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Basic principles of radiobiology, radiotherapy, and radiosurgery

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Spinal metastases are the most common spinal tumor, occurring in more than 100,000 patients in the United States per year [1,2]. Breast, lung, prostate, hematopoietic, and renal primary cancers account for most extradural spinal metastases because of the prevalence of these neoplasms and their predilection to spread to bone. Most metastatic spine tumors are bone metastases as opposed to metastatic deposits to the dura or spinal cord itself. Radiotherapy has been used in the treatment of such tumors for many decades. Although a "standard" treatment regimen may be considered to be a total dose of 30 Gy in 10 equal daily fractions, this may not always be considered to be the optimal course of treatment. It is absolutely essential for treating (or perhaps referring) physicians to appreciate the concepts of dose fractionation and biologically effective dose (BED) fully before recommending or embarking on altered fractionation schemes, whether this means a mixture of doses per fraction or the application of a single high dose of radiation. The BED for tumor as well as normal tissue (ie, spinal cord) must be taken into account. The following reviews the basic principles of radiobiology and the application thereof to the treatment of metastatic spine tumors. The most important concepts of dose fractionation and the concept of BED as well as spinal cord tolerance to single and multiple doses of radiotherapy are emphasized. Basic principles of treatment planning for radiotherapy and radiosurgery are outlined.

Basic principles of radiobiology

The probability of cell survival after single doses of ionizing radiation is a function of absorbed dose measured in gray units. The shape of the mammalian cell survival curve obtained after irradiation in culture (Fig. 1) shows little variation between cell lines [3]. The characteristic shape includes a low-dose shoulder region, followed by a steeply sloped, or more continuously bending, portion at higher doses. An interpretation of the shoulder region is the accumulation of sublethal damage at low doses and lethality resulting from the interaction of two or more such sublethal lesions [4–6]. A simple model for cell killing by ionizing radiation assumes that DNA is the target molecule and that a double-strand break in the DNA is necessary and sufficient to cause cell death (defined as loss of ability to divide). A double-strand break may be produced by a single-particle track or by the interaction of two single-strand breaks occurring closely in space and time (Fig. 2). Single-strand breaks alone may be repaired and therefore represent sublethal damage. Such a model is described by the linear quadratic formula:

$$SF = e - (\alpha D + \beta D^2)$$

where SF is surviving fraction, D is dose of radiation in gray units [7], α is the coefficient related to single-event cell killing, and β is the coefficient related to cell killing through the

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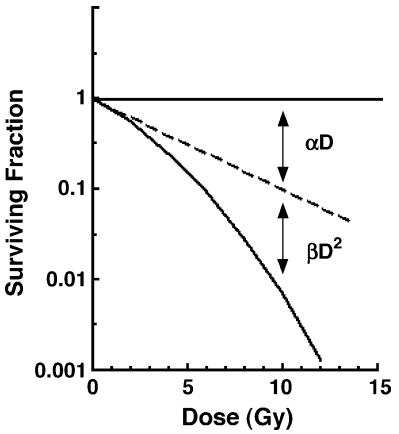

Fig. 1. Mammalian cell survival curve after x-ray irradiation (*solid line*). The α/β is 10 Gy, a dose at which there is equal contribution to cell killing by single events (αD, *dashed line*) and interaction of sublethal events (βD^2).

interaction of sublethal events. The ratio α/β is a measure of the relative contributions of these two components to overall cell kill, and α/β is the dose at which overall cell killing is equally caused by these two components, or $\alpha D = \beta D^2$ or $D = \alpha/\beta$.

Most mammalian cell survival curves, including those derived from human metastatic cancers, after x-ray irradiation may be fit well to the linear quadratic model [8,9]. Cell survival after a single dose of radiation in vitro reflects the intrinsic radiosensitivity of a particular cell type to a particular type of radiation [9].

A larger α/β indicates relatively little contribution from the interaction of sublethal events. A low α/β indicates a greater contribution from this type of reparable lesion. Because sublethal damage may be repaired after a dose of radiation, cells with a lower α/β ratio are spared to a greater extent by fractionation than are cell types with a larger α/β (Fig. 3). This is the basis for fractionated radiotherapy. Tumors and other rapidly proliferating tissues (eg, skin, mucosa, bone marrow) demonstrate high α/β on the order of 10 Gy, whereas many normal tissues, including those of the central nervous system (CNS), have lower α/β [6,10].

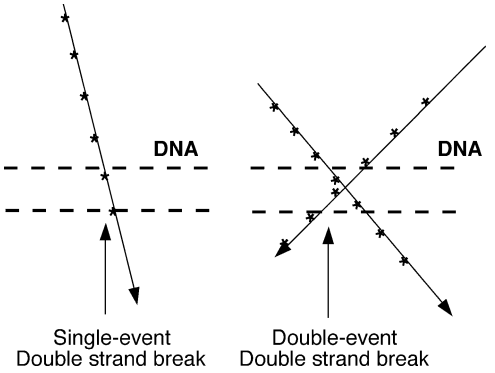

Fig. 2. Diagrammatic representation of double-strand break production by a single photon or interaction of damage produced by two photon tracks.

Normal tissue radiobiology

Therapeutic ratio

The radiation oncologist must be concerned not only with effects of treatment on tumor but with normal tissue effects. The normal tissues of particular interest in the treatment of metastatic spine tumors are the spinal cord and peripheral nerve roots. Also of interest are effects on the vasculature within normal and tumor tissue.

The probability of an undesirable normal tissue effect after radiotherapy is, like tumor control probability, a function of dose. This is represented graphically as a sigmoid-shaped curve similar to that obtained for tumor cure (Fig. 4). Curves for a wide variety of normal tissue end points have been generated. Although each has a similar shape, the relative placement of these curves along the dose axis may be quite different. In clinical radiotherapy, the relative positions of the curves for tumor cure and normal tissue complication defines what is known as the therapeutic ratio. The therapeutic ratio may be calculated as

$$\text{Probability of Tumor Cure}/\text{Probability of Complication}$$

An optimal therapeutic ratio would be described by curves that allow 100% tumor cure without appreciable probability of normal tissue complication (see Fig. 4A). The opposite extreme would be exemplified by a tumor requiring high-dose radiation for cure located within a critical normal structure with a low tolerance to radiation (see Fig. 4B). The tolerance dose for specific tissues is a function of the volume irradiated, the total dose and dose per fraction used, and the level of risk acceptable [11–14]. For example, the total dose to cause necrosis of the spinal cord in 5% of patients treated with a single dose of radiosurgery is vastly different than the dose associated with

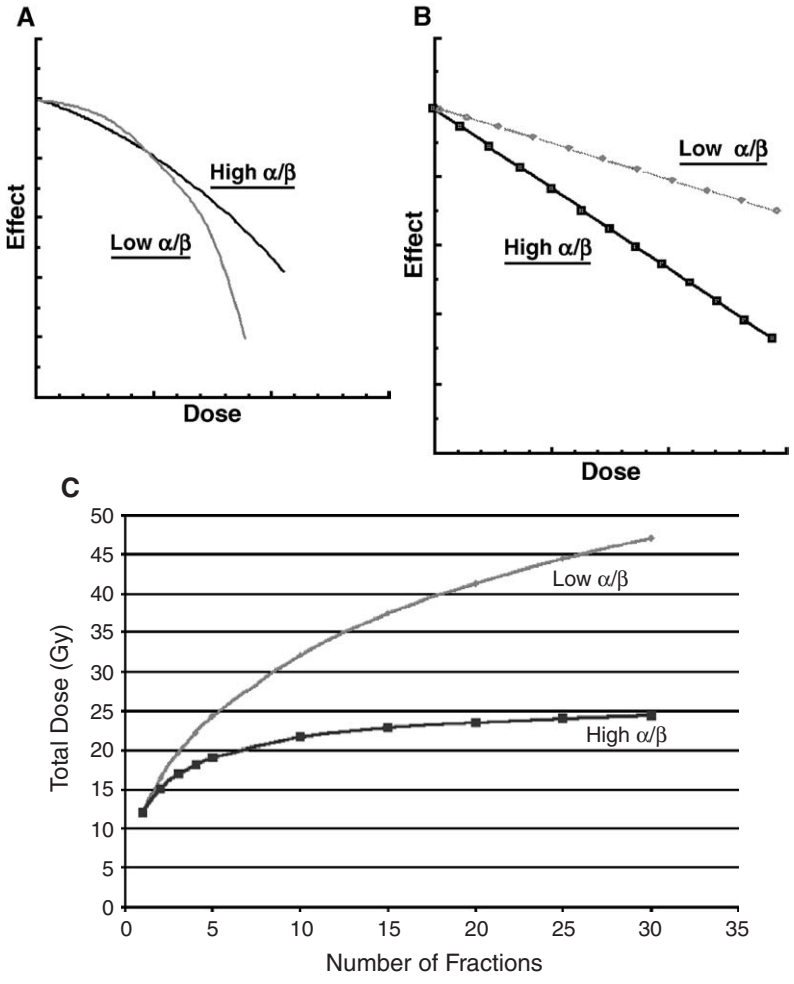

Fig. 3. (*A*) Schematic single dose-effect curve for tissue types with high α/β (early responding tissues and tumors) and low α/β (late responding tissues, including the central nervous system). The largest differential favoring sparing of late-responding tissues is in the low-dose region of the curves. (*B*)When low daily doses are used as in standard fractionation, this small differential effect is amplified. (*C*) Isoeffect curves for tissues with low α/β (2 Gy) and high α/β (10 Gy). Any point on the curves has a biologically effective dose (BED) equivalent to 12 Gy in a single fraction. The area between the curves represents opportunity for increasing the therapeutic ratio by delivering a higher BED to tumor while respecting normal tissue tolerance.

the same risk when conventional fractionation (1.8–2.0 cGy per day) is used [15].

Radiation tolerance of normal tissues of the spinal cord

In general, normal tissue effects are divided into those occurring early, during, or within weeks of radiation and those occurring late or months to years after radiation. Early effects are generally related to effects on rapidly proliferating tissues, such as skin, bone marrow, and mucosal surfaces. Late effects are related to changes in slowly proliferating or nonproliferating tissues, such as brain, spinal cord, and peripheral nerve.

Acute reactions associated with irradiation of the spine are usually not severe. Potential acute effects of irradiation of spinal metastases are associated with increased edema causing or exacerbating existing systems as a result of cord compression. These effects are usually minimized by administration of corticosteroids [16]. Any patient with impending or existing cord impingement should be started on high-dose

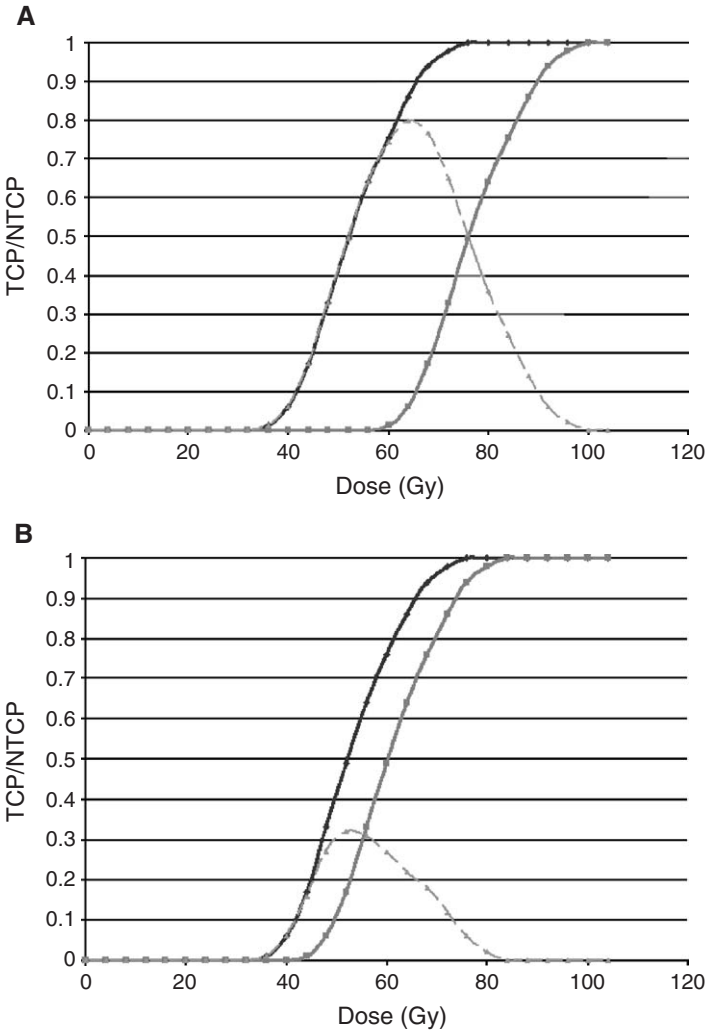

Fig. 4. Curves schematically comparing doses required for tumor control and those associated with significant normal tissue damage. (*A*) Depiction of a relatively favorable situation in which a dose regimen resulting in a high rate of tumor control would produce an acceptable rate of significant normal tissue damage. The dotted curve represents the probability of an uncomplicated cure. (*B*) An unfavorable situation in which the treatment is less likely to cure many tumors without substantial risk of normal tissue injury. Modifications of the treatment regimen that separate the curves in a favorable manner are said to increase the therapeutic ratio.

corticosteroids before radiotherapy. Neurosurgical intervention should also be considered in these cases [17].

Subacute effects of CNS irradiation are related to transient demyelination mediated by radiation injury to oligodendrocytes or through alterations in capillary permeability. The clinical manifestations are transient radiation myelopathy or L'hermitte's syndrome after spinal cord irradiation [18]. This is a self-limiting process, but patients may benefit from administration of steroids. Development of L'hermitte's syndrome does not portend frank myelopathy and is usually associated with an extended length of cord being irradiated, such as in the treatment of patients with Hodgkin's disease [18,19].

True myelopathy manifesting the late effects of spinal cord irradiation occurs within several months or up to many years after treatment. Radiation tolerance of the spinal cord is a

dose-limiting factor in the treatment of many malignancies, including intrinsic spinal cord tumors; spinous metastases; and carcinoma of the head and neck, esophagus, and lung. The risk of spinal cord injury increases with increasing dose per fraction and total radiation dose. Radiation-associated myelopathy may occur within months of radiotherapy and be transient in nature or may have a delayed time of onset and be permanent in nature. The mechanism of spinal cord injury after radiation may involve vascular effects or white matter damage. A dual mechanism of action has been suggested. Extensive demyelination is associated with damage to oligodendrocytes. This process corresponds to a shorter latent period, and effects may be transient or progressive, leading to white matter necrosis. A separate mechanism involves damage to the vascular endothelium. Resultant changes in permeability may induce white matter injury and lead to necrosis [16].

Wara et al [20] described the time-dose relation for radiation-induced spinal cord injury. They used an effect single dose (ED), where

$$ED = D(cGy) \times N^{-0.377} \times T^{-0.058}$$

Based on this formula, the authors suggested that doses of 2000 cGy in 5 fractions, 3000 cGy in 10 fractions, and 5000 cGy in 20 fractions were safe. This corresponds to an ED of about 1000 cGy and was believed to be associated with a 1% incidence of myelopathy. In practice, the risk may be much lower. Data from experiments in Rhesus monkeys estimate the doses for 50% ED (ED_{50}) and 1% myelopathy to be 76 and 59 Gy, respectively [14]. These results are in good agreement with the existing clinical data. In a review of patients receiving radiotherapy to the cervical spine, Marcus and Million [21] found that 2 of 1112 (0.18%) patients receiving a dose of 30 to 60 Gy in standard daily fractions developed myelopathy. It has been estimated that the dose of standard fractionated radiotherapy that would be associated with a 5% incidence of spinal cord injury is 57 to 61 Gy in standard fractions of 1.8 to 2.0 Gy [22]. It must be kept in mind that these data apply to standard daily fractionated radiotherapy. Estimates of tolerance of the spinal cord to single doses of radiation may be derived from modeling and extrapolation of clinical data to be in the range of 10 Gy [20]. A recent report of palliative hypofractionated radiotherapy for lung cancer found no myelopathy after single doses of 8.5 Gy to the thoracic spinal cord [23]. Myelopathy in children after radiotherapy is rarely reported [24]. Despite lack of evidence, spinal cord tolerance is usually considered to be 10% less in the pediatric population [14].

Reirradiation of spinal cord

With the development of more efficacious systemic therapies, patients with metastatic cancers are living longer and radiation oncologists may be more frequently faced with local failures within or marginal failures adjacent to previously irradiated spinal cord. Most clinical experience with reirradiation of brain tumors and optic nerves and chiasm suggest a long-term recovery from radiation damage to the CNS [25–28].

Experimental data in rodents suggest that long-term recovery of spinal cord damage after single or fractionated doses of radiation also occurs [29–33]. Ang [34] has conducted experiments in Rhesus monkeys indicating approximately 75% recovery of occult radiation injury 2 years after administration of 44 Gy in 20 fractions (Table 1). In practice, these data must be used judiciously, keeping irradiated spinal cord volume to a minimum, taking advantage of the sparing effects of fractionation, and fully informing the patient of risks involved with reirradiation.

Effects of dose fractionation on response to radiation therapy

The radiotherapy of spinal metastases has historically used standard fractionation protocols with doses per fraction of 2 to 4 Gy and total

Table 1
Incidence of myelopathy in the cervical spinal cord of Rhesus monkeys with or without pretreatment of 44 Gy in 20 fractions

Pretreatment	Total dose (Gy)	Incidence of myelopathy
0	70.4	3/15
0	77	3/6
0	83.6	7/8
44 Gy	83.6	0/4
44 Gy	92.4	0/4
44 Gy	101.2	1/4
44 Gy	110	1/4

From Ang KK. Clinical application of laboratory data on neurotoxicity. In: Wiegel T, Hinkelbein W, Brock M, Hoell T, editors. Controversies in neuro-oncology. Basel: Karger; 1999. p. 253–64; with permission.

doses of 20 to 40 Gy. Recently, there has been interest in using single doses of radiation to treat some spinous metastases. The rationale for each of these approaches is quite different and requires a thorough understanding of the effects of dose fractionation on response of tumor and normal tissues to radiation. The indications for single-fraction treatment should also take into account a comparative analysis of the efficacy and toxicity of fractionated treatment as well as the relative costs of the different treatments.

The effects of dose fractionation have long been known to influence the outcome of radiotherapy. The effects of fractionated radiotherapy are dependent on the total dose, the size of each fraction, the interval between fractions, and the overall time of treatment. The relative contributions of each of these factors vary depending on the end point of interest. These effects can be explained on the basis of four radiobiologic principles: repair of sublethal damage, reoxygenation of hypoxic cells, reassortment of proliferating cells in the cell cycle, and repopulation [35]. The rationale for fractionated radiotherapy is based on differential effects between normal tissues and tumors with respect to these processes.

Repair of sublethal damage, as discussed previously, is manifested by the shoulder of the dose response curve. The α/β is a measure of the relative contributions of reparable and irreparable damage. Tissues with a low α/β have a relatively high proportion of reparable (β-type) damage. These tissues are significantly spared as the number of fractions is increased, because the number of interfraction intervals and opportunity for repair of sublethal damage increases [6,7,36]. In addition, because the term for β-type damage is a function of D^2, lower doses per fraction are relatively less effective in tissues with a low α/β. Tissues with high α/β have a relatively small contribution from β-type damage and are spared to a lesser extent by dose fractionation [36]. The shapes of dose-effect curves for tissues with low and high α/β indicate the largest differential advantage at low doses per fraction (see Fig. 3A).

The effect of repair alone on the BED of fractionated radiotherapy is dramatic. Fractionation spares all tissues; therefore, as the number of fractions is increased, the total dose required for an equivalent biologic effect is increased (see Fig. 3C). The magnitude of the increase in total dose required is a strong function of α/β, however. Fractionation remains the most effective measure to increase the therapeutic ratio.

Reoxygenation of hypoxic cells has been demonstrated in all tumors with a significant radiobiologically hypoxic population [37]. Oxygen is the most potent known radiosensitizer of mammalian cells, increasing the dose for dose efficiency of ionizing radiation by a factor of 3. After a dose of radiation, relatively sensitive oxygenated cells are preferentially killed and their numbers are diminished. Therefore, the hypoxic fraction immediately after a dose of radiation is increased and may approach 100%. Over a period of 12 to 24 hours, however, the tumor demonstrates reoxygenation and returns to have the original hypoxic fraction [4]. This principle indicates the important role of fractionation in combating hypoxic cell radioresistance. This is an effect demonstrated in tumors only, because normal tissues contain no radiobiologically hypoxic cells.

Cellular radiosensitivity varies over the cell cycle by a factor on the order of 3 [38]. After a single dose of radiation, a cycling population of cells will have lost a larger proportion of cells in radiosensitive phases of the cell cycle (G_2 and M). Over a period of 4 to 6 hours, the cell population resumes cycling and redistribution of cells from relatively resistant phases to more sensitive phases of the cell cycle takes place. This effect has an advantage for tumor cell killing only and would not apply to noncycling normal tissues.

Although radiotherapy causes a cell cycle delay in late G_2, this delay is usually only a maximum of several hours [4,39]. Therefore, during the interfraction interval, tumor and cycling normal tissues may proliferate and repopulate, partially compensating for killing by the previous radiation dose. For normal tissues, this is a favorable compensatory mechanism. For tumors, it is counterproductive to the goal of eradication of the tumor. In rapidly proliferating tumors, it may be necessary to increase the dose per fraction or to decrease the interfraction interval to overcome the effects of tumor repopulation.

Specific data for primate spinal cord indicate an α/β of approximately 2 Gy [34]. The kinetics of repair of sublethal damage after irradiation of the spinal cord have been found to fit a biexponential model with a fast component of repair (half-life of damage of 0.7 hour) and a slower component of repair (half-life of damage of 3.8 hours) [40]. A higher than expected incidence of myelopathy has been observed in a human clinical protocol delivering three daily doses of radiotherapy at 8-hour intervals [41]. To achieve full benefit from interfraction repair of spinal cord, once-

daily dosing is recommended. Reduction of the interfraction interval from 24 hours to 6 to 8 hours requires a 10% to 15% reduction in spinal cord dose from expected tolerance doses over a standard course of radiotherapy [14].

Altered fractionation: biologically effective dose

The biologic effect of a regimen of radiotherapy depends on the total dose (D), the dose per fraction (d), and the overall time (t) taken to deliver the total dose, D. For single doses, the BED may be derived from the linear quadratic formula:

$$\mathrm{BED}(\mathrm{Gy}_{\alpha/\beta}) = \mathrm{D}(1 + \mathrm{d} \div \alpha/\beta)$$

where for the special case of a single fraction, d = D. BED is expressed as a dose in $\mathrm{Gy}_{\alpha/\beta}$ and is useful in comparing BEDs for different dose schedules in tissue with a particular α/β. When dose is fractionated, D = nd, where n is equal to the number of fractions of dose, d, and the equation should also take into account the overall time of treatment (T) [42]:

$$\mathrm{BED}(\mathrm{Gy}_{\alpha/\beta}) = \mathrm{nd}(1 + \mathrm{d} \div \alpha/\beta) - \gamma\mathrm{T}$$

For most late responding normal tissues, particularly for nerve and spinal cord, the time factor is negligible. For most tumors, the time factor depends on the potential doubling time of the tumor cells and perhaps hypoxic fraction. In practice, the time factor for most tumors is about 60 cGy per day [43]. The formula for BED can be used to compare dose regimens of varying total doses and dose per fraction in a particular tissue. Likewise, the equation may be used to determine the isoeffective total doses, D, associated with different doses per fraction d:

$$\mathrm{D}_1/\mathrm{D}_2 = (\alpha/\beta + \mathrm{d}_2) \div (\alpha/\beta + \mathrm{d}_1)$$

Standard radiotherapy for spinal metastases

Most radiotherapy treatments delivered in the United States use the linear accelerator. Historically, these units have replaced the orthovoltage x-ray units and the cobalt 60 units. The major advantages of the more modern units relate to the higher energies that are available and interfacing of computer verification systems that allow the daily delivery of precise treatments through multiple complex field arrangements. Coupled with modern imaging and computed tomography (CT)- or magnetic resonance imaging (MRI)-based treatment planning, modern radiotherapy more reliably delivers therapeutic doses to the tumor volume while excluding normal tissues from the high-dose region. Together, these are the most effective means of increasing the therapeutic ratio [44].

Treatment planning

Careful treatment planning is an essential component of optimum delivery of modern radiotherapy. Patients with painful spinal metastases should be staged with bone scans and MRI of the clinically suspicious area. For patients with neurologic compromise, MRI of the entire spine is optimal. For spine tumors, CT-based treatment planning for radiotherapy offers the most precise information regarding the location of tumor and critical normal structures. Definition of the volume to treat is a critical step in the planning process. Before the CT/MRI era, it was standard practice in radiation oncology to treat the offending vertebral body(ies) with a "margin" of two bodies above and two bodies below. This was done for two reasons: because there was uncertainty using contemporary technology to deliver treatment accurately to the correct vertebral body and because recurrences were found most often to be contiguous with previously irradiated vertebral bodies. Modern imaging, treatment planning, and delivery systems make it possible to define the area requiring treatment, immobilize the patient, and accurately deliver a highly conformal dose of radiation to virtually any region of the body. The vertebral column is especially amenable to precise treatment because it is well visualized radiographically and there is virtually no motion with normal respiration.

Results of radiotherapy for spinal metastases

Certainly, for most patients with metastatic spine disease, standard radiotherapeutic approaches have to be considered the standard of care. Patients are normally treated with a relatively short course consisting of 10 treatment sessions delivering a total dose of 30 Gy, the most commonly used regimen in the United States. For patients with a low burden of systemic cancer, higher total doses may be given: 37.5 Gy in 15 fractions or 40 Gy in 20 fractions.

Randomized trials treating osseous metastases with various dose regimens have not identified

a significant difference in palliation of bone pain for various regimens ranging from 8 Gy in 1 fraction to 30 Gy in 10 fractions [45–48]. These studies do indicate a significantly higher reirradiation rate for patients treated with a single fraction (20%–25%) compared with fractionated regimens (7%–12%), however [49]. In a recently completed randomized trial (RTOG 97-14), patients with either prostate or breast cancer and painful osseous metastatic sites were randomized to receive either 8 Gy in a single fraction or 30 Gy in 10 fractions for palliation. Median survival of this group was 9 months. By 3 months after treatment, 50% of patients reported mild or no pain and one third of patients were completely off narcotic pain medications. There were no statistically significant differences in any of the end points studied between the single-fraction treatment and the 10-fraction treatment except that the single-fraction group experienced less acute toxicity and required in-field retreatment more often (18% versus 9% at 3 years) [50].

The efficacy of palliative radiation for spinal metastases and spinal cord compressions is well established. Conventional external beam radiotherapy has been shown to improve bone pain in approximately 80% to 90% of patients with metastatic bony disease [51]. In a series of 80 patients, Loeffler et al [52] reported an incidence of in-field recurrence of 11.3%, similar to that found for other osseous metastases. Wazer and Willett [53] reported that patients treated with radiotherapy for vertebral body metastases from prostate cancer had a relatively long mean survival time of 18.2 to 27.2 months and required retreatment anywhere in the spinal axis in 22% of cases. They emphasized that the customary margin of two vertebral bodies may compromise the ability to deliver future treatment.

Spinal cord compression is a preterminal event in most patients. Sorensen et al [54] retrospectively reviewed data from 345 patients with metastatic spinal cord compression treated with radiation (43%), laminectomy (31%), or laminectomy followed by radiation (26%). The median survival in this study was 3.1 months. Seventy-eight percent of ambulatory patients treated with radiation alone retained the ability to walk, whereas 16% of nonambulatory patients and 4% of paralytic patients treated with radiation alone regained the ability to walk. For patients treated with laminectomy followed by radiation, 83% of ambulatory patients remained ambulatory, whereas 29% of nonambulatory patients and 13% of paralytic patients regained the ability to walk. Ability to ambulate after radiotherapy was prognostic for a median survival of 1.5 versus 7 months for nonambulatory and ambulatory patients, respectively. The success of standard palliative radiotherapy has been confirmed in a multivariate analysis from a prospective cohort study of patients with spinal cord compression. Ambulatory status was maintained or achieved in 100% of patients who were ambulatory before treatment, 35% of those paretic before treatment, and 7% of those paraplegic before treatment [55].

Recent data underscore the importance of surgery in conjunction with radiation in treating spinal cord compressions. Patchell et al [17] randomized 101 patients with cord compressions to surgery, followed by radiotherapy (surgery group) or radiotherapy alone (radiation group). All patients received 30 Gy of radiation and were treated according to the same corticosteroid protocol. In all cases, the goal for surgery was to remove as much tumor as possible to provide immediate decompression and to stabilize the spine. The study was stopped after interim analysis revealed that patients treated with surgery retained the ability to walk significantly longer than those treated with radiation alone (median: 126 days versus 35 days; $P = 0.006$). Of the 32 nonambulatory patients enrolled (16 in each group), 56% regained the ability to walk in the surgery group versus 19% in the radiation group ($P = 0.03$). Patients in the surgery group also maintained continence significantly longer than patients in the radiation group. There was a trend toward longer survival in the surgery group (median: 129 days versus 100 days; $P = 0.08$). Those in the surgery group required significantly fewer steroids and narcotics.

Principles of radiosurgery for spinal metastases

Radiosurgery refers to the delivery of a single high dose of ionizing radiation to a focal target. There are an increasing number of centers in the United States performing this type of treatment. Recently, there has been interest in applying the experience with intracranial radiosurgery to spinal metastases. The most common delivery systems for radiosurgery to the spine are modified linear accelerators (Novalis, BrainLAB Inc., Chicago, IL) and a robotic linear accelerator (CyberKnife, Accuray, Sunnyvale, CA). The details of each of these technologies are discussed in separate articles in this issue. Radiobiologically, radiosurgery

is at the opposite end of the spectrum from daily fractionated radiotherapy. The advantages of fractionation outlined previously are forfeited by the delivery of a single dose, because there is no interfraction interval during which repair, reoxygenation, redistribution, or repopulation can occur. The focal nature of radiosurgery may provide a safe and potentially efficacious treatment for small-volume localized disease, however [56]. Complication rates after spine radiosurgery are clearly related to the dose delivered to spinal cord and peripheral nerve roots. The single high-dose treatment tends to enhance late effects selectively based on the linear quadratic formulation.

The rationale for fractionated radiotherapy is based on the radiobiologic principles outlined previously. The rationale for radiosurgery is the exquisite localization of dose to the tumor and the delivery of relatively low doses of radiation to the surrounding tissues. This approach should allow the delivery of a higher BED to the metastatic deposit while respecting spinal cord tolerance. The physical hallmark of radiosurgery

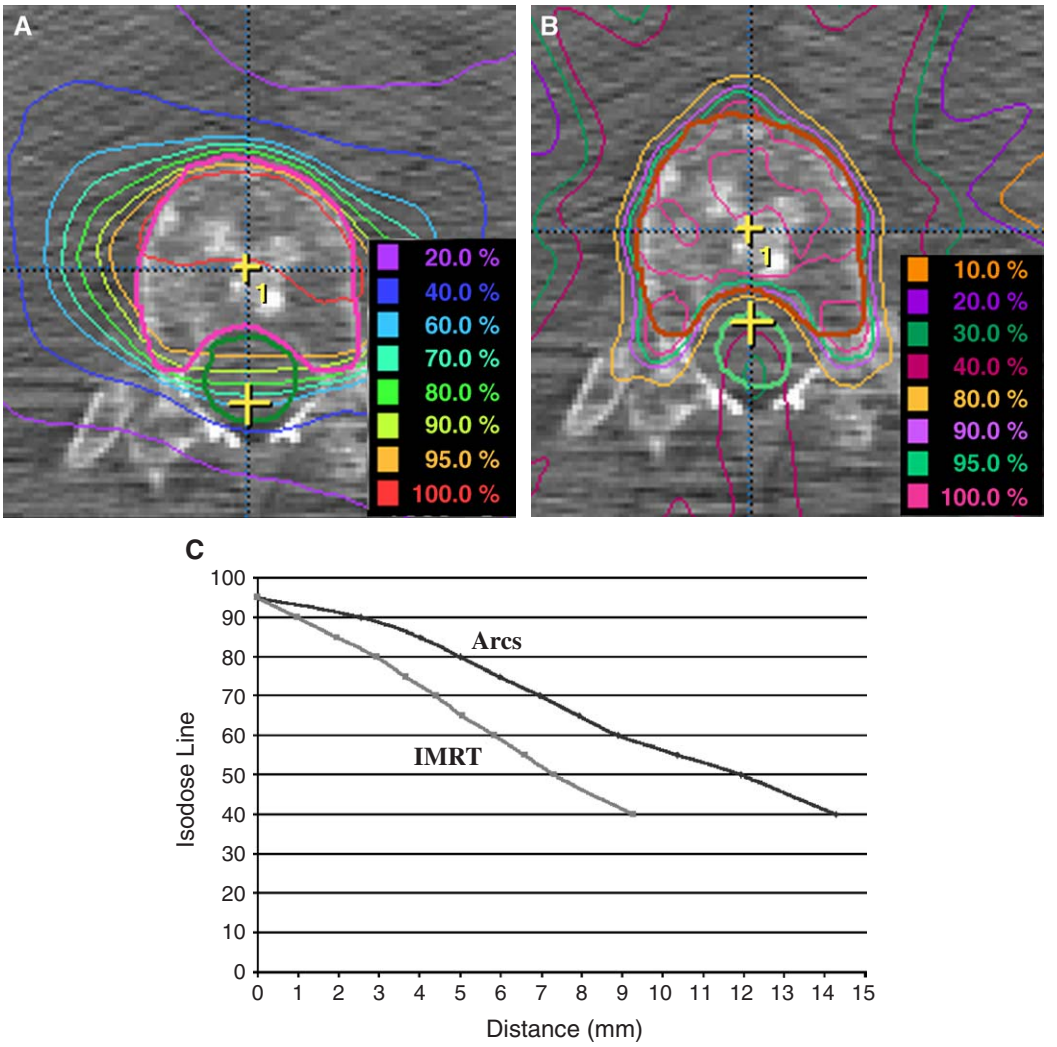

Fig. 5. (*A*) Dose volume histogram for tumor (vertebral body) treated with arcs or intensity-modulated radiotherapy (IMRT). (*B*) Dose volume histogram for spinal cord treated with arcs or IMRT. Note the excellent coverage of the tumor volume with either plan but the superiority of spinal cord sparing with IMRT. Also note (*C*) the steep dose gradient, which requires excellent immobilization and verification of patient position.

is a dose distribution with a rapid dose fall-off outside the intended target (Fig. 5). This may be accomplished through a series of arcs centered about the geometric center of the target (isocenter) or a series of intersecting shaped and fixed beams [56]. This technique does not usually provide adequate protection of the spinal cord (see Fig. 5). Intensity-modulated radiotherapy (IMRT) is used to further steepen the dose gradient between the vertebral body and spinal cord (see Fig. 5; Fig. 6) [57]. Such a gradient relies on reliable patient positioning and immobilization. With single doses, small errors may make a significant difference in BED to the spinal cord, because total dose and dose per fraction increase (Fig. 7). Details and early clinical results of spinal radiosurgery are discussed elsewhere in this issue.

Spinal radiosurgery may be of benefit to some patients with metastatic spine disease. Indications may include patients with a previous history of spinal irradiation or discrete low-volume disease. The patient's overall prognosis, the added cost over that of standard treatment, and the expected benefit to the patient need to be considered.

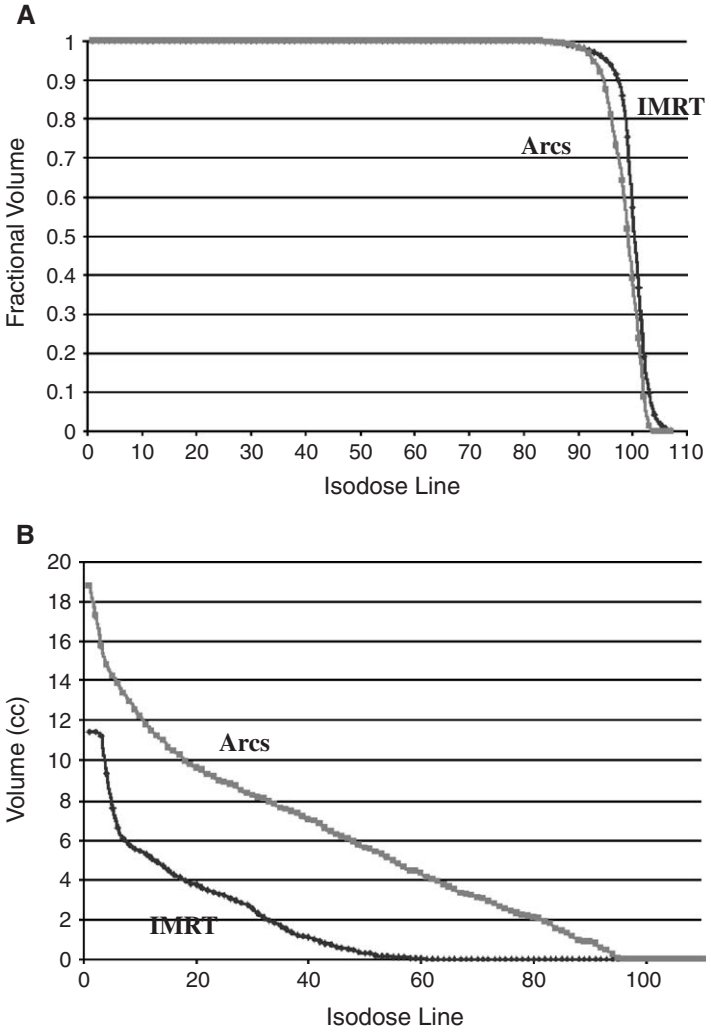

Fig. 6. Isodose plans for stereotactic treatment of metastasis to a vertebral body. (*A*) Results of arc therapy. Note the steep dose gradient into the spinal cord but lack of concavity, providing further sparing of the spinal cord. (*B*) Intensity-modulated radiotherapy (IMRT) plan. Note concavity of the isodose lines around the spinal cord. (*C*) Dose fall-off into the region of the spinal cord on arc plan and IMRT plan.

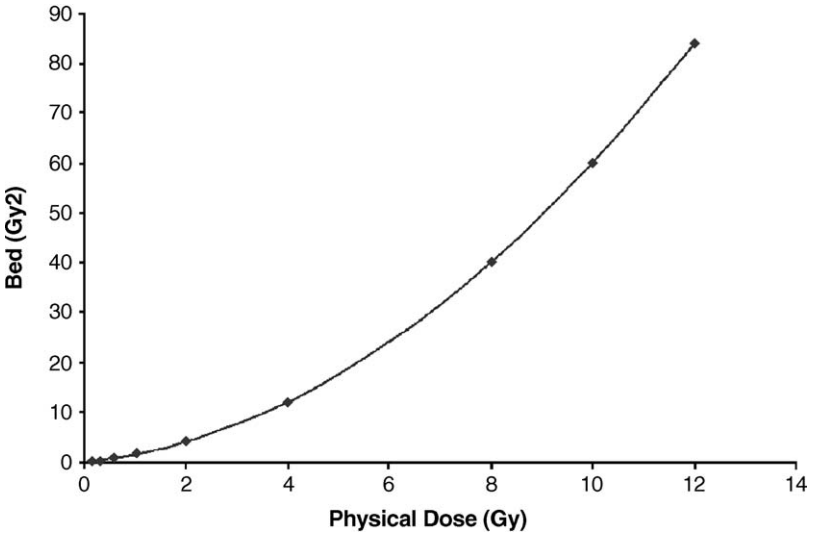

Fig. 7. Plot of physical dose versus biologically effective dose (BED) for single treatments. If patient motion or setup error puts the spinal cord into a higher isodose line, the BED can be greatly increased.

Randomized trials are necessary to clearly define indications and the population of patients likely to benefit from spinal radiosurgery.

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