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CONTROVERSIES IN RADIOTHERAPY OF METASTATIC BONE DISEASE

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Abstract

Metastatic bone (MB) disease is a common manifestation of advanced cancer. Although bone metastases can be asymptomatic, in more than two thirds of patients they cause pain, as well as a wide spectrum of complications, including pathological fractures, spinal cord and nerve root compressions, hypercalcaemia and mobility impairment; greatly reducing the patients' quality of life. Radiotherapy has since long proved to be an effective modality for treatment of bone metastases, resulting in palliation in up to 80% patients. Despite the extensive research in this area, many controversial issues still remain. The authors conducted a critical review of the publications on several of these issues, including the mechanisms of action of radiotherapy, dose-response relationship, optimal fractionation regimens, irradiation techniques, response assessment.

The conclusion was drawn that in line with the current clinical evidence, there are no substantial differences between various fractionation schedules in terms of analgesic effect. However, in consideration of other endpoints, MF regimens may provide better effect than SF; this is a subject for future clinical research. Currently, besides the clinical evidence, the routine practice in radiotherapy departments is strongly influenced by other disease-non-specific factors, including the factors that are physician-related (country of training, location, and type of practice, professional membership affiliation, etc.) and policy/community-related (type of reimbursement, available recourses).

A brief description of the practice in palliative radiotherapy for bone metastases in the Radiotherapy Department of the National Center of Oncology is presented.

Keywords: bone metastasis, palliative radiotherapy, fractionation.

Background. One of the most frequent manifestations of advanced cancer is metastatic bone disease, which is clinically apparent in 14–70% of all cancer patients, and has been reported to occur in 70–85% of autopsy material [*Jeremic B., 2001*]. The most common localizations that develop bone metastases (BM) are breast and prostate carcinomas with an incidence of 73% and 68%, respectively. In addition, lung, thyroid, and renal carcinoma develop metastases to bone in about 30-40% of cases [*Coleman R.E., 2006*]. With advances in effective systemic treatment during the last 2 decades, the survival of patients with BM has improved substantially, and it is estimated that the prevalence of patients with BM has doubled during this period of time [*Chow E. et al., 2006*]. Although BM can be asymptomatic, in more than two thirds of patients they cause pain, as well as a wide spectrum of complications, including pathological fractures, spinal cord and nerve root compressions, hypercalcaemia and mobility impairment, greatly reducing the patients' quality of life. Radiotherapy (RT) has since long proved to be an effective modality for treatment of BM and their accompanying symptoms [*Lievens Y. et al., 2000*], resulting in palliation in up to 80% of patients [*Criteria , 2007*]. Nowadays, palliative RT for metastatic bone disease accounts up to 30- 40% of the daily workload in radiation oncology departments [*Foro A. et al., 2008*].

While the efficacy of RT in treatment of metastatic bone disease is unanimously recognized, many issues in this area still remain controversial.

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We conducted a review of the literature to explore the current state of some of these issues.

Mechanisms of Action and Dose–Response Relationship. Though local RT is successful in most patients with BM, the exact mechanisms of action remain uncertain [*Hoskin P., 2007*]. Certain features of the response (rapid pain relief after the first few procedures, effectiveness of low doses) suggest that tumour shrinkage is not the only mechanism of RT. analgesic action The striking clinical observation that some patients experience symptom relief within 24 hours after the irradiation leads to the hypothesis that early reacting, very sensitive cells and the molecules they produce are involved in this response [*Vakaet L., Boterberg T., 2004*]. Obvious candidate cells are the inflammatory cells that are largely present in the BM micro-environment. The reduction of inflammatory cells by ionizing radiation inhibits the release of chemical pain mediators and is probably responsible for the rapid reaction seen in some patients. Other candidate cells are the osteoclasts. The effect of anti-osteoclastic drugs, such as bisphosphonates, on bone pain hints to the prominent role of the osteoclast in mediating bone pain and the possibility thereof to be one of the targets of radiotherapy. Indeed, it has been demonstrated that urinary markers of bone resorption (and thus osteoclastic activity) and pain relief after radiation treatment correlated [*Hoskin P.J. et al., 2000*]. On the other hand, it was shown that the reaction of osteoclasts was a subject to a clear dose-response relationship, and in the first weeks after exposure to moderate doses of ionizing radiation the number of osteoclasts did not reduce [*Tsay T. et al., 1999*]. Thus, the role of osteoclast inhibition in early response to radiation and pain control at low doses is not certain.

It is clear that one can distinguish 2 different components of bone pain, "biological pain" caused by the changes in the tumor micro-environment and stimulation of chemical pain receptors and "mechanical pain" produced by the tumor stress on mechanical pain receptors [*Ratanatharathorn V. et al., 1999*]. Hence, if for biological pain there might be no clear dose response relationship, for mechanical pain control a large number of tumour cells must be killed, which is a dose dependent process, according to current radiobiological concepts.

Clinical data on dose response relationship in the palliative RT for BM are contentious. Two randomized trials comparing different single fraction regimens [*Hoskin P. et al*., 1992; *Jeremic B. et al.*, 1998] found clear advantage of higher dose regimens (8 *Gy* in 1 fraction) to lower ones (4 *Gy* x 1 and 6 *Gy* x 1) in the term of pain control. However, the differences disappear in higher dose range, and in multifraction comparisons, as was shown in other trials. The situation changes, if other endpoints are considered. As reported by S. Koswig and V. Budach, though 8 *Gy* in one fraction and 30 *Gy* in 10 fractions were equivalent for pain control, in consideration of recalcification a fractionated regimen was superior to the single fraction (173% *vs* 120%) [*Koswig S., Budach. V., 1999*]. This means that if the goal of RT is not only the pain control, but also bone stabilization, fractionated regimens might be more advantageous.

Optimal Dose Fractionation. Despite the extensive research in this area, the issue of the optimal fractionation remains unclear. It is of note that more than 100 different fractionation schedules have been recommended for the palliation of BM, ranging from a single 3 *Gy* to 60 *Gy* in 20 fractions [*Fairchild A.. et al, 2009*]. Multiple randomized controlled trials (RCT) have been conducted during the last 2.5 decades, addressed to comparison of different single-fraction (SF) and multifraction (MF) irradiation schedules for treatment of painful BM.

In their systematic review published in 1999, V. Ratanahtarathorn and co-authors analyzed the data from 12 randomized dose fractionation trials with inclusion of about 2700 patients [*Ratanatharathorn V. et al., 1999*]. The authors concluded that, overall, higher dose fractionated treatment regimens produced a better frequency, magnitude, and duration of palliative response than lower dose single-fraction regimens. In contrast to this, in reviews no difference in palliative response between SF and MF regimens was found [*McQuay H. et al., 1997; Jeremic B., 2001*].

In the meta-analysis [*Sze W. et al., 2004*] 11 RCT's were included, with 3487 painful sites. Patients treated with SF-RT and MF-RT showed similar rates of overall response (60% vs 59%) and complete response (34% vs 32%). Patients treated by SF-RT had a higher re-irradiation rate (21.5%) compared to 7.4% of patients in the MF-RT arm.

The pathological fracture rate was also higher in SF arm patients (3% vs 1.6). The authors concluded that single fraction radiotherapy was as effective as multifraction radiotherapy in relieving metastatic bone pain.

The conclusion of another meta-analysis published by J. Wu and co-authors in 2002 was the same [*Wu J. et al., 2003*].

The most recent systemic review, which included all published reports from 16 major RCT's, comparing SF (8-12 *Gy* x 1) or MF (15-30 *Gy* in 3-10 fractions) schedules was published by Chow and co-authors in 2007 [*Chow E. et al., 2007*]. Overall, data of more than 5000 patients were analyzed: the overall response (OR) rate and compete response (CR) rate for pain control were similar for SF and MF schedules (58% *vs*. 59% and 23% *vs*. 24%, respectively). The authors found statistically significant 2.5-fold higher retreatment rates in SF arm patients (20% *vs*. 8%, P<0.00001), as well as a slight, statistically non-significant increase in pathological fracture and spinal cord compression rates (3.8% *vs* 2.8%, P=0.75 and 2.8% *vs*. 1.9%, P=0.13, respectively). There were no differences observed in acute toxicities between the two arms. Furthermore, detailed analysis of subgroups within the Dutch Bone Metastasis Study in patients with different primaries, with either long or short term survival, or with only spinal metastases, showed equal pain control after a single 8 *Gy* compared with 24 *Gy* in 6 fractions, and no subgroup was identified that clearly benefited more from MF-RT [*Van der Linden Y. et al., 2006; 2009*].

Most of the randomized trials also showed the superiority of SF irradiation in terms of optimal recourse management, cost-effectiveness, and patient convenience.

It might be expected that all these data provide evidence enough for the implementation of SF-RT as the new standard of RT for the treatment of BM. However, according to recent surveys, in spite of clinical practice the guidelines and consensus documents published since 1999, only 11-42% of radiation oncologists use SF schedules in daily practice, and the situation does not seem to change substantially during this period [*Fairchild A. et al*., *2009*]. Indeed, 30 *Gy* in 10 fractions remains the most common schedule in the USA and Asia, 20 *Gy* in 5 fractions in Canada and Australia/NZ, and a single 8 *Gy* is a common choice only in Europe and UK.

According to surveys [*Lievens Y. et al., 2000* ***a****; 2000b; Fairchild A. et al., 2009*], besides the clinical evidence, there are multiple factors strongly influencing the palliative RT practice. Contrary to the literature evidence, patients' condition, site of the metastasis and expected outcome were most important factors for fractionation preference. Other independent factors were country of training, location and type of practice, professional membership affiliation, as well as the type of reimbursement in a country. Interestingly, while SF regimens seemed more convenient to patients, the majority of them preferred fractionated RT to SF, and practical aspects of treatment such as traveling distance, remaining at home, shortness of treatment, were less important [*Shakespeare T. et al., 2003; Szumacher E. et al., 2005; Bradley N. et al., 2007*].

In our opinion, some skepticism towards the quality of the evidence from the randomized fractionation trials might be of importance as well. In their paper, specifically questioning the quality of randomized trials on palliative RT for BM, T. Shakespeare and co-authors concluded that overall quality of dose-fractionation trials was poor (the median score 1 of 5, range 0-3) and irrespective of whether this is due to poor design or poor reporting, the ability to interpret the study results was hindered [*Shakespeare T. et al., 2005*]. One of the reasons for this, besides heterogeneous inclusion criteria and absence of double blinding, were different response assessment tools.

Response Assessment. The criteria of complete response (CR), partial response (PR) and overall response (OR) to the palliative RT vary substantially in different trials. On the other hand, response rates to RT are a function of endpoint definitions, and different conclusions can be drawn, even within the same trial depending on the stringency of the definition [*Wu J. et al.,* 2002; *Chow E. et al., 2007*]. For example, in a randomized Canadian trial comparing the efficacy of a single 8 *Gy* to 20 *Gy* in 5 daily fractions in the treatment of BM, more patients in multiple fractionations received significant pain relief, defined as reduction in the pain score at the treated site with reduced analgesics or a pain score of zero at the treated site without an increase in analgesics. In contrast, when response was defined as pain

relief alone regardless of analgesic consumption, the two regimens gave the same response rates. In hopes of promoting consistency in future trials, the International Bone Metastases Consensus Working Party formed specific end points for RT trials in 2002. According to them, complete response (CR) was defined as a pain score of zero at the treated site with no concomitant increase in analgesic intake. Partial response (PR) was defined as a pain reduction of 2 or more at the treated site on a 0 to 10 scale without analgesic increase, or analgesic reduction of 25% or more from the baseline without an increase in pain. The international consensus endpoints took into account both the patient's pain score and analgesic consumption [*Chow E. et al., 2002*]. However, the role and optimal instruments of assessment of other endpoints had not been clearly stated. On the other hand, it might be expected that properly assessed functional status and quality of life, radiological signs of bone remineralization (thus, bone stabilization), jointly with the pain control, can better define the treatment outcome, at least in patients with long expected survival. Many practitioners can remember patients with complete response in the terms of pain control after the course of local RT for BM, which either developed severe stiffness in major joints, or fracture of long bones, several months after the completion of the treatment, resulting in substantial impairment of the quality of life. So, did they really achieve complete response?

Radiotherapy for Asymptomatic Bone Metastases. According to Perez and Brady's "Principles and Practice of Radiation Oncology", "the ideal patient for the best long-term benefit of radiation therapy is one with a metastasis to bone detected by a change in bone scan before symptoms of the metastasis develop"[*Perez C., 1998*], i.e., a patient with asymptomatic BM. Completely different approach has been pointed out in the paper by D.R. Clohisy, according to which the watchful waiting is a treatment of choice for asymptomatic patients, and RT is added when skeletal lesions become painful [*Clohisy D., 2003*]. However, in a good deal of cases the first manifestations of skeletal metastases are the symptoms of vertebral collapse, metastatic spinal cord compression, and pathological fractures. On the other hand, about 30-40% of patients do not respond to radiotherapy to painful sites. Thus, there might be a subgroup of asymptomatic patients that would fairly benefit from RT. Moreover, RT might serve as a potentially curative modality of local treatment for solitary BM when combined with the systemic agents in some patients. Interestingly, the literature hardly provides any specific data on the role of local RT in the management of asymptomatic BM, with the exception of the cases when there is apparent risk for pathological fracture, and physicians very often rely on their subjective sense when defining indications for irradiation of asymptomatic bone lesions.

Irradiation Techniques. The conventional simulator based RT is widely accepted as a standard approach for BM when megavoltage X-rays are used. The treatment fields should cover the painful site with a 2 to 3 *cm* margin. Other considerations are that when treating the spine field edges should ideally be at intervertebral spaces and the field symmetrical about the midline unless there is a significant paraspinal soft tissue mass. The treatment portals should cover at least one vertebral body both above and below the tender one. For many situations a single field will be adequate with the dose prescribed as the incident 100% dose either on the surface or at build-up depth for megavoltage beams. For deeper bones, particularly long bones and the pelvis, anterior and posterior parallel opposed fields will be used with the dose described to the intersection point [*Chow E. et al*., 2002; *Foro A. et al., 2008*]. The dose homogeneity in target volumes is considered less important in palliative treatments. On the other hand, as shown by R. Barton and co-authors, the dose received by the vertebrae could vary by up to 50% with changes in the prescription depth and energy [*Barton R. et al., 2002*]. This can be more considerable when treating thick patients, and when Co60 units are used, which is not uncommon in many countries. As shown in another report by the authors of the present paper, in some situations, during conventional irradiation for spinal and pelvic metastases, tolerant levels for some normal tissues can be exceeded; that is why we suggested a 3 field technique for irradiation of the spinal metastases with CT based planning [*Karamyan S. et al., 2008*]. Quite a different situation was discussed in another paper [*Lo S. et al., 2009*]. With the recent advance of new technologies in radiotherapy, highly conformal RT techniques, such as three-dimensional conformal radiotherapy (3D-CRT), intensity

modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), become increasingly popular. Compared to conventional RT, these techniques are superior in sparing of normal tissues and critical structures in the close neighborhood of target volume, and give additional opportunity for dose escalation, which in turn may improve local control. However, highly conformal RT is extremely demanding on the radiotherapy department resources as it requires considerable expertise and training with the use of costly modern linear accelerators equipped with image guidance, dedicated modern body immobilization devices, more labour-intensive treatment planning and delivery processes and individualized quality assurance measures for each plan. The patient is subjected to robust immobilization with near-rigid body immobilization devices, and patients with significant pain symptoms may not be able to tolerate the procedure given that treatment typically takes 45 minutes or longer. Furthermore, these techniques cannot be used in emergency settings such as malignant spinal cord compression. When high dose radiation is delivered using highly conformal techniques, the risk of complications may also increase as even small errors can result in dosimetric uncertainties with overdose of the adjacent organs-at-risk. For example, radiation-induced myelopathy has been reported and represents an unacceptable complication for the palliative patient. Other complications including vertebral compression fractures, which are relatively rare in the setting of conventional radiotherapy, have also been reported in patients who undergo SBRT for spinal metastasis.

Our Practice. Radiotherapy department of the National Center of Oncology (Yerevan, Armenia) is the main source of radiation oncology services in the country. About 100-120 patients with bone metastases are treated with local RT annually, that constitutes about 7-10% of daily workload of the department. About 70% of these patients are those with breast cancer, other common primaries are lung and prostate. We normally use fractionated regimens, and most of the patients receive 30 *Gy* in 10 fractions or 20-24 *Gy* in 5-6 fractions. Single 8 *Gy* is used rarely, when the sole goal of RT is pain relief. Though conventional simulator-based planning is widely used, we prefer CT based planning with target volume delineation, when available. The pain response to the treatment is generally measured by physician-based scales at the end of the treatment and in 3-4 weeks after the completion of RT. Patient-based assessment tools will be implemented in the near future.

We believe, that certain clinical prognostic factors, such as the performance status, primary disease, histology, character, number and localization of bone lesions, presence of visceral metastases, concomitant specific treatment, etc. can be helpful in decision making to define the indications for local RT, optimal fractionation regimen, irradiation techniques, in accordance to expected survival and response to the treatment. Therefore, we consider the development of a complex of relevant prognostic factors to be a promising way for individualizing of the palliative RT of BM, hence improving the quality of palliative services to this large group of patients.

Conclusions

Radiotherapy remains the most important palliative treatment for localized bone pain. Despite the extensive research during the last 25 years, there are persisting controversies concerning to indications, dose fractionation, response assessment, dose response relationship, technical aspects of palliative radiotherapy for bone metastases. According to the current clinical evidence, there are no substantial differences between different fractionation schedules in terms of analgesic effect. However, in consideration of other endpoints MF regimens may provide better effect than SF, so future research will hopefully make this issue more definite. Currently, besides the clinical evidence the routine practice in radiotherapy departments is strongly influenced by other disease-non-specific factors, including the factors that are physician-related (country of training, location and type of practice, professional membership affiliation, etc.) and policy/community-related (type of reimbursement, available recourses).

References

1. *Barton R., Robinson G., Gutierrez E., Kirkbride P., McLean M.* Palliative radiation for vertebral metastases: The effect of variation in prescription parameters on the dose received at depth.. Int. J. Radiat. Oncol. Biol. Phys. 2002; 52 (4): 1083-1091.
2. *Bradley N.M., Husted J., Sey M.S., Husain A.F., Sinclair E., Harris K., Chow E.*Review of patterns of practice and patients' preferences in the treatment of bone metastases with palliative radiotherapy. Support Care Cancer. 2007; 15 (4): 373-385.
3. *Chow E., Harris K., Fan G., Tsao M. Sze W.M.* Palliative radiotherapy trials for bone metastases: a systematic review. J. Clin. Oncol. 2007; 25 (11): 1423-1436.
4. *Chow E., Hoskin P., van der Linden Y., Bottomley A., Velikova G.* Quality of life and symptom end points in palliative bone metastases trials. Clin. Oncol. (R. Coll. Radiol.). 2006; 18(1): 67-69.
5. *Chow E., Wu J.S.Y., Hoskin P., Coia L.R., Bentzen S.M., Blitzer P.H.* International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Radiotherapy and Oncology. 2002; 64 (3): 275-280.
6. *Clohisy D.R.* Metastatic bone disease: future directions. Clin. Orthop. Relat. Res. 2003; 415 (Suppl): S95-99.
7. *Coleman R.E.* Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006; 12(20; Pt 2): 6243s-6249s.
8. *Criteria* for Palliation of Bone Metastases – Clinical Applications. IAEA-TECDOC-1549. 2007: p. 9.
9. *Fairchild A., Barnes E., Ghosh S., Ben-Josef E., Roos D., Hartsell W., Holt T., Wu J., Janjan N., Chow E.* International Patterns of Practice in Palliative Radiotherapy for Painful Bone Metastases: Evidence-Based Practice? Int. J. Radiat. Oncol. Biol. Phys. 2009.
10. *Foro A.P, Fontanals A.V., Galceran J.C., Lynd F., Latiesas X,S,, de Dios N,R,, Castillejo A,R,, Bassols M,L,, Galan J,L,, Conejo I,M,, Lopez M,A,* Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiother. Oncol. 2008; 89(2): 150-155.
11. *Hoskin P.J.* Bisphosphonates and radiation therapy for palliation of metastatic bone disease. Cancer Treat. Rev. 2003; 29(4): 321-327.
12. *Hoskin P.J., Price P., Easton D., Regan J., Austin D., Palmer S., Yarnold J.R.* A prospective randomised trial of 4 Gy or 8 Gy single doses in the treatment of metastatic bone pain. Radiother. Oncol. 1992; 23 (2): 74-78.
13. *Hoskin P.J., Stratford M.R., Folkes L.K., Regan J., Yarnold J.R.* Effect of local radiotherapy for bone pain on urinary markers of osteoclast activity. Lancet. 2000; 355 (9213): 1428-1429.
14. *Jeremic B.* Single fraction external beam radiation therapy in the treatment of localized metastatic bone pain. A review. J. Pain Symptom Manage., 2001; 22(6): 1048-1058.
15. *Jeremic B., Shibamoto Y., Acimovic L., Milicic B., Milisavljevic S., Nikolic N., Aleksandrovic J. Igrutinovic I.* A randomized trial of three single-dose radiation therapy regimens in the treatment of metastatic bone pain. Int. J. Radiat. Oncol. Biol. Phys. 1998; 42 (1): 161-167.
16. *Karamyan S.K., Karamyan N.S., Mkrtchyan Z.S.* The alternative approach inplanning paliative radiotherapy (PRT) in case of lumbar spinemetastatic lesions. In: Proceedings of the Fifth Congress "NIS Oncologists and Radiologists". Tashkent. 2008. P. 496.
17. *Koswig S. and Budach. V.* Remineralization and pain relief in bone metastases after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study. Strahlenther. Onkol. 1999; 175 (10): 500-508.
18. *Lievens Y., Van den Bogaert W., Rijnders A., Kutcher G., Kesteloot K. et al.* Palliative radiotherapy practice within Western European countries: impact of the radiotherapy financing system? Radiother. Oncol. 2000 ***b***; 56 (3): 289-295.
19. *Lo S.S., Sahgal A., Hartsell W.F., Lutz S.T., Kardamakis D., Linden Y., Hoskin P.J.* The Treatment of Bone Metastasis with Highly Conformal Radiation Therapy: A Brave New World or a Costly Mistake? Clin. Oncol. (R. Coll. Radiol.).

20. *McQuay H.J., Carroll D., and Moore R.A.* Radiotherapy for painful bone metastases: a systematic review. Clin. Oncol. (R .Coll. Radiol.).1997; 9(3): 150-154.

21. *Perez C.A.* (ed.) Perez and Brady's Principles and Practice of Radiation Oncology. 3rd ed. 1998. Lippincott-Raven. 2205p.

22. *Ratanatharathorn V., Powers W.E., Moss W.T., Perez C.A.* Bone metastasis: review and critical analysis of random allocation trials of local field treatment. Int. J. Radiat. Oncol. Biol. Phys. 1999; 44(1): 1-18.

23. *Shakespeare T.P., Lu J.J., Back M.F., Liang S., Mukherjee R.K., Wynne C.J.* Patient preference for radiotherapy fractionation schedule in the palliation of painful bone metastases. J. Clin. Oncol. 2003; 21 (11): 2156-2162.

24. *Shakespeare T.P., Thiagarajan A., and Gebski V.* Evaluation of the quality of radiotherapy randomized trials for painful bone metastases. Cancer. 2005; 103 (9): 1976-1981.

25. *Sze W.M., Shelley M., Held I., Mason M.* Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. Cochrane Database Syst. Rev. 2004 (2): CD004721.

26. *Szumacher E., Llewellyn-Thomas H., Fransen E., Chow E., DeBoer G., Danjoux C., Hayter C., Barnes E., Andersson L.* Treatment of bone metastases with palliative radiotherapy: patients' treatment preferences. Int. J. Radiat. Oncol. Biol. Phys. 2005; 61 (5): 1473-1481.

27. *Tsay T.P., Chen M.H., and Oyen O.J.* Osteoclast activation and recruitment after application of orthodontic force. Am. J. Orthod. Dentofacial Orthop. 1999; 115 (3): 323-330.

28. *Vakaet L.A. and Boterberg T.* Pain control by ionizing radiation of bone metastasis. Int. J. Dev. Biol. 2004; 48 (5-6): 599-606.

29. *Van der Linden Y., Roos D., Lutz S., Fairchild A.* International Variations in Radiotherapy Fractionation for Bone Metastases: Geographic Borders Define Practice Patterns? Clin. Oncol. (R. Coll. Radiol.). 2009.

30. *Van der Linden Y.M., Steenland E., van Houwelingen H.C., Post W.J., Oei B., Marijnen C.A., Leer J.W.* Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. Radiother. Oncol. 2006; 78 (3): 245-253.

31. *Wu J.S.*, *Wong R, Johnston M., Bezjak A., Whelan T*. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. Int. J. Radiat. Oncol. Biol. Phys. 2003; 55(3): 594-605.

32. *Wu J.S., Bezjak A., Chow E., Kirkbride P.* Primary treatment endpoint following palliative radiotherapy for painful bone metastases: need for a consensus definition? Clin. Oncol. (R. Coll. Radiol.). 2002; 14 (1): 70-77.