Finding a Way Forward in Parathyroid Carcinoma

By Joe Munch

Among the rarest of the rare malignancies, parathyroid carcinoma poses myriad diagnostic and treatment challenges. Owing to its extreme rarity, very little is known about the mechanisms driving parathyroid carcinoma, let alone how to target them; and survival rates have not budged in decades. However, researchers at The University of Texas MD Anderson Cancer Center are working to change this.

“This is an exciting time to be treating patients with this disease, because we are finally gaining the ability to combine an earlier diagnosis, more precise surgery, a better discernment of aggressive tumors, and the potential for targeted therapy,” said Nancy Perrier, M.D., a professor in the Department of Surgical Oncology and chief of the Section of Surgical Endocrinology. “Historically, parathyroid carcinoma was an unusual diagnosis with few therapeutic options other than the management of high serum calcium levels. But now we have something more to offer.”

Diagnosis difficulty

Parathyroid carcinoma occurs in approximately one out of every 2 million people; it has no predilection for men or women. Because parathyroid carcinoma can be clinically indistinguishable from benign causes of hyperparathyroidism, the cancer often remains unidentified until after it has metastasized and the opportunity to effectively treat it has passed.

“Some of these tumors are smoldering—they recur locally and persistently, and they do so over several decades. Others are very locally aggressive, and others metastasize,” Dr. Perrier said.

Parathyroid tumors account for most cases of primary hyperparathyroidism. Worldwide, 85%–95% of these cases are attributable to benign adenomas; fewer than 3% are attribut-
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able to parathyroid carcinomas. Unsurprisingly, primary hyperparathyroidism is the initial clinical presentation of parathyroid carcinoma, with symptoms of hypercalcemia predominating. These symptoms may include fatigue, weakness, confusion, bone pain, and pathologic fracture.

According to Dr. Perrier, any patient who presents with symptoms of hypercalcemia should be given a thorough diagnostic workup. Such a workup includes laboratory assessments of serum calcium and parathyroid hormone levels, neck ultrasonography to assess local disease, and both functional and anatomical imaging. In some cases, nuclear medicine imaging techniques such as sestamibi/single-photon emission computed tomography (CT) or positron emission tomography are used to assess the primary tumor and for systemic evaluation.

“Parathyroid cancer is very rare, and it’s hard to know what to look for,” said Naifa Busaidy, M.D., an associate professor in the Department of Endocrine Neoplasia and Hormonal Disorders. However, some signs should increase the index of suspicion for parathyroid carcinoma. The effects of hypercalcemia may be more pronounced in patients with parathyroid carcinoma than in those with benign disease and include serum calcium levels higher than 13 mg/dL or parathyroid hormone levels more than 2 times the upper limit of the normal range. Also, evidence of bone involvement (e.g., subperiosteal bone resorption, “salt and pepper” skull, or osteitis fibrosa cystica) is more common with carcinoma. A neck mass that is palpable (rare in cases of benign disease) or that on ultrasonography is cystic or larger than would be expected in the case of benign disease also should increase one’s suspicion of carcinoma.

However, there is no test or set of characteristics to definitively differentiate parathyroid carcinoma from benign disease preoperatively. The only definitive marker of parathyroid carcinoma, metastatic disease, is seldom seen at the initial presentation. And fine-needle aspiration is strongly discouraged because cytological features alone do not differentiate benign from malignant parathyroid cells.

Rather, the diagnosis is usually made intraoperatively, when the parathyroid surgeon finds that the mass is larger, firmer, grayer, and more attached to surrounding structures than would be expected in the case of benign disease. Pathological analysis of the surgical specimen is performed to identify architectural features of malignancy, especially invasion into adjacent tissues and vessels. However, parathyroid carcinoma does not have a specific set of markers to distinguish it from benign disease, and a tumor may have only one or two pathological features indicative of malignancy. Thus, many cases cannot be definitively classified as malignant and are considered parathyroid neoplasms of uncertain malignant potential.

According to Michelle Williams, M.D., an associate professor in the Department of Pathology, caution is used before making a diagnosis of parathyroid carcinoma to ensure that the sampled tissue isn’t a more common condition with atypical features, such as fibrosis from a previous procedure.

Cytology alone is insufficient to differentiate parathyroid carcinoma from benign disease. Unlike many other types of cancer cells, most parathyroid carcinoma cells show only subtle morphological changes compared with normal cells. “In some cancers, such as squamous carcinoma, the cells themselves look ugly,” Dr. Williams said. “But in parathyroid carcinoma, the cells more closely resemble normal cells, which is why it can be difficult to figure out what the biology is by cytology alone.”

Ancillary tests used to help strengthen the case for or against a diagnosis of parathyroid carcinoma include staining cells for parafibromin and Ki-67 expression. Compared with normal parathyroid cells, parathyroid carcinoma cells tend to have loss of parafibromin expression and higher levels of Ki-67 expression. Although neither test alone is conclusive, Dr. Williams said, “These tests help us characterize what the cells are doing in borderline cases.”

Assessing for mutations in CDC73 (formerly called HRPT2), the gene for parafibromin, also may be informative. Patients with mutations in this gene may have hereditary syndromes associated with parathyroid carcinoma. Used in combination with abnormal pathological findings, a positive result on genetic testing for CDC73 mutations would support a diagnosis of parathyroid carcinoma.

Few treatment options

Surgery is currently the only definitive treatment for parathyroid carcinoma. Performed early in the disease process, when the cancer is localized, en bloc resection to completely remove all tumor cells offers a chance at a cure. “Having a suspicion about the tumor preoperatively is important because it allows planning for the initial operation to be appropriate,” Dr. Perrier said. Whereas only about a third of the patients who are diagnosed before or during surgery—and thus undergo en bloc resection—have a recurrence, more than half of those who are diagnosed after surgery—who do not undergo en bloc resection—have a recurrence.

“Often, it’s only after the patient has a recurrence that carcinoma is diagnosed,” Dr. Perrier said. “At that point, local recurrence in proximity to vital structures often makes surgical treatment less effective, and essentially, we’ve missed our window of opportunity to provide localized tumor control.”

Prophylactic, large, lateral neck dissections are unnecessary, Dr. Perrier said, because parathyroid carcinoma doesn’t kill by multiple recurrences of nodal disease; rather, death is usually caused by the debilitating effects of severe hypercalcemia.

“The right thing to do is to remove the tumor in continuity with anything else it might be attached to, without disrupting the tumor capsule and leaving microscopic disease behind,” Dr. Perrier said. “What’s not needed is aggressive lymph node dissection and surrounding prophylactic surgery. That
doesn’t seem to affect survival.”

Fifty percent of parathyroid carcinoma patients have recurrent disease within 5 years after the initial oncological resection. While many recurrences are locoregional, 30%-40% involve distant metastases in the lung(s), liver, and/or bone(s), which require multiple surgeries to control the tumor burden. “Because of the high rate of recurrence, we know that surgery alone is not enough in every case. But we don’t have any adjuvant therapy to control the metastatic disease,” said Angelica Silva, M.D., a postdoctoral fellow in the Department of Surgical Oncology.

Cytotoxic chemotherapy regimens have no effect on parathyroid carcinoma, and the risks of postoperative radiation therapy often outweigh the treatment’s benefits.

“In the past, we thought that giving local radiation would help, but that comes with too many side effects,” Dr. Silva said, “and it does nothing for improving survival because it doesn’t influence metastatic disease.”

Because of the disease’s propensity to recur, parathyroid carcinoma patients must be monitored for life after their disease has been resected. The follow-up for patients with parathyroid carcinoma is the same as that for patients with hyperparathyroidism. Serum calcium and parathyroid hormone levels are assessed regularly; a sudden increase in either level would prompt additional investigation with imaging studies. However, there is no established algorithm for follow-up imaging, and whether one imaging modality is better than another for detecting recurrent local or distant metastatic disease is unknown. Typically, however, cervical ultrasonography is performed to assess for local recurrence; if no disease is found in the neck, then a CT study of the lungs, the most common site of metastasis, is performed. Abdominal imaging may be performed if the CT study reveals the lungs to be disease-free.

The main challenge in treating patients with unresectable or recurrent disease is managing their profound hypercalcemia. According to Dr. Perrier,
these patients’ hypercalcemia eventually manifests as fatigue, arthralgia, cloudy thinking, and changes in mood, memory, and concentration.

Bisphosphonates are given to protect bone against the risk of fracture, and calcimimetics are given to keep serum calcium levels down. However, Dr. Perrier said, these agents do not affect the parathyroid hormone level, and their effects are not durable.

Finding some answers

Investigating parathyroid carcinoma has not been easy. Studies of the disease have been largely limited to case reports, case series, and small, single-institution retrospective analyses.

MD Anderson sees about 12 parathyroid carcinoma patients per year—the largest experience in the country, if not the world, according to Dr. Perrier. Recognizing this, Dr. Silva, who was training in Chile at the time, reached out to Dr. Perrier in 2014 to explore the possibility of working together to find new and effective treatments for parathyroid carcinoma. In 2015, she completed her training and came to MD Anderson to focus solely on parathyroid carcinoma. Since her arrival, she has worked with Dr. Perrier and others to initiate programs aimed at better understanding and treating the disease.

International consortium

Dr. Silva has established an international consortium to facilitate the study of parathyroid carcinoma. In addition to MD Anderson and other U.S. institutions, the consortium includes groups based in the United Kingdom, Australia, Spain, and the Netherlands and continues to grow.

“It’s an uncommon disease, but it’s also potentially lethal. We need to find a specific treatment to control this disease, and a collaborative effort is needed,” Dr. Silva said.

The main objective of the consortium is to share knowledge and discoveries about the disease, along with cell and tumor samples. “Different groups have worked on this very rare disease, but we need to put together all the information,” Dr. Silva said. “This is the first time we’ve tried to create a big picture of the disease, from making the diagnosis to finding options for controlling it.”

Biomarker studies

One main component of MD Anderson’s push to understand more about parathyroid carcinoma is an institutional review of all parathyroid carcinomas. In 2015, she has worked with Dr. Perrier and others to initiate programs aimed at better understanding and treating the disease.

“Historically, parathyroid carcinoma was an unusual diagnosis with few therapeutic options… but now we have something more to offer.”

— Dr. Nancy Perrier

“and this will help us provide earlier, more effective treatment.”

Genomic profiling

Genomic profiling, too, plays an increasingly large role in determining how to best approach parathyroid carcinoma. At MD Anderson, all parathyroid cancers archived between 1986 and 2015 are being subjected to genomic profiling, which should identify genes the tumors commonly express and help reveal the pathways underlying the disease. Tissues are also being banked to look at additional genes and underlying changes that may point to causes of the disease or that can be used to help guide treatment.

“Currently, we don’t know what genes these tumors have in common,” Dr. Perrier said. “Once we have those data and can perform computational analysis, we can design a panel on a platform for genomic profiling and tailor treatment according to the results.”

Creating new therapies may not be necessary. “We already have targeted therapies, such as vaccines and antibodies, that were created for other kinds of tumors,” Dr. Silva said.

The whole-genome exon sequencing data should be available soon, Dr. Perrier said, meaning that before long her team may have something other than surgery to offer parathyroid carcinoma patients. In the meantime, patients may be eligible for clinical trials on the basis of their individual tumor’s characteristics (see “A Patient’s Perspective,” p. 3).

Immunogenic profiling

In a pilot program of immunogenic profiling that was recently initiated by Dr. Silva and her colleagues, 45 parathyroid tumors will be analyzed to investigate the differences in the tumor environment according to the presence or absence of tumor-infiltrating lymphocytes and programmed death ligand 1 expression on parathyroid tumors.

“We need to look at the tumor’s mutational status,” Dr. Busaidy said. “We’re also working with the immunotherapy group here and looking at tumors’ immune signatures to see if
they’re likely to respond to immunotherapy or if they need priming before they’ll respond. And we have a few patients with parathyroid carcinoma who have responded to antiangiogenic therapy, so that is something else we’re looking into.”

Moving forward

Adding to the improvements in parathyroid carcinoma treatment and research that may result from the initiatives at MD Anderson, the American Joint Committee on Cancer will soon offer staging guidelines for parathyroid carcinoma.

“The new staging guidelines mean that there will be a patient-based registry, and we will be able to accumulate information and develop survival curves to predict and better understand who we need to treat more aggressively and when,” Dr. Perrier said. “Up to now, we’ve only been able to attempt this at individual institutions because we haven’t had a collective effort of looking at clusters of tumors and because of their rarity.”

Despite the vast amount of work required to move forward in parathyroid carcinoma, the outlook is generally positive.

“It takes an effort to look at a rare disease like this to figure out how we can improve the diagnosis and treatment,” Dr. Williams said. “Working together, we can certainly make strides.”

Studies Explore Screening for HPV-Related Anal and Oropharyngeal Cancers

By Bryan Tutt

No consensus screening guidelines exist for human papillomavirus (HPV)–related cancers other than cervical cancer. As a step toward establishing such guidelines, studies under way or in the planning stages at The University of Texas MD Anderson Cancer Center will test various strategies for early detection of specific HPV-related cancers in populations believed to be at high risk.

Although HPV is known to cause oropharyngeal, penile, anal, cervical, vaginal, and vulvar cancers, only cervical cancer has established screening guidelines and a reliable test—the Pap test—that can detect early cancer or precancerous dysplasia.

“The Pap test can detect precancerous tissue and prevent cervical cancer,” said Erich Sturgis, M.D., M.P.H., a professor in the Department of Head and Neck Surgery and the Department of Epidemiology. “But we don’t have such a test for oropharyngeal or anal cancer.”

Dr. Sturgis and his colleagues hope to provide data for such tests in clinical trials that will screen people at high risk for HPV-related anal or oropharyngeal cancers. One such trial is currently enrolling women, and another will soon begin enrolling men.

Screening for anal cancers in women

Patients who have HPV-related cervical, vaginal, or vulvar carcinomas are believed to be at high risk for HPV-related anal carcinoma; however, the rates of anal cancers in these patients remain unclear. An ongoing clinical trial seeks to determine the prevalence of anal cancer in women who have cervical, vaginal, or vulvar cancer or dysplasia and compare methods of screening for HPV-related anal cancer and dysplasia.

The clinical trial, known as the Prevalence of Anal Dysplasia and Anal Cancer in Women with Cervical, Vaginal, and Vulvar Dysplasia and Cancer (PANDA) trial (No. 2014-0021), is now enrolling patients at MD Anderson, its regional care centers, and Lyndon B. Johnson Hospital in Houston.

Kathleen Schmeler, M.D., an associate professor in the Department of Gynecologic Oncology and Reproductive Medicine, and Craig Messick, M.D.,
an assistant professor in the Department of Surgical Oncology’s Section of Colon and Rectal Surgery, are the co–principal investigators of the PANDA trial. “Dr. Messick and I share several patients with both anal and cervical or vulvar cancer, and this made us realize that maybe we should be screening women with gynecological cancers for anal cancer,” Dr. Schmeler said. “That’s why we’re doing this study.”

Dr. Schmeler said that current anal cancer care, without standardized screening, is similar to the state of cervical cancer care before the advent of the Pap test. “Most of the time, people are diagnosed with anal cancer when it is symptomatic, after the cancer is advanced and has led to another problem,” she said. “That’s how cervical cancer used to be, but since the Pap test became standard, we’re finding cervical cancer in the preinvasive phase or at an early stage. We’d like to do the same thing with anal cancer.”

The PANDA trial eventually will enroll 500 patients. Eligible for the trial are women 18 years or older who have invasive squamous cell carcinoma or high-grade dysplasia of the cervix, vagina, or vulva. Excluded from the trial are women who are pregnant or have a history of dysplasia or invasive carcinoma of the anus or anal canal.

In addition to the standard tests related to their gynecological cancer or dysplasia, patients in the study undergo screening for anal cancer or dysplasia by an anal Pap test, anal HPV test, and high-resolution anoscopy. Patients with abnormal findings on any of these screening tests are referred to Dr. Messick’s group for further evaluation and care.

Besides showing the prevalence of HPV-related anal dysplasia and cancer in this high-risk population of women, data from the study will provide information about the sensitivity and specificity of anal Pap tests, anal HPV tests, and anoscopy. “We know there are women at high risk for anal cancer,” Dr. Schmeler said. “We want to find out how often and the most effective way to screen these women.”

### Screening for oropharyngeal cancers in men

As the PANDA trial seeks to provide data that could lead to routine screening guidelines for HPV-related anal cancers, Dr. Sturgis is helping organize a trial to provide similar data for HPV-related oropharyngeal cancers. Because both oropharyngeal HPV infections and HPV-related oropharyngeal cancers are more common in men than in women, Dr. Sturgis’s trial will enroll men only, specifically those in their 50s.

The trial will soon begin enrolling participants at several locations in the Houston area. Participants will fill out a questionnaire about tobacco and alcohol use as well as sexual behavior, and cell samples for HPV testing will be obtained from the throat with a “swish and spit” technique. Blood will also be drawn to test for antibodies to early (E) antigens of HPV type 16 in the serum.

“Our previous research showed a very strong link between antibodies to HPV-16 E6 and E7 antigens in the serum and oropharyngeal cancer,” Dr. Sturgis said. “We estimate that 1%–2% of the men in our trial will test positive for these antibodies.”

Men whose serological tests are positive for antibodies to HPV-16 E6 or E7 antigens will be sent to MD Anderson for further HPV and cancer screening, as will an equal number of men who test negative for the antibodies. Both groups will undergo standard clinical examinations of the throat, anus, and penis and standard ultrasound examination of the neck lymph nodes. The anal exams will include standard high-resolution anoscopy and a newer technique, high-resolution microendoscopy, as well as selective brushings to obtain cells for standard and novel HPV tests.

The main focus of the trial, however, will be oropharyngeal cancers. “We will use some experimental approaches to see if imaging can identify early oropharyngeal cancers before they are visible to the naked eye,” Dr. Sturgis said. One technique that may be used in the study, optical coherence tomography, is commonly used in ophthalmology but not to detect oropharyngeal cancers. Another, narrow band imaging, has been used with endoscopy to detect early gastric tumors.

The study will also involve taking cell samples from the tonsils and the base of the tongue to look for HPV that has been integrated into the human genome. Integrated HPV is typically the first step of tumorigenesis in HPV-related cancers. Although the U.S. HPV vaccination rate has improved, it lags behind the rates of many countries. The statistics above show the percentages of eligible females who have received the complete series of three vaccinations. The U.S. Centers for Disease Control and Prevention recommends HPV vaccination for both males and females 11–26 years old. Source: Institut Català d’Oncologia Information Centre on HPV and Cancer.
What You Should Know About Drug Advertisements

Prescription drug ads may not tell the whole story

If you watch television or read magazines, it’s likely that you have seen advertisements for prescription drugs. While these ads can help raise awareness about certain medical conditions, their contents should be taken with a grain of salt. When you see an ad for a prescription drug, here are some things to consider.

Limited regulation

The U.S. Food and Drug Administration (FDA) requires televised drug ads to include the following information:
- the drug’s brand name and generic name (for example, the drug with the brand name Lyrica has the generic name pregabalin),
- at least one FDA-approved use for the drug,
- the drug’s major risks and side effects, and
- detailed information about how the drug works (including drug interactions and less serious side effects) or at least two sources (such as a Web site or toll-free telephone number) where people can get such information.

However, the FDA’s power to regulate advertising is limited. Ads are not submitted to the FDA for approval before they are used. Instead, the FDA takes action after they learn that a prescription drug ad might be breaking the law—examples of this include stating that a drug can treat diseases that it is not approved to treat by the FDA and making claims about the drug’s effectiveness that are not supported by evidence. This means that the general public could see ads that violate the law before the FDA can remove the ads from circulation. That said, large-scale advertising campaigns are expensive, so it is unlikely that a drug company would intentionally release ads that do not follow the FDA’s regulations.

Besides requiring a drug company to remove ads that violate the law, the FDA may ask the company to publish a correction, or the FDA may take the company to court. These actions are taken if the misleading information could pose a risk to people’s health.

Side effects and risks

Federal law requires televised prescription drug ads to list the drug’s most severe risks, such as life-threatening drug interactions and allergic reactions, but televised ads do not have to list all the drug’s side effects. Print ads must list all known side effects and major drug interactions, but these lists can be confusing and hard to read. The lack of emphasis on side effects and interactions can lead consumers to believe that a drug is a good fit when it may not be.

Consumers should keep in mind that detailed information about a drug in a print ad is no substitute for a doctor’s advice. Things you may not even think about—such as grapefruit juice, herbal supplements, or nonprescription pain relievers—can interact with prescription medications. Your doctor can tell you if any medications you take or medical conditions you have might interact with or cause side effects from a particular drug.

Habit-forming drugs

Many prescription drugs, such as narcotic pain relievers and certain antidepressants, can be habit-forming. People who take these drugs may become dependent on them. This means that once they start taking a drug, it’s hard to stop. When they do stop, they’re likely to experience unpleasant withdrawal symptoms.

The ad for a habit-forming drug might not directly say that the drug is habit-forming. Instead, the ad may advise potential users of the drug that they should not stop taking it without talking to their doctor first. The ad may also warn patients with a history of substance abuse that they should not take the drug.

Costs and other concerns

Ads are not required to tell you how much a prescription drug costs or whether a generic equivalent (the same drug without the brand name) is available. Brand-name medications are typically more expensive than their generic equivalents, even though both versions contain the same ingredients and meet the FDA standards for safety and quality. In addition, newer brand-name drugs tend to be more expensive than older brand-name drugs.

Critics of prescription drug ads say the ads encourage patients to ask for expensive brand-name drugs when a less expensive option might work just as well. Many conditions can be treated with several different drugs, and your doctor may prescribe a different drug than the one you’ve seen advertised to treat your condition. It may be necessary to try more than one drug before finding a treatment that works for you. You should talk to your doctor about all your treatment options and go over their costs and benefits.

– E. Nielsen

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• Visit www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising

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Screening for HPV-Related Cancers

“The central question is, can we establish a screening mechanism for HPV-related oropharyngeal cancer?”

– Dr. Erich Sturgis

related cancer. Dr. Sturgis said, “This will be the first screening application of testing for integrated HPV.”

Participants will be followed up for 5 years. The head and neck examination and imaging studies will be repeated every 6 months, but the anal and penile tests will not be repeated.

The two goals of the trial are, first, to see whether serological HPV testing in a high-risk group is an effective screening tool and, second, to see which tests are most effective for detecting early HPV-related cancers. In the meantime, Dr. Sturgis urges physicians to encourage men in their 50s to participate in his trial.

Likewise, Dr. Schmeler said she hopes physicians will encourage their patients who have had one HPV-related gynecological cancer to consider participating in her clinical trial. “Since there are no guidelines for anal cancer screening, this study is a good option for physicians with patients who are at risk.”

Encouraging HPV testing

Other MD Anderson researchers are looking into the role of HPV testing in cancer screening and prevention. In one trial scheduled to begin enrolling patients this fall (No. 2015-0795, led by Jessica Hwang, M.D., an associate professor in the Department of General Internal Medicine), patients who have received allogeneic stem cell transplants will undergo HPV testing in the anatomic areas associated with HPV-related cancers. Studies have shown that such patients are at a high risk of HPV-related cancers.

Dr. Hwang’s study, together with the studies led by Drs. Sturgis and Schmeler and Messick, may provide data that will enable the early detection of HPV-related cancers. In the meantime, Dr. Sturgis urges physicians to encourage men in their 50s to participate in his trial.

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