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Original Article

Tumour Volume and Dose Influence Outcome after Surgery and High-dose Photon Radiotherapy for Chordoma and Chondrosarcoma of the Skull Base and Spine

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Abstract

Aims: To evaluate the long-term outcomes of patients with chordoma and low-grade chondrosarcoma after surgery and high-dose radiotherapy.
Materials and methods: High-dose photon radiotherapy was delivered to 28 patients at the Neuro-oncology Unit at Addenbrooke's Hospital (Cambridge, UK) between 1996 and 2016. Twenty-four patients were treated with curative intent, 17 with chordoma, seven with low-grade chondrosarcoma, with a median dose of 65 Gy (range 65–70 Gy). Local control and survival rates were calculated using the Kaplan–Meier method.
Results: The median follow-up was 83 months (range 7–205 months). The 5 year disease-specific survival for chordoma patients treated with radical intent was 85%; the local control rate was 74%. The 5 year disease-specific survival for chondrosarcoma patients treated with radical intent was 100%; the local control rate was 83%. The mean planning target volume (PTV) was 274.6 ml (median 124.7 ml). A PTV of 110 ml or less was a good predictor of local control, with 100% sensitivity and 63% specificity. For patients treated with radical intent, this threshold of 110 ml or less for the PTV revealed a statistically significant difference when comparing local control with disease recurrence ($P = 0.019$, Fisher's exact test). Our data also suggest that the probability of disease control may be partly related to both target volume and radiotherapy dose.
Conclusion: Our results show that refined high-dose photon radiotherapy, following tumour resection by a specialist surgical team, is effective in the long-term control of chordoma and low-grade chondrosarcoma, even in the presence of metal reconstruction. The results presented here will provide a useful source for comparison between high-dose photon therapy and proton beam therapy in a UK setting, in order to establish best practice for the management of chordoma and low-grade chondrosarcoma.

Key words: Chondrosarcoma; chordoma; local control; radiotherapy; tumour volume

Introduction

Chordomas and chondrosarcomas are rare malignant tumours occurring in all ages. Chordomas develop from cellular remnants of the embryonic notochord, arising along the length of the spine, commonly in the sacrum (50%) and skull base (35%) [1]. Chondrosarcomas originate from cartilaginous elements of primitive mesenchymal cells [2]. Characteristically, chordomas grow slowly but have a high tendency for local recurrence [3] and metastases occur in 30–40% of patients [4,5]; outcome is generally poorer compared with low-grade chondrosarcoma [6].

Both tumours are rare, with a combined incidence of 0.8–1 per million per year in the UK (Dr David Greenberg,

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Eastern Knowledge and Intelligence Team, personal communication). The rarity, relative radio-resistance and frequently challenging anatomy make management difficult. Treatment is usually with surgery followed by radiotherapy [2,6–8]; aiming for complete macroscopic excision is important, as residual postoperative tumour volume may predict local control [9–12]. An association with preoperative tumour volume has also been shown [13]. Even when complete surgical removal is achieved, residual microscopic disease is common, making subsequent radiotherapy important [14].

Tumour proximity to critical dose-limiting normal tissues makes both surgery and radiotherapy challenging. Metal implants, frequently required as part of surgical reconstruction, may compound this complexity during both the planning and the delivery of radiotherapy. Image degradation can hamper target volume delineation and affect the calculation of voxel-by-voxel stopping power within crucial sections of the image, while proton dosimetry can be significantly affected [8,15]. The TD_{50} (dose required to achieve local control in 50% of tumours) for chordoma is around 65 Gy, irrespective of modality [16]. Achieving this can be difficult without exceeding normal tissue dose constraints. The heterogeneity of resection extent, timing and delivery of radiotherapy, as well as technical developments during the lengthy follow-up periods of many case series, makes optimal dose definition problematic. Nonetheless, the most successful outcomes seem to be with carbon ion, proton beam therapy (PBT) and high-dose photon treatments [8,9,16,17]; recently a best practice paper has also been published on recurrent chordoma [18].

The National Health Service currently funds some UK patients to travel abroad for PBT and a service will be available at The Christie NHS Foundation Trust in Manchester from 2018. However, PBT is less effective in patients who require metal reconstruction during surgery [19]. X-ray beams are considerably less perturbed by metal, especially when multiple beams or rotational therapy are used.

Our group has previously published work reviewing outcomes for patients with chordoma or chondrosarcoma following surgery and high-dose photon therapy [17]. In this present study, we extend our previous report with a larger patient cohort and longer follow-up, in order to evaluate prognostic features, contribute to the development of effective management strategies and provide a basis for comparison with PBT when it becomes available in the UK.

Patients and Methods

Study Approval

This study was registered and approved as a service evaluation with the local oncology directorate and audit department, reference number PRN5089, and therefore did not require ethical approval. Trust guidelines for data protection were adhered to in data collection and analysis.

Patient Cohort

All patients aged 16 years and over, with a diagnosis of chordoma or low-grade chondrosarcoma, who were referred to the Neuro-oncology Unit at Addenbrooke's Hospital between October 1996 and May 2016 were reviewed. In this 20 year period, 45 patients were referred. Ten patients were excluded, the most common reason being tumour site, as three patients had sacral tumours, which require a different treatment paradigm (Supplementary Table S1), leaving 35 for analysis. This analysis includes a brief overview of seven patients referred for PBT abroad (three to the Paul Scherrer Institute, Switzerland, four to the University of Florida, Proton Therapy Institute). Thirty-four patients underwent maximal surgical debulking. One patient declined supportive blood products, so surgical intervention was inappropriate.

Twenty-three cases were histologically confirmed as chordoma and 11 as chondrosarcoma. The patient who did not undergo biopsy was classified as having chordoma based on radiological appearances. Metal reconstruction was required in eight of the 24 patients treated radically, and in two of the palliative patients. Radical treatment was with curative intent and palliative treatment was given with no expectation of cure. Patient details are summarised in Table 1. The mean age was 53 years (range 17–83 years). The age distribution is presented in Supplementary Figure S1.

Radiotherapy Treatment

Patients were immobilised using a Gill-Thomas-Cosman re-locatable stereotactic frame or thermoplastic shells. From 2007, image guidance was used, with daily imaging and positional correction (DIPC) using a zero action level approach [22]. Target volume delineation was based on a combination of pre- and postoperative magnetic resonance imaging and diagnostic computed tomography imaging to demonstrate bone detail. After the installation of TomoTherapy equipment, a pre-treatment megavoltage computed tomography was carried out to help target volume delineation in patients with metal reconstruction, because this virtually abolishes metal artefact [21].

Radiotherapy treatment was given in one, two or three phases, due to changing techniques over time. Residual tumour, or the area deemed to be at highest risk of recurrence, received the maximal dose. Patients 20 and 21 were treated with two-dimensional planning, supplemented in one by a spherical stereotactic boost. Patient 1 received 62 Gy in 31 fractions using a rotational plan with a central axis beam block [20]. Conformal radiotherapy was introduced in 1998 and thereafter patients received 65 Gy in 39 fractions, at 1.67 Gy per fraction; some were treated with plans including arcs. In 2007 image-guided intensity-modulated radiotherapy (IG-IMRT) using helical tomotherapy was introduced. All patients treated on the TomoTherapy HiArt™ units underwent DIPC [22,23]. Superior dose distributions with IMRT allowed dose escalation, first to