

Editor's note:

“Palliative Radiotherapy Column” features articles emphasizing the critical role of radiotherapy in palliative care. Chairs to the columns are Dr. Edward L.W. Chow from Odette Cancer Centre, Sunnybrook Health Sciences Centre in Toronto and Dr. Stephen Lutz from Blanchard Valley Regional Cancer Center in Findlay, gathering a group of promising researchers in the field to make it an excellent column. The column includes original research manuscripts and timely review articles and perspectives relating to palliative radiotherapy, editorials and commentaries on recently published trials and studies.

Palliative Radiotherapy Column (Review Article)

Radiotherapy for neuropathic pain due to bone metastases

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Abstract: Neuropathic bone pain (NBP) due to bone metastases is estimated to affect about 15-25% of cancer patients experiencing pain. Numerous randomized trials have shown that single or multiple fraction radiotherapy (RT) for painful bone metastases produces intention-to-treat overall response rates (RRs) of approximately 60%, but there are few data on RT for NBP, *per se*. One randomized trial, Trans Tasman Radiation Oncology Group (TROG) 96.05 showed similar outcomes for NBP, although a single 8 Gy fraction was not proven to be as effective as fractionated treatment (20 Gy in five fractions), with RRs of 53% and 61%, respectively. A recent small, single institution series reported a comparable overall RR for NBP using a variety of fractionation schedules. Although TROG 96.05 found no statistically significant difference in the rates of re-treatment, spinal cord compression, or pathological fracture at the index site by arm, one subsequent single institution retrospective review cautioned against using single fractions for spine (the skeletal site causing the vast majority of NBP), particularly in the presence of high “spinal instability” scores. In that study, single fractions were associated with more spinal adverse events (including symptomatic vertebral compression fracture and spinal cord compression) than fractionated schedules. Although re-irradiation of bone metastases is feasible and moderately effective, there are no outcome data specific to re-treatment of NBP. In summary, NBP may appropriately be treated with fractionated RT, although single fractions may also be reasonable for patients with poor performance status and/or limited expected survival, and in centers with prolonged waiting times for fractionated treatment, given that re-treatment is possible for either. In addition, multiple fractions may be preferable for vertebral metastases in the setting of high “spinal instability” risk.

Keywords: Bone metastases; neuropathic pain; palliative radiotherapy; review

Submitted Aug 17, 2015. Accepted for publication Aug 19, 2015.

doi: 10.3978/j.issn.2224-5820.2015.08.03

View this article at: <http://dx.doi.org/10.3978/j.issn.2224-5820.2015.08.03>

Introduction

Numerous randomized controlled trials have confirmed the effectiveness of radiotherapy (RT) to palliate painful bone metastases. Perhaps surprisingly, a single moderately large dose, typically 8 Gy, achieves similar intention-to-treat overall response rates (RRs) to higher dose fractionated schedules (e.g., 20-30 Gy in 5-10 fractions), namely around 60%. For assessable patients (i.e., excluding drop-out), the RRs are correspondingly higher, but still statistically equivalent for single *vs.* multiple fractions (72-74%). There are also no statistically significant differences in the rates of complete and partial pain response, pathological fracture or spinal cord compression at the treated site, or any notable differences in acute toxicity. Although re-irradiation rates are usually higher after single fractions (20% *vs.* 8%), this may partly be explained by the reluctance of radiation oncologists to re-treat after higher (fractionated) doses (1).

However, the vast majority of these randomized trials either excluded or did not explicitly identify patients whose bone pain had a neuropathic component, referred to here as “neuropathic bone pain” (NBP). Neuropathic pain is typically described using terms such as burning, tingling, searing, stabbing, shooting, electric shocks or pins and needles and is experienced in a superficial dermatomal distribution supplied by peripheral or cranial sensory nerves. It may be associated with altered sensation in the same distribution (e.g., hypoesthesia, hyperesthesia, paresthesia, allodynia). This is in contradistinction to localized bone pain experienced at the site of the osseous metastasis, although the latter can be associated with nearby pain due to secondary (protective) muscle spasm e.g., paravertebral pain and tenderness overlying the erector spinae muscles adjacent to vertebral metastases. Neuropathic pain may also be confused with pain referred in a “sclerotomal” distribution e.g., hip pain radiating down the thigh to the knee. This is due to the fact that the sensory nerves supplying joints also supply the muscles and bones acting about the joint. This pain tends to be perceived as deep rather than cutaneous, and without the troublesome neuropathic features listed above (2).

The prevalence of neuropathic pain

Neuropathic pain is a common and under-recognised source of distress in cancer patients (3). Although medications are first line treatment, neuropathic pain is notoriously resistant to pharmacological intervention. Its causes include tumour

(malignant bone or soft tissue mass irritating adjacent nerves via elaboration of pain mediators, or by directly compressing the nerves), treatment (surgery, chemotherapy, RT), and comorbid conditions (e.g., post-herpetic neuralgia, diabetic neuropathy). The prevalence of neuropathic pain (pure or mixed nociceptive/neuropathic) for cancer patients experiencing pain in various oncology settings is around 30-40% (3-5). “Tumour”, the majority being bone metastases, constitutes the commonest cause. Hence, NBP accounts for approximately 15-25% of pain in this population overall (5,6), and (personal communication, N Nakamura, Aug 2015).

The NBP trial

Considering its prevalence, and the frequent use of RT to palliate bone pain in general, surprisingly little has been published about the role of RT for NBP. Only one randomized trial has explicitly addressed this question viz. Trans Tasman Radiation Oncology Group (TROG) 96.05 (7). At the time of trial development in 1995, the definition of neuropathic pain by the International Association for the Study of Pain (IASP) was “pain initiated or caused by a primary lesion or dysfunction in the nervous system” (8), concise but not particularly helpful clinically. For the purposes of trial eligibility, NBP was therefore defined empirically as pain or dysesthesia radiating superficially along the distribution of peripheral nerve(s) compressed or irritated proximally by the presence of a bone metastasis in the vicinity of the nerve(s), often accompanied by sensory changes in the same dermatomal distribution. The index bone lesion needed to be visible on plain X-ray and/or bone scan, with no other metastases along the same distribution which might serve as an alternative explanation for the putative NBP. This was the conventional 2-D planning era, when RT fields were marked on simulation radiographs rather than targeted on computer work stations using planning CTs. It was also prior to routine availability of MRI. Accordingly, 3-D diagnostic imaging was not mandated in TROG 96.05. Other major eligibility criteria were known malignancy, no change in systemic treatment within 6 weeks before or anticipated within 4 weeks after RT, and no clinical or radiological evidence of cord/cauda equina compression. The primary endpoints were pain response within 2 months of commencement of RT and time to pain progression treatment failure (TTF).

Interestingly in retrospect, the above study definition was very similar to the most recent update from the Neuropathic Pain Special Interest Group (NeuPSIG) of the

IASP as pain arising as a direct consequence of a lesion or disease affecting the somatosensory (i.e., afferent) part of the nervous system, as distinct from the motor (efferent) or autonomic components. Additionally, the confidence with which a diagnosis of neuropathic pain can be made is graded as “possible”, “probable” or “definite” based upon four criteria viz. plausible pain distribution, history suggesting an appropriate index lesion or disease, sensory signs confined to the corresponding innervation region, and confirmatory diagnostic tests (9). Although it is very difficult to be certain retrospectively that neuropathic pain is present, every effort was made during the conduct of TROG 96.05 to confirm patient eligibility by stringent source data verification case sampling (10,11).

Between 1996 and 2002, 272 NBP patients from 15 Australian, New Zealand and UK centres were randomized to a single 8 Gy (8 Gy/1) or 20 Gy in five fractions (20 Gy/5). The index sites were spine 89%, rib 9% and others 2%; commonest primary cancers were lung 31%, prostate 29% and breast 8%; 72% of patients were male and the median age was 67 years (range, 29-89 years). Median survival was 4.8 mo (95% CI, 4.2-5.7 mo) with no significant difference between trial arms.

The intention-to-treat overall RRs (95% CI) were 53% (45-62%) for 8 Gy/1 and 61% (53-70%) for 20 Gy/5 (P=0.18). The complete RRs were 26% vs. 27%, respectively (P=0.89). The estimated median TTFs were 2.4 and 3.7 mo, respectively, with the comparison of TTF curves of borderline significance (log-rank P=0.056). Excluding 38 invaluable patients, the corresponding overall RRs for assessable patients were 61% (52-70%) and 72% (63-80%), respectively. There were no statistically significant differences in the rates of re-treatment, cord compression or pathological fracture at the index site by trial arm. Toxicity was generally absent or mild, with only “flare effect” (temporary worsening of pain after treatment) somewhat worse following 8 Gy/1.

The analysis and interpretation of this non-inferiority trial was complex, but the conclusion was that, although 8 Gy/1 was not statistically significantly worse than 20 Gy/5, nor was it shown to be as effective (the quantitatively small differences were generally in favour of 20 Gy/5). Accordingly, the recommendation was that 20 Gy/5 may generally be the preferable option for NBP, but that 8 Gy/1 may be reasonable for patients with poor performance status and/or short expected survival, or in centres with long waiting times for fractionated treatment.

This, of course, raised the question as to whether higher

dose treatment (e.g., 30 Gy/10) may be more effective for NBP. A Canadian led project was initiated in 2011 to explore this possibility, but for a variety of reasons, was eventually abandoned during development, and the issue remains unresolved at the time of writing.

A post-hoc subset analysis of TROG 96.05 comparing the costs of RT delivery, analgesia and hospital admissions following either one or five fractions of RT for NBP in the Australian setting, verified that the former is cheaper overall. The potential savings per patient in 2000/01 Australian dollars from using single fractions was approximately \$1,000 (range about \$750-\$1,500 on sensitivity analysis) (12).

Other relevant literature

Non-randomized data on RT for NBP

One recent, Japanese single center series of 87 patients compared RT for bone metastases with and without neuropathic features. Fractionation schedules were 8 Gy/1, 20 Gy/5, or 30 Gy/10 at clinicians' discretion. The overall RRs for the 64 evaluable patients in the two groups with and without NBP were 59% (95% CI, 33-82%) vs. 55% (95% CI, 40-70%), respectively (personal communication, N Nakamura, Aug 2015). Noting that the confidence intervals were wide, and that patient selection and definition of response differed from those used in TROG 96.05, the RR of 59% for assessable patients with NBP was comparable to the 67% overall RR for assessable patients in TROG 96.05 (7). Taken together, these data suggest that the response of NBP to RT is similar to that of pain from the general bone metastases patient population (1).

RT for spine metastases

Of obvious concern in treating spine metastases with single fraction RT is whether the low dose relative to fractionated RT is enough to prevent development of complications such as vertebral crush fracture or spinal cord compression. As noted above, both meta-analyses of the randomized bone metastases fractionation trials overall (1), and TROG 96.05 in particular (where 89% of index sites were spine) (7), have been reassuring in this respect.

However, a recently published single institution retrospective review of 299 spine metastases treated with RT (13) found significantly more spinal adverse events at the index site (defined as symptomatic vertebral fracture, hospitalisation for site-related pain, salvage surgery,

interventional procedure, new neurological symptoms or cord compression) after a single fraction than after multiple fractions [hazard ratio (HR) =2.8 (1.5-5.2), $P=0.001$ on multivariate analysis]. In particular, the crude rates of cord compression were 10.6% *vs.* 1.7% ($P=0.003$), and symptomatic vertebral fracture were 13.6% *vs.* 3.0% ($P=0.01$), respectively. The other major finding of this study was that it confirmed spinal adverse events after RT are significantly associated with the so-called Spinal Instability Neoplastic Score (SINS). This classification system, published in 2010, was based upon the summation of six sub-scores relating to site, pain, structural & radiological features, to give a total between 0 and 18 for the risk of spinal instability (13). Its predictive value after RT had not previously been assessed. On multivariate analysis, patients with a SINS ≥ 11 had higher risk of spinal adverse events than those with a SINS < 11 [HR =2.5 (1.3-4.9), $P=0.007$]. Although a little over half of the patients in this series were considered retrospectively to have neuropathic pain, the analysis did not focus specifically upon the issue of NBP. However, these data do caution against using single fractions for spine metastases in patients with high SINS, especially those with longer predicted survival, while further studies examining this question are awaited.

Re-irradiation for NBP

In TROG 96.05, 73 of the 272 randomized patients were re-irradiated. The crude re-treatment rates were 29% for 8 Gy/1 *vs.* 24% for 20 Gy/5 ($P=0.41$). A wide range of schedules were used for the second RT course at clinicians' discretion, most commonly 8 Gy/1 or 20 Gy/5. However, because patients were off-study following TTF, response to re-irradiation was not formally assessed.

A Canadian-led international, non-inferiority trial (NCIC SC.20) subsequently randomized 850 patients to 8 Gy/1 or 20 Gy/5 for re-irradiation of bone metastases previously treated with RT (14). The intention-to-treat overall RRs were 28% and 32% ($P=0.21$), and the per-protocol overall RRs were 45% and 51% ($P=0.17$), respectively. Multiple fractions were associated with more acute toxicity (lack of appetite and diarrhea) but there were no statistically significant differences in the rates of pathological fracture or cord compression at the index site by arm. As was the case with TROG 96.05, the statistical analysis was complicated, but interestingly, the results also tended to slightly favour 20 Gy/5 numerically. Although 8 Gy/1 was non-inferior to 20 Gy/5 by trial criteria based upon the intention-to-

treat RRs, this conclusion was not robust to per-protocol analysis. Accordingly, the authors suggested that trade-offs between efficacy and toxicity might exist. However, neuropathic features were not explicitly identified in NCIC SC.20, and although it is plausible that the findings would apply to re-treatment of NBP, this is currently unknown.

In summary, NBP is common in cancer patients experiencing pain. Limited data on the use of palliative RT for NBP suggest that it responds similarly to pain from bone metastases in general, but there appears to be a stronger case for the use of fractionated schedules to treat NBP. Nevertheless, single fractions are a reasonable option for some patient sub-sets.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Roos DE. Radiotherapy for neuropathic pain due to bone metastases. *Ann Palliat Med* 2015;4(4):220-224. doi: 10.3978/j.issn.2224-5820.2015.08.03