

## The use of radiation in the management of spinal metastases

Clare M. Faul and John C. Flickinger

*Department of Radiation Oncology University of Pittsburgh, School of Medicine, Pittsburgh P.A. 15213, USA*

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### Introduction

Skeletal metastases occur in the majority of patients with systemic cancer [47, 48]. However only between 5–10% will develop symptomatic spinal cord or cauda equina compression in their lifetime [49]. In one study by Lenz and Fried in autopsies on 168 patients with breast cancer 59% had evidence of spinal metastases however only 9% had developed spinal cord compression [50]. Primary histology's leading to skeletal metastases in adults are breast, lung, prostate, kidney, lymphoma, myeloma and carcinomas of unknown origin in order of frequency and neuroblastoma, Ewing's sarcoma, osteogenic sarcoma and rhabdomyosarcoma in children [51, 52, 53]. Despite autopsy findings showing that metastases most often involve the lumbar spine in clinical practice symptomatic metastases most often affect the thoracic spine followed by the lumbar spine and least often the cervical spine [47].

### *Clinical features*

Pain is the most striking symptom in over 80% of patients. Because of the devastating consequences of delay in diagnosis of spinal metastases with the potential for development of symptomatic spinal cord compression one must have a high index of suspicion and new onset of back pain be regarded as skeletal metastases until proven otherwise in a patient with a diagnosis of cancer [53, 54].

Spread to the epidural space may occur by a number of different methods. Direct spread from an in-

volved vertebra is the commonest followed by spread through the intervertebral foramina from adjacent nodes as in lymphoma, haematogenous spread or by direct compression by pathological fracture or fracture dislocation [55, 56].

After the development of pain the development of signs of spinal cord compression if it does occur can take anywhere from 7 weeks to 6 months [57]. The duration of pain is longer with breast cancer than with lung cancer or lymphoma which is dependent on the underlying tumor biology.

Spinal cord compression produces a classical clinical syndrome. Pain is usually localized at first but persistent and usually progressive. Radicular pain one of the first signs of spinal cord compression is caused by compression of nerve roots. Radicular pain is usually unilateral in patients with cervical or lumbar involvement and bilateral in patients with thoracic involvement. The site of radicular pain corresponds to the level of obstruction in the majority of patients. Further symptoms include the development of a sensory loss corresponding to a skin dermatome, weakness, unsteadiness, sensory symptoms, alteration in bowel or bladder function which all progress to complete and irreversible paralysis unless prompt therapy is instigated [58, 59].

### *Investigations*

The investigation of the patient with spinal metastases should be tailored to the individual clinical situation. Factors such as the clinical symptoms and signs, duration of onset of symptoms, and overall

condition and prognosis of the patient should be taken into account.

Plain X-rays positive in about 85–90% of patients presenting spinal metastases are a quick and economic investigative procedure [60, 61]. Radioisotope bone scan is another useful test and sensitivity is about 85% however false positives can range up to 20%. Bone scans have the advantage of showing the full extent of disease [61].

What further tests are needed depends on the clinical situation. If X-rays and scans are normal and patient has pain, computerized tomography looking at the spine, intervertebral foramina, and vertebral soft tissues may be helpful [62]. Magnetic resonance imaging is now considered the most sensitive test for vertebral metastases although because of cost factors should be used if clinically indicated. MR imaging can detect vertebral metastases earlier than plain x-ray or bone scan. Extra spinal lesions can also be readily detected. The whole spinal axis can be visualized and extent of disease characterized in sagittal plane as compared to CT [63, 64].

In a patient with clinically suspicious signs of spinal cord compression the test that will confirm the diagnosis and that is the most readily available should be performed. Myelography is the gold standard at present. It is as sensitive as MR in the diagnosis of spinal cord compression in most studies. The disadvantages are that it is an invasive procedure and if complete block is seen a second puncture is needed to assess the superior extent of the block [65].

MR imaging is now increasingly being used in the diagnosis of spinal cord compression. It is useful for the diagnosis of early cord lesions and because the spine can be viewed in the sagittal plane the exact extent of the lesion can be determined in comparison to other studies. This is very useful for the delineation of treatment ports in radiation treatment. The other advantage is the fact that it is non invasive. Disadvantages include cost and patient tolerance issues [63, 64].

### **Radiobiology and radiation myelopathy**

A critical component in the discussion of the use of

external beam radiation in the management of spinal metastases relates to the tolerance of the spinal cord to radiation. Permanent radiation injury (radiation myelopathy) is a devastating consequence of radiation with no effective treatment. In the following discussion a number of factors that influence radiation tolerance of the spinal cord and future implications of irradiation will be discussed.

Radiation myelopathy can either occur as a transitory syndrome (L'hermitte's sign), a delayed progressive syndrome, an acute rapid onset paralysis or a lower motor neurone syndrome [1].

Lhermitte's sign occurs relatively infrequently. In a series of 2901 patients treated to the cervical spinal cord 3.6% developed the sign and none developed progressive symptoms. Only two factors were associated with the development of Lhermitte's sign total dose  $\geq 5000$  cGy and higher dose per fraction [2].

Lhermitte's sign is usually characterized by a momentary 'shock like' parasthesia radiating from the neck to the extremities precipitated by flexion of the neck. The syndrome develops in the majority of cases within average of 3–4 months and the symptoms usually resolve after a further 3–6 months. Not all patients get complete recovery and progressive myelopathy may develop especially if large doses are delivered to the spinal cord [3].

Progressive radiation myelopathy usually appears late, with an average latent period of 20 months. The latent period appears shorter with larger doses and in children and longer with lumbar myelopathy [1, 3].

Deficits may be partial or progressive and symptoms range from numbness, Brown-Sequard syndrome to complete paralysis. The neurological changes are almost always irreversible [4].

Occasionally radiation myelopathy may present as an acutely developing paralysis thought to be from infarction of the cord at high total doses [1].

Lumbar myelopathy is characterized by lower motor neurone signs in the lower extremities [5].

The site of radiation injury is the white matter and may result from demyelination or from changes in the intramedullary vasculature or both together [6].

Demyelination occurs at a shorter latent period than vascular injury explaining the recognized bi-

modal distribution of radiation injury [6]. The two peaks are usually separated by about 17 months. Experimental and clinical data have confirmed higher doses are associated with the demyelination injury [6].

The target cell for development of radiation myelopathy is unknown. Recent evidence has suggested that the astrocyte plays an important part in both injury and repair of c.n.s. damage [7]. Astrocytes are components of the immune system and are involved in cytokine production. Tumor necrosis factor is cytotoxic and is associated with demyelinating illnesses and may be a factor in the production of radiation myelopathy. Other factors associated with the development of radiation injury include the presence of plasminogen activator inhibitor-1, decrease in myelin basic protein and decrease in level of glial derived nexin [10, 11]. Interrupting these processes may prevent the development of radiation myelitis in the future [10, 44, 45].

An interesting recent animal study found that hyperbaric oxygen slowed the development of radiation myelitis when given prophylactically 6 weeks after irradiation [8]. Other agents investigated in animals have shown some effect in protecting the spinal cord from radiation damage and include, pretreatment with methotrexate in rats, and post radiation administration of vasoactive drugs [9, 10, 11].

The diagnosis of myelitis is usually made on clinical grounds however recently magnetic resonance imaging is proving effective in diagnosis. Distinct localized abnormalities corresponding to the level of myelopathy clinically can be seen and other conditions excluded [2, 13]. Pallis first determined that myelopathy only be diagnosed if the following criteria were met – a) the spinal cord should be radiated at the level of myelopathy, b) the cord should be within the treatment port, and c) other causes of myelopathy should be excluded [15].

Apart from clinically evident myelopathy patients treated to the spinal cord have shown evidence of subclinical myelopathy years after treatment. Reduction in spinal conduction velocity has been noted in both animals and humans [14].

## **Dose, fractionation and tolerance**

Experimental models have shown that spinal cord tolerance is critically dependent on dose per fraction as well as overall dose and duration of treatment. Clinical data is limited by the use of conservative doses to the spinal cord, poor dosimetry in the past and short follow up of patients [20].

Since the mid 1940's various estimates on tolerance levels of the spinal cord have been produced along with mathematical models to explain them. The first study by Boden in 1948 suggested that the maximum cord dose should be 3500–4500 cGy in 21 days [16]. Atkins and Tretter later confirmed by Phillips's reported that the dose per fraction rather than the overall treatment time was the critical factor in the development of myelopathy. A tolerance level of 50 Gy in 25 fractions was suggested [17, 18]. Currently it is believed that at standard fractionation (1.8–2 Gy/fr) 45 Gy produces a less than 0.2% risk of myelopathy and a 5% risk occurs at a dose level of 51–61 Gy [19, 20].

Recent studies have confirmed the increased tolerance of cervical spinal cord. In 72 patients who received > 5500 cGy to some portion of spinal cord 5% developed neurological changes [21]. 1/53 patients receiving > 5600 cGy, 0/75 who received > 5000 cGy and 2/471 patients that received between 4500–5000 cGy to at least 2 cm of cord developed myelopathy [22, 23].

Several mathematical models have been used to account for the radiobiological effect of fractionation to allow for comparisons between different schedules. The first widely used model was the Nominal Standard Dose or N.S.D. formula (see Table 2) which calculates a theoretical single dose equivalent for early skin reactions. After this formula came into widespread use it became clear that late reacting normal tissue injury such as spinal cord injury was much more sensitive than acute responding tissues to the dose per fraction. Other variants of this model were proposed to be used specifically for neural tissue (Neuret) [32].

The Linear Quadratic Formula is now gaining increasing use to account for fractionation effects (see Table 2). With this formula the cell kill from radiation is described as a combined linear and quad-

ratio function of dose per fraction possibly mirroring single and double hit kinetics. The degree to which radiation injury (cell kill of stem cell targets) depends upon fractionation is expressed by the alpha-beta ratio. Late responding tissues such as spinal cord have low alpha-beta ratios (1.5–3) while acute responding tissues (skin and some tumors) have higher ratios (around 10) [1].

Certainly when the dose per fraction is increased above 2 Gy the risk of myelopathy is substantially increased despite lower overall doses.

Dische *et al.* reported a 11% risk of myelopathy at doses per fraction of 5 Gy and total doses of 33.5–35.3 Gy [41]. Hatlevol *et al.* reported a 29% incidence of myelopathy at 6 Gy fraction size and overall doses of 38 Gy [42].

The effect of doses per fraction below 1.8 Gy has become increasingly important especially since the report of 4 cases of myelopathy from C.H.A.R.T. experience and 2 cases from an altered fractionation scheme in Canada [27, 46]. Experiments on animals had suggested that at these low doses per fraction the spinal cord should have been spared [24–26]. It is now believed that repair of sublethal spinal cord damage may take longer than predicted and the short interfraction time in the above studies contributed to the increased level of myelopathy seen rather than reduced sparing at low doses per fraction [27]. Experiments have shown that delivering 2 fractions at 6 or 8 hours intervals instead of 24 hours reduced the tolerance of the spinal cord by 16.5 and 13.5% respectively [28]. If the spinal cord is included in multiple daily fractionation schemes it should not receive more than 40 Gy [29].

The influence of length of spinal cord irradiated on the subsequent development of myelopathy has been less well studied. Experimental data on irradiating increasing lengths of spinal cord in rodents has shown a significant increase in incidence of myelopathy at similar doses and fractionation [30].

Clinical evidence of increased risk of myelopathy with larger field sizes is sparse.

The first paper alluding to this fact was from Boden who suggested > 10 cm of cord could tolerate 38 Gy in 17 fractions compared to 50 Gy to less than 8 cm of cord [16]. Pallis also suggested that cord length's of > 10 cm tolerated 3300 cGy compared to

4300 cGy for lengths < 10 cm [15]. Abbatucci *et al.* suggested that > 5 cm cord could tolerate no more than 50 Gy in 25 fractions compared to 60 Gy for lengths of cord below this [31]. There was no myelopathy noted at this dose level. Further clinical data is sparse therefore no firm recommendations on tolerance levels with respect to length of cord can be given.

Tolerance of the thoracic spinal cord to radiation is thought to be less than other cord levels. This was based on a number of cases of myelopathy reported with unconventional thoracic radiation for lung or esophageal primaries [32]. Some cases had received a higher spinal cord than tumor dose because of the technique used. However Lambert and Phillip's found tolerance levels similar to those reported for the cervical cord [4, 18]. The supposed poorer vascular supply reported to be reason behind this poorer tolerance has not been substantiated. Therefore at present there is no objective reason to support poorer tolerance to radiation of the thoracic spinal cord.

Repeat irradiation of the spinal cord is an area of particular interest at present although data is limited. Animal data have suggested long term recovery of radiation damage in the rat spinal cord model which is dependent on time [34]. The level of initial damage influences the subsequent development of radiation injury. At 4 weeks there was a significant recovery in initial damage in the lumbar cord of rats and at 8 weeks of the cervical spine. Longer intervals were needed for sparing of late vascular injury [35]. Also the pathology of initial damage and subsequent damage was similar suggesting a similar mechanism of injury [34].

Data has also suggested that radiation sensitivity of re-irradiated rodents was similar to un-irradiated controls. In a study on the monkey spinal cord it was shown that late vascular damage showed a less recovery than white matter damage [36]. Age of the animal at the time of radiation was also shown to influence recovery. Recovery was faster but tolerance to retreatment less [37]. The doses to which the cord can be retreated varies between species and time intervals between treatment. Maximum total doses (initial + retreatment dose) range from 130% of ETD (extrapolated tolerance dose) for rats to 145% of ETD for primate cord.

Clinical data also suggest significant recovery of spinal cord with time. Cumulative doses of up to 80–90 Gy with standard fractionation does not invariably produce myelopathy. 3/22 patients treated for recurrent nasopharyngeal carcinoma developed myelopathy [38]. A second study on re-radiation of Hodgkin's disease patients showed that in 5 patients followed for 10 years who received spinal doses of between 50–70 Gy none developed myelopathy although some developed minor neurological symptoms [39]. Current recommendations on length of time to re-treatment are not available as yet although it is felt that less than 2 years is risky.

The influence of host factors on the development of myelopathy is not fully understood. The reports of myelopathy developing in patients receiving relatively low spinal cord doses lend support to individual sensitivity being important in the development of radiation damage. Both hypertension and hypotension have been reported to accentuate radiation damage [43]. This has not been substantiated by other investigators. Concurrent chemotherapy and radiation has resulted in reduced radiation tolerance of the cord perhaps by reduction in repair of sublethal damage [40].

### Radiation technique

Radiation therapy has long been the initial therapy of choice for spinal metastases. The aim of therapy is to palliate pain and prevent irreversible neurological complications. In a patient without clinical suspicion of spinal cord compression radiation can relieve pain in up to 80% of cases. Radiation technique, doses and field size are tailored to the individual patient [54, 67].

Different treatment techniques are used depend-

Table 1. Depth of spinal cord and vertebral body below the skin surface

Site	Depth of spinal cord	Depth of vertebral body
Cervical spine	4–5 cm	5–6 cm
Thoracic spine	4–5 cm	6–7 cm
Lumbar spine	7 cm	9–10 cm

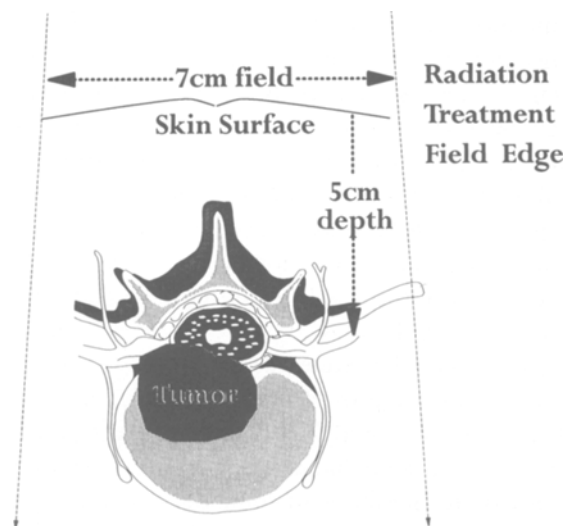


Fig. 1. Cross sectional drawing of a typical radiation field setup for treatment of a spinal metastasis.

ing on the level of spinal column treated. Lesions of the cervical vertebrae are treated with the patient supine using parallel opposed lateral fields avoiding irradiating the oropharynx [67]. This also allows for easier set up of the patient. Thoracic vertebrae are usually treated by a single direct posterior field with the patient lying prone if possible. If not the patient is treated supine with a posterior field through the treatment couch [54, 57].

Lumbar vertebrae can be treated by a single direct posterior field, parallel opposed technique or by two posterior oblique fields depending on physician preference and clinical situation. The first technique is simpler to set up but has the disadvantage of higher exit dose to bowel.

The tumor dose delivered must be delivered to the vertebrae and therefore with a single field technique must be prescribed at a certain depth below the skin surface (see Fig. 1). Varying depths of vertebrae below skin surface are given in Table 1.

The radiation field sizes depends on the extent of metastases and level of involvement.

Usually the affected vertebrae plus two superior and two inferior vertebrae are included in the treatment field. The width of the treatment field is usually 7–8 cm or to include the transverse processes. This is to allow for treatment variables such as patient movement, set up variables and diagnostic

limitations of exact extent of disease. The upper and lower border should include the whole vertebrae to allow for precise documentation of treatment fields in case further radiation is needed. Verification films and tattoos are used also for this purpose [72, 74]. Because M.R. imaging can better delineate the extent of metastases in the spine and sagittally along the spine smaller radiation fields can be used to spare more normal tissue resulting in less toxicity to the patient [63].

There is no definite evidence of a dose response relationship for pain relief.

The R.T.O.G. study on relief of painful bony metastases suggested that higher doses of radiation increased the likelihood of complete pain relief [68]. A prospective randomized trial from Britain however showed equal pain relief with a tumor dose of 8 Gy in a single fraction as compared to 30 Gy given in 10 fractions [69]. Also they did not detect a difference in duration of pain relief. A further study comparing a dose of 8 Gy single fraction to 4 Gy single fraction showed a significantly better pain response in the 8 Gy arm (at 4 weeks 76% vs 53% pain relief) at 8 weeks the response was similar however, 40% of patients had treatment to spinal column. Although follow up was short they did not report neurological complications [70].

Most centers still use more fractionated treatments to the spinal column because of the worry of spinal cord tolerance which has been discussed earlier. Usual doses and fractionation include 30 Gy in 10 fractions or 20 Gy in 5 fractions which produce similar levels of pain relief. Lower doses per fraction and longer treatment times may be appropriate in a patient with a relatively good prognosis after development of spinal metastases such as in breast cancer to allow for retreatment if needed. However

in a patient with a poor overall prognosis a single fraction may be very efficacious in palliation.

Complications are few and are restricted to a small risk of acute bone pain flare that is temporary, a mild risk of nausea in patients with exit doses through the upper abdomen, oesophagitis, skin erythema and diarrhea are all rare [68–70].

The effect of tumor histology on the response of bone metastases to radiation is controversial. Although it was felt that some histology's were 'radio-resistant' and did not respond to radiation recent data has not confirmed this fact. A large prospective study from Britain already mentioned did not show any influence of tumor histology on response rates [69, 70]. A further study from Japan showed that in a series of patients with bony metastases from renal carcinoma thought to be radioresistant radiotherapy relieved pain in 79% of cases [71].

Multiple vertebral involvement presents a challenging management problem.

Large fields may be used but tolerance of spinal cord must be kept in mind and doses and doses per fraction reduced accordingly. Limitation of therapy machines is also a factor at large field sizes with the added complication of overlapping fields and potential for overdosing the spinal cord. Also if multiple vertebral metastases are involved there is a high likelihood of other symptomatic bony metastases being present that need treatment [47]. Treatment methods to overcome these problems include hemibody irradiation and strontium therapy [76, 78].

Hemibody irradiation refers to a technique whereby a single fraction of radiation is given to a large surface area of the patient (one half of the body) followed in many cases by a repeat treatment to the other half after a break of 4–6 weeks [74, 76].

It is utilized for the palliation of widespread pain-

Table 2. Radiobiological formulas to account for fractionation

Name	Formula
Nominal standard dose (NSD)	$NSD = D n(-0.22')t(-0.11)$
Neuret	$Neuret = D n(-0.37)t(-0.058)$
Linear quadratic ETD = extrapolated tolerance dose	$ETD = D(1 + d/(\alpha\beta))$

where D = total dose, d = dose per fraction, n = number of fractions and t = treatment time in days.  
 $\alpha\beta$  = alphabeta ratio.

ful bony metastases and saves the inconvenience of multiple hospital visits.

The patients are treated with a linear accelerator at extended FSD and fields outlined depending on the sites of disease. The upper limit of the lower field is usually at the level of the iliac crests. Because of lung toxicity the dose to the upper hemibody treatment has been reduced from 1000 cGy to 600 cGy and lung correction factors are used. For lower hemibody treatments the specified dose is usually 800 cGy. The break of 4–6 weeks between treatments is because of hematological toxicity. Although hematological recovery is usually complete by 4 weeks prolonged pancytopenia has been reported especially in heavily pretreated patients. The acute syndrome of nausea vomiting and fatigue is usually alleviated by premedication. Patients also benefit from hydration prior to treatment [73, 74].

Results from centers that regularly use this technique have shown rapid pain relief usually within 24 hours even in patients that have already received radiation. Duration of pain relief has been reported to last up to 3 months or more. Long term complications are few and the main limitations to this technique are lung and hematological tolerance [73].

Strontium-89 therapy has recently been found to provide palliation of widespread bony metastases without major toxicity. Strontium-89 chloride is an injectible isotope that localizes to bony metastases and because of its properties penetrates minimally into soft tissue thus reducing toxicity. Advantages include a half life of 50 days, and an up to 25 fold increased affinity for bony metastases as compared to normal bone [75, 77, 78].

Clinical trials have shown that strontium-89 can provide pain relief in 50–80% of patients treated. Also a Canadian study showed that adjuvant use of strontium-89 after external beam radiation provided increased duration of pain relief as compared to radiation alone (35.3 weeks vs 20.3 weeks) [77]. Duration of response of strontium-89 is reported to be as long as 6 months. Clinical indications for strontium are a) patients with bony metastases from prostate or breast cancer, b) more than one site of disease, c) adequate bone marrow reserve and d) life expectancy of greater than 3 months for radiation protection issues. Although strontium is recom-

mended for the above named malignancies it may be effective in other malignancies that metastasize to bone. A fall in post treatment P.S.A. levels has been reported in patients with prostate cancer [78].

Usual doses are 148 MBq (4 mCi) of strontium-89 which has an activity of 1 mCi/ml by slow intravenous injection. Up to 6 injections of strontium-89 can be given however if the first injection is not beneficial subsequent injections are less likely to be effective.

Complications include a 10% risk of bone pain flare, a significant risk of hematological toxicity especially a drop in platelet counts that are usually temporary and cost issues [75].

High energy transfer (LET) radiation refers to the use of particles that deliver substantially more energy per unit length than does megavoltage photons used in conventional radiation. Neutrons have resulted in radiation injury at high doses. Reported neurological complications range from 9% to 20%. Recommended doses delivered to the cord range between 1050–1100 cGy (n gamma). Charged particle beams such as protons (low LET) and alpha or helium particles (high LET) have finite path lengths and sharp beam edges that allow for radiation close to the spinal cord with relative dose sparing of the cord itself. This technique is useful for repeat radiation or initial high dose radiation of spinal metastases and chordomas [76].

### **Radiation therapy of spinal cord compression**

Because of the devastating consequences of delay in management of spinal cord compression and resulting irreversible neurological deficit it is important to identify patients earlier in the course of their disease [57]. As discussed myelography, CT myelography and MRI are all useful in the diagnosis however because of accuracy and patient tolerance MR imaging is increasingly becoming the investigative procedure of choice in centers with access to it. Also MR imaging has the advantage of being able to image the entire spine which is useful for radiation planning as multiple lesions not suspected clinically can occur in up to 30% of cases [63, 64].

With the increasing diagnosis of very early le-

sions with 'minimal impingement of the cord' and no neurological signs there is sparse data on the optimum management. Do these patients need emergent radiotherapy or do they need steroid coverage? These are all questions that need to be answered in the future. It is quite probable that these early lesions were treated by standard radiation for bony metastases in the past without neurological compromise in the series that have reported long term results although this cannot be determined without reservation [67–70].

Emergent management of symptomatic spinal cord compression is needed as maintenance of ambulation is higher when therapy is initiated early prior to the development of irreversible neurological deficits. Once the clinical diagnosis of symptomatic spinal cord compression is made high dose steroids are usually recommended prior to myelography/MR imaging to prevent further neurological compromise. The need for steroids and the dosage remains controversial. Animal studies have shown reduced epidural swelling after high dose steroids with transient clinical improvement [79, 80]. A randomized trial of high dose steroids (100 mgIV) compared to more conventional dose (10 mgIV) both followed by 4 mg every 4 hours by Vecht failed to show any significant difference between the two schedules [81]. Steroids have been shown to improve pain and transiently improve the clinical status of patients in most studies however as the majority of patients receive steroids the outcome of patients not receiving steroids is unknown [80]. Data has shown that response to steroids predict for radioresponsiveness suggesting an initial similar mechanism of action.

Although the optimum definitive management for metastatic epidural spinal cord compression is not known radiation therapy is increasingly being used as first line treatment. The objection to radiation in the past was due to the observation that some patients signs worsened on treatment. This was felt to be secondary to radiation induced edema and further compression of the cord. An elegant study on rats by Rubin refuted this argument [82]. Even after high doses of radiation per fraction no tumor swelling was noted. Any edema seen was counterbalanced by cell loss [82]. Therefore the

need to combine steroids with radiation in the treatment of spinal cord compression is not definite. Most clinicians would do so especially if there is a high degree of block.

Radiation therapy has a proven record in the definitive treatment of spinal cord compression and except in a few circumstances should be the therapy of choice. Decompressive laminectomy the previous first line therapy has been superseded by radiation or in specific cases by anterior decompression and stabilization. This resulted from poor results, significant risk of neurological deterioration with spinal instability and an up to 10% mortality rate [83].

#### *Dose and fractionation*

Once the diagnosis has been confirmed the usual procedure is to initiate radiation therapy within 24 Hr. in order to prevent further neurological compromise. The majority of centers also cover the patient with high dose steroids. The optimal dose and fractionation schedule for spinal cord compression remains unknown.

Experimental work by Kato *et al.* on the mechanism of epidural spinal cord compression showed that in early stages the venous plexus is compressed and as the level of mechanical compression increases spinal cord blood flow decreases until loss of cord function ensues [84].

Increasingly high daily dose fractionation schedules are being used. This approach was based on initial experimental data from Rubin [82]. Two fractionation schedules were compared in 20 rats (group 1 received low dose per fraction – 100 cGy  $\times$  10 = 1000 cGy, and group 2 received high dose per fraction – 500 Cgy  $\times$  3 = 1500 cGy). The major difference between the two groups was in the time to response. There was faster tumor regression in the high daily fractionation group with earlier neurological recovery. In the low dose per fraction group the recovery was slower however the majority of rats did improve. There was a suggestion that because of the slow response there was a risk of further neurological progression before the effect of radiation was seen in the low dose per fraction



group. Although there is no prospective comparison clinically between the two fractionation schedules centers using the high dose per fraction schedule have shown similar results as above when compared retrospectively.

Greenberg *et al.* from the Memorial Sloan Kettering hospital has compared retrospectively the effect of a high dose per fraction schedule to their previous standard fractionation schedule. They found that with 500 cGy per fraction  $\times$  3 days followed by a rest of 4 days and further 300 cGy per fraction over 5 days there was no significant difference in outcome when compared with their previous series. There was a hint of a better response for 'radioresistant tumors' but the numbers were small [85]. Other studies have shown although results were good with this regime there was no significant difference when compared to 3000 cGy  $\times$  10 treatments [86, 88]. The Greenberg protocol is increasingly being used especially for tumors felt to be less responsive to radiation (lung, renal cell, colon) or if a high degree of block is seen on myelography.

For more 'radioresponsive' (lymphoma, myeloma, breast and prostate) tumors standard fractionation schedules have produced excellent results and allow for the prospect of retreatment [87].

The use of 'hypofractionation' schedules high single fractions of radiation for the treatment of spinal cord compression is controversial mainly because of spinal cord tolerance issues. However a number of centers have used this schedule with satisfactory results. Interesting the results show equal response of more radioresistant tumors and quick and high levels of pain relief [88, 89]. This technique may be useful for patients with a poor prognosis for survival or in patients with long standing complete paralysis where chances of response are low.

Whether there is a relationship between overall dose and functional outcome is difficult to determine from the series reported. In one series there seemed to be a better outcome with higher doses with a significant difference reported when patients received greater or less than 2000 cGy in 5 fractions [90].

% Regaining and/or Retaining Ambulation

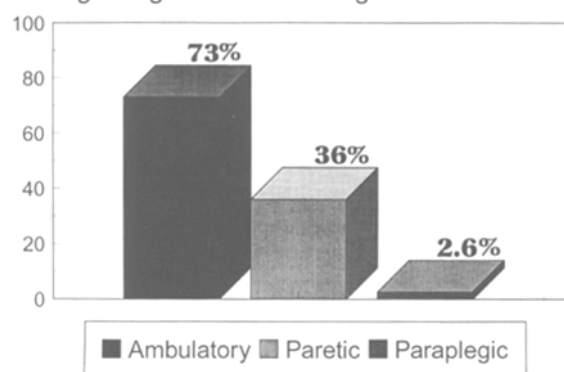


Fig. 2. Functional results following irradiation according to the neurological status prior to treatment (Gilbert RW, Kim VH: *Ann Neurol* 3: 40, 1978).

### Prognostic factors

The most important prognostic factor in all series (both radiation and surgery) that determines functional outcome is the level of neurological deficit prior to commencing therapy. The majority of ambulatory patients retain walking ability post radiation. Overall response to radiation related to the degree of deficit is outlined in Fig. 2. Once complete loss of power has occurred the response to radiation is very poor with an average recovery rate to ambulation of 3% [92]. The only exception to this is with highly radiosensitive tumors i.e. lymphomas. Some studies have suggested that the outcome of paraparetic patients is better with primary surgery mainly because of the fear of further deterioration while radiation is taking effect. This theoretical concern has not been substantiated in the literature [91].

Although most series concur that responses after 72 hours of documented complete paralysis are minimal in one series of 15 patients with complete paralysis 5 recovered ambulatory function. In this series it was noted that the time to note recovery was late and in 3/5 patients was only seen at the 6 month follow up visit [93]. This is consistent with some animal data. Slow onset of paralysis also correlates with improved functional results after radiation. This is thought to be due to fact that slow onset of paralysis results in less ischaemia than acute onset. However the neurological grade has a

greater influence on prognosis than symptom progression rate [91, 92].

Other poor prognostic factors include autonomic dysfunction which is correlated with a high degree of neurological deficit. Ambulatory rates following radiation when sphincter dysfunction is present ranges about 30%. Recovery of autonomic function varies with levels reported of 40–50%. Autonomic dysfunction also correlates with a poorer outcome after surgery [12, 86].

The influence of tumor histology on choice of therapy remains controversial. Although so called 'radioresistant' tumors were thought to be best managed by surgery a number of radiation studies have not shown that tumor histology influences outcome [93, 94, 96]. Other studies have shown poor results with radiation when these tumor types were associated with a high grade of neurological deficit [86–88]. However a recent review of 31 surgical and radiotherapy series with over 2300 patients found that tumor radiosensitivity was associated with the aggressiveness of the tumor, overall functional results were similar despite primary management and suggested that tumor histology should not influence the choice of therapy [91].

The degree of myelographic block an indicator of the extent of tumor within the spinal canal does not always correlate with the degree of neurological deficit [87]. In some radiation series it is associated with poorer functional outcome and in others not. In the only prospective series comparing radiation with surgery although numbers were small there was no significant outcome when patients were stratified according to the degree of block [95].

The optimum first line therapy when vertebral collapse is present remains controversial. A large prospective study by Marazano found no influence of vertebral collapse on outcome after primary radiation [87].

Other studies have shown a poor outcome with radiation for this entity although partial collapse, i.e. less than 50%, did not seem to influence prognosis [97].

Primary surgery was not without hazard with vertebral collapse in the past with the risk of further destabilizing the spine. More recently anterior de-

compression with stabilization has been used and may result in better outcome for this entity [100].

Radiation is usually offered to the patient post surgery to prevent tumor regrowth and has been shown to improve ultimate functional outcome. Standard radiation fractionation schedules rather than high dose schedules are recommended [98, 99].

### **In conclusion**

The optimum management of spinal metastases is early diagnosis and initiation of therapy prior to neurological deficit. The choice of either radiation or surgery as primary management of spinal cord compression remains controversial. The only prospective trial although numbers are small show no significant difference in functional outcome between laminectomy and radiation [50]. Other retrospective series have also suggested similar results however with reduced toxicity in the radiation arm. Anterior decompression has not been adequately tested against radiation. However because this population has a poor prognosis with average survivals of less than one year in most series, radiation is increasingly being used as first line therapy in the majority of centers.

Results show that maintenance of ambulation occurs in up to 80% of patients when radiation is initiated while the patient is still ambulatory. Results are less favorable when patients are not ambulatory prior to initiating therapy [12, 42, 43].

Surgery is reserved for patients with no diagnosis or for patients that deteriorate during radiation. Other prognostic factors such as degree of block, vertebral collapse and tumor histology have not definitively been shown to influence the choice of therapy [87, 96, 97].

When treating the spinal cord with radiation the radio-sensitivity of the cord must always be kept in mind. Recent radiobiological data has suggested that the spinal cord has a higher tolerance than previously believed [21, 22]. Exciting data has also come from studies looking at tolerance to repeat radiation implying that re-irradiation of the spine may be possible in the future [34, 36]. This holds out

the opportunity in the future to re-irradiate after repeat spinal cord compression safely.

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*Address for offprints:* C.M. Faul, Magee Womens Hospital, Dept Radiation Oncology, Fobes & Halket Street Pittsburgh, PA 15213, USA