(Scott noted that they didn’t invent these concepts. “These are all things that have been studied by different people over the last 30 or 40 years.”) According to Scott, developing a mathematical model will help define both the concentration of CTCs and their phenotypic distribution at any given point in the network, as well as organ-specific filtration values. “We recognize that each of these biological processes is probably disease- and even patient-specific,” he said. To parameterize this model, Scott said, researchers will need to characterize and count CTCs taken from one patient at different times and from different points in this network.

A complete understanding of the model will also yield information about the behavior of the system as a whole, Scott continued. Specifically, researchers will be able to calculate the average lifespan of a CTC in a patient’s circulation with minimal measurements. “Although this seems to be a simple calculation, the scientific literature on this topic is substantially conflicted, with reports of cells lasting on the order of years in some patients but less than 24 hours in others,” said Scott.

The researchers wrote that even this seemingly simple factor will differ between patients and cancer types and will lead to many questions:

- Could there be a “circulator” phenotype that avoids arrest with extreme efficiency that can explain long dormancy periods?
- Could this cell type be targeted?
- Could such a cell type be mechanically filtered out?

“This example,” they wrote, “represents one of the many new pieces of information that we are on the brink of understanding through mathematical models that could inform treatment decision-making paradigms.”

Am F. Chambers, Ph.D., Canada research chair and oncology professor at the University of Western Ontario, applauds their efforts to better understand metastases. However, she disputes some of their findings. “The authors propose that there may be a CTC ‘circulator’ phenotype that would enable CTCs to survive in the circulation for years,” said Chambers. “However, the available evidence suggests that an individual CTC’s half-life in the circulation is on the order of minutes to hours. There is no evidence that individual CTCs can survive for years in the circulation.”

Even so, Chambers said the authors have synthesized from the literature many key factors that deserve further study and measurement. “This is great, because we need physicists and other disciplines to think about this kind of stuff. Overall, I believe it will contribute to a better understanding of metastases.”

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Looking Treatment Complications in the Mouth

By Norra MacReady

Complications of the mouth occur in many cancer patients—often without warning—leaving a particularly sour taste in patients’ mouths.

Perhaps the disconnect exists because mountains of information are pushed on individuals who often are still reeling from the diagnosis, said radiation oncologist Mohan Suntha, M.D., professor of radiation oncology at the University of Maryland in Baltimore. “They’re told about the aggressive, multidisciplinary approach to their disease, and they’re told about the side effects, some of which can be dramatic. My best guess is that the dental issues are raised at that time, but when you add them to that laundry list, it’s easy to see how they drop to the bottom, given everything else the patient has to think about. So when they start to experience the dental complications, they say, ‘I was never told about this.’ That’s one reason why a dental evaluation is so important: It’s hard to ignore the issue when you’re actually being referred to the dentist.”

Oral side effects occur in virtually all patients receiving radiation for head and neck malignancies, in approximately 80% of hematopoietic stem cell transplant recipients, and in nearly 40% of chemotherapy patients. Effects range from mild and transient to severe and persistent, sometimes even permanent. “Almost every cancer therapy has associated oral complications, even if the cancer is distant from the mouth,” said Timothy Meiller, D.D.S., Ph.D., professor of oncology and diagnostic sciences at the University of Maryland and the Marlene and Stuart Greenebaum Cancer Center.

Effects to Watch For

Radiation brings the most substantial complications. A standard dose of head-and-neck radiation is 70 gray (Gy), but salivary glands may be damaged at doses as low as 26 Gy, Suntha explained. Saliva protects against oral infection and tooth decay, so the dry mouth (xerostomia) resulting from salivary gland damage increases risk of cavities and infection, including fungal infections such as candidiasis.

One of the most serious complications of head-and-neck radiation is osteoradionecrosis of the jaw, in which the bone loses its mucosal covering and deteriorates, said Cherry Estilo, D.M.D., of the Memorial Sloan–Kettering Cancer Center in New York. Symptoms include pain, swelling of the oral tissues, exposure of the bone, tooth
malocclusion, oral cutaneous fistulae, and trismus, or difficulty opening the mouth owing to soft tissue swelling or fibrosis. Mucositis, resulting from irradiation or ulceration of the oral mucosa, is another potential effect.

Along with their inherent discomfort, these conditions can complicate the management of any coexisting dental issues. “That’s why, if a patient is scheduled to undergo high-dose radiation therapy for head and neck cancer, it is imperative that [he or she] see a knowledgeable dentist to identify any potential sources of problems,” Estilo noted. “For example, if a patient has a loose or infected tooth or a lot of cavities, those teeth should be treated as soon as possible.”

The effects of these complications may extend far beyond the oral cavity. “Mucositis can impair a patient’s nutritional status and may be associated with weight loss,” said Mahnaz Fatahzadeh, B.Sc., D.M.D., M.S.D., Dip. A.B.O.M., associate professor of oral medicine in the Department of Diagnostic Sciences at New Jersey Dental School in Newark. In severe cases, “patients sometimes need a feeding tube while they are undergoing treatment because they cannot maintain adequate oral intake.”

Among patients with substantial preexisting dental problems, “If you don’t deal with those issues before they start treatment, imagine how hard it will be after radiation if they have difficulty opening their mouth. I had a patient who could open his mouth only 1 cm and had to be on a liquid diet. Management of severe postradiation trismus can be very challenging and at times possible only with surgical intervention. Prevention is key.”

Chemotherapy produces many of the same oral side effects as radiation, said Sol Silverman, D.D.S., professor of oral medicine at the University of California, San Francisco. “No matter what the tumor type, we may see dental issues,” such as mucositis and xerostomia. Bisphosphonates, prescribed to lower the risk of fractures associated with bone metastases of multiple myeloma as well as some forms of breast and prostate cancer, may also cause osteonecrosis. “The risk is low, but clinicians should alert patients to the possibility that they might have a problem so they can have a dental exam before starting treatment.”

Graft-versus-host disease, which sometimes occurs in patients who underwent bone marrow transplantation to treat certain hematological cancers, may also cause problems with salivation and mucositis, Fatahzadeh added.

Prophylaxis
Shielding vulnerable structures may spare patients from the worst side effects of radiation, Meiller said. Intensity-modulated radiation therapy, in which the dose of radiation varies during treatment, also protects healthy tissue. Several drugs are available that, if started early enough, may help maintain the quantity of salivary flow, but so far no way exists to prevent radiation-induced changes in salivary quality, or longer-term problems that may arise.

Similarly, Meiller noted that no way yet exists to prevent the mucositis or inflammation from chemotherapy. “We’re always trying to find therapies for mucositis:

“Dental professionals can get the mouth into optimal condition so we can minimize or prevent complications during treatment.”

It’s a hot topic of research,” he explained. Sucking on ice chips during a bolus administration of chemotherapy constricts the oral blood vessels and may keep the drug from accumulating in the oral mucosa. But it cannot prevent the drug from entering vessels of the gastrointestinal tract or other organs—so the protective effect, though real, is small.

Pretreatment Exam
Time permitting, a thorough dental examination and treatment of outstanding problems, including pulling teeth or filling cavities, is one of the most important prophylactic measures. “Dental professionals can get the mouth into optimal condition so we can minimize or prevent complications during treatment,” Silverman said. They try to determine whether tooth extraction is essential or, if the patient has periodontal disease, whether he or she needs deep scaling or aggressive hygiene before starting treatment, he pointed out.

Patients who require radiation often undergo fluoridation treatment beforehand, with the expectation that they continue throughout treatment and for the rest of their lives, Fatahzadeh said. She suggested that clinicians emphasize the importance of preemptive dental care by assessing what she called the patient’s “dental IQ”: the level of his or her understanding of dental issues, including the importance of oral hygiene to overall health. “You have to explain things at a level the patient understands and appreciates.”

Meiller urges dentists to become involved in a cancer patient’s care as soon as possible. “Getting any outstanding oral disease issues under control early on is essential,” he warned. After all, “healthy patients do better.”