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Review Article

'Who', 'when' and 'how' in re-irradiation of recurrent painful bone metastases

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ABSTRACT

Re-irradiation of painful bony metastases is increasingly performed since patients are receiving better systemic treatments and having longer life expectancy, and may also be due to the increase use of initial single fraction radiotherapy. However, randomized control trial on the efficacy of re-irradiation is lacking. A recent meta-analysis concluded with a 58% response rate for pain relief by re-irradiation of symptomatic bone metastases. In this review, the effectiveness of re-irradiation in terms of clinical and economical aspects, and clinical questions on who, when, and how to re-irradiate would be discussed. A brief review of other treatment options and comparison with re-irradiation of bone metastases would be performed.

1. Re-irradiation of symptomatic recurrent painful bone metastases

Radiotherapy to painful bony metastases is undoubtedly useful in pain relief. It was demonstrated on a recent updated systemic review [1] that the effectiveness in pain relief is comparable for single-fraction (SF) and multi-fraction (MF) radiotherapy. It was found that 11–42% and 0–24% of patients given SF and MF treatment respectively would eventually require retreatment [2]. The re-irradiation rate is significantly higher in patients with single fraction radiotherapy (2.6 fold, 20% versus 9% in the SF arm versus the MF arm respectively) [1]. On the other hand, with increased effectiveness of systemic cancer treatment, patients nowadays have longer life expectancy. Thus, bone re-irradiation is increasingly considered. A recent systematic review and meta-analysis by Huisman et al. [3] included 2694 patients treated with re-irradiation from 4 Gy up to 26 Gy, 2–8 Gy per fraction daily. It showed an overall pain response of 58%.

Toxicities are the major concern for re-irradiation. Huisman et al. [3] reviewed the toxicities from various studies, and reported that toxicity data was only available in three studies from Jeremic et al. in 1999 [4]and 2002 [5], and van der Linden et al. in 2004 [6] respectively. Jeremic et al. 1999 [4] reported that there was no serious acute toxicity ($\geq$RTOG grade 3). Pathological fractures were reported in 3/135 (2%) patients and spinal cord compression in 3/135 (2%) patients.. The main side effect was mainly gastrointestinal (grade 1 or 2 nausea and vomiting) in 18% (25/135). The same group in 2002 [5] reported there was no acute or late high-grade toxicity (>3), no pathological fractures or spinal cord compression. Van den Linden et al. [6] reported retreatment toxicities in both single-fraction (SF) versus multi-fraction (MF) treatment groups with Rotterdam Symptom Checklist. Most SF and MF patients reported no or only mild nausea and vomiting. Nausea score 4 (very bad) was reported in 12% of MF patients vs. 6% of SF patients ($p=0.39$). Vomiting score 4 (very bad) was reported in 1 MF patient and 2 SF patients ($p=0.49$). Severe tiredness was reported in 18% of SF patients and 27% of MF patients ($p=0.41$). Overall, it seems that re-irradiation is a tolerable treatment.

Cost effectiveness is another major concern for the governments in countries with public health system. Van-den Hout WB et al. at Netherlands [7] did a cost utility analysis showing the cost of radiation treatment including re-treatment for bone metastases using SF versus MF were €2438 versus €3311 respectively. RTOG 9714 groups showed the expected mean cost was US $1009 and US $2322 for treating with 8 Gy/1 Fr and 30 Gy/10 Fr respectively [8]. It is evident that SF is more cost effective than MF treatment. Physicians are therefore advised to consider more single fractioned radiotherapy on uncomplicated bone

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metastases based on the similar efficacy and cost effectiveness. Even taking into account of higher re-treatment rate using initial SF radiotherapy, the cost is still lower than performing initial SF and retreatment with MF radiotherapy [7].

In palliative medicine, maintaining the quality of life (QOL) is the most important goal of both patients and palliative physicians. However, there is no trial addressing the QOL of patient receiving re-irradiation for their painful bone metastases. The development of EORTC-QLQ BM22 [9] would probably standardize the outcomes on QOL in upcoming trials, and hopefully, we will have a better idea on how re-irradiation improves the QOL of patients in quantitative means. A simplified treatment plan would definitely help in improving the QOL of patient. Successful re-irradiation to painful bony sites may potentially minimize the use of analgesics. Thus, patients would definitely benefit in terms of improving their QOL.

2. Re-irradiation of other organs

Re-irradiation of other body sites is increasingly attempted by physicians worldwide. However, randomized control trials are again lacking. The response rate of re-irradiating each site varies. Table 1 shows a comparison of response rate of re-irradiating different organs.

Late toxicities are challenging for physicians. Tissue tolerance of various organs had been discussed by Nieder et al. [10] in 2000. Having said that toxicities were observed after exceeding a certain cumulative dose at BED at 2 Gy, oncologists often try their best to stretch the maximal tolerance of major organs by using better dose painting technique to minimize dose to organs at risk, and at the same time giving the best local control with irradiation. Dose constraints of the brain stem and brain tolerance in re-treatment of head and neck cancer recurrences were well documented on RTOG 9610 and 9911 protocols, though long term results of complications are awaited. Comparing re-irradiating organs with painful bone metastases especially non-axial bones, there is much less concern for late complications of bones.

3. Alternatives in treating bone pain recurrence

Huisman et al. [3] suggested physicians to explore more on other sorts of treatment including radionuclides and bone targeting therapy. It is therefore worthwhile to understand more on the response rate and cost effective of other alternatives in comparison with that of re-irradiation of bone metastases.

3.1. Analgesics

Pain management with oral analgesics is usually conducted according to World Health Organization (WHO) analgesic ladder, and it provides adequate pain control in 80–90% of patient [11]. Cost of oral analgesics varies. The cost of commonly used analgesics such as acetaminophen, NSAID, codeine, tramadol and morphine sirup is usually low with less than $15 US dollars per day. It is more costly for fentanyl patches in cases of difficult pain control (A 100-microgram patch of fentanyl costs between $60 and $75 US dollars). However, the side effects of analgesics will cause considerable nuisance to patients' QOL. Common side effects of opioid drugs include nausea and vomiting, constipation and dry mouth. Significant side effects of NSAIDs include risk of peptic ulcer and bleeding. The quality of life is greatly jeopardized by complicated schedule of analgesics and their side effects, especially in elderly patients having co-morbidities already given multiple medications. Therefore, it is desirable to minimize analgesics. Moreover, mechanical pain and breakthrough pain are often difficult to control with regular analgesics. Thus, many patients prefer to minimize mobilization if they suffer from mechanical bone pain, which subsequently lead to debilitation and other undesired complications such as bed sores, chest infection and depression. These patients may need localized treatment, for example, radiotherapy, surgery or nerve blocks for controlling baseline pain.

3.2. Bone modifying agents

Bisphosphonates have been widely used in the past decade. It was shown to be effective in reducing skeletal related events (SREs) in breast cancer using zoledronic acid by 41% compared with placebo [12], by 11% in prostate cancer [13]. FDA approved its indications in reducing hypercalcaemia in malignancy, in multiple myelomas, and in bone metastases of solid tumors [14]. In terms of pain relief, marked pain relief (defined as a two-point decrease lasting for $<=6$ weeks) was reported by Conte et al. [15] in 44% of pamidronate patients and in 30% of controls in breast cancer patients with bone metastases ($p=0.025$). Wheinfurt et al. [16] reported that patients receiving zoledronic acid had a 33% chance of a favorable pain relief, compared with 25% for patients receiving placebo in prostate cancers with bone metastases ($p=0.04$; 95% CI 0.5%–15.6%). A meta-analysis conducted by Wong et al. [17] reviewing 30 randomized control trials concluded with favorable likelihood of pain relief and analgesic reduction at week 4 and week 12. Bisphosphonates are undoubtedly useful for multiple painful bony sites beyond localized treatment. However, side effects including renal toxicity, osteonecrosis of jaw (ONJ), and hypocalcaemia are well known. The mean time to occurrence of ONJ was found to be 1.8 years after the most potent bisphosphonate zoledronic acid [18]. Therefore, many physicians are cautious for its long term use. For

Table 1
Re-irradiation in different body parts

Organ/ Trials	First RT fractionation/dosage	Second RT fractionation/ dosage	Response rate
Brain Akiba T et al. 2012 [29] N=31	30 Gy/10 Fr	3-4 Gy/1–20 Fr	68% (symptomatic improvement) 55% tumor RR
Brain Sadikov E et al. 2007 [30] N=72	20 Gy/5 Fr	15–25 Gy, 2–3 Gy per fraction	31%
Brain Hazuka MB et al. 1988 [31] N=44	30–36 Gy (at 1.5–4.0 Gy/fraction)	6–36 Gy at 2.0–4.0 Gy/fraction	27% neurological improvement
Head & Neck Review by Mendenhall et al. 2008 [32] NPC: N=406 Non-NPC: N=772	NPC*: 60–70 Gy Non-NPC:	NPC: with brachytherapy or SRS. Dose varies Non-NPC	(local control) NPC:47-89% Second relapse: 33% Non-NPC: 4–81% loco-regional control
Spinal Cord Maranzano et al. 2011 [33] N=24	8–16 Gy/1–2 Fr	4–20 Gy, 3–8 Gy per fraction	85.7% in ambulant patients 0% in non-ambulant patients
Lung Critical review by Jeremic et al. 2011 [34] N=307	30–78 Gy	4–60 Gy	48–81% (symptom improvement)

* NPC: nasopharyngeal carcinoma.

pain recurrence after completing a course of bisphosphonate, other alternatives have to be considered.

A novel fully human monoclonal antibody, denosumab, seems to be a promising bone modifying agent. It inhibits the maturation of osteoclasts by binding to and inhibiting RANKL. Cleeland et al. [19] reported its superior outcome in alleviating pain, and also a statistically significant 4-month delay in progression to moderate to severe pain in patient with no or mild pain at baseline with denosumab compared with zoledronic acid. A meta-analysis published in similar period by Sun et al. [20] reviewed seven reports from three randomized controlled trials involving 5723 patients and showed that denosumab significantly delayed time to first on-study SRE [hazard ratio (HR)=0.83; 95% CI, 0.76-0.90, $P<0.001$], time to multiple SRE (HR=0.83; 95% CI, 0.76–0.90, $P<0.001$), and pain worsening (HR=0.92; 95% CI, 0.86-0.99, $p=0.026$) for patients with bone metastases compared with zoledronic acid, yet similar result in pain improvement. It was approved by FDA for increasing bone mass in patients at high risk for fracture including androgen deprivation therapy (ADT) for non-metastatic prostate cancer or adjuvant aromatase inhibitor (AI) therapy for breast cancer [21].

In terms of cost effectiveness, Cartel et al. [22] reported that cost of denosumab and zoledronic acid including drug, administration and monitoring to be US $25,016 and $15,994 per patient respectively. The cost per quality-adjusted life year (QALY) gained was US $644,000. There was an incremental cost/quality-adjusted life year (QALY) gained > US $600,000 by denosumab, which is far higher than what is considered to be good value for a medical intervention ($50,000–$100,000/QALY). Overall, both zoledronic acid and denusomab are expensive. Patients with multiple sites of complicated bone metastases would benefit from both. However, re-irradiation of isolated painful uncomplicated bony sites would be much more cost effective.

3.3. *Optimizing systemic treatment*

Optimizing systemic treatment may improve symptoms including bone pain and also perhaps improve progression free survival and overall survival. Various new chemotherapy, targeted agents and hormonal therapy are available. Response rates of frequently used systemic treatment in the three commonest cancers are shown on Table 2. However, the patient should be fit to receive such systemic treatment as it will also cause significant side effects affecting the patient's quality of life. In addition, the cost of chemotherapy and new targeted agents remain to be a huge burden to the government and also patients especially in countries that patients need to pay for their own drugs. Vergnenègre et al. [23] reported the cost of docetaxel and pemetrexed in second line treatment of metastatic non-small cell lung cancer were €9709 ± €6272 and €13,436 ± €6508 respectively. The cost-utility was €32,652/quality-adjusted life year for docetaxel and €40,980/quality-adjusted life year for pemetrexed respectively. It is again considerably more costly than delivering palliative radiotherapy treatment. Taking non-small cell lung cancer treatment as an example, even with low response rate and high cost of second line chemotherapy, it is still widely prescribed in metastatic cancer patients for its potential survival benefit.

4. Re-irradiation of bone metastases is efficacious

Overall, re-irradiation of bone metastases is much less costly, having high response rate and low toxicities compared with other alternatives. It is definitely worthwhile to consider re-irradiation in uncomplicated isolated bone metastases having pain recurrence. More understanding on 'who', 'when' and 'how' to re-irradiate bone metastases would be important.

5. Who, when and how to re-irradiate recurrent painful bone metastases

'Who' would likely respond to re-treatment? Jeremic et al. [4] conducted a prospective trial with 4 Gy in one fraction after initial 4 Gy single fraction treatment with a response rate of 74%. Those who initially had a complete response were more likely to achieve another complete response then those with partial response ($p=0.042$), and those with initial partial response were also more likely to achieve another partial response ($p=0.00054$). Even for non-responders, 46% did have a partial or complete response with re-irradiation. Jeremic et al. [5] later conducted another study on 25 patients who receive 4Gy in one fraction after given single fraction radiotherapy (4, 6, or 8 Gy plus 4 Gy) for twice, suggested a response rate of 84%, and 67% in previous responders and non – responders respectively. It seems that both initial responders and non- responders would benefit from re-irradiation for one or more times. Van den Linden et al. [6] reported that the pain score before retreatment significantly predicted retreatment ($P<0.001$). Retreatment for non-responders was successful in 66% SF vs. 33% MF patients ($p=0.13$), and retreatment for progression was successful in 70% SF vs. 57% MF patients ($p=0.24$). However, with the background that SF is as effective as MF treatment in terms of pain response [1], SF is encouraged to be implemented as first line treatment in uncomplicated bone metastases, thus higher response rate of re-treatment may be anticipated in subsequent trials. Overall, it seems that no matter SF or MF treatment was initially given and whether patients responded initially, those presented with recurrence of bone pain would definitely worth being considered for re-irradiation. Those who responded initially may benefit more.

On the other hand, it was also shown that multi-fraction long-course radiotherapy results in better re-calcification and fewer recurrences of spinal cord compression within the irradiated spinal region [24,25]. In case of recurrence, Nieder et al. [10] reviewed that re-irradiation of the spinal cord to a cumulative biological equivalent dose (BED) of 130 to 135 Gy2 was safe when the initial

Table 2
Response rates of commonly used first line and second line systemic therapy

Organ/Systemic treatment	Response rate of 1st line treatment	Response rate of 2nd line treatment
Breast Chemotherapy	42%–72% [35–38] (Docetaxel) 73% (FAC) [39]	42% (retry Docetaxel) [40] 30% (Gemcitabine/Vinorelbine) [41] 30% (Capecitabine) [42]
Breast Hormone	30% (Letrozole) 20% (Tamoxifen) [43]	30.7% (Exemestane + GnRH agonist in pre-menopausal women) [44] 14.3% (Fulvestrant) [45]
Lung Chemotherapy	30.6% (Pemetrexed/Cisplatin) 28.2% (Gemcitabine/cisplatin) [46]	12% (Docetaxel) [47]
Colorectal Chemotherapy + Targeted therapy	64% (Oxaliplatin + Cetuximab) [48]	10.8% (FOLFIRI) 22.9% (FOLIFIRI + Cetuximab) [49]

dose did not exceed 90 Gy2. Therefore, for patients with spinal cord compression or who are at risk of spinal cord compression, a more protracted initial course of radiotherapy is recommended in order to avoid unsalvageable recurrence and complicated calculation during retreatment in patients with good performance status.

'When' to give re-irradiation? It is also generally recommended to consider re-irradiation after at least 4 weeks in patients not responding to initial radiation [26], and definitely at the time when pain recurs. When organs at risk are in-field of re-treatment portal, tissue tolerance has to be taken into consideration. However, as the time for recovery is still unknown, exact tolerance of organs at risk during retreatment is uncertain and more studies are warranted in this aspect.

'How' to give re-irradiation? Jeremic et al. [4] found that there was no difference in efficacy for 4, 6 or 8 Gy in single fraction after an initial 4 Gy single-fraction treatment. Mithal et al. [27] reported the outcomes of 105 patients with 57 out of 280 individual painful sites retreated. The pain response was 87%, in which 74% [17–23] responded with SF treatment and 91% [31–34] responded with MF treatment. The number of patients was small to draw a conclusion if MF was superior compared with SF treatment for re-irradiation. However, in cases when organs at risk are in field, careful calculation to tissue tolerance for the dose fractionation has to be taken into account.

The most optimal situations and the best way to give re-irradiation to bone metastases are still unknown. The results of an ongoing study phase III study NCIC CTG SC20 [28] should be able to answer more on 'how' to deliver re-irradiation. The study included patients with initial radiation dose to the extremities/ ribs/ pelvis with either single or multi-fractionation and only excluded patients with initial dose of 24 Gy in 6 fractions, 27 Gy in 8 fractions or 30 Gy in 10 fractions to the spine or any part of the pelvis encompassing small or large bowel and/or the rectum.

6. Conclusion

Re-irradiation for uncomplicated painful bony sites is highly recommended for its high response rate, favorable toxicity profile and low cost compared with other types of treatment. It also potentially decreases the use of analgesics. Patients' quality of life would certainly be improved. Results of SC 20 are awaited in order to know more on the most optimal way to conduct re-irradiation.

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References

[1] Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clinical Oncology 2012;24(2):112–24.
[2] Chow E, Harris K, Fan G, Tsao M, Sze W. Palliative radiotherapy trials for bone metastases: a systemic review. Journal of Clinical Oncology 2007;25(11): 1423–36.
[3] Huisman Merel, Marice AAJ, van den Bosch, Joost WWijlemans, Marco van Vulpen, Yvette M, van der Linden, Helana MVerkooijen. Effectiveness of reirradiation for painful bone metastases: a systemic review and meta-analysis. International Journal of Radiation Oncology, Biology, Physics 2012;84(1):8–14.
[4] Jeremic B, Shibamoto Y, Igrutinovic I. Single 4 Gy re-irradiation for painful bone metastasis following single fraction radiotherapy. Radiotherapy and Oncology 1999;52(2):123–7.
[5] Jeremic B, Shibamoto Y, Igrutinovic I. Second single 4 Gy reirradiation for painful bone metastases. Journal of Pain and Symptom Management 2002;23(1):26–30.
[6] van der Linden YM, Lok JJ, Steenland E, Martijn H, van Houwelingen H, Marijnen CA, Leer JW. Dutch Bone Metastasis Study Group. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. International Journal of Radiation Oncology, Biology, Physics 2004;59(2):528–37 Jun1 2004;59(2):528–37.
[7] van den Hout WB, van der Linden YM, Steenland E, Wiggenraad RG, Kievit J, de Haes H, Leer JW. Single- versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial. Journal of the National Cancer Institute 2003;95(3):222–9.
[8] Konski A, James J, Hartsell W, et al. Economic analysis of radiation therapy oncology group. 97-14: multiple versus single fraction radiation treatment of patients with bone metastases. American Journal of Clinical Oncology 2009;32:423–8.
[9] Chow Edward, Hird Amanda, Velikova Galina, Johnson Colin, Dewolf Linda, Bezjak Andrea, Wu Jackson, Shafiq Jesmin, Sezer Orhan, Kardamakis Dimitrios, van der Linden Yvette, Ma Brigette, Castro Monica, Arnalot Palmira Foro, Ahmedzai Sam, Clemons Mark, Hoskin Peter, Yee Albert, Brundage Michael, Bottomley Andrew. On behalf of the EORTC Quality of Life Group. The European organization for research and treatment of cancer quality of life questionnaire for patients with bone metastases: The EORTC QLQ-BM22. European Journal of Cancer 2009;45(7):1146–52.
[10] Carsten Nieder, Luka Milas, K. Klan Ang. Tissue Tolerance to Reirradiation. Seminars in Radiation Oncology;10(3) July pp. 200–9.
[11] 〈www.who.int/cancer/palliative/painladder/en〉.
[12] Schmidt RL, Stockler M. Bisphosphonates for breast cancer. Cochrane Database of Systematic Reviews 2005;(3):CD003474.
[13] Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. Journal of the National Cancer Institute 2004;96:879–82.
[14] 〈http://www.fda.gov/ohrms/dockets/ac/02/briefing/3827b1_02_novartis-newAppendix%203.htm〉.
[15] Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, Bonneterre J, Francini G, Ford JM. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. Journal of Clinical Oncology 1996;14(9):2552–9.
[16] Weinfurt KP, Anstrom KJ, Castel LD, Schulman KA, Saad F. Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer. Annals of Oncology 2006;17(6):986–9.
[17] Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database of Systematic Reviews 2002(2):CD002068.
[18] Palaska Pinelopi Kleio, Cartsos Vassiliki, Zavras Athanasios I. Bisphosphonates and time to osteonecrosis development. The Oncologist 2009;14:1154–66.
[19] Cleeland CS, Body JJ, Stopeck A, von Moos R, Fallowfield L, Mathias SD, Patrick DL, Clemons M, Tonkin K, Masuda N, Lipton A, de Boer R, Salvagni S, Oliveira CT, Qian Y, Jiang Q, Dansey R, Braun A, Chung K. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer 2012, Sep 5. http://dx.doi.org/10.1002/cncr.27789, [Epub ahead of print].
[20] Sun L, Yu S. Efficacy and safety of denosumab versus zoledronic acid in patients with bone metastases: a systemic review and meta-analysis. American Journal of Clinical Oncology 2012 Oct 8 [Epub ahead of print].
[21] 〈http://www.cancer.gov/cancertopics/druginfo/fda-denosumab〉.
[22] Carter JA, Snedecor SJ, Kaura S, Botteman M. Cost-effectiveness of zoledronic acid (ZOL) versus denosumab (Dmab) in prevention of skeletal-related events (SREs) in metastatic breast cancer (mBC). Journal of Clinical Oncology 2011;29 ASCO Annual Meeting Abstract no: 9025 ,2011 (suppl; abstr 9025).
[23] Vergnenegre A, Corre R, Berard H, Paillotin D, Dujon C, Robinet G, Crequit J, Bota S, Thomas P, Chouaid C. 0506 GFPC Team. Cost-effectiveness of second-line chemotherapy for non-small cell lung cancer: an economic, randomized, prospective, multicenter phase III trial comparing docetaxel and pemetrexed: the GFPC 05-06 study. Journal of Thoracic Oncology 2011;6(1):161–8.
[24] Rades D, Schild SE, Abrahm JL. Treatment of painful bone metastases. Nature Reviews Clinical Oncology 2010;7(4):220–9.
[25] Rades D. Dose-fractionation schedules for radiotherapy of bone metastases. Breast Care (Basel) 2010;5(5):339–44.
[26] Chow E, Hoskin P, Mitera G, Zeng L, Lutz S, Roos D, Hahn C, van der Linden Y, Hartsell W, Kumar E. International bone metastases consensus working party. update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. International Journal of Radiation Oncology, Biology, Physics 2012;82(5):1730–7.
[27] Mithal N, Needham P, Hoskin P. Retreatment with radiotherapy for painful bone metastases. International Journal of Radiation Oncology, Biology, Physics 1994;29(5):1011–4.
[28] Chow E, Hoskin PJ, Wu J, Roos D, van der Linden Y, Hartsell W, Vieth R, Wilson C, Pater J. A phase III international randomized trial comparing single with multiple fractions for re-irradiation of painful bone metastases: National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) SC 20. Clinical Oncology (Royal College of Radiologists (Great Britain)) 2006;18(2):125–8.
[29] Akiba T, Kunieda E, Kogawa A, Komatsu T, Tamai Y, Ohizumi Y. Re-irradiation for metastatic brain tumors with whole-brain radiotherapy. Japanese Journal of Clinical Oncology 2012;42(4):264–9.
[30] Sadikov E, Bezjak A, Yi QL, Wells W, Dawson L, Millar BA, Laperriere N. Value of whole brain re-irradiation for brain metastases—single center experience. Clinical Oncology (Royal College of Radiologists (Great Britain)) 2007;19(7):532–8.

[31] Hazuka MB, Kinzie JJ. Brain metastases: results and effects of re-irradiation. International Journal of Radiation Oncology, Biology, Physics 1988;15(2): 433–7.
[32] Mendenhall WM, Mendenhall CM, Malyapa RS, Palta JR, Mendenhall NP. Re-irradiation of head and neck carcinoma. American Journal of Clinical Oncology August 2008;31(4):393–8. http://dx.doi.org/10.1097/COC.0b013e3181637398.
[33] Maranzano Ernesto, Trippa Fabio, Casale Michelina, Anselmo Paola, Rossi Romina. Reirradiation of metastatic spinal cord compression: definitive results of two randomized trials. Radiotherapy and Oncology 2011;98:234–7.
[34] Brainislav Jeremi c, Gregory MMVidetic. Chest reirradiation with external beam radiotherapy for locally recurrent non-small-cell lung cancer. International Journal of Radiation Oncology, Biology, Physics 2011;80(4):969–77.
[35] Bergh J, Bondarenko IM, Lichinitser MR, Liljegren A, Greil R, Voytko NL, Makhson AN, Cortes J, Lortholary A, Bischoff J, Chan A, Delaloge S, Huang X, Kern KA, Giorgetti C. First-line treatment of advanced breast cancer with sunitinib in combination with docetaxel versus docetaxel alone: results of a prospective, randomized phase III study. Journal of Clinical Oncology 2012;30(9):921–9.
[36] Stemmler HJ, Harbeck N, Gröll de I, Vehling U, Rauthe G, Abenhardt W, Artmann A, Sommer H, Meerpohl HG, Kiechle M, Heinemann V. Prospective multicenter randomized phase III study of weekly versus standard docetaxel (D2) for first-line treatment of metastatic breast cancer. Oncology 2010;79(3–4): 197–203.
[37] Valero V, Forbes J, Pegram MD, Pienkowski T, Eiermann W, von Minckwitz G, Roche H, Martin M, Crown J, Mackey JR, Fumoleau P, Rolski J, Mrsic-Krmpotic Z, Jagiello-Gruszfeld A, Riva A, Buyse M, Taupin H, Sauter G, Press MF, Slamon DJ. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. Journal of Clinical Oncology 2011;29(2):149–56.
[38] Trudeau ME. Phase I–II studies of docetaxel as a single agent in the treatment of metastatic breast cancer. Seminars in Oncology 1999;3(Suppl. 8):S21–26.
[39] Hortobagyi GN, Gutterman JU, Blumenschein GR, Tashima CK, Burgess MA, Einhorn L, Buzdar AU, Richman SP, Hersh EM. Combination chemoimmunotherapy of metastatic breast cancer with 5-fluorouracil, adriamycin, cyclophosphamide, and BCG. Cancer 1979;44(5):1955–62.
[40] Toulmonde M, Madranges N, Brouste V, Donamaria C, Macgrogan G, Durand M, Bonnefoi H, Mauriac L, Debled M. Docetaxel rechallenge after a first response in non-resistant metastatic breast cancer: significant activity with manageable toxicity. Breast Cancer Research and Treatment 2012;134(1):325–32.
[41] Kim HJ, Kim JS, Seo MD, Oh SY, Oh DY, Kim JH, Lee SH, Kim DW, Im SA, Kim TY, Heo DS, Bang YJ. Gemcitabine and vinorelbine combination chemotherapy in anthracycline- and taxane-pretreated advanced breast cancer. Cancer Research and Treatment 2008;40(2):81–6.
[42] Gilabert M, Bertucci F, Esterni B, Madroszyk A, Tarpin C, Jacquemier J, Extra JM, Viens P, Gonçalves A. Capecitabine after anthracycline and taxane exposure in HER2-negative metastatic breast cancer patients: response, survival and prognostic factors. Anticancer Research 2011;31(3):1079–86.
[43] Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleeboom HP, Jänicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Lassus M, Verbeek JA, Staffler B, Chaudri-Ross HA, Dugan M. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. Journal of Clinical Oncology 2001;19(10):2596–606.
[44] Kim SH, Park IH, Lee H, Lee KS, Nam BH, Ro J. Efficacy of exemestane after nonsteroidal aromatase inhibitor use in metastatic breast cancer patients. Asian Pacific Journal of Cancer Prevention 2012;13(3):979–83.
[45] Ingle JN, Suman VJ, Rowland KM, Mirchandani D, Bernath AM, Camoriano JK, Fishkin PA, Nikcevich DA, Perez EA. North Central Cancer Treatment Group Trial N0032. Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Group Trial N0032. Journal of Clinical Oncology 2006;24(7): 1052–6.
[46] Scagliotti Giorgio Vittorio, Parikh Purvish, Pawel Joachim von, Biesma Bonne, Vansteenkiste Johan, Manegold Christian, Serwatowski Piotr, Gatzemeier Ulrich, Digumarti Raghunadharao, Zukin Mauro, Lee Jin S, Mellemgaard Anders, Park Keunchil, Patil Shehkar, Rolski Janusz, Goksel Tuncay, Marinis Filippo de, Simms Lorinda, Sugarman Katherine P, Gandara David. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non–small-cell lung cancer. Journal of Clinical Oncology 2008;26(21):3543–51.
[47] Fossella FV. Docetaxel for previously treated non-small-cell lung cancer. Oncology (Williston Park) 2002;6(Suppl. 6):S45–51.
[48] Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, Idziaszczyk S, Harris R, Fisher D, Kenny SL, Kay E, Mitchell JK, Madi A, Jasani B, James MD, Bridgewater J, Kennedy MJ, Claes B, Lambrechts D, Kaplan R, Cheadle JP. MRC COIN Trial Investigators. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomized phase 3 MRC COIN trial. Lancet 2011;377(9783):2103–14.
[49] Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. New England journal of medicine 2004;351(4):337–45.