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The influence of intramedullary nailing upon the development of metastases in the treatment of an impending pathological fracture: an experimental study

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An experimental model has been developed in which the effects of a pathological fracture and intramedullary nailing on metastatic spread have been investigated. The endpoint used was the production of lung metastases in rats inoculated intracortically with a rhabdomyosarcoma. We have found that a pathological fracture markedly increases the incidence of lung metastases and that intramedullary nailing, by decreasing the incidence of fractures, decreases the incidence of lung metastases. The surgical procedure itself does not increase the incidence significantly. It is concluded that in metastatic disease prophylactic nailing of an impending pathological fracture is the treament of choice.

Introduction

Rieder and Schumann [17] discussed a patient who developed a pathological fracture, due to metastasis of carcinoma of the breast. This fracture was treated by means of an intramedullary nail, after which the patient developed lesions in the trochanteric area. Based on this finding, the authors suggested that this surgical intervention had a metastasis-promoting effect. Haase [8] similarly reported that tumour cells were disseminated by a Küntscher nail inserted for a pathological femur fracture in a case of metastatic hypernephroma. These case reports and the publications of Peltier [15, 16] have popularized the hypothesis of acceleration of metastatic growth by intramedullary nailing. However, there is no experimental evidence and there are also insufficient clinical data on which to base this supposition. The advantages of doing an internal fixation are potentially great if it can be shown that no significant increase in metastases follows. Because we were interested to see if internal fixation of an impending pathological fracture has a metastasis-promoting effect, and whether other factors (e.g. fracturation) could play a significant role, we developed an animal-experimental model to investigate the influence of internal fixation on metastases formation.

Material and methods

Tumour

The rhabdomyosarcoma had arisen in the jaw musculature of an irradiated WAG/Rij rat in 1962. After alternate culturing *in vitro* and inoculation of cultured cells from selected clones with uniform growth patterns into young animals, a transplantable tumour system designated as R-1 and with constant growth

characteristics resulted. The tumour volume-doubling time is approximately 4 days [1]. A total of 96 male (WAG/Rij × BN/Bi-Rij)F_1 rats aged 22–28 weeks were inoculated on day 0 with sarcoma tissue. The tumour material weighing ± 5 mg was inserted intramedullary at the level of the intermediate and distal third of the right femur as follows. After the lateral part of the femur was dissected free over a distance of ± 1 cm, a hole 2 mm in diameter was drilled into the lateral cortex. This was followed by excochleation of the bone marrow over a distance of ± 0·5 cm with a bent probe, thus forming an intramedullary cavity. Then a 5 mg piece of tumour was inserted. The defect in the cortex was closed with bone wax and the skin with clamps. The inoculation was performed under general ether anaesthesia.

Osteosynthesis

As intramedullary pins, disposable injection needles with filed point (Terumo 18 G × $1\frac{1}{2}$) were used. The technique was as follows. Through a small incision, the abductors were split and the top of the major trochanter was cleared. The next step was to drill the bone cortex with a 1·2 mm drill. A space was then made in the bone marrow with disposable 23 G and 21 G diameter injection needles. The osteosynthesis was finally performed by inserting a needle with a filed point. The part of the needle above the major trochanter was cut off. After this procedure, the muscles were joined with catgut stitches and the skin finally closed with clamps.

Exarticulation

After tying the large vessels in the groin, the hip joint was approached surgically from its medial aspect. The head of the femur was dislocated from the acetabulum and the muscles attached to the femur were cut off at the origin. The skin was closed with clamps. All surgical procedures were performed under general ether anaesthesia.

Endpoints and statistical evaluation

The tumour-bearing leg was radiographically monitored every two weeks (figure 1). For the determination of lung metastases, rats were sacrificed. As by sacrificing the animals at too early a stage many lung metastases that were present but too small could have passed unnoticed, and as too late a sacrifice could have resulted in premature death due to massive lung metastases, 50 per cent were killed and examined for lung metastases on day 121 and the rest on day 156. The lungs were fixed in Bouin's solution and the number of visible metastases on the surface (magnified 4 times) was established. At the same time, all right femurs of animals without demonstrable lung metastases were examined histologically for the presence of rhabdomyosarcoma. Regional lymph node metastases or metastases in other organs were never observed. A total of 14 out of 96 rats were excluded from the final analysis: eight of these did not develop tumour growth and the tumour inoculation in six was apparently not properly performed, as they developed tumour extending into the soft tissue of the leg within 14 days after inoculation. Fisher's test was used for statistical evaluation.

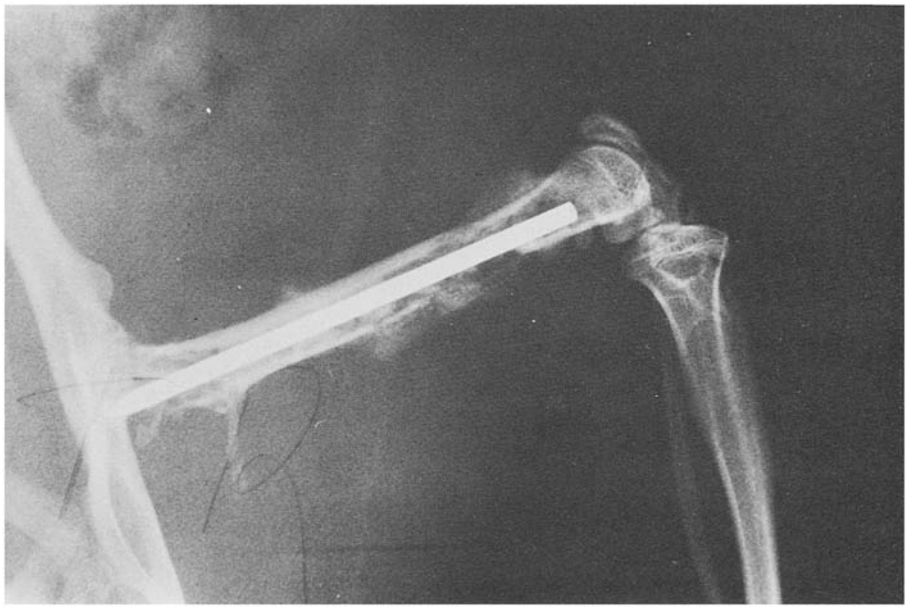

Figure 1. X-ray of the right femur of a rat 45 days after osteosynthesis. The tumour has involved the cortex.

Experimental design

After tumour inoculation, the rats were randomly divided into four groups of 24 animals each:

(I) Control group	No further treatment.
(II) Osteosynthesis group	Intramedullary fixation to be inserted on day 42.
(III) Exarticulated group	The tumour-bearing leg to be exarticulated on day 45.
(IV) Combined treatment group	Intramedullary fixation on day 42 will be followed by exarticulation on day 45.

From the difference in the number of rats with lung metastases in the control and osteosynthesis groups, the effect of osteosynthesis on the development of lung metastases was determined.

From the difference in the number of rats with lung metastases in the exarticulated and combined treatment groups, it was possible to determine the effect of fixing the pin itself on the development of lung metastases.

Results

Significantly more animals with lung metastases at sacrifice were found to be present in group I than in group II (table 1).

In neither group did this incidence differ between animals sacrificed at day 121 and those sacrificed at day 156 (group I: 7/11 and 7/10; group II: 3/11 and 4/11, respectively). For animals having developed lung metastases it is shown (figure 2) that the number of lung metastases per rat in group I is significantly greater than in

Group	Lung metastases	
	Present	Absent
Control (I) ($n=21$)	14 (67 per cent) $p=0{\cdot}03$	7
Osteosynthesis (II) ($n=22$)	7 (32 per cent)	15
Exarticulated (III) ($n=19$)	0 (0 per cent) $p=0{\cdot}10$	19
Combined treatment (IV) ($n=20$)	4 (20 per cent)	16

Table 1. Incidence of lung metastases according to group.

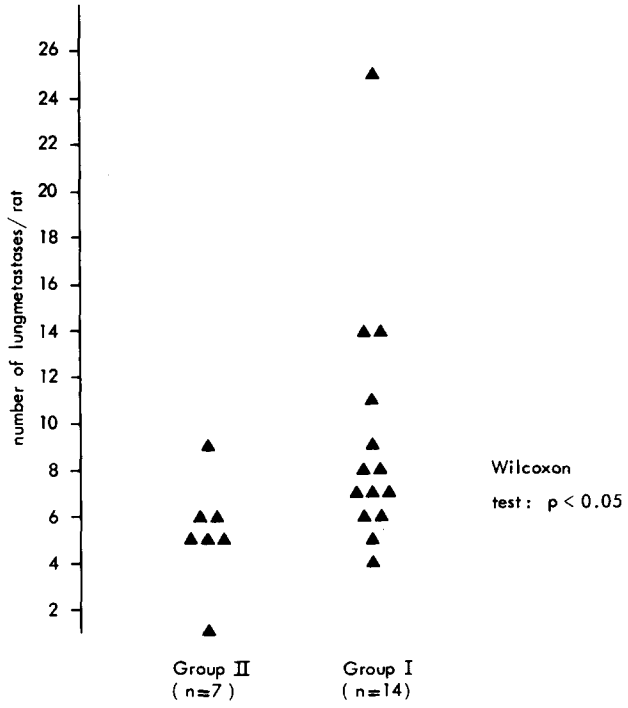

Figure 2. Number of lung metastases/rat in group I (control group) compared with group II (osteosynthesis group).

group II. No difference regarding these numbers between the two sacrifice dates was apparent.

Table 2 gives numbers of animals according to degree of cortical involvement for groups I and II. The percentage of animals which spontaneously developed fractures in group I is significantly greater than in group II (Fisher's test: $p<0{\cdot}005$).

In table 3 the incidence of lung metastases in relation to the occurrence of fracture is given for groups I and II. In both groups all animals which showed a fracture

Cortical involvement	Control group (I) ($n=21$)	Osteosynthesis (II) ($n=22$)
None	2	3
<50 per cent	6	7
>50–99 per cent	2	10
100 per cent fracture	11 (52 per cent)	2 (9 per cent)

Table 2. Comparison of degree of cortical involvement in groups I (control group) and II (osteosynthesis group).

		Control group (I) ($n=21$)		Osteosynthesis group (II) ($n=22$)
Rats with fracture	11		2	
Number of them with metastases		11 (100 per cent)		2 (100 per cent)
		$p=0{\cdot}001$		$p=0{\cdot}09$
Rats without fracture	10		20	
Number of them with metastases		3 (30 per cent)		5 (25 per cent)

Table 3. Correlation between the incidence of lung metastases and pathological fractures.

developed lung metastases. In case of no fracture, the percentage of rats with lung metastases was significantly less and did not differ between groups I and II.

In table 1 the number of animals showing lung metastases are compared for groups III and IV. While 20 per cent of animals in group IV showed lung metastases at sacrifice, this percentage was 0 in group III. This difference, however, is not statistically significant ($p=0{\cdot}10$, Fisher's test).

Discussion

The occurrence of spontaneous fractures is significantly related to the incidence of lung metastases (table 3). The number of animals developing fractures is significantly reduced by prophylactic osteosynthesis (table 2). This explains why the incidence of lung metastases in prophylactic treated rats is significantly lower than in non-treated animals (table 1). In this study the possible increased risk of metastases by the procedure of inserting the femur pin (table 1), appears to be smaller than the risk of fracture and its variably-associated occurrence of metastases in case of no prophylactic osteosynthesis. Since there exists the possibility of treating pathological fractures by osteosynthesis, it has been pointed out in the literature, largely through the pioneer work of Peltier [15, 16] which was confirmed by others, that the danger of this type of therapy is the development of the spread of tumour cells [5, 12].

Peltier [15] showed that bacteria in glass tubes half-filled with a mixture of agar and milk (tryptase-peptonized) had spread to the distal column of agar, after the insertion of an intramedullary nail. Also, from Peltier's second *in vitro* experiment, it was evident that erythrocytes tagged with ^{32}P, which were at the mid-point of the tibia, had spread proximally and distally due to the intramedullary nailing, and were

pressed outwardly by the foramina nutricia. He also showed that a pressure of 380 mmHg could be reached by intramedullary nailing, especially if the hammer blows followed quickly, one upon the other [16].

On the basis of these experiments, Peltier concluded that intramedullary nailing of pathological fractures might similarly result in the spread of tumour cells and might lead to metastases elsewhere, so that serious consideration must be given in planning the treatment. The fact that there is a connection between the performance of osteosynthesis in the treatment of pathological fractures and tumour cell dissemination was demonstrated in the positive results from his experiments and confirmed clinically in humans by other workers.

Junge [11] found after treating eight patients by the Küntscher nail following pathological femur fracture, that histologic tumour cells were present in three of these on the place where the nail was driven in. He found no evidence of systemic metastases due to this action.

Zickel and Mouradian [22] described one patient with an intramedullary tumour spread after fixation of a pathological fracture. Hoare [10] revealed malignant cells in the vena cava during an osteosynthesis, and Harrington *et al.* [9] found that after 375 operations for pathological fractures, in one instance a metastasis appeared in the operation wound.

Contrary to the above-mentioned authors, who stressed the possible risks of osteosynthesis, there are also many publications covering more than 1000 osteosyntheses due to pathological fracture, which show no evidence that this action accelerates the process of metastasis.

In 185 patients we have operated for an (impending) pathological fracture, we did not find any evidence of acceleration of the metastatic growth [2]. Junge [11], followed by Knutson and Spratt [13], could not show any difference in survival rate between two groups of patients with pathological fractures, treated either by osteosynthesis or conservative management. Further, in our own patient groups, the life expectancy was unaffected by the operation [2].

The above-mentioned experiments of Peltier [15, 16] did not, however, escape criticism. Fundamental objections were, for instance, made by Wehner [21] who argued that tumour cells are not to be compared with bacteria and erythrocytes. Furthermore, most tumour cells which come into circulation during osteosynthesis [10] are immediately destroyed, without evidence of metastasizing [14]. Francis [7] wrote that the appearance of lesions on the distal side of the metastases, were probably subclinically already present. Bremner and Jelliffe [3] and Devas *et al.* [4] pointed out the possibility that the occurrence of a pathological fracture itself influences the process of metastasis. Finally, the chance of metastasis acceleration may well be enhanced if fixation of the fracture is badly done [20].

Notwithstanding the comprehensive available literature, the question whether osteosynthesis accelerates metastasis is still being raised. Wehner [21], and Stoffella *et al.* [19] advise drilling the marrow-cavity up to and above the tumour, to prevent tumour cell dissemination as much as possible. Devas *et al.* [4] proposed that surgical management of a pathological fracture is indicated only if bone metastasis elsewhere is obvious, while Douglas *et al.* [5] concluded that the unjustified risk of accelerating dissemination by osteosynthesis, is probably the reason why relatively only a few prophylactic operations are performed.

Our study consisted of an investigation into examining how far osteosynthesis will stimulate the development of metastasis. Roentgenographic evidence was used

to estimate the cortical involvement because in cases (humans) where this is more than 50 per cent, pathological fracture occurred in 66 per cent of patients [6]. In our study, pathological fracture was prevented by inserting a femur nail which significantly reduced the number of animals with lung metastases and the number of lung metastases per animal. Hence we were able to demonstrate that the presence of a pathological fracture stimulates development of metastasis, thus supporting the ideas of Tachdjian and Compere [20] and Rinecker and Dölle [18]. It is evident that the influence of the procedure of osteosynthesis itself on the process of metastasis is small.

Based on our data from animal model experiments and clinical osteosyntheses, and data from the literature, it can be concluded that prophylactic osteosynthesis in the prevention of pathological fracture is preferable in spite of the risk of acceleration of metastatic development. When it is also taken into account that the operation reduces pain, enables patients to be ambulant more quickly and for longer, and is technically simpler with few complications, then we feel that it is justified to say that prophylactic osteosynthesis of an impending pathological fracture is the treatment of choice.

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