Secondary Malignancies after Radiation Therapy

A rare but serious potential side effect of radiation therapy is induction of a secondary malignancy – that is, creation of a new cancer resulting from cancer treatment. Many patients that have experienced cancer are already at higher risk for developing a second cancer in greatest part due to genetics and carcinogenic exposures (for example, smoking). However the term “secondary” implies that a new cancer arising after treatment of a first cancer was triggered by the initial therapy. The most common type of cancer caused by radiation is a sarcoma, which is typically a cancer of muscle, bone, or blood vessel origin.

Descriptions of second cancers date far back in the medical literature. Dr. Cahan and colleagues reported their clinical observation of “Sarcoma Arising in Irradiated Bone” in 1948, and articulated the following three criteria characteristic of cancers caused by radiation therapy: 1) histologic features of first cancer and secondary cancer are different, 2) secondary cancer is within the area previously treated with radiation, and 3) the secondary cancer has a latency period of 5 years – that is, the secondary cancer develops five years or later after the first. These criteria are not set in stone, but stand as a good general reference when trying to deduce whether a cancer was likely secondary to radiation.

Secondary cancers are caused by injury to the DNA of irradiated cells in such a way that genetic programming is altered to favor abnormal cellular growth and proliferation. In general it takes many years for secondary cancers to develop. Many factors contribute to the risk for radiation carcinogenesis – some are specific to the patient and some are specific to radiotherapy treatment. Patients that are younger and smokers tend to be at higher risk for secondary cancers. Three important contributing factors specific to radiation therapy include the total radiation dose, the volume of irradiated tissue, and the type of tissue irradiated.

With regard to radiation dose, the probability of carcinogenesis increases with increasing radiation dose within a certain range, however the severity of the induced malignancy is not influenced by dose – known as a stochastic phenomenon. At very high dose, stereotactic radiosurgery data supports that there may be a lower risk for induction of a secondary malignancy, because of a very high probability of complete cellular kill in the high dose radiation field – that is, no damaged cells with a potential for malignant transformation survive, and fewer cells are exposed to an intermediate dose exposure. A completely safe minimum dose threshold, below which there is zero risk for radiation carcinogenesis does not appear to exist. However, at some threshold as described in the last commentary entitled “Radiation 101 – Background,” the risk of developing a cancer from radiation drops to the very low risk associated with the level of natural background radiation to which we are exposed every day. Thus we generally consider a safe level of radiation to be on the order of a few multiples of background radiation dose.

The overall risk for developing a radiation related malignancy has historically been best described among breast cancer patients. As noted above, it often takes many years for development of secondary malignancies – breast cancer is a disease in which many patients undergo treatment with radiation, and fortunately, most breast cancer patients are cured of
their disease and live for many years after treatment. It is late during this survivorship that a small fraction of patients may develop a secondary malignancy – because the risk is so small, thousands of patients must be studied in order to detect any increase in risk.

After radiation therapy for breast cancer, the risk of sarcoma, lung cancer, and other breast cancers have been described in the medical literature. From France, we have reports on thousands of women treated with radiation therapy for breast cancer over the last few decades. The French have reported a risk of developing sarcoma in the range from 0.28% to 0.48%. With regard to lung cancer, data from the United States and Sweden indicates that patients treated before the mid 1980's were noted to have approximately a 0.5% increase in the risk of developing lung cancer – almost all secondary lung cancers appear to be in smokers. However, among patients treated in the last 30 years, this increased risk of lung cancer has disappeared. With regard to whether women are at increased risk for secondary breast cancers, data is too conflicting to draw firm conclusions. It appears that with older techniques, younger women may have been at a slightly elevated risk of developing a second breast cancer.

Considering secondary malignancy risks across all cancer sites, a recent review in the journal Lancet Oncology examines the secondary malignancy risk among 647,672 patients age 20 and older with cancers originating at 15 anatomic sites throughout the body. Both patients treated without and with radiation therapy were included in the analysis. Among all patients, 60,271 (9%) developed a second solid cancer, of which 3,266 were estimated to be related to radiotherapy, corresponding to a risk of five excess cancers per 1,000 patients treated with radiotherapy at 15 years after diagnosis. The authors appropriately concluded that a relatively small proportion of second cancers are related to radiotherapy in adults, suggesting that most are due to other factors such as lifestyle, carcinogenic exposures, and genetics. Highlighting the differences in risk across cancer sites, only 4% of second cancers originating in or around the eye were related to radiation therapy, yet 24% of second cancers following treatment of primary testicular cancer in men were related to radiation therapy. Of note, it is relatively uncommon nowadays to undergo radiation therapy for testicular cancer – surgery and chemotherapy are the most common forms of current treatment.

Generally, the risk of developing a radiation induced malignancy after treatment of cancer is very small, though certainly a scary thought. Remarkably though, radiotherapy related cancers account for a small minority of second cancers which develop in patients after treatment for a first cancer. In the Lancet study above, nearly 10% of cancer patients developed second cancers, but only 0.5% of patients developed cancers which seemed likely to be radiotherapy related. In discussion with cancer patients, radiation oncologists strive to balance the often highly effective cancer controlling benefit of radiation with the risk of secondary malignancy, as well as other possible side effects of treatment. Thankfully, with modern radiation techniques, the risk of causing a secondary malignancy is less than that demonstrated in historical studies, due to higher precision radiation targeting.