In My Own Time

Osteosarcoma

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British Medical Journal, 1979, **2**, 536-537

I remember her so well—a pretty girl of 17. Her name was Jane, and she was already a patient in the ward when I became house surgeon to the surgical unit at The Middlesex Hospital in 1950. I have often remembered her ordeal over the years, for she was the first of many patients I have seen with an osteogenic sarcoma of the lower femur. She was to be my introduction to the unfolding tragedy associated with this diagnosis. I remember the late Sir Gordon Gordon-Taylor being consulted, and the anguish before the inevitable amputation. The greatest tragedy, however, came later when my six months on the unit was almost up. Jane was readmitted, this time with multiple metastases. She died a few months later. Amputation had achieved nothing; it seemed merely to have been an additional source of misery before her inevitable death soon afterwards.

Amputation and radiotherapy

At that time amputation was virtually the only treatment available for malignant bone tumours. Radiotherapy with the low-voltage machines then in use often not only failed to control the tumour, but also damaged the surrounding skin and soft tissues; even adjacent normal bone could be so badly affected that it was not uncommon for pathological fractures to occur. Radiotherapy, however, was destined to become popular again —particularly in Britain, where men like the late Sir Stanford Cade and Sir Brian Windeyer led the world in using the newly introduced super-voltage *x*-ray equipment. It was not long before they showed that osteosarcoma could be made to respond without unacceptable tissue damage. Amputation alone achieved some success, and about one in five patients survived. The other four, my patient Jane among them, were subjected to what seemed to be an unnecessarily mutilating operation a few months before death.

By the time I was a junior registrar, surgeons—hitherto disenchanted with radiotherapists' earlier efforts—seemed more inclined to accept the new super-voltage irradiation. Radiotherapists themselves, to whom many patients were referred direct, knew that their new technique resulted in tumour regression in most of them. Many surgeons, however, continued to amputate in spite of this. For most patients, though, it came too late to save their lives because long before diagnosis, they already had widespread but invisible micrometastases in their lungs. Such early amputation did at least spare them the unpleasant effects of a course of irradiation but, perhaps more important, spared them the possibility of painful local post-irradiation recurrence with pathological fracture, or even tumour fungation, shortly before their eventual death from disseminated disease.

In spite of the initial good results, radiotherapy, for all its recent improvements, was never able to ensure total destruction of the tumour. Indeed, it was soon shown that after a full course about one-third of the limbs later amputated showed histological evidence of apparently viable malignant cells within the original tumour. Most radiotherapists soon accepted that, although their newer technique was capable of producing an early excellent clinical and radiological response, many tumours returned later—often very much later.

For the next 20 years, the treatment of osteosarcoma for most patients depended on the acceptance that usually irradiation alone could at least control the primary tumour for six to 12 months. Primary amputation was largely abandoned, and the patient dying with lung metastases a few months afterwards became a rarity. Irradiation was used as a holding treatment. The late Sir Stanford Cade of Westminster Hospital must be given credit for devising this humane regimen. He rightly assumed that initial treatment with a full course of megavoltage irradiation was, at least for the first six months, as effective as total tumour ablation by amputation. Thus, by treating all patients in this way, unnecessary amputation could be avoided in those already doomed because of invisible lung metastases. He advised amputation, so essential for long-term survival, only in those shown most likely to survive by an absence of visible lung deposits six months or so after radiotherapy.

This Cade regimen was widely accepted in the United Kingdom, and has now been shown to have produced results equal to those of invariable early amputation. All those who survived had to have an amputation, but most of the others—for whom it would have been of no value—were spared this horror. There were, of course, many problems with this regimen. Some tumours did not respond; others, on whom amputation was not performed because of metastases, developed painful local recurrence. There was also the difficulty of explaining to parents the necessity for amputation in an apparently healthy child six months after what seemed to have been dramatically successful treatment to the limb; indeed, several refused. For these reasons some surgeons, particularly those away from the major radiotherapy centres, continued to advise primary amputation.

In the United States, too, there was never great enthusiasm for irradiation in any form. In Britain, however, the Cade regimen became much more popular than primary ablation. Had my patient Jane presented a few years later, she would almost certainly have been spared such mutilating surgery. Unfortunately, her chance of survival with radiotherapy instead would have been no better, for we now know that, in spite of sparing many from surgery, no more survived and four out of every five succumbed. One must not forget, however, that survival alone was not our only aim. Comfort, during what was for most patients the last few months of life, was also important. Cade, by devising his regimen, spared many from

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amputation. Irradiation became, and remains to this day, a potent weapon in the relief of pain from metastases. Painful local recurrence could be treated by late palliative amputation.

Prophylactic chemotherapy

The great change in treatment during the past five years has been the realisation that several of the known chemotherapeutic agents, such as methotrexate and doxorubicin, when given in higher doses than hitherto, could cause the regression of metastatic osteosarcoma, and therefore probably also the destruction of many of the micrometastases present (but not visible) early in the disease. Unfortunately, such cytotoxic agents are much less effective in the presence of bulk disease so that they must be started soon after amputation to achieve their earliest maximum effect. Unfortunately, therefore, when amputation is necessary, it must now be advised early. This is then followed by a course of appropriate adjuvant chemotherapy—not pleasant, but undoubtedly effective in altering the course of the disease. It is still much too early to know how much the chances of survival have increased, but certainly patients live longer and metastases develop much later than they used to. Whereas in the past most patients died within two years, now lung metastases sometimes develop later than this. For this reason, it is still not known just how effective this adjuvant treatment will eventually prove to be.

Many drugs are under trial: methotrexate is one of the most effective and, together with vincristine and doxorubicin, is recommended in Britain in the Medical Research Council's national trial of treatment. A so-called "moderate" dose of 200 mgm^2 is recommended, and early results indicate that at this level it is as effective and, of course, much safer than the higher dose originally recommended—which is still widely used in the United States. At present, there seems little difference in the early results reported from the trials of different drug regimens which are in progress throughout the world. It is impossible to predict ultimate survival figures, but opinion suggests that the rate may be doubled. With such a rare tumour it is encouraging that so many large co-operative trials of treatment are now in progress, for only in this way will the most effective regimen be determined within a reasonable time. In Britain, for example, the Medical Research Council's trial has received such widespread support from clinicians that already it is among the largest at present in progress.

Local resection and prosthetic replacement

When I qualified, amputation was advised for almost all patients with primary malignant tumours of the limb bones. There followed a long period when such mutilation was reserved only for those apparently free from disseminated disease six months after super-voltage irradiation. Now, amputation is once again advised as the primary treatment to eliminate bulk disease and thus give the chemotherapeutic agents the best possible chance of destroying invisible micrometastases.

Nowadays, however, the local resection and prosthetic replacement of all or part of the large limb bones and adjacent joints is possible. In the case of such malignant tumours as osteosarcoma, with widespread soft tissue extension, such local resection at present seems unlikely to be adequate. In the case of less malignant tumours, this emerging surgical technique can sometimes replace amputation. Chondrosarcomas and the much rarer more circumscribed variety of osteosarcoma, the juxtacortical osteosarcoma, may now be treated in this way. Usually it is the femur that is concerned when the knee or hip is replaced together with half the shaft, the replacement prosthesis being made individually from measurements from preoperative *x*-ray films. When there is more extensive intramedullary disease, it may be necessary to remove the whole bone and replace the joints at either end. Thanks to the early pioneer work of Burrows and Scales, and the recent advances in joint replacement surgery, this is now possible.

Although such local resection at present seems unwise in osteosarcoma, limited trial—particularly in the arm, where amputation is particularly abhorrent—is justified. No one, however, underestimates the possible risks, but with modern adjuvant chemotherapy there remains at least hope that, in future, prosthetic replacement may more often become a substitute for amputation.

Lung metastases

Until recently the development of even a solitary lung metastasis was regarded as the inevitable harbinger of early death. There is now ample evidence that in some patients the local resection of one, or perhaps two, such metastases may be all that is required to rid the patient of the last remaining trace of disease. Such patients must be few, but no longer should a single lung deposit be regarded in this way. Resection is not normally considered unless a metastasis has remained solitary for two or three months. Otherwise, of course, a great many unnecessary thoracotomies would be performed. Even so, the removal of a single deposit, perhaps repeated once, is well worth while and there are today many patients, several of my own among them, who owe their lives to the removal of a lung metastasis. Indeed, 15 years ago, I well remember writing to the chairman of a local housing committee on behalf of one of my patients who, six months after amputation, had developed a metastatic deposit in one lung. She lived in miserable conditions with her husband and 2-year-old daughter in one room. I explained that she had but a few months to live and requested that she be given priority on the local authority housing list so that, for a few months at least, the family could live happily in comfort. My letter had the required effect: within a week they were in a brand-new council house. Shortly afterwards, the metastasis was removed and I heard from her recently: she is very well, now with three children, and still in the same council house.

Fortunately, osteosarcoma is a rare disease, but it is particularly unpleasant; not only because of its virulence, but because so often its victims are young. Over the last 30 years, the greatest potential therapeutic advance has come during the last five—as prophylactic adjuvant chemotherapy has evolved. Unfortunately, the early high hopes have proved overoptimistic, but hope in the foreseeable future still lies with improvements in, and a better understanding of, chemotherapy. Perhaps the day is not too far off when more patients may benefit from local resection and prosthetic replacement and be spared the horror of amputation. Certainly, if Jane had presented now, some 30 years later, she would have lived longer and probably had about twice the chance of survival. Perhaps it is too much to hope that her successors will fare better than other patients with malignant disease, but let us hope that at least they will be spared amputation.

WORDS Drugs, poisons, diseases, and injuries that cause death are said to be fatal or lethal. Why fatal? In Greek mythology there were three Fates. These ladies controlled the thread of life. Clotho spun the thread and Lachesis mixed the strands of good and evil fortune. She passed it on to Atropos who cut the thread of life. *A-tropos*, no turning; she could not be turned aside from her task. Hence, atropine from *atropa belladonna*, the deadly nightshade. The fates were concerned not only with death, but with birth and the course of one's life. So perhaps fatal is not a suitable word for something causing death, and lethal (L *letalis*; *letus*, death) is the better choice. Anything to do with the river Lethe?