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REVIEW ARTICLE

BONE METASTASIS

Prognosis, diagnosis and treatment

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Abstract

Carcinoma of the breast, lung or prostate cause the majority of all bone metastases. Prolonged survival is common in patients with breast or prostate tumours. Different types of treatment may significantly increase the quality of life. Single-dose or fractionated radiation therapy may be effective, and 70 to 90 per cent of patients obtain partial or complete relief from pain. Surgery followed by irradiation is indicated in most patients with pathologic femur fractures. Immediate surgical treatment, either alone or combined with radiation therapy, may prevent paraparesis in patients with incipient cord compression. For neoplasms sensitive to systemic therapy such treatment should often be added to local treatment.

Key words: Bone neoplasms, metastases; therapy.

Most patients with bone metastases have their primaries in the breast, lung, or prostate, and a considerable proportion of patients with these three diagnoses will develop osseous metastases (45). ABRAMS et coll. (1) found bone metastases in 27 per cent of autopsied patients with carcinomas. Other autopsy studies report bone metastases in 47 to 85 per cent of women dying from breast cancer, in 33 to 85 per cent of patients with prostatic cancer, and in 32 to 60 per cent of patients with lung cancer (86). With scintigraphy, bone metastases were detected in 43 to 67 per cent of common human malignancies including tumours arising from the gastrointestinal tract (86).

The prognosis for patients with bone metastasis is serious, which must be taken into account when treatment is planned. Overtreatment in the terminally ill must be avoided. However, many patients may live for years and greatly benefit from active treatment. Survival rates for patients with bone metastasis from carcinomas of the breast, prostate, and lung vary within wide limits.

Breast cancer survival. Median survival following detection of distant metastases from breast cancer is about 1 to 2 years (46, 59, 81), and survival at 5 years from diagnosis, for stage IV patients, is 13 per cent (14). Survival in the subgroup with only osseous metastases is better, with a median survival of 4 years (81). Other reports confirm that patients with their first metastases located in bone have a favourable prognosis compared with patients with other initial metastatic sites (17, 59), and the tumour in these patients is also more commonly hormone-receptor positive (17).

Prostate cancer survival. Survival at 5 years from diagnosis, for distant metastases, has been reported to be 17 per cent. Median survival for such patients younger than 65 years was in this study 2 years, for those aged 65 to 75 years 18 months, and for patients older than 75 years only one year (14).

Lung cancer survival. Median survival for lung cancer patients with bone metastases is only about 3 months (43), and less than 2 per cent survive for 5 years (14). However, for patients with small cell anaplastic carcinoma survival may be prolonged after chemotherapy (83).

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Survival for other malignancies. Median survival for patients with multiple skeletal metastases from renal carcinoma is approximately one year. About 30 per cent of the patients with a solitary osseous metastasis survive for 5 years (88). Survival for malignant melanoma with bony spread is only 3 to 5 months (25, 85), and expected survival in patients with bone metastases from colorectal carcinoma averages 13 months (7). Nearly all patients with skeletal metastases from carcinoma of the cervix are dead within 18 months (10). Among patients with bone metastases of unknown origin a median survival of 3 to 6 months has been reported (60), while patients with multiple myeloma survive for 2 to 3 years (65).

Distribution of bone metastases. At least 80 per cent of the bone metastases are found in the spine, ribs, pelvis, or the proximal parts of the femur or humerus. It is thought that blood-borne tumour cells reach the bone marrow mainly through the paravertebral venous plexus (70). In one report on 319 patients with breast cancer, the proportion of metastatic sites in the spine : femur : pelvis : humerus was found to be approximately 4.8 : 2.8 : 2.6 : 1 (59). Skeletal carcinoma metastases distal to the elbows and knees are unusual (47, 94) and may indicate a primary sarcoma, especially in patients with no known primary tumour.

Renal adenocarcinoma may produce a solitary metastasis in 2 to 4 per cent of the patients (64, 89), and such solitary metastases may occasionally be located in bone. Following aggressive local therapy, 30 to 40 per cent of the patients survive for 5 years (50, 88). Few if any other common human tumours produce solitary bone metastases.

Diagnosis

Symptoms. Pain, which may be nocturnal or worse at rest, is the cardinal sign. However, more than one third of the patients with skeletal metastases from breast (28) or prostate carcinoma (78) are free from pain. Using bone scintigraphy FRONT et coll. (28) found that only one third of the metastatic sites in patients with breast cancer were painful. In some patients pain may begin weeks or months before the lesions can be detected at radiography. On the other hand, an unexpected pathologic fracture may be the first sign of bone metastasis.

Biochemical tests. Serum alkaline phosphatase is elevated in 80 per cent of patients with skeletal metastases from prostate carcinoma (78) and in 32 to 53 per cent of patients with bone lesions from breast cancer (19, 67). Serum acid phosphatase is increased in 60 to 70 per cent of patients with distant metastases from prostate carcinoma (78), but may also be elevated in serum from patients with other types of bone metastasis (93). Thus, increased levels are not pathognomonic for prostatic origin of the bone metastases (93).

Radiologic evaluation. Radiography is less sensitive but more specific than scintigraphy for the detection of bone metastases. At least 30 to 50 per cent of the mineral content in a metastatic lesion must be lost before radiologic detection is possible. Lesions smaller than 1.5 cm in cancellous bone may be undetectable, while cortical lesions are usually discernible at an earlier stage (2). CT scanning may detect lesions as small as 3 to 5 mm and also detect pathologic changes in adjacent tissues (42), the medullary cavity, or the spinal canal (41, 42). Most bone metastases are lytic, and a distinct periosteal reaction is less common than in primary bone malignancies (61). Metastases located in vertebral bodies do not affect the intervertebral discs, in contrast to osteomyelitis (2). However, primary bone tumours, osteomyelitis, or Paget's disease of bone may sometimes be radiographically misinterpreted as bone metastases.

Metastatic breast carcinoma produces lytic or mixed lytic-sclerotic lesions which often become sclerotic after successful local or systemic therapy (2). Survey radiography of the skull, chest, spine, and pelvis will detect at least 90 per cent of radiologically overt skeletal metastases from breast cancer (67).

Prostate cancer yields nodular or diffuse sclerotic metastases initially typically located in pelvis or spine. Occasionally, however, mixed lytic-sclerotic or even lytic lesions are seen.

Bone metastases from lung cancer are usually lytic. In one third of the cases, however, and in most patients with carcinoid tumours, the metastases are sclerotic (2). Some patients with bone metastases from lung cancer develop excentrically lytic lesions with one-sided destruction of cortical bone (22). Usually, metastatic lesions grow outwards from the medullary cavity (2).

Bone scintigraphy. Scintigraphy is very sensitive for the detection of skeletal metastases. However, it has rather low specificity, and metastatic disease therefore often needs to be confirmed by radiography or biopsy (8, 56). Lytic lesions in plasmocytoma or myelomatosis often escape scintigraphic detection (56). This is also the case for up to 8 per cent of the lytic lesions in carcinomas (8).

Biopsy. Solitary skeletal lesions may be the first sign of malignant disease. The possibility of a primary bone tumour must be kept in mind, and an open bone biopsy may be necessary for a definite diagnosis. Drill biopsy from a vertebral body can be performed with local anaesthesia under fluoroscopic control (15).

Skeletal metastases of unknown origin. In approximately 10 to 15 per cent of patients with bone metastases the primary source is unknown at the time of presentation (2). Extensive and time-consuming investigations to find an asymptomatic primary tumour in such patients have a low yield (60) and are often of marginal therapeutic benefit to the patient (60, 82). However, it is important to diagnose tumour diseases where effective systemic therapy is available. In most cases, histologic or cytologic confirmation of the malignant nature of the lesion(s) is necessary.

Therapy

Philosophy of management. Since cure is usually not possible, the treatment of bone metastases should be palliative and if possible also prevent the development of pathologic fractures. Management of an individual patient may include combinations of cytotoxic or hormonal treatment, surgery, and radiation therapy (62). In addition, spinal cord compression caused by metastatic disease should if possible be prevented by surgery alone or combined with radiation therapy (9, 72).

Systemic therapy with hormonal or cytotoxic agents. Endocrine therapy or chemotherapy may help patients with tumours sensitive to systemic treatment (27), and should often be added to local treatment.

Estrogens or bilateral orchidectomy can be expected to give pain relief in 70 to 80 per cent of previously untreated patients with skeletal metastases from prostate carcinoma (49, 51). Orchidectomy is often preferred in patients with co-existing cardiovascular disease (4, 49).

One third of unselected women with metastatic cancer of the breast will benefit from hormonal therapy, and at least 50 per cent of women with hormone-receptor positive tumours will respond to hormonal manipulation (castration, tamoxifen, aminoglutethimide, gestagens, glucocorticoids (39, 87). Patients with relapse after an initial remission following one type of hormonal treatment may often respond also to a second type of hormonal treatment. Hypercalcemia may complicate hormonal therapy, but may be successfully treated by forced diuresis, glucocorticoids, calcitonin, or mithramycin (5, 84).

Several cytotoxic drugs are of proven efficacy in breast cancer (32, 39, 74) and chemotherapy should often be considered for palliation of metastatic disease.

Small cell lung cancer as a rule responds to cytotoxic drugs (83), while these are less efficient in other types of lung cancer (92). Hodgkin's disease (57), non-Hodgkin lymphomas (18), multiple myeloma (65), or germinal cell tumours in testicles (21), ovaries (80), or the mediastinum (33) may be efficiently treated by combination chemotherapy. Differentiated carcinomas of the thyroid may respond to radioiodide treatment, but metastatic thyroid carcinomas located in bone carry a serious prognosis (13).

Surgical treatment of bone metastases. Patients with femoral lytic lesions exceeding 2.5 cm in diameter, or with destruction of more than 50 per cent of the femoral cortex, have a high risk of fracture (24, 37) and should be treated with prophylactic internal fixation followed by irradiation (40, 52, 53).

Fractures through metastatic bone are common in patients with metastatic carcinoma of the breast (29, 34, 53), lung, and prostate (24, 29). Large metastases from tumours of the kidney or thyroid, or multiple myeloma, may be highly vascular and bleed profusely during surgery. Preoperative angiographic embolization of tumour vessels may reduce the considerable surgical risk in these patients (16, 88). Large defects due to lytic lesions may be stabilised by the use of methylacrylate (52) which retains its mechanical properties after therapeutic irradiation (23). Radiation therapy is usually necessary in order to control local tumour growth (12, 29), but renders bone grafting ineffective (37) and reduces callus formation (12). Nevertheless, bony union is consistently achieved provided the fracture is properly stabilised (12, 29, 35, 37).

Metastatic bone lesions are frequently located proximally in the extremities, and so are the fractures. In the upper extremity, fractures are located almost exclusively in the humerus, and are usually adequately managed by bracing and radiation therapy (29, 63). Some shaft fractures may need internal fixation (29).

Metastatic lesions located in the lumbar spine may cause instability of the vertebral column. Insertion of Harrington's rods may stabilise the spine in these patients (36). Another alternative is the use of a corset and radiation therapy.

Rapidly developing signs of compression of the spinal cord by metastatic disease is a therapeutic emergency. In many of these patients paraparesis can be avoided by emergency laminectomy, by radiation therapy or by combined treatment (9, 54, 72).

It is also possible to decompress the spinal canal by an anterior approach and reconstruct the vertebral body with methylacrylate and internal fixation (38). Of 100 patients reported by LIVINGSTON & PERRIN (54), 58 were able to walk after laminectomy, and 40 walked and were urine continent 6 months later. Even after transient paraplegia—a very serious prognostic sign with regard to neurologic recovery—1/3 of patients with cord compression caused by multiple myeloma recovered partly or fully. Median survival in these patients was 30 months (6). More than half of 322 patients with skeletal metastases reported by SCHABERG & GAINOR (77) had vertebral lesions, and 20 per cent of these patients developed cord compression. In patients with slowly developing signs of spinal cord compression caused by radiation sensitive and chemotherapy sensitive lesions (as myeloma, Hodgkin's disease and non-Hodgkin lymphoma) laminectomy can often be avoided and a good result obtained by combined radiation therapy and chemotherapy.

Fractures in metastatic lesions in the proximal femur are often best managed by inserting a prosthesis (37, 52, 53), since these fractures heal slowly if at all following conventional therapy (29). Acetabular defects caused by metastatic disease can be filled with methylacrylate strengthened with metal mesh (35). Femoral shaft fractures should whenever possible be surgically stabilised (63). The combination of internal fixation and methylacrylate may render surgical stabilisation of otherwise unstable fractures feasible and is recommended in many fractures of the lower extremity.

Radiation therapy. Radiation therapy is well suited for palliative treatment of metastases in any bone. Orthovol-

tage equipment with beam energy in the 150 to 300 kV range can often be used successfully.

After irradiation to therapeutic doses, some degree of hyperemia and osteoporosis may develop, followed by increased bone remodelling; finally the disturbed bone metabolism gradually returns to normal (48). During the hyperemic-osteoporotic period the risk of pathologic fracture may increase (29). Due to hyperemia or increased bone remodelling, irradiated bones may show increased radioisotope uptake or radiologic abnormalities (9) which may be confused with metastatic disease.

Irradiation kills the destructive tumour cells and thus makes healing possible (29). Tumour cell necrosis is followed by growth of loose vascular connective tissue which produces osteoid material, and lytic lesions may heal within 2 months (55). However, irradiation also delays normal chondrogenesis and osteogenesis in an irradiated pathologic fracture. Bone grafts do not 'take' after irradiation (37), and healing of pathologic fractures may be prolonged. BLAKE (9) advises against doses exceeding 30 to 40 Gy since higher doses may compromise fracture healing. However, it has been clearly demonstrated that experimental fractures do heal following irradiation to 20 Gy in two weeks provided the fractures are adequately stabilised by internal fixation (12). Patients with stable fractures caused by breast cancer also easily achieve bony union after radiation therapy (20, 59). HARRINGTON (35, 37) used doses of 22 Gy in 4 days and reported that at least 85 per cent of the patients achieved bony union provided the fractures were surgically stabilised. Doses of 30 Gy in two weeks following insertion of a hip joint prosthesis are also well tolerated (35).

The radiation portals should encompass the painful site or demonstrable symptomatic bony lesions detected by scintigraphy or radiography. Usually, one vertebral body cranial and caudal to a metastatic site are included when irradiating lesions in the spine. When treating lesions in long bones, a margin of 3 to 4 cm or the nearest joint is incorporated in the radiation fields. Patients with pain caused by diffuse skeletal metastases from breast, prostatic or pulmonary neoplasms may in 60 to 80 per cent of cases obtain pain relief within 2 days after a single half-body fraction of 6 to 10 Gy (73, 76).

No obvious difference in pain relief was seen between patients treated with a single fraction in the dose range 4 to 15 Gy (44, 66, 91) or fractionated treatment with total doses of 20 Gy in one week, 30 Gy in 2 weeks, 40.5 Gy in 3 weeks, or 60 Gy in 6 weeks (3, 31, 68, 69, 79, 90). Complete or partial pain relief is obtained in 70 to 90 per cent of all patients within 2 weeks regardless of treatment regime (26, 30, 31, 66, 69, 90, 91). However, damage to normal tissues within the irradiation volume is reduced if fraction doses exceeding 2.5 to 3 Gy are avoided (26).

To avoid impairment of bone growth in children doses in excess of 15 to 25 Gy should be avoided in long bones, spine, acetabulum, or orbits. Epiphyseal growth zones are very sensitive to radiation (75), and should if possible not be irradiated in children when long-term survival is possible.

Since bone metastases generally retain the inherent radiation sensitivity of the primary tumour, treatment results may show some variation according to the tumour of origin. However, this variation is less than would be expected (26, 31), and pain relief is often achieved even in quite radiation resistant neoplasms such as renal carcinoma and melanoma.

Although the patient's survival may not be prolonged by treatment of symptomatic skeletal metastases, the quality of life is improved in the majority of patients and the occasional patients with a solitary plasmocytoma (58) or primary lymphoma (71) of bone may be cured.

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