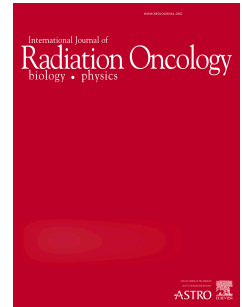


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The potential of proton therapy to reduce acute haematological toxicity in concurrent chemoradiotherapy for oesophageal cancer

Samantha Warren^a, Christopher N Hurt^b, Thomas Crosby^c, Mike Partridge^a, Maria A Hawkins^a

^a CRUK/MRC Oxford Institute for Radiation Oncology, Gray Laboratories, University of Oxford, Oxford, OX3 7DQ, UK

^b Wales Cancer Trials Unit, School of Medicine, Heath Park, Cardiff, CF14 4YS, UK

^c Velindre Cancer Centre, Velindre Hospital, Cardiff, CF14 2TL, UK

Author for correspondence:

Samantha Warren

CRUK/MRC Oxford Institute for Radiation Oncology, Gray Laboratories, University of Oxford, Oxford, OX3 7DQ, UK

warren_samantha@hotmail.com

Tel: +441865857043

Fax: +441865857127

Short title: proton therapy for reducing bone marrow toxicity

Summary:

Radiotherapy dose escalation is predicted to improve local tumour control in oesophageal cancer, yet any increase in acute haematological toxicity (HT) could limit the predicted improvement in patient outcome. We investigated the bone marrow dose of VMAT, proton plans, and marrow-sparing VMAT plans for oesophageal tumours. Improved marrow sparing was possible with VMAT, but only protons showed significant sparing for bone V_{10Gy} and bone mean dose, especially for patients with larger PTV size.

Abstract:

Radiotherapy dose escalation using a simultaneous integrated boost (SIB) is predicted to improve local tumour control in oesophageal cancer, yet any increase in acute haematological toxicity (HT) could limit the predicted improvement in patient outcome. Proton therapy has been shown to significantly reduce HT in lung cancer patients receiving concurrent chemotherapy, we therefore investigated the potential of bone marrow sparing with protons for oesophageal tumours.

21 mid-oesophageal cancer patients treated with conformal radiotherapy (3D50) were selected. Two surrogates for bone marrow were created by outlining thoracic bones (bone) and only the body of the thoracic vertebrae (TV) in Eclipse (Varian). The % overlap of TV with the PTV was recorded for each patient. Additional plans were created retrospectively: a volumetric modulated arctherapy plan (VMAT50) with the same dose as 3D50; a VMAT SIB plan with a dose prescription of 62.5 Gy to the high risk sub-region within the planning treatment volume (VMAT62.5); a re-optimised TV sparing VMAT plan (VMAT62.5bm) and a proton therapy plan (SFO62.5) with the same SIB dose prescription. Bone and TV dose-metrics were recorded and compared across all plans and variation with respect to PTV size and % overlap for each patient was studied.

3D50 plans show the highest bone mean dose and TV V_{30Gy} values for each patient. VMAT plans irradiate a larger bone V_{10Gy} volume than 3D50 plans. Re-optimised VMAT62.5bm plans showed improved sparing of the TV volume, but only proton plans showed significant sparing for bone V_{10Gy} and bone mean dose, especially for patients with larger PTV size.

Background

Oesophageal cancer is the 6th most common cause of death worldwide, representing 5% of total cancer deaths in 2012 (1). Whilst surgery offers the best outcomes for patients with oesophageal cancer, only 10-20% of patients with non-metastatic disease are eligible for surgical treatment. Definitive concurrent chemoradiotherapy (dCRT) is therefore recognised as a valuable treatment option for many patients, and the recent XXXX trial (ISRCT number XXXX) reported good outcomes in the standard dCRT arm (cisplatin / 5FU with 50Gy/25 fractions) with 2-yr OS of 56%, with haematological toxicity (HT) grade ≥ 3 the most commonly reported acute side effect (28% of patients) (2) with only 53% of the patients completing chemotherapy at full dose. Radiotherapy dose escalation using a simultaneous integrated boost (SIB) is predicted to further improve local tumour control in these patients (3). Treatment planning studies for mid-oesophageal cancer patients suggested that a boost dose of 62.5Gy/25 fractions could be achieved using either photons (4) or protons (5) without exceeding dose constraints for heart, cord and lung. A pilot study treating 25 patients with photons has described safe escalation of 62.5Gy/25 fractions to a PET-guided GTV boost volume (6). Conversely, any increase in radiotherapy dose may cause an increase in HT due to higher bone marrow irradiation. This could reduce treatment intensity by interrupting delivery or reducing dose of concurrent chemotherapy, and limit any predicted improvement in patient outcome.

Studies of patients who have received fractionated radiotherapy indicate that below around 50Gy, bone marrow has a large capacity for repair and regeneration (although this may take many months or even years) (7). Longitudinal FLT-PET imaging of pelvic cancer patients suggests that acute HT may occur at low doses (4Gy), whilst bone exposed to

>35Gy exhibits chronic toxicity, with reduced bone marrow recovery 1 year post treatment (8).

Most data concerning the risk of HT and bone marrow irradiation has been collected from studies of anal cancer (9) or cervical cancer (10, 11), where the large planning treatment volumes (PTV) are often abutting or overlapping the pelvic bones (pelvis, sacrum, lumbar spine) which combined contain around 50% of the body's active bone marrow. Dose-volume metrics such as mean pelvic bone dose and pelvic bone V_{10Gy} and V_{20Gy} (where V_{xGy} represents the % volume of the bone receiving xGy or above) have been linked to risk of Grade ≥ 2 leukopenia and neutropenia (10), when the external contour of the pelvic bony structures was used as a surrogate for bone marrow irradiation. Intensity modulated radiotherapy techniques (IMRT and VMAT) can be used in treatment of these tumour sites for improved pelvic bone marrow sparing, and reduced HT in cervical cancer (12) have been reported, as well as reductions in HT for anal cancer (13) treated with IMRT and scanned proton therapy (14). These delivery techniques can also be combined with functional imaging to identify active bone marrow regions within the pelvis to guide dose optimisation (11, 15, 16). Dose to sub-sites of the pelvic bone (such as lumbosacral spine, which contains 25% of bone marrow) have also been identified as important predictors of HT (17), and preferential dose sparing to a sub region of pelvic bone may be more easily achieved.

HT is also observed in patients receiving chemoradiotherapy for thoracic malignancies (2, 18, 19), where approximately 35% of the active bone marrow is found (20). Reduced proliferation of irradiated bone marrow in thoracic spine after only 2Gy has also been detected using FLT-PET imaging for lung cancer patients receiving chemoradiotherapy (21).

A recent study of 52 lung cancer patients treated with 3D conformal and IMRT found thoracic vertebrae dose parameters (mean dose, $V_{20\text{Gy}}$ and $V_{30\text{Gy}}$) to be associated with risk of grade ≥ 3 leukopenia (22), and a study of 41 oesophageal cancer patients investigated similar dose-volume parameters (thoracic vertebrae mean dose, $V_{20\text{Gy}}$ and $V_{10\text{Gy}}$) to propose cut-off values to avoid grade ≥ 3 leukopenia (23). The size and position of target volumes also means that the potential for dose sparing of bone marrow in the thorax may be greater than for the pelvis, especially if IMRT, VMAT or proton therapy are used. While these techniques may improve the conformality of the high dose region, the distribution of low doses (5-15 Gy) is very different with IMRT or VMAT compared to 3D conformal radiotherapy. Proton therapy plans have demonstrated a reduction in bone $V_{10\text{Gy}}$ by 30% and 27% compared to 3D and IMRT plans respectively (24) and reduced HT for lung cancer patients treated with passive scattering protontherapy has been reported (25).

Given the proximity and anatomical location of the oesophagus in relationship to the vertebral bodies and the technological capabilities of modern linear accelerators, the potential for bone marrow sparing for individual patients also merits further investigation. This study therefore compares the dose-volume metrics for thoracic bone structures in order to identify differences in dose distribution for a representative group of mid-oesophageal cancer patients from conformal, VMAT and proton therapy treatment techniques. The potential for re-optimising VMAT plans to improve bone marrow sparing or of selecting patients for treatment with proton therapy is also illustrated by comparing dosimetric parameters for individual patients.

Materials and Methods

21 patients treated with definitive chemoradiotherapy for mid-oesophageal cancer from the XXXX clinical trial previously used for modelling dose escalation and proton treatment delivery were further investigated. (4, 5). These patients with mean planning treatment volume (PTV) size of 327 cm^3 (range $140\text{-}591 \text{ cm}^3$) were randomly selected previously (ref 4 and 5) to be a representative subset of the entire XXXX trial database where mean PTV is 334 cm^3 .

The trial-derived gross tumour volumes (GTVs) were used for each patient, and each GTV was extended along the oesophagus manually by $\pm 2\text{cm}$ cranial-caudally. The clinical target volume (CTV_{50Gy}) was created using an additional radial margin of 1cm , and there was no elective node irradiation. A further 1cm margin was added to generate PTV_{50Gy} which received a dose prescription of 50 Gy in 25 fractions for the standard dose plans. For the plans with a simultaneous integrated boost (SIB) dose prescription of 62.5 Gy in 25 fractions, CTV_{62.5Gy} was considered identical to GTV, and PTV_{62.5Gy} was then generated using an isotropic margin of 0.5cm to allow dose fall off from 62.5Gy to 50Gy .

A surrogate for bone marrow (bone) was created by outlining the thoracic vertebrae (T1-T12 inclusive), sternum, scapulae, ribs and clavicles using the automatic thresholding tool in Eclipse (Varian). A separate volume for the body of the thoracic vertebrae T1 to T12 was created (TV). The dose calculated from the 3D conformal plan (3D50) of typically 4-fields (ANT/POST and LAT/OBL) was available, and was used to record dose to bone and TV.

Additional treatment plans were created retrospectively in Eclipse using the volumetric modulated arctherapy technique (VMAT) and for dose-escalated plans using VMAT and proton therapy. All arctherapy plans consisted of 2 complete 360° arcs (clockwise and counter-clockwise) of 6MV : initially, one plan with the same standard dose prescription as

the original treatment plan (VMAT50), and a dose-escalated VMAT plan (VMAT62.5) with a simultaneous integrated boost (SIB) dose prescription of 62.5 Gy in 25 fractions to the high risk sub-region within the PTV were created (4).

A 3-field spot-scanning proton therapy plan 70-250MeV using single field optimisation (SFO62.5) was created with the same SIB dose prescription using an ANT and POST-OBLIQUE beam arrangement to improve heart and lung sparing (26). Additional field-specific proximal and distal margins of 0.3 to 0.5 cm were applied to PTV_{50Gy} to account for 3.5% range error (5). The same dose-volume constraints for plan optimisation, target coverage and dose to organs at risk (heart, lung, spinal cord) were initially applied to VMAT and proton plans, and no explicit dose constraints for bone marrow sparing were initially used. Dose distributions obtained for these four plans are shown in Figure 1.

Subsequently, a dose-escalated and bone-marrow sparing VMAT plan was created for each patient to reduce dose to bone marrow (VMAT62.5bm). Using *all* the thoracic bone structures (T1-T12, sternum, scapulae, ribs and clavicles) as an optimisation volume was deemed impractical, and reduction of dose was applied only to the TV volume non-overlapping with the PTV, by using a mean dose constraint and additional dose-volume constraints in the 10-30 Gy region for this sub-structure. The proton plans were not re-optimised for bone marrow sparing, given the sharp dose fall-off around the target adjacent to the TV volume, and the already low dose to the other thoracic bone structures.

For all plans, Bone mean dose, V_{20Gy} and V_{10Gy} and TV mean dose, TV V_{20Gy} and TV V_{10Gy} , Lung mean dose and V_{20Gy} and heart mean dose and V_{30Gy} dose-metrics were recorded. Tests for statistical significance were carried out in SPSS v 20 (IBM) using the Wilcoxon signed rank test for pairwise comparison of dose-volume metrics using the different

irradiation techniques. To better understand the parameters (e.g. PTV size, number of vertebrae irradiated (NV) or % TV overlap) which might affect the potential for bone marrow sparing when re-optimising the VMAT62.5 plans, differences in the dose-volume metrics achieved for SFO vs VMAT62.5 and for SFO vs VMAT62.5bm were examined for individual patients, in order to assess the benefits of proton therapy to improve bone marrow sparing, and these were tested using the Pearson correlation.

Results

The dose distribution data are compared quantitatively for all patients for each technique and shown in Figure 2 and in Supplementary Table 1: the 3D50 plans generated the highest bone mean dose (median value 12.1 Gy, interquartile range (IQR) 10.1-12.5%) and bone V_{20Gy} (median 27.5%, IQR 23.2 – 28.8%). There was no *clinically* significant difference (i.e. <2 Gy in absolute dose or <5% in V_{xGy}) between the original VMAT₅₀ and VMAT_{62.5} plans for any of the dosimetric parameters, suggesting that dose escalation with VMAT could be achieved without a clinically significant increase in bone marrow irradiation for all patients. Both original VMAT plans generated a slightly higher median bone V_{10Gy} (VMAT50 median 35.3%, IQR 30.1-41.0% and VMAT62.5 median 37.9%, IQR 31.6-41.8%) than 3D50 plans (median bone V_{10Gy} 33.4%, IQR 29.5-36.4% with Wilcoxon signed rank test $z = -2.172$, $p = .030$, compared to VMAT50). There was no clinically significant difference in TV mean dose between the photon techniques, and differences in TV V_{20Gy} were modest between 3D (median 51.5%, IQR 45.5-57.0%) and the VMAT plans (VMAT50 median 46.0%, IQR 43.3-54.4% and VMAT62.5 median 47.5%, IQR 44.5-55.3%). Median TV V_{10Gy} for this group of patients was similar for 3D50 plans (median 54.3%, IQR 47.9-58.5%), VMAT50 plans (median 50.7%, IQR 46.6-57.5%) and median 51.0%, IQR 47.7-58.4% for VMAT62.5, although VMAT62.5bm plans showed a small reduction in TV V_{10Gy} with median 45.5% (IQR

41.2-51.1%), and this was similar in magnitude to the TV V_{10Gy} sparing of SFO62.5 plans with median TV V_{10Gy} 47.1 % (IQR 42.5-52.1%).

In contrast, SFO62.5 showed clinically significant sparing (>2 Gy in absolute dose or $> 5\%$ in V_{xGy}) for many bone volume parameters compared to the photon techniques, notably for bone mean dose (median 5.7 Gy, IQR 4.9-6.5 Gy) and bone V_{10Gy} (median 23.0%, IQR 20.0-26.0%) and In comparison with the VMAT62.5 plans, the median value for TV mean dose was reduced by > 3 Gy, to 17.6 Gy (IQR 15.0-19.8 Gy) for the proton planning technique. These differences in SFO62.5 vs VMAT62.5 plans were also found to be highly statistically significant ($Z=-4.015$, $p<.001$). Although for the overall *group* of patients, the SFO62.5 plans had similar TV V_{10Gy} values (median 47.1 % (IQR 42.5-52.1%) to the VMAT62.5bm plans, indicating that the smaller TV and PTV overlap can also be beneficial for TV sparing in the VMAT62.5bm plans. However, the minimum TV V_{10Gy} value (19.5%) for patients with the smallest TV overlap in the PTV was much smaller for the proton plans than for VMAT62.5bm (33.0%).

Dose-volume parameters for heart and lung are also shown in Figure 2, indicating that dose escalation may be achieved with only a small increase in mean dose to lung, and that proton plans produce significant sparing of heart, lung and bone marrow structures compared to VMAT and conformal techniques, as described previously (5).

Notwithstanding the overall trends observed, there was considerable variation in bone marrow dose-volume metrics for individual patients, as shown in Figure 3. The correlation of mean dose for bone and TV with factors such as number of vertebrae(NV) irradiated, % TV overlap in the PTV (where median overlap was 7.0%, IQR 5.0-10.5%), and PTV size is also examined. For both bone and TV, although there is a general trend to higher dose with a

larger NV, this is not a sufficiently unique value to clearly differentiate patients at most risk of higher bone marrow irradiation, regardless of technique.

Variations in bone mean dose (and bone V_{20Gy} , V_{10Gy} , data not shown) with the different treatment techniques appear most clearly linked to PTV size. For the bone mean dose, a general increase in dose with PTV size is seen for the 3D50, VMAT50 and VMAT62.5 plans. For 16/21 patients, the V_{10Gy} dose was higher with VMAT50 plans than the 3D50 plans due to the increased low-dose bath generated by the arctherapy technique. Only the proton plans were able to reduce dose-volume metrics for *all* patients compared to all the 3D and VMAT plans, and especially when PTV size is above 300cm³.

The trend to higher TV mean dose (also higher TV V_{20Gy} and TV V_{10Gy} , data not shown) with larger overlap was more pronounced for the proton plans, such that for this series of patients, proton therapy may have a limited ability to spare TV above ~8 % TV overlap.

Applying the TV dose-volume cut-off values to predict risk of grade ≥ 3 leukopenia proposed by Lee et al (23) and Deek et al (22) are shown in Table 1, which shows the number of patients (absolute and % of group) exceeding the threshold values for each treatment technique. The cut-off values proposed by Lee (23) and Deek et al (22) are different, but the trends observed are the same: the SFO and VMAT62.5bm plans show the lowest risk of haematological toxicity, greatly reduced compared to the 3D50, VMAT50 and standard VMAT62.5 plan.

When re-optimising VMAT treatment plans to explicitly spare bone marrow, the PTV size, % overlap of the thoracic vertebrae and proximity and overlap of PTV with other organs at risk (such as heart, lung and spinal cord) were critical. For one patient (with the highest TV overlap with PTV of 13.7%) and also close proximity of the PTV to the spinal cord, better

bone marrow sparing for VMAT62.5bm was impossible, without exceeding dose constraints for other organs at risk. Dose to bones and to TV are compared for each patient for SFO62.5 vs VMAT62.5 and for SFO62.5 vs VMAT62.5bm in Figure 4. SFO62.5 plans compared to the *original* VMAT plans reduced mean dose to the bones by a median value of 4.5 Gy, (IQR 3.6-5.4Gy) ($Z=-4.015$, $p<.001$), or by median 3.1 Gy (IQR 2.6-3.6 Gy)) ($p=.002$) compared to the re-optimised VMAT62.5bm plans. Proton plans were better at sparing low dose, even compared to the re-optimised VMAT plans, with median 11.4% absolute reduction of bones V_{10Gy} ($Z=-3.92$, $p<.001$). For patients with PTV size above 300cm^3 , this reduction in % V_{10Gy} with protons was $>7\%$.

Differences in TV mean dose and TV V_{20Gy} as a function of % TV overlap for SFO vs VMAT62.5 and for SFO vs VMAT62.5bm are also shown in Figure 4. The median gain in TV mean dose with proton therapy vs the original VMAT62.5 plan is 4.6 Gy (IQR 2.9-6.4 Gy) correlated with %TV overlap (Pearson correlation, $r = -0.726$, $n=21$, $p<.001$). However, on re-optimisation (VMAT62.5bm plans), this difference in mean dose is median 0.6 Gy (IQR 0.1-1.5 Gy) ($r = -0.230$, $n=20$, $p=.329$). For TV V_{20Gy} , SFO62.5 vs VMAT62.5 gave an absolute difference of 11.6% (IQR 5.9-18.9%) correlated with % TV overlap ($r=-0.796$, $n=21$, $p<.001$). On re-optimisation of the VMAT plans, the median reduction with SFO62.5 is now 0.2% (IQR -1.9 to 1.3%), and does not appear to be correlated with either % TV overlap ($r=-.125$, $n=20$, $p=.601$), or PTV size (not shown).

Discussion

Our data show that in a representative group of mid-oesophageal cancer patients, bone marrow irradiation is highly dependent on the radiotherapy treatment technique. We have demonstrated that using VMAT or protons, reduction of dose to bone and TV occurs in the

20-30Gy range, as compared to the 3D conformal treatments used in the XXXX trial. Proton therapy plans offer the greatest potential for reduced irradiation of *all* thoracic bone structures, in particular for patients with larger PTV size ($> 300\text{cm}^3$ in this study), and was especially useful in sparing the low dose region around 10 Gy, which was not possible with VMAT plans.

We have also demonstrated that significant TV sparing in the 20-30Gy dose region is possible by re-optimising VMAT plans, even with dose escalation. Optimal treatment plans (using either protons or photons) would be best achieved using multi-criteria optimisation methods, to balance dose sparing of bone marrow with dose constraints to heart, lungs and spinal cord for each individual patient, although this is outside the scope of this current work. Use of patient-specific beam arrangements for the proton therapy plans could also change the dose distribution in the region of the thoracic vertebrae, and the conclusions from this study might not be applicable when using different beam geometries for treatment. Furthermore, proton plan robustness to respiratory and cardiac motion should also be analysed for different beam geometries – although this would require detailed information on both the timescale of the spot delivery, and of each patient's breathing and cardiac motion. Our threshold limit of 300 cm^3 PTV for greatest potential benefit of proton therapy may also depend on the CTV and PTV margins used, and may not be directly applicable to other target volume delineation protocols

One of the limitations of this study is a lack of consensus in the dose-volume parameters to predict HT, both in the organ-at-risk delineation, and in the dose-volume threshold. We have used values from the literature for thoracic tumours (NSCLCC and oesophagus), and whilst values for mean TV dose are similar (23.9 Gy – 25.9 Gy) the values for TV $V_{20\text{Gy}}$ vary much more (56.0% - 70%).

Using TV dose values from Deek et al (22) as a threshold to predict leukopenia varied between 19 and 38% for the 3D conformal plans which is broadly in line with the 28% rate of HT observed in the standard arm of the XXXX trial (2). Predicted toxicity rates for VMAT (10% - 29% and SFO (0% - 10%) plans were much lower. However, cut-off values from Lee (23) predicted much lower incidence of grade >3 leukopenia for all treatment techniques, with a maximum of 14% of 3D50 patients predicted to experience HT.

There are some notable differences between these two studies, and also the patient cohort investigated here which might influence the risk of HT, such as different chemotherapy regimens and different radiotherapy dose prescription and technique. The clinical data from Lee et al describe pre-operative oesophageal cancer patients receiving 2 cycles of neoadjuvant CRT (cisplatin and 5FU) to a maximum dose of 48 Gy, whilst the standard arm of the XXXX trial prescribed 2 cycles of induction chemotherapy (cisplatin and 5FU) prior to further 2 cycles concurrent CRT to 50Gy. The PTV size in the study of Lee is also much larger (median 519 cm³, range 300-1426 cm³) than in our study, possibly due to the elective node irradiation, which might also effect the dose distribution in the region of the vertebrae.

The use of different chemotherapy agents could have a significant effect on HT, and data from pelvic IMRT suggests that use of cisplatin and 5FU causes significantly less HT than MMC (27). We would anticipate similar effects for thoracic tumours, and not only the chemotherapy agent, but also the timing and dosage of chemotherapy could alter the dose tolerance of thoracic bone marrow.

The benefit of protontherapy, and/or the re-optimisation of photon plans depends on whether irradiation of *all* bone in the thorax region or just the thoracic vertebrae body are most important for haematological toxicity. There is evidence from FLT-PET imaging that

the proportion and distribution of active bone marrow in the thorax varies considerably with age and gender (28). A limitation of our study is that we have used the external bone contour as a surrogate for active bone marrow, although the distribution of the active marrow might be very different for each patient, and will influence the active bone marrow sparing possibilities for each individual patient. The idea of a compensatory response in non-irradiated bone has also been proposed (11) and sparing a sufficient bone marrow reserve from even low doses in the thoracic region would suggest that protons should be used, especially for patients with a small absolute bone volume or receiving intense concurrent chemotherapy regimens. Future work would ideally require imaging of active bone marrow for each patient, to identify the region of active bone marrow to be spared, and to select patients who would benefit sufficiently from re-optimised photon plans, or those who require proton planning to reduce their risk of acute haematological toxicity.

Conclusion

VMAT plans can reduce thoracic bone marrow dose in the 20-30 Gy range for mid-oesophageal cancer patients, but irradiate a larger bone $V_{10\text{Gy}}$ volume than conformal plans. Re-optimised VMAT plans showed improved sparing of the TV volume, but only proton plans showed significant sparing for bone $V_{10\text{Gy}}$ and bone mean dose, especially for patients with larger PTV size.

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Figure and tables

Figure 1 Dose distributions for a typical mid-oesophageal cancer patient illustrating a) conformal plan (3D50), b) standard dose VMAT plan (VMAT50), c) a dose-escalated VMAT plan (VMAT62.5) and d) a dose-escalated spot-scanning proton plan (SFO62.5). Bone is outlined in orange, PTV_{50Gy} in yellow, PTV_{62.5Gy} in red. The dose colour wash is from 10Gy (blue) to 40Gy (green) to 65Gy (red).

Figure 2 Box plots comparing the dose-volume parameters for Bone, TV, heart and lung obtained for the 3D50, VMAT50, VMAT62.5, SFO62.5 and VMAT62.5bm (optimised for bone marrow sparing) treatment plans for the group of 21 patients.

Figure 3 A comparison of bone and TV mean dose for individual patients as a function of number of vertebrae (NV), PTV size or % TV overlap. Dose metrics for 3D50 conformal (open grey circles), VMAT50 (open grey triangles), VMAT62.5 (open black squares) and SFO62.5 (solid black diamonds).

Figure 4 A comparison of dose-volume metrics for individual patients for Bone as a function of PTV size (a and b) and TV (c and d) as a function of % TV overlap. The solid circles indicate the differences in the SFO62.5 and original VMAT62.5 plans, and the open diamonds the difference with the re-optimised bone marrow sparing VMAT62.5bm plans.

Table 1 The number of patients in this cohort predicted to be at risk of grade ≥ 3 leukopenia using the threshold dose-volume metrics for the thoracic vertebrae (TV) taken from Lee (23) and Deek (22). Values are shown as the absolute number of patients, and a % of the group of 21 studied.

Supplementary table Dose volume value for bone and TV volumes for the group of 21 mid-oesophageal cancer patients for 3D50 conformal, VMAT50, VMAT62.5, VMAT62.5bm and SFO62.5 plans. Values in **BOLD** indicate differences of potential clinical significance (i.e. > 2Gy in dose or > 5% in V_{xGy}). Statistical test data are presented with no correction for multiple testing, but values in *italics* indicate $p < .001$.

Grade ≥ 3 leukopenia cut-off	3D50	VMAT50	Treatment plan		
			VMAT62.5	SFO62.5	VMAT62.5bm
Lee TV mean < 25.9 Gy	3 (14%)	2 (10%)	2 (10%)	0	0
Lee TV V_{20Gy} < 70%	1 (5%)	1 (5%)	1 (5%)	0	0
Lee TV V_{10Gy} < 77%	1 (5%)	1 (5%)	0	0	0
Deek TV mean < 23.9 Gy	8 (38%)	3 (14%)	6 (29%)	2 (10%)	1 (5%)
Deek TV V_{20Gy} < 56.0%	5 (24%)	4 (19%)	4 (19%)	0	0
Deek TV V_{30Gy} < 52.1%	6 (29%)	2 (10%)	2 (10%)	0	0

Table 1

Figure 1

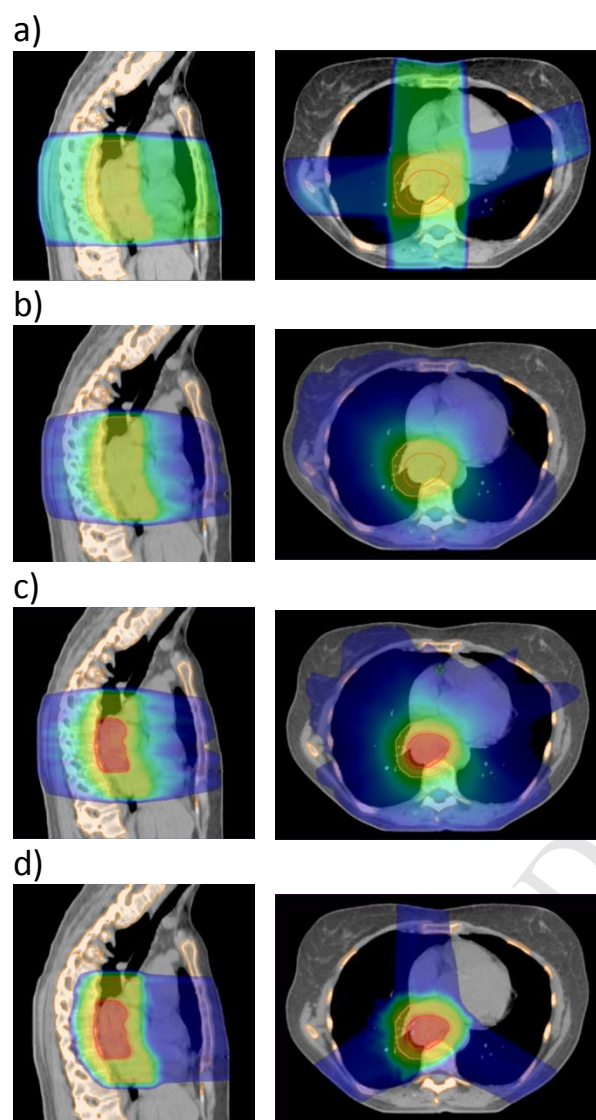


Figure 2

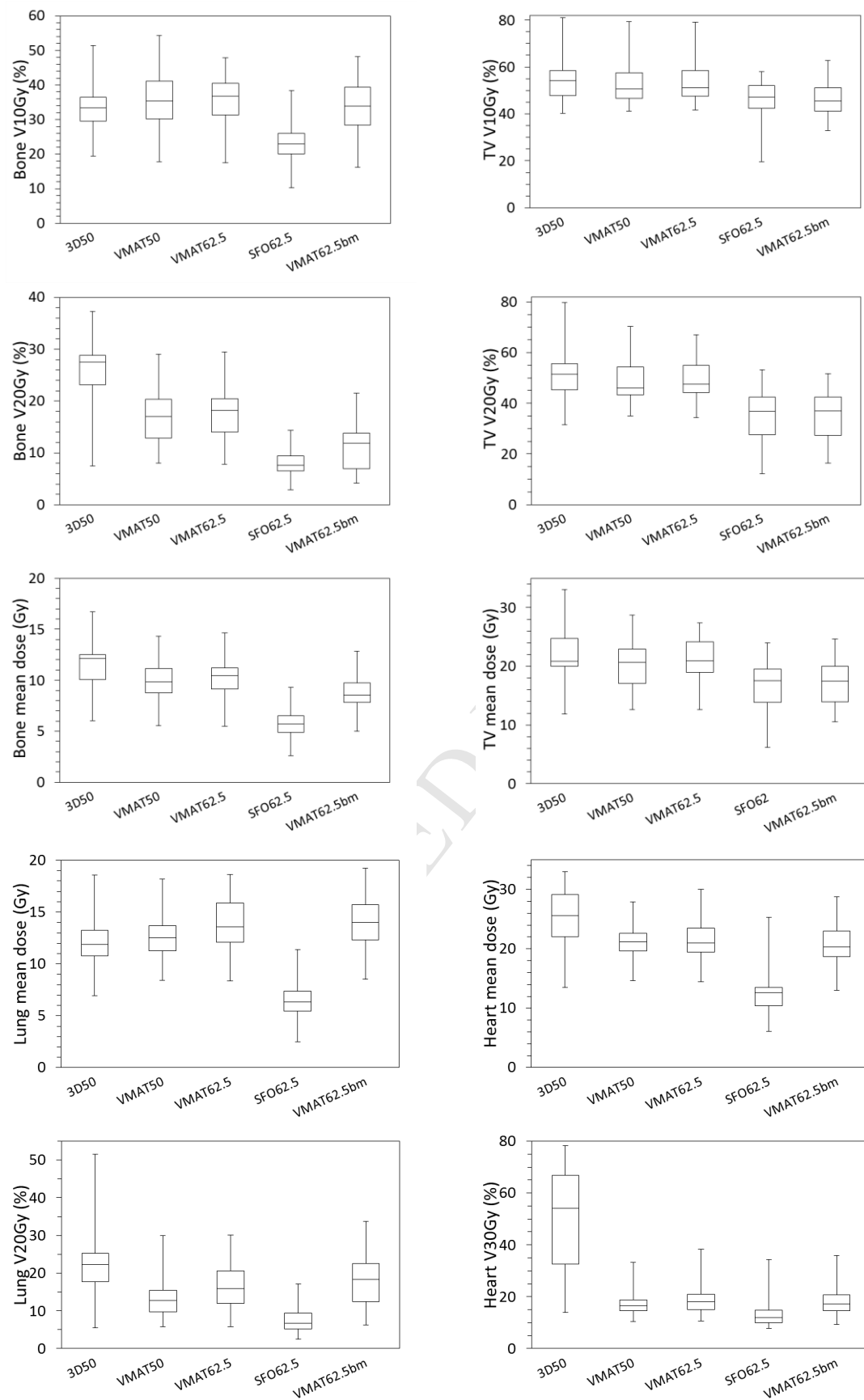
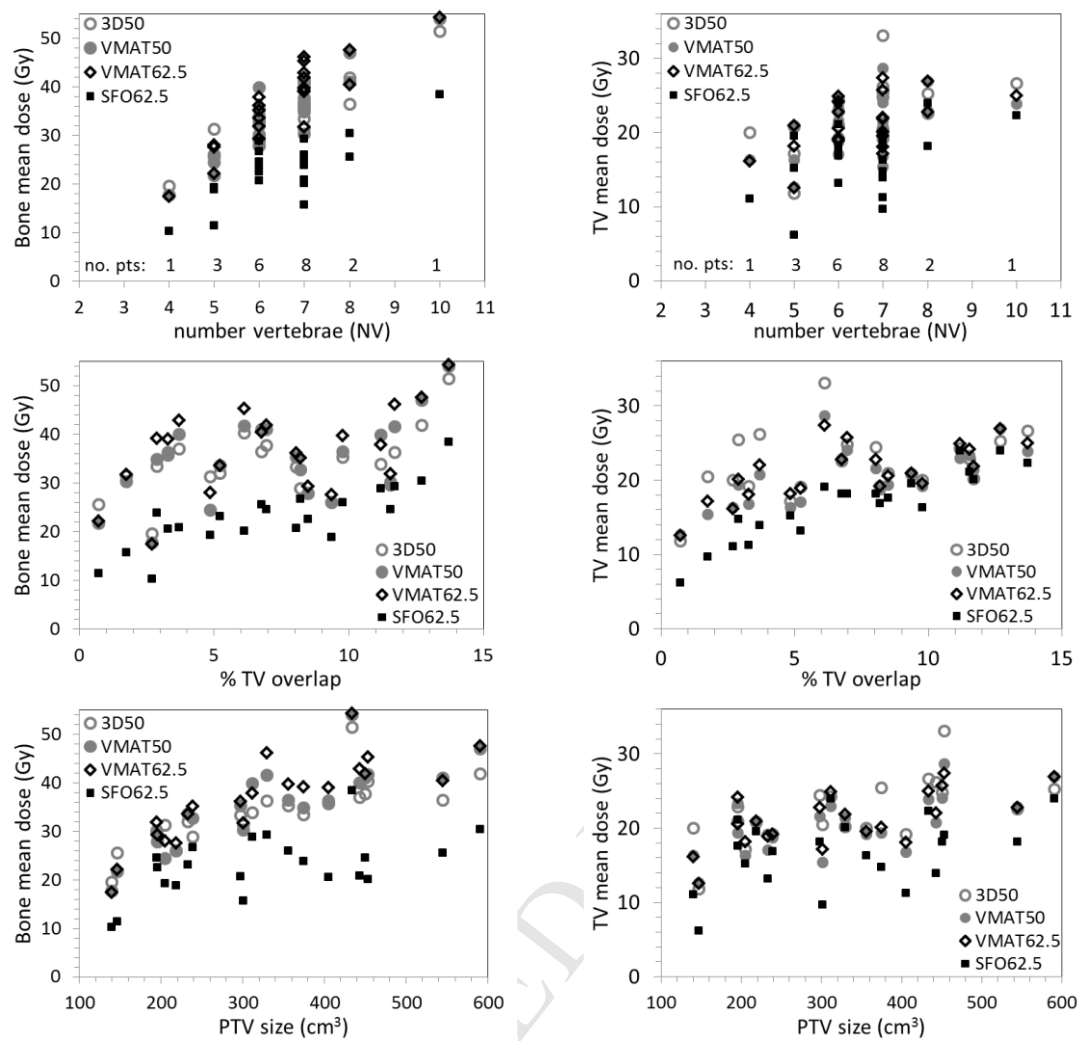
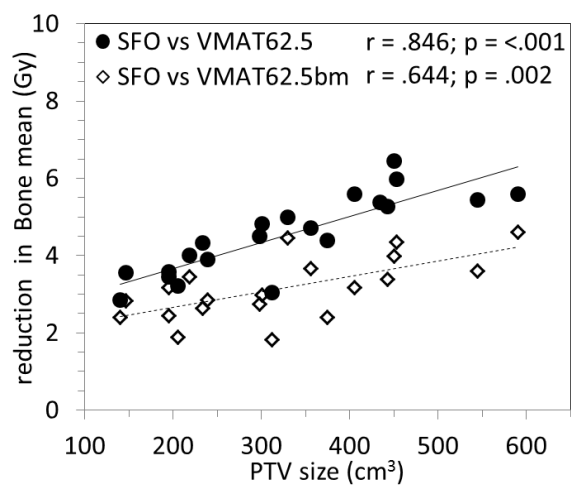


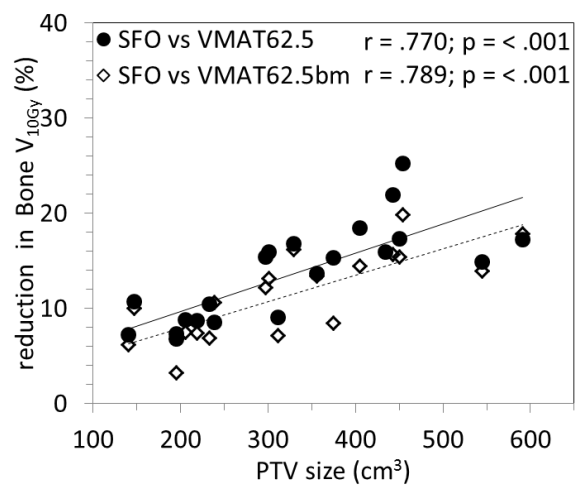
Figure 3



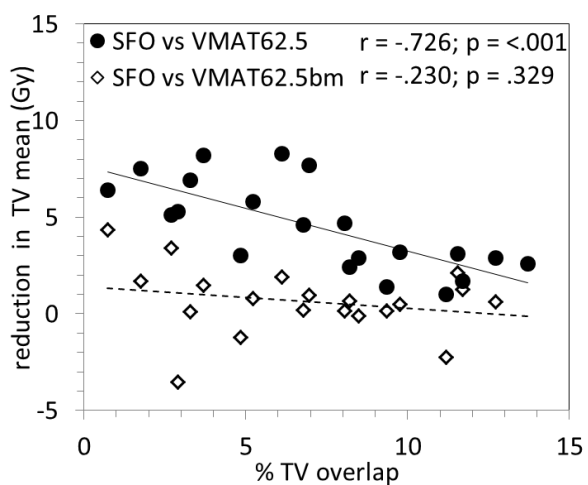
a)



b)



c)



d)

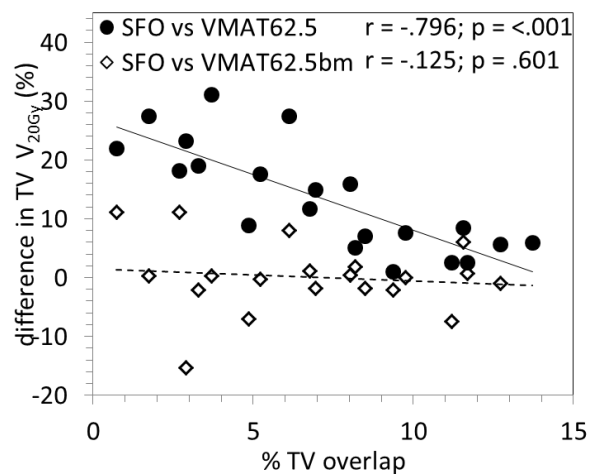


Figure 4