The value of image-guided intensity-modulated radiotherapy in challenging clinical settings

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Objective: To illustrate the wider potential scope of image-guided intensity-modulated radiotherapy (IG-IMRT), outside of the "standard" indications for IMRT.

Methods: Nine challenging clinical cases were selected. All were treated with radical intent, although it was accepted that in several of the cases the probability of cure was low. IMRT alone was not adequate owing to the close proximity of the target to organs at risk, the risk of geographical miss, or the need to tighten planning margins, making image-guided radiotherapy an essential integral part of the treatment. Discrepancies between the initial planning scan and the daily on-treatment megavoltage CT were recorded for each case. The three-dimensional displacement was compared with the margin used to create the planning target volume (PTV).

Results: All but one patient achieved local control. Three patients developed metastatic disease but benefited from good local palliation; two have since died. A further patient died of an unrelated condition. Four patients are alive and well. Toxicity was low in all cases. Without daily image guidance, the PTV margin would have been insufficient to ensure complete coverage in 49% of fractions. It was inadequate by >3 mm in 19% of fractions, and by >5 mm in 9%.

Conclusion: IG-IMRT ensures accurate dose delivery to treat the target and avoid critical structures, acting as daily quality assurance for the delivery of complex IMRT plans. These patients could not have been adequately treated without image guidance.

Advances in knowledge: IG-IMRT can offer improved outcomes in less common clinical situations, where conventional techniques would provide suboptimal treatment.

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The recent advances in radiation delivery can improve tumour control probability and reduce treatment-related toxicity. The use of intensity-modulated radiotherapy (IMRT) allows for an improved radiation dose distribution compared with conventional techniques, ensuring safe dose escalation in selected cases. However, IMRT treatments are less forgiving of set-up inaccuracies owing to steep dose gradients. The integration of image-guided radiotherapy (IGRT) to the IMRT workflow (IG-IMRT) not only enables correction for set-up errors in real time but also permits tighter planning margins.

Currently, there is limited evidence on the clinical benefits of IGRT. In addition, patients need to be clinically prioritised for IMRT, owing to limited capacity in the UK. This report illustrates the wider potential of IG-IMRT, where the integration of an IG-IMRT approach allows for radiation treatment which would be considered as non-feasible with conventional techniques.

The success of radiotherapy in ablating a tumour depends principally on the total radiation dose, but this dose is limited by the tolerance of the surrounding normal tissues. Techniques such as three-dimensional conformal

radiotherapy (3D-CRT) and, more recently, IMRT have allowed for a reduction in normal tissue dose, and therefore toxicity, for a given level of tumour dose. In turn, this may allow for dose escalation, with the expectation of a higher probability of tumour control. In some circumstances, IMRT enables treatment which might previously have been entirely impossible because of toxicity.

There is now excellent evidence of the clinical value of IMRT in reducing toxicity by sparing the dose to the surrounding healthy tissue in various tumour sites [1–6]. These results are consistent with the fundamental proof of principle that better dose distributions lead to improved outcomes.

One of the capabilities of IMRT is the ability to deliver very steep dose gradients where the target lies close to a critical normal structure. The dose may drop rapidly over just a few millimetres (e.g. 12 Gy over 3 mm), which may have important clinical value. However, it also makes IMRT less forgiving of set-up inaccuracies. In this situation, some form of image guidance to verify that the gradient is correctly located before treatment is desirable, for the dual goals of achieving an adequate target dose (avoiding geographical miss) and minimising the dose to normal tissues (avoiding excess toxicity). IGRT therefore acts as a quality assurance measure for the delivery of high-quality IMRT [7].

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The existence of discrepancies (positional errors) in patient set-up, resulting from a combination of systematic and random errors, is well understood [8, 9]. For a mobile structure, such as the prostate, this also includes an important contribution from random day-to-day variation in the position of the prostate within the patient [10]. Image guidance has been revolutionised by the integration of online imaging capability on linear accelerators, with full software integration for image matching and positional correction. It allows for correction of positional discrepancies in real time, before treatment, so that each daily treatment can be accurately targeted, potentially allowing for tighter planning margins or greater security of target coverage. It also provides an opportunity for treatment adaptation based on changes in tumour volume or patient anatomy [11, 12]. IGRT also has a role in quantifying positional discrepancies. It is likely that IGRT will at least contribute to more reliable target volume coverage, as well as a reduction in dose to the surrounding normal tissue [11, 13]. In this way, IGRT is complementary to IMRT. However, caution is required, given that IGRT does not necessarily allow for planning target volume (PTV) margin reduction [14].

Initial estimates for the expansion of the national IMRT programme suggested that 33% of radical fractions should be delivered with IMRT to maximise the clinical benefit from radiotherapy [15]. This figure of one-third was composed of 24% inverse-planned IMRT cases and 9% forward-planned IMRT cases. These figures have been helpful in developing the national service, but may need to be revised upwards. Significant progress is being made in the roll out of IMRT in the UK [16]. In general, the experience of centres treating with IMRT is that it has wider applicability, particularly when combined with IGRT

[17–19]. Nevertheless, limitations in capacity are common, so it is necessary to prioritise those cases for which IG-IMRT is considered likely to give the greatest benefit. For tumours in the head and neck, the close proximity of the target to other structures makes IMRT an attractive option, and the evidence for reduction in long-term side effects with IMRT is most notable in this site. Image guidance is attractive for mobile internal targets such as the prostate [10, 18]. Many other sites may also benefit from the combined techniques.

The process of clinical prioritisation is a key component of IMRT service implementation [18, 20–24]. This is simple for tumour sites where evidence of benefit exists. However, it may not be possible to generate such evidence for all tumour sites, nor should this be expected. In addition, there are situations in which it is impossible to achieve a worthwhile tumour dose without the use of IMRT. In our initial IG-IMRT series this amounted to 5% of cases [18].

We report on a group of challenging clinical cases (Table 1) in which we believe IG-IMRT offered advantages over “standard” conformal treatment. These cases illustrate the wider potential scope of IG-IMRT outside of the standard indications for IMRT.

There are different technical solutions for IG-IMRT and we used the TomoTherapy HiArt™ system (TomoTherapy Inc., Madison, WI) for IG-IMRT delivery. The concepts described here also apply to other platforms using rotational therapy.

Patients and methods

All patients were treated in our department between January 2009 and January 2011. During this period an

Table 1. Illustrative cases and reasoning for the choice of image-guided intensity-modulated radiotherapy (IG-IMRT)

Case	Diagnosis	Age (years)	Summary and reasoning for use of IG-IMRT	F/U (months)	Local recurrence	Metastatic disease	Outcome
1	Pelvic Ewing's sarcoma	18	Radical treatment, sparing normal tissue structures	24	No	No	Alive
2	Chest wall chondrosarcoma	18	Radical treatment for patient with normal anatomy, where radical treatment was not possible with CRT owing to OAR constraints	24	No	Yes	Alive
3	Prostate adenocarcinoma	53	Radical treatment for patient with challenging (abnormal) anatomy	21	No	No	Alive
4	Carcinoma of the larynx (post op)	54	Radical treatment for patient with challenging (abnormal) anatomy	1	No	No	Died
5	Prostate and rectal adenocarcinomas	76	Radical treatment of synchronous tumours simultaneously	23	No	Yes	Died
6	Carcinoma of the cervical oesophagus	68	Radical treatment following previous radiotherapy (occurrence of a different tumour)	13	No	No	Alive
7	Nasopharyngeal carcinoma	60	Radical retreatment (recurrence of the same tumour)	15	Yes	No	Alive
8	Carcinoma of the cervix	38	Radical retreatment (recurrence of the same tumour)	15	No	Yes	Died
9	Vertebral chordoma	39	Substitute for proton therapy in patients with metal reconstruction	30	No	No	Alive

CRT, conformal radiotherapy; F/U, follow-up; OAR, organ at risk; post op, post operation.

average of 443 cases per year were treated on our 2 TomoTherapy units, out of approximately 1930 radical cases (23%). We expect approximately 20 cases per year (*i.e.* 5% [18]) to have difficult clinical scenarios requiring IG-IMRT outside of the conventional indications. Patients were immobilised using site-specific immobilisation techniques and planning scans were acquired on a CT scanner with a 3-mm slice thickness. The target volume and organs at risk (OARs) were outlined as per department protocols. The PTV and planning organ at risk volume (PRV) margins were modified in selected cases because all patients received daily image guidance prior to treatment delivery. The PTV and PRV margins are described in more detail with the individual cases, and listed in Table 2.

Image acquisition on TomoTherapy

For each patient each day, a fan beam megavoltage CT (MVCT) scan was acquired, with an in-plane resolution of 0.78 mm at the bore centre, using a mean beam energy of 0.75 MeV [25]. The scan length was kept as short as possible, with a nominal slice thickness of 6 mm. The typical imaging dose was 0.9 cGy for a 6-mm slice thickness.

Image matching

The daily MVCT image was compared with the imported kilovoltage CT planning scan, using pre-agreed match structures. Image matching was led by a radiographer and performed in two steps, as described previously [18]. First, a rapid automated match was undertaken, measuring discrepancies in all six translational and rotational directions, to exclude any gross error in the patient's position. Second, the matching was repeated rapidly with four degrees of freedom, measuring discrepancies in all translational directions plus roll, which can be corrected on the TomoTherapy units. The automated matching was then refined manually and optimised by the treatment radiographers. Action levels for positional correction were set at 1 mm for translations and 1° for roll, which represents the resolution of the couch controls. In reality, virtually all patients had daily corrections applied. The positional corrections were recorded in an in-house bespoke database.

Assessment of image guidance

To determine the practical importance of online IGRT in these cases, the frequency with which the clinical target volume (CTV) would be outside of the PTV margin under a lesser image guidance regime was determined. The PTV margin was used as a surrogate for the 95% isodose. The hypothetical comparison regimen consisted of online IGRT for the first three fractions, with the mean correction so determined applied to the remaining fractions without further imaging [26]. For this comparison, only translational shifts were considered, although the translational impact of the applied roll correction was also accounted for when the target

Table 2. Summary of fractionation schedules and margins used for each case, with three-dimensional (3D) positional errors and estimates of the percentage of fractions where the clinical target volume (CTV) position would have been outside the planning target volume (PTV) margin used, compared with "first three fraction" correction image-guided radiotherapy

Case	Primary tumour	Total dose (Gy)	Number of fractions	CTV-PTV margin (mm)	PRV cord (mm)	Average 3D displacement (mm)	% of fractions where the CTV-PTV margin would have been inadequate	% of fractions where the CTV-PTV margin would have been inadequate by >3 mm	% of fractions where the CTV-PTV margin would have been inadequate by >5 mm
1	Ewings sarcoma, right ileum	64	30	8	N/A	5.3	17	0=	0
2	Chondrosarcoma, chest wall	60	30	8	Canal ^a	2.2	0	0	0
3	Prostate	60/48	20	5-10 ^b	N/A	6.1	70	15	5
4	Larynx (post op)	60	30	5	3	11.9	90	67	47
5	Rectum	50/45	25	20	N/A	5.2	56	24	12
6	Prostate	64/52	25	5-10 ^b					
7	Cervical oesophagus (post op)	60	30	5	3	6.0	67	27	3
8	Nasopharynx (recurrence)	50	30	3	3	2.1	17	0	0
9	Cervix, PA nodal recurrence	60	30	5	3	4.8	41	17	3
9	Chordoma, T12	70	39	5	1 ^c	5.9	80	21	10

N/A, not applicable; PA, para-aortic; post op, post operation; PRV, planning organ at risk volume.

^aFor this case, the whole spinal canal was outlined, which produced a small margin on the cord itself. The cord was entirely within the PTV, but planned to receive a slightly lower dose (54 Gy) than the remaining bulk of the PTV, defined as the PTV-PRV.

^bFor Cases 3 and 5 (prostate carcinoma), the smaller CTV-PTV margin of 5 mm is used for the calculations.

^cFor Case 9 the CTV-PTV margin was constrained to the PRV, which had a margin of 1 mm around the spinal cord, and therefore had an effective posterior margin of 1 mm for some of the volume.

volume was significantly distant from the centre of the data set. For each patient, the mean 3D error resulting from the lesser image guidance regime was calculated, along with the percentage of fractions in which the 3D error was greater than the CTV-PTV margin and the percentage in which the 3D error exceeded the CTV-PTV margin by >3 mm or >5 mm, respectively.

In Cases 2 and 9, the PTV extended into the spinal cord PRV. In each case an additional volume was produced: the PTV-PRV. This was used for planning. For Case 9, the effective posterior margin for much of the PTV was 1 mm, and the analysis treats any posterior shift of >1 mm as compromising CTV coverage.

Case examples

A summary of the cases and rationale for the use of IG-IMRT is given in Table 1. The set-up errors for the individual cases, which were corrected before treatment, are presented in Table 2.

Radical treatment, sparing normal tissue structures

Case 1

An 18-year-old female presented with localised Ewing's sarcoma of the right iliac bone. Prior to starting vincristine, ifosfamide, doxorubicin and etoposide (VIDE) chemotherapy, she was commenced on a luteinising hormone releasing hormone agonist to produce transient ovarian suppression during chemotherapy, as a means of preserving ovarian function [27]. Because radiotherapy was also required, both ovaries were moved out of the pelvis laparoscopically to avoid radiotherapy damage to ovarian function.

In contouring the target volumes, a CTV-PTV margin of 8 mm was used [28]. The whole pre-chemotherapy volume was treated to 54 Gy, the iliac bone to 60 Gy, and the post-chemotherapy residual disease to 64 Gy, delivered in 30 fractions using IMRT.

The target volume was in close proximity to the utero-vaginal complex. IMRT allowed for the sculpting of a

high dose away from the central pelvic area (Figure 1). The addition of image guidance allowed for a reduction of the CTV-PTV margin, from a conventional 20 mm (as per the European Ewing Tumour Working Initiative of National Groups protocol [29]) to 8 mm. The result of the combination of image guidance and IMRT was that the planned dose to the utero-vaginal complex was <19 Gy, with the potential for preservation of long-term function for fertility. In addition, the security of the target volume coverage was maximised. After 24 months' follow-up the patient remained disease free and pelvic ultrasound demonstrated normal uterine vasculature and blood flow.

Radical treatment for patients with normal anatomy but where radical treatment is not possible with CRT owing to OAR constraints

Case 2

An 18-year-old male presented with a $13 \times 10 \times 11$ cm right upper chest wall mass eroding the ribs, and encroaching into the spinal canal with impending spinal cord compression at T2-T3. He was treated with surgical posterior spinal decompression and debulking of the tumour from the spinal canal with fixation from C5 to T6. This was followed by right thoracotomy, excision of the chest wall lesion and excision of a new 3×2 cm tumour at T2. The early appearance of the new lesion suggested rapid tumour growth. Histology confirmed grade 3 chondrosarcoma. The patient was treated with six cycles of VIDE chemotherapy followed by high-dose radiotherapy.

The pre-operative tumour bed extended along the pleura of the right lung anteriorly, and around the spinal cord posteriorly. Given the double curvature of the target around the chest wall (axially and superoinferiorly), and the proximity of the spinal cord, a dose of ≥ 60 Gy was considered impossible to deliver safely using 3D-CRT without breaching OAR (lung and spinal cord) constraints. IMRT allowed for the pre-operative pleural-based tumour bed to be covered to 60 Gy, and the spinal canal to 54 Gy, in 30 fractions (Figure 2).

Figure 1. Case 1, pelvic Ewing's sarcoma.

Figure 2. Case 2, chest wall chondrosarcoma.

To plan this treatment, the CTV was expanded into the PTV with a margin of 8 mm [28], and the spinal canal was outlined as the cord PRV. Where the PTV overlapped the PRV, a new target volume was produced—the PTV–PRV—by subtracting the overlap region. This new volume was used for planning, although the priority was given to the dose limit of the PRV.

24 months following the completion of radiotherapy, the patient's local disease remained controlled and he is ambulant with no neurological deficit. Unfortunately, he is now receiving further treatment for metastatic sarcoma.

Radical treatments for patients with challenging anatomy

Case 3

A 53-year-old male with a T1c (MRI T_2) N0 M0 Gleason 3+4 prostate adenocarcinoma with a presenting prostate-specific antigen (PSA) of 10.9 ng ml^{-1} was referred for consideration of radical radiotherapy. His weight was 148 kg, with a body mass index (BMI, measured by mass in kilograms divided by height in metres squared) of >40 . Neither brachytherapy nor fiducial marker insertion were felt to be technically feasible, but there was also concern regarding the accuracy of positioning using either skin marks or pelvic bone verification because of his size. Therefore, the decision was made to use daily online volumetric image guidance. He was treated with IG-IMRT

to a dose of 60 Gy in 20 fractions over 4 weeks. The standard CTV–PTV margin of 10 mm was used (Figure 3).

Our calculations suggest that, without daily image guidance, 70% of the treatment fractions would have been positioned beyond the PTV margin, with a consequent reduction in dose to the prostate (Table 2). It is likely that this would have compromised local tumour control. The patient remained well 21 months following radiotherapy, with no long-term toxicities and with biochemical PSA control.

Case 4

A 54-year-old male underwent a total laryngectomy for a T4a N0 M0 supraglottic squamous cell carcinoma of the larynx. Post-operative treatment was recommended to optimise local control. However, the patient also suffered from severe ankylosing spondylitis, with significant kyphosis, and was unable to lie flat or hold his neck in a neutral position. Conventional immobilisation thus proved to be impossible. He was therefore immobilised using a vacuum bag technique. His performance status and comorbidities were considered to be contraindications to chemotherapy, so he received 60 Gy in 30 fractions over 6 weeks with IG-IMRT (Figure 4).

The 5-mm CTV–PTV margin for head and neck cancer in our unit is based on the use of a thermoplastic immobilisation shell. If vacuum bags alone are used for immobilisation, the CTV–PTV margin would normally require a significant increase to accommodate lower set-up precision. In this patient the minimum distance from

Figure 3. Case 3, prostate adenocarcinoma.

Figure 4. Case 4, carcinoma of the larynx.

the PTV to the spinal cord PRV was 1.5 mm. Using daily image guidance, we were able to keep a CTV-PTV margin of 5 mm while also respecting the cord PRV, allowing for safe delivery of the prescribed dose to the target volume without compromising the OARs. Unfortunately the patient died of pneumonia shortly after completion of radiotherapy.

Radical simultaneous treatment of synchronous tumours

Case 5

A fit 76-year-old male was found to have a rectal adenocarcinoma following investigation for rectal bleeding. MRI revealed a T3 tumour within 1 mm of the circumferential margin, but also a suspicious prostate lesion. Subsequent biopsy confirmed a synchronous T2 N0 Gleason 4+5 prostate adenocarcinoma.

Radiotherapy with androgen deprivation was considered to be the optimum treatment for the patient's high-risk prostate carcinoma, and long course pre-operative chemoradiotherapy for his high-risk rectal carcinoma. It was decided to treat both tumours simultaneously with IG-IMRT (Figure 5). He was commenced on goserelin implants and, in addition, received 3 months' neoadjuvant chemotherapy, per the EXPERT trial [30].

The simultaneous treatment of prostate and rectal carcinomas requires IMRT, to allow for synchronous delivery of different doses to the two target areas with a steep dose gradient between the two. This patient received 64 Gy in 25 fractions over 5 weeks to his

prostate (equivalent dose in 2 Gy fractions=74 Gy using an α/β ratio of 1.5 [31]); and 45 Gy in 25 fractions to the mesorectum, boosting the rectal gross tumour volume (GTV) to 50 Gy. However, both the prostate and the rectum are mobile organs. We used image guidance with the prostate protocol correction to ensure that the prostate remained within the high-dose region, and in addition confirmed that the rectal tumour was adequately covered by the treatment isodose for each fraction, avoiding geographical miss.

The patient went on to have a Hartmann's procedure, the histology showing no residual invasive adenocarcinoma—ypT0 ypN0 (0/22). He continued on adjuvant androgen deprivation with excellent PSA control. Unfortunately he developed lung and liver metastases from his rectal tumour, although with local control maintained, and died 23 months later.

Radical treatment following previous radiotherapy (for a different tumour)

Case 6

A 68-year-old female was diagnosed with a cervical oesophagus squamous cell carcinoma. 11 years previously she had received prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine and methotrexate chemotherapy for a mediastinal sclerosing B-cell non-Hodgkin lymphoma, followed by 40 Gy in 20 fractions over 4 weeks to a mini-mantle field, at another centre. It was not possible to retrieve the details pertaining to her previous radiotherapy.

Figure 5. Case 5, prostate and rectal adenocarcinomas.

The current tumour was situated within the previous treatment field. She underwent a pharyngolaryngectomy and oesophagectomy with a radial forearm free flap reconstruction. Histopathology confirmed a pT3 N0 moderately differentiated squamous cell carcinoma with extensive perineural invasion, and a close circumferential margin posteriorly. Post-operative radiotherapy was recommended to a dose of 60 Gy in 30 fractions over 6 weeks. Other comorbidities precluded the use of concurrent cisplatin.

Assuming a spinal cord tolerance of 48 Gy in 2-Gy fractions [32], and at least 50% recovery of the spinal cord following the previous radiotherapy [33], this treatment was planned with a dose constraint of 28 Gy to the spinal cord PRV. We used a 5-mm margin for CTV-PTV, as is standard for head and neck radiotherapy in our centre, and a spinal cord PRV margin of 3 mm. With IMRT our plan achieved a maximum dose of 26 Gy to the cord PRV (Figure 6).

The PRV spinal cord came within 9 mm of the 60 Gy volume. Daily image guidance allowed for more accurate targeting, and ensured that the spinal cord did not stray into the high-dose volume, allowing the treatment to be delivered safely. The patient was free of disease recurrence 13 months following radiotherapy.

Radical retreatments (recurrence of the same tumour)

Case 7

A 60-year-old male with a T4 N1 M0 nasopharyngeal carcinoma received radiotherapy to a total dose of 68 Gy in 34 fractions over 7 weeks with concomitant cisplatin in 2005. This was delivered using lateral parallel opposed fields to cover the primary tumour, matched to an anterior split neck field, with added electron fields to treat the posterior neck, a technique conventional at that time. The boost to the primary site (Phase 3) was delivered conformally, with a CTV-PTV margin of 5 mm. The patient had a complete response and remained disease free for 5 years.

Unfortunately, he then presented with a 15-mm recurrent nasopharyngeal carcinoma anterior to the right side of the lateral mass of C1 and the skull base. The previous plan was available and analysis showed a maximum dose to the spinal cord of $42.2 \text{ Gy} \pm 5\%$, although the contribution of the electron fields was not included in this dose calculation. It was decided to proceed with re-irradiation to the local disease.

The patient was treated radically with IG-IMRT to a dose of 50 Gy in 30 fractions over 6 weeks. The OARs included the spinal cord and brain stem, as well as both

Figure 6. Case 6, carcinoma of the cervical oesophagus.

globes and optic nerves, and both temporal lobes. It was accepted that the recurrent tumour was too close to the right temporal lobe for the dose to be limited. The aim was to constrain the brain stem to <13 Gy and all other OARs to <10 Gy to potentially reduce the risk of both acute and long-term toxicities (Figure 7).

A GTV-CTV margin of 5 mm, edited around bone, and a CTV-PTV margin of 3 mm, rather than the more conventional 5 mm, were used. IMRT allowed for a steep dose gradient between the target volume and OARs. Daily image guidance and set-up correction allowed the CTV-PTV margin to be reduced, achieving dose constraints for the OARs, while still confidently delivering a high dose to the PTV. The minimum distance from the 50-Gy volume to the brain stem PRV was 3 mm.

Unfortunately the patient developed a further recurrence within the re-irradiated volume 12 months after the completion of radiotherapy, and has commenced palliative chemotherapy. He has no late neurological toxicities at 15 months' follow-up.

Case 8

A 38-year-old female with an International Federation of Gynecology and Obstetrics Stage IIA squamous cell carcinoma of the cervix, grade 2, was treated with radical radiotherapy. She received 45 Gy in 25 fractions over 5 weeks, delivered using a three-field technique, with weekly cisplatin. The superior border of the pelvic field was the L4-L5 junction. This was followed by three high-dose-rate Ir-192 brachytherapy insertions, delivering a total of 20.5 Gy to Point A over 8 days.

4 months after completion of radiotherapy she developed multiple enlarged para-aortic lymph nodes and an 11-mm retrocaval lymph node. There was no evidence of distant metastases or local recurrence. Further radiotherapy, extending the treated volume to include the involved nodes, was felt to be her best chance of achieving long-term local control, with perhaps a small probability of overall cure. She received 60 Gy in 30 fractions over 6 weeks with concomitant weekly cisplatin.

Over the majority of the length of the target volume, the 60-Gy PTV was within 14 mm of the cord PRV. The spinal nerve roots had previously received a relatively high radiotherapy dose, so the dose was sculpted away to avoid overlap. Part of the small bowel had previously received 45 Gy, and in some places more, owing to the contribution of brachytherapy. The median retreatment dose was of the order of 15 Gy. The median dose to the kidneys and liver was estimated to be 15 Gy.

Owing to the target abutting the previous treatment volume and the potential for significant gastrointestinal side effects, she was treated with IG-IMRT (Figure 8). Her mean (corrected) 3D displacement was 4.8 mm (Table 2). Difficulties in set-up reproducibility because of disease-related back pain contributed to this.

Treatment was tolerated extremely well. She continued her normal activities throughout, with fatigue being the only significant problem towards the end of treatment. Unfortunately, she developed metastatic disease from which she died 15 months after completing treatment. At the time of her death, both pelvic and para-aortic regions remained disease free and she had no reported long-term side effects from her radiotherapy.

Figure 7. Case 7, recurrent nasopharyngeal carcinoma.

Figure 8. Case 8, cervical carcinoma.

Substitute for proton therapy in patients with metal reconstruction

Case 9

A 39-year-old male had a resection and metal reconstruction for a chordoma of the T12 vertebra, and was subsequently referred to our centre for consideration of post-operative radiotherapy. Proton therapy was not considered appropriate because his reconstruction contained significant metalwork [34, 35].

High-dose, high-precision irradiation with photons provides an alternative to proton therapy [36]. In our patient, the distance between the spinal cord and the posterior vertebral body was 4 mm. The CTV included the vertebral body, the pedicles, and the intervertebral spaces that had contained soft-tissue extension of the tumour pre-operatively. This volume was grown by 5 mm to produce a PTV. A second volume, the PTV-PRV, was produced by growing the PTV up to the spinal cord PRV, and this was used for planning. The spinal cord PRV was constructed with a 1-mm margin around the spinal cord itself.

With the addition of daily image guidance and positional correction prior to delivering treatment, the dose to the spinal cord can be calculated accurately and minimised, while ensuring treatment accuracy. This patient received 70 Gy in 39 fractions over 8 weeks. The maximum dose to the spinal cord PRV was constrained to <58.6 Gy (equivalent to ~54 Gy in 30 fractions using an α/β ratio of 2) (Figure 9).

Clearly, without daily imaging with positional correction combined with IMRT, this plan could not have been safely delivered (Table 2). The patient tolerated treatment extremely well, returned to work and remained free of recurrence and toxicity 30 months following radiotherapy.

Discussion

These cases have been selected to illustrate the role of IG-IMRT as a potential radiotherapy solution in difficult clinical scenarios. All of these patients were treated with radical intent, although it was accepted that for many the probability of cure was low. The role of high-dose radiotherapy in providing adequate palliation, including achieving sustained local control, must not be discounted, and we believe the addition of image guidance to IMRT provided benefit even in those patients who subsequently relapsed.

There are common themes throughout these nine cases. Many illustrate how we have used IG-IMRT in situations where the PTV is in close proximity to OARs. With IMRT, it is possible to produce plans that keep to the required dose constraints, but concerns over organ motion and set-up inaccuracy mean that, without image guidance, it is not possible to be confident in the accuracy of the dose delivery. With steep dose gradients, even movement of a few millimetres can compromise

Figure 9. Case 9, vertebral chordoma.

both the dose to the target and the dose received by the OARs, potentially exceeding their tolerance.

Although advantages of IMRT over CRT have been demonstrated [1–6], it is unlikely that the degree of clinical benefit from the integration of IGRT and IMRT will ever be tested in a large randomised clinical trial. We await the results of the IG-IMRT substudy within the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial which is currently ongoing [30, www.controlled-trials.com/ISRCTN97182923/97182923]. Image guidance permits confident dose delivery, tackling the issue of accuracy [7]. In addition to knowing that tight dose constraints for OARs have been safely achieved, it can allow for a reduction in the standard CTV–PTV margins without geographical miss, thus limiting the dose to OARs still further, although caution is needed [14].

In Case 1, the patient with the pelvic Ewing's sarcoma, the CTV–PTV margin was reduced from 20 to 8 mm, thus minimising the uterine dose. There is a significant risk of permanent infertility at doses above 20–30 Gy to the uterus, with increased rate of miscarriage [37]. There are also data to support improved local control with higher doses in Ewing's sarcoma, suggesting a dose–response relationship [38, 39]. With image guidance, this reduced

uterine dose was achieved without compromising the dose to the intended target.

The spinal cord is clearly a significant OAR. In Case 2, the patient with the chest wall chondrosarcoma, the PTV extended into the spinal canal, and the aim was to constrain the cord dose to 54 Gy. Lung dose constraints were also an important consideration. With IG-IMRT the patient received a high radical dose (60 Gy) without the OARs being compromised. Without image guidance, this patient would have been treated to a lower dose, hence reducing the likelihood of achieving local control and preservation of neurological function.

We have illustrated the use of an IG-IMRT solution in the presence of challenging anatomy in cases involving a high BMI and severe ankylosing spondylitis. There are other clinical scenarios where this approach may be valuable. For example, breast irradiation in the context of pectus excavatum is not uncommon, and the use of IG-IMRT in this situation has already been described [40].

Case 3 illustrates the problem of geographical miss in obese patients undergoing prostate radiotherapy. Obesity has been reported as an independent predicting factor for biochemical failure after external beam radiotherapy [41], but not brachytherapy [42]. This may be because of a large variation between skin markers

relative to bone structures, leading to partial geographical miss, and hence loss of biochemical control. Recently published data on prostate shifts for 117 patients treated with image guidance showed a strong correlation between BMIs >35, patient weight and standard deviation of daily shift in the left–right direction ($p < 0.01$) [43]. Without IG-IMRT, our patient would not have received the entire prescribed dose to the target. It is noted that 60 Gy in 20 fractions is not a standard dose fractionation schedule for prostate cancer outside of the CHHiP trial [30], but was used for pragmatic reasons in this patient owing to the considerable distance he travelled for daily radiotherapy.

Geographical miss was also a major concern when irradiating the synchronous rectal and prostate tumours in Case 5. It required the confident delivery of different doses to two separate targets. IMRT shaped the dose appropriately. With IGRT correction based on prostate position, coverage of the rectal tumour was ensured by an adequate PTV.

IMRT is becoming much more widely used for the treatment of head and neck carcinomas. A rigid thermoplastic shell is required for immobilisation, and typically achieves an accuracy of 5 mm [44]. Flexible thermoplastic materials (*e.g.* Orfit Industries, Wijnegem, Belgium) can achieve similar accuracy to a rigid poly(methyl methacrylate) shell, but they may shrink with time, which can alter their properties if used over several weeks. Vacuum bags are usually reserved for cases where immobilisation is less critical, for example in palliative treatments, or for limb immobilisation where larger margins are used, because they do not afford great precision. There are no published data on the sole use of vacuum bags in head and neck cancer radiotherapy, because their inaccuracy precludes their use in this cohort of patients. However, the addition of image guidance compensated for the poor immobilisation in the patient with ankylosing spondylitis, permitting a radical dose without the need for an increased CTV–PTV margin, and keeping the spinal cord within tolerance (Case 4).

For retreatments in the head and neck, it is even more important to be sure of the dose received by OARs, to minimise the risk of long-term toxicities [45]. Again, the spinal cord is a crucial structure in this respect. The degree of spinal cord recovery following previous radiotherapy is hard to quantify, but animal studies have shown recovery of >50% at 2 years [33], and this figure is a commonly used conservative estimate in clinical practice. This value is likely to be affected by other factors, such as the use of chemotherapy. For the patient with a second malignancy within a previous radiotherapy field (Case 6), image guidance allowed for the confident delivery of post-operative radiotherapy, knowing that the spinal cord was well within our retreatment dose limit of 28 Gy.

Recurrent nasopharyngeal carcinoma, as in Case 7, can be treated by surgery, brachytherapy or re-irradiation. In this patient it was felt that surgery would result in unacceptable morbidity. Brachytherapy, although a reasonable option in a patient with a small recurrence and a long disease-free interval, has fallen out of favour in the UK, owing in part to a lack of technical expertise. Re-irradiation using external beam radiotherapy can achieve good results but at the expense of considerable toxicity. In

a large Hong Kong series [46], the incidence of late toxicities at 12 months was 70%, with grade 3 toxicities of 25%. That series used a varying GTV–PTV margin of 2–10 mm, depending on the proximity to OARs. It demonstrated good long-term control of rT1–3 tumours using a dose of 50–60 Gy. As the most pressing issue was the reduction in dose to the previously treated normal tissue, we used image guidance to allow a reduction in the CTV–PTV margin from 5 to 3 mm. The aim was to give this patient the best chance of long-term control, but with the hope of minimising long-term sequelae.

Case 8, which involved irradiating para-aortic lymph nodes in a patient treated for cervical cancer, presented a challenge owing to the areas of overlap with the previously irradiated spinal cord, the potential of increased bowel toxicity, and the difficulty in accurate positioning in the presence of significant back pain. Standard radical treatment of the para-aortic nodes was limited to 45 Gy in 25 fractions by small bowel, spinal cord and kidney tolerances. With concomitant cisplatin, this approach resulted in 5-year survival rates of 30% in asymptomatic patients, but poor outcomes in those presenting with symptomatic disease [47]. There is evidence that dose escalation improves tumour control and subsequently survival, but this requires at least a proportion of the radiation dose to be planned conformally to reduce the dose to the small bowel [48]. This is a considerably more toxic treatment in terms of both acute and long-term morbidity, with gastrointestinal side effects most prevalent. Image guidance permitted an increased dose of 60 Gy to be accurately delivered while maintaining dose constraints, and resulted in minimal acute toxicity.

To attain long-term control in chordoma, as in Case 9, high-dose radiotherapy is required, typically ≥ 65 –70 Gy [36, 49]. The close proximity to the spinal cord makes this difficult to achieve while keeping to dose constraints for the cord (54 Gy) and other OARs. Proton therapy allows for high-intensity, highly localised deposition of energy at a fixed depth, making it ideal for cases such as this [34, 49, 50]. The presence of a metal reconstruction reduces the effectiveness of proton therapy [49], and constitutes a contraindication. Artefacts caused by the metal implants may cause difficulty with target volume definition and delineation, precise localisation of spinal cord and accurate dose computation. We have used MVCT as part of the imaging for planning to overcome these problems. Conformal irradiation with photons provides an alternative to proton therapy, and has produced encouraging results [36, 51]. With the addition of daily image guidance and positional correction prior to delivering treatment, the dose to the spinal cord can be calculated accurately and minimised, while ensuring treatment accuracy.

For all of these cases the daily discrepancies between the initial planning scan and the on-treatment MVCT were recorded, and it is possible to calculate the daily 3D displacement and compare this with the margin used to create the PTV. To avoid overestimating the added value of IG-IMRT, these daily displacements were compared with a hypothetical regimen that used image guidance for the first three fractions only, and then applied the resulting systematic correction to the remaining fractions. Table 2 illustrates the proportion of fractions where the chosen planning margin would not have been enough to ensure adequate irradiation of the target.

This provides numerical support for the use of IG-IMRT in these patients.

In this challenging group, the percentage of fractions where the chosen CTV-PTV margin was not sufficient without daily imaging and correction to ensure complete coverage by the 95% isodose averaged at 49% (range 0–90%). Without our daily corrective strategy, the CTV-PTV margin would have been inadequate by >3 mm in an average of 19% of fractions (range 0–67%), and by >5 mm in 9% of fractions (range 0–47%). Clearly, the patient with ankylosing spondylitis and suboptimal immobilisation (Case 4) would have posed an insurmountable problem without the use of IG-IMRT, given that even increasing the CTV-PTV margin by a further 5 mm would not have ensured adequate treatment, and would have compromised the spinal cord. It is worth noting that even in Case 2, in which the calculations revealed no clear benefit of continuing daily imaging (Table 2), these results could not have been predicted in advance of treatment. What image guidance adds in this case is the confidence of accurate dose delivery, acting as daily quality assurance for the delivery of the complex IMRT plan.

One may argue against the use of IG-IMRT for these patients given that the final clinical outcome in several was poor (see Table 1), with several patients developing or dying of metastatic disease. However, most had aggressive disease with poor prognosis, and IG-IMRT provided good palliation by achieving local control, for all except one patient. Toxicity was low in all the patients and the treatment could not have been safely attempted without IG-IMRT.

Conclusion

These challenging cases illustrate areas where IG-IMRT has afforded advantages over either conformal radiotherapy or IMRT alone. Although not the only solution, we believe TomoTherapy has afforded greater precision, enabling confident delivery of radiotherapy to the intended target while minimising the dose to OARs, preventing geographical miss and, in some instances, allowing for tighter planning margins. The use of IG-IMRT should be considered in clinically challenging situations where conventional techniques provide sub-optimal treatment.

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References

1. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, et al. Xerostomia and quality of life after intensity-modulated radiotherapy *vs* conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys* 2006;66:981–91.
2. Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, et al; Breast Technology Group. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. *Radiother Oncol* 2007;82:254–64.
3. Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. *Lancet Oncol* 2008;9:367–75.
4. Staffurth J. A review of the clinical evidence for intensity modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010;22:643–57.
5. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;12:127–36.
6. Barnett GC, Wilkinson JS, Moody AM, Wilson CB, Twyman N, Wishart GC, et al. Randomized controlled trial of forward-planned intensity modulated radiotherapy for early breast cancer: interim results at 2 years. *Int J Radiat Oncol Biol Phys* 2012;82:715–23.
7. Bujold A, Craig T, Jaffray D, Dawson LA. Image-guided radiotherapy: has it influenced patient outcomes? *Semin Radiat Oncol* 2012;22:50–61.
8. BIR Working Party. Geometric uncertainties in radiotherapy—defining the planning target volume. London, UK: British Institute of Radiology; 2003.
9. Royal College of Radiologists, Society and College of Radiographers, Institute of Physics and Engineering in Medicine. On target: ensuring geometric accuracy in radiotherapy. London, UK: Royal College of Radiologists; 2008.
10. Rimmer YL, Burnet NG, Routsis DS, Twyman N, Hoole AC, Treeby J, et al. Practical issues in the implementation of image-guided radiotherapy for the treatment of prostate cancer within a UK department. *Clin Oncol (R Coll Radiol)* 2008;20:22–30.
11. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. *J Clin Oncol* 2007;25:938–46.
12. Verellen D, De Ridder M, Storme G. A (short) history of image-guided radiotherapy. *Radiother Oncol* 2008;86:4–13.
13. Verellen D, Ridder MD, Linthout N, Tournel K, Soete G, Storme G. Innovations in image-guided radiotherapy. *Nat Rev Cancer* 2007;7:949–60.
14. Engels B, Soete G, Verellen D, Storme G. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. *Int J Radiat Oncol Biol Phys* 2009;74:388–91.
15. Williams MV, Cooper T, Mackay R, Staffurth J, Routsis D, Burnet NG. The implementation of intensity-modulated radiotherapy in the UK. *Clin Oncol (R Coll Radiol)* 2010;22:623–8.

16. Mayles WPM, Cooper T, Mackay R, Staffurth J, Williams M. Progress with intensity-modulated radiotherapy implementation in the UK. *Clin Oncol (R Coll Radiol)* 2012;24:543–4.
17. Sterzing F, Schubert K, Sroka-Perez G, Kalz J, Debus J, Herfarth K. Helical tomotherapy. Experiences of the first 150 patients in Heidelberg. *Strahlenther Onkol* 2008;184: 8–14.
18. Burnet NG, Adams EJ, Fairfoul J, Tudor GSJ, Hoole ACF, Routsis DS, et al. Practical aspects of implementation of helical tomotherapy for intensity-modulated and image-guided radiotherapy. *Clin Oncol (R Coll Radiol)* 2010;22: 294–312.
19. Giraud P, Kantor G, Yassa M, Zefkili S, Dejean C, Lisbona A, et al. Two-year clinical experience with tomotherapy: the French national cancer institute project on implementing new technology. *Cancer Invest* 2011;29:557–63.
20. Ting JY, Scarbrough TJ. Intensity-modulated radiation therapy and image-guided radiation therapy: small clinic implementation. *Hematol Oncol Clin North Am* 2006;20:63–86.
21. Welsh JS, Lock M, Harari PM, Tomé WA, Fowler J, Mackie TR, et al. Clinical implementation of adaptive helical tomotherapy: a unique approach to image-guided intensity modulated radiotherapy. *Technol Cancer Res Treat* 2006;5:465–79.
22. Whittton A, Warde P, Sharpe M, Oliver TK, Bak K, Leszczynski K, et al. Organisational standards for the delivery of intensity-modulated radiation therapy in Ontario. *Clin Oncol (R Coll Radiol)* 2009;21:192–203.
23. Smith D, MacDougall N, Monk J, Sibtain A, Powell ME, Plowman PN. First quinquennial review of intensity-modulated radiotherapy at St Bartholomew's Hospital, London. *Clin Oncol (R Coll Radiol)* 2010;22:666–74.
24. Chatterjee S, Mott JH, Smyth G, Dickson S, Dobrowsky W, Kelly CG. Clinical challenges in the implementation of a tomotherapy service for head and neck cancer patients in a regional UK radiotherapy centre. *Br J Radiol* 2011;84: 358–66.
25. Yartsev S, Kron T, Van Dyk J. Tomotherapy as a tool in image-guided radiation therapy (IGRT): theoretical and technological aspects. *Biomed Imaging Interv J* 2007;3:e16.
26. Houghton F, Benson RJ, Tudor GS, Fairfoul F, Gemmill J, Dean JC, et al. An assessment of action levels in imaging strategies in head and neck cancer using TomoTherapy. Are our margins adequate in the absence of image guidance? *Clin Oncol (R Coll Radiol)* 2009;21:720–7.
27. Urruticoechea A, Arnedos M, Walsh G, Dowsett M, Smith IE. Ovarian protection with goserelin during adjuvant chemotherapy for pre-menopausal women with early breast cancer (EBC). *Breast Cancer Res Treat* 2008;110:411–16.
28. Li XA, Qi XS, Pitterle M, Kalakota K, Mueller K, Erickson B, et al. Interfractional variations in patient setup and anatomic change assessed by daily computed tomography. *Int J Radiat Oncol Biol Phys* 2007;68:581–91.
29. ClinicalTrials.gov [homepage on the internet]. Washington D.C.: National Institute of Health; 1997 [cited October 2011]. Available from: <http://www.clinicaltrials.gov>
30. Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a Phase 2 trial. *Lancet Oncol* 2010;11:241–8.
31. Khoo VS, Dearnaley DP. Question of dose, fractionation and technique: ingredients for testing hypofractionation in prostate cancer—the CHHiP trial. *Clin Oncol (R Coll Radiol)* 2008;20:12–14.
32. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose–volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys* 2010;76(Suppl. 3):S42–9.
33. Kian Ang K, Guo-Liang J, Feng Y, Clifton Stephens L, Tucker SL, Price RE. Extent and kinetics of recovery of occult spinal cord injury. *J Radiat Oncol Biol Phys* 2001;50:1013–20.
34. Rutz HP, Weber DC, Sugahara S, Timmermann B, Lomax AJ, Bolsi A, et al. Extracranial chordoma: outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation. *Int J Radiat Oncol Biol Phys* 2007;67:512–20.
35. nhs.uk [homepage on the internet]. London, UK: NHS Specialised Services [cited March 2012]. Available from: <http://www.specialisedservices.nhs.uk/info/proton-beam-therapy>
36. Potluri S, Jefferies SJ, Jena R, Harris F, Burton KE, Prevost AT, et al. Residual post-operative tumour volume predicts outcome after high dose radiotherapy for chordoma and chondrosarcoma of the skull base and spine. *Clin Oncol (R Coll Radiol)* 2011;23:199–208.
37. rcog.org.uk [homepage on the internet]. London, UK: Royal College of Physicians, Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists; 2007 [cited October 2011]. Available from: <http://www.rcog.org.uk/womens-health/clinical-guidance/effects-cancer-treatment-reproductive-function-guidance-management>
38. Burnet NG, Bliss JM, Harmer CL. The impact of radiotherapy dose on local control of Ewings sarcoma of bone. *Sarcoma* 1997;1:31–8.
39. Paulino AC, Nguyen TX, Mai WY, Teh BS, Wen BC. Dose response and local control using radiotherapy in non-metastatic Ewing sarcoma. *Pediatr Blood Cancer* 2007;49:145–8.
40. Kirby R, Burnet N, Routsis D, Lenane M. A case of post-operative breast irradiation on a patient with pectus excavatum. *Synergy Imaging & Therapy Practice*, [serial on the internet]. October 2009 [cited March 2012];24:[4 pp.]. Available from: <http://content.yudu.com/Library/A1gr1e/SynergyMImagingTherap/resources/8.htm>
41. Stroup SP, Cullen J, Auge BK, L'Esperance JO, Kang SK. Effect of obesity on prostate-specific antigen recurrence after radiation therapy for localized prostate cancer as measured by the 2006 Radiation Therapy Oncology Group—American Society for Therapeutic Radiation and Oncology (RTOG-ASTRO) Phoenix Consensus Definition. *Cancer* 2007;110:1003–9.
42. Merrick GS, Galbreath RW, Butler WM, Wallner KE, Allen ZA, Adamovich E. Obesity is not predictive of overall survival following permanent prostate brachytherapy. *Am J Clin Oncol (R Coll Radiol)* 2007;30:588–96.
43. Wong JR, Zhanrong G, Merrick S, Wilson P, Uematsu M, Woo K, et al. Potential for higher treatment failure in obese patients: correlation of elevated body mass index and increased daily prostate deviations from the radiation beam isocentres in an analysis of 1465 computed tomographic images. *Int J Radiat Oncol Biol Phys* 2009;75:49–55.
44. Hanna CL, Slade S, Mason MD, Burnet NG. Translating radiotherapy clinical target volumes into planning target volumes for bladder and brain tumour patients. *Clin Oncol (R Coll Radiol)* 1999;11:93–8.
45. Sulman EP, Schwartz DL, Thuy TL, Kian Ang K, Morrison WH, Rosenthal D, et al. IMRT reirradiation of head and neck cancer—disease control and morbidity outcomes. *J Radiat Oncol Biol Phys* 2009;73:399–409.
46. Chua DTT, Sham JST, Leung LHT, Au GKH. Reirradiation of nasopharyngeal carcinoma with intensity-modulated radiotherapy. *Radiother Oncol* 2005;77:290–4.
47. Singh AK, Grigsby PW, Rader JS, Mutch DG, Powell MA. Cervix carcinoma, concurrent chemoradiotherapy, and salvage of isolated paraaortic lymph node recurrence. *Int J Radiat Oncol Biol Phys* 2005;61:450–5.

48. Kim YS, Kim JH, Ahn SD, Lee S-W, Shin SS, Nam J-H, et al. High-dose extended-field irradiation and high-dose rate brachytherapy with concurrent chemotherapy for cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2009;74:1522–8.
49. Ares C, Hug EB, Lomax AJ, Bolsi A, Timmermann B, Rutz HP, et al. Effectiveness and safety of spot scanning proton radiotherapy for chordomas and chondrosarcomas of the skull base: first long term report. *J Radiat Oncol Biol Phys* 2009;75:1111–18.
50. Delaney TF, Liebsch NJ, Pedlow FX, Adams J, Dean S, Yeap BY, et al. Phase II study of high dose photon/proton radiotherapy in the management of spine sarcomas. *Int J Radiat Oncol Biol Phys* 2009;74:732–9.
51. Foweraker KL, Burton KE, Maynard SE, Jena R, Jefferies SJ, Laing RJ, et al. Skull base surgery and neurosurgery collaborators. High-dose radiotherapy in the management of chordoma and chondrosarcoma of the skull base and cervical spine: Part 1—clinical outcomes. *Clin Oncol (R Coll Radiol)* 2007;19:509–16.