“FRACTIONATED” Radiation Therapy: Why Weeks of Treatment?

For many patients, it comes as a surprise when their radiation oncologist explains a recommendation for a five to seven week course of radiation therapy with daily treatments on a Monday through Friday schedule. The rationale for splitting a prescribed radiation dose into sometimes upwards of 35 or 40 treatments is two-fold: to maximize the good effect of radiation (killing cancer cells), and to minimize any negative effect of radiation (scarring of neighboring normal healthy tissues).

An oversimplified analogy which illustrates the concept in everyday terms is a February trip by a fair skinned Pacific Northwesterner to Hawaii. That fair skinned man or woman has been indoors much of the winter, without much sun exposure due to cloudy skies and rainy days. Picture what would happen if that individual arrived in Maui, headed straight for the beach, and spent the entire first ten hour day snorkeling and surfing in nothing except a bathing suit. How would that person look the next day? Exactly right… sunburned!

In contrast, consider if that same individual had taken the approach of limiting their snorkeling and surfing sun exposure to 30 minutes per day. Over a few weeks, they would likely develop a reasonable tan. Now, our “patient” is optimizing the beneficial effects of the sun (Vitamin D, and it simply feels good) and hopefully minimizing the detrimental effects of the sun (skin damage).

This example is designed simply to illustrate a point that most of us already know from everyday living on our sun-warmed earth – dividing radiation exposure into small amounts delivered over a briefly extended period, instead of a large single exposure, can result in a more favorable outcome. As I physician I am obliged to point out that medically and technically, this analogy is flawed. In truth, even limited sun exposure can be detrimental to the skin and increase the risk of skin cancer and accelerate aging effects. Further, the ultraviolet radiation of sunlight is quite different from the higher energy X-rays and Gamma rays used in therapeutic radiation. Ultraviolet light damages skin cells in a somewhat different manner at the level of cellular DNA and generally does not penetrate below the skin; whereas therapeutic radiation can be deeply penetrating and even pass right through the human body. Regardless of these limitations of our Hawaiian vacation example, it depicts the concept well.

In the medical field, dividing radiation into multiple smaller doses is referred to as fractionation. The first technical studies describing the beneficial effects of radiation fractionation date back to France in the 1920’s and 1930’s. Scientific investigators experimented with radiation dose delivery to the testes of rams. In these experiments, the testes were the model of a tumor, as they contained many rapidly proliferating cells (like a cancer); the surrounding skin was the model for adjacent normal healthy tissue. They found that sterilization of the testes could not be accomplished with a single dose of radiation without causing extensive skin damage to the scrotum of the ram. However, when radiation was delivered over a period of weeks, sterilization of the testes was accomplished with minimal adverse effect to the scrotal skin. Since these animal experiments, many clinical studies in human patients have confirmed the
validity of these fractionation models and determined the optimal radiation dose per day and total radiation dose to kill a tumor with minimal risk of harming a patient.

On a cellular level, four important biologic processes are occurring after each radiation treatment, which produce the benefit of fractionated radiotherapy:

1. **Repair of sublethal DNA damage by normal cells.** Radiation damage to cancer cells is the result of DNA strand breaks. Normal cells have better DNA repair machinery. Fractionated treatment preferentially allows normal cells to repair sublethal DNA damage.

2. **Repopulation of normal healthy cells.** The time interval between radiation fractions allows normal cells to grow, divide, and therefore continue normal function at the level of tissues and organs.

3. **Reassortment of tumor cells into more radiosensitive phases of the cell cycle.** Cancer cells have varying sensitivity to radiation depending on their current phase of the cell cycle. In between treatments, some proportion of cells will cycle into a more sensitive phase, rendering them more susceptible to radiation damage.

4. **Reoxygenation of tumor cells.** The majority of radiation damage to the DNA of cancer cells occurs through a free radical mechanism that is enhanced by oxygen. The time interval between fractions allows additional perfusion of oxygen into areas of the tumor that tend to have low levels of oxygen (that is, hypoxic regions), leading to an enhanced effect of radiation in the tumor.

For approximately eight decades, physicians have discovered and employed the radiobiologic principles described above to optimize radiotherapy treatment with fractionation in regard to curing cancer and preventing side effects. However, particularly in the last 10 years, imaging technology and tumor tracking capability have improved dramatically and led to exciting advancements in radiation therapy. Now, physicians can target tumors with tiny, image guided radiation beamlets which deposit high radiation doses precisely in a tumor target, and spare neighboring tissues the high radiation dose. This type of high dose image guided treatment is often referred to as stereotactic radiotherapy. In the modern setting of stereotactic treatment, healthy tissues neighboring a tumor are no longer receiving significantly high radiation doses such that there is significant benefit to fractionation. Further, with modern technology, physicians are able to significantly increase the radiation dose to the tumor to records levels. In some cases, stereotactic radiotherapy treatment has led to higher cure rates, and even lower rates of side effects.

Whether traditional fractionated radiation therapy or stereotactic radiation therapy is the best treatment for an individual patient depends on many factors, including size of the tumor, location of the tumor, proximity to critical organs (such as the kidneys or spinal cord) and whether nearby lymph nodes are involved or are at risk of harboring microscopic disease – all of which are important factors focused upon by a radiation oncologist.
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