

Dosimetric comparison of volumetric modulated arc therapy and three dimensional conformal radiotherapy in the adjuvant setting for the management of gastric cancer: target volume coverage and normal tissue sparing

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Declaration

By submitting this thesis, I declare that the entirety of the work contained therein is my own original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Abstract

Background: Whilst the benefit of adjuvant radiotherapy in gastric cancer is known, the optimal means of delivery, including two dimensional conventional, three dimensional conformal radiotherapy, intensity modulated radiotherapy and volumetric modulated arc therapy is less certain. The purpose of this study is to assess and compare volumetric modulated arc therapy (VMAT) and three dimensional conformal radiotherapy (3DCRT) plans in adjuvant radiation of gastric cancer. **Methods and materials:** 8 patients who received adjuvant radiotherapy for gastric cancer using a 3DCRT technique were replanned with VMAT. The same CT data sets and contoured structures were used. The parameters used to compare planning target volume coverage included conformity index, uniformity index, homogeneity index, maximum dose and percentage of target volume receiving at least 95% of prescribed dose. The parameters used to compare organ at risk sparing included mean dose, maximum dose and the percentage of the volume of the organ at risk receiving more than its tolerance dose as defined by QUANTEC. Statistical analysis was performed with a paired t-test. **Results:** VMAT achieved better target volume coverage and improved conformity and uniformity indexes. VMAT achieved decreased percentage of the volume of the liver receiving more than its tolerance dose as well as maximum dose but no difference in mean dose. There was no difference between VMAT and 3DCRT for the left and right kidneys and spinal cord in terms of the defined parameters. **Conclusion:** This study showed that VMAT is superior to 3DCRT for radiotherapy in the adjuvant setting for gastric cancer with regard to target volume coverage as well as liver sparing.

However, there was no benefit for other organs at risk, namely the left and right kidneys and spinal cord. Clinical studies are required to further define the benefit of VMAT in adjuvant radiotherapy for gastric cancer.

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Abbreviations

3DCRT – three dimensional conformal radiotherapy

CI – conformity index

CT – computed tomography

Dmax – maximum dose

Dmean – mean dose

HDK – higher dose kidney

HI – homogeneity index

IMRT – intensity modulated radiotherapy

LDK – lower dose kidney

OAR – organ at risk

PTV – planning target volume

QUANTEC – Quantitative analysis of normal tissue effects in the clinic

TNM – tumor node metastasis staging

UI – uniformity index

VMAT – volumetric modulated arc therapy

Introduction

Gastric cancer remains one of the leading causes of cancer mortality worldwide. Data from the GLOBOCAN [1] database shows gastric cancer to be the third leading cause of cancer mortality worldwide with 8.8% of total cancer mortality in 2012. This is despite a marked decline in incidence over the last few decades. The age adjusted incidence rate of gastric cancer in South Africa is 5.09/100 000, making it the fifth most common cancer in this country. The prognosis of gastric cancer is poor with 2002 TNM stage groupings showing a 58% 5 year overall survival for stage IB disease, 34% for stage II, 20% for stage IIIA and 8% for stage IIIB [2, 3]. This burden of mortality has encouraged the study of surgical technique as well as adjuvant therapies in the hope of improving these outcomes. The role of surgery and adjuvant chemoradiation was established as one of the primary approaches to the management of nonmetastatic gastric cancer in the Intergroup 0116 study [4]. It was shown that post operative chemoradiation improved median overall survival from 27 months to 36 months. In this trial, a two dimensional conventional approach was used to deliver radiotherapy (45Gy in 1.8Gy fractions delivered daily five times per week). Acute grade III and grade IV toxicities were reported in 41% and 32% respectively. Late toxicity has not been reported. The proven clinical benefit for radiotherapy is therefore tempered by this toxicity.

The target volume used in post operative radiotherapy for gastric cancer includes regional lymph nodes, the tumour bed, site of anastomosis and gastric remnant if any. The planning target volume (PTV) therefore encroaches on

surrounding critical organs including the liver, spinal cord, left and right kidney. The need for increased conformity and organ at risk sparing in adjuvant radiotherapy of gastric cancer has prompted interest in and investigation of other radiotherapy techniques. Prior dosimetric studies have been undertaken to evaluate the potential benefit of three dimensional conformal radiotherapy (3DCRT), intensity modulated (IMRT) and volumetric modulated arc therapy (VMAT) [5-13]. These have shown mixed results. Whilst the balance of evidence favours a dosimetric advantage for 3DCRT over two dimensional conventional radiotherapy, the benefit of IMRT over 3DCRT is less assured. Certain studies suggest a dosimetric benefit for IMRT over 3DCRT whilst others propose no benefit or only a marginal benefit. In addition, little data exists regarding the use of VMAT in adjuvant radiotherapy of gastric cancer [5].

The purpose of this study is to dosimetrically evaluate and compare VMAT and 3DCRT in adjuvant radiotherapy of gastric cancer. PTV coverage and organ at risk sparing are reported.

Literature Review

The role of radiotherapy in gastric cancer in the post operative setting was established by Macdonald et al [4]. In this seminal paper, 556 pts with T1-T4,N0-1 gastric or esophagogastric junction tumors were randomised to observation or chemoradiation postoperatively. The majority were T3 or T4 tumors (68%) and 85% were node positive. The benefit for adjuvant radiotherapy was evidenced by a 5 year overall survival benefit of 43% versus 28% in the observation group. An in depth analysis of this and other studies evaluating the role of adjuvant radiotherapy in gastric cancer is beyond the scope of this paper but this important data is presented here to provide the necessary context. In this study, a two dimensional conventional technique was used to deliver the radiotherapy. Since then, other techniques have been employed in adjuvant radiotherapy of gastric cancer with the aim of achieving improved conformity and organ at risk sparing [5-13]. These include three dimensional conformal radiotherapy, intensity modulated radiotherapy and volumetric modulated arc therapy. The primary objective of this literature review is to critically assess the published literature with regard to adjuvant radiotherapy techniques used in gastric cancer. Specifically, dosimetric evaluation for target volume coverage and organ at risk sparing was sought. It was expected and subsequently proven that little evidence existed in the literature regarding volumetric modulated arc therapy in adjuvant radiotherapy of gastric cancer. Comparatively, though still limited, more

evidence was available with respect to other techniques including three dimensional conformal radiotherapy and intensity modulated radiotherapy.

An online search using University of Cape Town libraries was performed. The keywords chosen included “radiotherapy” and “gastric”. 48 results were obtained. Inclusion criteria included studies which evaluated radiotherapy techniques in the adjuvant setting for gastric cancer. All studies which evaluated dosimetric benefit, regardless of technique, were included. Exclusion criteria included studies evaluating non adenocarcinoma histology, non gastric primary tumors, clinical studies that did not specifically evaluate dosimetric differences between radiotherapy techniques, intraoperative radiotherapy and radiotherapy not given in the adjuvant setting.

As noted, the available literature evaluating volumetric modulated arc therapy in adjuvant radiotherapy for gastric cancer is scant. In the Wang study [5], 12 patients were retrospectively analysed with comparison made between single arc VMAT, 3DCRT and IMRT. They reported improved target volume conformity for VMAT and IMRT compared to 3DCRT, with a superior conformity index 0.82 ± 0.03 and 0.82 ± 0.03 for IMRT and VMAT respectively compared to 0.69 ± 0.03 for 3DCRT, $p < 0.001$. The maximum and mean doses to the target volume were significantly higher for both VMAT and IMRT. The mean Dmax for VMAT and IMRT was 57.86Gy and 57.24Gy respectively. With regard to organ at risk sparing, they showed benefit for VMAT and IMRT for both the liver and left kidney over 3DCRT. The left kidney mean dose, V20 and V30 as well as the liver V20 and V30 were all reduced for VMAT and IMRT over 3DCRT. No significant

difference was seen for liver mean dose. Of note in this study, the benefit of VMAT over IMRT was limited to the reduced V20 of the liver. The Wang study [5] is one of the first papers to evaluate the role of VMAT in adjuvant radiotherapy of gastric cancer and this initial reported experience lays down a marker for comparison and further study.

With respect to 3DCRT in adjuvant radiotherapy for gastric cancer, there is conflicting evidence in the literature. A systematic review published by Morganti [6] suggests that the advantage of 3DCRT over conventional radiotherapy is not proven. In terms of target volume coverage, a “minimal advantage” was seen for 3DCRT. In terms of organs at risk, the liver was better spared by conventional radiotherapy. The left kidney was better spared by 3DCRT and the right kidney was equivocal between the two techniques. In contrast to these findings, Leong et al (2005) demonstrated improved target volume coverage and reduced doses for the right and left kidney and spinal cord for 3DCRT compared to conventional radiotherapy with an antero-posterior postero-anterior (AP/PA) beam arrangement [7]. In this study, a split field monoisocentric technique was employed. 99% of the planning target volume received 95% of the prescribed dose with the conformal technique compared to 93% with the 2D technique. Of note here is coverage of the PTV with 98% of the prescribed dose - 95% for the conformal technique and, significantly inferior, 71% for the AP-PA technique. The spinal cord dose was reduced with 3DCRT. The doses to one third and two thirds of the spinal cord were 17 and 3 Gy, respectively, for the conformal technique, and 45 and 6 Gy for the AP-PA technique. Sparing of the right kidney was achieved with 3DCRT

with one third and two thirds of the right kidney receiving 18 and 6 Gy, respectively, for the conformal technique, and 35 and 4 Gy for the AP-PA technique. Similarly, sparing of the left kidney was achieved with 3DCRT – 18Gy to one third and 5Gy to two thirds for 3DCRT and 40Gy to 1/3rd and 5Gy to 2/3rd for the conventional technique. The dose to the liver was higher with 3DCRT compared to the AP/PA technique though still below tolerance (mean dose 22Gy for 3DCRT and 14Gy for AP-PA). These results clearly demonstrate a dosimetric benefit for 3DCRT with improved target volume coverage and organ at risk sparing for the defined structures. These findings have been replicated by others. Soyfer et al [11] showed a dosimetric benefit for 3DCRT in terms of kidney sparing. In this study, three arms were compared i.e. conventional AP-PA, 4 field box technique and “experimental” noncoplanar 3DCRT. A distinction was made for dosimetric purposes between the higher dose kidney (HDK) and the lower dose kidney (LDK). The mean dose to the higher dose kidney was 19.25 Gy in the experimental arm, 20.58 Gy with the four-field box technique and 24.59 Gy with AP-PA technique. Comparison of the mean dose between the experimental plan and the AP-PA plan showed a statistically significant benefit for the experimental plan. In terms of the other organs at risk, a benefit for the spinal cord was seen with the 3DCRT plan. In a similar fashion to Leong, Soyfer showed decreased dose to the liver with the conventional AP-PA technique. In summary, therefore, there is a balance of evidence favouring a dosimetric benefit for 3DCRT over a conventional 2D technique. The systematic review discussed, however, points to a “minimal advantage” offered by 3DCRT.

With regard to IMRT in adjuvant radiotherapy for gastric cancer, there is again limited and conflicting evidence. Milano et al (2006) compared conventional AP-PA (2 field), 3 field 3DCRT and IMRT techniques dosimetrically and also reported early clinical outcomes in seven patients [8]. In this study, the prescription dose was 50.4Gy, escalated from the standard 45Gy based on the Intergroup trial [4]. IMRT was shown to be superior to 3DCRT with reduced dose to the liver and right kidney. The right kidney mean dose was 26.7% (percentage of prescription dose) in the 3DCRT arm compared to 18.9% for IMRT. The right kidney volume receiving greater than threshold dose (V20) also showed benefit for IMRT – 20.9% for 3DCRT compared to 11.6% for IMRT. Similarly, the mean dose to the liver was reduced with IMRT (44.6% of prescription dose compared to 67.9% for 3DCRT). The liver volume receiving greater than the threshold dose (V30) was also reduced with 63.6% for 3DCRT compared to 18.9% for IMRT. Planning target volume coverage was evaluated by mean PTV dose and the volume receiving 55.4Gy and maximum dose. The IMRT plans had a higher mean PTV dose as well as volume receiving >55.4Gy, though neither finding was statistically significant. The maximum dose with IMRT was, however, increased and this was statistically significant compared to the 3DCRT technique and the two field technique. The Milano paper went on to report clinical outcomes, specifically acute toxicities, in this group. Despite a higher prescription dose than that used in the Intergroup trial, there was no grade 3 or worse acute toxicity. In addition, all patients completed their planned course of chemoradiotherapy. This is in contrast to the Intergroup trial in which 33% experienced grade 3 or worse gastrointestinal toxicity and 64% completed treatment uninterrupted. The Milano paper, therefore, suggests both

a dosimetric and clinical benefit for IMRT over other techniques including 3DCRT.

Minn [9] adds weight to the argument for the benefit of IMRT over 3DCRT. In similar fashion to the Milano paper, both dosimetric and clinical outcomes were reported. In this study, 57 patients were evaluated – 26 of whom received 3DCRT and 31 received IMRT. Of interest here, the mean kidney dose (bilateral kidneys) was increased in the IMRT group compared to the 3DCRT group (13.9Gy vs 11.1Gy, $p = 0.05$) but the V20 was reduced for the IMRT group. The V20 for the IMRT group was 17.5% compared to 22% for 3DCRT with a p value of 0.17. In this study, serum creatinine was measured and compared pre-treatment to most recent. The median creatinine was unchanged in the IMRT group (0.8mg/dl) but increased in the 3DCRT group from 0.8mg/dl to 1.0 mg/dl. This was statistically significant with a p value of 0.02. This suggests that the V20 is perhaps a more useful dosimetric endpoint than mean dose in predicting clinical outcomes. Benefit for the liver as an organ at risk was also shown in this study with the median liver mean dose for IMRT being 13.6Gy compared to 18.6Gy for 3DCRT. $p=0.19$. The median liver V30 was 16.1% for IMRT and 28% for 3DCRT ($p < 0.001$).

In terms of clinical outcomes, no difference was seen in 2 year overall survival or locoregional recurrence. Grade 2 acute toxicity was similar between the two groups although more treatment interruptions were required in the 3DCRT group. This paper therefore shows a dosimetric benefit for the liver and possible benefit for the kidneys with IMRT. An important limitation in this study, however, is the fact that IMRT and 3DCRT plans and dose volume

histograms were not compared for individual patients but rather as two groups. As a result, potential variables were inherent including target volume definition, field design, patient anatomy and the individual preferences of treating physicians. PTV coverage was not evaluated in this study.

Ringash [12] published an article which sought to address the potential advantage of IMRT over 3DCRT using somewhat dissimilar methods to the previously mentioned papers. In this study of twenty patients, patients who had previously received 3DCRT were replanned using IMRT. Two blinded radiation oncologists were then presented with dose volume histograms and organ dose summaries. Dose distributions and digitally reconstructed radiographs were not provided. IMRT was the preferred plan in 89% of cases. The blinded reviewers felt that IMRT provided better planning target volume coverage in 86% of cases. Organs at risk were also thought to be spared preferentially with IMRT – 74% of cases for spinal cord, 69% of cases for kidneys, 71% of cases for liver and 69% of cases for the heart. These statistics are difficult to relate to the available literature as they reflect distinctly dissimilar endpoints from those published in other studies. However, these findings do add weight to the argument in favour of benefit of IMRT over 3DCRT. This paper does also report the median doses received by the organs at risk (OAR) – dose to 20%, 50% and 80% of the volume of each OAR is presented. Using D50 as a surrogate, dose to 50% of the liver (17.29 vs. 27.97), left kidney (15.50 vs. 16.06 Gy) and heart (12.89 vs. 15.50 Gy), were lower with IMRT than with the conformal plans.

The study by Chung [13] also supports the dosimetric benefit of IMRT over 3DCRT. In this study of ten patients, IMRT had an increased PTV V45 (volume of the PTV receiving >45Gy) of 95% versus 72% for 3DCRT. No difference was noted for the left and right kidneys between 3DCRT and IMRT. The liver was preferentially spared with IMRT – V30 of 24.5% for IMRT versus 40.2% for 3DCRT with a p value <0.001. The mean dose was also improved with IMRT 22.7Gy versus 26.3Gy (p <0.001). Of note in this study, the plans were also sent to a centre experienced in IMRT, namely the University of California San Francisco (UCSF) for replanning. UCSF was able to achieve lower left kidney V20 and right kidney V20 than the IMRT plans of Chung. They also achieved lower liver mean dose than the IMRT plans of Chung. This study therefore highlights two aspects. Firstly, the benefit of IMRT over 3DCRT is shown in terms of liver sparing and PTV coverage. It must be stated here, however, that the endpoint chosen to evaluate PTV coverage is not as robust as, for example, indexes evaluating conformity, homogeneity and uniformity. Secondly, the improvement in plans achieved by an experienced centre demonstrates the dependence of IMRT planning on individual users. This effect cannot be underestimated when interpreting dosimetric data that originates in many different sites with varying levels of experience and expertise.

The Alani [10] article of 2009 compared 3DCRT and IMRT dosimetrically with similar endpoints to those mentioned in the other studies. 14 patients were included. All these patients had been treated with a noncoplanar four field arrangement. This is a departure from the coplanar approach utilised in other trials. IMRT plans were then generated for comparison. PTV coverage was

“satisfactory” for both approaches based on 95% isodose coverage. In this trial, a clinical distinction was made between high and low dose kidney, not simply left and right. Mean kidney dose to the high dose kidney was 12.8Gy for IMRT and 25.6Gy for 3DCRT. The V20 for the high dose kidney was 17% for IMRT compared to 39% for 3DCRT. In terms of the low dose kidney, the mean dose was 11.3Gy for IMRT versus 21.2Gy for 3DCRT, with a V20 of 7% for IMRT and 17% for 3DCRT. These results depict a benefit for IMRT over 3DCRT in terms of kidney sparing. Despite the statistical significance shown, the authors do question however the clinical relevance of this benefit. Of course, this can only be evaluated in a clinical study and this question remains unanswered. Of note in this paper is the mean dose to the liver. They achieved a mean dose of 31Gy for IMRT and 25Gy for 3DCRT. The statistical relevance of, never mind the reasons for, this finding is not discussed in the paper. In summary, the authors note that IMRT confers only a “marginal benefit” over 3DCRT and should be considered only in those patients with underlying kidney disease or risk factors for its development. The authors also assert that the noncoplanar beam arrangement approach is a “valuable tool” and suggest that the benefit of IMRT over 3DCRT seen in other reports, as discussed previously, “may have been exaggerated”.

All studies with dosimetric comparisons were included regardless of the methods of comparison. A challenge faced when interpreting the available data, therefore, was the variety of methods used in the different studies to evaluate target volume coverage and organ at risk sparing. The endpoints used were heterogeneous. Evaluation and comparison of target volume coverage was

variably done on the basis of percentage of the target volume covered by the 95% isodose line, conformity, uniformity and homogeneity indexes. The parameters used to compare organ at risk sparing also varied. This makes cross trial comparison and interpretation of the data difficult – a standard template of comparison with predefined parameters would make analysis of the data as a whole more meaningful. However, the comparative value for individual articles remains useful.

In summary, whilst the balance of evidence favours a dosimetric advantage for 3DCRT over two dimensional conventional radiotherapy, the benefit of IMRT over 3DCRT is less certain. Little data exists in the literature regarding the use of volumetric modulated arc therapy in gastric cancer and the data presented by Wang [5] is, to our knowledge, the first study to evaluate the role of VMAT in gastric cancer.

Methods

Eight patients were identified who met the inclusion criteria. This included patients seen at the Department of Radiation Oncology, Groote Schuur Hospital between 2009-2013 with pathologically proven gastric adenocarcinoma. All patients had undergone surgery as the primary modality of treatment followed by adjuvant three dimensional conformal radiotherapy. Exclusion criteria included patients with metastatic disease, patients who received two dimensional conventional radiotherapy, non adenocarcinoma histology and oesophageal or oesophagogastric junction tumors.

These patients had all been previously treated with 3DCRT using the Varian ® Clinac 23Ex and treatment planning was done using the Pinnacle ® treatment planning software. The same CT data sets and segmented structures, including planning target volume and organs at risk, were duplicated to create a template for this analysis. The prescribed dose-fractionation schedule conformed to the international standard of 45Gy in 1.8Gy fractions described in Intergroup 0116 [4]. The 3DCRT plans typically consisted of 3 and 4 coplanar fields optimised by forward planning. Dose prescription was to the International Commission on Radiation Units and Measurements (ICRU) reference point. Beam weighting, energy, angles and multileaf collimator position were optimised for each of these treatment plans. All patients had an assessment of renal function with pre-treatment glomerular filtration rate and renogram.

Volumetric modulated arc therapy plans were then generated for each of the patients within the Pinnacle® (Phillips Medical System, Madison, Wisconsin) treatment planning system. The dose prescription was to the ICRU reference point. Single arc VMAT was utilised for all patients. An initial template of constraints was applied to all eight patients. Modification of these constraints was done as necessary to optimise the plans i.e. minimise dose to organs at risk without compromising PTV coverage. The planning criteria for organs at risk conformed closely to QUANTEC tolerance guidelines. The initial constraints applied were as follows:

1. PTV – 95% prescribed dose to 98% of the PTV. Dmax 107% of prescribed dose.
2. Liver – V30 <30%
3. Left kidney – V23 <30%
4. Right kidney – V23 <30%
5. Spinal cord – Dmax <45Gy

The parameters used to compare planning target volume coverage of the 3DCRT and VMAT plans included conformity index, uniformity index, homogeneity index, mean dose, maximum dose and percentage of target volume receiving at least 95% of prescribed dose (TV95%). The indexes are defined as follows:

1. Conformity index – defined by the following formula. $(TV95/TV) \times (TV95/V95)$. TV95 is the volume of the target covered by the 95% isodose curve. TV is the total target volume. V95 is the volume of tissue

covered by the 95% isodose line. The conformity index ranges from 0 to 1, with 1 being the ideal value [14].

2. Uniformity index – defined as $D5/D95$. D5 is the minimum dose to 5% of the PTV. D95 is the minimum dose to 95% of the PTV. The lower the index, the more uniform the plan [15].
3. Homogeneity index – defined as the difference in PTV dose between D1 and D99 divided by the prescription dose. The lower the index, the more homogenous the plan [16-18].

The parameters used to compare organ at risk sparing for 3DCRT and VMAT included maximum dose, mean dose and percentage of volume of organ at risk (OAR) receiving a dose more than its tolerance limit as defined by QUANTEC. This was done for each organ at risk, namely left and right kidney, liver and spinal cord. The specific parameters were as follows:

1. Liver – Dmax (maximum dose), Dmean (mean dose to the organ), V30 (volume of the organ receiving more than 30Gy)
2. Right and left kidney – Dmax, Dmean, V23 (volume of the organ receiving more than 23Gy)
3. Spinal cord - Dmax

Dose volume histograms were also used to compare treatment plans. All data was captured into an electronic Microsoft Excel ® database. Personal identifiers were removed. Descriptive statistics including mean and standard deviation

was used to summarise results. Statistical analysis was performed with a paired t-test and a p value of $p < 0.05$ was set for statistical significance.

Results

Both the 3DCRT and VMAT approaches produced acceptable plans, both in terms of PTV coverage and organ at risk tolerances i.e. dose distributions and dose volume histograms were satisfactory for all plans.

In terms of PTV coverage, VMAT was shown to be superior with respect to the conformity and uniformity indexes, TV95 as well as maximum dose. No difference was seen with regard to the homogeneity index or PTV mean dose:

1. The mean conformity index for 3DCRT was 0.73 with 95% CI 0.71-0.75 and the mean conformity index for VMAT was 0.77 with a 95% CI 0.73-0.81. This was statistically significant with a p value of 0.02.
2. The mean uniformity index for 3DCRT was 1.13 (95% CI 1.11-1.14) compared to a mean of 1.10 for VMAT (95% CI 1.09-1.11), p = 0.021.
3. The TV95 for VMAT was superior with a mean 3DCRT TV95 of 96.79 (95% CI 95.72-97.87) compared to the VMAT TV95 mean of 97.53 (95% CI 96.8-98.26) with a p 0.0049.
4. In terms of maximum dose (Dmax), VMAT achieved a statistically significant lower dose. The 3DCRT mean PTV Dmax was 112% (95% CI 109.8-114.2) compared to VMAT mean 110.5% (95% CI 108.9-112), p = 0.005.

5. In terms of the homogeneity index, no difference was seen between 3DCRT and VMAT. The mean homogeneity index for 3DCRT was 0.17 (95% CI 0.14-0.21) and VMAT was 0.17 (95% CI 0.14-0.20) p = 0.54.
6. No difference was seen in the PTV mean dose – 103.4% (95% CI 102.4-104.4) for 3DCRT and 104% (95% CI 102.9-105%) for VMAT, p = 0.11.

Table 1: Comparison of the PTV parameters

	3D-CRT	VMAT	
	Mean (95% CI)	Mean (95% CI)	p Value
Conformity Index	0.73 (0.71-0.75)	0.77 (0.73-0.81)	0.02
Uniformity Index	1.13 (1.11-1.14)	1.10 (1.09-1.11)	0.021
Homogeneity Index	0.17 (0.14-0.21)	0.17 (0.14-0.20)	0.54
TV95	96.79% (95.72-97.87)	97.53% (96.8-98.26)	0.0049
Dmax	112% (109.8-114.2)	110.5% (108.9-112)	0.005
PTV Mean	103.4% (102.4-104.4)	104% (102.9-105)	0.11

CI = confidence interval

Conformity index, uniformity index, homogeneity index and TV95 calculated as described under Methods

In terms of organ at risk sparing, VMAT was superior to 3DCRT for the liver Dmax and V30 though no difference was shown for Dmean. No difference was seen for the left and right kidney or spinal cord:

1. Liver – the mean Dmax for 3DCRT was 49.7Gy (95% CI 48.6Gy-50.8Gy) compared to the VMAT mean of 48.9Gy (95% CI 48Gy-49.9Gy), $p = 0.01$. The V30 for VMAT was also superior to 3DCRT. The 3DCRT mean V30 was 34.2Gy (95% CI 25.9 – 42.6Gy) compared to 24.2Gy for VMAT (95% CI 21.2-27.2Gy), $p = 0.013$. No statistically significant difference was shown in terms of the mean dose to the liver, with 3DCRT achieving a mean of 22.1Gy (95% CI 20.4 – 23.8Gy) and VMAT achieving a mean of 21.7Gy (95% CI 20.2 – 23.2Gy), $p = 0.38$.
2. Right kidney – no difference was shown for any of the defined parameters. The mean Dmax for 3DCRT was 33.1Gy (95% CI 22.9 – 43.3Gy) compared to the VMAT Dmax of 34.3Gy (95% CI 25.8 – 42.7Gy), $p = 0.39$. The mean dose for 3DCRT was 10.2Gy (95% CI 5.9 – 14.4Gy) compared to VMAT 11.4Gy (95% CI 7.4 -15.4Gy) with a nonsignificant difference. The mean for both 3DCRT and VMAT are well within tolerance. The 3DCRT V23 was 6.8Gy compared to 8.6Gy for VMAT (nonsignificant).
3. Left Kidney – the clinical relevance of the defined parameters in the left kidney should be understood in context. In terms of the planning approach for both the forward and inverse plans in the present study, the typical dose constraints one would apply were purposefully disregarded. This is based on the clinical decision to accept a higher dose

to the left kidney with the intention of maximal sparing of the contralateral kidney. No difference was seen in terms of Dmax or V23. The 3DCRT mean Dmax was 48Gy compared to 47.8Gy, a nonsignificant difference. The V23 for 3DCRT was 70.7Gy and 64.7 for VMAT, statistically nonsignificant. A benefit for the left kidney mean dose was shown for VMAT over 3DCRT. The mean dose achieved with 3DCRT was 30.6Gy (95% CI 21 – 40.3Gy) compared to 28.6Gy (95% CI 18.9 – 38Gy), $p = 0.02$.

4. Spinal cord – no difference was seen for the spinal cord Dmax, with 34.2Gy (95% CI 25.9 – 42.4Gy) for 3DCRT versus 40.1 (95% CI 37 – 43.2Gy) for VMAT, a nonsignificant difference.

Table 2: Comparison of the OAR parameters

	3D-CRT	VMAT	
	Mean (95% CI)	Mean (95% CI)	p Value
Liver			
V30 ^Ψ	34.2% (25.9-42.6)	24.2% (21.2-27.2)	0.013
Dmax	49.7Gy (48.6-50.8)	48.9Gy (48-49.9)	0.01
Mean	22.1Gy (20.4-23.8)	21.7Gy (20.2-23.2)	0.38
Right kidney			
V23 [#]	6.8% (1.3-14.9)	8.6% (2.2-14.9)	0.246
Dmax	33.1Gy (22.9-43.3)	34.3Gy (25.8-42.7)	0.39
Mean	10.2Gy (5.9-14.4)	11.4Gy (7.4-15.4)	0.06
Left kidney			
V23 [#]	70.7% (46.6-94.9)	64.7% (35.4-94.1)	0.104
Dmax	47.9Gy (46.9-49)	47.8Gy (47.1-48.6)	0.707
Mean	30.67Gy (21-40.34)	28.6Gy (19-38.2)	0.02
Spinal Cord			
Dmax	34.2Gy (25.9-42.4)	40.1Gy (37-43.2)	0.052
CI = confidence interval			
^Ψ The volume of the liver that received more than 30Gy			
[#] The volume of the kidney that received more than 23Gy			

Representative isodose distributions and dose volume histograms are shown below for comparative purposes.

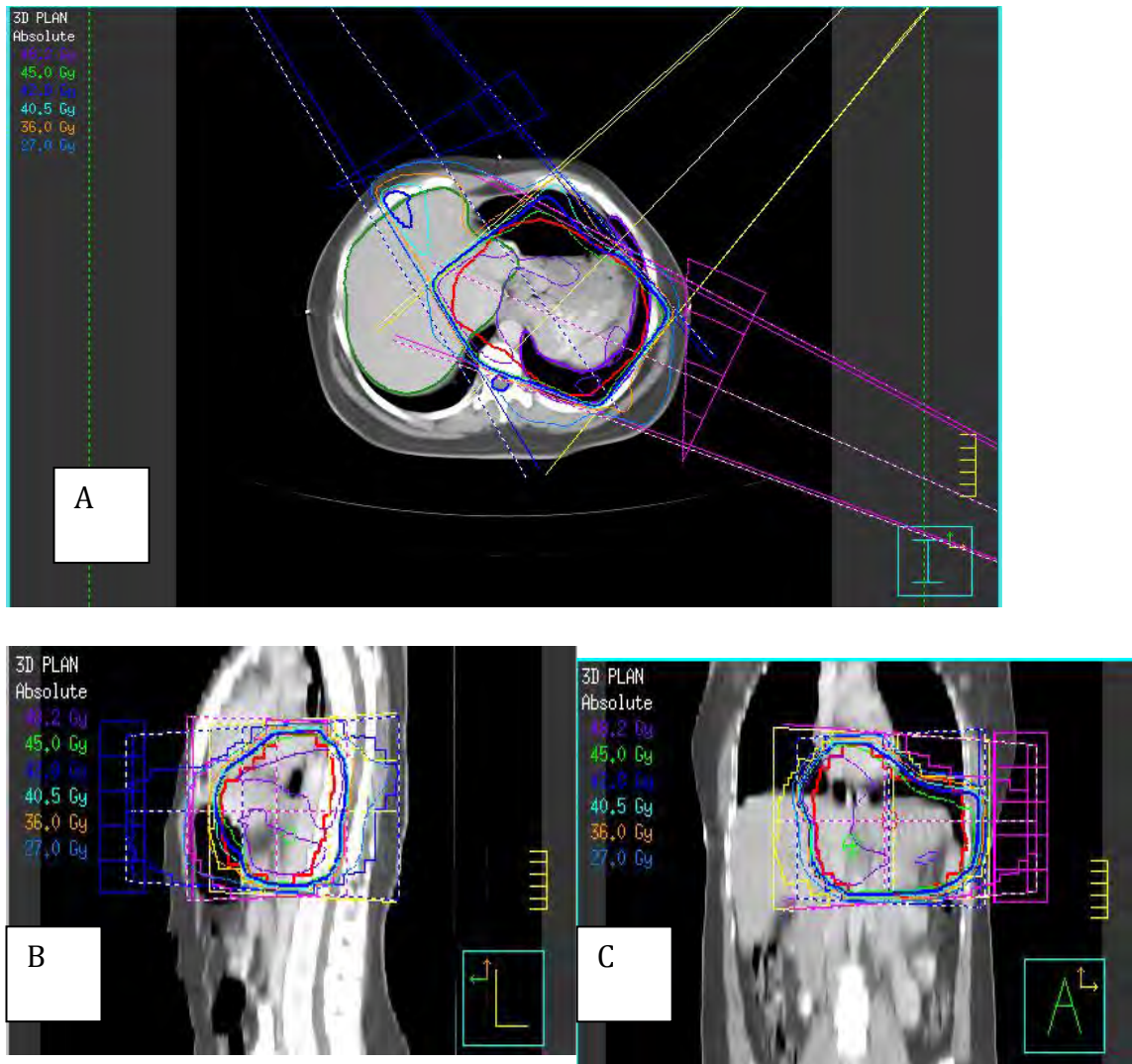


Figure 1. 3DCRT - Isodose curves and beam arrangement in axial (A), sagittal (B) and coronal (C) planes.

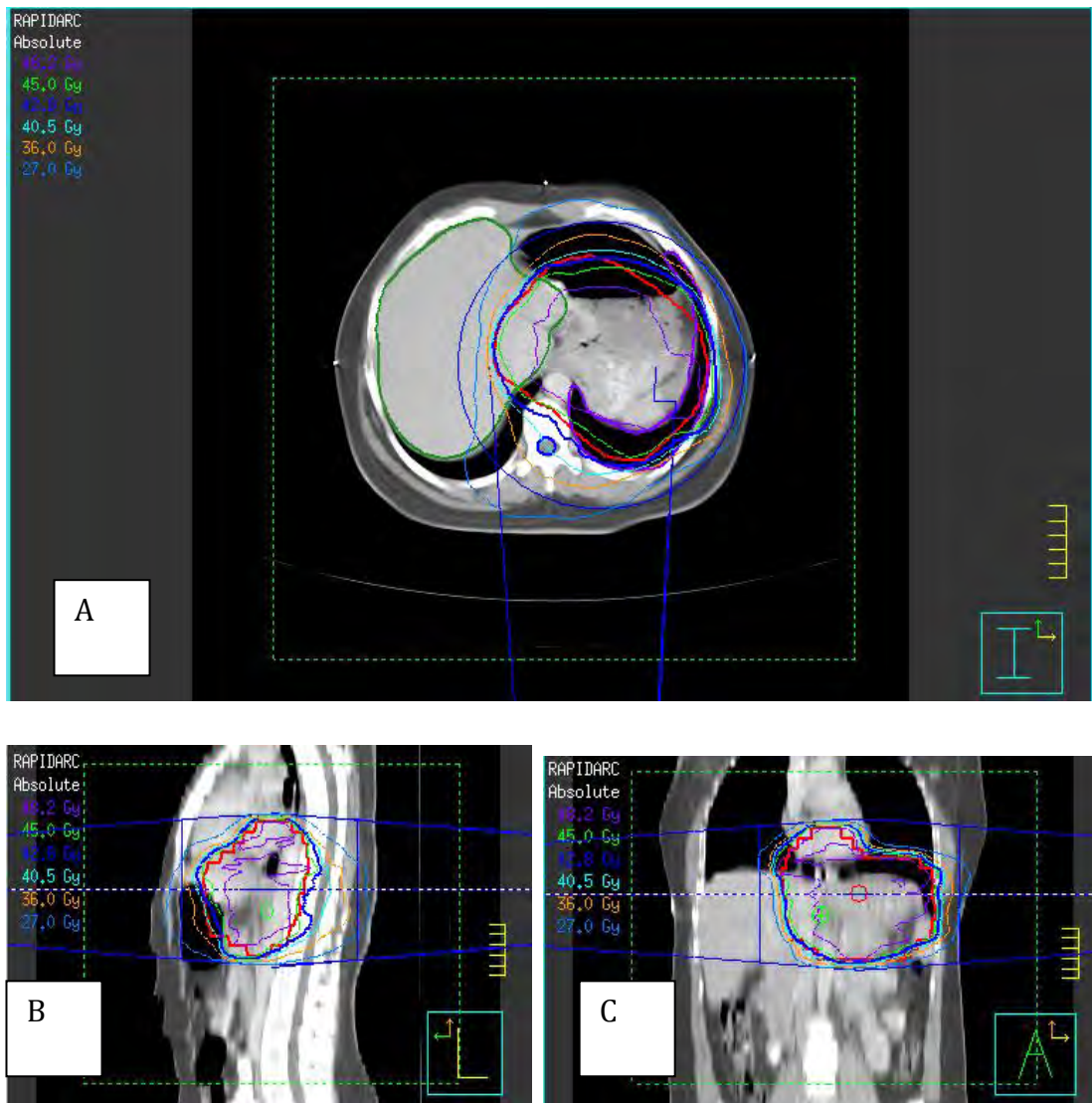
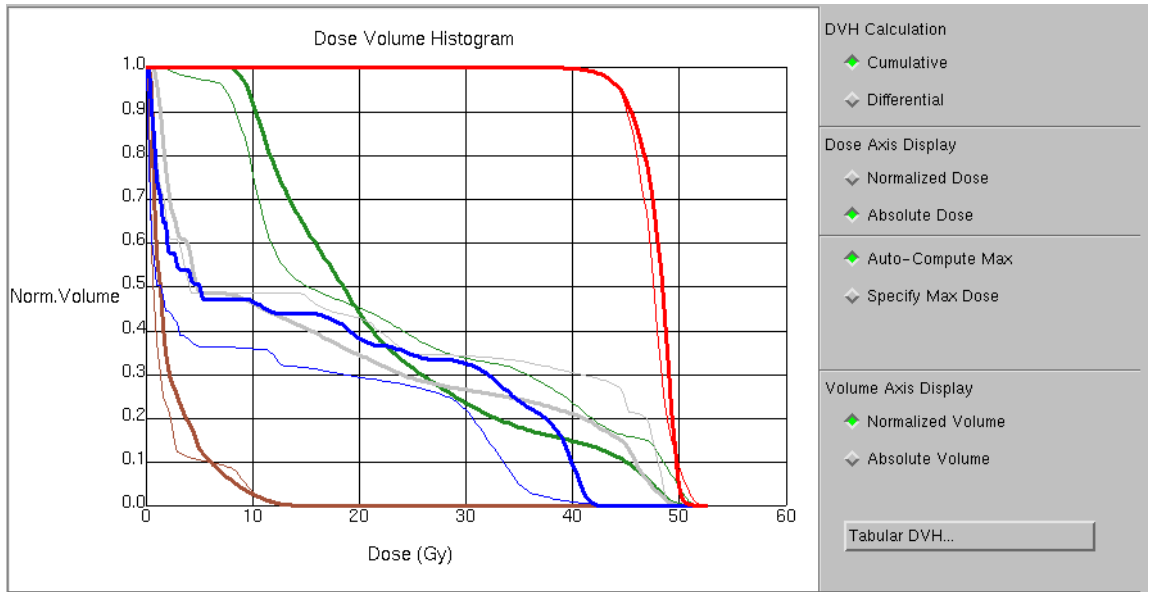


Figure 2. VMAT – Isodose curves in axial (A), sagittal (B), and coronal (C) planes.



ROI Statistics										Compute
Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max	Generalized EUD	
<input type="checkbox"/>	LIVER	3D PLAN	1.13	52.20	23.24	15.65	0.00 %	0.00 %	--	
<input checked="" type="checkbox"/>	LIVER	RAPIDARC	7.06	50.32	22.31	12.12	0.00 %	0.00 %	--	
<input type="checkbox"/>	LT KIDNEY	3D PLAN	0.43	49.26	19.31	20.04	0.00 %	0.00 %	--	
<input type="checkbox"/>	LT KIDNEY	RAPIDARC	0.84	49.69	16.56	17.53	0.00 %	0.00 %	--	
<input type="checkbox"/>	RT KIDNEY	3D PLAN	0.21	12.50	1.78	2.69	0.00 %	0.00 %	--	
<input checked="" type="checkbox"/>	RT KIDNEY	RAPIDARC	0.41	13.71	2.37	2.54	0.00 %	0.00 %	--	
<input type="checkbox"/>	S CORD	3D PLAN	0.05	44.72	10.78	14.10	0.00 %	0.00 %	--	
<input checked="" type="checkbox"/>	S CORD	RAPIDARC	0.30	42.29	13.02	16.08	17.42 %	0.00 %	--	
<input type="checkbox"/>	ptv	3D PLAN	38.17	52.50	47.46	1.89	0.00 %	0.00 %	--	
<input type="checkbox"/>	ptv	RAPIDARC	33.05	51.31	47.93	1.84	0.00 %	0.00 %	--	

Figure 3. Dose volume histogram comparing 3DCRT (thin solid) and VMAT (thick solid) in a representative patient.

Discussion

Primary surgery and adjuvant chemoradiation for gastric cancer is an established approach since Macdonald's seminal paper [4]. Following this, the Smalley consensus report advocated parallel opposed fields as "the most practical arrangement for the overwhelming majority of postoperative adjuvant radiotherapy cases" [19]. However, given the rate of acute grade III and IV toxicities, specifically 41% and 32% in the Macdonald trial, in addition to poor survival rates in gastric cancer, efforts have been made to improve the radiotherapy component of gastric cancer treatment. Subsequent studies evaluating different techniques of radiotherapy, including three dimensional conformal radiotherapy and intensity modulated radiotherapy, have yielded mixed results [5-13]. Whilst the balance of evidence favours a dosimetric advantage for 3DCRT over two dimensional conventional radiotherapy, the benefit of IMRT over 3DCRT is less certain. Little data exists in the literature regarding the use of volumetric modulated arc therapy in gastric cancer. The data presented by Wang [5] is, to our knowledge, the first study to evaluate the role of VMAT in adjuvant radiotherapy of gastric cancer.

Currently at our institution, three dimensional conformal radiotherapy is offered to all gastric cancer patients in the adjuvant setting. The dosimetric benefits shown in this study contend that VMAT is superior to three dimensional conformal radiotherapy for adjuvant radiotherapy of gastric cancer. We observed a benefit for VMAT with superior PTV coverage, as

evidenced by improved conformity, uniformity, volume of PTV covered by the 95% isodose and a lower Dmax. In addition, improved organ at risk sparing, specifically for the liver, was achieved with VMAT. This was shown in terms of a reduced V30 and Dmax. No difference was observed with regard to the other organs at risk, namely left and right kidney and spinal cord. In comparison to Wang, we have similarly confirmed the benefit of VMAT in terms of PTV coverage and liver sparing. In contrast, however, we were not able to show a dosimetric benefit for either the left or right kidney with VMAT. The basis for this lack of benefit may include several reasons. As demonstrated by Chung, improvement in plans can be achieved by a centre more experienced in intensity modulated radiotherapy [13]. Secondly, the clinical decision to accept doses beyond tolerance to one kidney, with the express intention of maximal sparing of the contralateral kidney, must be factored in. Cross trial comparison must take these aspects into account.

The role of radiotherapy in gastric cancer must also be considered in a resource constrained setting. In an environment where time on the Linac is precious, the benefit of reduced treatment times is an important factor. Radiotherapy departments such as ours who face these challenges would welcome any potential gains that VMAT might offer in this regard. Whilst treatment times might be reduced, however, the increased burden of quality assurance for VMAT compared to 3DCRT would be an equally important factor to consider in a resource constrained environment. Clinical studies are needed to further evaluate these particular aspects.

Based on these observations, the possible clinical benefits must be considered. Whilst these benefits cannot be truly known outside a clinical trial, the potential for reduced treatment related toxicity is clear. In addition, there is also potentially less need to sacrifice, possibly tumoricidal, total dose to meet surrounding organ at risk tolerances. Indeed, there is the possibility of dose escalation with more conformal techniques. Situations which warrant this consideration include incomplete resection or nodal extracapsular extension. In a disease fraught with poor outcomes and significant treatment related morbidity, any meaningful improvement in radiotherapy technique and delivery will be welcomed. Volumetric modulated arc therapy in the adjuvant setting for gastric cancer warrants further clinical study.

Competing interests

The authors declare that they have no competing interests.

Authors contributions

Dr Reddy was responsible for conception and design of the study, data acquisition, analysis and interpretation as well as drafting the manuscript.

Dr Robertson supervised the study from conception and critically appraised the draft and final manuscripts.

Acknowledgements

My thanks go to my supervisor Dr B Robertson for her steadfast guidance and the medical physics team at Groote Schuur Hospital and Theresa Binz for their support throughout.

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Appendix A: Ethics Approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: linsey.samuels@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

06 November 2013

HREC REF: 684/2013

Dr B Reddy
c/o Dr B Robertson
Radiation Oncology
GSH

Dear Dr Reddy

PROJECT TITLE: DOSIMETRIC COMPARISON OF VOLUMETRIC MEDIATED ARC THERAPY AND 3D CONFORMAL RADIOTHERAPY IN THE ADJUVANT SETTING FOR THE MANAGEMENT OF GASTRIC CANCER: TARGET VOLUME COVERAGE AND NORMAL TISSUE SPARING

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

HREC REF 684/2013

Appendix B: Instructions for Authors - Radiation Oncology Journal

Submission process

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

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Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

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During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the 'About [Radiation Oncology](#)' page, and to declare any potential competing interests. You will be also asked to provide the contact details (including email addresses) of potential peer reviewers for your manuscript. These should be experts in their field, who will be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same research institution. Suggested reviewers will be considered alongside potential reviewers recommended by the Editor-in-Chief and/or Editorial Board members.

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If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF.

For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

Preparing main manuscript text

General guidelines of the journal's style and language are given below.

Title page

The title page should:

- provide the title of the article

- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

Abstract

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background**, the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your research reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

Keywords

Three to ten keywords representing the main content of the article.

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The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

Methods

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see 'About this journal'.

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The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

Conclusions

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

Competing interests

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

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- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
- Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

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In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

According to ICMJE guidelines, An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

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Acknowledgements

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Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, datasets, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE. Citations in the reference list should include all named authors, up to the first 30 before adding '*et al.*'..

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of ab initio three-dimensional prediction, secondary structure, and contacts prediction. *Proteins* 1999, **43**(Suppl 3):149-170.

In press article

Kharitonov SA, Barnes PJ: **Clinical aspects of exhaled nitric oxide.** *Eur Respir J*, in press.

Published abstract

Zvaifler NJ, Burger JA, Marinova-Mutafchieva L, Taylor P, Maini RN: **Mesenchymal cells, stromal derived factor-1 and rheumatoid arthritis [abstract].** *Arthritis Rheum* 1999, **42**:s250.

Article within conference proceedings

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Book chapter, or article within a book

Schnepf E: **From prey via endosymbiont to plastids: comparative studies in dinoflagellates.** In *Origins of Plastids. Volume 2.* 2nd edition. Edited by Lewin RA. New York: Chapman and Hall; 1993:53-76.

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Whole conference proceedings

Smith Y (Ed): *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore*. Stoneham: Butterworth-Heinemann; 1996.

Complete book

Margulis L: *Origin of Eukaryotic Cells*. New Haven: Yale University Press; 1970.

Monograph or book in a series

Hunninghake GW, Gadek JE: **The alveolar macrophage**. In *Cultured Human Cells and Tissues*. Edited by Harris TJR. New York: Academic Press; 1995:54-56.
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The Mouse Tumor Biology Database

[<http://tumor.informatics.jax.org/mtbwi/index.do>]

Link / URL with author(s)

Corpas M: **The Crowdfunding Genome Project: a personal genomics community with open source values**

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Dataset with persistent identifier

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<http://dx.doi.org/10.5524/100012>.

Clinical trial registration record with persistent identifier

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Current Controlled Trials. <http://dx.doi.org/10.1186/ISRCTN22153967>

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There is no charge for the use of color figures.

Please read our **figure preparation guidelines** for detailed instructions on maximising the quality of your **figures**.

Formats

The following file formats can be accepted:

- PDF (preferred format for diagrams)
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Figure legends

The legends should be included in the main manuscript text file at the end of the document, rather than being a part of the figure file. For each figure, the following information should be provided: Figure number (in sequence, using Arabic numerals - i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words); detailed legend, up to 300 words.

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Allowable formats - EPS, PDF (for line drawings), PNG, TIFF (for photographs and screen dumps), JPEG, BMP, DOC, PPT, CDX, TGF (ISIS/Draw).

Preparing tables

Each table should be numbered and cited in sequence using Arabic numerals (i.e. Table 1, 2, 3 etc.). Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Detailed legends may then follow, but they should be concise. Tables should always be cited in text in consecutive numerical order.

Smaller tables considered to be integral to the manuscript can be pasted into the end of the document text file, in A4 portrait or landscape format. These will be typeset and displayed in the final published form of the article. Such tables should be formatted using the 'Table object' in a word processing program to ensure that columns of data are kept aligned when the file is sent electronically for review; this will not always be the case if columns are generated by simply using tabs to separate text. Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell display as black lines. Commas should not be used to indicate numerical values. Color and shading may not be used; parts of the table can be highlighted using symbols or bold text, the

meaning of which should be explained in a table legend. Tables should not be embedded as figures or spreadsheet files.

Larger datasets or tables too wide for a landscape page can be uploaded separately as additional files. Additional files will not be displayed in the final, laid-out PDF of the article, but a link will be provided to the files as supplied by the author.

Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). As with all files, please use the standard file extensions.

Preparing additional files

Although *Radiation Oncology* does not restrict the length and quantity of data included in an article, we encourage authors to provide datasets, tables, movies, or other information as additional files.

Please note: All Additional files **will be published** along with the article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files should be sent by email to radiationoncology@biomedcentral.com, quoting the Manuscript ID number.

Results that would otherwise be indicated as "data not shown" can and should be included as additional files. Since many weblinks and URLs rapidly become broken, *Radiation Oncology* requires that supporting data are included as

additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission.

Additional files can be in any format, and will be downloadable from the final published article as supplied by the author. We recommend CSV rather than PDF for tabular data.

Certain supported files formats are recognized and can be displayed to the user in the browser. These include most movie formats (for users with the Quicktime plugin), mini-websites prepared according to our guidelines, chemical structure files (MOL, PDB), geographic data files (KML).

If additional material is provided, please list the following information in a separate section of the manuscript text:

- File name (e.g. Additional file 1)
- File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)
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Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

Additional file formats

Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

- Additional documentation
 - PDF (Adobe Acrobat)
- Animations
 - SWF (Shockwave Flash)
- Movies
 - MP4 (MPEG 4)
 - MOV (Quicktime)
- Tabular data
 - XLS, XLSX (Excel Spreadsheet)
 - CSV (Comma separated values)

As with figure files, files should be given the standard file extensions.

Mini-websites

Small self-contained websites can be submitted as additional files, in such a way that they will be browsable from within the full text HTML version of the article.

In order to do this, please follow these instructions:

1. Create a folder containing a starting file called index.html (or index.htm) in the root.

2. Put all files necessary for viewing the mini-website within the folder, or sub-folders.
3. Ensure that all links are relative (ie "images/picture.jpg" rather than "/images/picture.jpg" or "http://yourdomain.net/images/picture.jpg" or "C:\Documents and Settings\username\My Documents\mini-website\images\picture.jpg") and no link is longer than 255 characters.
4. Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.
5. Compress the folder into a ZIP, check the file size is under 20 MB, ensure that index.html is in the root of the ZIP, and that the file has .zip extension, then submit as an additional file with your article.

Style and language

General

Currently, *Radiation Oncology* can only accept manuscripts written in English. Spelling should be US English or British English, but not a mixture.

There is no explicit limit on the length of articles submitted, but authors are encouraged to be concise.

Radiation Oncology will not edit submitted manuscripts for style or language; reviewers may advise rejection of a manuscript if it is compromised by grammatical errors. Authors are advised to write clearly and simply, and to have their article checked by colleagues before submission. In-house copyediting will be minimal. Non-native speakers of English may choose to make use of a copyediting service.

Help and advice on scientific writing

The abstract is one of the most important parts of a manuscript. For guidance, please visit our page on [Writing titles and abstracts for scientific articles](#).

Tim Albert has produced for BioMed Central a [list of tips](#) for writing a scientific manuscript. *American Scientist* also provides a list of resources for science writing. For more detailed guidance on preparing a manuscript and writing in English, please visit the [BioMed Central author academy](#).

Abbreviations

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

Typography

- Please use double line spacing.
- Type the text unjustified, without hyphenating words at line breaks.

- Use hard returns only to end headings and paragraphs, not to rearrange lines.
- Capitalize only the first word, and proper nouns, in the title.
- All pages should be numbered.
- Use the *Radiation Oncology* [reference format](#).
- Footnotes are not allowed, but endnotes are permitted.
- Please do not format the text in multiple columns.
- Greek and other special characters may be included. If you are unable to reproduce a particular special character, please type out the name of the symbol in full. **Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF.**

Units

SI units should be used throughout (liter and molar are permitted, however).'