

Early Oral Cancer Discovery: Technique or Technology? A Personal Opinion.

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Kelly was a 33-year-old mother of two daughters, college graduate, and stay-at-home mom. She exercised regularly, loved the outdoors, and never had an association with tobacco or alcohol in her lifetime. People commented on her radiant smile, and she was a regular at her dentist's office for cleanings and check ups. Tom—a 44-year-old father of a son just entering college—wanted to be a professional ball player when he was younger. His family called him a “gym rat” since he loved to work out, run in marathons, and compete in cycling events. He, too, was a regular at his dental office, though his hygienist said he took such good care of his mouth, there was little for her to do during his twice a year visits. He was a never smoker, and alcohol was also not a big part of his life. Both died within the last 18 months from oral cancer after difficult and extensive treatments were unable to stop the ravages of the disease. I came to know both of them as they entered the uncertain world of cancer patients and posted regularly on the Oral Cancer Foundation's survivor/patient web forum (www.oralcancer.org). Note that I did not use some euphemism for

death like passed away, etc. These deaths were drawn out, painful, and emotionally devastating for the patients and their families. They endured almost 2 years of radiation, chemotherapy, salvage surgery, open draining fistulas on their faces and necks, loss of speech and the ability to eat, as well as the emotional devastation and high levels of physical pain that accompanied the impending death. But of all the facts that I could speak to regarding these two extraordinary individuals, all the emotional points that I could make about their courage during their fight, the families they left behind, or the graphic description of their physical demise, the one aspect that bothers me the most—and which brings me the greatest sorrow—is that they were both initially diagnosed as late-stage cancers. In spite of their visits to members of both the medical and dental community on a regular basis, neither had even heard of oral cancer before their own diagnosis, nor been screened for it. Worse, their stories of late discovery and untimely death are hardly unique. The dental and medical communities are letting people like Kelly and Tom down every day.

Despite oral cancer following a series of well-defined cellular and visible tissue transformations and precancerous states, the easy access to the environment in which the disease occurs, and the ability to often identify these early manifestations or very early malignant disease states with the naked eye or via palpation of the tissues, approximately 70% of oral cancer is discovered as late stage 3 and 4 disease. These late stages are accompanied by dismal survival rates. Those who do survive suffer significant morbidity and permanent quality-of-life issues. This situation

has existed for many decades without improvement. The mortality rate of about 50% at 5 years postdiagnosis has also remained unchanged. It is a rate that exceeds that of cancers we hear much more about, even other squamous cell carcinomas (SCC) such as cervical cancer. This is not a surprise when you look at the SEER numbers, which reveal early staging to be the most predictive component of survival. However, that is dependent on early discovery, which is still not taking place. While many people are concerned with discovery and treatment of precursor conditions (as they should be), the SEER database reveals that significant survival advantages exist only if the actual cancerous disease state is found in early stages. This is particularly disturbing considering early SCCs, which make up about 85% of all oral cancers, are highly vulnerable to existing treatment modalities when found and addressed as early stage disease. Survival rates in the 80% to 90% range accompany early stage detection. While many discuss the value or importance of finding and treating precancerous conditions, we are not even finding early stage cancerous tissues with any regularity. The obstacles to progress remain the same: a lack of a national policy or standard of care from those institutions capable of establishing one; a professional dental and medical community which is not fully engaged or embracing the concept of opportunistic screening for oral cancer; and a general population that is largely unaware of its existence or the lifestyle risk factors that contribute to it, let alone the early warning signs that it is entering their lives.

THE CERVICAL CANCER EXPERIENCE AND ITS LESSON

In the late 1940s cervical cancer was a major killer of women in the United States, but a decade later the mortality rate from the disease had dropped by approximately 70%. This is probably one of the greatest success stories we can showcase in the world of cancer, and you would think that a breakthrough treatment was responsible. But there was no miracle drug or treatment. This precipitous drop came from something as simple as opportunistic screening. The adoption of a standardized examination by the medical community, an effort by public

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health services and medical professionals to educate the at-risk population and provide the examination, and the compliance of patients to engage in an annual screening brought cervical cancer's mortality rate down to a number that is significantly lower than that of oral cancer today. Lest anyone doubt what was responsible for this change, they need only look at developing nations around the world today where opportunistic screenings for cervical cancer are not a matter of routine, and see that cervical cancer still ranks as a high mortality rate disease in those locations. Given this successful and cost effective model for reducing the death rate, one has to wonder why we have not learned from it in the world of oral cancer. A cervical examination mirrors the oral cancer examination in many respects. It is visual, tactile, and brush cytology or other biopsies are used to collect samples of suspect tissues for examination. The same precancerous tissue changes occur, and the trained eye of the examiner when looking for leukoplakias and other precursors has been the tool of success. By finding cervical precancers and early stage disease, SCC of the cervix is no longer high on the list of killers in the United States. While I use cervical cancer as the model for this discussion because it is also a SCC, it doesn't matter which cancer you select when discussing reductions in mortality rates. In those cancers where we have made the greatest progress in fatality reduction, you will always find public awareness and early detection to be the primary causes of benefit. Colon, prostate, cervical, skin, and breast cancers all have demonstrable cause and effect relationships of this nature. The equation which matches a biological location that lends itself to early discovery, early stage detection of the disease, and vulnerability of that disease to existing treatment modalities has been our most successful formula. Oral cancer meets all these criteria. Given this, it is obvious that we could and should be doing more.

A CHANGING DEMOGRAPHIC AND ITS IMPLICATIONS

Historically, the dental and medical community has looked at a stereotypical "high risk" patient population when considering who should be screened for oral cancer.

The fastest growing segment of the oral cancer population is people between 20 and 50 years old who are non-smokers. This simply means that previous assumptions about whom we are to screen are no longer valid.

We have all been taught that this population is over 50 years old, predominantly male, twice as many African Americans than whites, smokers, and heavy alcohol users. While I am known to berate the dental community for lack of involvement, in their defense, they only see about 60% of the population each year. However, there is no evidence that the remaining 40% bear the load of the nearly 31,000 cases diagnosed in the United States in 2006. Clearly there are economic, social, and geographic barriers causing disparities in health care that affect portions of our population. But focus groups and surveys conducted by the Oral Cancer Foundation lead us to believe that infrequent opportunistic screenings of existing patient populations is a main contributing factor to the lack of early discovery. This is compounded by a lack of knowledge of trends in populations at risk, and a belief by many dental professionals that oral cancer is a rare disease, in spite of the fact that it takes a life in the United States every hour of the day, 365 days a year.

Consider the primary causative agent for oral cancer—tobacco. Numerous groups ranging from the US Department of Agriculture to the American Lung Association have reported that the use of tobacco in most of its forms has seen a steady decline in the United States for the last decade. This is not to infer that anyone doubts that it is still a significant cause of health issues and death, but the number of users in the United States has seen progressive decline. Alcohol use as another major risk factor for oral cancers has remained relatively constant during the same decade. Considering that the incidence rate of oral cancers during

that same time period has remained constant, and even slightly increased in 2006, something has changed. You cannot have a decline of the primary cause and an increase (or maintenance of the number) in the incidence rate without a replacement etiology. Given this basic premise, what does this say about the high-risk population for oral cancer? It means that while the historic group continues to be at high risk, a new sub-population that is at high risk has entered the equation in a significant way. This begs the question; can we easily identify them and clearly state today who is at high risk?

HUMAN PAPILOMA VIRUS AND ORAL CANCER

In the last few years, published studies out of Johns Hopkins and other reputable institutions around the world have clearly shown the relationship between several oncogenic forms of the human papilloma virus (HPV) such as HPV 16 and oral and oropharyngeal cancers. The transference of this virus between individuals through sexual contact has also been clearly demonstrated. While there are over 100 variations of HPV, perhaps a dozen or so have shown this oncogenic capability. Given HPV 16's well-defined ties to another SCC (cervical cancer) and the ease of its transfer through sexual contact, we likely have our primary replacement etiology. HPV oncogenes expressed in either squamous cells of the cervix or the oral environment are involved in the cells' transformation and immortalization. They are causes for the progression towards malignancy when other common risk factors are eliminated. Epidemiological studies have underlined

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that HPVs are the primary etiological factor for cervical cancer. While the demonstration of HPV as a causative agent in oral cancer is no longer in question, it may have further involvement in the transformation to malignancy initiated through other etiologies, as found in tumors that are primarily of tobacco use origin. HPV is at minimum a co-factor and a facilitator. While we do not know how many individuals will contract the oncogenic forms of HPV in their lifetimes, the American Social Health Association estimates that over 75% of sexually active people will be infected with HPVs at some point in their lifetime, as it is the most common sexually transferred disease in the United States. As of now, over 20 million Americans are carriers of the virus, with 6.2 million new carriers being added per year, mainly in the group between 15 and 24 years old. Given this data, it is necessary to include the consideration of HPV when we discuss screening the high-risk population for oral cancer. The fastest growing segment of the oral cancer population is people between 20 and 50 years old who are non-smokers. They fall out of the typical stereotypes in many ways, including race, age, and gender, as well as economic and education backgrounds. This simply means that previous assumptions about whom we are to screen are no longer valid. In my opinion, anyone old enough to have had sexual activity or who has engaged in the use of tobacco needs to be examined opportunistically on an annual basis.

THE IMPACT OF TECHNOLOGY

Recent progress in the world of technology and the introduction of it into the dental marketplace has enhanced the early

detection of suspect tissues in the oral environment. While we are still at the very beginning of the learning curve of interpretation by generalists in dentistry and medicine, technologies based on cellular reflectance and fluorescence are aiding involved individuals in the visualization of some of the less obvious early manifestations of both precancerous and early malignant disease states. Work is currently moving rapidly on vital stains and lights which reveal tissue states of importance. For instance, visualization of high-risk cellular transformations such as the loss of heterozygosity, when combined with other factors, can be predictive in nature and are near our understanding and ability to utilize. We are entering a genomic era that will yield strategies for determining which early disease states will actually progress to cancer and produce technologies that will target change in these cells to prevent that transformation. Clearly the most recent work elucidating the use of adjunctive devices to define dysplasia or disease outside the bounds of what was previously considered an adequate surgical margin has profound ramifications.

It is an exciting time for science and oral cancers. But any of these devices as a stand-alone technology is useless. In the end, it is the non-complacent practitioner who is involved in routinely examining all of their patient population, educated in what they are looking at, using their own eyes and incorporating a tactile component to the exam, that will make the difference. Adjunctive devices are just that, and not the primary mechanism at this time for identifying suspect tissues. Currently, not enough of the medical and dental communities are engaged in the screening process at the most basic

level. These devices will not realize their promise and potential if we cannot involve individuals in the entire screening process. I hope that I have clearly made the point that none of these tools would have saved the lives of Kelly, Tom, or thousands of other patients who were initially diagnosed with late-stage disease. It is not about technology or tools; it is about informed involvement in the process. While I herald the introduction of the many adjunctive devices, we must do more at the most basic levels.

Separate from engagement in the discovery process itself, there needs to be consensus and standards for conduct as it relates to custody of the patient once suspect tissue is discovered. Timelines must be determined when definitive diagnosis must be obtained vs continued observation, referral for second opinions solicited, and what warrants the current gold standard biopsy and when. Delay is deadly. I take particular exception to professionals who wish to place the responsibility of late diagnosis on the patients themselves, who present when a lump in their neck appears, or when a lesion of significant size in their mouth becomes apparent to them. This premise negates the value of the opportunistic screening process. As a late stage 4 cancer patient who was dentally aware and regularly seeing dental professionals, I had no discomfort and was not aware of any symptoms until that cervical node presented painlessly. One of the real dangers from this disease is that in its early, highly survivable stages it is rarely painful and only through an opportunistic discovery during a regular oral examination would it be found.

Despite the potential of adjunctive devices and the science they represent, the most important contribution made by industry may be the most basic: money. The marketing dollars spent by their manufacturers has begun to create professional awareness—even desire—to be involved in the screening process. And while some claim that the professional's conversion to the screening process is motivated as much by the creation of a new profit center as providing the best service to the patient populations, it matters not to me, as the end result will hopefully be the same. More patients will obtain screenings, more disease will be found at early stages, and more lives will be saved.