Factors affecting dose distribution in Hepatocellular carcinoma in cases treated by 3 Dimensional Conformal Radiotherapy (3DCRT)

Azza Helal, PhD[1]; Mohamed Farouk Mostafa, MD[2]; Abbas Omar, MD[2]

(1) Medical Physics Unit, Diagnostic Imaging Department, Faculty of Medicine, Alexandria University
(2) Clinical Oncology Department, Faculty of Medicine, Alexandria University

✉ *Corresponding Author: Dr Azza Helal, PhD*
Medical Physics Unit, Diagnostic Imaging Department
Faculty of Medicine, Alexandria University
E-mail: helals2002@yahoo.com

Key words: Hepatocellular carcinoma, Three-dimensional conformal radiotherapy, Dose distribution, OARs tolerance dose.

ISSN: 2070-254X

Abstract

Introduction: The dose distribution of 3DCRT planning depends on number of beams, geometry of target volume, number and tolerance of surrounding organs at risk (OARs).
Aim: To study the interacting effects of target volume, OAR geometry and planning parameters on the resulting dose distribution in the target volume and OARs for 3DCRT plans for patients with advanced non metastatic hepatocellular carcinoma (HCC). It also aims at identifying which combination of these factors influencing the dose volume parameters and dose distribution and the selection of beam number among patients with HCC.
Methods: CT studies of 30 patients with unresectable HCC were planned using different number, direction and energy of photon fields. The volume and length of planning target volume (PTV), volume of whole and healthy liver and the ratio of the volume of PTV to whole liver volume were calculated. Linear regression was used to identify which combination of the anatomic factors influences the dose distribution and selected beam number.
Results: The favorable factors for optimum plan were small target volume 369cc, short target length 8cm and small PTV/ liver volume 16.8 and healthy liver volume 2183cc-3631cc and the use of multiple beams which is limited by volume of PTV, PTV/ liver volume ratio (small) and site of tumor (left lobe).
Conclusion: 3DCRT dose distribution is strongly dependent not only on geometrical relationship between target and critical organs but also on number of beams used. The size of the effect varies with all factors together.
I declare that there is no conflict of interest with any financial organization regarding the material in this manuscript.

Introduction

The usual presentation of Hepatocellular carcinoma (HCC) is advanced disease where surgery has no role. In such patients radiotherapy (RT) is indicated in those who have contraindication for or failed trans-arterial chemo-embolization (TACE).[1–5].

Many radiotherapy techniques are available, such as 3DCRT, intensity-modulated RT (IMRT) and image-guided RT (IGRT). 3DCRT is the most commonly used radiotherapy technique.[2]

Radiotherapy for whole liver has played a limited role because the radiation tolerance of the whole liver is approximately 30 Gy. Radiation-induced liver disease (RILD) is the result of whole liver irradiation (25-30Gy). To deliver higher doses of radiation, the dose should be conformed to the hepatic lesion with minimal damage to surrounding normal liver parenchyma [2,3,6,7]

Two important factors should be considered. First, the cephalo-caudal movement of the liver[6] , which can be solved by adding enough margin around the tumor to create PTV [8,9] , by the use of IGRT, and by active breathing control[10,11]. The second factor is the proximity of the liver to other radiosensitive organs such as kidneys, spinal cord and intestines that makes the possibility of conforming the dose to the tumor shape with sparing OARs difficult. So the balance between target dose coverage & sparing of critical organs should be controlled. [2]

In previous work the unfavorable anatomic parameters for each DVP for different target volumes and OARs in IMRT of head and neck & prostate cancer patients were found [12-15]

In the present study we extended the work to show that as the anatomic factors affect the dose distribution of IMRT plans, they could also affect the dose distribution for 3DCRT plan for liver cancer as well.

Aim

To study the interacting effects of target volume, OAR geometry and planning parameters on the resulting dose distribution in the target volume and OARs for 3DCRT plans for patients with advanced non metastatic hepatocellular carcinoma (HCC) unfit for interventional therapy. It also aimed at identifying which combination of these factors influencing the dose volume parameters and dose distribution and the selection of beam number among patients with HCC.

Methods

From January 2010 till April 2012 thirty patients with locally advanced non metastatic HCC unfit for trans arterial chemoembolization (TACE), were referred to the Alexandria Clinical Oncology Department for 3DCRT to the hepatic mass and portal vein thrombus (if present). CT simulation was performed in supine position with 2-3mm slice thickness. Then the CT data were transferred to treatment planning system (Precise Elekta) where required structures were contoured. They include GTV (high CT value area in early phase contrast-enhanced CT image), CTV (1cm margin around the GTV) & PTV (0.5cm & 1.5cm margin to the CTV in axial and craniocaudal axes) respectively.

Whole liver, healthy liver (total liver volume minus PTV), kidneys and spinal cord were also contoured. The volume & length of PTV, volume of whole and healthy liver and the ratio of the volume of PTV to whole liver volume were calculated.

All CT scans were planned with 6MV photon beam in 10 patients and 15 MV in 20 patients. This is according to the depth of the tumor from the surface[3]. For each patient, optimum plan was carried out using different number (2-5) and directions of photon fields to encompass the PTV and to well spare nearby OARs. MLCs were used for all cases to shape the beam and to spare OARs as possible.

For all plans, isodose distributions and DVHs were generated. The optimum plan was evaluated by PTV dose coverage (minimum and maximum dose), conformity and inhomogeneity within PTV and sparing of OARs. OARs sparing was assessed using the mean dose for whole liver (28-30Gy), healthy liver (23-26 Gy) and kidneys (20-23Gy for one kidney) and the maximum point dose of spinal cord (≤ 45 Gy).[3,8].

This study had approval of Institutional Review Board as a retrospective one in which confidentially of records was considered.

Statistical analysis

For all plans, data were recorded, compared and analyzed statistically using excel sheet 2003 & linear regression models by SPSS software, version 18.

Results

Clinico-pathologic data of 30 HCC patients are shown in table 1.

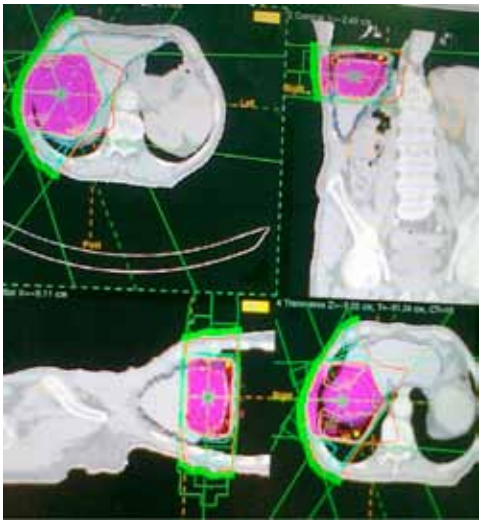
Table 1: Clinico-pathologic data

	Number (%)
Age	
mean	57.1 years
range	40-75 years
Sex	
male	26 (86.6)
female	4
Performance status	
0	5
1	18 (60)
2	7
Site	
right lobe	16 (53)
left lobe	14
Portal vein thrombosis	20 (66.6)
Alpha fetoprotein level elevation above normal	28 (93)
Size of the mass	
< 5 cm	5
5-10 cm	8
> 10 cm	17 (56.6)
Hepatitis C positivity	18 (60)
Hepatitis B Positivity	5 (16.6)
Okuda stage [16]	
I	7
II	18 (60)
III	5

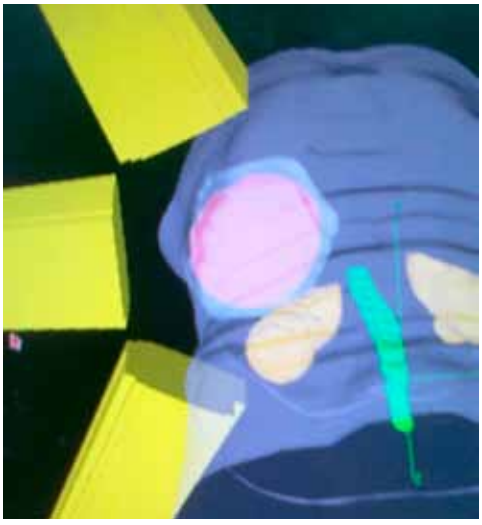
The number of beams that achieved the optimum plan was two, three, four and five beams in 1, 17, 6 & 6 patients respectively. The most common beam arrangements were three fields (right anterior oblique, right posterior oblique and right lateral) for right lobe tumors and four to five fields (right anterior oblique, right posterior oblique/ posterior, right lateral and left anterior oblique) for left lobe tumors. In 4 cases the tumor was present in build up so a bolus of 1-1.5 cm was used to improve target coverage. Different doses were prescribed; 50Gy in 12 patients, then as far as the dose to OARs did not exceed the tolerance the dose was escalated to 54Gy in 3 patients and to 60Gy in 14 patients. In one case the dose reduced to 45 Gy to avoid exceeding the tolerance dose of spinal cord.

Dose distribution

For all patients, the optimum plan was achieved; the average of min dose was 95%, the average of dose gradient within PTV was 13% and also, the 95% dose wash matched well the PTV shape (figure 1 (a & b) and figure 2).
Regarding the dose to OARs, all DVPs were within their tolerance. The average of mean dose to right, left kidney, whole and healthy liver was 29%, 4%, 58% and 48% respectively while the average of spinal cord max. point dose was 32%. The average of body max dose was 109%. Table2 shows the numeric findings from the DVH analysis of the PTVs and OARs.



a



b

Fig 1: Typical dose distribution displayed in axial, coronal & sagittal views for 3DCRT using; three coplanar gantry angles for a patient with HCC (a) and the room eye view of the same patient (b). Both show the colour wash of 95% of the dose (pink in a & white in b) match well the PTV shape.

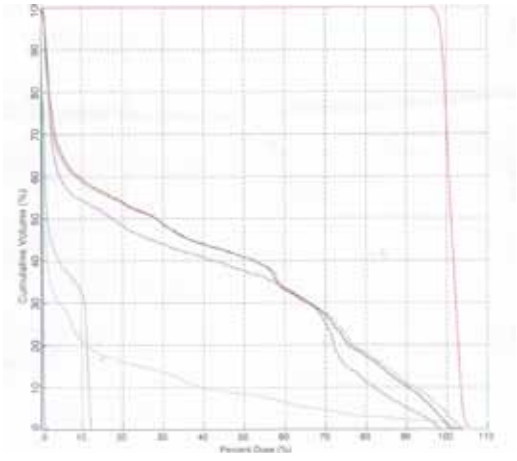


Fig 2: Dose volume histograms in percentage for PTV and different OARs for 3DCRT plan for a case with HCC. PTV is shown in red, whole liver in pink, healthy liver in black, kidneys in blue, spinal cord in dark green and body in light green.

Table 2: The mean doses for PTV & OARs for 3DCRT of 30 cases with HCC. It also shows dose inhomogeneity within PTV and body maximum dose. All are in percentage.

.	PTV min dose	PTV max. dose	% dose Inhomo-geneity	RT kidney mean dose	Lt kidney mean dose	Healthy liver mean dose	Whole liver mean dose	S. cord max dose	Body max dose
Min	95	103	7	0	0	12	18	3	103
Max	98	114	19	105	15	82	91	99	115
Aver-age	95	109	13	29	4	48	58	32	109

Study of the effects of target volume / OAR geometry & number of beams on dose distribution within target volume & OARs

Table 3: Summary of Min, Max. and average of volume of PTV and its length, whole liver volume, healthy liver volume and PTV/Liver volume ratio for 30 patients with HCC.

	PTV (cc)	PTV (cm)	Whole Liver (cc)	Healthy liver (cc)	Ratio PTV/Liver volume
Min.	68	4.5	955	605	4.5
Max	2062	23	4449	3631	160
Average	685	10	2170	1777	35

Number of beams

All right lobe tumors were treated using three beams (fig 1 a & b) except in one case the tumor was irradiated using two fields (AP & PA) as the size of the tumor was very large extending posteriorly (2062cc). All left lobe tumors were treated using four or five beams except in two cases (the size of the tumor was large 1032cc & 1356cc) the tumor was irradiated using two lateral and an anterior fields.

Table 4 summarizes the significant negative correlations between different anatomic factors and number of beams. These factors accounted for 38%, 24% and 23% of the change in the number of beams (R^2 explains the proportion of variation in the number of beams due to the variation in each anatomic factor). Position of PTV (Right or left lobe) also explained 20% of the changes of number of beams (R= 0.47, R^2=0.20 & P =0.009). (Not tabulated)

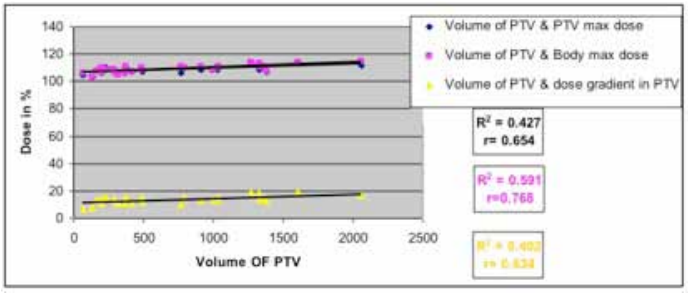
Table 4: Summary of significant negative correlations between different anatomic factors and number of beams. R, R^2 and P values are shown.

	PTV Volume	PTV Length	Ratio PTV/Liver volume
No of beams			
R	-0.637	-0.516	-0.502
R^2	**0.38**	**0.24**	**0.23**
P value	<0.001	0.004	0.005

Table 5 and figure 3 summarize the significant correlation between different anatomic factors and number of beams with each DVP. It also shows the proportion of variation in each DVP due to the variation in each anatomic factor or number of beam (R^2). For example; the variation in the volume of PTV accounted for 59% of the variation in body max dose.

Table 5: The correlation between different anatomic factors and number of beams with each DVP. R, R^2 and P values are shown.

DVPs	PTV Volume	PTV Length	Healthy liver Volume	Ratio PTV/ Liver volume	No of beams
PTV Max dose					
R	0.654	0.466		0.602	-0.569
R^2	**0.42**	**0.19**		**0.34**	**0.30**
P value	<0.001	0.009		<0.001	0.001
Dose gradient					
R	0.634	0.485		0.592	-0.578
R^2	**0.40**	**0.21**		**0.33**	**0.31**
P value	<0.001	0.007		0.001	0.001
Rt kidney mean dose					
R	0.654	0.592		0.669	-0.407
R^2	**0.41**	**0.33**		**0.44**	**0.14**
P value	<0.001	0.001		<0.001	0.025
Lt kidney mean dose					
R	0.418		-0.511	0.669	-0.481
R^2	**0.15**		**0.23**	**0.43**	**0.20**
P value	0.021		0.004	<0.001	0.007
Whole liver mean dose					
R	0.620	0.588	-0.714	0.696	-0.499
R^2	**0.36**	**0.32**	**0.51**	**0.47**	**0.22**
P value	<0.001	0.001	<0.001	<0.001	0.005
Healthy liver mean dose					
R	0.559	0.518	-0.675	0.689	-0.423
R^2	**0.29**	**0.24**	**0.45**	**0.46**	**0.15**
P value	<0.001	0.003	<0.001	<0.001	0.02
SC. max dose					
R	0.468			0.636	
R^2	**0.19**			**0.40**	
P value	0.009			<0.001	
Body max dose					
R	0.768	0.575		0.592	-0.717
R^2	**0.59**	**0.31**		**0.33**	**0.50**
P value	<0.001	0.001		0.001	<0.001



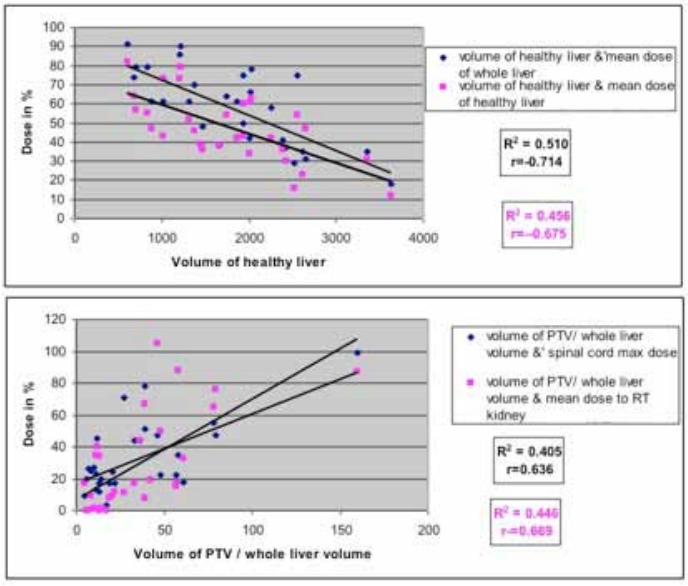


Figure 3 Scatter plot shows different correlations. The data are fitted by linear regression. R and R^2 are also shown

Table 6 shows the best combination of the factors (predictors) that most effectively influenced the variation in each of DVPs and selection of number of beams; ratio of PTV/ liver volume, volume of PTV, and no of beams are significant predictors for PTV max dose (explained 44% of its variation). Ratio of PTV/ liver volume, number of beams, volume of PTV & length of PTV are significant predictors for dose gradient (explained 41% of its variation). Ratio of PTV/ liver volume & length of PTV are significant predictors for mean dose of right kidney (explained 48% of its variation). Ratio of PTV/ liver volume, number of beams, volume of healthy liver & length of PTV are significant predictors for left kidney mean dose (explained 44% of its variation). Volume of PTV, volume of healthy liver & length of PTV are significant predictors for mean dose of whole liver (explained 75% of its variation). Volume of PTV, volume of healthy liver & length of PTV are significant predictors for mean dose of healthy liver (explained 63% of its variation). Ratio of PTV/ liver volume is the significant predictors for spinal cord max dose (explained 34% of its variation). Length of PTV, volume of PTV, and no of beams are significant predictors for body max dose (explained 66% of its variation). Volume of PTV and its position are significant predictors for selection of number of beams (explained 62% of its variation).

Table 6: The significant predictors and the total % of variation (R^2) for each DVP & selected number of beams accounted by these predictors combination.

DVP	PTV Max dose	Dose gradient	Rt kidney mean dose	Lt kidney mean dose	Whole liver mean dose
Predictors	PTV Volume PTV/Liver volume No of beams	PTV Volume PTV Length PTV/Liver volume No of beams	PTV Length PTV/Liver volume	PTV Length PTV/Liver volume No of beams Healthy liver Volume	PTV Volume PTV Length Healthy liver Volume
R, P value	0.70, <0.001	0.70, 0.001	0.72, 0.001	0.72, 0.001	0.88 , <0.001
R^2	**0.44**	**0.41**	**0.48**	**0.44**	**0.75**

DVP		Healthy liver mean dose	SC. max dose	Body max dose	No of beams
Predictors		PTV Volume PTV Length Healthy liver Volume	PTV/Liver volume	PTV Volume PTV Length No of beams	PTV Volume position
R, P value		0.82, <0.001	0.64, <0.001	0.83, <0.001	0.80, <0.001
R^2		**0.63**	**0.34**	**0.66**	**0.62**

To determine the favorable factors that influence DVPs and so the dose distribution of optimum plans, the selected patients were classified into 4 groups according to the dose prescription (50, 54, 60 & 45 Gy for groups 1 to 4 respectively). Then to assess the differences between the four groups the anatomic factors that might significantly affect liver mean dose (Ratio of PTV/ liver volume, volume of PTV & length of PTV and volume of healthy liver) were statistically analyzed using one way ANOVA.

For the volume of PTV, the lowest mean value was for group 3 (369cc) and the highest mean value was for group 4, 1 & 2 (1608cc, 900cc & 989cc). The differences in the value between 4 groups was statistically significant (p=0.007) For the length of PTV, the lowest mean value was for group 3 (8cm) and the highest mean value was for group 4 & 1 (16cm & 12cm). The differences in the value between 4 groups was statistically significant (p=0.018)

For the ratio of volume of PTV/ whole liver volume, the lowest mean value was for group 3 (16.8) and the highest mean value was for group 4 & 1 (160 & 43.5). The differences in the value between 4 groups was statistically significant (p<0.001). For the healthy liver volume, the lowest mean value was for group 1 & 4 (1436cc & 605cc) and the highest mean value was for group 3 (2183.7cc). The differences in the value between 4 groups was statistically significant (p=0.028) So we determined that the favorable factors which produce optimum plan in which the dose can be escalated up to 60 Gy were in group 3 (small target volume 369cc, short target length 8cm and small PTV/ liver volume 16.8 and healthy liver volume 2183cc up to 3631cc). The use of multiple beams was also considered the favorable factor for the plan but this was limited by volume of PTV, PTV/ liver volume ratio (small) and the site of tumor (left lobe). For left lobe PTV, if the volume exceeded 482cc 3 beams were used, if the volume was <400cc, 4 and 5 beams was used. On the other hand, for tumors of the right lobe three beams were used whatever the size of the tumor (even for very small tumor).

Discussion

The dose distribution is strongly dependent on many interacting factors such as number of beams, geometry of target volume and geometry, number and tolerance of surrounding organs at risk.[17,18,19] Kuo et al[3] compared three different radiotherapy techniques; volumetric intensity-modulated Arc therapy, IMRT and 3DCRT using 4 -5 fields; the average dose prescribed was 49.4Gy. Compared to his work, the target coverage was better in our work ($V_{100\%}$ was 95% compared to 76.81 ± 5.95) but PTV dose homogeneity was better in his work compared to ours (average 1.3% compared to 13% in our work). This difference in homogeneity, is due to difference in the way of calculation as we calculated it as the difference between maximum and minimum dose and they calculated as $D_{5\%}$ / $D_{95\%}$, and by applying their equation, ours was 1.2% which is very comparable to their result. The average of the mean dose to healthy liver was comparable to our results (44% compared to 48% in our study), while the average of the mean dose to left & right kidney was higher in their work 23% & 30% respectively compared to 4% & 29% in our work. The dose to spinal cord was also far lower in our work compared to their work (32%. max point dose compared to 79% max. dose at 1% volume ($D_{1\%}$). This might be due to difference in the size of target volume. It was smaller in our study, the mean of PTV was 685cc (range, 68cc-2062cc) compared with 1734 cm^3 (range, 859.6-3253.4 cm^3) in their work.

In ZHANG Li et al[20] work; the mean dose to normal liver ranged from 32-50% of the prescribed dose compared to 48% in our work. This study determined the significant predictors that affect each DVP and the number of beams. In a previous study[13-15] we investigated the effect of patient anatomy on IMRT dose distribution for patients with head and neck and prostate cancer. For patients with head and neck cancer; the volume of PTV and percentage of parotid overlap with PTV were the most significant predictors for PTV coverage and parotid sparing. For patients with prostate cancer; rectum volume and percentage of rectum overlap with PTV were significant predictors for rectum DVPs and bladder volume and percentage of bladder overlap with PTV were significant predictors for bladder DVPs.

Asselen et al [21] correlated each 1mm increase in the margin around CTV to produce the PTV with a 1.3Gy increase in the parotid mean dose in head and neck cancer patients. Hsiung et al[22] reported that a large target volume and a small minimum separation between the target volume and OAR are two important factors for unfavorable results. Hsiung et al [23] found a correlation between minimum distance between the target and brain stem and the maximum overlap of the target and brain stem and target $D_{5\%}$.

Asteruldoeu et al[24] found a correlation between the relative overlap parotid volume and the parotid mean dose difference. Hunt et al[25] found that the PTV uniformity and the maximum dose to the OAR exceeding the constraints for small minimum separation between the spinal cord and the target. Changing the number of beams is one of the most important parameters to be adjusted to improve the dose distribution. The optimal number of beams in a treatment plan depends on a complex combination of a number of factors. [26] In this study using multiple beams causes a decrease in PTV and body max dose, mean dose of right, left kidney, whole and healthy liver and dose gradient within PTV. This will result in delivering the dose to the target with an increase in the amount of surrounding tissues exposed to a low dose and a decrease in the volume of the tissues exposed to a high dose. This results in improvement in the dose distribution. Hence the greater the number of the fields, the more conformal is the plan not just to the target volume but to the sensitive structures as well [18,19,26] Samuelsson et al[26] found that the treatment plan was improved when the number of beams was increased as the mean dose in the PTV became smaller and the absorbed dose to the OAR was also reduced.

Although we choose to study the effect of number of beams on the dose distribution, other beam parameters such as beam energy, wedges, beam overlap and the use of bolus could affect the maximum dose to PTV, dose gradient and body max dose. Added to that the beam direction and number of OARs and its tolerance and how they are close to PTV could also affect the dose to OARs as the mean dose to kidneys, spinal cord and liver.

This work presents a detailed study for the effect of patient anatomy on the dose distributions for 3DCRT plans in cases with HCC. With the knowledge of the favourable and unfavourable anatomic parameters for each DVP, it is possible to predict the results regarding the target coverage and OAR dose distribution. This work will also help to determine the optimum number and direction of beams for different tumour site and size. It shows us whether it will be of benefit to use multiple beams or not for specific patient geometries.

Conclusion

As for IMRT, the dose distribution of 3DCRT plan is strongly dependent not only on the geometrical relationship between target and critical organs but also on number of beams used. The size of the effect varies with all factors together.

References

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012; 379: 1245-55.
2. Ik Jae Lee and Jinsil Seong. The Optimal Selection of Radiotherapy Treatment for Hepatocellular Carcinoma. Gut and Liver 2012 ; (2): 139-48
3. Yu-Cheng Kuo, Ying-Ming Chiu, Wen-Pin Shih, Hsiao-Wei Yu, Chia-Wen Chen, Pei-Fong Wong, Wei-Chan Lin, and Jeng-Jong Hwang. Volumetric intensity-modulated Arc (RapidArc) therapy for primary hepatocellular carcinoma: comparison with intensity-modulated radiotherapy and 3-D conformal radiotherapy. Radiat Oncol. 2011; 6: 76.
4. R. CABRERA & D. R. NELSON Review article: the management of hepatocellular carcinoma. Aliment Pharmacol Ther 2010; 31:461–76.
5. Judith Meza-Junco a, Aldo J. Montano-Loza b, David M. Liu c,d, Michael B. Sawyer a, Vincent G. Bain b, Locoregional radiological treatment for hepatocellular carcinoma; Which, when and how? / Cancer Treatment Reviews 2012; 38 : 54–62
6. Carlo Greco, Gianpiero Catalano, Alfio Di Grazia, and Roberto Orecchia. Radiotherapy of Liver Malignancies. From Whole Liver Irradiation to Stereotactic Hypofractionated Radiotherapy. Tumori 2004; 90: 73-9.
7. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 2002; 53:810–21.
8. Li Zhang, Mian Xi, Xiao-Wu Deng, Qiao-Qiao Li, Xiao-Yan Huang and Meng-Zhong Liu. Four-dimensional CT-based evaluation of volumetric modulated arc therapy for abdominal lymph node metastasis from hepatocellular carcinoma. Journal of Radiation Research 2012; 01: 1–8
9. ICRU report 62. Prescribing, recording, and reporting photon beam therapy. (Suppl. to ICRU report 50): Bethesda, MD: The International Commission on Radiation Units and Measurements, Nov. 1999.
10. Wong JW, Sharpe MB, Jaffray DA, Kini VR, Robertson JM, Stromberg JS, Martinez AA: The use of active breathing control (ABC) to reduce margin for breathing motion. Int J Radiat Oncol Biol Phys1999; 44: 911-19.
11. Dawson LA, Brock KK, Kazanjian S, Fitch D, McGinn CJ, Lawrence TS, Ten Haken RK, Balter J: The reproducibility of organ position using active breathing control (ABC) during liver radiotherapy. Int J Radiat Oncol Biol Phys 2001; 51:1410-21.
12. Helal, A.M., Przeslak, A.J., Sundar, S., & Perkins, A.C. (2006). The effect of target volume / OAR geometry on the dose distribution within rectum and bladder for IMRT treatment of prostate cancer. (Poster) in NCRI cancer conference; 8th –11th October 2006; Birmingham. UK.
13. Helal A.M, Przeslak, A.J., Morgan, DAL & Perkins, A.C. (2007). The effect of patient geometry on the dose distributions for IMRT plans of head and neck cancer. (Poster) in 4th Radiation Oncology Conference; 19th –21st March 2007; Edinburgh, UK.
14. Helal, A.M., Przeslak, A.J., Sundar, S., & Perkins, A.C. (2007). Patient geometry and applicability of class solution for optimised Intensity Modulated Radiotherapy dose distributions for prostate cancer. (Poster) in prostate cancer symposium; 22nd –24th February; Florida, USA
15. Helal A M. (2007). The Effect of Patient Anatomy on Optimized Intensity Modulated Radiotherapy Dose Distributions for Head and Neck and Prostate Cancer. PHD Thesis. Nottingham University.UK
16. A Grieco, M Pompili, G Caminiti, L Miele, M Covino, B Alfei, G L Rapaccini and G. Gasbarrini. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. *Gut* 2005;54:411-18
17. Petra, A. Intensity modulated radiotherapy treatment planning with OMP/ TMS for head and neck carcinomas in the ARTSCAN study. Master of Science thesis 2004. Lund University.UK
18. Kessler, M.L, Mcshan, D.A., Epelman, M.A., Vineberg, K.A., Eisbruch, A., Lawrence, T.S & Fraass, B.A. Costlets: A generalised approach to cost function for automated optimization of IMRT treatment plans. Optimisation and engineering 2005; 6: 421-48.
19. Beavis, A. W. Is tomotherapy the future of IMRT? Br J Radiol 2004; 77: 285 95.
20. ZHANG Li, XI Mian, SUN Wen-zhao, LIANG Jian, HUANG Xiao-yan, LIU Meng-zhong. Dosimetric Comparison of 3DCRT, Static IMRT, and VMAT for Hepatocellular Carcinoma. Journal of sun yat Sen University 2012; 33 (3): 402-6
21. Asselen, B.V., Dehnad, H., Raaijmakers, C.P., Roesink, J.M., Lagendijk, J.J., Terhaard, C.H. The dose to the parotid glands with IMRT for oropharyngeal tumours: The effect of reduction of positioning margins. Radiother Oncol 2002; 64:197–204.
22. Hsiung, C.Y., Yorke, E.D., Chui, C.S., Hunt, M.A., Ling, C.C., Huang, E.Y., Wang, C.J., Chen, H.C., Yeh, S.A., Hsu, H.C. & Amols, H.I. Intensity modulated radiotherapy versus conventional three dimensional conformal radiotherapy for boost or salvage treatment of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2002; 53: 638-47.
23. Hsiung, C.Y., Hunt, M.A., Yorke, E.D., Chui, C.S., Hu, J., Xiong, J.P., Ling, C.C., Lo, S.K., Wang, C.J., Huang, E.Y. & Amolsm, H.I. Intensity-modulated radiotherapy as the boost or salvage treatment of nasopharyngeal carcinoma: The appropriate parameters in the inverse planning and the effects of patient's anatomic factors on the planning results. Radiother Oncol 2005; 77:53-7.
24. Astreinidou, E., Dehnad, H., Terhaard, C.H. & Raaijmakers, C.P. Level II nodes and radiation induced xerostomia. Int J Radiat Oncol Biol Phys 2004; 58: 124-31.
25. Hunt, M.A., Hsiung, C.Y., Spirou, S.V., Chui, C.S., Amols, H.I. & Ling, C.C. Evaluation of concave dose distributions created using an inverse planning system. Int J Radiat Oncol Biol Phys 2002; 54: 953-62.
26. Samuelsson, A. & Johansson, K.A. Intensity modulated radiotherapy treatment planning for dynamic multileaf collimator delivery: influence of different parameters on dose distribution. Radiother Oncol 2003; 66: 19-28.