

Original Article

High-dose Radiotherapy in the Management of Chordoma and Chondrosarcoma of the Skull Base and Cervical Spine: Part 1 of Clinical Outcomes

K. L. Foweraker*, K. E. Burton*, S. E. Maynard*, R. Jena*, S. J. Jefferies*,
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Aims: Patients with chordoma and chondrosarcoma in the skull base present a complex multidisciplinary problem. These tumours are rare and occur in difficult anatomical regions. We reviewed the local control and survival of patients treated in our centre.

Materials and methods: Between 1996 and 2005, 12 adult cases of chordoma (nine) and chondrosarcoma (three) in the skull base or cervical spine were treated in our centre. The median follow-up is currently 38 months. One patient was treated with palliative intent. In 10 cases the prescription dose was 65 Gy in 39 fractions. The target volumes were measured, and the target maximum and minimum doses and the equivalent uniform dose (EUD) for the phase I plans were recorded.

Results: Local control was achieved in 11 of 12 cases. One chordoma patient failed locally, and one other died of metastatic disease despite local control. The 3- and 5-year cause-specific survival for the series was 88 and 75%, respectively. The mean phase I planning target volume (PTV) was 120.4 cm³. The median minimum dose in the phase I PTV was 81.0%. The median EUD (expressed as a percentage of the prescribed dose) for the phase I PTV, calculated using a value for the exponent a of 1.15, was 98.3%. The phase I EUD was below 80% in two of the 12 cases.

Conclusions: Our results confirm a need for aggressive local surgery and high-dose radiotherapy, and endorse multidisciplinary working. Although charged particle therapy is accepted as providing optimal treatment plans, in eight of our patients travel abroad would not have been feasible. This series provides encouraging results for carefully planned photon conformal radiotherapy, carried out in close collaboration with a specialist surgical team. Foweraker, K. L. *et al.* (2007). *Clinical Oncology* 19, 509–516

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Introduction

The management of patients with chordoma and chondrosarcoma in the skull base is a complex multidisciplinary problem. These tumours are rare, and are said to account for 1–4% of all malignant tumours of bone [1]. Chordomas are about twice as common as chondrosarcomas. The incidence seems to be in the range of 0.5–1 cases per million population per year, so that as few as 30–60 cases occur in the UK per annum. They can occur at any age and have a slight male preponderance. Their anatomical

location, as well as their rarity, adds to the difficulty of treatment.

Chordomas are thought to arise from remnants of the notochord, and occur most frequently in the skull base and upper cervical spine or in the sacrum. They can, however, occur along the whole length of the spine. Although chordomas are thought to arise from notochord structures, within the skull base they typically lie adjacent to the midline rather than in an exact midline position. They are typically, although not invariably, slow-growing tumours, but are locally aggressive, destroying bone and invading nearby soft tissue structures. Chondrosarcomas also occur in the skull base, and are thought to arise from cartilaginous elements in the skull base near to fused joints such as the petro-clival junction. The major problem from these tumours is local invasion and the high tendency for local

¹ Skull base surgery and neurosurgery collaborators: P. Axon^x, D.G. Hardy^y, R.W. Kirollos^y, R. Macfarlane^y, D.A. Moffat^x, J.D. Pickard^y.

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Conclusions: Our results confirm a need for aggressive local surgery and high-dose radiotherapy, and endorse multidisciplinary working. Although charged particle therapy is accepted as providing optimal treatment plans, in eight of our patients travel abroad would not have been feasible. This series provides encouraging results for carefully planned photon conformal radiotherapy, carried out in close collaboration with a specialist surgical team. Foweraker, K. L. *et al.* (2007). *Clinical Oncology* 19, 509–516

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recurrence. However, they do have malignant potential and can metastasise. Chordomas are more likely to metastasise than chondrosarcomas, although this is relatively uncommon. The growth rates of both tumour types are characteristically very slow, although after multiple surgical procedures, an acceleration of growth rates can be observed.

There is reasonable evidence that the best treatment for these skull base and upper cervical spine tumours is with a combination of surgery and radiotherapy [2e4]. These tumours are considered to be relatively radiation resistant, requiring high doses for successful control [5e7]. Between 60 and 65 Gy is considered a minimum useful dose, but higher doses have been favoured in some series, particularly where this is made possible by treatment using charged particle irradiation [8e12]. Not all series have shown a dose-response relationship [13,14], but it is difficult to assess the optimal radiation dose as the available data often have variation in the degree of surgical resection, the multiplicity of surgical procedures and of the postoperative policy used for the timing, delivery and quality of the radiotherapy. Many published series go back over many years and therefore include patients treated with non-conformal photon radiotherapy or combinations of photon and proton treatments. On balance, it seems probable that a dose response is present, and that high doses, in excess of 60e65 Gy (or equivalent) are required.

Surgical resection of skull base and cervical spine tumours is challenging, and requires specialist skull base surgical techniques. Surgery for skull base tumours poses a risk of damage to normal structures, including the spinal cord and cranial nerves. These same normal tissue structures also impose a limitation on the external beam radiotherapy dose, which adds an additional difficulty as these tumours are relatively radio-resistant.

We examined the results of a small series of patients from our centre with chordoma and chondrosarcoma, in which 10 of 12 were treated with radical surgical resection and all then received high-dose (photon) radiotherapy, to review the outcome from this multidisciplinary approach.

Patients and Methods

All cases of chordoma and skull base chondrosarcoma in patients aged 16 years and over were collected between October 1996 and the end of December 2005. During this period, 18 cases were referred to our centre. There were three sacral tumours and one in the thoracic spine, which have not been included here. Of the remaining 14 cases, one was a patient who had been previously irradiated and further radiotherapy was not advised; one other was an 80-year-old man who declined any treatment. Therefore, 12 cases within the skull base and upper cervical spine were included in this review, which represents the experience of a large oncology centre working in close association with a neurosurgical service on the same site. In all cases, maximum possible surgery was carried out, considering the anatomical location of the tumour and the general fitness

of the patient. In most cases, either extensive removal or macroscopic excision was achieved. One patient declined supportive blood products and therefore no surgical intervention was carried out and the diagnosis was made on imaging alone. The surgery was carried out by members of a specialist skull base team based in our centre, comprising neurosurgeons, ear-nose-throat surgeons and pituitary surgeons. Details of the cases are given in Table 1, which includes a description of the extent of tumour resection. Of the 12 cases, there was histological confirmation of eight chordomas and three chondrosarcomas. The final case did not have a tissue diagnosis (patient declined surgery), but was classified as chordoma on radiological appearance. Ten of the 12 cases involved the skull base with or without the upper cervical spine. In this series, the mean age was 49.2 years (Table 1); the age distribution is shown in Fig. 1. The median follow-up for this series is currently 38 months (range 8.4e107.5) from the completion of radiotherapy; see Table 2 for details.

All 12 patients were referred via the neuro-oncology or skull base multidisciplinary teams for postoperative radiotherapy. The decision to give photon radiotherapy locally was made based on a number of considerations and will be detailed further in the discussion. Treatment was typically given in two or three phases, with the preoperative tumour bed receiving 50e60 Gy and an additional boost being delivered to residual tumour or the area deemed at highest risk, up to a maximum of 65 Gy. Ten of the 12 cases received a prescription dose of 65 Gy, given in 39 fractions (Table 2). Organs at risk (OARs) were outlined and included. The spinal cord, optic apparatus and brainstem were given the following dose constraints: spinal cord and optic apparatus 50 Gy in 30 fractions; brainstem 55 Gy in 33 fractions. The OARs were given priority over the target dose. Where appropriate, patients were immobilised in the relocatable stereotactic frame in order to minimise the planning target volume (PTV) margin. To benefit from the frame, patients must be able to co-operate, be physically able, have normal sensation in the face and mouth, and have tumours located above the level of the frame (for details see [15]). Five patients did not fulfil these criteria. Therefore, they were immobilised in a thermoplastic shell.

In two of the patients it was impossible to deliver 65 Gy safely to the PTV. In the first, patient 10, one of the earliest patients in the series, there was possible residual microscopic disease on the odontoid peg. The preoperative tumour bed received 55 Gy in 33 fractions. In the second phase, the odontoid peg received 5 Gy to the 90% isodose in three fractions using stereotactic arcs.

The second patient to receive less than 65 Gy was treated with palliative intent (patient 1). In this case, the chordoma wrapped entirely around the spinal cord, touching it in much of the circumference. Although the patient underwent apparently macroscopic removal at surgery, there was noted to be significant disease present at the time of radiotherapy planning. The treatment was delivered using rotation therapy with a central axis beam block such that the maximal spinal cord dose was 80%. This

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Table 1 e Patient details

Patient	Age	Gender	Tumour	Site	Surgery
1	76	Male	Chordoma	C2eC4	Macroscopic removal*
2	35	Female	Chordoma	Skull base	Near-total removal
3	39	Female	Chordoma	Skull base	Macroscopic removal
4	60	Male	Chordoma	Sphenoid bone	Transphenoidal biopsy
5	46	Female	Chordoma	C1eC4	Macroscopic removal
6	83	Male	Chordoma	Clivus	Transphenoidal biopsy
7	59	Male	Chordoma	Skull base	No surgery ^y
8	33	Male	Chordoma	Petrous bone	Near-total removal
9	18	Male	Chordoma	Clivus, C1e2	Macroscopic removal
10	43	Female	Chondrosarcoma	Clivus, C1	Near-total removal (well differentiated)
11	50	Female	Chondrosarcoma	Petrous bone	Near-total removal (moderately differentiated)
12	55	Male	Chondrosarcoma	Petrous bone	Macroscopic removal (poorly differentiated)

*Large volume of disease at radiotherapy due to early re-growth of tumour before planning. ^yPatient declined supportive transfusions e no biopsy or other surgery carried out.

therefore delivered a prescription dose of 62 Gy in 31 fractions to the isocentre within the target volume. This patient subsequently recurred locally 2 years later and was retreated with a further 57 Gy. For further details see [16]. The patient developed further local recurrence 25 months after treatment, but subsequently died from a myocardial infarction.

This series was reviewed with respect to the dosimetry of both target volumes and normal tissue structures. Briefly, the dose prescription was noted and the variation in PTV dose recorded, including the minimum and maximum doses. In addition, the equivalent uniform dose (EUD) was calculated. This was implemented in our in-house Addenbrooke's Radiotherapy Planning System (ARPS) according to the generalised EUD formulation developed by Niemierko [17,18]. Table 3 shows details of the size of the gross tumour volume (GTV) and the PTV, with maximum and minimum doses and the EUD for the phase I PTV. Further details of the dosimetry, including normal tissue doses, in these 12 cases will be presented separately.

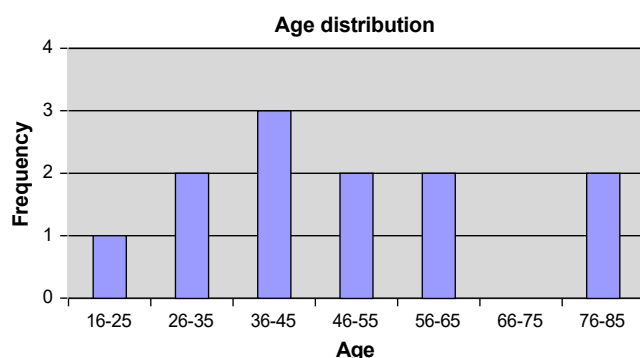


Fig. 1 e Age distribution of 12 (adult) chordoma/chondrosarcoma patients.

Results

The outcome data for the 12 patients are shown in Table 2. Local control was achieved in 11 of 12 cases after primary treatment. In the patient who failed locally (patient 1), the first recurrence of chordoma occurred 23 months after the completion of radiotherapy. He was re-irradiated but developed a further local recurrence 25 months after his second treatment. He then died of an unrelated myocardial infarction 5 months later, with disease present. His total survival time from the completion of his original radiotherapy treatment was 58 months [16].

A further patient developed locoregional lymph node metastases 7 months after her surgery and radiotherapy and then progressed to more widespread dissemination, before dying of disease 20 months after treatment, albeit with apparent local control. In addition to the cases detailed above, one other patient has died from unrelated gastric carcinoma, 21 months after the completion of radiotherapy for chordoma, which was still controlled. The remaining patients are all currently disease free at the last review.

Figure 2 shows the survival curve for cause-specific survival by histological subtype. The 3-year cause-specific survival for our series is 88%, with a 5-year value of 75%. In the analysis of cause-specific survival, we considered the patient who died of a myocardial infarction but had evidence of chordoma recurrence at the time as a chordoma death as this is more representative. The 3- and 5-year disease-free survival for the chordoma patients alone is 80% at present, although only one chordoma patient has reached 5 years of follow-up. All three chondrosarcoma patients are alive and disease free, and two have follow-up in excess of 8 years. Figure 3 shows overall survival by histological subtype for our patients, including the non-chordoma death from gastric cancer.

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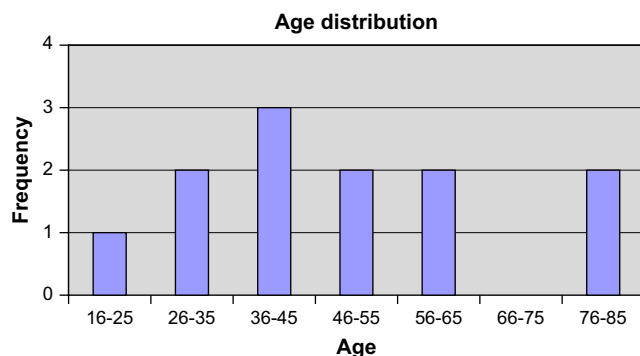


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Table 2 e Details of tumour control

Patient	Prescribed dose (Gy)	Post-radiotherapy follow-up (months)	Recurrence	Current status	Time to recurrence (months)	Time to death (months)
1	62	57.5	Yes e local	Dead*	22.7	57.5
2	65	69.0	No	Alive		
3	65	41.0	No	Alive		
4	65	42.7	No	Alive		
5	65	19.7	Yes e metastases only	Dead	6.7	19.7
6	65	21.6	No	Dead ^y		21.6
7	65	34.7	No	Alive		
8	65	23.6	No	Alive		
9	65	8.4	No	Alive		
10	60	107.5	No	Alive		
11	65	98.2	No	Alive		
12	65	17.5	No	Alive		

*Cause of death myocardial infarction (chordoma present). ^yCause of death gastric carcinoma (local control of chordoma).

Both patients who have died with disease suffered from chordoma, whereas the three patients with chondrosarcoma are all still alive and disease free. The histology of these three chondrosarcoma patients included one each of well-differentiated, moderately differentiated and poorly differentiated tumours. This differs from the series reported from the Heidelberg group [10], using carbon ions, which only included well-differentiated tumours d again with our small numbers this is an observation, but does not give further conclusions.

Tables 2 and 3 detail the size of the target volume and the radiation dose prescribed and delivered to the initial phase target volume for the 12 cases. In six cases there was no macroscopic residual tumour remaining at the time of radiotherapy planning (i.e. GTV $\frac{1}{4}$ 0 cm³), but in two cases, including the patient treated with palliative intent, the GTV was large. The mean GTV for the whole series was 15.2 cm³. The size of the phase I PTV was much larger in most cases, in order to encompass the original tumour bed. The mean phase I PTV was 134.4 cm³.

We used the phase I PTV for dose evaluation. Compared with a prescribed dose of 100%, the median maximum dose was 105.6%; the median minimum dose was 81.0%. The median EUD for the phase I PTV, calculated using a value for the exponent α of 15 (discussed below), was 98.3%. The phase I EUD was below 80% in two cases, one of which had a very large (residual) GTV and a large accompanying PTV (patient 1). This patient failed locally. The other patient with a low EUD had no residual gross tumour, and remains disease free, albeit with an early follow-up of 8.4 months.

The patients currently under review have no evidence of late radiation damage to the brain, spinal cord or optic apparatus, and no documented evidence of pituitary dysfunction thus far.

Discussion

The rarity of skull base tumours and their location make both surgery and radiotherapy technically difficult. Their relative resistance to radiotherapy imposes an additional

Table 3 e Details of radiotherapy including phase 1 target volume coverage

Patient	Total dose (Gy)/fraction	Phase I dose/fraction	GTV target volume (cm ³)	PTV (1) target volume (cm ³)	PTV (1) Maximum dose (%)	Minimum dose (%)	EUD (%)
1	62/31	62/31	76.3	201.0	105.3	41.7	65.9
2	65/39	50/30	13.5	70.4	105.3	82.9	98.5
3	65/39	50/30	8.2	107.5	105.6	90.2	98.0
4	65/39	50/30	59.7	116.9	109.5	91.3	99.1
5	65/39	65/39	0	204.4	111.4	60.4	86.8
6	65/39	50/30	18.1	68.9	108.8	90.1	100.6
7	65/39	65/39	7.1	41.2	104.5	88.8	99.3
8	65/39	60/36	0	18.6	102.1	88.7	98.8
9	65/39	55/33	0	203.7	103.1	19.3	32.3
10	60/36	55/33	0	288.7	110.2	79.0	100.0
11	65/39	50/30	0	67.6	105.5	75.9	95.4
12	65/39	60/36	0	224.3	106.1	64.1	90.1

GTV, gross tumour volume; PTV, planning target volume; EUD, equivalent uniform dose. For EUD calculation: α $\frac{1}{4}$ 15. PTVs larger than 200 cm³ are shown in italic; minimum doses and EUDs less than 80% are shown in bold.

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5	65	19.7	Yes – metastases only	Dead	6.7	19.7
6	65	21.6	No	Dead†		21.6
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9	65	8.4	No	Alive		
10	60	107.5	No	Alive		
11	65	98.2	No	Alive		
12	65	17.5	No	Alive		

*Cause of death myocardial infarction (chordoma present). †Cause of death gastric carcinoma (local control of chordoma).

Both patients who have died with disease suffered from chordoma, whereas the three patients with chondrosarcoma are all still alive and disease free. The histology of these three chondrosarcoma patients included one each of well-differentiated, moderately differentiated and poorly differentiated tumours. This differs from the series reported from the Heidelberg group [10], using carbon ions, which only included well-differentiated tumours — again with our small numbers this is an observation, but does not give further conclusions.

Tables 2 and 3 detail the size of the target volume and the radiation dose prescribed and delivered to the initial phase target volume for the 12 cases. In six cases there was no macroscopic residual tumour remaining at the time of radiotherapy planning (i.e. GTV = 0 cm³), but in two cases, including the patient treated with palliative intent, the GTV was large. The mean GTV for the whole series was 15.2 cm³. The size of the phase I PTV was much larger in most cases, in order to encompass the original tumour bed. The mean phase I PTV was 134.4 cm³.

We used the phase I PTV for dose evaluation. Compared with a prescribed dose of 100%, the median maximum dose was 105.6%; the median minimum dose was 81.0%. The median EUD for the phase I PTV, calculated using a value for the exponent a of -15 (discussed below), was 98.3%. The phase I EUD was below 80% in two cases, one of which had a very large (residual) GTV and a large accompanying PTV (patient 1). This patient failed locally. The other patient with a low EUD had no residual gross tumour, and remains disease free, albeit with an early follow-up of 8.4 months.

The patients currently under review have no evidence of late radiation damage to the brain, spinal cord or optic apparatus, and no documented evidence of pituitary dysfunction thus far.

Discussion

The rarity of skull base tumours and their location make both surgery and radiotherapy technically difficult. Their relative resistance to radiotherapy imposes an additional

Table 3 – Details of radiotherapy including phase 1 target volume coverage

Patient	Total dose (Gy)/fraction	Phase I dose/fraction	GTV target volume (cm ³)	PTV (1) target volume (cm ³)	PTV (1) Maximum dose (%)	Minimum dose (%)	EUD (%)
1	62/31	62/31	76.3	201.0	105.3	41.7	65.9
2	65/39	50/30	13.5	70.4	105.3	82.9	98.5
3	65/39	50/30	8.2	107.5	105.6	90.2	98.0
4	65/39	50/30	59.7	116.9	109.5	91.3	99.1
5	65/39	65/39	0	204.4	111.4	60.4	86.8
6	65/39	50/30	18.1	68.9	108.8	90.1	100.6
7	65/39	65/39	7.1	41.2	104.5	88.8	99.3
8	65/39	60/36	0	18.6	102.1	88.7	98.8
9	65/39	55/33	0	203.7	103.1	19.3	32.3
10	60/36	55/33	0	288.7	110.2	79.0	100.0
11	65/39	50/30	0	67.6	105.5	75.9	95.4
12	65/39	60/36	0	224.3	106.1	64.1	90.1

GTV, gross tumour volume; PTV, planning target volume; EUD, equivalent uniform dose. For EUD calculation: $a = -15$. PTVs larger than 200 cm³ are shown in italic; minimum doses and EUDs less than 80% are shown in bold.

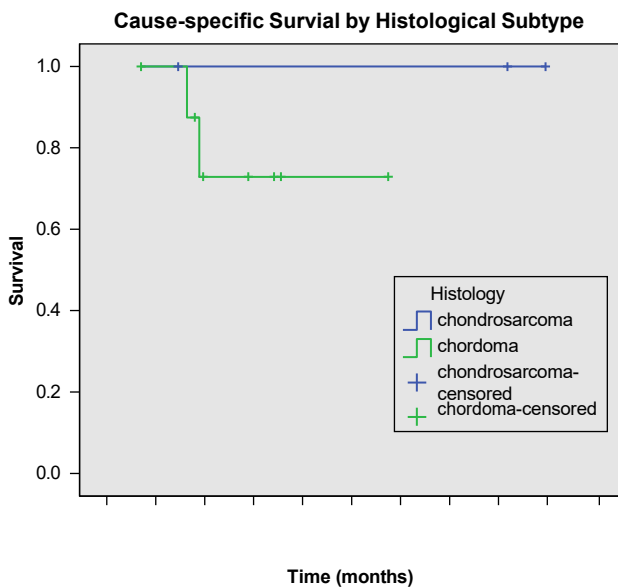


Fig. 2 e Kaplan-Meier plot showing disease-free survival by histological subtype.

difficulty. A review of recent published studies suggests that maximal surgery followed by high-dose radiation therapy should be the standard of care for these patients.

This paper details our single centre experience of high-dose postoperative radiotherapy delivered using photon radiation to 12 cases of skull base tumours. The results are encouraging, although follow-up remains relatively short, at a median time of 3 years and from past publications it can be seen that the fall off in survival continues inexorably for chordomas.

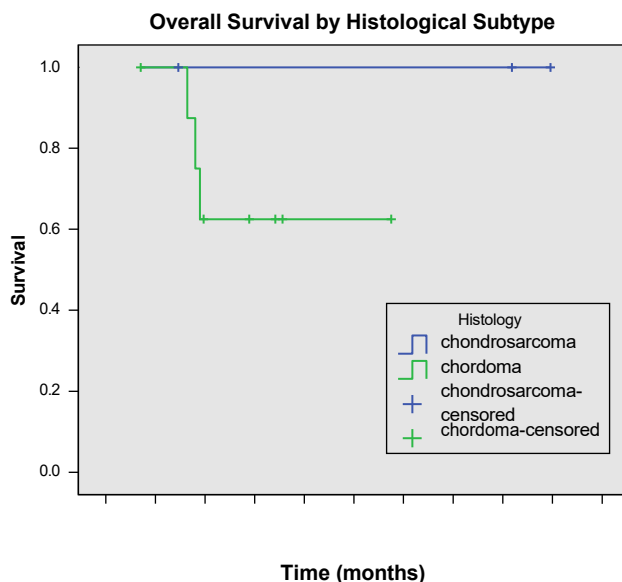


Fig. 3 e Kaplan-Meier plot showing overall survival by histological subtype.

Clinical Series

In our series of 12 patients, 11 achieved local control (defined by no clinical or radiological evidence of recurrence at the primary site at the most recent follow-up visit). The patient who failed had a very large, rapidly growing recurrence after surgery, which was abutting the spinal cord. The details have been outlined above, but with a survival of almost 5 years from the first treatment, this case suggests a useful role for radiotherapy as a palliative treatment, provided high doses are used.

Sadly, one patient with chordoma developed metastatic disease, which proved unresponsive to any further treatment. Metastasis occurred early after radiotherapy, despite local control being maintained. This raises the possibility of microscopic dissemination before surgery and radiotherapy. Earlier diagnosis and treatment is the only method that might have improved her outcome.

A third patient died of gastric cancer, with no evidence of recurrence of his chordoma. The remainder of the patients were disease free at the last review, with a median follow-up of 3 years. It is also important that none of the patients has so far developed late normal tissue toxicity affecting the brain, spinal cord or optic pathways. Most had PTVs located below the level of the pituitary, and none has experienced pituitary dysfunction.

The Boston group [11] have found gender to be an independent predictor of local control for skull base but not spinal chordomas, with men doing significantly better than women. Our series, of five women and seven men, was too small to draw any conclusions about outcome according to gender.

On review of published studies regarding the outcome of skull base tumours, a number of points are apparent regarding surgery and radiotherapy. It is clear that surgery alone is not curative; it is, however, important to achieve maximal debulking, and studies have shown improved local control with radical (total or near-total) resection [4,19,20]. This also delivers a reduction in the GTV, which facilitates radiotherapy planning. However the risk of damage to adjacent structures from surgery must be taken into account [4,19]. It is preferable to have a specialist skull base surgical team to provide optimal surgery, both to optimise tumour resection and minimise co-morbidity.

The excellent results in our small series are undoubtedly due in part to high-quality surgery preceding radiotherapy and prompt referral for radiotherapy, thus avoiding a 'wait and see' approach with subsequent radiotherapy to an established recurrence or after further surgical attempts. Most of our patients had either complete or near-total resection of their tumour, and in six cases no postoperative GTV was present. In only two patients was there a substantial residual volume post-surgical resection (Table 3). Therefore, the treatment strategy outlined here might be less successful in patients with larger residual tumour volumes. It may also be the case that selection has played a role in this series <1 patients with more advanced disease may not necessarily have been referred to the skull base team, although we doubt that this has occurred.

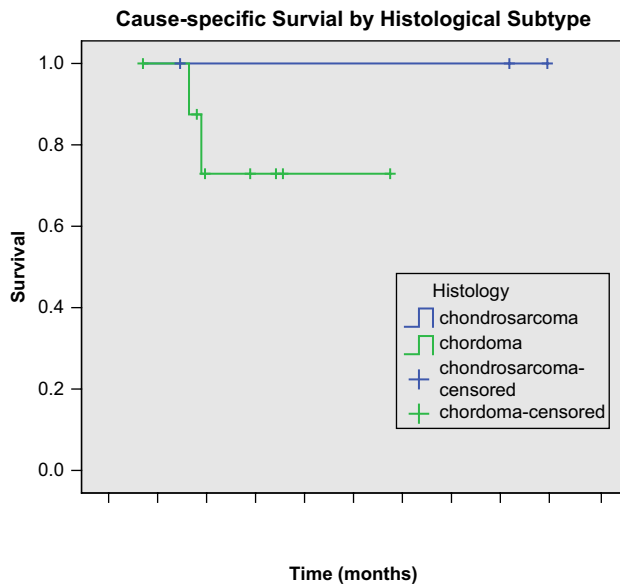


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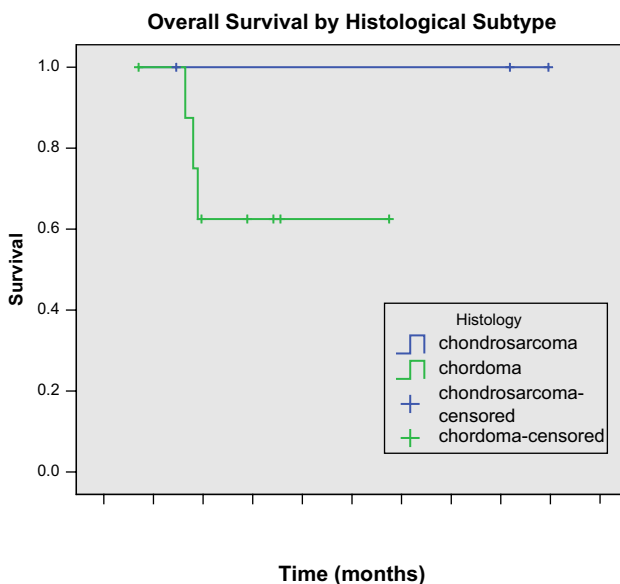


Fig. 3 — Kaplan–Meier plot showing overall survival by histological subtype.

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Radiotherapy given after surgical resection seems to add to the local control of these skull base tumours. The optimal dose for local control of chordoma is not defined, although increasingly a dose-response relationship is suggested, with improved outcome at doses over 60–65 Gy [5,7,9,11,21]. In a review from the Paris group, where patients were treated with a combination of 75% photons and 25% proton radiation, the median total dose was 67 cobalt Gray equivalent (CGE), delivered to the GTV [9]. CGE is obtained by multiplying the proton dose (Gy) by 1.1, which represents the average relative biological effectiveness of protons relative to ^{60}Co . The results from the Paris group showed 2- and 5-year overall survival of 94.3 and 80.5%, respectively; the local control rate was 86.3% at 2 years. The Heidelberg data [10] for carbon ion radiotherapy delivered a median dose of 60 CGE, again to the GTV, but treatment was given in 20 fractions over 20 days (i.e. a highly accelerated programme). They showed local control rates of 81% for chordoma and 100% for chondrosarcoma at 3 years; the actuarial 3-year overall survival for all patients was 91%. The Boston group [11] delivered a median dose of 68.9 CGE but over a protracted duration using 1.8 Gy per fraction five times per week. Their local control rates were 59% at 5 years and 44% at 10 years of follow-up.

In our series, a planned dose of 65 Gy was possible for 10 of the 12 cases, and 62 and 60 Gy for the remaining two cases. This radiotherapy was given with photons throughout, using a combination of static fields and arcs. An immobilisation device was always used, and where appropriate this was a relocatable stereotactic frame. Because six of the 12 cases had no postoperative GTV present, it is difficult to compare doses directly between our series and published reports, where the dose to the GTV is a parameter used to define the dose.

Prescribed Dose and Dose Homogeneity

It is increasingly apparent in this group of tumours that the prescribed dose does not correlate well with outcome and local control. Rather, it is the minimum dose delivered to the target that reflects outcome better than the maximum, mean or median dose [11]. The homogeneity of the dose across the target volume seems to correlate strongly with local control in these tumours. A particularly useful measure of the homogeneity of the delivered dose is described by the EUD. The concept of the EUD is a biologically equivalent dose that if given uniformly would result in the same tumour cell kill as the actual delivered inhomogeneous dose distribution [17]. The larger the EUD, the higher the tumour control probability. Other studies have highlighted the correlation of dose uniformity within the target volume [22]. It is often the dose constraints to OARs adjacent to the target volume that lead to compromise in the homogeneity of the delivered dose and consequently reduce the predicted tumour control probability.

For the EUD calculation, we used a value of 15 (A. Niermiero, pers. commun.) for the exponent α in the generalised EUD formulation [17,18]. The choice of this

value gives relative weighting to areas of low dose within the target volume, and is the best estimate by the Boston group of the value of α for chordoma and chondrosarcoma (A. Niermiero, pers. commun.).

Overall, the dose homogeneity within the phase I PTV was good, with mean and median EUDs of 88.7 and 98.3% of the prescribed dose, respectively (Table 3). It is interesting to note that in our series the one patient to develop local recurrence so far had rapid re-growth of his tumour after surgery and therefore had a significant GTV at the time of radiotherapy planning. On review of his dosimetry, the minimum dose to the PTV was 41.7% (the second lowest value of the 12 cases) and the EUD was 65.9% – also the second lowest value seen in this series. Thus, his case combined the largest volume of tumour with a low value of EUD, albeit in a palliative setting. The patient who developed metastatic disease also had a low value for the minimum dose to the PTV (60.4%), but the EUD was more acceptable at 86.8%.

The most recently treated chordoma patient (patient 9) had a very low minimum dose and EUD (19.3 and 32.3%, respectively). He had no residual tumour after surgery (i.e. GTV ¼ 0). This patient had very severe learning difficulties and required enteral feeding via a percutaneous endoscopic gastrostomy tube. Radiation treatment abroad was not considered feasible and this was the most acceptable plan achievable with conformal radiotherapy.

Charged Particle Radiotherapy

An additional method for improving the physical dose distribution of radiation treatment for these tumours is the use of charged particles, especially protons. There is increasing interest in particle radiotherapy, particularly in difficult tumour sites and paediatric cases [23]. A number of published studies support the use of protons, or carbon ions, for skull base tumour radiotherapy [10,12], although in some centres the reality is often a combination of photon and particle radiation due to time constraints of the particle facility [8,9,11]. However, the advent of advanced imaging, planning and delivery of photon radiotherapy over the past one to two decades has provided opportunities for delivering high doses safely for patients with skull base and cervical spine tumours. Under some conditions, advanced photon radiotherapy may be sufficient [4], and may be necessary for UK patients who are unsuitable for referral abroad. It seems probable that dose distributions will be superior with proton or carbon ion radiotherapy, even if dose plans are deemed ‘acceptable’ with photons. The implication is that there should be better tumour control and/or fewer side-effects, such as contralateral hearing loss/brain atrophy and radiation-induced second malignancies.

The use of particle radiotherapy in patients with these tumours is also supported by the National Institute for Health and Clinical Excellence (NICE). The Evidence Review in Improving Outcomes for People with Brain and Other CNS Tumours [24] considers that proton radiotherapy is the current standard of care for patients with chordomas and

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