Radiobiological Principles Underlying Stereotactic Radiation Therapy

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Introduction

Since the Gamma Knife was first conceived in 1968, primarily for arterial and functional lesions [1], single-fractioned stereotactic radiation therapy* has been increasingly used to treat a variety of cerebral lesions. By 1985, an alternative modality was available for stereotactic radiation therapy, using a linear accelerator (linac) and a stereotactic head frame [4, 5]. Recently, the CyberKnife, a frameless robotic system, has been developed for stereotactic radiation therapy [6], and intensity-modulated stereotactic radiation therapy [7, 8] is now entering clinical practice.

In its early use, stereotactic radiation therapy was always applied in single fractions (i.e., radiosurgery), so its benefits were entirely related to its ability to irradiate target volumes with excellent dose distributions. By about 1990, however, several groups [9–15] began to consider the potential biological advantages of fractionated stereotactic radiotherapy, stimulated also by the development of relocatable stereotactic head frames for linac-based treatments [11, 12, 16].

As we will discuss, new technology has made it increasingly practical to fractionate a stereotactic treatment, and the use of fractionated stereotactic radiotherapy has indeed increased steadily over the past 15 years, as illustrated by more than 700 publications documented in PubMed/Medline on this modality. We will review here the radiobiological principles underlying stereotactic radiation therapy and their applications to single or multifractioned radiotherapy of the three main types of lesions that might be treated with this modality: malignant tumors, benign tumors, and vascular disorders. In that little is known about the radiobiological rationale behind radiotherapy for functional disorders, this area will not be covered. A complementary review on the clinical aspects of fractionated stereotactic radiotherapy has been published by Tomé and colleagues [17].

The Three R’s of Radiobiology: Reoxygenation, Repair, and Repopulation

All these three radiobiological phenomena relate ultimately to cell-killing processes, the assumption being that this is the primary (though not the only) mechanism by which all radiotherapy both produces tumor control and induces side effects. Of course, there are a variety of mechanisms that lead to cell killing, and a variety of relevant target cells, but underlying all radiotherapeutic response remains cell killing [18].

Reoxygenation

The first radiobiological principle of importance here is that malignant tumors, even those of limited size, almost always contain a proportion of hypoxic cells that, because of their deficiency in oxygen, are highly resistant to killing by X- or γ-rays [19]. Examples are shown in Figure 5-1, showing hypoxic regions in sections of small tumors derived from human glioma xenograph lines.

Figure 5-2 shows a dose-response curve, derived from the classic studies of Powers and Tolmach [20], illustrating the fraction of cells surviving in very small tumors in a mouse irradiated in a single fraction in vivo, and subsequently assayed by transplantation to other animals. The cellular survival curve is characterized by two distinct components; the slopes of the two components differing by a factor of 2 to 3. Up to doses of several Gy, the response is dominated by the killing of aerobic cells, whereas, for higher doses, the killing of hypoxic cells dominates. It is apparent that irradiating partially hypoxic tumors with a single large dose of several tens of Gy is a futile exercise if the goal is sterilization, because the hypoxic cells will not be adequately depopulated with a dose of this size. Figure 5-3 gives rough estimates, based on in vitro data, of the single fraction dose to sterilize a 30-mm-diameter tumor, with and without a hypoxic component [21].

* Note the term stereotactic radiation therapy will be used here to apply both to single-fraction treatment (often called radiosurgery) and to multiple-fractioned stereotactic radiotherapy. There is still debate about the most appropriate terminology [2, 3].
Tumors, however, exhibit a characteristic known as reoxygenation, whereby, between fractionated doses of X- or γ-rays, tumors tend to reestablish their original pattern and proportion of oxygenated and hypoxic cells [22] (Fig. 5-4). In a fractionated regime, therefore, each X- or γ-ray dose predominately kills aerobic cells, and the interval between treatments allows hypoxic cells to reestablish their oxygenated state.

**Repair**

The second radiobiological principle is repair. It has been well established for many decades that protracting or fractionating an acute exposure reduces the level of cell killing. An example is shown in Figure 5-5 [23]. If all tissues were equally affected by changes in protraction or fractionation, then there would be no radiotherapeutic significance to fractionation beyond the need to increase the dose to compensate for the increased cellular repair.

There is, however, a wealth of experimental evidence indicating that there is a difference in shape between the dose-response relationship characteristic of early-responding tissues and tumors and late-responding tissues. The inference from experiments in animals, which is confirmed in clinical practice, is that the dose-response relationship for late-responding tissues is more “curvy” than that for early-responding tissues, as shown in Figure 5-6.

In mathematical terms, if the dose-survival relationship is expressed in terms of a linear-quadratic relation,

\[ S = \exp(-\alpha D - \beta D^2), \]