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Improvement of lung sparing and health tissue by using different IMRT techniques in mid esophageal cancer

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ABSTRACT

The present study is designed to evaluate the feasibility of beam intensity modulation on treatment planning of the mid esophagus to reduce normal lung doses, by comparing different intensity modulated radiotherapy (IMRT) techniques. For this purpose, four mid esophageal cancer cases are selected randomly. Eight IMRT plans are generated for each case with the same dose-volume constraints but with different beam numbers and arrangements. Local optimization using regular structures drawn automatically around the planning target volume (PTV) with margins from 0.5-1.5 cm are performed. IMRT plans are evaluated with respect to $PTV_{95\%}$, homogeneity index (HI), and conformity index (CI) and dose optimization to irradiate normal structures, with statistical comparison made between the types of plans using the One Way ANOVA test. The obtained results of IMRT using seven beam plans show the best coverage for PTV with tolerable doses for the organ at risks (OARs) but the beam orientation is very critical for the seven beams plans. Increasing beam numbers from 7Bs to 13Bs do not show significant differences in the PTV coverage whereas increasing the mean lung doses. The PTV coverage ($PTV_{95\%}$) is up to 97.9% for all plans, with $P < 0.05$. The mean heart dose (MHD) does not exceed 36.26 ± 0.99 Gy with $P < 0.05$. Spinal cord does not exceed 44.85 ±2.02 Gy with $P > 0.05$. For lung doses, all plans are accepted except 3Bs plan which has 21.3 ± 4.13 Gy which lead to the plan evaluation depends on CI and HI. IMRT improved the homogeneity indices from 0.10 ± 0.03 to 0.13 ± 0.03 for 13Bs and 7Bs(R), respectively ($P < 0.05$), conformity indices are improved as number of beams reduced from 13Bs to 7Bs with adding ring (1.37 ± 0.01 and 1.02 ± 0.10, respectively, with $P < 0.05$). In conclusion, the dose–volume of exposed normal lung can be reduced with 13Bs and 7Bs(R) IMRT plans, but, the best conformity is achieved by 7Bs(R) without effect on OARs.

KEYWORDS

Intensity modulated radiotherapy (IMRT);
Esophageal cancer;
Optimum orientation of beams;
Normal tissue sparing;
Organ at risks.

INTRODUCTION

The goal of radiotherapy for esophageal cancer is to ensure appropriate coverage of the targeted structures while minimizing irradiation of normal tissues. One study found higher rates of postoperative pulmonary complications, such as pneumonia and acute respiratory distress syndrome, when higher lung volumes received low doses of lung radiation preoperatively: the pulmonary complication rate was 35% when the volume of lung receiving e" 10 Gy (V_{10}) wase"40 and 8% when V_{10} was <40% (P=0.014).[1] In that study, the treatment plan used conventional radiotherapy techniques, usually two-dimensional techniques using simulation films. Three-dimensional conformal radiotherapy (3DCRT) techniques have been shown to improve tumor targeting and to reduce irradiation of surrounding normal tissues, especially the lung[2].

Conformal radiotherapy techniques offer the potential to deliver higher doses of radiation to esophageal tumors[3], and this may improve local tumor control. However, concerns regarding late normal tissue damage to the lung parenchyma and spinal cord remain a concern. Intensity modulated radiotherapy (IMRT) allows complex dose distributions to be produced, and can reduce the dose to radiosensitive organs close to the tumor[4]. The predicted benefit of IMRT for esophageal carcinoma, where the PTV is cylindrical, is relatively small compared to other tumor sites where the PTV is concave[5].

Further improvement on dose conformity and normal tissue sparing can be accomplished by using IMRT.[6] With IMRT, the possible gains over 3DCRT could come from reduced toxicity and delivery of a higher dose to target volumes. Use of IMRT for specific disease sites, including the prostate and the head and neck, has been investigated extensively and has become part of standard practice at many institutions[6]. However, very few studies have assessed whether IMRT is suitable or effective for treating esophageal cancer, partly because of the concern that IMRT may spread radiation at low doses to large volumes of normal lung tissue, which could be detrimental to radiosensitive structures. Only three reports have been published so far on the use of IMRT for esophageal cancer[7-9]. In two earlier studies[7,8], Nutting et al. showed 9Bs-IMRT plans were equivalent compared with3DCRT plans regarding planning target volume (PTV), dose homogeneity and mean lung dose (MLD). However, 4Bs-IMRTplans with the same beam orientation as the 3DCRT plans increased PTV dose homogeneity and reduced the mean lung dose. A more recent report from Wu et al.[9] found that IMRT could be an effective tool to reduce volume of lung irradiated above 25 Gy for mid-thoracic esophageal cancers. Apparently, more extensive studies are needed to explore the potential gains of IMRT with respect to dosimetric improvements, before embarking on a clinical trial.

In the present work, a pilot study investigating the feasibility of using IMRT for cases of mid thoracic esophageal cancers is completed, which typically involves higher lung volume being irradiated than cervical esophageal cancers. We determined whether IMRT could reduce dose delivered to normal lung by different IMRT techniques. Eight types of IMRT beam arrangements were made to assess optimal beam angles. Through this study, the establish IMRT treatment strategies for esophagus cancers, and obtain preliminary results for designing future clinical trials is intended.

MATERIALS AND METHODS

For the present study, four mid esophageal cancer cases are selected randomly, which typically involves higher lung and heart volume being irradiated than cervical esophageal cancers. Celiac nodes and low abdomen organ at risks, such as kidney and stomach, are usually not involved in the radiation field for middle thoracic esophageal cancer, which differs from that of distal esophageal cancer. Therefore, the target volume of middle esophageal cancer is much more regular than those of cervical and distal esophageal cancer.

All of the patients had tumors involving the upper and cervical esophagus. Through treatment simulation session, CT images of the entire thorax were obtained using 3 mm slice spacing, including the entire lung, spinal cord and heart. Images are obtained with the patient in the supine position. Patients fixed with thermoplastic sheets (Radon & Sinmad) thermoplastic material. The planning target volumes (PTV) and organs at risk (OARs) are delineated by radiation oncologist on the CT slices using contouring option in the Xio, 4.7, treatment planning system (Xio, TPS). The Elekta Xio, Version 4.70 treatment planning is depending on aper-

TABLE 1 : The gantry angles for each plan category

Number of beams	Gantry angles
3Bs	0^o , 120^o, 240^o
5Bs	0^o , 72^o, 144^o , 216^o , 288^o
7Bs	0^o , 52^o, 103^o , 154^o , 206^o, 257^o , 308^o
9Bs	0^o , 40^o, 80^o , 120^o , 160^o, 200^o , 240^o , 280^o , 320^o
13Bs	0^o , 28^o, 55^o , 83^o , 111^o, 139^o , 167^o , 195^o , 223^o, 251^o , 279^o , 307^o , 335^o
7Bs(30)	30^o , 82^o, 134^o , 186^o , 238^o, 290^o , 342^o
7Bs(60)	60^o , 112^o, 164^o , 216^o , 268^o, 320^o ,372^o
7Bs(R)	0^o , 52^o, 103^o , 154^o , 206^o, 257^o , 308^o

TABLE 2 : IMRT average constraints to mid esophageal cancer

Structure	Type	Rank	Objective	Dose (Gy)	Volume (%)	Weight	Power
PTV	Target	1	Maximum	53	0	300	2.6
			Minimum	51	100	300	2.8
Spinal cord	OAR	2	Maximum	35	0	100	2.0
Heart	OAR	4	Dose volume	38	25	100	2.0
Right lung	OAR	3	Dose volume	35	5	100	2.0
			Dose volume	8	15	100	2.0
			Dose volume	6	30	100	2.0
Left lung	OAR	3	Dose volume	35	5	100	2.0
			Dose volume	8	15	100	2.0
			Dose volume	6	30	100	2.0
R1	OAR	6	Maximum	47	0	100	2.3
R2	OAR	7	Maximum	41	0	100	2.3
R3	OAR	8	Maximum	35	0	100	2.3

ture based inverse planning. The aperture based inverse planning (or direct aperture inverse planning "DAO") with standard superposition algorithm is used for dose calculations. For each patient two different treatment volumes are defined, clinical tumor volume esophagus (GTV + Margin). The margins are expanded based on the institutional protocol for IMRT, i.e., 1 cm along the transverse direction, 1 cm along the cranial caudal direction, 1 cm anteriorly, and 0.5 cm posteriorly. GTV = primary lesion and involved LN; CTV = GTV + subclinical disease (regional LN and sub-mucosal). The planning target volume (PTV) is (CTV + Margin) 4 cm proximal/distal and 1 cm radial (did not modify CTVs for the present study). Eight treatment plans with different beams number (Bs): 3Bs, 5Bs, 7Bs, 9Bs, 13Bs 7Bs(30), 7Bs(60) and 7Bs(R), are generated for each case. The effect of beam directions and local optimization are studied with the 7Bs plans, where the started angles are changed from 0o to 30o and 60o, as well as, three rings are drawn around the PTV with margins 0.5, 1and 1.5 cm, respectively, as automatic margins from the PTV [7Bs, 7Bs(30), 7Bs(60) and 7Bs(R)].

TABLE 1 summarizes the number of beams and gantry angles for each plan category. The target dose is 50.4 Gy delivered in 28 fractions. The IMRT plans are generated using equispaced beams, 6 MV photon energy of Elekta Precise linear accelerator.

The treatment planning parameters used to ensure coverage of the PTV are presented in TABLE 2. A structure called 'normal tissue' is created to include all of the tissues enclosed by the external contour (patient skin) minus the expanded PTV. The planning objectives for this structure are generally prioritized in the following order: PTV, lung, spinal cord, heart and rings. The full inverse planning process of the IMRT plans for the 7Bs is carried 25 times, during which the priority, ranking order and treatment planning dose constraints for each organ are adjusted to obtain plans with results congruent with the planning goals. The treatment-planning software uses a superposition based inverse planning algorithm to generate optimal beam modulation satisfying the physicist specified dose objectives and constraints. The goal of optimization was to minimize the overall cost of objective function (i.e., the function of the difference between the desired and calculated doses for the target and all specified critical organs). After the inverse planning, the leaf motion required for the accelerator (Elekta Precise linear accelerator, with motorized MLCs) was generated for each IMRT plan by using the sliding-window technique.14 The final dose distribution in each plan is normalized to 95% coverage of the PTV receiving the prescribed dose (50.4 Gy in 28 fractions).

The plans are evaluated and compared to each other according to the following parameters:

1. Isodose distribution.
2. Homogeneity index (HI) of PTV.
3. Conformity index (CI) of PTV.
4. The $PTV_{95\%}$.
5. Lung dose.
6. Maximum dose to spinal cord.
7. Mean heart dose.

Statistical significance of each comparison was assessed using a One Way ANOVA test.

RESULTS AND DISCUSSION

The present study addressed whether different IMRT techniques for esophageal cancer can be used to achieve higher PTV coverage and reduce OAR specially the volume of lung irradiated even at low doses of 5 to 30 Gy. This goal is achieved with all types of IMRT plans, which also reduced $V_{30\,Gy}$(%) and MLD.

PTV isodose distributions

The isodose lines are displayed on an absolute dose scale and the isodose levels of 50.4 Gy (95% of prescribed dose) are observed (images not shown). The isodose distributions on axial images for different IMRT plans in the isocenter of PTV for one of the cases are under study. Treatment plans are produced using odd of equispaced non-opposed coplanar beams starting with a direct anterior beam with adding ring provide the optimal IMRT dose distribution. The effect of the ring on the high dose outside the PTV is studied for the seven field's plans. From the isodose line points of view the fewer beams plans (3Bs and 5Bs) cannot accepted where a large normal tissue is included in high dose regions, including isodose lines 95 and 90%, respectively, of the prescribed dose. For the other plans of higher treatment beams from 7Bs of different arrangement to the 13Bs, the high isodose line of 100 and 95% is compatible with the PTV. The best compatibility of 95% isodose with PTV is performed when dose optimized using ring is introduced to the planning optimization.

The mean dose to the PTV for the four cases of mid esophageal cancer and the standard division (SD) are listed in TABLE 3.

The homogeneity indices (HI) of PTV

The homogeneity index is defined as: HI = (D2% - D98%)/D50%, where D2% (maximum dose), D98% (minimum dose), and D50% (mean dose), correspond to the dose delivered to 2, 98 and 50% of the PTV, respectively. HI values greater than 1.5 indicate that the maximum and minimum doses exceeding the ICRU83[10] guide line for plan acceptance and, thus, a greater degree of dose heterogeneity in the PTV. HI of zero represents the ideal plan homogeneity indices mean is 0.09 for 7Bs and 7Bs(30) with $P < 0.05$ which represent the best homogenous plans (TABLE 3). The improvements in HI are statistically significant; the magnitudes of the differences are small and within the acceptable range. Figure 1 shows the relation between the numbers of beams and mean homogeneity indices (HI) for different IMRT plans in the PTV for the four cases.

Conformity indices (CI) of PTV

Conformity index is defined as: $CI = (V_{98\%} / PTV_{98\%})$, where $V_{98\%}$ is the volume enclosed by the

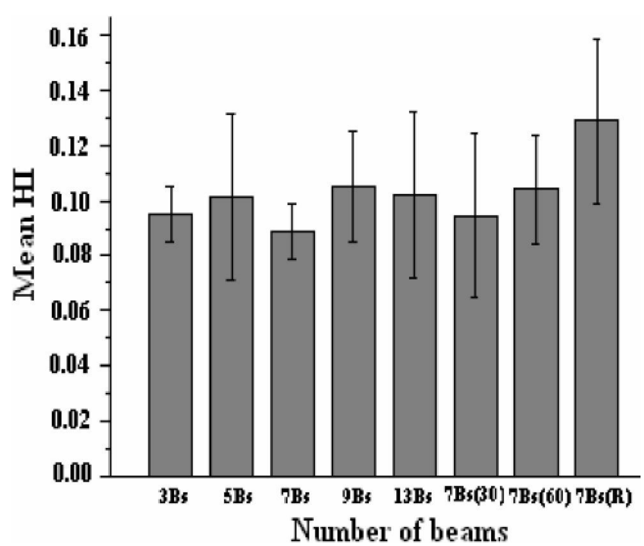

Figure 1 : The relation between the number of beams and mean HI.

TABLE 3 : The mean results for different IMRT plans of the mid thoracic esophageal cancer patients (mean ± SD)

Structure and Parameters	3Bs	5Bs	7Bs	9Bs	13Bs	7Bs(30)	7Bs(60)	7Bs(R)	P-Value
PTV D_2% (Gy)±SD D_{50}% (Gy)±SD D_{98}% (Gy)±SD	54.75±0.64 52.29±0.41 49.77±0.07	55.27±1.66 52.82±0.97 49.92±0.05	54.53±0.84 52.47±0.85 49.87±0.51	53.18±1.32 52.67±0.80 49.64±0.66	54.83±1.20 52.37±0.57 49.49±0.32	54.6±1.99 52.27±0.62 49.65±0.69	55.16±1.48 52.35±0.75 49.71±0.57 0.10±0.02 1.30±0.18	55.22±1.79 52.42±0.85 48.46±0.37	0.988 0.961 0.005
$PTV_{95\%}$ (Gy)±SD	99.90±0.31	100.90±0.26	100.10±0.42	99.90±0.30	99.40±0.43	99.70±0.50	99.90±0.35	97.90±0.54	0.002
Mean HI±SD	0.10±0. 01	0.10±0.03	0.09±0.01	0.11±0.02	0.10±0.03	0.09±0.03	0.10±0.02	0.13±0.03	0.003
Mean CI±SD	1.72±0. 20	1.31±0.21	1.26±0.16	1.32±0.27	1.37±0.10	1.41±0.10	1.30±0.18	1.02±0.10	0.003
Lung MLD (Gy) $V_{5\,Gy}$(%) $V_{10\,Gy}$(%) V_{20Gy}(%) $V_{30\,Gy}$(%)	13.76±0.83 83.10±26.22 50.20±28.39 21.30±4.13 9.40±3.92	13.17±0.88 88.80±27.55 49.00±10.21 19.40±3.41 6.90±2.33	12.49±0.58 86.20±29.43 45.70±8.39 17.00±1.81 7.80±2.36	12.02±0.57 82.70±68.07 40.50±7.46 16.20±1.73 7.60±1.74	11.75±0.53 84.50±38.95 37.00±11.83 15.20±1.22 7.90±2.67	12.48±0.54 81.80±35.29 45.30±3.21 17.60±2.48 7.80±2.19	12.41±0.44 85.10±59.50 42.90±10.16 17.00±1.82 8.40±3.84	14.94±0.53 95.50±33.36 76..90±4.90 17.00±0.42 5.20±1.01	0.000 0.001 0.008 0.041 0.050
Spinal cord Max dose (Gy)	44.85±2.04	44.30±2.76	43.42±2.18	43.22±2.82	44.27±1.22	43.19±1.70	43.98±1.95	41.76±1.67	0.544
Heart Mean heart dose (Gy)	32.78±5.42	32.48±0.50	33.78±1.46	35.87±2.09	36.26±0.99	35.42±0.65	35.37±2.55	27.94±4.13	0.007

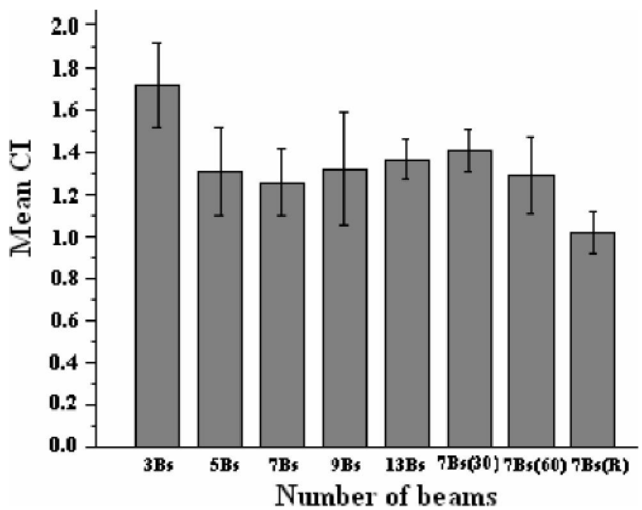

Figure 2 : The relation between the number of beams and mean CI.

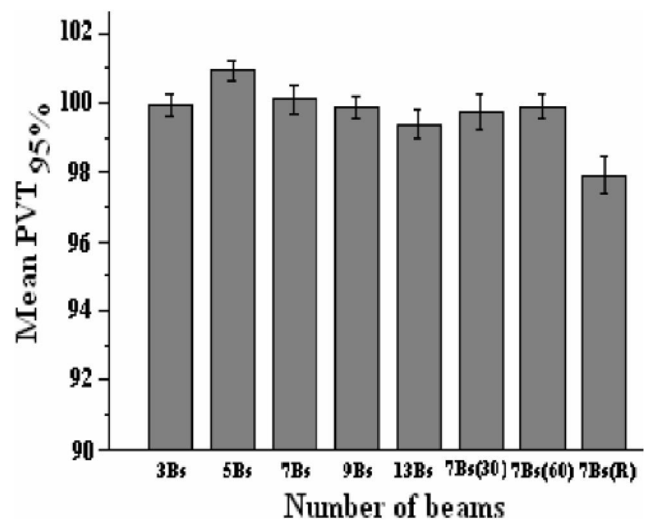

Figure 3 : The relation between the number of beams and mean $PTV_{95\%}$.

98% of prescribed dose cloud. CI is usually e” 1. Larger values indicate greater volumes of the prescription dose delivered outside the PTV (i.e., less dose conformity of the PTV). A conformity index of one represents the ideal situation that the target volume coincides exactly with the treatment volume. From the obtained results, the plan with three equispaced coplanar intensity modulated beam 3Bs could not meet the requirement of dose conformity. This might be due to the fact that the beam directions are not optimized, the conformity is improved as the number of intensity modulated beams increased, but the improvement is marginal when beam number is over five. As expected, the high dose conformity of the target volumes in IMRT plans are generally improved by using ring to 7Bs and it gives the ideal conformity than 9Bs and 13Bs. Figure 2 shows the relation between the number of beams and conformity indices (CI) for different IMRT plans in the PTV for the four cases.

The improvement in CI with the 7Bs(R) plans is statistically significant, so decrease the number of beams to 7Bs with adding ring is better than increasing the number of beams (TABLE 3) where the volume covered by 98% of the prescribed dose is about 157% of the $PTV_{98\%}$.

The $PTV_{95\%}$

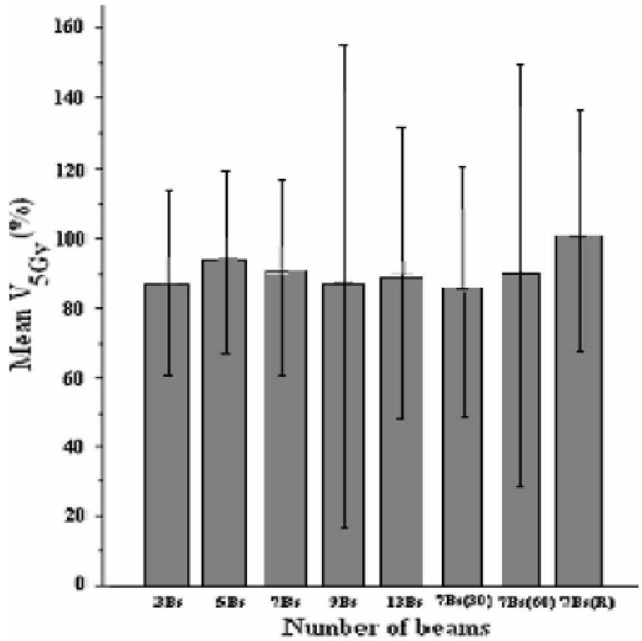

Figure 4 : The relation between the number of beams and mean $V_{5 Gy}$(%).

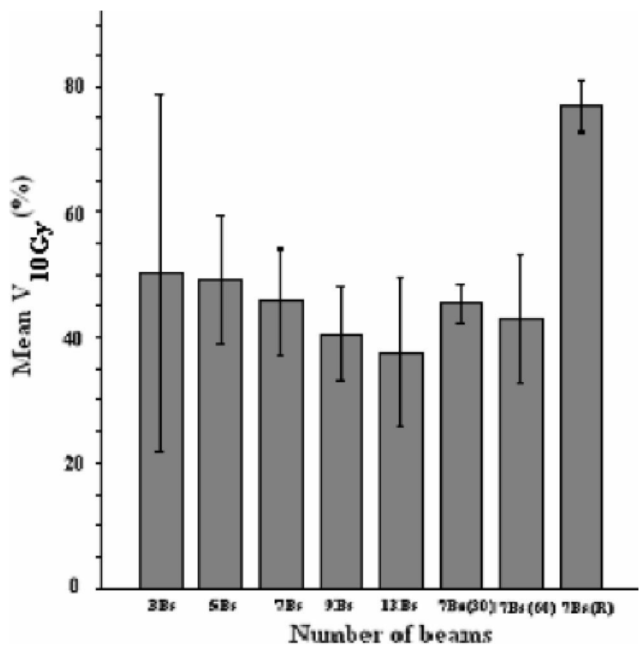

Figure 5 : The relation between the number of beams and Mean $V_{10 Gy}$(%).

The planning target volume (PTV) is defined by ICRU report 50 as a geometrical concept[11], used to select appropriate beam sizes and beam arrangements. Clinically, a plan is normally acceptable if the 95% isodose surface covers the PTV. The goal of the study is to investigate the validity of using the PTV coverage for plan evaluation, PTV95 = 100% for the prescribed dose. The targets' dose coverage in all plans is 97.9%, this come from the high conformity. Using ring, it is possible to reduce the number of IMB required to produce this benefit from 13Bs to 7Bs beams without loss of target coverage or dose homogeneity (TABLE 3). Small, statistically significant differences in mean PTV dose are noted between the different techniques. Figure 3 shows the relation between the number of beams and $PTV_{95\%}$ coverage for different IMRT plans in the PTV for the four cases. The plan is accepted when $PTV_{95\%}$ is covered with 98% of the prescribed dose for 7Bs(R).

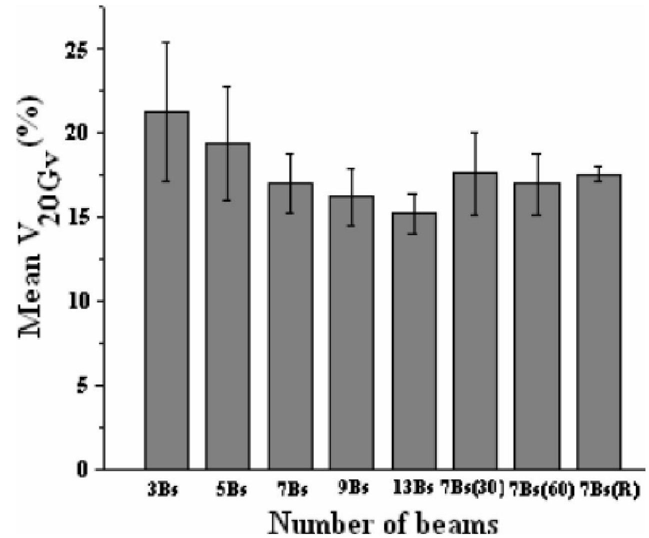

Figure 6 : The relation between the number of beams and Mean $V_{20 Gy}$(%).

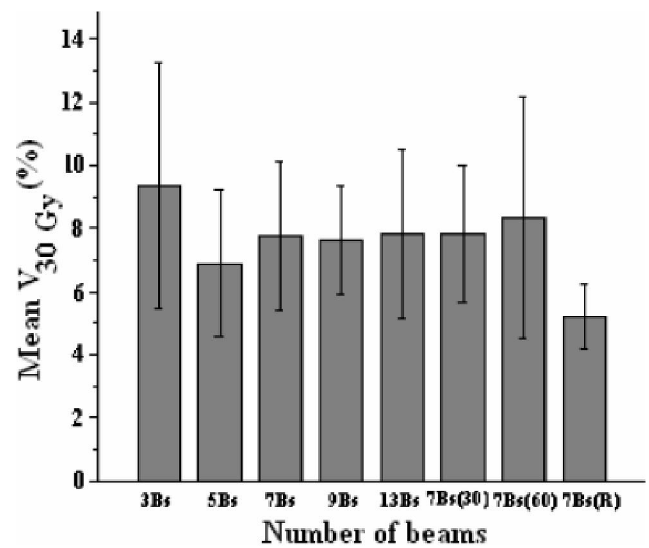

Figure 7 : The relation between number of beams and Mean $V_{30 Gy}$(%).

OARs "dose optimization"

Lung doses

$V_{5 Gy}$(%) is defined as the volume of lung receiving 5Gy, whereas in mid thoracic esophageal cancer, which typically involves higher lung and heart volume being

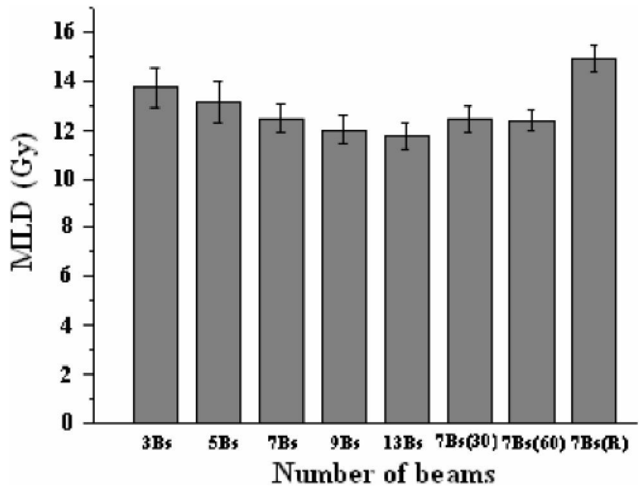

Figure 8 : The relation between the number of beams and MLD.

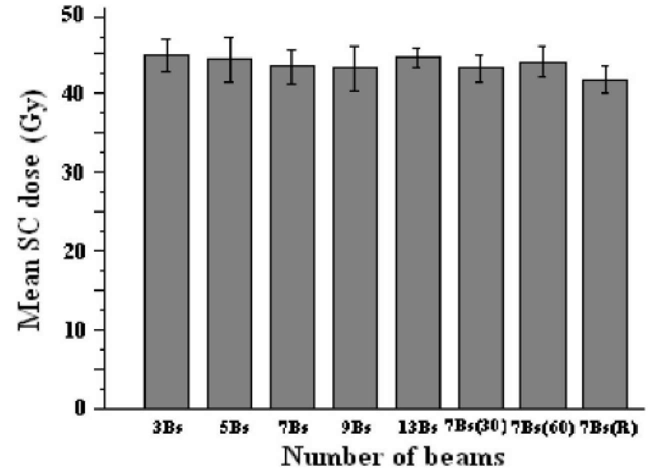

Figure 9 : The relation between the number of beams and mean SC dose.

irradiated than cervical esophageal cancers. The results obtained in Figure 4 show that for low dose regions there is no significant improvement with increasing treatment beams, where introducing ring in to dose optimization with 7Bs plans resulted in increasing $V_{5\,Gy}$(%). $V_{10\,Gy}$(%) of the lung, and this can be understood by analyzing the other parameter $V_{20\,Gy}$(%), $V_{30\,Gy}$(%) of lung doses and so the dose for other critical organs specially the mean heart dose. Global view of the lung dose results show that increasing treatment beams lead to decreasing the lung dose as presented in Figure 5 and Figure 6. Although plan optimization using ring increase low dose for lung, the high dose regions is decreased (Figure 7) which resulted in slight increase in the mean lung dose (Figure 8). The P value for the lung dose parameter using One Way ANOVA test were $P < 0.05$ which considered significant (TABLE 3).

Dose to spinal cord

In the mid esophageal cancer where spinal cord is far off the target volume, all the treatment plans have an acceptable and tolerable doses for spinal cord. Figure 9 shows that the introducing the ring to plan optimization reduced the dose for spinal cord so the physicist should use the local optimization to control the high dose outside the PTV. The local optimization is mandatory in case of there is large distance between the PTV and the critical structure. In addition, Figure 9 shows the relation between the number of beams and maximum dose to spinal cord for different IMRT plans for the four cases. All of the plans had a maximum spinal cord dose of d" 44.9 Gy except for7Bs(R) IMRT plan, which have a maximum dose of 41.7 Gy, and represents the best plan to meet the SC requirement. The comparison for all plans with maximum dose to spinal cord and its significant value are presented in TABLE 3. All doses are obtained at 0.2% of spinal cord volume.

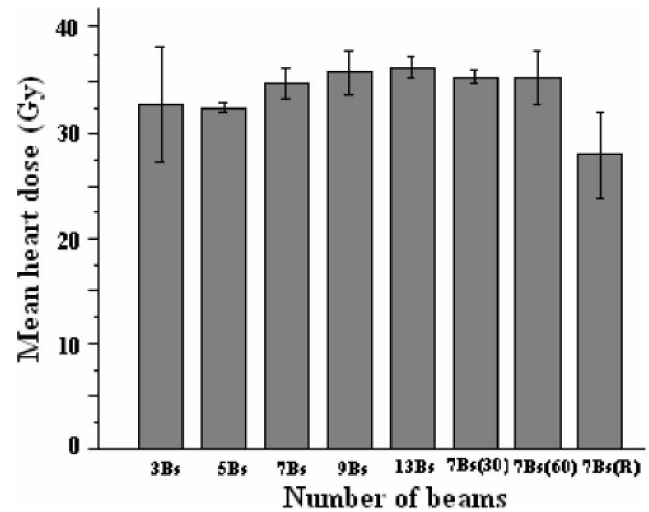

Figure 10 : The relation between the number of beams and mean heart dose.

Mean heart dose

The effects of different IMRT plans on the heart are also explored. Statistical differences are found between the different IMRT plans on evaluation of the assigned endpoints for this structure. The results obtained show that using ring for IMRT dose optimization resulted in redistribution dose inside the patient, this is present in the high dose region reduction for lung (Figure 7), spinal cord (Figure 9), and heart (Figure 10). Figure 10 shows the relation between the number of beams and mean heart dose for different IMRT plans

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for the four cases. The comparison for all plans with mean heart dose (MHD) and its significant value are presented in TABLE 3.

CONCLUSION

The comparisons between different IMRT techniques demonstrated that 7B(R) reduces the mean lung dose, and improves PTV homogeneity with best conformity. Moreover, dose–volume of exposed normal lung can be reduced with 13Bs and 7Bs(R) IMRT plans, but, the best conformity is achieved by 7Bs(R) without effect on OARs.

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