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Comparison of deliverable IMRT and VMAT for spine metastases using a simultaneous integrated boost

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Objective: To effectively treat spine metastases, significant dose must be delivered to regions surrounding the spinal cord. We present a study comparing both step-and-shoot intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques to deliver a concomitant hypofractionated prescription dose to the diseased region and to the involved vertebrae.

Methods: Seven-field IMRT and a single arc VMAT were inversely planned on five (two cervical and three thoracic) spinal metastatic patients. Planning target volumes PTV_m (macroscopic) and PTV_e (elective involved vertebrae) and associated organs at risk were localised. Mean doses of 35 Gy to PTV_m and 20 Gy to PTV_e were prescribed in five fractions. Dose statistics, estimated delivery time and results of verification using Delta⁴ (ScandiDos, Uppsala, Sweden) were compared.

Results: Deliverable plans were achieved with both IMRT and VMAT. The coverage to PTV

was similar for both IMRT and VMAT ($p=0.5$) and the dose to the regions adjacent to the spinal cord was 1% higher with VMAT ($p=0.04$). The mean delivery time for VMAT was 3.5 min compared with 10.5 min for IMRT. Fewer monitor units were required to deliver IMRT than to deliver VMAT. The median (range) percentage of measured points with a γ -index <1 with 3%/3 mm was 100 (99.9–100)% for IMRT and 100 (88.5–100)% for VMAT.

Conclusion: Both VMAT and IMRT can deliver the concomitant hypofractionated regime proposed, and both offer different benefits in dose delivery. IMRT is currently preferred for its superior pre-treatment verification results and shorter planning times.

Advances in knowledge: This study explores the feasibility of delivering tumouricidal doses of radiation to metastatic spine disease in the vicinity of the spinal cord.

Approximately one-third of all patients with cancer will develop bone metastases [1], and approximately 70% of these patients will have metastases involving the vertebral column. Radiation therapy plays an important role in the treatment of symptomatic vertebral metastases, including palliation of pain, control or prevention of neurological symptoms and prevention of pathological fractures, especially in patients who are frail, have limited life expectancy owing to the underlying burden of malignancy and can be at a high risk of surgical morbidity. Many studies have shown that conventional irradiation doses are insufficient for achieving long-term control of the metastatic tumour and that retreatment may be needed, but this is practised in a few patients only [2]. Higher biological equivalent dose (BED, 65–80 Gy) appears to be associated with a higher progression-free survival and reduced in-field recurrence [3].

Radiosurgical or hypofractionated treatments are expected to better control the spinal tumour with the consequence of more rapid and durable pain relief. The recent availability of image-guided radiotherapy can enable the increase in radiation dose deliverable to a spinal tumour [4], while at the same time limiting the radiation dose delivered to the spinal cord [5]. The majority of trials and institutions favour radiosurgical (single fraction) techniques owing to patient comfort and an outpatient, single-fraction treatment in the context of limited life expectancy. Although the local tumour and pain control have been reported in 80–90% of the patients with low rates of severe toxicity owing to the immediate proximity of vertebral metastases to the spinal cord, the single fraction dose deliverable is limited by the tolerance of the spinal cord, [6–8]. Consequently, many study protocols exclude tumours within a distance of <3 mm to the spinal cord, including the current randomised Radiation Therapy Oncology Group (RTOG) 0631 trial [9], which compares radiosurgery (16 Gy in one fraction) with conventional radiotherapy (8 Gy in one fraction). By excluding this region, the study precludes patients who are at the highest risk of cord compression. Additionally, two local failure sites can be attributed to the radiosurgical approach: (i) at the epidural space because of the sparing of the spinal cord—and adjacent epidural tumour involvement—from high biological doses of radiosurgery and (ii) in untreated parts of the vertebra, which are spared from the high single-fraction dose [10].

We would like to start a prospective study to see the effect of a concomitant hypofractionation radiotherapy regime to treat spine metastases. The length of irradiated spinal cord is reduced by treating the involved vertebra only, preserving bone marrow function and facilitating continuation of chemotherapy. The protocol will be unique in two aspects to avoid limitations of the radio-surgical single-fraction approach: (i) based on the linear quadratic model, hypofractionated (≥ 5 fractions) treatment will allow higher biologically effective doses to the tumour directly adjacent to the spinal cord than radio-surgical protocols (the multifraction approach is also supported by Rades et al [11] who described a significantly higher recurrence rate in the lower dose protocols after 1-year follow-up) and (ii) additionally, failures at the epidural interface shall be avoided by the use of a simultaneous integrated boost concept, and the whole involved vertebra will be treated with a second dose level (conventional dose) to avoid recurrences in the untreated parts of the vertebra. Preliminary results from the University Hospital Wuerzburg with dose-intensified irradiation using 20 fractions of 3 Gy are promising and support the hypothesis of this study [12].

To treat these patients, however, we must be able to deliver the hypofractionation dose prescription to the planning target volumes (PTVs) without compromising the spinal cord. Therefore, we present a planning study, a precursor to the proposed spine metastases prospective study, to compare step-and-shoot intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) plans to treat spine metastases and the involved vertebrae, as the dose prescription proposed cannot be delivered using conventional radiotherapy methods. The plans are compared in terms of dose volume statistics with PTVs and organs at risk (OAR), treatment delivery time and pre-treatment verification results. Furthermore, we concentrate on trying to deliver adequate dose to the regions just outside of the spinal cord.

MATERIALS AND METHODS

Patients

Five consecutive spine metastases patients treated at The Royal Marsden NHS Foundation Trust, Sutton, UK, between September and December 2011 were retrospectively identified (Table 1a). Patients were scanned in the supine position, with ankle stocks for comfort, on a Philips large bore CT Scanner (Philips Medical Systems,

Table 1. (a) Patient demographics and (b) planning objectives for PTVs and OAR. Doses are in Grays and volumes are in percent

Patient	Age (years)	Location of metastases	GTVm (cm ³)	GTVe (cm ³)
1	77	C6	1.15	23.19
2	68	C7	2.78	25.61
3	64	T10	2.70	47.09
4	72	T8	6.79	41.63
5	49	T9	1.22	36.38

(b)

	$D_{95\%}$	$D_{90\%}$	$D_{50\%}$
PTVm	—	33.2	35.0
PTVe	20.0	—	20.0
	$D_{\max(1\text{ cm}^3)}$	D_{mean}	Maximum dose/volume
PRVsc	23.8	—	—
Kidney	—	<10.0	$V_{10\text{ Gy}} < 10\%$
Oesophagus	24.0	—	
Liver	—	<20.0	$V_5\text{ Gy} \leq 5\%$

D , dose; $D_{\max(1\text{ cm}^3)}$, maximum dose to 1 cm³ of structure; GTVe, elective gross tumour volume; GTVm, macroscopic gross tumour volume; OAR, organs at risk; PRVsc, planning risk volume of the spinal cord; PTV, planning target volume; PTVe, elective PTV; PTVm, macroscopic PTV; V , volume.

Cleveland, OH). Cervical spine patients were immobilised using a head–shoulder thermoplastic shell. All CT planning scans were acquired with 2-mm slice thickness and contoured and planned on a Pinnacle³ treatment planning system v. 9.0 (Philips Radiation Oncology Systems, Madison, WI).

Target and organ definition

Macroscopic gross tumour volumes (GTVm) and involved vertebra GTV, otherwise referred to as the elective GTV (GTVe), were delineated on the planning CT image with the aid of a diagnostic MR scan (Table 1a). The macroscopic PTV (PTVm) was the GTVm with a uniform 3-mm margin to account for potential microscopic spread and inter- and intrafractional positional uncertainties. The elective PTV (PTVe) was the entire vertebra of the involved levels with a 2-mm uniform margin to account for variability in treatment set-up and internal target motion, with the PTVm subtracted. PTVm–sc, defined as PTVm minus a 3-mm expansion of the spinal cord, was also created. To assess adequate dose delivery to regions adjacent to the spinal cord, a 3-mm ring around the spinal cord (SCring) was also created.

The spinal cord was delineated with the aid of the diagnostic T_1 and/or T_2 weighted MRI data set. A 1-mm uniform margin of the spinal cord was added to create planning risk volume of the spinal cord. Other required normal tissue contours varied according to the level of spinal irradiation. The oesophagus was delineated including the outer muscular layers to the fatty adventitia and extended 2 cm above and below the level of the PTV. The lungs were auto-contoured and checked by the radiation oncologist. Both kidneys including the entire renal parenchyma and the visible collecting system were also delineated. The entire liver was contoured from the hepatic dome to the inferior border. Remaining volume at risk (RVR) was created with patient exterior contour outlined 1 cm above and below the level of the PTV with all clinical target volume and OAR subtracted from it.

Radiotherapy planning and evaluation

Pinnacle³ v. 9.0 was used to create seven-field step-and-shoot IMRT plans for all patients, based on a 6 MV Beam Modulator linear accelerator (Elekta AB, Stockholm, Sweden). Figure 1 shows the beam angles used for cervical spine (top) and thoracic spine (bottom)

Figure 1. Isodoses (as shown in legend) are shown on axial (top) and sagittal (bottom) slices of VMAT (left) and IMRT (right) plans for c-spine and t-spine patients. PTV_m – sc is indicated by the short arrows; PTV_e is indicated by the long arrows. The axial IMRT slices show the beam angles that were used for the c- and t-spine plans. The beam angles for the c-spine IMRT plan were 155°, 106°, 55°, 0°, 305°, 254°, 205° and for the t-spine IMRT plan were 180°, 150°, 115°, 80°, 280°, 245°, 210°. c-spine, cervical spine; IMRT, intensity modulated radiotherapy; PTV_e, elective planning target volume; PTV_m – sc, macroscopic planning target volume minus a 3-mm expansion of the spinal cord; t-spine, thoracic spine; VMAT, volumetric modulated arc therapy.

patients. Collimator angle for each beam was chosen to best conform to the PTV as well as to shield OAR. The number of segments per beam was kept to a minimum [median (range) = 5 (3–7)]. VMAT was planned using Pinnacle³ v. 9.0 SmartArc. A single counter-clockwise gantry arc from 179° to 181° according to the International Electrotechnical Commission standard IEC 61217 was observed to be most adequate and was used for all patients. The control point spacing was set to 2° and maximum allowable delivery time was set to be 180 s. A collimator angle of 2–3° was used to minimise the effects of interleaf leakage. Both IMRT and VMAT plans were produced with inverse planning objectives, as shown in Table 1b. Three annuli were created, and dose objectives were set to conform the dose distribution to the PTV and minimise dose to the surrounding tissue. In the inverse planning optimisation process, priority was given to PTV and spinal cord objectives. The plans were deemed to have reached their optimal planning potential when PRVsc dose constraint was met without causing detrimental effect to the PTV dose distribution. A mean dose of 35 Gy in five fractions was prescribed to PTVm – sc, and a mean dose of 20 Gy in five fractions was prescribed to PTVe. Final-dose calculation was on a dose grid size of 0.25 cm and was performed with collapsed cone convolution algorithm.

Dose distributions and dose volume histograms (DVHs) for all the organs outlined and for each technique for all patients were compared. Conformity index (CI) was the ratio of 95% isodose volume to the PTV. Clinical dose and volume objectives for PTVs and OAR were based on the BED as shown in Table 1b. We have used an α/β of 2 for the spinal cord late effects [13], using the linear quadratic model. Although there are limitations to the BED model within the high dose-per-fraction range [14], this model is widely used in clinical practice and is based on the least number of assumptions. The probability of radiation myelopathy with the constraints chosen is approximately 3% [15].

As the coverage of the PTVm – sc was crucially dependent on the shape and location of the target volume in relationship to critical OAR, the goal of 90% coverage with 95% of the prescribed dose may not be achievable in all patients, and the difference between the achieved and desirable coverage was therefore studied. Although the dose inhomogeneity in the PTV was not a priority, any dose >105% of the prescription

was planned such that it occurred primarily within the PTV and not within normal tissues outside the target volume. A statistical significance level of $p < 0.05$ is reported, using a non-parametric-related samples Wilcoxon signed-ranks test. The samples were considered to be related because a single CT scan was used for both conventional and VMAT plans, and a non-parametric test was chosen because the sample sizes were small and not of a normal distribution.

Monitor unit (MU) efficiency, *i.e.* the ratio of MU to dose (cGy) per fraction, was also compared between the plans. To test the feasibility of delivering the plans produced, all plans were recalculated for a volume representing the Delta⁴ (ScandiDos, Uppsala, Sweden). The plans were then delivered and the dose measured using the two crossed planes of diodes in the measurement phantom. A diode spacing was 0.5 cm in the central 6×6 cm and 1.0 cm in the outer regions. The agreement of the total dose delivered to the diode detectors and the recalculated three-dimensional dose distribution were then evaluated using the percentage of measured points with a γ -index of <1 with 3% dose difference, and 3-mm distance to agreement was used [16,17]. To compare the estimated delivery times, beam-on times were extracted from the record and used to verify system (MOSAIQ; Elekta AB) files after phantom verification.

RESULTS

All VMAT and IMRT plans meet the spinal cord tolerance dose. Figure 1 shows the dose distribution of cervical and thoracic spine patients, which is similar for both VMAT and IMRT. Dose coverage is similar for VMAT compared with IMRT plans for both PTVm – sc and PTVe ($p=0.5$). However, the dose is better conformed with VMAT than IMRT (see CI in Table 2). $D_{50\%}$ does not deviate from the prescription dose of 35 Gy for both VMAT and IMRT plans for all patients. However, VMAT $D_{90\%}$ and $D_{95\%}$ are, on average, higher (1.5% and 1.6% for PTVm – sc and 1.2% and 0.9% for PTVe, respectively) than for IMRT (Figure 2). Most of the patient plans did not meet the PTVm – sc $V_{95\%} > 90\%$ constraint because of the proximity and shape of the PTVm around the spinal cord. Dose to the regions surrounding the spinal cord, *i.e.* dose to the SCring is shown in Table 2. The doses delivered to this region are similar to that of the PTVe dose (Table 2), and, for both the SCring and the PTVe, VMAT achieves a higher mean dose than that of IMRT ($p=0.04$). Dose distributions (Figure 1)

Table 2. Median (range) CI ($V_{95\%}/\text{PTV}$) and dose statistics for PTVm – sc, PTVe, PRVsc, SCring and RVR are shown. Doses are in Grays and volumes are in percent

ROI		VMAT	IMRT
CI	$V_{95\%}/\text{PTV}$	1.30 (1.02–1.96)	1.54 (1.20–2.41)
PTVm – sc	$D_{95\%}$	31.4 (31.3–32.9)	30.7 (30.3–32.4)
	$D_{90\%}$	32.8 (32.2–33.6)	31.9 (31.5–33.3)
	$V_{95\%}$	87.1 (81.0–92.5)	82.6 (77.6–90.2)
PTVe	$D_{95\%}$	19.8 (19.5–20.3)	19.8 (19.4–19.9)
	$D_{90\%}$	20.4 (19.8–20.9)	20.1 (19.8–20.6)
	$V_{95\%}$	99.3 (98.6–99.6)	99.6 (99.2–100.0)
PRVsc	$D_{1\text{ cm}^3}$	22.5 (21.9–23.5)	22.0 (21.9–22.2)
SCring	D_{min}	18.1 (15.8–19.6)	19.2 (18.2–19.5)
	D_{mean}	23.2 (22.3–25.1)	23.0 (22.5–24.4)
RVR	$V_{10\text{ Gy}}$	11.0 (9.4–18.9)	14.6 (9.8–36.6)
	D_{mean}	5.1 (4.4–6.1)	4.9 (3.8–7.8)

D , dose; CI, conformity index; IMRT, intensity modulated radiotherapy; PRVsc, planning risk volume of the spinal cord; PTV, planning target volume; PTVe, elective PTV; PTVm – sc, macroscopic PTV minus a 3-mm expansion of the spinal cord; ROI, region of interest; RVR, remaining volume at risk; SCring, ring around the spinal cord; V , volume; VMAT, volumetric modulated arc therapy.

show that the acceptable coverage was achieved with both IMRT and VMAT.

As the OAR were dependent on the location of the spine metastases, individual patient DVHs are presented here (Figure 3). Both VMAT and IMRT deliver doses to the PTV without compromising the OAR dose objectives. However, there are differences in the doses to the OAR between the two plans, most notably the dose to the heart in Patient 4, where the IMRT plan has a more favourable dose distribution. The RVR $V_{10\text{ Gy}}$ is 3.6% lower with VMAT than with IMRT plans ($p=0.04$). However, D_{mean} is similar ($p=0.9$, Table 2).

The estimated treatment delivery time for VMAT is approximately 3.5 min compared with 10.5 min for IMRT. The γ -test results are shown in Table 3, and, with the exception of one plan (Patient 4 VMAT), all plans are shown to be acceptable. The number of MUs needed for IMRT is much smaller (average MU efficiency of 1.93) compared with VMAT plans (2.73). Table 3 lists the number of MUs used for all VMAT and IMRT plans.

DISCUSSION

We have successfully created plans that can deliver the doses required for the hypofractionation trial proposed

here for spine metastases. The complexities of radiotherapy dose and target definition in spine stereotactic body radiation therapy (SBRT) have not yet been fully defined, and the majority of data in terms of efficacy and safety are provided by retrospective studies; therefore a prospective study of multiple-fraction spine SBRT is warranted. Weksberg et al [18] produced a generalisable class solution to plan spine metastases, but only the involved vertebra was treated to a single dose. Other studies reported using VMAT or IMRT for treating spine metastases [19–26]. However, all the studies were on treating a single volume, and two studies [19, 20] were on reirradiation where the prescription dose is dependent on the initial treatment. Wu et al [22] and Kuijper et al [23] used highly modulated plans as they used high numbers of MUs (approximately 8000 MU) to deliver 16 Gy and they did not test delivery. Ma et al [24] showed through multi-institutional data that different apparatuses offer better delivery depending on the increasing number of vertebral bodies being treated. To date, there are no prospective data with the dose (with the simultaneous boost schema) and fractionation scheme studied here. Therefore, direct randomisation with current palliative radiotherapy regimes would be difficult to undertake. We hypothesise that an improved tumour control could be achieved when compared with single fraction radiosurgery as the equivalent

Figure 2. $D_{x\%}$, doses to specified PTVm – sc (top) and PTVe (bottom), are plotted for VMAT and IMRT. p -values in key are comparing the specified VMAT and IMRT dose statistics. IMRT, intensity modulated radiotherapy; PTVe, elective planning target volume; PTVm – sc, macroscopic planning target volume minus a 3-mm expansion of the spinal cord; VMAT, volumetric modulated arc therapy.

dose delivered to the tumour is slightly higher—61 Gy equivalent dose in 2-Gy fractions (EQD2) vs 42 Gy EQD2 using an α/β of 10—calculated within limitations of the linear quadratic model. The higher dose delivered could also have an impact on the development of marginal recurrences, seen in up to 12% of patients treated with single-fraction stereotactic radiosurgery [27], and a reduced risk of vertebral collapse, currently estimated at 11–20% [28].

The results show different benefits with IMRT and VMAT plans. Both plans can adequately cover both PTVm and PTVe to the prescribed dose, and there is a significant dose that is delivered to the regions adjacent to the spinal cord. However, there are differences between the two plans. The planning times required for IMRT are much lower than that of the VMAT plans. This is mainly because of the computational speed of the optimisation process, which is

Figure 3. Individual patient dose volume histograms are plotted for (from top to bottom) PTVm – sc, PTVe, oesophagus, heart and lungs and kidney and liver. As only partial oesophagus was localised, absolute volume is plotted. IMRT, intensity modulated radiotherapy; pt, patient; PTVe, elective planning target volume; PTVm – sc, macroscopic planning target volume minus a 3-mm expansion of the spinal cord; VMAT, volumetric modulated arc therapy.

Table 3. Pre-treatment verification data for VMAT and IMRT (left). The percentage of measured points with a γ -index of <1 with 3% dose difference and 3-mm distance to agreement was used. Number of monitor units are listed for VMAT and IMRT (right)

Patient	γ -test		Number of monitor units	
	VMAT (%)	IMRT (%)	VMAT	IMRT
1	100	100	1906	1362
2	93.4	100	1709	1510
3	100	100	2064	1310
4	88.5	100	2006	1401
5	100	99.0	1859	1167

IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.

much slower in VMAT than in IMRT for the planning system used here. Both plans are, however, achievable in the short planning timeframe that is needed in spinal treatments. To be specific, it is feasible, with the aid of some automatic scripts in place, to produce both types of plans in a few hours.

There are, however, concerns regarding both plans. Owing to the requirement of larger dose per fraction and the nature of step-and-shoot IMRT delivery, the time required to deliver this plan is significantly higher than with VMAT plans. There are benefits to IMRT over VMAT in terms of MU efficiency, and, also, IMRT plans verified better than VMAT owing to being less modulated; satisfactory IMRT plans have been produced with relatively low numbers of segments (approximately 35 segments). The normal tissue dose differences are observed using RVR, and this shows that VMAT is better in terms of $V_{10\text{ Gy}}$. We did not study very low dose levels as the RVR was kept to a minimal size in order to keep the calculation times and the planning system memory to a reasonable level. However, as the number of MUs needed for VMAT is higher, there is an assumption that those plans produce larger volumes of normal tissues that receive low scatter doses. This may not be of great concern for this patient population. Although short delivery time for VMAT is highly desirable, with the addition of required verification imaging, this advantage is not so evident. Also, for Patient 4, very small apertures were present in the VMAT plan as more optimisations were required to produce an adequate clinical plan. This in turn has contributed to worse pre-treatment verification results for VMAT compared with IMRT. In addition, we can currently perform *in vivo* dosimetry using an electronic portal imaging device for

IMRT but not for VMAT patients, and therefore we would like to start the prospective treatment study with IMRT.

We have used an “optimal” collimator twist on IMRT beams to best conform to PTV and shield OAR. However, with VMAT, only a nominal collimator angle has been chosen in order to minimise the interleaf leakage for VMAT. Two studies [29,30] have shown that there are gains to be had in optimising collimator angles. Mancosu et al [29] compared multiple collimator angles for single and double RapidArc VMAT (Varian Medical Systems, Inc., Palo Alto, CA) and showed that choosing a certain angle may be beneficial in reducing dose to the cord. However, it is difficult to be conclusive in the clinical benefit of these angles as they have studied collimator angles on single data sets involving one to three involved vertebrae. Zhang et al’s [30] proposal of a collimator trajectory optimisation adds another degree of freedom in VMAT planning, but to implement this clinically, hardware and software limitations such as the speed of multileaf collimator (MLC) travel need to be improved.

Cervical spine patients require head–shoulder thermoplastic immobilisation devices and thoracic spine patients’ set up is very similar to that of conventional methods, *i.e.* using a thin mattress, knee supports and a lung board to keep their arms up if possible. Dahele et al [31] showed that, with appropriate imaging protocols, the intrafractional spinal movement is minimal, and therefore we do not propose any stereotactic compression methods to be used for the prospective study. Radiological precision will be of importance, including localisation of the metastatic volume as well

as the spinal cord, and a planning MRI is most probably needed.

CONCLUSIONS

IMRT and VMAT can be planned to deliver concomitant hypofractionated doses to the metastatic and involved vertebrae volumes without compromising the region immediately around the spinal cord in the short

planning time frame that is required. Both types of plans present different benefits, which will be useful in individualising treatment plans with respect to individual patient needs. The current plan is to use IMRT as the pre-treatment verification results were better than that of VMAT and the planning times are much shorter owing to the longer optimisation planning system times in VMAT.

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