Radiation Therapy in Patients with Collagen Vascular Disease (Scleroderma, Lupus, and others)

When patients first meet with a radiation oncologist, their physician may be interested in knowing about any history of collagen vascular disease. For patients with collagen vascular disease, the concern among physicians is that radiation therapy may cause a worsening of symptoms and potentially lead to unusually severe side effects in the long term (months to years) following radiation therapy.

Collagen vascular disease includes a wide spectrum of medical diagnoses, including scleroderma, systemic lupus erythematosus (“lupus”), rheumatoid arthritis, dermatomyositis, Sjogren syndrome, and mixed connective tissue disorder, among others. The uniting and underlying theme among all of these diagnoses is abnormal regulation of the immune system, such that one’s immune system mistakenly mounts an attack on a healthy part of the body. This abnormal immune system attack of one’s self is referred to as an “autoimmune” process. It is the specific area(s) of the body involved and some specific variations in the biologic pathways involved (identified with laboratory blood testing) which help associate a specific set of symptoms with one of the above specific diagnoses. Typically, in all of these disease processes, one of the targets of the immune system is collagen – which serves as the cellular foundation for many organs, as well aspects of blood vessels, thus the term collagen vascular disease.

Let’s digress to some medical jargon decoding, which will also help explain interplay of radiation therapy with the collagen vascular disease process. First, terms with the suffix “-itis” indicate inflammation – associated with swelling, congestion, irritation, pain, and redness. Arthritis is inflammation of the joints. Dermatomyositis is inflammation skin (dermo-) and muscles (myo-). We are all familiar with these symptoms, having experienced them in at least a minor degree with the common cold’s inflammation of the upper respiratory tract, or the sensation of pain and swelling of the bone and muscles when one bangs their knee or bumps their head. Second, the terms sclero- and fibro- indicate scarring and hardening of tissues and organs (remember that the skin is an organ too). Similarly, we have all experienced scarring to a minor degree – think of a blister on your hand or foot that slowly evolves to a callus: it is tough, dense, and stiff – very different from the supple, flexible, and soft skin that preceded the skin blister. Inflammation typically precedes scarring (like the blister preceding the callus).

All of the collagen vascular diseases have abnormal activation of the immune system, so that they cause inflammation and scarring in varying degrees. In some of the collagen vascular diseases, the inflammation is more of the problem. In other diseases, the inflammation smolders more so than flames, and the resultant scarring accumulates, predominates, and causes symptoms.

By name, it is often not obvious which of the collagen vascular diseases affects which parts of the body. As is typically the case in medicine, these medical conditions may carry the names of the first person to describe them in the medical literature – or reference their initial clinical impressions of the disease. For example, while it may be clear that rheumatoid arthritis
involves the joints (as we are all quite familiar with the term arthritis), one would likely never
guess that Sjogren syndrome involves dryness of the eyes and mouth as a result of abnormal
immune attack of the tear and salivary glands, as it is named for Henrik Sjogren, an eye
physician who described the disease in the last century. Further, systemic lupus erythematosisis
was named in part for a characteristic rash which may be present over the nose and cheek
region in a similar distribution to that of the coloring of a wolf’s face (hence, *lupus*, latin for
wolf). Interestingly, however, the abnormal inflammation associated with lupus can affect ANY
part of the body. Wikipedia and other online resources do a good job in describing generally
the features of most of the connective tissue disorders.

Interestingly, the human body’s normal tissues and organs respond to radiation therapy with a
process of early inflammation (during radiation therapy and for weeks afterwards) and later,
potentially scarring (or “fibrosis”), months to years after radiation therapy. The degree of
potential scarring long term is related to the dose of radiation, the amount of an organ or tissue
in the treatment region, and the radiation technique. Particularly with modern radiation therapy
techniques, late scarring and fibrosis can be minimized.

You have likely now deduced why the radiation oncologist is interested to know whether a
patient has been diagnosed with a collagen vascular disease: the concern is that the
inflammation caused by the radiation may overlap with and be magnified by the already
heightened inflammation present in the body related to the collagen vascular disease, and as a
result, that short term inflammation and long term scarring may be much worse than typically
expected if the patient’s immune system is already triggering too much inflammation and
scarring on its own.

Which patients with collagen vascular disease are at heightened risk with radiation therapy has
been recently well reviewed by Dr. Jennifer Wo and Dr. Alphonse Taghian of the
Massachusetts General Hospital in a pivotal article (IJORBP, 2007). They chronicle early case
reports from the 1980s in which patients with variants of scleroderma and lupus were reported
to have severe side effects following treatment with radiation therapy, including nerve, skin,
muscle, bone and lung damage. These reports were taken very seriously by the medical
community, leading to a 1992 American College of Radiology treatment guideline stating that
“history of collagen vascular diseases is a relative contraindication to breast conservation
treatment because published reports indicated that such patients tolerate irradiation poorly.”

During the 1990s and through 2010, multiple additional reports have been published examining
the effect of radiation therapy among patients with rheumatoid arthritis, lupus, scleroderma,
polymyositis, dermatomyositis, and to a lesser extent other collagen vascular diseases. Some
articles reported similar concerning outcome for collagen vascular disease patients as those of
the prior decade. A number of these reports matched the collagen vascular disease patients to
patients without collagen vascular disease, but otherwise similar cancers and similar courses
of radiotherapy. The results of these studies were mixed, though surprisingly, short term and
long term side effects were generally less than expected. Patients with collagen vascular
disease had moderately elevated risks of short term and long term complications, and only in
one study did the increased late toxicities meet statistical significance. In the largest
retrospective study during this period, patients with rheumatoid arthritis did not appear to have
increased risk of long term complications. Across multiple studies, it seemed as though patients with scleroderma had the worst outcome and most significantly different outcome, though it is difficult to fully assess the data, given that very limited numbers of scleroderma patients were included in these studies (which does make sense, as many patients with the disease were no longer treated based on earlier case reports).

In the U.S., further current reports on radiation therapy in patients with scleroderma and lupus have been published by the radiation oncology group at the Mayo clinic. For both groups of patients serious long term side effects were present in approximately one-third of patients with these collagen vascular diseases.

The biological basis for the increased side effects seen in collagen vascular disease patients treated with radiation therapy is not clear. Many postulate on the themes of vascular injury and triggers of abnormal collagen production in the body, but the exact molecular pathways which lead to an exacerbation of side effects are not well known. One common pathway shared between radiation reaction and collagen vascular disease, in particular, in patients with scleroderma, is high levels of a molecule known as transforming growth factor beta – which is strongly associated with increased rates of fibrosis.

Overall, the literature to date indicates that patients with collagen vascular disease are at higher risk for short term and long term side effects associated with radiation therapy. Patients with scleroderma appear to be at the highest risk, although increased side effects with lupus and other diseases have been documented as well. The rates of increased complications among patients with rheumatoid arthritis seem to be lowest – generally near that for the general population. Fortunately, in the larger reported series of patients, it appears that the most serious side effects occur in a minority of patients with active collagen vascular disease, and not in the majority of these patients.

Important for the collagen vascular disease patient and their physicians is careful consideration of the risks and benefits of radiotherapy, given the particular cancer scenario for an individual patient. Indeed, radiation therapy may carry higher risks for certain patients with collagen vascular disease, but for many patients, it may still be the best treatment option if they have a cancer that is very difficult to treat otherwise. Fortunately, too, radiotherapy techniques have dramatically changed for the better over the last four decades. In the modern era, radiation oncologists are able to minimize radiation dose to normal, healthy tissues: that was not often possible for patients treated decades ago, and is of particular benefit for collagen vascular disease patients with increased susceptibility to side effects of radiation treatment.