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ORIGINAL PAPER

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The development of bone metastases as the first sign of metastatic spread in patients with primary solid tumours

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Abstract The purpose of this retrospective study was to investigate the incidence of bone metastases as the first sign of metastatic spread in patients with primary solid malignant tumours. Between January 1987 and December 1998, we treated 867 patients suffering from primary solid malignant tumours. Their average age was 67 (range: 30–96) years and all were thoroughly investigated with a complete physical examination and laboratory tests as well as imaging studies and bone scans. No bone metastases were found at the time of the initial diagnosis, and the patients were then re-assessed every 6 months for the first 5 years and then once a year. We found that, regardless of treatment, bone metastases appeared in a certain number of patients and that after excluding patients with prostate cancer a bone metastasis was the first sign of "recurrence" in 1.3% of the patients with a known primary solid malignant tumour.

Résumé Le but de cette é tude r é trospective é tait de rapporter la fr é quence des m é tastases osseuses comme premier signe m é tastatique, chez des patients ayant une tumeur solide primitive connue. De janvier 1987 à décembre 1998 nous avons traité 867 malades souffrant de tumeurs solides primitives. Leur âge moyen était de 67 (30–96) ans. Tous les malades ont eu un examen complet y compris les études d'imagerie et la scintigraphie osseuse. Aucune métastase osseuse n'a été trouvé au diagnostic initial. Les malades ont été évalués tous les 6 mois pendant les 5 premières années et ensuite une fois par an. Sans tenir compte du traitement, nous avons constaté que les métastases osseuses apparaissaient chez un certain nombre de malades. En excluant les malades avec un cancer prostatique, les métastases osseuses étaient le premier signe de récidive chez 1,3% des malades avec une tumeur solide primitive connue.

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Introduction

As medical and scientific advances lead to major gains in life expectancy, the prevalence of chronic diseases, including cancer, continues to increase. High expectation for the treatment of primary tumours, together with careful clinical follow-up, also reveals an increase in bone metastases. The exact incidence of skeletal metastasis is unknown, and rates from necropsy studies are not accurate, as patients dying in hospital with terminal metastatic disease are an un-representative sample.

The distribution of bone metastases reflects the pattern of the haematogenous spread of tumour cells from primary tumours, and surgeons are often faced with complex surgical problems as they have to deal with both a primary tumour and its metastatic spread.

The purpose of our retrospective study was to report the incidence of bone metastases as the first sign of metastatic disease in patients with a known primary solid malignant tumour.

Material and methods

The records of 867 patients with various primary solid malignant tumours treated at our institution between 1987 and 1998 were reviewed. The average age was 67.7 (range: 30–96) years, and there were 400 men and 467 women. On admission, all the patients were graded according to Karnofsky's performance status [7]. This method allows patients to be classified in relation to any impairment of their daily living activities. It can be used both to follow the course of the illness and to assess the prognosis for individual patients. The lower the Karnofsky status, the worse the chances of survival and the quality of life.

Assessment of the primary tumours included clinical, laboratory and radiographic examinations, together with CT scans and bone scan imaging studies in all patients. CT scans of the abdomen were used for accurate diagnosis of solid tumours of major organs. In patients with gastro-intestinal disease, endoscopic examinations or conventional radiographs were performed in order to diagnose the exact location of the primary tumour. However, patients with prostatic cancer were excluded from the study and were referred to another institution, as we did not have the necessary equipment to treat these patients. Table 1 shows the location of solid tumours. No evidence of any bone metastases was found at the initial presentation.

Of the 867 patients with adequate records, 45 had been treated by chemotherapy or radiation either alone or in combination, and 822 by operation. Surgical removal was assessed according to the margins that could be achieved. These were graded as residual tumour status zero (R0) when no macroscopic disease was left behind, (R1) if there was residual microscopic disease and (R2) if macroscopic disease was left behind because complete operative resection had not been possible.

In addition to surgery, 398 out of 822 patients (48.4%) received adjuvant therapy (chemotherapy, radiation, or both) while the remaining 424 (51.6%) did not, either because these therapies were unlikely to be helpful or because there were severe contraindications or even patients' refusals. After their primary treatment, every patient was assessed every 6 months for the first 5 years and then once a year. The mean follow-up was 23.2 (range: 2–170) months and included complete clinical, laboratory, radiographic, and CT examinations. The chi-square test was used to determine whether the distribution of variables was statistically important. The possibility of recurrence was calculated using the Hazard proportion analysis, and the log-rank test was used for statistical comparison of recurrence probabilities. A p value <0.05 was considered statistically significant.

Table 1 Location of primary tumours

Location	Frequency	Percent
Colorectal	247	28.5
Gastric	187	21.6
Breast	111	12.8
Pancreatic	82	9.5
Ovarian	55	6.3
Liver	36	4.2
Gall bladder	33	3.8
Renal	21	2.4
Sarcoma	17	2.0
Bile-duct	15	1.7
Gi-lymphoma	14	1.6
Thyroid	11	1.3
Lung	9	1.0
Oesophageal	9	1.0
Melanoma	8	0.9
Corpus uteri	7	0.8
Peritoneal	3	0.3
Mesothelioma	2	0.2
Total	867	100.0

Results

According to their Karnofsky performance status, 665 patients were graded as 90–100%, 147 patients as 70–80%, 50 as 50–60%, two as 20–40% and three as 10–20%. The hospital mortality rate was found to be 12.7% (110 out of 867). Of 822 patients who underwent surgery, 571 (69.5%) had R0 resection, 28 patients (3.4%) had R1 and 223 patients (27.1%) had R2 resection.

The overall recurrence rate was 18% (156 out of 867), and a bone metastasis was found as the first sign of disease recurrence in ten out of 757 patients (1.3%). The primary malignant tumour was in the colon or rectum in two patients, the breast in five and the stomach in three (Table 2). One patient (case 5) presented with a pathological hip fracture, and another (case 4) suffered a compression fracture of the third lumbar vertebra. At 2 and 4 months respectively after their latest follow-up, CT-scan imaging revealed a metastasis in two other patients (cases 6 and 9). In our other patients, clinical examinations and plain radiography revealed the metastases.

Study of the results showed no statistically significant difference between the disease recurrence rate and patient gender. But when disease recurrence was compared to the patients' initial Karnofsky performance status, the difference was statistically significant (p=0.000). In addition, a statistically significant difference was also found between post-operative residual tumour (R0, R1, R2), and disease recurrence rate (p=0.000). Recurrence was found to be statistically significant when compared to post-operative adjuvant therapy that had been performed in the patients (p=0.001).

Table 2 Patients with bone metastases as first sign of recurrence. *DSF* disease-free survival

No.	Gender	Age	Primary location	DFS (months)	Metastatic location
1	F	59	Stomach	2	Lumbar spine
2	M	51	Stomach	5	Lumbar spine
3	F	64	Breast	7	Multiple
4	F	54	Breast	8	Lumbar spine
5	M	67	Colorectal	10	Multiple
6	M	70	Stomach	16	Lumbar spine
7	F	40	Breast	17	Multiple
8	M	57	Colorectal	27	Hip
9	F	81	Breast	40	Lumbar spine
10	F	46	Breast	44	Lumbar spine

In patients with bone metastases, the most common location was in the lumbar spine. The mean disease-free survival period was 17.2 (minimum 2, maximum 44) months, and no correlation was found between the exact location of any bone metastasis and patient gender. In addition, no statistically significant difference was found between the exact location of a bone metastasis, the residual tumour status (R0, R1, R2) and the primary tumour location. There was also no correlation between the exact metastatic location and the disease-free survival time. Although there was a statistically significant difference between the pattern of recurrence (distant, regional) and adjuvant therapy (p=0.001), the difference was not statistically significant when adjuvant therapy and the exact location of bone metastases were compared.

Discussion

The exact incidence of bone metastases is still unknown, although the skeleton is one of the favourite sites for the metastasis of many malignant neoplasms [3]. It has been shown that approximately 60–84% of cancer patients who die of known tumours had developed bone metastases [9],but these figures are based on autopsy findings with gross examination and limited sampling. On the other hand, 10% of cancer patients appear with bone metastases as the first sign of the disease [1, 8], and in a majority of patients, the primary tumours are of the breast, prostate, or lungs [1, 10, 12]. Thus, it is apparent that the incidence and prevalence of bone metastases are difficult to determine with accuracy, and there are no studies concerning the incidence of bone metastasis as the first sign of generalised metastatic disease.

Metastases in bone are usually osteolytic, and the most common sites of involvement are the vertebrae (thoracic, lumbar, and cervical) [13], pelvis, femur, humerus and ribs [8]. Plain radiographs are not particularly sensitive in identifying early metastatic lesions [13]and fail to detect about 20–25% of skeletal spread [4]. Computed tomography or magnetic resonance imaging are not only helpful in demonstrating the extent of bone destruction but are also of great importance in diagnosing primary lesions [2]. Bone scanning is the most useful study in assessing patients with suspected metastatic skeletal disease because of its ability to detect asymptomatic disease approximately 4 months on average before a lesion can be identified by plain radiography [6].

Malignant tumours of the breast, prostate or lungs carry the highest risk of developing osseous metastases in contrast to intra-coelomic tumours, the spread of which tends to remain in the abdominal cavity [11].

In this study, all patients underwent complete clinical, laboratory and radiographic examinations, CT scans and bone scans, and no evidence of bone metastases was found at the initial diagnosis. This would indicate that regardless of treatment, bone metastases will appear in a certain number of patients. It has been stated that most metastases occur approximately 1 year after diagnosis [3] and that the most common site of bone metastases is the vertebrae [5]. In our study, bone metastases occurred approximately 17 months after initial diagnosis of the solid tumours, and the majority of bone metastases were in the lumbar spine (Table 2).

The very low rate of metastases in this study could be attributed to the supposition that cancer patients, especially those with residual macroscopic disease (R2) die of causes related or unrelated to their illness before developing loco-regional or distant metastases. Moreover, the very low incidence of bone metastases as the first metastatic sign (1.3%) in this study could possibly be explained by the fact that the great majority of the cases concerned intra-abdominal tumours.

Pain is the predominant symptom of skeletal metastasis. Therefore, it could be argued that, after the initial diagnosis and treatment, follow-up screening for all cancer patients without evidence of bone metastases and in the absence of skeletal pain should include a complete clinical and laboratory examination including tumour markers. In cases where clinical and laboratory investigations reveal abnormalities while other imaging studies fail to detect a metastasis, bone scans should then be used to search for real or possibly potential skeletal metastatic disease.

This is a retrospective review and patients with prostate cancer are not included, although it is well documented that prostate cancer is among the gamut of tumours carrying the highest risk of developing bone metastases. It should also be stated that the incidence and distribution of bone metastases would change significantly in centres where more patients with kidney, lung and prostate cancer are treated. Therefore, our study has limitations in its interpretations and findings. However, this preliminary work does provide data that can be useful for conducting a more scientific assessment of the problem.

In conclusion, as this study showed, and with the exclusion of patients with prostate cancer, 1.3% of other cancer patients with known primary tumours will present with bone metastases as the first sign of metastatic disease.

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