Methodology report RL Prostaat PICO5

# key question

**Uitgangsvraag:** Welke behandeling is geïndiceerd voor pijnlijke botmetastasen bij patiënten met een gemetastaseerd castratie-resistent prostaatcarcinoom?

**P** Patiënten met gemetastaseerd castratie-resistent prostaatcarcinoom (mCRPC) en pijnlijke botmetastasen

**I** Radiotherapie (uitwendige)

**C** Geen behandeling of een (of meer) van de andere behandelingen

**O** Reductie van pijnklachten, Kwaliteit van leven, Toxiciteit,

# golden hits

**1.** Meeuse JJ, van der Linden YM, van Tienhoven G, et al. *Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastases Study.* Cancer, 2010 Jun 1; 116(11): 2716-2725.

**2.** Chow E, Zeng L, Salvo N, et al. *Update of the systematic review of palliative radiotherapy trials for bone metastases.* Clin Oncol (R Coll Radiol), 2012 Mar; 24(2): 112-124.

**3.** Westhoff PG, de Graeff A, Reyners AK, et al. *Effect of age on response to palliative radiotherapy and quality of life in patients with painful bone metastases.* Radiother Oncol, 2014 May; 111(2): 264-269.

**4.** Sze WM, 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

# Search strategy

The searches were run on 21 June 2015 Ovid Medline, Ovid Embase, Cochrane (all libraries) were searched. Detailed search strings are given below. The searches were limited to 2001-2015, English and Dutch. Study types: systematic reviews, meta-analysis and RCTs.

# Search results

The Medline search yielded 179 hits, while the search in Embase yielded 251 hits, Cochrane yielded 93 hits.

After merging the search files into one file and removal of the duplicates 512 records were screened on title and abstract. Of these 282 were excluded. The most important reasons for exclusion was that studies were

1. Patient population
2. Intervention

Of the remaining 230 studies, the full text was retrieved. Based on the full text, an additional 229 studies were excluded. Table 4.1 provides an overview of the studies, with the reason for exclusion.

# **Table 4.1 Full text screening and reasons for in- and exclusion**

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Reference** | **Included / Excluded** | **Reasons** |
| #1 | Amouzegar-Hashemi, F., et al., *Single versus multiple fractions of palliative radiotherapy for bone metastases: A randomized clinical trial in Iranian patients.* Current Oncology, 2008. **15**(3): p. 36-39. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #2 | Atahan, L., et al. *Zoledronic acid concurrent with either high- or reduced-dose palliative radiotherapy in the management of the breast cancer patients with bone metastases: a phase IV randomized clinical study*. Supportive care in cancer, 2010. **18**, 691-8 DOI: 10.1007/s00520-009-0663-x. | Excluded | Solely patients with breast cancer included. |
| #3 | Baczyk, M., et al., *A prospective randomized trial: A comparison of the analgesic effect and toxicity of 153Sm radioisotope treatment in monotherapy and combined therapy including local external beam radiotherapy (EBRT) among metastatic castrate resistance prostate cancer (mCRPC) patients with painful bone metastases.* Neoplasma, 2013. **60**(3): p. 328-333. | Excluded | Comparison is 153sm isotope + EBRT versus 153sm isotopes |
| #4 | Badzio, A., et al., *20 Gy in five fractions versus 8 Gy in one fraction in palliative radiotherapy of bone metastases. A multicenter randomized study.* Nowotwory, 2003. **53**(3): p. 261-264. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #5 | Becker-Schiebe, M. and W. Hoffmann, *Single versus fractionated reirradiation in bone metastases.* Onkologe, 2014. **20**(4): p. 373-375. | Excluded | Written in German |
| #6 | Berwouts, D., et al., *Biological 18[F]-FDG-PET image-guided dose painting by numbers for painful uncomplicated bone metastases: A 3-arm randomized phase II trial.* Radiotherapy and Oncology, 2015. **115**(2): p. 272-278. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #7 | Chow, E., et al., *Effect of re-irradiation for painful bone metastases on urinary markers of osteoclast activity (NCIC CTG SC.20U).* Radiotherapy and Oncology, 2015. **115**(1): p. 141-148. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #8 | Chow, E., et al., *Palliative radiotherapy trials for bone metastases: A systematic review.* Journal of Clinical Oncology, 2007. **25**(11): p. 1423-1436. | Excluded | Effect of treatment not stratified among different types of cancer included. Additionally, not clear what types of cancers are included. |
| #9 | Chow, E., et al. *Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial*. The Lancet. Oncology, 2014. **15**, 164-71 DOI: 10.1016/S1470-2045(13)70556-4. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #10 | Chow, E., et al. *Impact of reirradiation of painful osseous metastases on quality of life and function: a secondary analysis of the NCIC CTG SC.20 randomized trial*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2014. **32**, 3867-73 DOI: 10.1200/JCO.2014.57.6264. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #11 | Chow, E., et al., *Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial.* Lancet Oncology, 2014. **15**(2): p. 164-71. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #12 | Chow, E., et al., *Update on the systematic review in palliative radiotherapy trials for bone metastases.* Supportive Care in Cancer, 2011. **19**(2): p. S145. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #13 | Christensen, M.H. and L.J. Petersen *Radionuclide treatment of painful bone metastases in patients with breast cancer: a systematic review*. Cancer treatment reviews, 2012. **38**, 164-71 DOI: 10.1016/j.ctrv.2011.05.008. | Excluded | Systematic review that includes non-RCTs, concerns radionuclide, and does not stratify among different types of cancer |
| #14 | D'Angelo, G., et al., *Targeted bone-seeking radiopharmaceuticals for the palliation of bone pain from skeletal metastases: A systematic review and meta-analysis.* European Journal of Nuclear Medicine and Molecular Imaging, 2012. **39**: p. S293. | Excluded | Abstract |
| #15 | D'Angelo, G., et al., *Targeted "bone-seeking" radiopharmaceuticals for palliative treatment of bone metastases: A systematic review and meta-analysis.* Quarterly Journal of Nuclear Medicine and Molecular Imaging, 2012. **56**(6): p. 538-543. | Excluded | Systematic review that concerns radioisotopes (89Sr-chloride and 153Sm-EDTMP). |
| #16 | Dennis, K., et al., *Single fraction conventional external beam radiation therapy for bone metastases: A systematic review of randomised controlled trials.* Radiotherapy and Oncology, 2013. **106**(1): p. 5-14. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #17 | Deodato, F., et al., *Stereotactic Radiosurgery (SRS) with Volumetric Modulated Arc Therapy (VMAT): Interim Results of a Multi-arm Phase I Trial (DESTROY-2).* Clinical Oncology, 2014. **26**(12): p. 748-756. | Excluded | Single-arm study |
| #18 | El Hawwari, B. and A. Telfah, *Comparison of 8gy single fraction radiotherapy versus 20gy in five fractions or 30gy in 10 fractions for the treatment of metastatic bone pain.* Annals of Oncology, 2012. **23**: p. ix462. | Excluded | Abstract |
| #19 | Foro Arnalot, P., et al., *Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction.* Radiotherapy and Oncology, 2008. **89**(2): p. 150-155. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #20 | Hamouda, W.E., W. Roshdy, and M. Teema *Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases*. Gulf journal of oncology, 2007. **1**, 35-41. | Excluded | Comparison is single or multifraction radiotherapy |
| #21 | Harstell, W.F., et al., *Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases.* Journal of the National Cancer Institute, 2005. **97**(11): p. 798-804. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #22 | Hoskin, P., et al., *Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: A prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial.* The Lancet Oncology, 2014. **15**(12): p. 1397-1406. | Excluded | Comparison is radium-223 versus matching placebo. |
| #23 | Howell, D.D., et al. *Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14*. Cancer, 2013. **119**, 888-96 DOI: 10.1002/cncr.27616. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #24 | Huisman, M., et al., *Effectiveness of reirradiation for painful bone metastases: A systematic review and meta-analysis.* International Journal of Radiation Oncology Biology Physics, 2012. **84**(1): p. 8-14. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #25 | Kaasa, S., et al., *Prospective randomised multicenter trial on single fraction radiotherapy (8 Gynull1) versus multiple fractions (3 Gynull10) in the treatment of painful bone metastases.* Radiotherapy and Oncology, 2006. **79**(3): p. 278-284. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #26 | Kamada, T., et al., *Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas.* Journal of Clinical Oncology, 2002. **20**(22): p. 4466-71. | Excluded | No prostate cancer patients included. |
| #27 | Klimo, P., et al. *A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease (Structured abstract)*. Neuro-Oncology, 2005. **7**, 64-76. | Excluded | Systematic review including non-RCTs. In addition, effect of treatment not stratified among different types of cancer included. |
| #28 | Konski, A., et al. *Continuing evidence for poorer treatment outcomes for single male patients: retreatment data from RTOG 97-14*. International journal of radiation oncology, biology, physics, 2006. **66**, 229-33 DOI: 10.1016/j.ijrobp.2006.04.005. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #29 | Linden, Y.M., et al. *Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy*. Cancer, 2005. **103**, 320-8 DOI: 10.1002/cncr.20756. | Excluded | Comparison is single versus multifraction radiotherapy |
| #30 | Linden, Y.M., et al. *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**, 528-37 DOI: 10.1016/j.ijrobp.2003.10.006. | Excluded | Comparison is single versus multifraction radiotherapy |
| #31 | Linden, Y.M., et al. *Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study*. Radiotherapy and oncology, 2006. **78**, 245-53 DOI: 10.1016/j.radonc.2006.02.007. | Excluded | Duplicate |
| #32 | Loblaw, D.A., et al. *Pain flare in patients with bone metastases after palliative radiotherapy--a nested randomized control trial*. Supportive care in cancer, 2007. **15**, 451-5 DOI: 10.1007/s00520-006-0166-y. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #33 | Lutz, S., et al., *Palliative radiotherapy for bone metastases: An ASTRO evidence-based guideline.* International Journal of Radiation Oncology Biology Physics, 2011. **79**(4): p. 965-976. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #34 | Manas, A., et al., *Randomised study of single dose (8 Gy vs. 6 Gy) of analgesic radiotherapy plus zoledronic acid in patients with bone metastases.* Clinical and Translational Oncology, 2008. **10**(5): p. 281-287. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #35 | Mao, S., et al., *Employing the treatment-free interval of intermittent androgen ablation to screen candidate prostate cancer therapies.* Prostate, 2007. **67**(15): p. 1677-1685. | Excluded | Comparison is IM862 versus placebo |
| #36 | McDonald, R., et al., *International patterns of practice in radiotherapy for bone metastases: A review of the literature.* Journal of Bone Oncology, 2014. **3**(3-4): p. 96-102. | Excluded | Review without pooled analysis for the outcomes of interest. |
| #37 | Meeuse, J.J., et al. *Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastasis Study*. Cancer, 2010. **116**, 2716-25 DOI: 10.1002/cncr.25062. | Excluded | Comparison is single versus multifraction radiotherapy |
| #38 | Nilsson, S., et al., *Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases.* Clinical Genitourinary Cancer, 2013. **11**(1): p. 20-26. | Excluded | Comparison is radium-223 versus placebo |
| #39 | Nilsson, S., et al., *Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study.* Lancet Oncology, 2007. **8**(7): p. 587-594. | Excluded | Comparison is radium-223 versus placebo |
| #40 | Oosterhof, G.O., et al. *Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group*. European urology, 2003. **44**, 519-26. | Included | **Design**: RCT**Patients:** patients with painful bone metastases of hormone-resistant prostate cancer**Intervention:** local radiotherapy **Control:** Strontium89 Chloride |
| #41 | Pandit-Taskar, N., et al., *Antibody mass escalation study in patients with castration-resistant prostate cancer using 111In-J591: lesion detectability and dosimetric projections for 90Y radioimmunotherapy.* Journal of Nuclear Medicine, 2008. **49**(7): p. 1066-74. | Excluded | No RCT |
| #42 | Parker, C., et al., *Alpha emitter radium-223 and survival in metastatic prostate cancer.* New England Journal of Medicine, 2013. **369**(3): p. 213-223. | Excluded | Comparison is radium-223 versus placebo |
| #43 | Parker, C.C., et al. *A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer*. European urology, 2013. **63**, 189-97 DOI: 10.1016/j.eururo.2012.09.008. | Excluded | Comparison is radium-223 versus placebo |
| #44 | Rades, D., et al., *Improved posttreatment functional outcome is associated with better survival in patients irradiated for metastatic spinal cord compression.* International Journal of Radiation Oncology, Biology, Physics, 2007. **67**(5): p. 1506-9. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #45 | Ricci, S., et al., *Clinical benefit of bone-targeted radiometabolic therapy with 153Sm-EDTMP combined with chemotherapy in patients with metastatic hormone-refractory prostate cancer.* European Journal of Nuclear Medicine & Molecular Imaging, 2007. **34**(7): p. 1023-30. | Excluded | Comparison is 153Sm-EDTMP versus chemotherapy |
| #46 | Roos, D.E., et al., *Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05).* Radiotherapy and Oncology, 2005. **75**(1): p. 54-63. | Excluded | Comparison is single versus multifraction radiotherapy |
| #47 | Salazar, O.M., et al., *Fractionated half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomized Phase III trial of the International Atomic Energy Agency (IAEA).* International Journal of Radiation Oncology, Biology, Physics, 2001. **50**(3): p. 765-75. | Excluded | Comparison is single versus multifraction radiotherapy |
| #48 | Sarkar, S.K., et al., *Multiple and single fraction palliative radiotherapy in bone secondaries - A prospective study.* Indian Journal of Radiology and Imaging, 2002. **12**(2): p. 281-284. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #49 | Sartor, O., et al. *Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial*. The Lancet. Oncology, 2014. **15**, 738-46 DOI: 10.1016/S1470-2045(14)70183-4. | Excluded | Comparison is radium-223 versus placebo |
| #50 | Sciuto, R., et al. *Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients*. Breast cancer research and treatment, 2001. **66**, 101-9. | Excluded | Comparison is 148 MBq 89Sr i.v versus  |
| #51 | Sciuto, R., et al., *Effects of low-dose cisplatin on 89Sr therapy for painful bone metastases from prostate cancer: A randomized clinical trial.* Journal of Nuclear Medicine, 2002. **43**(1): p. 79-86. | Excluded | Comparison is 148 MBq 89Sr i.v versus |
| #52 | Shakespeare, T.P., A. Thiagarajan, and V. Gebski, *Evaluation of the quality of radiotherapy randomized trials for painful bone metastases: Implications for future research design and reporting.* Cancer, 2005. **103**(9): p. 1976-1981. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #53 | Smeland, S., et al., *Role of strontium-89 as adjuvant to palliative external beam radiotherapy is questionable: results of a double-blind randomized study.* International Journal of Radiation Oncology, Biology, Physics, 2003. **56**(5): p. 1397-404. | Excluded | Comparison is 89Sr versus placebo |
| #54 | Sze, W.M., et al., *Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials.* Cochrane Database of Systematic Reviews, 2004(2): p. CD004721. | Excluded | Comparison is single versus multifraction radiotherapy |
| #55 | van den Hout, W.B., et al., *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): p. 222-229. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #56 | Van Der Linden, Y.M., et al., *Prediction of survival in patients with metastases in the spinal column: Results based on a randomized trial of radiotherapy.* Cancer, 2005. **103**(2): p. 320-328. | Excluded | Effect of treatment not stratified among the two groups treated (control / intervention combined) |
| #57 | Van Der Linden, Y.M., et al., *Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: Results from a randomised trial.* Radiotherapy and Oncology, 2003. **69**(1): p. 21-31. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #58 | Van Der Linden, Y.M., et al., *Single-dose irradiation of painful bone metastases is as effective as multiple fractions. Outcome of the Dutch Bone Metastasis Study.* Nederlands Tijdschrift voor Geneeskunde, 2002. **146**(35): p. 1645-1650. | Excluded | Comparison is single versus multifraction radiotherapy |
| #59 | van der Linden, Y.M., et al., *Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: Results on survival in the Dutch Bone Metastasis Study.* Radiotherapy and Oncology, 2006. **78**(3): p. 245-253. | Excluded | Comparison is single versus multifraction radiotherapy |
| #60 | Van Oorschot, B. and D. Rades, *External-beam radiotherapy for pain control. Update - Bone metastases.* Onkologe, 2014. **20**(9): p. 853-859. | Excluded | Written in German |
| #61 | Westhoff, P.G., et al., *Dexamethasone for the prevention of a pain flare after palliative radiotherapy for painful bone metastases: A multicenter double-blind placebo-controlled randomized trial.* BMC Cancer, 2014. **14**(1). | Excluded | Protocol |
| #62 | Wong, E., et al., *Re-irradiation for painful bone metastases-a systematic review.* Supportive Care in Cancer, 2014. **22**(1): p. S127. | Excluded | Abstract |
| #63 | Wong, K.H., et al., *Results of a phase II clinical trial of 2-fractionated half-body irradiation in treatment of patients with multiple painful bony metastases.* Journal of the Hong Kong College of Radiologists, 2005. **8**(3): p. 162-171. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #64 | Yeoh, E.E.K., et al., *Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: Early results of a Phase III randomized trial.* International Journal of Radiation Oncology Biology Physics, 2003. **55**(4): p. 943-955. | Excluded | Patients without metastases |
| #65 | Yoon, F. and G.C. Morton, *Single fraction radiotherapy versus multiple fraction radiotherapy for bone metastases in prostate cancer patients: Comparative effectiveness.* Cancer Management and Research, 2014. **6**: p. 451-457. | Excluded | Comparison is single versus multifraction radiotherapy |
| #66 | Zhou, S.F., et al., *Interoperative radiotherapy of seventy-two cases of early breast cancer patients during breast-conserving surgery.* Asian Pacific Journal of Cancer Prevention: Apjcp, 2012. **13**(4): p. 1131-5. | Excluded | Breast cancer patients |
| #67 | Zhu, X.B., Z.M. Ye, and Z.G. Tao, *Zoledronic acid in combination with radiotherapy in treatment of bone metastases.* Journal of Practical Oncology, 2015. **30**(2): p. 179-182. | Excluded | Article in Chinese |

**Full-text evaluation of included studies in Cochrane review, Sze, 2004 (N = 13)**

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Reference** | **Included / Excluded** | **Reasons** |
| #1 | *8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party.* Radiother Oncol, 1999. **52**(2): p. 111-21. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #2 | Cole, D.J., *A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases.* Clin Oncol (R Coll Radiol), 1989. **1**(2): p. 59-62. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #3 | Foro P, Algara M, Reig A, Lacruz M, Valls A. Randomized prospective trial comparing three schedules of palliative radiotherapy. Preliminary results. [Spanish]. Oncologia1998;21(11):55–60. | Excluded | Article in Spanish |
| #4 | Foro P, Algara M, Reig A, Lacruz, A Valls. Randomized prospective trial comparing three schedules of palliative radiotherapy. Preliminary results. [Spanish]. Oncologia 1998;21(11):55–60. | Excluded | Article in Spanish |
| #5 | Gaze, M.N., et al., Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. Radiother Oncol, 1997. 45(2): p. 109-16.PMID: 9423999 | Excluded | Comparison is single versus multifraction radiotherapy |
| #6 | Kagei, K., et al., *[A randomized trial of single and multifraction radiation therapy for bone metastasis: a preliminary report].* Gan No Rinsho, 1990. **36**(15): p. 2553-8. | Excluded | Article in Chinese |
| #7 | Koswig, S. and V. Budach, *[Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study].* Strahlenther Onkol, 1999. **175**(10): p. 500-8. | Excluded | Written in German |
| #8 | Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases.Radiotherapy Oncology 1998;47(3):233–40. | Excluded | Effect of treatment not stratified among different types of cancer included. |
| #9 | Ozsaran Z, Yalman D, Anacak Y, Esassolak M, Haydaroglu A. Palliative radiotherapy in bone metastases: Results of a randomized trial comparing three fractionation schedules. Journal BUON 2001;6:43–48. | Excluded | Comparison is single versus multifraction radiotherapy |
| #10 | Ozsaran Z, Yalman D, Anacak Y, Esassolak M, Haydaroglu A. Palliative radiotherapy in bone metastases: Results of a randomized trial comparing three fractionation schedules. Journal of BUON 2001;6. | Excluded | Duplicate |
| #11 | Price, P., et al., *Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases.* Radiother Oncol, 1986. **6**(4): p. 247-55.PMID: 3775071 | Excluded | Comparison is single versus multifraction radiotherapy |
| #12 | Steenland, E., et al., *The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study.* Radiother Oncol, 1999. **52**(2): p. 101-9.PMID: 10577695 | Excluded | Comparison is single versus multifraction radiotherapy |
| #13 | Warde PR, Kirkbride P, Panzarella T. Single fraction vs fractionated radiation therapy in the palliation of skeletal metastases - a randomised phase III trial.“ International Journal of Radiation Oncology, Biology, Physics 48(3 Suppl. Proceedings of the American Society of Clinical Oncology 2001; 20:abstract 1538. | Excluded | Abstract |

**Full-text evaluation of included studies in Sze, 2003 (N = 12)**

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Reference** | **Included / Excluded** | **Reasons** |
| #1 | Koswig S, Budach V. Recalcification and pain relief followingradiotherapy for bone metastases. A randomized trial of twodifferent fractionation schedules (10\_3Gy vs 1\_8 Gy) [inGerman]. *Strahlenther Onkol* 1999;175:500–508. | Excluded | Written in German |
| #2 | Gaze MN, Kelly CG, Kerr GR, et al. Pain relief and qualityof life following radiotherapy for bone metastases: a randomisedtrial of two fractionation schedules. Radiother Oncol 1997;45:109–116. | Excluded | Duplicate |
| #3 | Ozsaran Z, Yalman D, Anacak Y, et al. Palliative radiotherapy inbone metastases: results of a randomized trial comparing threefractionation schedules. J Balkan Union Oncol 2001;6:43–48 | Excluded | Duplicate |
| #4 | Foro P, Algara M, Reig A, *et al*. Randomized prospective trialcomparing three schedules of palliative radiotherapy [in Spanish].Preliminary results. *Oncologia* 1998;21:55–60. | Excluded | Written in Spanish |
| #5 | Bone Pain Trial Working Party. 8 Gy single fraction radiotherapyfor the treatment of metastatic skeletal pain: randomised comparisonwith a multifraction schedule over 12 months of patientfollow-up. Radiother Oncol 1999;52:111–121. | Excluded | Duplicate |
| #6 | Kagei K, Suzuki K, Shirato H, et al. A randomized trial ofsingle and multifraction radiation therapy for bone metastasis: apreliminary report. Gan No Rinsho 1990;36:2553–2558 | Excluded | Written in Chinese |
| #7 | Nielsen OS, Bentzen SM, Sandberg E, *et al*. Randomized trial ofsingle dose versus fractionated palliative radiotherapy of bonemetastases. *Radiother Oncol* 1998;47:233–240. | Excluded | Duplicate |
| #8 | Price P, Hoskin PJ, Easton D, et al. Prospective randomised trial ofsingle and multifraction radiotherapy schedules in the treatment ofpainful bony metastases. Radiother Oncol 1986;6:247–255. | Excluded | Duplicate |
| #9 | Steenland E, Leer JW, van Houwelingen H, *et al*. The effect of asingle fraction compared to multiple fractions on painful bonemetastases: a global analysis of the Dutch Bone Metastasis Study.*Radiother Oncol* 1999;52:101–109. | Excluded | Duplicate |
| #10 | Sarkar SK, Sarkar S, Pahari B, *et al*. Multiple and single fractionpalliative radiotherapy in bone secondaries-a prospective study.*Indian J Radiol Imaging* 2002;12:281–284. | Excluded | Duplicate |
| #11 | Cole DJ. A randomized trial of a single treatment versus conventionalfractionation in the palliative radiotherapy of painful bonemetastases. Clin Oncol 1989;1:59–62. | Excluded | Duplicate |
| #12 | Warde PR, Kirkbride P, Panzarella T, *et al*. Single fraction vsfractionated radiation therapy in the palliation of skeletalmetastases—a randomised phase III trial. *Proceedings American**Society of Clinical Oncology* 2001;20: abstract 1538. | Excluded | Conference abstract |
| #13 | Warde PR, Kirkbride P, Panzarella T, *et al*. A randomised trialcomparing the efficacy of a single radiation fraction with fractionatedradiation therapy in the palliation of skeletal metastases. *Int J**Radiat Oncol Biol Phys* 2002;48(suppl 3):185. | Excluded | Conference abstract |

**Full-text evaluation of excluded studies in Sze (because comparison is different schemes multiple fraction or single fraction), 2003 (N = 14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Reference** | **Included / Excluded** | **Reasons** |
| #1 | Blitzer PH. Reanalysis of the RTOG study of the palliation ofsymptomatic osseous metastasis. *Cancer* 1985;55:1468–1472.PMID: 2579716 | Excluded | Comparison is different schemes of radiotherapy |
| #2 | Borojevic N, Golubicic I, Radosˇevic-Jelic L. The responsivnessof bone metastases in breast cancer patients to radiotherapy:Prospective study comparing six different fractionation schedules.Eur J Cancer 1999;34:1326 [abstract]. | Excluded | Conference abstract |
| #3 | Foro P, Algara M, Reig A, *et al*. Randomized clinical trialcomparing two schedules of treatment for painful bone metastases[abstract]. 6 vs 8 Gy single doses. *Radiother Oncol* 1998;48:834. | Excluded | Conference abstract |
| #4 | Hirokawa Y, Wadasaki K, Kashiwado K, et al. A multiinstitutionalprospective randomized study of radiation therapy ofbone metastases. Nippon Igaku Hoshasen Gakkai Zasshi 1988;48:1425–1431. | Excluded | Article in Japanese |
| #5 | Hoskin PJ, Price P, Easton D, et al. A prospective randomised trialof 4 Gy or 8 Gy single doses in the treatment of metastatic bonepain. Radiother Oncol 1992;23:74–78.PMID: 1372126 | Excluded | Comparison is different schemes of radiotherapy |
| #6 | Jeremic B, Shibamoto Y, Acimovic L, *et al*. A randomized trial ofthree single-dose radiation therapy regimens in the treatment ofmetastatic bone pain. *Int J Radiat Oncol Biol Phys* 1998;42:161–167.PMID: 9747834 | Excluded | Comparison is different schemes of radiotherapy |
| #7 | Madsen EL. Painful bone metastasis: efficacy of radiotherapyassessed by the patients: a randomized trial comparing 4 Gy\_6versus 10 Gy\_2. *Int J Radiat Oncol Biol Phys* 1983;9:1775–1779.PMID: 6198311 | Excluded | Comparison is different schemes of radiotherapy |
| #8 | Maranzano E, Frattegiani I, Piro F, et al. Randomized trial ofshort-course versus split-course radiotherapy (RT) in metastaticspinal cord compression (MSCC). An interim analysis [abstract].Radiother Oncol 2000;56:62. | Excluded | Conference abstract |
| #9 | Niewald M, Tkocz HJ, Abel U, et al. Rapid course radiationtherapy vs. more standard treatment: a randomized trial for bonemetastases. Int J Radiat Oncol Biol Phys 1996;36:1085–1089.PMID: 8985030 | Excluded | Comparison is different schemes of radiotherapy |
| #10 | Okawa T, Kita M, Goto M, et al. Randomized prospective clinicalstudy of small, large and twice-a-day fraction radiotherapy forpainful bone metastases. Radiother Oncol 1988;13:99–104.PMID: 2462264 | Excluded | Comparison is different schemes of radiotherapy |
| #11 | Poulter CA, Cosmatos D, Rubin P, *et al*. A report of RTOG 8206:a phase III study of whether the addition of single dose hemibodyirradiation to standard fractionated local field irradiation is moreeffective than local field irradiation alone in the treatment ofsymptomatic osseous metastases. *Int J Radiat Oncol Biol Phys*1992;23:207–214.PMID: 1374061 | Excluded | Comparison is different schemes of radiotherapy |
| #12 | Rasmusson B, Vejborg I, Jensen AB, et al. Irradiation of bonemetastases in breast cancer patients: a randomized study with1 year follow-up. Radiother Oncol 1995;34:179–184.PMID: 7631024 | Excluded | Comparison is different schemes of radiotherapy |
| #13 | Salazar OM, Sandhu T, da Motta NW, *et al*. Fractionatedhalf-body irradiation (HBI) for the rapid palliation of widespread,symptomatic, metastatic bone disease: a randomized Phase III trialof the International Atomic Energy Agency (IAEA). *Int J Radiat**Oncol Biol Phys* 2001;50:765–775. | Excluded | Duplicate |
| #14 | Tong D, Gillick L, Hendrickson FR. The palliation of symptomaticosseous metastases: final results of the Study by theRadiation Therapy Oncology Group. *Cancer* 1982;50:893–899.PMID: 6178497 | Excluded | Comparison is different schemes of radiotherapy |

**Full-text evaluation of included studies in Chow et al, 2007 & Chow et al, 2012 (N = 25)**

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Reference** | **Included / Excluded** | **Reasons** |
| #1 | Amouzegar-Hashemi F, Behrouzi H, Kazemian A, et al. Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. Curr Oncol 2008;15:151.PMID: 18596887 | Excluded | Comparison is single versus multifraction radiotherapy |
| #2 | Hamouda WE, Roshdy W, Teema M. Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases. Gulf J Oncol 2007;1:35e41. | Excluded | Duplicate |
| #3 | El-Shenshawy H, Kandeel A, El-Essawy S. The effect of a single fraction compared to multiple fractions radiotherapy on painful bone metastases with evaluation of computed tomography bone density in osteolytic bone metastases. Bull Alex Fac Med 2006;42:439. | Excluded | Comparison is single versus multifraction radiotherapy |
| #4 | Foro Arnalot P, Fontanals AV, Galceran JC, et al. 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;89:150e155. | Excluded | Duplicate |
| #5 | Safwat E, El-Nahas T, Metwally H, et al. Palliative fractionated radiotherapy for bone metastases clinical and biological assessment of single versus multiple fractions. J Egypt Natl Cancer Inst 2007;19:21e27.PMID: 18839032 | Excluded | Comparison is single versus multifraction radiotherapy |
| #6 | Sande TA, Ruenes R, Lund JA, et al. Long-term follow-up of cancer patients receiving radiotherapy for bone metastases: results from a randomised multicentre trial. Radiother Oncol 2009;91:261e266.PMID: 19307034 | Excluded | Comparison is single versus multifraction radiotherapy |
| #7 | Sarkar SK, Sarkar S, Pahari B, et al: Multipleand single fraction palliative radiotherapy in bonesecondaries: A prospective study. Ind J Radiol Imag12:281-284, 2002 | Excluded | Duplicate |
| #8 | Altundag˘ MB, U¨ c¸ er AR, C¸ alikog˘lu T, et al:Single (500 cGy, 800 cGy) and multifraction (300 X10 cGy) radiotherapy schedules in the treatmentof painful bone metastases. Turkish Journal ofHematology-Oncology 12:16-21, 2002 | Excluded | Written in Turkish |
| #9 | Badzio A, Senkus-Konefka E, Jereczek-FossaBA, et al: 20 Gy in five fractions versus 8 Gy in onefraction in palliative radiotherapy of bone metastases.A multicentre randomized study. Journal ofOncology 53:261-264, 2003 | Excluded | Duplicate |
| #10 | Hartsell WF, Scott CB, Watkins Bruner D, etal: Randomized trial of short- versus long-courseradiotherapy for palliation of painful bone metastases.J Natl Cancer Inst 97:798-804, 2005 | Excluded | Comparison is single versus multifraction radiotherapy |
| #11 | Roos DE, Turner SL, O’Brien PC, et al: Randomizedtrial of 8 Gy in 1 versus 20 Gy in 5 fractionsof radiotherapy for neuropathic pain due to bonemetastases (Trans-Tasman Radiation OncologyGroup, TROG 96.05). Radiother Oncol 75:54-63,2005 | Excluded | Duplicate |
| #12 | Kaasa S, Brenne E, Lund J, et al: Prospectiverandomized multicentre trial on single fraction radiotherapy(8 Gy X 1) versus multiple fractions (3 Gy X10) in the treatment of painful bone metastases:Phase III randomized trial. Radiother Oncol 79:278-284, 2006 | Excluded | Duplicate |
| #13 | Haddad P, Behrouzi H, Amouzegar-HashemiF, et al: Single versus multiple fractions of palliativeradiotherapy for bone metastases: A randomizedclinical trial in Iranian patients. Radiother Oncol 80:S65, 2006 (abstr 223) | Excluded | Conference abstract |
| #14 | Steenland E, Leer JW, Van Houwelingen H, etal: The effect of a single fraction compared tomultiple fractions on painful bone metastases: Aglobal analysis of the Dutch Bone Metastasis Study.Radiother Oncol 52:101-109, 1999 | Excluded | Duplicate |
| #15 | van der Linden YM, Lok JJ, Steenland E, et al:Single fraction radiotherapy is efficacious: A furtheranalysis of the Dutch Bone Metastasis Study controllingfor the influence of retreatment. Int J RadiatOncol Biol Phys 59:528-537, 2004 | Excluded | Duplicate |
| #16 | Gaze MN, Kelly CG, Kerr GR, et al: Pain reliefand quality of life following radiotherapy for bonemetastases: A randomized trial of two fractionationschedules. Radiother Oncol 45:109-116, 1997 | Excluded | Duplicate |
| #17 | Bone Pain Trial Working Party: 8 Gy singlefraction radiotherapy for the treatment of metastaticskeletal pain: Randomized comparison with a multifractionschedule over 12 months of patient followup.Bone Pain Trial Working Party. Radiother Oncol52:111-121, 1999 | Excluded | Duplicate |
| #18 | Foro P, Algara M, Reig A, et al: Randomizedprospective trial comparing three schedules of palliativeradiotherapy: Preliminary results. Oncologia21:55-60, 1998 | Excluded | Article in Spanish |
| #19 | Ozsaran Z, Yalman D, Anacek Y, et al: Palliativeradiotherapy in bone metastases: Results of arandomized trial comparing three fractionationschedules. Journal of BUON 6:43-48, 2001 | Excluded | Duplicate |
| #20 | Price P, Hoskin PJ, Easton D, et al: Prospectiverandomized trial of single and multifractionradiotherapy schedules in the treatment of painfulbony metastases. Radiother Oncol 6:247-255,1986 | Excluded | Duplicate |
| #21 | Cole DJ: A randomized trial of a single treatmentversus conventional fractionation in thepalliative radiotherapy of painful bone metastases.Clin Oncol 1:59-62, 1989 | Excluded | Duplicate |
| #22 | Kagei K, Suzuki K, Shirato H, et al: A randomizedtrial of single and multifraction radiation therapyfor bone metastasis: A preliminary report. Gan NoRinsho 36:2553-2558, 1990 | Excluded | Written in Chinese |
| #23 | Nielsen OS, Bentzen SM, Sandberg E, et al:Randomized trial of single dose versus fractionatedpalliative radiotherapy of bone metastases. RadiotherOncol 47:233-240, 1998 | Excluded | Duplicate |
| #24 | Koswig S, Budach V: Recalcification and painrelief following radiotherapy for bone metastases: Arandomized trial of 2 different fractionation schedules(10 X 3 Gy vs. 1 X 8 Gy). Strahlenther Onkol175:500-508, 1999 | Excluded | Written in German |
| #25 | Kirkbride P, Warde P, Panzarella A, et al: Arandomized trial comparing the efficacy of singlefraction radiation therapy plus ondansetron withfractionated radiation therapy in the palliation ofskeletal metastases. Int J Radiat Oncol Biol Phys48:185, 2000 (suppl 3) | Excluded | Conference abstract |

**Full-text evaluation of included studies in Wu et al, 2003 (N = 16)**

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Reference** | **Included / Excluded** | **Reasons** |
| #1 | Kirkbride P, Warde P, Panzarella A, et al. A randomised trialcomparing the efficacy of single fraction radiation therapyplus ondansetron with fractionated radiation therapy in thepalliation of skeletal metastases [Abstract]. Int J Radiat OncolBiol Phys 2000;48(3 Suppl):185. | Excluded | Duplicate |
| #2 | Bone Pain Trial Working Party. 8 Gy single fraction radiotherapyfor the treatment of metastatic skeletal pain: Randomisedcomparison with a multifraction schedule over 12 monthsof patient follow-up. Radiother Oncol 1999;52:111–121. | Excluded | Duplicate |
| #3 | Steenland E, Leer JW, van Houwelingen H, et al. The effectof a single fraction compared to multiple fractions on painfulbone metastases: A global analysis of the Dutch Bone MetastasisStudy. Radiother Oncol 1999;52:101–109. | Excluded | Duplicate |
| #4 | Koswig S, Budach V. Remineralization and pain relief in bonemetastases after different radiotherapy fractions (10 times 3Gy vs. 1 time 8 Gy). A prospective study [in German].Strahlenther Onkol 1999;175:500–508. | Excluded | Written in German |
| #5 | Nielsen OS, Bentzen SM, Sandberg E, et al. Randomized trial of single dose versus fractionated palliative radiotherapy ofbone metastases. Radiother Oncol 1998;47:233–240. | Excluded | Duplicate |
| #6 | Gaze MN, Kelly CG, Kerr GR, et al. Pain relief and quality oflife following radiotherapy for bone metastases: A randomisedtrial of two fractionation schedules. Radiother Oncol 1997;45:109–116. | Excluded | Duplicate |
| #7 | Cole DJ. A randomized trial of a single treatment versusconventional fractionation in the palliative radiotherapy ofpainful bone metastases. Clin Oncol (R Coll Radiol) 1989;1:59–62. | Excluded | Duplicate |
| #8 | Price P, Hoskin PJ, Easton D, et al. Prospective randomisedtrial of single and multifraction radiotherapy schedules in thetreatment of painful bony metastases. Radiother Oncol 1986;6:247–255. | Excluded | Duplicate |
| #9 | Niewald M, Tkocz HJ, Abel U, et al. Rapid course radiationtherapy vs. more standard treatment: A randomized trial forbone metastases. Int J Radiat Oncol Biol Phys 1996;36:1085–1089. | Excluded | Duplicate |
| #10 | Rasmusson B, Vejborg I, Jensen AB, et al. Irradiation of bonemetastases in breast cancer patients: A randomized study with1 year follow-up. Radiother Oncol 1995;34:179–184. | Excluded | Duplicate |
| #11 | Hirokawa Y, Wadasaki K, Kashiwado K, et al. A multiinstitutionalprospective randomized study of radiation therapyof bone metastases [Japanese]. Nippon Igaku HoshasenGakkai Zasshi 1988;48:1425–1431. | Excluded | Article in Japanese |
| #12 | Okawa T, Kita M, Goto M, et al. Randomized prospectiveclinical study of small, large and twice-a-day fraction radiotherapyfor painful bone metastases. Radiother Oncol 1988;13:99–104 | Excluded | Duplicate |
| #13 | Madsen EL. Painful bone metastasis: Efficacy of radiotherapyassessed by the patients—A randomized trial comparing 4Gy x 6 versus 10 Gy x 2 Int J Radiat Oncol Biol Phys1983;9:1775–1779. | Excluded | Duplicate |
| #14 | Tong D, Gillick L, Hendrickson FR. The palliation of symptomaticosseous metastases: Final results of the Study by theRadiation Therapy Oncology Group. Cancer 1982;50:893–899. | Excluded | Duplicate |
| #15 | Jeremic B, Shibamoto Y, Acimovic L, et al. A randomizedtrial of three single-dose radiation therapy regimens in thetreatment of metastatic bone pain. Int J Radiat Oncol BiolPhys 1998;42:161–167. | Excluded | Duplicate |
| #16 | Hoskin PJ, Price P, Easton D, et al. A prospective randomisedtrial of 4 Gy or 8 Gy single doses in the treatment of metastaticbone pain. Radiother Oncol 1992;23:74–78. | Excluded | Article in Japanese |

Appendix

**Search strategies**

**Medline via OVID**

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomized controlled trials/
4. Random allocation/
5. Double blind method/
6. Single blind method/
7. clinical trial.pt.
8. exp Clinical trial/
9. (clin$ adj25 trial$).tw.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
11. Placebos/
12. placebos.tw.
13. random.tw.
14. Research design/
15. Comparative study/
16. exp Evaluation studies/
17. Follow up studies/
18. Prospective studies/
19. (control$ or prospectiv$ or volunteer$).tw.
20. or/1-19
21. limit 20 to animal
22. limit 20 to human
23. 21 and 22
24. 21 not 23
25. 20 not 24
26. exp Bone Neoplasms/
27. (Osseous metastasis or Osseous metastases).mp.
28. 26 or 27
29. 25 and 28
30. (radiotherapy or irradiation or radiation).mp.
31. 29 and 30
32. 31 and 32 **179**

**Embase**

1. 'bone marrow cancer'/exp
2. 'bone metastasis'/exp
3. #1 OR #2
4. radiotherapy OR irradiation OR radiation
5. #3 AND #4
6. pain OR analges\*
7. #5 AND #6
8. #7 AND [humans]/lim
9. #7 AND [animals]/lim
10. #8 AND #9
11. #8 NOT #10
12. #7 AND #11
13. #7 AND #11 AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim) AND [2001-2015]/py **251**

**Cochrane**

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomized controlled trials
4. Random allocation
5. Double blind method
6. Single blind method
7. clinical trial.pt.
8. MeSH descriptor: [Clinical Trial] explode all trees
9. (clin\* adj trial\*).tw.
10. ((singl\* or doubl\* or trebl\* or tripl\*) and (blind\* or mask\*)).tw.
11. Placebos
12. placebos.tw.
13. random.tw.
14. research design
15. comparative study
16. MeSH descriptor: [Evaluation Studies] explode all trees
17. Follow up studies
18. Prospective studies
19. (control\* or prospectiv\* or volunteer\*).tw.
20. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21. #20 and animal
22. #20 and human
23. #21 and #22
24. #21 not #23
25. #20 not #24
26. MeSH descriptor: [Bone Neoplasms] explode all trees
27. Osseous metastasis or Osseous metastases
28. #26 or #27
29. #25 and #28
30. Radiotherapy or irradiation or radiation
31. #29 and #30
32. Pain or analges\*

34. #31 and #32 **93**