16. **Skeletal Metastases**

Introduction

Skeletal metastases are common in advanced neoplastic diseases. About 50 per cent of all cancer patients get metastases, and about half of them get metastases in the skeleton. Carcinomas of the breast, prostate and bronchi account for approximately 80 per cent of all bone metastases. In about 50–70 per cent of the patients, bone metastases give rise to signs and symptoms, such as skeletal or neuropathic pain, pathological fractures, hypercalcemia, nerve root damage, and spinal cord compression [37]. Metastases to the skeleton are usually multiple; solitary metastases appear in less than 10 per cent of the cases. More than 80 per cent of the metastases are found in the axial skeleton, i.e. the vertebral column and the pelvis. The localization pattern of bone metastases does not depend on the histopathological type of tumour. However, tumours in the pelvic organs (prostate, bladder, rectum, uterus) are prone to metastases to the pelvic skeleton. Pathological fractures occur in 8–30 per cent and most often in the femur. Hypercalcemia occurs in approximately 10 per cent, and spinal cord compression in about 5 per cent of the patients.

Within a metastatic bone lesion, there is usually a marked activity of a great variety of cells. There are not only the neoplastic cells, that are responsible for this activity, but also osteoclasts, osteoblasts, and inflammatory cells, including macrophages. High osteoclastic activity results in osteolytic lesions as seen in the radiologic images, whereas predominantly osteoblast activity gives rise to osteosclerotic lesions. However, in most bone metastases, both osteolytic and osteosclerotic activities are going on simultaneously.

The most common symptom is pain. It is present in about 75 per cent of the patients. Skeletal pain is thought to be elicited by a combination of mechanical and biochemical factors. As a result of local bone destruction, there may be an activation of pain receptors in local nerves. Macro- and microfractures may contribute, as well as the loss of bone strength and stiffness. Increased blood flow to the metastatic lesions promotes

inflammatory response, with release of cytokines by both the tumour cells and the surrounding normal cells.

The treatment intention in bone metastases is in most cases palliation. Only exceptionally it is curative and then, the patient usually has a solitary metastases.

Median survival time is usually about 3–12 months. However, there are patients, particularly breast cancer patients, who may survive for several years. The goals of treatment are to attain – for shorter or longer time periods – relief of pain, preservation of mobility and function, maintenance of skeletal integrity and preservation of quality of life. Specific antitumoural treatment, such as cytotoxic chemotherapy and hormone manipulation, are first-line therapies. In addition several other modalities can be used, as local radiotherapy [4,14,16,17,25,27] and/or systemic radiotherapy [17,27,42,52]. The use of orthopedic intervention with osteosynthetic devices and, in particular for patients with long term prognosis, prosthetic reconstructions are of great importance [20,28, 43,65], as well as the use of various drugs, including analgesics and bisphosphonates [10,15,23].

Summary of the earlier report, SBU 129/2

The synthesis of the literature on radiotherapy in the previous SBU report, 129/2, published 1996, was based on 171 scientific reports, including 13 randomized studies, 24 prospective investigations, and 79 retrospective studies. Together, all these investigations involved 13 054 patients. The literature on which the report was based, was covered until 1994.

The main issues focused upon were bone pain palliation, fracture prevention and treatment, as well as spinal cord compression. For pain palliation, the treatment modalities looked upon were, in addition to external beam radiation, therapy with local and half-body field, systemic radiotherapy by means of radionuclides and treatment with bisphosphonates.

Conclusions

- Radiotherapy has been well documented as a method for alleviating pain, but the mechanisms underlying this effect are largely unknown.
- When used for pain palliation, radiotherapy achieves freedom from pain – or substantial alleviation of pain – in nearly all cases, with few side effects.
- Half-body irradiation is effective in treating multiple metastatic sites and should be considered for use more frequently. However, this increases the requirements on equipment, dosimetry, and hospital beds.
- Systemic radiotherapy with radionuclides may be indicated for generalized skeletal pain.
- The role of radiotherapy in preventing or healing fractures is not fully evaluated. Optimum dose levels and fractionation schedules have not been established.
- Early radiotherapy for spinal cord compression may prevent symptoms from becoming worse, but the effects on existing paralysis are modest.

Discussion

In the SBU 129/2 report it was underlined, that metastases from most carcinomas, with few exceptions, had to be treated with a palliative intent and that the most common symptom is pain. Thus, one of the main end points should be the effect of the therapeutic intervention on pain, measured as pain relief (partial and/or complete) and its duration. Local radiotherapy (RT) was found to have a documented effect on pain, with moderate side effects. There were only few randomized controlled trials. The RT procedure varied between the centers, and it was difficult to compare the results obtained. In most patients, with advanced stage of the disease, it was difficult to conduct large randomized studies with a follow-up period of at least one year. In addition, the lack of adequate methods for evaluation of pain relief contributed to the unclarity of the results. Thus, dose levels and fractionating schedules used for RT for pain relief often turned-out to be based on so-called empirical knowledge, with regard to both the patients' individual characteristics and the local institutional practice.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
C	3/1 258	7/1 110	3/138	**13/2 506**
P	4/554	15/903	5/165	**24/1 622**
R	3/2 353	39/4 930	37/1 643	**79/8 926**
L	15	18	3	**36**
O	1	14	4	**19**
Total	**26/4 165**	**93/6 943**	**52/1 946**	**171/13 054**

Assessment of new literature

Search methods and selections

The search of the literature was performed according to the directions decided by SBU. The reports were identified by searching in Medline and the Cochrane Library. The time period chosen was from January 1, 1994, to October 1, 2001. The search criteria used were: full report in a peer-reviewed scientific journal, dealing with clinical investigations, including meta-analysis, randomized controlled trials (RCT), as well as prospective and retrospective studies. In addition, some review articles were included.

In all, 145 reports were retrieved, which initially seemed to fulfil most of these criteria. However, out of these 145 reports, a closer scrutiny revealed, that only 65 of them fulfilled the SBU selection criteria.

The reasons for exclusion of 80 abstracts and articles from further analysis in the present review were grouped as follows:

Group
A: Reviews of categories L2/L3: 13
B: Short comments: 2
C: Basic, non-clinical, scientific investigations: 15
D: Experimental phase I–II studies: 12
E: Studies based on small patient materials: 16
F: Investigations with topics not relevant for this study: 20
G: Duplicate publications: 2

Overview of new studies

The occurrence of skeletal metastases still demands a palliative therapeutic setting [4,6,16,17,33,53]. There were no reports, where treatment was given with curative intention. As previously reported, there are long-term survivors. Patients with solitary metastases have better prognosis than those with multiple ones. Patients with skeletal metastases from carcinoma of the breast have, as a rule, longer survival time periods than others.

Radiotherapy (RT)

Local RT of bone pain

Overview 1a. Fractionation and dose (after the list of references)

The relief of bone pain by means of locally applied RT has been focused upon during these last few years. Of high relevance were eight randomized studies [18,29,35,45,46,49,58,60], and five larger prospective studies [3,12,26,63,64]. The fractionation schedules used were quite different; the lowest single fraction was 4 Gy, the highest 10 Gy. The multifractions used were between 1.8 Gy and 5 Gy, given 4 to 23 times. The results confirm those of SBU 129/2 that local RT has a well documented effect on metastatic bone pain [14,25].

As regards the concept "complete pain response", it was difficult to evaluate the reported results, as the assessments of the patients' pain and the criteria of response that were used were markedly different [44,58,60].

As to the concept "overall pain relief" (OPR), its frequency was reported to vary between 59 per cent and 90 per cent. The pain-relieving effect reported with 4 Gy single fractions was significantly lower than that of other fraction schedules [12,29]. The lowest pain-relieving single fraction seemed to be 6 Gy [29]. Excluding the results obtained of the 4 Gy single treatment, the mean rate of OPR was 84 per cent. All studies, with exception of one non-randomized study [3], showed that OPR did not seem to depend on the fractionation schedules used [12,18,26,29,35, 45,46,49,58,60,63,64]. The duration of OPR was reported in 9 out of the 13 studies. There were great differences between the time periods for evaluation and how the results were assessed. The large randomized clinical trials (RCT) reported a median time to progression of five and six months after RT [58], and first increase of pain score in 40 per cent of the patients

after one year [60]. The results reported in the other studies did not show a significantly longer time to pain progression. Time to pain progression did not depend on the fractionation schedules used.

The number of re-treatments was stated in 7 of the 13 studies. The frequency reported varied between 2 per cent and 44 per cent. In the two large RCTs, the percentages of re-treated patients in the different groups were 7 and 25 [58], and 10 and 23 [60], respectively. Re-treatment was thus, significantly higher in the single fraction group than in the multifraction. The reasons for these differences were not obvious.

The well-known side effects of local RT were found to be mild. The occurrence of spinal cord compressions (SCC) was reported in 4 out of the 13 studies. It was not always clearly stated, whether the cord compressions occurred at the index fields. The incidences reported were low, 1–2 per cent, in the large RCT studies [58,60], and without any differences between the various treatment groups. The smaller studies reported incidences of SCC of 8–9 per cent and again without significant differences in between the treatment groups [29,64].

Occurrence of pathological fractures was reported in 6 out of the 13 studies. The incidence reported varied from 1 per cent to 10 per cent. Low incidence (1–4 per cent) were reported in the two large RCTs [58,60]. In both of them, patients treated with a single RT fraction had two to three times higher incidence of pathological fractures than those treated with multifraction schedules.

Analgesic reports were not sensitive enough to allow any decisions of the RT response over a time period of 12 months [60].

When QoL measurements were made, no significant differences between treatment groups were shown [58].

The cost difference between single and multifraction treatment groups was 8 per cent when the costs for re-treatment were included [58].

There is only one report studying the end point of skeletal remineralisation of osteolytic metastases [35]. After six months the remineralisation was significantly better in the patients in the multifraction group compared to those of the single fraction group.

Overview 1b. Half body irradiation (HBI) of bone pain (after the list of references)

In a recent randomized study [54] it has been shown that overall pain relief, side effects and QoL, were the same, irrespective of whether the patients had obtained "standard" treatment, 3 Gy x 5, or 3 Gy x 2 or 4 Gy x 2 in one day. Overall pain relief was about 90 per cent and occurred within three to eight days. Duration of pain relief was, however, significantly longer in the group who had obtained 3 Gy x 5 then in the other two groups.

In one retrospective study, mainly based on patients with nasopharyngeal skeletal metastases, HBI was used [13]. Whith a single dose of 7 Gy and above, pain relief was attained in 70 per cent of the patients; the effect was smaller with lower doses.

Other reports and systematic reviews on local RT and bone pain

(These reports not shown in overview)

In 1999, there was one report, including pooled data from RCTs published between 1982–1992 [7]. The main focus of that study was to find out, whether or not there might be a dose-response relationship between the biological effective dose (BED) and the response rate of patients with bone pain relief. The end point used in that data analysis was complete pain relief. The study demonstrated no dose-response relation between RT dose and early (four weeks) complete pain relief. However, for late (3–6 months) complete pain relief, the results showed a clearcut relationship between response rates and BED: the higher the BED the higher the number of patients with late complete pain relief.

In one publication the results of 12 RCT were reviewed [50]. The main purpose was to determine which fractionation schedules used in local RT that gave best results as regards complete pain relief and prevention of disability for the remaining life of the patient. Five out of the 12 studies were published since 1994 [18,29,45,46,49], (Overview 1a). It was concluded that methodological differences between the reports seem to contribute to unclear results with respect to pain relief, complete pain relief and duration of pain relief. One additional report was dealing with the same issue, re-investigating ten RCT [30]. Four out of these ten

studies were published since 1994 [18,45,46,49]. This review concluded that a single dose of 8 Gy was effective for partial or complete pain relief in about 80 per cent of the patients.

Recently, one systematic review from the Cochrane Library was published on palliation of metastatic bone pain with local RT and systemic radionuclides [44]. The review included nine RCT published before 1994, comprising 1 895 patients, and four studies, published since 1994, including 769 patients, [18,45,46,49], (Overview 1a). The results showed that local RT was clearly effective at reducing pain. Overall pain relief was assessed to be about 66 per cent. There was no evidence of any difference in efficacy between different fractionation schedules used.

The literature shows that:

- The treatment of skeletal metastases is, with few exceptions, palliative.
- Local RT gives overall bone pain relief in more than 80 per cent of the patients.
- In general, the overall pain relief does not depend on the fractionation schedules used. The lowest pain-relieving single fraction seemed to be 6 Gy.
- Half a year after local RT, at least half of the patients, who initially got overall pain relief, are still free from pain.
- The number of re-treatments is low, but significantly higher in patients given a single fraction RT than multifraction RT. The reason for this has to be clarified.
- In general, side effects of local RT are mild.
- Complications, such as spinal cord compression and pathological fractures at the index fields, are rare.
- The results of local RT, when related to the concept of complete pain relief, still remain to be settled.
- The difference in costs between single and multifraction RT is small, when the costs for re-treatment are included.

- Remineralisation of osteolytic bone lesions seems to be dose-dependent. A more fractionated schedule is obviously advantageous.
- The pathophysiological mechanisms behind metastatic skeletal pain and the mechanisms of pain relief with RT still remain to be more closely investigated.

Local RT of spinal cord compression (SCC)

Overview 2 (after the list of references)

The present review includes one retrospective study [32], and four prospective non-randomized studies [22,31,40,41]. The total number of patients studied is limitied. Details concerning radiotherapy methods are not always given. In most of the reports, conventional fractionation schedules were used. There was, however, one study using single fractions of 8 Gy once weekly x 2. The results did not differ significantly from those with multiple fractions, but the patient material was selected [40]. In general, earlier statements of SBU 129/2 were confirmed [14,27,28].

The literature shows that:

- Early diagnosis and therapy are the two most important predictors of the final outcome of SCC.
- When the SCC diagnosis is late, the outcome depends on the radioresponsiveness of the tumour.
- After RT, one third of the number of non-walking SCC patients improve to attain the ability to walk.
- There is only a minority (about 10 per cent) of the totally paralytic patients who regain the ability to walk.
- A slow onset of the SCC symptoms seems to facilitate recovery after RT.
- Controlled studies are needed in order to clarify treatment schedules for the different subgroups of SCC patients.

Surgical treatment of pathological fractures with or without RT

Overview 3 (after the list of references)

There were only two retrospective reports focusing on this issue [21,62]. Postoperative RT was shown to be the only significant predictor of normal use of legs or arms after surgical intervention [62]. When patients were operated upon with prosthetic replacement of the proximal femur, post-operative RT seems to prevent new bone formation around the prosthetic implants [21].

The literature shows that:

- There is evidence that local RT after stabilizing surgical treatment of pathological fractures is of significant benefit for the patients' outcome.
- However, the indications for giving local RT after prosthetic replacements need to be better clarified.

Systemic radionuclide therapy of bone metastases

Overview 4 (after the list of references)

During the last few years, the role of radionuclides in the treatment of bone pain has been extensively studied. A review of the relevant reports revealed three RCTs [48,51,57], ten prospective [1,2,5,11,34,36,38,39, 47, 56,61] and one retrospective study [19]. In five of these studies, less than 50 patients were included. The radionuclides most often used in patients with advanced metastatic diseases were 89 Strontium (^{89}Sr) (Metastron®), 153 Samarium (^{153}Sm) (Lexidronam®), and 186 Renium (^{186}Re). Some of the studies were dose-finding phase I–II reports [2,61]. Most of the more complete investigations were made in patients with several types of tumours. However, carcinomas of the prostate, breast and bronchi predominated.

The OPR was reported to be between 60 and 80 per cent, with no significance between the different radionuclides used.

The onset of pain relief was found to differ with the type of radionuclide treatment; ^{89}Sr showed a median time of 15 days [5,36], whereas the effect of ^{153}Sm was reported to be within 2–7 days [1,2,51,57]. Two reports on ^{186}Re stated the onset to be between 7 and 20 days [34,56].

The duration of response varied considerably between the reports, but 2–4 months seemed to hold true for most of them.

In one RCT, in which bone pain relief by either local RT or HBI was compared with systemic radionuclide therapy with ^{89}Sr, in patients with hormone-independend prostate carcinoma, the efficacy in the treatment groups was found to be the same. However, as regards new pain sites reported by the patients, the number was lower in patients receiving ^{89}Sr than in those who got RT or HBI [48].

In almost all studies a mild and transient myelosuppression (WHO grade I–II) was reported, three to six weeks after treatment, depending on the radionuclide given.

There were two systematic reviews published, dealing with palliation of metastatic bone pain by use of systemic radionuclides [44,55]. The publication from the Cochrane Library [44] included seven reports about bone pain relief after different radionuclide treatment. There were three of them published since 1994 [48,51,56]. The other systematic review [55] included 14 reports, three of which after 1994 [2,51,57].

The literature shows that:

- The dose of ^{89}Sr (150–200 MBq) and ^{153}Sm (1.0 mCi/kg), suitable for patients with bone pain, seems now to be agreed upon.
- The overall bone pain relief by therapy with ^{89}Sr or ^{153}Sm occurs in about 60–80 per cent of the patients, with a response duration of 2–4 months.
- The onset of response by therapy with ^{89}Sr or ^{153}Sm occurs after 2–3, and 1–2 weeks, respectively.
- Reports of new pain sites are lower in patients treated with ^{89}Sr than in those who had been given RT or HBI.
- Side effects after one radionuclide treatment are mild to moderate, irrespective of the radionuclide chosen. However, the side effects of repeated treatments still remain to be studied.
- These data are valid for skeletal meastases from the two most common neoplastic diseases, namely prostate and mammary carcinomas. For skeletal metastases from other neoplastic diseases, corresponding data are still missing.

Bisphosphonate therapy

Overview 5 (after the list of references)

Because of their ability to inhibit osteoclast-induced bone resorption, bisphosphonates have been studied for the prevention and treatment of lytic bone lesions for more than a decade [10,15,23]. Patients with osteolytic metastases from breast carcinomas have been extensively investigated. The recommended treatment is pamidronate, 90 mg every fourth week, in women with pain caused by osteolytic bone lesions, concurrently with systemic chemotherapy and/or hormonal treatment [10,23]. The intent of this treatment was to decrease the prevalence of skeleton-related complications, including hypercalcemia.

The recent RCTs with pamidronate against placebo showed a significantly lower incidence of skeletal complications, both during one year's [24], and two years' [59] treatment. The time to first skeletal complication was significantly prolonged in the pamidronate-treated groups. Also the need for RT was significantly lower in the pamidronate-treated groups than in the placebo groups. Length of survival did not differ between the groups.

One recent RCT of the new potent bisphosphonate, zoledronic acid, has demonstrated that the need of RT was significantly reduced when 2.0 or 4.0 mg, every fourth week, was given [9]. The effect reported was equal to that of the standard treatment, viz. 90 mg of pamidronate every fourth week. The adverse effects were essentially the same in nature and frequency. The number of patients who discontinued treatment was high, mostly due to death or an adverse event. Most patients, about 70 per cent in the three zoledronic acid groups and 82 per cent in the pamidronate group, completed at least six months of study treatment. Zoledronic acid was given as a 5-minute infusion. The shorter administration time could in the clinical setting be of advantage. Almost a third of the patients in this study had multiple myeloma. Thus, the effects could be different in a study including only patients with carcinomas of the breast.

The literature shows that:

- Patients with myeloma or osteolytic lesions from carcinoma of the breast benefit from treatment with bisphosphonates in terms of a lower incidence of skeletal complications and lower increase of bone pain.
- The treatment is generally well tolerated. The side effects reported are vomiting and fatigue in about 10 per cent of the patients. A new potent bisphosphonate drug, zoledronic acid, has equal effects as the pamidronate treatment, and the same kinds of side effects and a similar incidence of them. A shorter administration time may be advantageous.
- Bisphosphonate treatment has not been shown to have any life-prolonging effect.

Literature

The synthesis of the literature in skeletal metastases is based upon 65 scientific reports: 16 RCTs, 20 prospective studies, and five retrospective studies with the details shown in the overviews 1–5. One systematic review [44], and one MASC application report [55] have also been scrutinized, as well as 22 larger reviews.

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	**2 = Moderate**	**3 = Low**	**Total**
C	8/3 487	8/1 767	–	**16/5 254**
P	5/540	11/1 751	4/109	**20/2 400**
R	1/119	3/144	1/134	**5/397**
L	13	5	–	**18**
O	1	3	–	**4**
Total	**28/4 146**	**30/3 662**	**5/243**	**63/8 051**

The two systematic reviews [44,55] were not classified in the table above.

Conclusions and comments

- Irradiation of skeletal metastases is, with few exceptions, a palliative treatment. ([4]L1, [6]O2, [16]L2, [17]L1, [33]L2, [53]O2).
- There is a strong evidence that radiotherapy of skeletal metastases gives an overall pain relief (complete and partial) in more than 80 per cent of the patients. ([3]P2, [12]P1, [18]C2, [26]P3, [29]C2, [35]C2, [45]C1, [46]C2, [49]C2, [58]C1, [60]C1, [63]P2, [64]P2).
- There is a strong evidence that the duration of pain relief in at least 50 per cent of the patients lasts for ≥6 months. ([3]P2, [18]C2, [26]P3, [29]C2, [45]C1, [46]C2, [49]C2, [58]C1, [60]C1).
- There is a strong evidence that pain relief, in terms of degree and duration, does not depend on the fractionation schedules applied. ([12]P1, [18]C2, [26]P3, [29]C2, [35]C2, [45]C1, [46]C2, [49]C2, [58]C1, [60]C1, [63]P2, [64]P2).
- Irrespective of the fractionation schedule used at irradiation, the number of later complications, such as spinal cord compression or pathological fractures, at the index fields are low. ([29]C2, [45]C1, [46]C2, [58]C1, [60]C1).
- There are some data showing that the cost difference between single and multifraction treatment is small. However, these data do not permit any firm conclusion. ([58]C1).
- Several reports indicate that both early diagnosis and early therapy of spinal cord compression are the two most important predictors of a favourable clinical outcome after radiotherapy. However, there are no controlled studies made. ([22]P1, [31]P2, [32]R2, [40]P2, [41]P2).
- When the diagnosis of spinal cord compression is late, a favourable outcome might depend on the radio-responsiveness of the tumour. The documentation is week and no conclusion can be drawn. ([41]P2).
- Some evidence exists, that a minor proportion of the totally paralytic patients can regain walking function after radiotherapy. ([22]P1).

- There is a strong evidence that the radionuclides ^{89}Sr and ^{153}Sm are efficient when they are used as a systemic treatment of generalized bone pain due to metastases from carcinomas of the prostate and breast. An overall bone pain relief occurs in about 60–80 per cent of the patients with a median response duration of 2–4 months. ([1]P2, [5]P2, [11]P2, [19]R1, [34]P3, [36]P1, [38]P3, [39]P3, [47]P2, [48]C1, [51]C2, [56]P1, [57]C1).
- There is a strong evidence that intravenous treatment with bisphosphonates in patients with myeloma and osteolytic bone metastases due to carcinoma of the breast significantly decreases the number of skeleton related events and bone pain. ([8]C2, [9]C2, [24]C1, [59]C1).

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Overview 1a *Skeletal metastases. Local radiotherapy of bone metastases – fractionation and dose.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Bone Pain Trial Working Party 1999 [60] C	**A:** 8 Gy/fr, 1 fr **B:** 4 Gy/fr, 5 fr, 20 Gy/1 w or 3 Gy, 10 fr, 30 Gy/2 w (only 8 pts got 3 Gy, 10 fr, 30/Gy/2 w)	761 pts A 383 B 378
Steenland 1999 [58] C	**A:** 8 Gy/fr, 1 fr **B:** 4 Gy/fr, 6 fr, 24 Gy/1 w	1 157 pts A 578 B 579 Mets to cervical spine excluded
Koswig 1999 [35] C	**A:** 8 Gy/fr, 1 fr **B:** 3 Gy/fr, 10 fr, 30 Gy/2 w	107 pts A 52 B 55
Jeremic 1998 [29] C	**A:** 4 Gy/fr, 1 fr **B:** 6 Gy/fr, 1 fr **C:** 8 Gy/fr, 1 fr	327 pts A 109 B 108 C 110

CPR: complete pain relief; d: day(s); fr: fraction: m: month(s); mets: metastases; NR: not reported; ns: not significant; OPR: overall pain relief (partial and complete); pts: patient(s); SCC: spinal cord compression; w: week(s); y: year(s)

Results					Conclusion/Comments
	OPR %	Duration	Retreatment %	SCC No pf pts	
Follow-up 1 y					The trial compared 8 Gy single fraction with a multifraction regimen (20 Gy or 30 Gy) with a randomization ratio 1:1. Pain assessment: 4-graded categorized scale. SCC: reported at the index field within 12 months. Pathological fractures: 7 cases in group A, 2 cases in group B. Use of analgesic drugs did not differ between the groups at any time of the study. **C1**
A	78	40% >12m	23	6 pts	
B+C:	78	No diff between the groups	10 p<0.001	4 pts	
Follow-up 2 y					Pain assessment: 11-pointed pain scale. Time to progression was effected of tumour histopathology (p<0.0001), breast carcinoma >prostate carcinoma >carcinoma of the bronchi or others. Pathological fractures: 4% in group A, and 2% in group B. QoL (Rotterdam symptom checklist) not significantly different between groups. Costs including retreatment was 8% higher for group B. **C1**
A	72	20 w	25	13 pts	
B	69	24 w	7	10 pts	
	ns	p<0.0001			
Follow-up 6 m					The main endpoint was remineralisation. **C2**
A	78	NR	NR	NR	
B	81				
	ns				
Remineralisation significantly better in group B with 1.7 x higher bone density vs 1.2 x in group A.					
Follow-up 2 m					Only patients with their first single bone metastases were included. Pain assessment: 4 point categorized pain scale. Pathological fractures occurred in 6, 7, and 7%, in group A, B, and C, respectively. **C2**
A	59*	42 w	42	4 pts	
B	73*	50 w	44	5 pts	
C	78*	47 w	38	4 pts	
*A vs B p<0.025					
*A vs C p<0.0019					

The table continues on the next page

Overview 1a *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Nielsen 1998 [45] C	**A:** 8 Gy/fr,1 fr **B:** 5 Gy/fr, 4 fr, 20 Gy/4 d	239 pts A 120 B 119
Gaze 1997 [18] C	**A:** 10 Gy/fr, 1 fr **B:** 4.5 Gy/fr, 5 fr, 22.5 Gy/1 w	265 pts A 134 B 131
Niewald 1996 [46] C	**A:** 4 Gy/fr, 5 fr, 20 Gy/1 w **B:** 2 Gy/fr, 15fr, 30 Gy/3 w	97 pts A 51 B 46
Rasmusson 1995 [49] C	**A:** 5 Gy/fr, 3 fr, 15 Gy/1 w **B:** 3 Gy/fr, 10 fr, 30 Gy/2 w	200 pts A 100 B 100 Only carcinoma of the breast
Arcangeli 1998 [3] P	**A:** 1.8–2 Gy/fr, 20–23 fr, 40 Gy/4–4.5 w **B:** 2.5–3 Gy/fr, 10–12 fr, 30 Gy/2–2.5 w **C:** 5–8 Gy/fr, 1–4 fr	255 pts A 64 B 102 C 89

Results OPR %		Duration	Retreatment %	SCC No pf pts	Conclusion/Comments
Follow-up 5 m					In both groups, 5% of the patients developed a pathological fracture. **C1**
A 62*	72**	60%>6 m	20	NR	
B 71*	82**	no diff	11	NR	
ns		between A and B	ns		
Pain assessment: Visual analogue scale (VAS)*, and a five-point categorized scale**.					
Follow-up 3 y					Re-entry of previously randomized pts was allowed. Pain assessment: five-point categorized scale. No differences in QoL (Spitzer index) or in the prevalence of anxiety/depression (HAD scale) between groups. **C2**
A	83	22.5 w	NR	NR	
B	89	24.9 w			
	ns	ns			
Follow-up 1 y					Pain assessment: 4 graded categorized scale. Analgesics used were not assessed. Pathological fractures: 4 pts in group A and 6 in group B. **C2**
A	77	35 w	2	NR	
B	86	35 w	2		
	ns				
Follow-up 1 y					Physicians were "blinded" as to which radiation treatment the patients had received. Pain assessment: 4-graded categorized scale. No sign. changes in consumption of analgesics within the two groups. **C2**
A	81	90%>12 m	NR	NR	
B	72	65%>12 m			
	ns	ns			
Follow-up: not clearly stated					Patient characteristics differed between the treatment groups. Pain assessment: VAS (0–10). Analgesic assessment: Five-point scale. CPR: VAS< 2 or 0 in the analgesic scale. A dose-response relationship for complete pain relief was also found. **P2**
A	91	Duration of	NR	NR	
B	83	pain relief			
C	62	sign longer			
p<0.05		for pts with CPR			

The table continues on the next page

Overview 1a *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Bremer 1999 [12] P	**A:** 4 Gy/fr, 1 fr **B:** 4 Gy/fr, 4 fr	131 pts A 45 B 86
Huguenin 1998 [26] P	**A:** 3 Gy/fr, 10 fr, 30 Gy/2 w **B:** 4 Gy/fr, 5 fr, 20 Gy/1 w **C:** 2 Gy/fr, 10 fr, 20 Gy/2 w	40 pts only malignant melanoma and renal cell carcinoma
Tombolini 1994 [63] P	**A:** 8 Gy/fr, 1 fr **B:** 5 Gy/fr, 4 fr, 20 Gy/4 d **C:** 4 Gy/fr, 5 fr, 20 Gy/w **D:** 3 Gy/fr, 10 fr, 30 Gy/2 w **E:** 2 Gy/fr, 20 fr, 40 Gy/4 w	103 pts A 48 B 7 C 15 D 20 E 13 Spinal mets Only
Uppelschoten 1995 [64] P	6 Gy/fr, 1 fr	211

Results					Conclusion/Comments
	OPR %	**Duration**	**Retreatment %**	**SCC No pf pts**	
Evaluated at 90 d					Pts with metastases in vertebrates, or other weight-bearing bone were excluded. Pain assessment: 4-point categorized scale. **P1**
A	55	3 m	NR	NR	
B	80	9 m			
p< 0.006		p<0.0001			
All groups					Small study. **P3**
	63*	2.4 m	NR	NR	
*No of pts and OPR in the different groups not shown.					
Follow-up 8 m					Most of the treatment was given with a 60-Co source. Pain assessment: 5-point categorized scale. Analgesic assessment not performed. Small numbers of patients in the different groups. **P2**
A	82	NR	4	NR	
B	85				
C	85				
D	80				
E	80				
	ns				
Follow-up 4 w					Re-entry of previously randomized patients was allowed. Pain assessment: 4-point categorized scale. Analgesic assessment: 4 categories. In-field pathological fractures occurred in 5 patients (8%). **P2**
	88	NR	18	4 pts	

Overview 1b *Skeletal metastases. Half Body Irradiation.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Salazar 2001 [54] C	**A:** 3 Gy/fr, 5 fr, 15 Gy/w **B:** 4 Gy/fr, 2 fr/d, 8 Gy/1 d **C:** 3 Gy/fr, 1 fr/d, 6 Gy/2 d	156 pts A 51 B 56 C 49
Chua 1994 [13] R	HBI: 1.5 Gy/min Treatment fields: 35–45 cm^2 Source skin distance: 80 cm Total doses: 4.5–8.0 Gy Median dose of 5 Gy to the upper half body, 7.0 Gy to the lower half body	134 pts

CPR: complete pain relief ; d: day(s); fr: fraction: HBI: half body irradiation; NR: not reported; ns: not significant; OPR: overall pain relief; QoL: quality of life; pts: patient(s); w: week(s)

Results				Conclusion/Comments
	OPR %	Duration	Retreatment	
A	91	155 days	NR	Lower HBI 79 pts, upper HBI 68 pts, middle HBI 9 pts. Pain relief occurred in 3 to 9 days, no diff between the groups. CPR: sign lower in group B than in groups A and C. QoL (RTOG grading system) no diff between the groups. **C1**
B	89	101		
C	94	112		
	ns	p<0.034		
Toxicity: grade 3–4 in totally 18 pts, no diff between the groups.				
	70	Relief lasted from a few weeks to several months	NR	38% had nasopharyngeal carcinoma. Pain assessment was not shown in detail. Pain relief occurred from 24 hours. Evaluation of side effects not reported. **R3**

Overview 2 *Skeletal metastases. Local radiotherapy of spinal cord compression.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Kida 2000 [32] R	1,8–5 Gy/fr to 20–51 Gy	52 pts Surgery considered contraindicated in all
Katagiri 1998 [31] P	2 Gy/fr, 40 Gy/4 w	82 pts
Maranzano 1997 [40] P	8 Gy/fr, 1 fr/w, 16 Gy/2 w The second fraction only given to responders or to pts with stable disease.	49 pts
Helweg-Larsen 1996 [22] P	4 Gy/fr, 7 fr consecutive days, 28 Gy/1 w	153 pts
Maranzano 1995 [41] P	3 Gy/fr, 10 fr, 30 Gy/2 w or 5 Gy/fr, 3 fr/w to 15 Gy 4 d rest, *3 Gy/fr, 5 fr, to 15 Gy, total dose 30 Gy/3 w *only given to responders	209 pts

CHT: chemotherapy; fr: fraction: RT: radiotherapy; pts: patient(s); w: week(s)

Results	Conclusion/Comments
In 7 of the 28 pts with neurological impairment, an improvement was seen. No improvement in pts who got RT >3 days after developing complete paralysis.	Methods of RT not stated in detail. **R2**
66% of the pts were neurologically stable or had improved, 67% achieved pain relief, and 64% had functional improvement. The treatment was often successful when primary tumours had responded to RT/CHT.	In 72% of the pts, the spinal lesions were multiple. Several types of tumours were included. In 62 pts combined RT and CHT were given. Data about CHT not shown. **P2**
Motor function response rate was 63%. Only 38% of non-walking pts improved. None of the paralytic pts regained ability to walk. Early treatment was an important predictor for good response to RT.	Only pts with low radio-responsive primary tumours or more radio-responsive ones with paresis, plegia, low performance status and/or short life expectancy were included. **P2**
Of 74 initially non-walking pts, 21 (28%) were ambulatory after RT. Among 43 totally paralytic pts, 9 gained walking function between 3 weeks and 20 months. Early treatment was most important for a good outcome. Slow rate of development of compression seemed to facilitate recovery.	The pts were included consecutively. **P1**
76% of the pts achieved full recovery or preserved walking ability. Early treatment was most important for a good outcome. When treatment was delayed, radiosensitive tumours still responded.	The pts were included consecutively. No of pts in the different RT schedules not reported. **P2**

Overview 3 *Skeletal metastases. Surgical treatment of pathological fractures with or without radiotherapy.*

Author Year (ref no) Design	Aim/ Study question			Patient population
Townsend 1994 [62] R	ST only, 29 pts:	femur humerus other sites	26 1 2	64 Several types of solid tumours.
	ST + RT, 35 pts:	femur humerus other sites	32 2 1	
	Time to postop RT mean 14 days Median RT dose 30 Gy			
Haentjens 1995 [21] R	ST only 19 pts: ST + RT 9 pts: In 2/9 pts RT given preoperatively	femur femur	19 9	28 Several types of solid tumours

pts: patient(s); RT: radiotherapy; ST: surgical treatment;

Results	Conclusion/Comments
Successful outcome = normal use of arm/leg: ST 4/29, 14% ST + RT 19/35, 54% $p<0.01$	Consecutive pts. Postoperative RT was the only significant predictor for a successful outcome. For review, 25 simulation films were available. Out of them, 21 were found to have included the entire orthopedic prosthesis. **R2**
No diff between ST only and ST + RT. 23/28 pts achived good function.	New bone formation around the prosthesis was limited to the ST group of pts only. Small study group. **R2**

Overview 4 *Skeletal metastases. Systemic radionuclide therapy of bone metastases.*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Piffanelli 2001 [47] P	**A:** 89-Sr, 148 MBq **B:** 186-Re-HEDP, 1295 MBq	610 pts A 527 B 83 Prostate ca
Kraeber-Bodéré 2000 [36] P	89-Sr, 150 MBq	94 pts Prostate ca, hormone refractory
Baziotis 1998 [5] P	89-Sr, 150 MBq	64 pts Breast ca
Lee 1996 [38] P	89-Sr, 3mCi (range 2.2–4.4)	28 pts Mainly prostate and breast ca
Quilty 1994 [48] C	A: 89-Sr, 200 MBq B: ocal RT C: 89-Sr, 200 MBq D: HBI	305 pts A 76 B 72 C 77 D 80 Prostate ca, hormone refractory

89-Sr: strontium 89; 153-Sm-EDTMP: 153-samarium-EDTMP; 186-Re-HEDP: 186-renium-HEDP; HBI: half body irradiation; KPS: Karnowsky performance scale; m: month(s); ns: not significant; NR: not reported; OPR: overall pain relief; PSA: prostata specific antigen; pts: patient(s); RT: radiotherapy;

Results				Conclusion/Comments
	OPR %	Onset of PR	Duration	
A B	80 82 ns	NR	NR	Criteria for treatment: Life expectancy was at least 6 m. KPS <30. WBC >2.4 x 10^9/L, Platelets ≥ 60 x 10^9/L. No correlation between response and pretherapeutic PSA levels. **P2**
	78	15 d (median)	0.3–18 m (median 2.5)	Criteria for treatment: Life expectancy was at least 3 m. WBC >2.5 x 10^9/L, Platelets ≥100 x 10^9/L. Response significantly longer in pts with moderate bone involvement than in pts with a more extensive one. Flare was observed in 23% of the pts. Hematological side effects mild. **P1**
Improvement of QoL in 65% of the pts.				
	81	10–20 d	NR	In 19% of the pts no pain relief. Platelets and WBC decreased to 70% of the pretreatment levels, 4–6 weeks after therapy. **P2**
	61	4 w (time to best response)	2–8 w	Six pts showed pain progression. Mean decrease at nadir was 32% for WBC, and 40% for plateles. Small study group. **P3**
Evaluation after 3 m A B C D	 66 61 66 64	NR	NR	Pts were stratified according to their suitability for either local RT or HBI. 89-Sr was superior to local RT and HBI in delaying the progression of pain to new sites. Side effects of 89-Sr treatment was generally transient. Nausea, vomiting, and diarrhoea, were significantly lower in the 89-Sr-groups than in the groups treated with local RT or HBI. **C1**
Fewer pts reported new pain sites after 89-Sr than after local RT or HBI, $p<0.05$.				

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Overview 4 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Bos 1994 [11] P	89-Sr, 150 MBq	28 pts Prostate ca, Hormone refracotry
Giammarile 1999 [19) R	85-Sr, 335 MBq (mean)	119 pts Mainly prostate and breast ca
Serafini 1998 [57] C	153-Sm-EDTMP **A:** 0.5 mCi/kg **B:** 1.0 mCi/kg **C:** Placebo (Double-blind)	118 pts A 40 B 39 C 39
Tian 1999 [61] P	153-Sm-EDTMP **A:** 18.5 MBq/kg **B:** 37.5 MBq/kg	105 pts A 35 B 70 Several types of ca
Alberts 1997 [2] P	153-Sm-EDTMP **A:** 0.75 mCi/kg **B:** 1.5 mCi/kg **C:** 3.0 mCi/kg	82 pts A 28 B 35 C 19 Mainly prostate, breast, lung ca

Results			Conclusion/Comments
OPR %	Onset of PR	Duration	
82	NR	3 m	Ambulatory treatment setting. No response, at all, was seen in three pts, two pts were not evaluated. Small study group. **P2**
72	NR	1–36 m (mean 4.3)	Best improvement in pts with early stage of metastatic disease, and in prostate cancer. No major hematological toxicity. No correlation between clinical response and estimated absorbed dose of 85-Sr delivered to metastases. **R1**
Follow-up 16 w A 60 B 70* C 40 * B vs A and C p <0.01	<1 w <1 w >1–4 w	all >12 w 2/3 >16 w <4 w	Only 30% of pts completed the 16 weeks of follow-up, the majority discontinued because of disease progression. Only group B showed significantly lower pain scores and reduction in opioid analgesic use, when compared with groups A and C. A mild and transient dose-related myelosuppression was seen. **C1**
83 No diff between groups	2–26 d (8.8 mean)	3–16 w (8.6 mean)	No serious side effects were reported. Small number of pts within the different groups of tumours. **P2**
78–95 no diff between groups	Within 2 d no diff between groups	40–56 d the longest duration in group B	Multiple doses were given to pts in groups A and B. Only 38% of the pts qualified for multiple treatments. No clear dose-response relationship. Toxicity increased with dosage. **P1**

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Overview 4 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Resche 1997 [51] C	153-Sm-EDTMP **A:** 0.5mCi/kg **B:** 1.0 mCi/kg	114 pts A 55 B 59 Several types of ca
Ahonen 1994 [1] P	153-Sm-EDTMP 330–1100 MBq	35 pts Mainly prostate and breast ca
Kolesnikov-Gauthier 2000 [34] P	186-Re-HEDP 1295 MBq	28 pts A 12 prostate ca B 16 breast ca
Liepe 2000 [39] P	188-Re-HEDP 1600–3459 MBq	15 pts Mainly prostate ca
Sciuto 2000 [56] P	186 Re-HEDP 1406 MBq (mean)	65 pts Mainly prostate ca

Results	OPR %	Onset of PR	Duration	Conclusion/Comments
A B	67 65	Within 1 w in both groups	NR	WBC and platelets reached nadir values at 3 or 4 w, and recovered by 8 w. No sign diff between the groups. Breast cancer pts in group B showed the best response and longer survival than those in group A, p-values not reported. **C2**
	80	Within 1 w	2–17 w (median)	Myelosuppression, WHO grade III, was observed in one patient. No accumulation of 153-Sm was detected outside the skeleton. Small study group. **P2**
A B	67 36	1–3 w 1–3 w	47 d 33 d	All pts had carcinomas resistent to chemo- and hormonal therapy. No major side effects reported. Small study group. **P3**
	80	NR	NR	Mild bone marrow toxicity, comparable to 186-Re-HEDP and 89-Sr. Small study group. **P3**
	80	Within 1	3 w–12 m (median 60 d)	No clinically evident acute side effects. WHO grade 1–2 haematologic toxicity. **P1**

Overview 5 *Skeletal metastases. Bisphosphonate therapy.*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Berenson 2001 [9] C (Double-blind)	Type of drug/dose Zoledronic acid **A:** 0.4 mg **B:** 2.0 mg **C:** 4.0 mg **D:** Pamidronate 90 mg Every 4th week	108 pts Multiple myeloma 172 pts Breast ca
Theriault 1999 [59] C (Double-blind)	Benefit of drug Pamidronate **A:** 90 mg, monthly **B:** Placebo	371 pts A 182 B 189 Breast ca, with at least one lytic metastases
Berenson 1998 [8] C (Double-blind)	Benefit of drug Pamidronate **A:** 90 mg, monthly **B:** Placebo	377 pts A 198 B 179 Multiple myeloma
Hortobagyi 1996 [24] C (Double-blind)	Benefit of drug Pamidronate **A:** 90 mg, monthly **B:** Placebo	380 pts A 185 B 195 Breast ca with at least one lytic metastases

NR: not reported; pts: patient(s); m: month(s); SRE: skeletal-related events (pathological fractures, SCC, orthopedic intervention, RT in connection with patholgical fractures or SCC, or hypercalcemia); RT: radiotherapy

	Results			Conclusion/Comments
	Need for RT, %	**SRE** %	**Time to first SRE, months**	
A	24	46	5.6	The pts included had osteolytic lesions. Zoledronic acid was given as a 5-minute infusion. Pamidronate was given as a 2-hour infusion. The need for RT to the skeleton was evaluated 10 m after treatment initiation. The number of patients who discontinued were in all 91. Zoledronic acid of 2.0–4.0 mg was at least as effective as pamidronate treatment of osteolytic metastases. **C2**
B	19	35	5.7	
C	21	33	7.7	
D	18	30	8.5	
B, C, D sign better than A, p <0.05				
No sign diff between B, C and D, respectively.				
Adverse events were similar in all treatment groups				
A	31	56	10.4	All pts had hormonal therapy. Pamidronate was given for two years. Evaluation was made 24 m after start. 37% in group A, and 34% in group B, completed the treatment. Frequency of vomiting and fatigue was 10% higher in group A. Pamidronate treatment have shown to reduce skeletal morbidity. Survival did not differ between the two groups. **C1**
B	40	67	6.9	
	p=0.058	p=0.027	p=0.049	
A	25	38	Numbers NR	Patients with stage III and at least one lytic lesion. The pts were stratified according to different chemotherapy in two groups. Pamidronate was given as a 2-hour infusion monthly for 21 cycles. The treatment was well tolerated. Long-term treatment with Pamidronate reduced skeletal related events and need for RT. **C2**
B	34	51	Numbers NR	
	p=0.06	p=0.015	p=0.016	
A	19	43	13.1	The pts received the drug in addition to chemotherapy. Treatment was given for 12 m. 48% of pts completed treatment. Evaluation was made 12 months after start. Pamidronate treatment have shown to reduce skeletal morbidity. **C1**
B	33	56	7	
	p=0.002	p=0.008	p=0.0005	