Palliative Radiotherapy in Modern Practice

Susan Wiltshire and Andrew Potter
Royal Adelaide Hospital, Adelaide, South Australia.
Email: susan.wiltshire@health.sa.gov.au

Abstract
Radiotherapy provides effective symptom relief for patients with metastatic disease. The type and duration of radiotherapy depends on various factors including the patient’s performance status and the symptom being palliated. Hypofractionated (shorter courses with larger doses per treatment) regimens are effective in relieving pain from metastatic bone disease and epidural spinal cord compression. Whole brain radiotherapy plays an important role in the management of brain metastases. More aggressive treatment with surgery, stereotactic radiosurgery, or high dose conventional radiotherapy may be appropriate for selected patients with a favourable prognosis.

Radiotherapy plays an important role in palliating the symptoms of metastatic disease. It is commonly employed to treat bone and cerebral metastases, as well as symptoms arising from the primary site of disease. Palliative treatments make up a significant proportion of a radiotherapy departments’ workload, typically accounting for 30-50% of treatments delivered. Potential benefits from any palliative treatment must be carefully balanced against toxicities and optimal resource utilisation. Ideally, palliative treatments are effective, cause minimal side-effects, consume few resources and have little or no negative impact on quality of life. Many factors need to be considered when deciding on appropriate palliative treatment and on how aggressively to treat individuals. Here we discuss the palliative radiotherapy treatments commonly employed, as well as highlight selected emerging technologies.

Bone metastases
Bone is a common site of metastatic disease, with as many as 80% of patients with solid tumours developing painful bony metastases during the course of their illness.1 Bone metastases are a particularly common manifestation of distant relapse from prostate, breast and lung cancers. They can cause severe and debilitating effects including pain, hypercalcaemia, pathological fracture and epidural spinal cord compression.

External beam radiotherapy can significantly reduce pain, with overall response rates of 60-70% and a complete response in one-third of patients.2 The most commonly used schedules for treatment of bone metastases are a single 8 Gy fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions. Three meta-analyses,3-5 and a recent update by Chow et al.,6 have demonstrated the efficacy of a single fraction compared to multiple fractions, with no difference in overall and complete response rates in patients with uncomplicated bone metastases. Dose fractionation choice does not significantly impact on pathological fracture or spinal cord compression rates at the irradiated site. Retreatment rates are higher after a single fraction (20% compared with 8%), however this may be due to radiation oncologists’ increased willingness to retreat after a previous single treatment.2 Single treatments have the advantage of being more convenient than fractionated courses, which is of particular importance in the palliative setting. Acute side-effects are generally similar between single and multiple treatment regimens; however several authors have reported more acute toxicities from multiple fractions.6-8 These findings have led to a single 8 Gy fraction being the recommended treatment for uncomplicated painful bone metastases in the recent American Society for Radiation Oncology guidelines,9 and by the UK Royal College of Radiologists.10 Despite the evidence, there continues to be a reluctance to prescribe a single fraction. As studies of patterns of practice in Australia and New Zealand demonstrate, radiation oncologists continue to favour fractionated courses.11 Surveys on an international scale also demonstrate this practice, with fractionated courses favoured over a single treatment, particularly in the US.12

Controversy remains regarding the optimal dose fractionation for certain subgroups of patients with bone metastases. Specific groups include patients deemed to have a relatively good prognosis, patients with bone metastases causing neuropathic pain and patients with ‘complicated’ lesions, ie. bone metastases causing a fracture, spinal cord compression, or with a soft tissue component. For patients deemed to have a better prognosis there is little evidence to support the use of multiple fractions. The RTOG (Radiation Therapy Oncology Group) 9714 trial,8 which compared a single 8 Gy fraction with 30 Gy in 10 fractions, included only patients with breast or prostate cancer, with 75% of patients having a Karnofsky performance status of ≥70. The authors found no dose response and concluded that a single fraction should be the standard treatment for all patients, including those with a favourable prognosis.

For patients with neuropathic pain from bony metastases, the optimal dose and fractionation schedule remains unclear.13 Only one randomised trial has addressed the issue comparing a single 8 Gy fraction with 20 Gy in 5 fractions, finding no significant difference in overall response rates.14 Outcome measures other than pain response were generally poorer in the single-fraction arm, including time to treatment failure. Although interpreting
the results with caution, the authors concluded that it was reasonable to recommend multiple fractions (where resources allow), except in cases of poor performance status, where a single fraction is appropriate.

**Stereotactic body radiotherapy (SBRT)** is emerging as a promising technique for carefully selected patients. Vertebral metastases commonly cause pain and if left untreated may lead to fracture and/or epidural spinal cord compression (ESCC). Conventional fractionated radiotherapy encompasses the tumour volume plus a margin to avoid geographical miss and treat subclinical disease extension. This approach limits the dose that can be delivered to the tumour, particularly in the setting of re-irradiation, due to dose constraints of adjacent normal tissue (most notably the spinal cord). Technological advances in radiotherapy planning and delivery, namely the advent of intensity modulated radiotherapy and image guided radiotherapy, have led to the emergence of SBRT as an alternative, more aggressive treatment option to conventional radiotherapy for selected patients with spinal metastases.

Spine SBRT typically involves one to five fractions of high dose radiation to the target volume while sparing the surrounding normal tissues. Common doses include 24 Gy in 3 fractions or 16 Gy in a single fraction. This allows delivery of four to six times the biologically effective dose of conventional external beam radiotherapy, with the aim of maximising local disease control and reducing re-treatment rates, while minimising the risk of radiation myelopathy. Vertebral metastases provide an ideal application for SBRT techniques given the anatomy of the spine and the potential morbidity associated with uncontrolled vertebral disease. SBRT is much more complex and resource intensive than conventional radiotherapy, with patient selection requiring a multidisciplinary approach. Hence this treatment is currently limited to patients with a good performance status, low volume of metastatic disease and ‘radio-resistant’ tumour histology.

Published data confirms the efficacy of SBRT, with response rates comparable to conventional radiotherapy and local control rates of 80-95%. However, current evidence remains limited to non-randomised trials and retrospective series. The clinical advantages of SBRT over conventional treatment remain controversial; a randomised RTOG trial (RTOG 0631) is currently underway to compare SBRT and conventional radiotherapy prospectively. Favourable dose distributions achievable with SBRT also show promise in the setting of re-irradiation of vertebral metastases.

**Epidural spinal cord compression**

ESCC is an important complication of metastatic disease involving the spine or epidural space. If left untreated, ESCC can lead to relentless pain and major neurological deficits. The goals of treatment are pain relief, neurological maintenance or recovery, and improving or maintaining quality of life. This should be achieved utilising treatments that are appropriate for the patient’s life expectancy and burden of disease. In general, patient survival with ESCC is three to six months. However, factors indicating a better prognosis include a solitary skeletal metastasis, absence of brain and visceral metastases, and a long interval between diagnosis of cancer and presentation with ESCC. The primary disease site is of prognostic value, with one report demonstrating poor survival with non-small cell lung cancer, (median survival 1.5 months), while myeloma had the best median survival at 6.7 months.

The ability to ambulate at presentation is not only an important quality of life factor but is of prognostic value, with several authors documenting significantly improved survival in patients able to mobilise after treatment. Rades et al also demonstrated that patients with a slower onset of motor deficits had favourable functional outcomes. The single most important prognostic factor for regaining or maintaining ambulation after treatment of an ESCC is pre-treatment neurologic status, highlighting the importance of prompt diagnosis and treatment.

Individualised treatment of ESCC requires consideration of prognosis, spinal stability, histology, presence of bony compression and previous spinal irradiation. Bony compression is a negative predictive factor for achieving ambulation after radiotherapy. Although there is limited evidence, it is generally accepted that bony compression and/or spinal instability represent relative indications for surgery.

In carefully selected patients, aggressive surgical debunking plus spinal stabilisation followed by radiotherapy, leads to higher ambulatory rates compared with radiotherapy alone. Patchell et al evaluated patients with a known diagnosis of cancer (other than lymphoma and primary spine tumours), a single level of cord compression, and paraplegia for no more than 48 hours. Patients received either radiotherapy alone (30 Gy in 10 fractions), or direct circumferential surgical decompression followed by the same radiotherapy. The study was terminated early after a planned interim analysis demonstrated that patients treated with surgery followed by radiotherapy had a significantly higher ambulatory rate (84% versus 57%) and retained the ability to walk significantly longer than those treated with radiotherapy alone (median 122 v 13 days). However, surgery is associated with considerable morbidity which must be considered when deciding on optimal treatment.

Neurologic progression during or directly after radiotherapy is another indication for surgical intervention. Patchell et al reported that 30% of patients who underwent surgical salvage following progression during or directly after radiotherapy, regained the ability to ambulate. However, surgery following radiotherapy was associated with a near doubling of toxicity compared with those who underwent surgery first.

Radiotherapy alone remains an important primary modality in the treatment of ESCC, as many patients are unsuitable for surgery due to medical co-morbidities, poor performance status, short life expectancy, or extensive spinal involvement. Pain from ESCC is expected to respond to radiotherapy in 60-80% of cases, but functional benefits are more variable. In a report by Maranzano et al, 90% of patients who were ambulant pre-treatment retained this ability and 30% of non-walking patients regained ability. However, none of the 17 paraplegic
patients improved with respect to ambulation. Patients with radiosensitive tumours, such as myeloma, seminoma, lymphoma and breast cancer, have a higher likelihood of functional recovery, even if paraplegic at presentation.

Optimal radiotherapy dose for treatment of ESCC remains uncertain. Various dose fractionation schedules have been reported, ranging from a single 8 Gy fraction to more protracted courses such as 30 Gy in 10 fractions. In patients with a good prognosis who are ineligible for surgery a more protracted course may be beneficial. A prospective, international non-randomised study of 231 patients treated with either short course (a single 8 Gy fraction or 20 Gy in 5 fractions) or long course (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions) radiotherapy, concluded that longer fractionation schemes improved progression-free survival (72% v 55%) and local control (77% v 61%) at 12 months. The radiotherapy schedule did not impact on overall survival or motor function post treatment. In addition, in a prospective study by Rades et al, 40 Gy in 20 fractions did not improve functional outcomes or ambulatory status compared to 30 Gy in 10 fractions. As such, the debate as to whether protracted courses are truly beneficial remains open and is currently being evaluated in a randomised trial (SCORAD III) comparing 20 Gy in 5 fractions to a single 8 Gy fraction.

Radiotherapy schedules for patients with a poor prognosis have been evaluated in two randomised control trials by Maranzano et al. The first compared 18 Gy in two fractions a week apart, with split course radiotherapy (15 Gy in three fractions, four day rest, followed by 15 Gy in five fractions) to a total dose of 30 Gy in two weeks. There was no significant difference in ability to ambulate, duration of ambulation, bladder function, overall survival, toxicity or pain relief. In the second study, patients were randomised to 16 Gy in two fractions over one week or a single 8 Gy fraction. The same outcomes were assessed with no difference shown between arms. Thus a single 8 Gy fraction is effective and safe in poor prognosis patients.

Brain metastases

Brain metastases are a common source of morbidity and mortality in cancer patients, affecting 20-40% of adults with systemic malignancy. The mainstay of treatment for brain metastases has been corticosteroids and whole brain radiotherapy (WBRT). In patients with multiple unresectable brain metastases, the use of WBRT increases the average survival from one month with corticosteroids alone, to three to six months. Similar to ESCC, prognosis is one of the key elements in deciding on the most appropriate treatment. Key parameters that determine survival after the diagnosis of brain metastases are performance status, the extent of extracranial disease and age – parameters included in recursive partitioning analysis prognostic classes. More recently, the prognostic importance of primary site and number of metastases have been recognised by inclusion in the Diagnosis-Specific Graded Prognostic Assessment.

The benefit of WBRT in poor prognosis patients has not been clearly established. A prospective observational study by Bezjak et al of patients treated with corticosteroids and WBRT found that only 19% of patients had improvement in their neurological symptoms or quality of life one month after radiotherapy. Nearly a third of patients had worse neurological symptoms and 27% were deceased at one month or soon after treatment. The authors proposed that the apparent lack of benefit from WBRT seen in their study may be related to the poor performance status of subjects and also questioned whether even short fractionation schedules of radiotherapy were appropriate for some patients. This question is currently being evaluated in a phase III randomised control trial assessing the impact of radiotherapy versus supportive care on quality of life and survival in patients with inoperable brain metastases from non-small cell lung carcinoma.

Patients with oligometastatic cerebral disease (ie.1-4 brain metastases), in the setting of otherwise favourable prognostic factors, may benefit from a more aggressive approach. Three randomised trials have addressed the utility of surgery in addition to WBRT for a solitary cerebral metastasis. Two of these trials demonstrated a survival advantage with the addition of surgery. The third trial showed no difference in median survival with the addition of surgery. This incongruent result may be due to inclusion criteria allowing patients with a Karnofsky performance status as low as 50. It is important to note that in the two positive trials, the survival was universally poor for patients with disseminated disease or advanced age. Thus, it appears that for some good prognosis patients with a resectable solitary cerebral metastasis, surgery can prolong survival relative to WBRT alone, however there is no evidence to support surgery for patients with a poor prognosis.

Similarly, stereotactic radiosurgery has been shown to prolong survival in selected patients. Stereotactic radiosurgery utilises multiple convergent beams to deliver a single high dose of radiation precisely to a target volume, with rapid dose fall to minimise the risk of damage to surrounding normal tissue. An RTOG trial of WBRT +/- radiosurgery in patients with 1-3 brain metastases showed an improvement in survival for patients with a solitary lesion. A randomised trial by Kondziolka et al of WBRT plus radiosurgery, versus WBRT alone, was terminated after accrual of just 27 patients when an interim analysis showed one-year local brain failure rates of 8% versus 100%, respectively. There was no difference in survival between the two arms; however this may be due to the small sample size or the inclusion of patients with 2-4 metastases.

The positive results of aggressive local therapy have raised the question of the additional benefit of WBRT. This issue has been examined in multiple randomised trials which have demonstrated that in oligometastatic patients ≤ 4 cerebral metastases), the addition of WBRT to local therapy leads to lower rates of intracranial failure (both at the original site of the metastasis and elsewhere in the brain), but does not improve survival.

Multiple studies have compared different radiation schedules of WBRT. Schedules examined include conventional fractionated regimens of 12 Gy in 2 fractions, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in 20 fractions and an
accelerated schedule of 40 Gy in 20 fractions delivered twice daily. Despite extreme heterogeneity in these schedules, there is no compelling evidence to demonstrate differences in survival, palliation, or toxicity. In the largest of these trials, performed by the RTOG, patients were assigned to 40 Gy in 20 fractions, 40 Gy in 15 fractions, 30 Gy in 15 fractions, 30 Gy in 10 fractions, or 20 Gy in 5 fractions. The overall response rate and median survival were equivalent in all arms. Patients treated with larger fractions over a shorter time responded more quickly, but the duration of clinical response and time to progression were similar in all treatment arms. This has led to 30 Gy in 10 fractions or 20 Gy in 5 fractions being accepted as standard fractionation for palliation of bone metastases.

Conclusion
Radiotherapy is an effective modality in palliating symptoms of metastatic disease and in certain circumstances may prolong survival. Treatments should be individualised based on the patient’s overall disease state and performance status, among other factors. In general, shorter fractionation schedules, or in the case of bony metastases a single fraction, provide effective treatment while minimising inconvenience for patients, and should be strongly considered as the treatment regimen for all palliative patients.

References


