioactive iodine, so avoiding overtreatment of disease that has a good prognosis is key. However, maintaining a balance and recognizing when more intensive treatment is appropriate is also important.

“Another challenge is being able to recognize patients in their initial presentation of DTC who are at higher risk of having disease recurrence or developing distant metastatic disease in the future and making sure that their initial treatment strategies are optimized,” said Wirth. “The best surgery [should be] done from the get-go. They [should] get radioactive iodine when it’s indicated and have proper follow-up, given that they’re at higher risk for recurrence.”

Next, Wirth discussed frontline treatment options, as well as the process of defining radioiodine-refractory DTC. She said that according to the American Thyroid Association, the 4 main criteria that may be used are¹:

- The thyroid cancer tissue does not allow concentration of radioactive iodine after treatment or with a scan using radioactive iodine.
- Some areas take up the radioactive iodine, but others do not.
- Disease progression occurs within a relatively short time, such as 12 or 14 months, despite radioactive iodine concentration.
- Thyroid cancer remains after

receipt of larger and larger amounts of radioactive iodine after previous evidence of radioactive iodine-avid disease.

Regarding dosing strategies, Wirth said that “it’s generally accepted that around 600 mCi or 800 mCi of radioactive iodine is the maximum that, in general, most people should be getting.”

Thyroid cancers are associated with various clinical and molecular features that predict greater or lesser likelihood of radioiodine-refractory disease. One classic variant of papillary thyroid cancer is usually more sensitive to radioactive iodine, whereas some subtypes of papillary thyroid cancer, most commonly the tall-cell variant, are more aggressive and less likely to respond to radioactive iodine. The same is true for disease with *BRAFV600E* mutations, Hurthle cell carcinomas, and poorly differentiated thyroid carcinomas, according to Wirth. In general, *BRAFV600E* is “one of the most common molecular features” indicating insensitivity to radioiodine, “especially if it’s coexistent with another mutation in the TERT promoter,” she said.

In dealing with DTCs, Wirth said that clinicians must decide between active surveillance and immediate treatment. Taking immediate action in patients who show symptoms is a no-brainer, said Wirth.

“On the other end of the spectrum are patients with very low-volume disease, where they’re clearly asymptomatic and they won’t be symptomatic anytime soon,” Wirth continued. “Most of us, in general, take the approach that we should at least follow those patients by active surveillance or disease monitoring for some time to get a handle on the disease.”

The biggest challenge, noted Wirth, comes with making decisions about patients with moderate volume, slow-growing disease or lower-volume, rapidly growing disease.

“There aren’t numbers, necessarily, that we can pin on this, but that’s where I

think it’s challenging,” Wirth said.

Data from the SELECT trial (NCT01321554) do offer some insight. Among patients with radioiodine-refractory disease and lung metastases as small as 1 cm, patients assigned to lenvatinib (Lenvima) experienced an overall survival benefit compared with those in a placebo group, even though 90% of the placebo group eventually crossed over during the study after a median of 4 months (HR, 0.3; 95% CI, 0.47-0.85; *P* = .0025).²

Molecular diagnostics are important in symptomatic patients, Wirth said. Clinicians can identify patients with *RET* or *NTRK* fusions, biomarkers for which FDA-approved therapeutics are readily available.

If patients have neither an actionable alteration nor a *BRAFV600E* mutation, Wirth said she and her colleagues recommend multikinase inhibitors. “In general, we don’t use BRAF-directed therapy off label. For patients who don’t have a *RET* or *NTRK* fusion driving their thyroid cancer, I will start patients on lenvatinib,” she said.

Sorafenib (Nexavar) may be a better choice than lenvatinib for patients who are dealing with hypertension, because study results indicate that lenvatinib leads to more grade 3/4 hypertension. Wirth emphasized the importance of “prehabilitation”—making sure patients have well-controlled blood pressure.

“If we see hypertension emerging, in general, we start antihypertensive therapy earlier rather than waiting to see how bad it’s going to get,” Wirth said.

Other toxicities include diarrhea, fatigue, hand-foot syndrome, and mild transaminitis. Additionally, diarrhea and fatigue can cause weight loss and muscle loss, so Wirth recommends emphasizing exercise and a healthy diet to patients.

Second-Line Treatment Options

Wirth next pointed to data from the COSMIC-113 trial (NCT03690388), indicating that cabozantinib (Cabometyx) offers a survival benefit to patients who progressed

following treatment with multikinase inhibitors or other drugs.³ Cabozantinib is currently approved for second-line treatment in radioiodine-refractory disease, although it may come with toxicities similar to those of multikinase inhibitors as well as unusual toxicities, such as loss of pigment in skin and hair.⁴ On the other hand, sorafenib does not have the data to support its use as second-line therapy, Wirth said.

“Of course, if genotype-directed therapies are available, those need to be worked in appropriately as well,” added Wirth. “For example, if a patient had a multikinase inhibitor in the first line and they have a *RET* or *NTRK* fusion, I would certainly use one of the *NTRK*- or *RET*-directed therapies prior to cabozantinib.”

Other options may be on the horizon, Wirth continued. An international trial

is currently underway to assess the use of dabrafenib (Tafinlar) and trametinib (Mekinist) in *BRAF*-mutated, radioiodine-refractory DTC. Also, next-generation *RET* and *TRK* inhibitors are in development, and investigators are evaluating the wider use of active surveillance for early-stage thyroid cancers.

Unmet needs still exist, of course. For one, Wirth said, current treatment options do not cure DTCs and most patients still experience disease progression. There may also be hope in “redifferentiation,” or altering radioiodine-refractory thyroid cancer cells, to make them receptive to radioiodine. Finally, Wirth said that the mechanisms of resistance to VEGF inhibitors are still poorly understood.

It can be difficult for oncologists to treat very rare cancers, Wirth admitted,

but sharing knowledge is very important and benefits both patients and clinicians. “I really like the old-fashioned phone-a-friend approach,” Wirth concluded. ■

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