We’ve Got a Treatment, but What’s the Disease?

or

A Brief History of Hypofractionation and its Relationship to Stereotactic Radiosurgery

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ABSTRACT

Hypofractionation has been a recurring issue during the near century-long history of radiation oncology. Coutard first introduced protracted dose-fraction regimens that uniquely allowed for the control of “deep” tumors. Subsequent studies have consistently shown that hypofractionation leads to an increase in complication rates and a paradoxical decrease in cure rates. There have, nonetheless, been several resurgences of interest in hypofractionation, based on titration of treatment for acute isoeffects and for the accommodation of an adjuvant treatment relating to presumed hypoxia-induced resistance, and more recently, stereotactic radiosurgery. In final analysis of the earlier studies, the same effects on cure and complication were noted and there was a return to multi-fractionation. Stereotactic radiosurgery is now being evaluated. Stereotactic radiosurgery takes hypofractionation to an extreme by use of a single, large fraction of radiation therapy. In doing so, the late effects radiation oncologists ordinarily strive to avoid are brought about intentionally, minimizing or even eliminating any therapeutic index within the treatment volume. Stereotactic radiosurgery has been used successfully for treatment of benign lesions such as arteriovenous malformations in which total volume necrosis of small dimensions appears to be efficacious therapy. Stereotactic radiosurgery has also recently been extrapolated to malignant tumors in the brain which require larger treatment volumes, but the data on outcome following such treatment remain sparse. Therapeutic index must be preserved to obviate an intolerable volume of necrosis and other late effects. The single fraction approach to stereotactic radiosurgery for cancer is vulnerable to the same radiobiological criticisms that have been a recurrent theme with hypofractionation. Fractionated stereotactic radiosurgery is far more consistent with the principles of conventional radiobiology and oncology and represents the quintessential application of three-dimensional treatment planning. Stereotactic radiosurgery is really stereotactic radiotherapy, and when applied in single fraction to the treatment of cancer, it is suboptimal radiation oncology. Its utilization is virtually predicated on the ability to perform another craniotomy to remove focal necrosis. The Oncologist 1996;1:1-7

The issue of hypofractionation in radiation oncology has resurfaced in the form of stereotactic radiosurgery (SRS), the delivery of a single, large fraction of external beam radiation therapy to a focal brain volume guided by three-dimensional (3D) imaging data. The technique was pioneered by the Swedish neurosurgeon Lars Leksell [1] in the pre-CT era. He used what Buschke described as a surgical approach to fractionation: the use of “...massive single-dose therapy based on the assumption that radiation therapy is effective in the treatment of cancer through its caustic effects—a slough in lieu of excision,” [2], even though fulguration has not been especially valuable therapy against neoplastic diseases. This is emphasized by the choice of the term “radiosurgery” and a virtual exclusion of radiation oncologists from involvement in the initial development of this form of treatment [3]. The deliberate creation of an area of necrosis is a foreign concept to most radiation oncologists, and the validity of it as cancer treatment seems doubtful. SRS technology became available in the USA in the mid-1980s following the advent of CT and advances in technique [4]. These developments and their clinical application appear to have been driven by new technologies in
3D imaging, computer software and the ability to modify existing external beam radiation therapy (EBRT) equipment [5]. This was in sharp contrast to progress in the mainstream of radiation therapy, which was driven by the hard-learned lessons of almost a century of empirical radiobiology and clinical radiation therapy. Specifically, this empiricism was based on the principle that maximizing the number of smaller-sized fractions leads to a greater therapeutic index and minimizes, especially, the development of late complications [6, 7]. Well-done clinical studies have shown consistently that hypofractionation leads not only to increased complications, but also to a decrease in local cancer control [8]. The hazards of hypofractionation have long been realized [2, 9, 10], but subtle differences in response between early- and late-responding normal tissues were not more keenly appreciated until the mid-1980s [11, 12]. This was coincident with the renewed interest in SRS, which appears to have been inexplicably extrapolated from treatment of arteriovenous malformations (AVMs) to the treatment of cancer with far more alacrity than scientific thought.

SRS was initially used for the treatment of functional disorders such as thalamotomies for Parkinson’s disease and intractable pain syndromes and capsulotomies for obsessive-compulsive disorders [3]. It was then used in place of or as an adjuvant to surgery for selected arteriovenous malformations (still the current principal use), and recently extrapolated to include the treatment of intracranial neoplasms, benign and malignant, primary and secondary. SRS has also been considered as an alternative for certain conventional neurosurgical procedures with high risk for neurological morbidity [13]. This includes the treatment of lesions in relatively inaccessible sites. We have learned, however, from the use of brachytherapy procedures for malignant gliomas, that there is a significant risk for symptomatic necrosis requiring reoperation. The requirement for possible surgical access limits the spatial applicability of stereotactic implantation [14]. This same principle should apply to SRS as well. (All of these principles assume that the area of necrosis will be confined over time exclusively to a tumor volume, an assumption for which there are few supporting data.)

SRS was, thus, initially focused on functionally deranged, but normal anatomic structures (e.g., thalamus), and then variations of normal anatomy (e.g., AVM), and then extrapolated to small benign tumors (e.g., pituitary adenomas, meningiomas), and more recently to cancers. A major leap in treatment philosophy was made from the production of the “destruction” (a term chosen by Leksell [1]) of a localizable normal anatomic structure or variant thereof to the treatment of malignant neoplasms. Single doses of 40 Gy or more were delivered to the endpoint of necrosis of a very well-defined, limited volume of brain [3], without regard to the achievement of therapeutic index or recognition of radiobiological principles. This may work well for small AVMs, but even if there are small differences in alpha-beta ratios between tumor and normal brain, fractionation may spare late effects [15, 16]. The therapeutic principles for the treatment of benign and malignant processes are dissimilar, as the larger treatment volumes required for malignant tumors do incorporate surrounding “normal” brain (typically infiltrated by neoplastic cells microscopically), which requires a reaction less than total volume necrosis and the preservation of a therapeutic index.

It was estimated that 70 radiosurgery treatment units (gamma-knife or linear accelerator [linac] based) were in use in 1991 throughout the USA, and radiosurgery treatment is now widely available across the nation [17]. We have a new form of treatment available, but its scope of application remains to be defined by careful research. There is a concern that there may be a “fatal attraction” between the availability of new technology and its immediate application, ignoring nearly a century of lessons about problems associated with hypofractionation.

Multiple fractions in radiation therapy were first used for pragmatic purposes because the low output of x-ray tubes in the first part of this century required single fractions several hours in duration or multiple daily fractions over an interval of several days to accomplish a desired effect, such as epilation [18]. Advances in technology came rapidly and the ability to deliver massive single doses was warmly welcomed. This came to characterize the first intentional approach to the fractionation of radiation therapy, as has been reviewed by Buschke [2] and by del Regado [10]. There were no data to support this approach to a new agent of unknown potency, and it reflected then-current medical and surgical conceptions of therapeutics. The surgical conception was that radiation therapy represented an alternative cutting tool, and the medical conception was that it resembled an antimicrobial agent but with specific anticancer activity and should be implemented with dose-intensity based on Erlich’s concept: Therapia Magna Sterilisans [19]. It was not until the now-famous ram testes irradiation experiments by Regaud and Nogier [20] that interest was piqued in more protracted time-dose fractionation. Male animals could be sterilized sparing scrotal tissue necrosis by applying three fractions of radiation, but a single fraction produced scrotal necrosis without sterility. This demonstrated the concept of the therapeutic ratio which was promptly applied to the treatment of cancer.

It was also recognized clinically that single fractions of radiation may have controlled skin cancers in some patients, although deep-seated tumors were not controlled until the more protracted fractionation scheme of Coutard was
applied to head and neck cancer [21]. The “Coutard method” was slow to come into common use, but an ASTR survey of US, Canadian, British and French radiation oncology facilities in the mid-1960s revealed that 94% used five to six fractions per week [22]. Protracted fractionation seemed to be accepted only reluctantly, however, as it was reported that “…the greatest cellcidual effect is obtained by single-dose fractionation; however, as a rule, the concomitant damage to normal tissues…is not well tolerated…and we are forced to fractionate” [22]. Equally important, but less acknowledged today, the early investigators of the twentieth century quickly recognized that with protracted exposures they could control many advanced lesions that they didn’t dream they could control with single doses. Hence, this represented the beginning of the radiobiological principles that explain the benefits of fractionation which we blithely accept today as the four R’s: repair, repopulation, reoxygenation and redistribution [23]. Thus, the mainstream of clinical radiation oncology acceded to fractionation based on the emerging principles of clinical and experimental radiobiology. It appears that despite an intellectual appreciation of radiobiological data the “extirpative approach” was still appealing, later fostering the acceptance of new hypofractionated treatment regimes.

The first major resurgence of hypofractionation developed out of the desire to express individual radiation therapy treatments in a standard fashion so that treatment results could be compared among different treatment facilities and so that some correction could be made in the case of treatment irregularity. Ellis introduced the concept of Nominal Standard Dose (NSD) [24], a proportionality constant of normal tissues related to the factors of time and number of fractions in order to calculate an isoeffective total dose based on Strandquist’s acute normal skin tolerance isoeffects [25]. NSD came into routine use and led to commonplace hypofractionation. Fletcher et al. [26] were among the first to warn that such comparisons could be misleading based on treatment experience. A decade of application led to a critical analysis of hypofractionation by Cox [8], who concluded that large doses per fraction, even if titrated to acute isoeffects in normal tissue, not only led to an increase in late effects, i.e., complications, but also to a paradoxical decrease in tumor control. Another corollary was that large, single-dose treatments were the least effective approach to the treatment of cancer, largely because single-dose treatment negates any opportunity of exploiting the four R’s of Withers [23].

Interest in hypofractionation was rekindled in the 1970s and derived from the need to modify standard time-dose fractionation regimens in order to accommodate various forms of concomitant therapy designed to address the problem of treatment resistance in radiation therapy [27]. This kind of thinking has typically centered around the issue of hypoxia and involved the use of hyperthermia, hyperbaric oxygen or hypoxic cell sensitizers. There was a desire to limit the radiation exposures to when it could be given with the study treatment. The toxicities and practical contingencies in the application of these secondary modalities led again to hypofractionation. There was a sufficient alteration of the standard time-dose fractionation of radiation therapy that treatment was rendered ineffective, and controls with standard fractionation were frequently neglected [28]. So, the conclusion is not necessarily that such sensitizers are not effective, but that any potential benefit may be negated when combined with inadequate radiation therapy, i.e., hypofractionation [27, 29]. Less toxic agents which can be administered frequently are clearly needed. In fact, positive results with fewer severe complications were reported within a subset of patients when daily, as opposed to twice-weekly, fractionation was used [30].

Once again, the issue of hypofractionation has more recently been raised in the form of SRS. It came into use in the USA in 1986 when a modified linear accelerator (linac) was adapted for SRS at the Joint Center for Radiation Therapy, and in 1987, when a gamma knife unit was installed at the University of Pittsburgh. Podgorsak et al. have compared the various available techniques [31]. Small volumes, usually <2-3 cc, were treated with the intention of producing gliosis, obliterator endarteritis or even necrosis. Necrosis is a desirable endpoint only if confined exclusively to the tumor; but, when larger volumes are treated for malignancy, surrounding normal brain is at risk for these same late reactions, which are more commonly thought of in the class of untoward late effects rather than desirable therapeutic effects. These are reactions that radiation oncologists ordinarily shun rather than seek. In addition, we must acknowledge significant ignorance about the variety of factors involved in the process of brain necrosis. We understand that “tolerance” has been exceeded, but the processes that permit necrosis to be confined or spread over larger areas are not well understood.

The critical parameters for SRS include the delivery of a large radiation dose to a well-defined volume with millimeter accuracy and very tight penumbra. The rate of dose fall-off with depth is related to the collimator diameter. For small volumes, e.g., <3 cc, 100% of the specified dose is delivered to the center of the volume, the edge defined at the 90% isodose curve, for example, and there is fall-off to the 10% isodose curve in about 5 mm [31]. It must be emphasized that the safety and efficacy of SRS for these 3 cc or smaller treatment volumes are primarily based on reports of treatment of AVMs in which the treatment volume may be totally replaced and virtually devoid of normal brain, and no margin of normal brain need be included in the treatment volume. This should not necessarily be extrapolated to malignant neoplasms, which typically have small fingers of
cells extending beyond the level of radiographic detection of the mass and infiltrating larger volumes of normal brain.

A single, large fraction of radiation therapy may be capable of several logs of cell-kill, whereas a multi-fractionated regimen should, in principle, lead to far greater logs of cell-kill unless such a large, single dose is given to produce a locally devastating effect, e.g., necrosis, without any therapeutic index within the treatment volume. A single dose of 25 Gy, if applied to mammalian cells with favorable cell-survival characteristics, will only kill at most about seven logs of cells under optimal circumstances [E. Glatstein, personal communication, 1994]. This is inadequate for the cure of any gross neoplasm. Single fraction SRS involves no therapeutic index in the induction of necrosis and is more consistent with an approach to the treatment of small benign lesions. Furthermore, it is possible to destroy only a small volume of intervening normal brain without dire consequences. Although treatment results for selected AVMs have been good and associated with low morbidity [32], it is highly unlikely that the same risk-benefit analysis will apply to the treatment of infiltrating cancers, which require a larger treatment volume than the radiographically apparent mass in contrast to benign lesions, which do not.

One of the reasons radiation therapy is effective as cancer treatment is because differences between tumor cells and normal tissues are exploited by the process of fractionation, i.e., the four R’s affect the outcome [23]. The goal is to preserve normal tissue and destroy tumor within the treatment volume, i.e., therapeutic index. If there are no alpha-beta differences to exploit as with AVMs, then a controlled late reaction confined to a limited volume may be effective radiation treatment. Do we really understand the process of necrosis well enough to predict its long-term extent reliably in 3D [33]? In the case of cancer, there are alpha-beta differences to exploit and there is no current indication to deviate from fractionated radiation therapy [15, 16]. A fractionated SRS boost to a small volume following standard fractionated external radiotherapy to a larger initial volume might optimize this approach. In fact, the question with cancer is: “What are the indications to fractionate more with multiple daily fractions?”

Fractionated SRS is possible by use of relocatable stereotactic head frames in an attempt to avoid some of the radiobiological disadvantages of single-dose hypofractionation [34, 35]. The potential goals of fractionating SRS include: 1) maintenance of a favorable therapeutic ratio, i.e., achievement of a biological effect short of total-volume necrosis, sparing normal cells, particularly important as the treatment volume increases; 2) maintenance of the degree of local control achieved by total-volume ablation by giving a higher total dose; 3) the use of different beam arrangements on different days with the intention of minimizing dose to surrounding normal tissue; and 4) minimizing the impact of geographic miss. If a single fraction were given but missed part of the tumor volume, the consequences would be more catastrophic than if missed in only one of several fractions. Fractionated SRS makes far more sense from the radiobiologic standpoint when malignant tumors are being treated in terms of cell killing and because the requisite larger volumes can be treated with less risk for complication. Single-fraction SRS may, on the other hand, be adequate for the treatment of AVMs in which the late obliterative effect on vascular structures is the intended goal [34]. Nonetheless, radiation oncologists must acknowledge that the central nervous system (CNS) is the least forgiving human organ system in terms of radiation injury and careful long-term follow-up studies are still few in number, even for AVMs. There are also several treatment volume questions in SRS which cannot be ignored.

Dose-volume issues in SRS for malignancy include: 1) that conformational treatment planning is used to spread out and minimize dose to surrounding normal brain; 2) that large volumes of normal brain are exposed to lower doses of radiation in the many entry and exit beams introducing an increase in the possibility of radiation-induced malignancy [36]; 3) that the low alpha-beta ratio for normal CNS structures implies that dose-per-fraction is the most critical determinant of tolerance [37]; 4) that the treatment volume includes the dominant mass and all micro-extensions; and 5) that there may be a nonuniform risk of complication in that more “eloquent” areas of the brain may more readily express injury than neurologically “silent” areas [38, 39]. Given these factors, attempts to estimate tolerance have been made with the integrated logistic formula which still requires clinical validation [33].

The definition of the appropriate treatment volume is a major issue in the SRS treatment of malignant brain tumors at two levels. In general, we can use imaging data to define the 3D spatial coordinates of benign lesions more accurately than malignant tumors which characteristically infiltrate beyond the demonstrable borders of the major mass [40]. The treatment volume for a malignant tumor is, therefore, a priori larger than for a benign tumor of equal radiographic image size. Since the risk of complications for CNS irradiation is proportional to both the volume of brain irradiated as well as the dose-per-fraction, SRS presents an increased probability for either complications or geographic miss.

The second volume issue is potential tumor multiplicity, particularly in the treatment of metastatic lesions. The conventional treatment for even a single brain metastasis is whole brain irradiation, with or without a radiation or surgical boost. The addition of whole brain irradiation following the gross total removal of a solitary brain metastasis leads to improved survival and decreased brain failure [41]. SRS treatment of multiple metastases with multiple isocenters has
been described, but the importance of whole brain irradiation has been confirmed by SRS studies [42]. There may be no advantage in the use of SRS over conventional radiation therapy for the treatment of metastatic disease except for dose escalation and retreatment. Given the poor long-term prognosis for these patients, the considerable expense involved, and the absence of a clear track record, the routine use of SRS for metastatic disease is, at the very least, questionable.

If SRS were used as a boost following fractionated EBRT, similar to intra-operative radiation therapy (IORT), it is unclear whether there would be benefit from dose escalation when applied to malignant gliomas. The Brain Tumor Study Group dose-escalation studies demonstrated a doseresponse relationship to 60 Gy [43]. Other studies with boosts to higher doses using EBRT, brachytherapy and neutrons have not consistently led to improved survival, and autopsy material demonstrated necrosis of both brain and tumor. Although we cannot directly extrapolate this EBRT experience to SRS with smaller volumes, it is not clear that SRS boosting for dose escalation for malignant gliomas following fractionated EBRT will be of major benefit. It appears that the therapeutic index may be maintained only through a limited dose range with larger treatment volumes.

There are also some serious ethical issues that must be raised. This new technology is often being applied to treatment of tumors with which there is no track record of success. In other words, research is being done; however, no one wishes to use that word because otherwise, third-party carriers would not pay for this treatment, and the financial support for such treatment would come to a screeching halt. Neurosurgeons and radiation oncologists will be held to task if they are not clearly telling patients of the unproved nature of this treatment in their exploration of this previously uncharted area of cancer therapy. Are patients being told of the results of modern conventional therapy when SRS is suggested for a meningioma or pituitary tumor? Is this new unproved treatment being presented to patients as an "established" or "conventional" or "standard" therapy? The potential for medicolegal action is obvious, and physicians should be exceptionally clear to patients on these issues, or else they risk legal redress. The consent form that the patient signs should be carefully reviewed for accuracy and honesty.

In summary, SRS allows for precision delivery of high dose-per-fraction EBRT to a well-defined small volume. SRS represents the quintessential application of 3D treatment planning. Usually, a single, large fraction is used deliberately producing an "intentional" late-effect, e.g., necrosis. This presupposes small volume and tight penumbra, as the risk of complications increases with the volume of necrosis and the volume of normal brain radiated to high dose. The guiding principles of radiobiology, the four R’s, have generally been ignored. From the standpoint of radiobiology, SRS is in principle more rightly applied to small benign lesions in which therapeutic response is due to a late effect in the spectrum of endarteritis-gliosis-necrosis. Success has in fact been achieved in the treatment of appropriately selected AVMs. Special attention must be paid to treatment within "eloquent" areas of the brain. When SRS is applied to the treatment of malignancy, there must be a larger treatment volume evoking a greater need for the preservation of therapeutic index. If a large treatment volume were subject to late effects, accidental or deliberate, the risk of complications would be unacceptable. How large a target volume can be “necrosed” without serious adverse consequences? Attempts have been made to obviate this issue by using SRS as a closed-head boost in the place of open implant or IORT, or by fractionating treatment using relocatable stereotactic head frames. Radiation oncologists learned (painfully) that hypofractionation leads to lower rates of tumor control and higher rates of complications. This was rediscovered when hypofractionated treatment was based on the acute isoeffects, as derived from NSD data, and yet again when hypofractionated treatment was used to accommodate an adjuvant treatment so that every rad given could be potentially augmented by radiation sensitizers.

The issue of hypofractionation in radiation oncology has once again been raised in the form of SRS. Single fraction SRS for AVMs and possibly some meningiomas may lead to results equal or superior to other forms of radiotherapy, although no long-term data have emerged as yet. Hypofractionated treatment may be good for these small benign lesions with no alpha-beta characteristics distinguishing themselves from surrounding normal structures and exploitable for therapeutic index. There may be a case to examine single fraction palliative SRS for patients with incurable metastases from the viewpoints of effectiveness of palliation, total expense, quality of life, duration of survival and need to retreat. But we have learned over and over again that hypofractionated radiation therapy is suboptimal cancer treatment for larger volumes incorporating critical normal structures. This is particularly important if there is any expectation for longer term patient survival. SRS is really stereotactic radiotherapy, and as practiced with a single exposure is not optimal curative cancer treatment. The therapeutic ratio between the control of malignant tumors and untoward late effects may be improved by fractionated SRS, even though the total number of fractions may remain small compared to standard external beam radiotherapy. Perhaps if our now more acute distinction between early and late effects had antedated the availability of SRS, there would now be a less “fatal attraction” for its unbridled use in the treatment of cancer.
REFERENCES


