The risks and benefits of radiotherapy with massive endoprosthetic replacement

Between 1966 and 2001, 1254 patients underwent excision of a bone tumour with endoprosthetic replacement. All patients who had radiotherapy were identified. Their clinical details were retrieved from their records.

A total of 63 patients (5%) had received adjunctive radiotherapy, 29 pre-operatively and 34 post-operatively. The mean post-operative Musculoskeletal Tumor Society scores of irradiated patients were significantly lower (log-rank test, p = 0.009). The infection rate in the group who had not been irradiated was 9.8% (117 of 1191), compared with 20.7% (6 of 29) in those who had pre-operative radiotherapy and 35.3% (12 of 34) in those who radiotherapy post-operatively. The infection-free survival rate at ten years was 85.5% for patients without radiotherapy, 74.1% for those who had pre-operative radiotherapy and 44.8% for those who had post-operative radiotherapy (log-rank test, p < 0.001). The ten-year limb salvage rate was 89% for those who did not have radiotherapy and 76% for those who did (log-rank test, p = 0.02).

Radiotherapy increased the risk of revision (log-rank test, p = 0.015). A total of ten amputations were necessary to control infection, of which nine were successful. Radiotherapy may be necessary for the treatment of a bone sarcoma but increases the risk of deep infection for which amputation may be the only solution.

The surgical treatment of most bone sarcomas requires some method of reconstruction to preserve the limb. Several methods are available; however, surgeons in the United Kingdom tend to favour endoprostheses because of their ability to return patients rapidly to full activity. This is particularly important when one in four patients will die within two years of diagnosis despite adjuvant chemotherapy.1

Neo-adjuvant chemotherapy has been in routine use for osteosarcoma, Ewing’s and spindle cell sarcomas since the 1980s. Pre-operative chemotherapy is followed by radiological re-staging, surgical excision, endoprosthetic reconstruction and post-operative chemotherapy. Adjuvant external beam radiotherapy is not routinely used in the management of primary malignancies of bone, but may be considered pre-operatively if the tumour is radiosensitive, for example a Ewing’s sarcoma that fails to respond to chemotherapy, or post-operatively if there is an inadequate surgical margin, a poor response to chemotherapy or local recurrence.

The use of endoprostheses is not without its risks, chief of which is deep peri-prosthetic infection. The long-term risk of this may be as high as 10%. It is best treated by two-stage revision.3,4

The aim of this study was to compare the functional outcome and risk of complication after endoprosthetic replacement for sarcoma between those who had adjunctive radiotherapy and those who did not. A secondary aim was to study the efficacy of surgery for infected endoprostheses in irradiated patients.

Patients and Methods

Between 1966 and 2001, a consecutive series of 1254 patients underwent excision of a bone tumour and endoprosthetic replacement. Their records were reviewed for their demographic details, diagnosis, site of tumour, operations performed, adjuvant therapy, percentage tumour necrosis, surgical complications, outcome, last follow-up date, metastases, local recurrence and mortality. A subset of patients who had undergone radiotherapy to the affected limb and had a subsequent deep peri-prosthetic infection were identified and analysed in depth. A deep infection was defined as clinical evidence of infection with a positive microbiological culture, or the presence of...
peri-prosthetic pus and histological evidence of infection at operation. Functional scores were prospectively recorded for a limited period using the Musculoskeletal Tumor Society (MSTS)\(^5\) system, but were only available for 158 patients (12.6%).

Statistical analysis was performed using Statview (SAS Institute, Berkeley, California). Kaplan-Meier survival analysis was used to generate implant survival curves and life tables. The effect of radiotherapy on infection, implant survival, function and local recurrence were compared using Kaplan-Meier survival curves (using log-rank tests), chi-squared tests and Cox regression analysis. Significance was set at \(p \leq 0.05\).

**Results**

The mean follow-up for the 1254 patients was 5.75 years (3 months to 33 years). A sub-group of 63 patients (5%) had radiotherapy to the affected limb. This was administered pre-operatively in 29 (usually for a Ewing’s sarcoma) and post-operatively in 34 (usually because of close surgical margins or a poor response to chemotherapy). The mean post-operative MSTS functional score of patients having radiotherapy was significantly lower; 81.3% (24.4 of 30 points, 151 patients) for those who did not have radiotherapy and 64% (19.2 of 30 points, seven of 13 patients surviving with implant) for those who did (chi-squared test, \(p = 0.009\), Fig. 1).

The risk of infection was significantly higher in the patients who had undergone radiotherapy (log-rank test, \(p < 0.0001\)). The crude rate of infection in patients who did not have radiotherapy was 9.8% (117 of 1191), compared with 20.7% (6 of 29) in those who had pre-operative radiotherapy and 35.3% (12 of 34) in those who had post-operative radiotherapy. However, when the actuarial infection rates were evaluated using Kaplan-Meier survival curves (Fig. 2), the infection-free survival rate at ten years was 85.5% for those who had not had radiotherapy, 74.1% for those who had undergone radiotherapy pre-operatively, and 44.8% for those that had received it post-operatively.

Patients who had radiotherapy had a higher risk of subsequent amputation (15.8%; (10 of 63) than those who did not (7.8%; 93 of 1191, chi-squared tests, \(p = 0.02\)). The rate of amputation in patients who underwent pre-operative radiotherapy was 17.2% (5 of 29) and for those who had post-operative radiotherapy 14.7% (5 of 34). By contrast, the actuarial ten-year limb salvage rate was significantly different, at 89% for those who had not had radiotherapy and 76% for those who had (log-rank test, \(p = 0.02\)). There was a further significant difference between the two groups: in the radiotherapy group the cause of amputation was local recurrence in 30% (3 of 10), compared with 63.4% (59 of 93) in the no radiotherapy group (log-rank test, \(p = 0.02\)).

The ten-year survival rate was significantly worse in the radiotherapy group (29%) than in the no radiotherapy group (58%, log-rank test, \(p < 0.001\); Fig. 3). The risk of locally recurrent disease, however, was not statistically different between groups (log-rank test, \(p = 0.11\)) on Kaplan-Meier analysis. With the numbers available, the relationship between poor response to chemotherapy, inadequate surgical margins and radiotherapy on local control of disease was less clear. Only a good percentage tumour necrosis (Hazard Ratio (HR) = 0.22, \(p < 0.0001\)) and surgical resection margins (inadequate (HR = 2.3, \(p = 0.0004\)), adequate (HR = 0.66, \(p = 0.04\)) compared with those whose margins were unknown (HR = 1) were significant on multivariate Cox regression analysis (Table I).
The survival of the implant to revision was also significantly shorter in the radiotherapy group (39% at ten years) than in the no radiotherapy group (64% at ten years; log-rank test, \( p = 0.015 \), Fig. 4).

In the subgroup of 18 patients who had a deep infection following radiotherapy, 13 had received neoadjuvant chemotherapy.

The most common presentation was by an acute abscess with a discharging sinus. The mean time from operation to infection was 24.3 months (0.25 to 100). The mean erythrocyte sedimentation rate at presentation was 77 mm/h (34 to 128) and the mean C-reactive protein 56 mg/l (40 to 80). The infecting organisms were coagulase-negative staphylococcus in eight patients, \textit{Staphylococcus aureus} in five, streptococci in four and \textit{Escherichia coli} in one. Causes of infection other than radiotherapy were advanced in ten patients, and included pre-operative infection in one, post-operative haematoma in one, subsequent lengthening in one, post-operative sepsicaemia in three, surgery for local recurrence in two, and revision in two.

All 18 patients were initially treated with intravenous antibiotics to which the organism was sensitive, but no infection was controlled by antibiotics alone. Debridement and lavage of the prosthesis was carried out in 12 patients but failed to eradicate the infection. Two patients underwent debridement with soft-tissue flap cover: one was successful. Two patients underwent a one-stage revision, one of which was successful, and six patients underwent a two-stage revision, of which half succeeded. A total of ten amputations were performed for control of sepsis, nine of which were successful in eradicating infection. Three patients elected to preserve their limb and continue with a chronically infected endoprosthesis, controlled with intermittent antibiotics. Only five of 18 (28%) patients presenting with an infected endoprosthetic replacement after radiotherapy, were cured of infection while retaining the affected limb.

**Discussion**

The complications of radiotherapy are familiar to all those involved in its use. It is known that the ionisation events and free radicals produced by radiation cause damage to vital cellular components.\(^6,7\) Radiation activates various cellular signalling pathways\(^8\) that lead to the expression and activation of pro-inflammatory and profibrotic cytokines,\(^9,11\) vascular injury\(^12\) and activation of the coagulase cascade.\(^13\) These changes may be involved in the development of oedema, inflammation, and the initiation of wound-healing,\(^14,17\) and can lead to stiffness of the

---

**Table I.** The incidence of locally recurrent disease in patients receiving radiotherapy

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>No radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known poor response to chemotherapy only (log-rank test, ( p = 0.07 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local recurrence</td>
<td>9</td>
<td>64</td>
</tr>
<tr>
<td>No local recurrence</td>
<td>11</td>
<td>262</td>
</tr>
<tr>
<td>Known inadequate surgical margins (log-rank test, ( p = 0.55 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local recurrence</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>No local recurrence</td>
<td>5</td>
<td>52</td>
</tr>
</tbody>
</table>
Radiotherapy is currently a necessary adjunct to the treatment of a bone sarcoma. It is, however, a harbinger of complications and, if associated with infection, poses a significant risk of amputation. Patients who need radiotherapy should be aware of the increased risk to their limb despite the potential benefit in local disease control.

References