When detected early, most cases of local cutaneous squamous cell carcinoma are easily treated and usually cured. But when they become more advanced, this second most common form of skin cancer can become dangerous. Our expert guide helps you navigate the next steps.
Imagine being a patient who has been through grueling treatments, including surgeries that are sometimes disfiguring, radiation or systemic therapies. You’re at a follow-up appointment, hopeful, when the doctor comes in, looks at you solemnly and says, “The cancer has recurred, and we’re almost out of options.” This scenario takes place too often and in many types of cancer — including some advanced cases of skin cancer. It happens less often than it used to, because of recent FDA approvals of new medications for melanoma and basal cell carcinoma (BCC). It still happens, however, in cases of advanced cutaneous squamous cell carcinoma (CSCC). As the medical community continues to advance its knowledge of how to fight cancer, the hope is that this could change.

IF YOU SPEND

the next hour reading this Journal, about 115 cases of cutaneous (which means “on the skin”) squamous cell carcinoma will be diagnosed in the U.S. That adds up to more than an estimated 1 million cases a year, in this country alone. (The Skin Cancer Foundation uses this statistic, based on a 2015 study in JAMA Dermatology.)

While fewer people develop cutaneous squamous cell carcinoma than basal cell carcinoma (BCC), the most common type of skin cancer, CSCC can be more dangerous. “While both types are sometimes lumped together as ‘nonmelanoma skin cancers,’ they are quite different in terms of risk,” says Michael R. Migden, MD, a Mohs surgeon, dermato-oncologist and associate professor in the Departments of Dermatology and Head and Neck Surgery at MD Anderson Cancer Center in Houston. “Cutaneous SCC has a higher potential than BCC to become locally advanced or metastatic.” In fact, based on studies showing that approximately 1.5 percent of patients with CSCC die of the disease, the Foundation estimates that as many as 15,000 people in the U.S. die from this cancer each year.

“It’s extremely important to raise more awareness about this,” says Nikhil I. Khushalani, MD, vice chair of the Department of Cutaneous Oncology at Moffitt Cancer Center in Tampa. “If you think of a pie chart, those deaths represent just a small portion of the pie, but it’s a very large pie.” While CSCC has a much lower mortality rate than melanoma, it may represent a higher total number.

While that may seem frightening, Dr. Khushalani says it’s also important to know that an estimated 95 percent of CSCCs are detected when they’re early stage or localized, which means they are typically located within the skin or the adjacent tissues below. “They are often curable with prompt treatment,” he says.

For the other approximately 5 percent, however, it gets more complicated. That’s an estimated 50,000 people in the U.S. each year who learn they have cutaneous squamous cell carcinoma that has advanced to a point that it may be very challenging to treat. This article is for them and their friends and families.
What exactly is cutaneous squamous cell carcinoma?
CSCC is an uncontrolled growth of abnormal cells arising from the squamous cells in the epidermis, the skin’s outermost layer. When these cells grow, they may appear as an elevated wart-like growth or scaly lesion, which might bleed. Sometimes the abnormal cells first form a type of precancer called an actinic keratosis, or AK. If left untreated, an AK can develop into a CSCC tumor.

Are there squamous cell cancers that aren’t on the skin?
Yes, squamous cells exist in many parts of the body, so there are other types of squamous cell carcinoma, says Dr. Migden. “The word ‘cutaneous’ means skin, and these cancers are different from squamous cell carcinomas you may have heard about in the mouth, throat, genitals or lungs, for example. Those may be linked to the human papillomavirus, smoking or other causes.” This article refers only to cutaneous squamous cell carcinoma.

What causes CSCC?
CSCC is primarily caused by cumulative, long-term exposure to ultraviolet (UV) light from the sun, which damages the DNA in skin cells. This damage causes mutations that can lead to cancer.
While people who have fair skin are more prone to CSCC, anyone who has had extensive sun exposure can develop the disease. In fact, CSCC is the most common skin cancer in African Americans. Indoor tanning, which also emits UV radiation, raises the risk. Those who have a UV-sensitive condition, such as xeroderma pigmentosum, are more vulnerable to CSCC. Having a suppressed immune system, including those who take medications after an organ transplant, dramatically increases the risk.

How is CSCC diagnosed?
When doctors suspect CSCC, they do a biopsy by removing a sample of the lesion and sending it to a lab for microscopic analysis. Since early detection is always best, it’s important to know your skin and what to look for, so you can play a key role. If something on your skin is new, changing or not healing over several weeks, show it to your doctor. The Skin Cancer Foundation recommends that all adults do monthly skin self-exams and schedule a full-body skin exam with a dermatologist annually, or more frequently if they have high risk factors, have had a previous skin cancer or have a spot that concerns them. Visit SkinCancer.org for photos and more information on prevention, early detection and treatment.

For many years, Mohs micrographic surgery has been the gold standard for treating many skin cancers. This technique used by Mohs surgeons examines 100 percent of the tissue margins, spares healthy tissue and leaves the smallest scar possible. In certain cases of advanced CSCC and other skin cancers, further surgery is no longer a treatment option. The American College of Mohs Surgery (ACMS) offers a rigorous fellowship to dermatology residents, now focusing on dermatologic oncology as well as surgery. “This recognizes the role of the surgical dermatologist in treating skin cancer throughout the disease spectrum,” says Dr. Migden.
WHEN CSCC BECOMES ADVANCED

“ADVANCED” is a broad term for CSCC that may have spread extensively or have resisted multiple treatments and recurred. Within that, there are two categories: locally advanced and metastatic. When CSCC progresses to either of these stages, your dermatologist or Mohs surgeon may recommend an evaluation by a multidisciplinary team. This team is made up of your original dermatologist or Mohs surgeon, plus additional physicians and surgeons from other specialties. This process helps to determine if and what further treatments might be warranted, or if the patient should be considered for a clinical trial, says Dr. Migden.

Locally Advanced CSCC

“_LOCALLY ADVANCED_” CSCC means the tumor at the primary site may be very large, or is burrowing down into nearby subcutaneous tissue, muscle or along nerves, making treatment more difficult, says Dr. Khushalani. There may also be situations where there would be significant morbidity or disfigurement from surgery, such as loss of most or all of a facial appendage such as the nose, the lips or an ear, eye or eyelid, or where there is no confidence in obtaining clear surgical margins. “Patients like these are not suitable candidates for surgery, which is why involving the multidisciplinary team is so critical,” adds Dr. Migden.

“Some patients may benefit from a combination of surgery, radiation, plus some form of systemic therapy,” says Dr. Khushalani. “Or in some cases, we may try to render the tumor smaller with pre-operative treatment and then take them to the operating room if they have had a good response.”

It is important to seek timely treatment to hopefully stop the cancer from spreading to other parts of the body and becoming metastatic. In some cases, though, surgery or radiation may no longer be a suitable treatment option. “The tumor may have recurred after surgery, sometimes after two or even three attempts,” says Dr. Migden. At this

CONSEQUENCES OF NEGLECT

CSCC can become advanced without any previous treatment. This may be due to neglect because someone is in denial about a lesion, is afraid of having surgery, doesn’t have access to care or can’t afford it, explains Dr. Migden. “I had a patient with a massive tumor who had lost his job. He was only a few years out from getting Medicare, so he decided to wait. But by the time he was eligible, the tumor was very advanced. He did not do well.”

Dr. Khushalani has observed similar problems. “Once a tumor starts developing and isn’t treated, it can grow and become disfiguring, so patients may stop going out and become isolated. Then they neglect themselves even further,” he says. This may be more common in people who don’t have health insurance. “I’ve seen patients who have not seen a physician for years, and they come in with very advanced disease. We often involve a social worker as part of the multidisciplinary team to help address these issues.”
stage, “all that scar tissue and inflammation may make it too difficult or impossible to define the margins for another surgery. It might need such massive surgery that it could cause loss of function in the area, would be extremely disfiguring or even life-threatening.”

Radiation, which may entail a six-week commitment, also has the potential for adverse side effects. “Some patients with advanced CSCC might have failed previous radiation, it may no longer be appropriate as a curative treatment or it may threaten loss of function, such as loss of vision,” Dr. Migden explains.

**Questions to ask your doctors:**
- Is radiation an option for me? If so, what should I expect, how many treatments are necessary and what are the side effects?
- Is surgery still an option, and if so, how can I minimize any potential dysfunction or disfigurement from it?
- What other treatment options can I consider? Is systemic therapy an option?
- Is there a clinical trial I might be eligible for?

### Metastatic CSCC

**CSCC HAS BECOME METASTATIC** when it has spread to other parts of the body, explains Dr. Khushalani. Radiation may still be an option, as well as systemic drugs, such as chemotherapy. “Now that the tumor cells have escaped from their original location and physically traveled, you want something systemic that can target all of these areas, including the microscopic metastasis that we cannot see on imaging.”

However, if the patient has already tried these treatments and they’ve failed, it may be time to consider participating in a clinical trial, says Dr. Migden. Your multidisciplinary team can evaluate what has been done so far, discuss potential treatments and come up with a plan.

Indeed, medical research is advancing in the cancer field with clinical trials investigating combinations of two or more treatments as well as newer approaches like immunotherapies, which harness your body’s immune system to fight cancer. If you have metastatic CSCC, it’s important to stay up to date on the latest developments, talk to your doctor and, above all, stay optimistic.

**Questions to ask your doctors:**
- What treatment options are viable at this point, and how do they work?
- What are the side effects of these treatments?
- What are the chances for success of each treatment option?
- Are there clinical studies that I might be eligible for?