RESEARCH PAPER

Validation of esophageal cancer treatment methods from 3D-CRT, IMRT, and Rapid Arc plans using custom Python software to compare radiobiological plans to normal tissue integral dosage

Sougoumarane Dashnamoorthy[1,2], Ebenezar Jeyasingh[2], Karthick Rajamanickam[1]

[1]Thangam Cancer Center, Namakkal, Tamil Nadu, India
[2]Department of Physics, Jamal Mohamed College (Autonomous), Affiliated to Bharathidasan University, Tiruchirappalli, Tamil Nadu, India

ABSTRACT

Background: The aim was to develop in-house software that is able to calculate and generate the biological plan evaluation of the esophagus treatment plan using the Niemierko model for normal tissue complication probability and tumor control probability. The Niemierko model can be applied for esophagus cancer treatment plan to estimate the tumor control probability (TCP) and the normal tissue complication probability (NTCP) using different planning techniques. The equivalent uniform dose (EUD) and effective volume parameters were compared with organ at risk. Subsequently, EUD and TCP parameter were compared with tumor volume for all five different planning techniques.

Materials and methods: Ten cases for esophageal cancer were included in this study. For each patient, five treatment plans were generated. The Anisotropic analytical algorithms (AAA) were used for dose calculation for the three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques. The in-house developed radiobiological plan evaluation software using python programming is used for this study which takes a dose volume histogram (DVH) text file as an input file for biological plan evaluation.

Results and Conclusion: EUD, NTCP, TCP and effective volume were calculated from the Niemierko model using the in-house developed python based software and compared with treatment monitor units (MU) with all five different treatment plan. The best technique is quantified as benchmarked out of other different qualities of treatment. The four field 3D-CRT treatment plan is found to be the best suited from the perspective of biological plan index evaluation among the other planning techniques.

Key words: esophageal cancer; IMRT; MU

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Introduction

The primary objective of radiation oncology is to get the best possible outcome with no radiation-related complications. The early stages of treatment delivery are greatly improved by using published articles and practical expertise in this area. In order to confirm that the prescribed dose was applied to the planned target volume (PTV) and optimal dose to organ at risk (OAR), the physician has depended

on a customary technique like dose volume histogram (DVH).

Using the integrated iso-dose lines, color wash, 95% prescribed dose to 95% PTV for target structures, and Quantitative Analysis of Normal Tissues Effects (QUANTEC) or Radiotherapy Oncology Group (RTOG) used for physical treatment plan evaluation [1, 2]. There have been numerous attempts to develop mathematical models for normal tissue complication probability (NTCP) and tumor control probability (TCP), which were first proposed in the early decades, since the physical plan evaluation appears to be more quantitative than qualitative (OAR). Due to their intricacy and technical needs, these models are usually disliked by clinicians who work in this area of research.

The radiobiological model started their own method of enhancing treatment assessment because of the development of computer ages. Since the 2000s, many pieces of software have been created and implemented to analyze the treatment plan biologically [3]. The majority of applications are created using MATLAB, and only a very small number is created using the programming languages C, Visual Basic, and Java. This is because the DVH has become one of the most effective tools for assisting clinicians in understanding the desired plan objectives in terms of the relationship between dose and volume.

Considering the relationship between biological index estimates and physical dose measures in terms of clinical outcomes can be both fascinating and beneficial clinically. In numerous conditions, such as correct DVH computation and appropriate radiobiological parameters, radiobiological modeling enables the evaluation of clinical outcomes, such as TCP and NTCP [4]. In this study, we used the Niemierko model to determine the equivalent uniform dose (EUD)/TCP and NTCP for three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT) plans for esophageal cancer.

For the treatment of esophageal cancer, several cutting-edge external beam radiotherapy techniques are used, such as 3D-CRT, IMRT, and VMAT, to increase target coverage and decrease doses to nearby healthy structures. The majority of the study was devoted to analyzing the DVH and the physical dose distribution in order to assess the treatment strategy. In terms of lung and cardiac toxicities, the high-end approaches of IMRT and VMAT significantly differ from 3D-CRT procedures; however, there is still no agreement on a preferred technique because the treatment strategy produces equivalent dosimetric performance [5]. It is crucial to examine different therapy indices based on radiobiology in terms of tumor control and normal tissue complications in order to accurately assess the treatment results.

We have created a powerful program using the Python programming language that is user-friendly and inputs DVH text files from the commercial planning systems along with radiobiological parameters to calculate and analyze radiotherapy (RT) plans based on the radiobiological indices produced by the application, such as TCP, NTCP, EUD, and effective volume. In addition, based on the calculated treatment monitor units (MU), the integral dose to the entire body from the treatment techniques was examined and compared with radiobiological indexes for superior treatment techniques [6].

Materials and methods

Plan evaluation software

This software is built on the powerful Python programming languages and runs on a 62 bit windows operating system capable of analyzing the text file format of DVH from the Eclipse Treatment Planning System (M/S Varian Medical System, United States) more effectively than other programming language like visual basic, C and Java due to the very special packages in python called Numpy arrays which store and retrieve the data in nanoseconds. The default DVH format that the application uses for calculation is differential, but also converts cumulative DVHs into differential by the user. The Niemierko model of EUD/TCP and NTCP were implemented in this study, used centigray (cGy) for dose and cubic centimeter (cc) for volume.

Simulation and treatment planning

The CT simulations were carried out with both arms raised above the head and the patient lying head first on the spine. From the flat tabletop of the GE Discovery IQ PET-CT scanner, spiral CT images were obtained from the upper

boundary of the hyoid bone to the diaphragm and then rebuilt with a 3 mm slice thickness. RTOG delineation criteria for adjuvant radiation were used to contour the clinical target volume of the esophagus [7, 8] and other organs at risk, including the heart, right lung, left lung, liver, and spinal cord.

Five plans, including IMRT with gantry angles: 36°, 108°, 180°, 235°, 325° (5 field), IMRT of gantry angles: 27°, 78°, 129°, 180°, 231°, 282°, 333° (7 filed), VMAT [9, 10] of arc 179.0 CCW 181 (single arc) with 600 MU/min radiation rate in Eclipse TPS, and 3D-CRT with 2 field — anterior posterior field, 3D-CRT with 4 field — bi-lateral with anterior posterior field, were generated for each patient on a Varian treatment planning system (TPS) with photon beams from a Clinax iX linear accelerator add-on with Millennium Multileaf Collimator (MLC) with 120 leaves (special resolution of 5 mm at isocenter from the central 20 cm and of 10 mm in the outer 2 x 10 cm of maximum leaf speed of 2.5 cm/s with leaf transmission of approx. 1.5%. The anisotropic analytical algorithm (AAA) from Varian Eclipse TPS version 15.6 was used to compute the dosage distribution with a grid resolution of 2.5 mm. The plan is normalized so that 95% of the PTV was covered by 100% of the given dose [11].

Biological dose analysis

Ten esophageal cancer cases treated at our Cancer Center for cancer care were selected for this study, which is approved by the research committee of the hospital. The tumor were staged and tabulated in Table 1. The main parameters used to compare the 3D-CRT, IMRT and VMAT were EUD, NTCP and TCP and total number of MU, normal tissue integral dose of each treatment plan.

Radiobiological model

For radiobiological model response evaluation, cumulative DVHs of calculated treatment plans were exported from the Eclipse in text format. The in-house developed software was used for radiobiological analysis. We utilized python based program to calculate Niemierko's equivalent uniform dose (EUD)-based NTCP and TCP values. According to Niemierko's phenomenological model, the EUD [12] is defined as:

$$gEUD = [\Sigma(V_iD_i)^a]^{1/a} \quad (3)$$

In equation (3), "a" is a unit less tissue-specific parameter that describes the volume effect specific to the normal structure or tumor of interest, and v_i is unitless and represents the ith partial volume receiving dose Di in Gy. Since the relative volume of the whole structure of interest corresponds to 1, the sum of all partial volumes v_i will equal 1.

The parameter for TCD_{50} and $\gamma50$ was taken from Okunieff's report [13]. Furthermore, the biologically equivalent physical dose of 2 Gy was defined as:

$$EQD = D\frac{\left(\frac{\alpha}{\beta} + \frac{D}{nf}\right)}{\left(\frac{\alpha}{\beta} + 2\right)} \quad (4)$$

Where nf and df = D/nf are the number of fractions and dose per fraction size of the treatment course, respectively. The α/β is the tissue-specific Linear Quadratic (LQ) parameter of the organ being exposed [14].

TCP Niemierko's EUD-based TCP [25] is defined as:

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma50}} \quad (5)$$

Where, TCD_{50} is the 50% efficiency dose when irradiated homogeneously, and the $\gamma50$ is a unit-

Table 1. Parameters used to calculate Niemierko's equivalent uniform dose (EUD)-based tumor control probability (TCP) and the normal tissue complication probability (NTCP)

Tissue	Volume type	Value	γ50 value	TD50 [Gy]	TCD50 [Gy]	α/β [Gy]	Slope [m]
Heart	Normal	3	3	48		2	0.10
Lung	Normal	1	2	24.5		3	0.18
Spinal cord	Normal	13	4	66.50		2	0.175
Liver	Normal	2	3	40		1.5	0.15
Esophagus	Tumor	−13	2.16		49	10	

TD — toxic dose; TCD — tumor control dose

less model parameter that is specific to the tumor of interest and describes the slope of the dose-response curve.

NTCP Niemierko's EUD-based NTCP [26] is defined as:

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD}\right)^{4\gamma50}} \quad (6)$$

Where TD50 is the tolerance dose for a 50% complication rate at a specific time interval (e.g. 5 years in the Emami et al. normal tissue tolerance data) when the whole organ of interest is homogeneously irradiated. The γ50 is a unitless model parameter that is specific to the normal structure of interest and describes the slope of the dose-response curve. All the parameters used for the calculation of NTCP and TCP were tabulated in Table 2.

Kutcher and Burman developed a volume reduction algorithm for the Lyman Model for an in-homogeneously irradiated OAR, the resulting model conventionally referred to as the Lyman Kutcher Burman model. In the Lyman-Kutcher-Burman (LKB) model for each irradiated fractional sub volume v_i irradiated to dose d_i and reference dose d ref, there corresponds to a partial effective volume v_{eff}. The partial effective volume is defined as that volume which, if it were the only volume irradiated and were irradiated to dose d_{reff}, would result in the same NTCP in the Lyman model as if volume vi were the only volume irradiated and were irradiated to dose d_i [15].

$$V_{eff} = v_i \left(\frac{d_i}{d_{ref}}\right)^{1/n} \quad (7)$$

Where the d_i is the dose delivered to the volume fraction v and n is the parameter related to organ response to radiation (n = 0, 1 for serial and parallel organs, respectively). The inhomogeneous dose irradiation is converted into equivalent uniform irradiation of a fraction V_{eff} of the organ treated at the reference dose (d_{ref}).

Statistical analyses

A two-tailed paired t test was performed to compute the p value, with a value of p < 0.5 signifying statistical significance. The results were reported as mean and standard deviation from an ANOVA. Complete data analysis is performed using the Windows version of the SPSS application, version 20.00.

Results

For each of the five planning strategies [16], the results of the NTCP, TCP, EUD, and effective volume estimates using Niemierko models of each patient are compiled in Table 1. According to Figure 1, the heart's NTCP is statistically significant (p < 0.001), the same in all 5 approaches, although the effective volume is much lower in Rapid Arc while the EUD is constant across all 5 procedures.

In Figure 2, the lung's NTCP is statistically significant (p < 0.001) to be equal across all five techniques, while the effective volume was comparably lower in 3D-CRT. However, the lung's EUD for the 4-field 3D and Rapid Arc is the same across all five techniques.

In Figure 3, the NTCP of the liver is statistically significant (p < 0.001), the same in all 5 approaches, as is the effective volume, but the EUD for the 4-field 3D and Rapid Arc is also statistically significant (p < 0.001) and the same in all 5 procedures.

In Figure 4, the NTCP for 3D-CRT approaches (p < 0.001) is statistically significant compared to IMRT and Rapid Arc (p > 0.05), and the effective volume is relatively very high in 3D-CRT, but the EUD for 4-field 3D and Rapid Arc is the same as that of other techniques.

The effective volume in all 5 techniques is proportional to the NTCP of the heart, lung, liver, and spinal cord, i.e., less effective volume — low NTCP, more effective volume — high NTCP. The mean EUD for 4-field 3D-CRT- and Rapid Arc techniques is equal, and their NTCP also remains the same in the lung, liver, and spinal cord. The NTCP for the heart is significantly the same in 4-field 3D-CRT, IMRT, and Rapid Arc compared to 2-field 3D-CRT techniques, while the NTCP for lung complications is the same in all five techniques, as is the NTCP for liver complications in all five techniques, as shown in Figure 5A–C.

MUs [17] were collected for delivery 4D integrated treatment console (4DITC) for 4-field 3D-CRT and Rapid Arc treatment and comparison graph is shown in Figure 5A. Due to its higher EUD as compared to those of IMRT-5, IMRT-7, and Rapid Arc, the 4-field 3D-CRT clearly delivered a higher tumor control probability than other approaches as shown in Figure 7. Additionally, the 4-field 3D-CRT's EUD of PTV is higher than

Table 2. Dosimetric results of organ at risk for all five different radiotherapy (RT) planning techniques

| | 3D-CRT | | | | | | IMRT | | | |
	2-field	p-value	4-field	p-value	5-field	p-value	7-field	p-value	Rapid Arc	p-value
NTCP (homogeneous)										
Heart	0.973 ± 0.017	0.001	0.9473 ± 0.04	0.001	0.9304 ± 0.06	0.001	0.9262 ± 0.06	0.001	0.9250 ± 0.05	0.001
Lung	1.00	0.001	1.00	0.001	1.00	0.001	1.00	0.001	1.00	0.001
Liver	0.712 ± 0.43	0.001	0.7707 ± 0.38	0.001	0.727 ± 0.42	0.001	0.7493 ± 0.34	0.001	0.74 ± 0.40	0.001
Spinal cord	0.194 ± 0.016	0.001	0.091 ± 0.091	0.001	0.052 ± 0.051	0.001	0.033 ± 0.033	0.001	0.034 ± 0.034	0.001
NTCP (heterogeneous)										
Heart	0.968 ± 0.020	0.001	0.9316 ± 0.05	0.001	0.924 ± 0.063	0.001	0.9049 ± 0.07	0.001	0.9074 ± 0.06	0.001
Lung	1.00	0.001	1.00	0.001	1.00	0.001	1.00	0.001	1.00	0.001
Liver	0.705 ± 0.44	0.001	0.7572 ± 0.39	0.001	0.718 ± 0.43	0.001	0.7439 ± 0.40	0.001	0.7244 ± 0.41	0.001
Spinal cord	0.163 ± 0.01	0.001	0.063 ± 0.37	0.001	0.043 ± 0.04	0.001	0.03 ± 0.02	0.001	0.024 ± 0.01	0.001
EUD										
Heart	3180.6 ± 984	0.001	2873.1 ± 49	0.001	3007 ± 1004	0.001	2694.7 ± 58	0.001	2879.2 ± 97	0.001
Lung	2205.7 ± 71	0.001	2278.9 ± 39	0.001	2180.6 ± 114	0.001	2137.4 ± 46	0.001	2283.8 ± 77	0.001
Liver	2548 ± 83	0.001	2632 ± 44	0.001	2480 ± 74	0.001	2469 ± 53	0.001	2638 ± 89	0.001
Spinal cord	3601 ± 119	0.001	3723 ± 64	0.001	3408 ± 330	0.001	3492 ± 75	0.001	3731 ± 126	0.001
Effective Volume										
Heart	65.81 ± 16.74	0.001	31.58 ± 14.66	0.001	28.08 ± 15.20	0.001	24.65 ± 11.39	0.001	20.76 ± 9.32	0.001
Lung	56.54 ± 31.59	0.001	81.52 ± 41.10	0.001	76.3 ± 38.34	0.001	90.97 ± 39.49	0.001	76.77 ± 39.27	0.001
Liver	21.05 ± 21	0.001	26.32 ± 29	0.02	18.91 ± 21	0.001	19.03 ± 22	0.001	16.8 ± 19	0.02
Spinal cord	2.41 ± 0.49	0.001	0.24 ± 0.55	0.20	0.24 ± 0.75	0.34	0.02 ± 0.06	0.34	0	
PTV	0.358 ± .07	0.001	0.453 ± .05	0.001	0.37 ± .08	0.001	0.362 ± .05	0.001	0.375 ± .02	0.001
EUD	4931 ± 237	0.001	5187 ± 187	0.001	4896 ± 175	0.001	4900 ± 149	0.001	4987 ± 133	0.001

3D-CRT — three-dimensional conformal radiation therapy; IMRT — intensity modulated radiation therapy; normal tissue complication probability; EUD — equivalent uniform dose; PTV — planned target volume
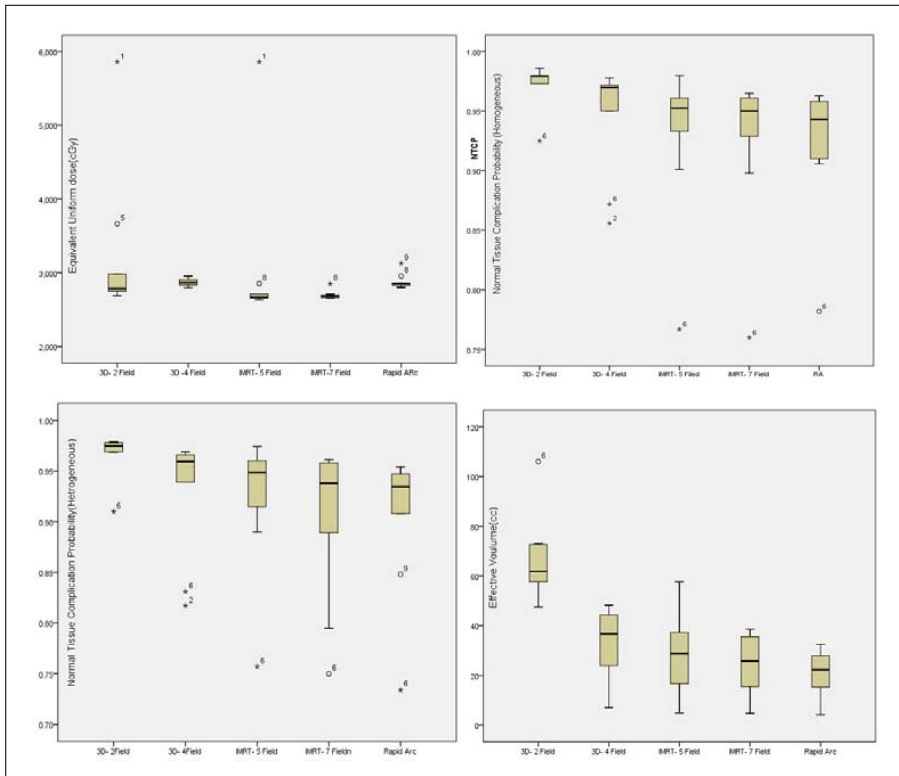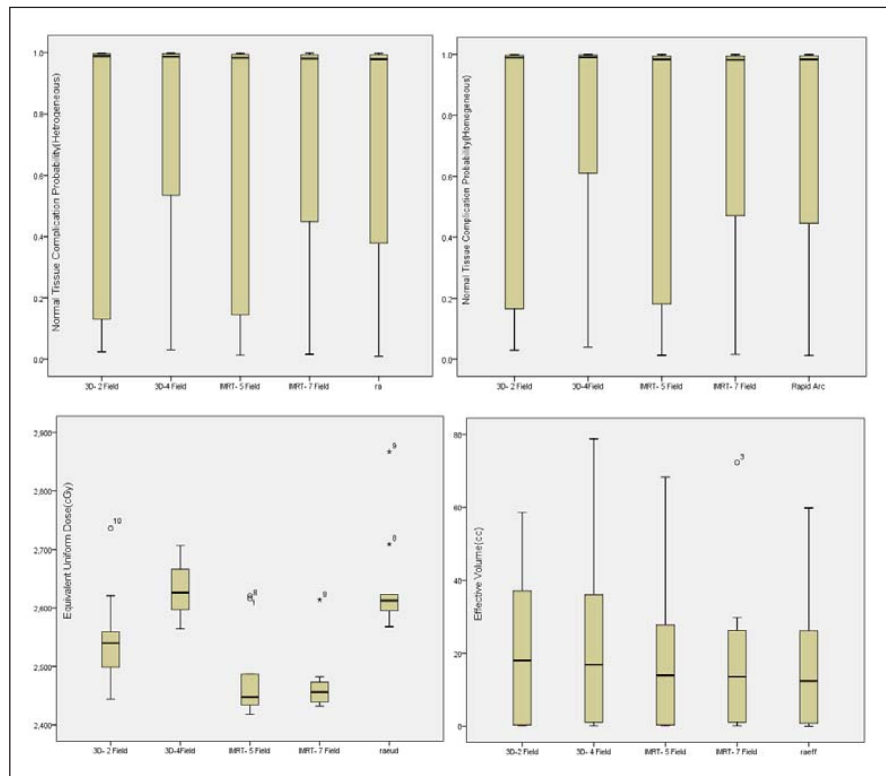
Figure 1. The normal tissue complication probability (NTCP), equivalent uniform dose (EUD) and effective volume of heart for five treatment planning techniques
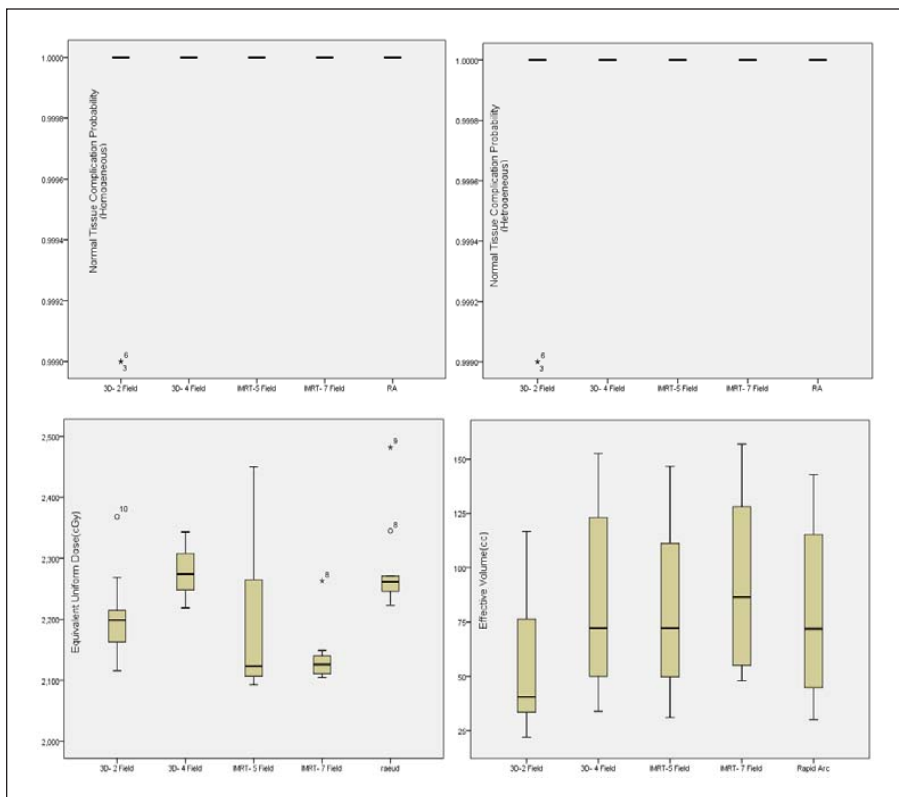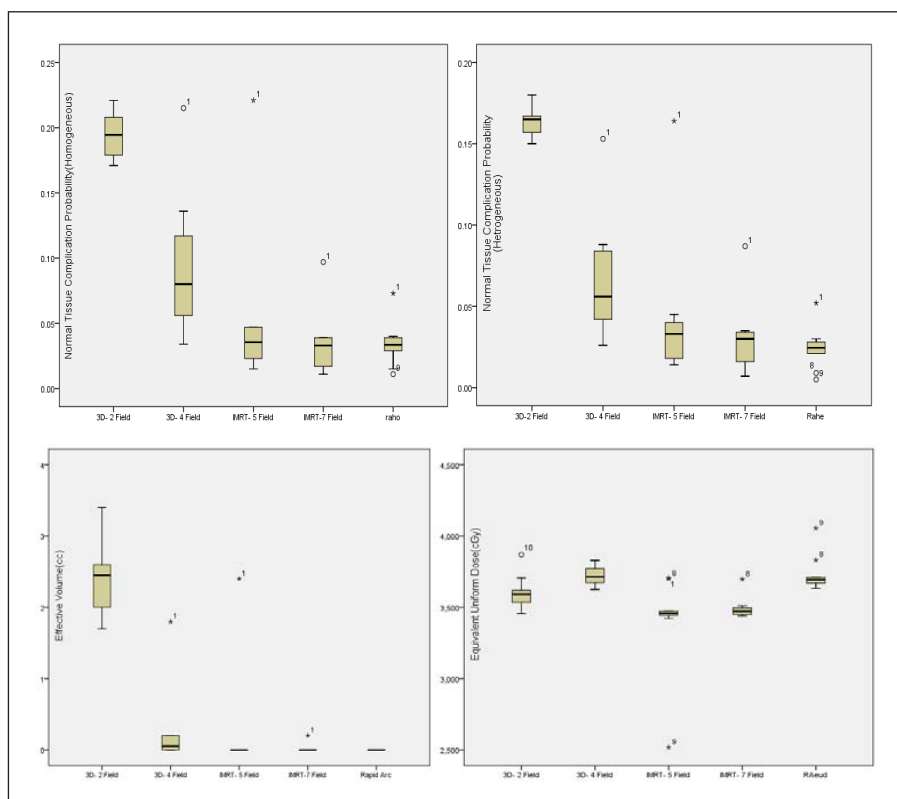

Figure 2. The normal tissue complication probability (NTCP), equivalent uniform dose (EUD) and effective volume of lung for five treatment planning techniques
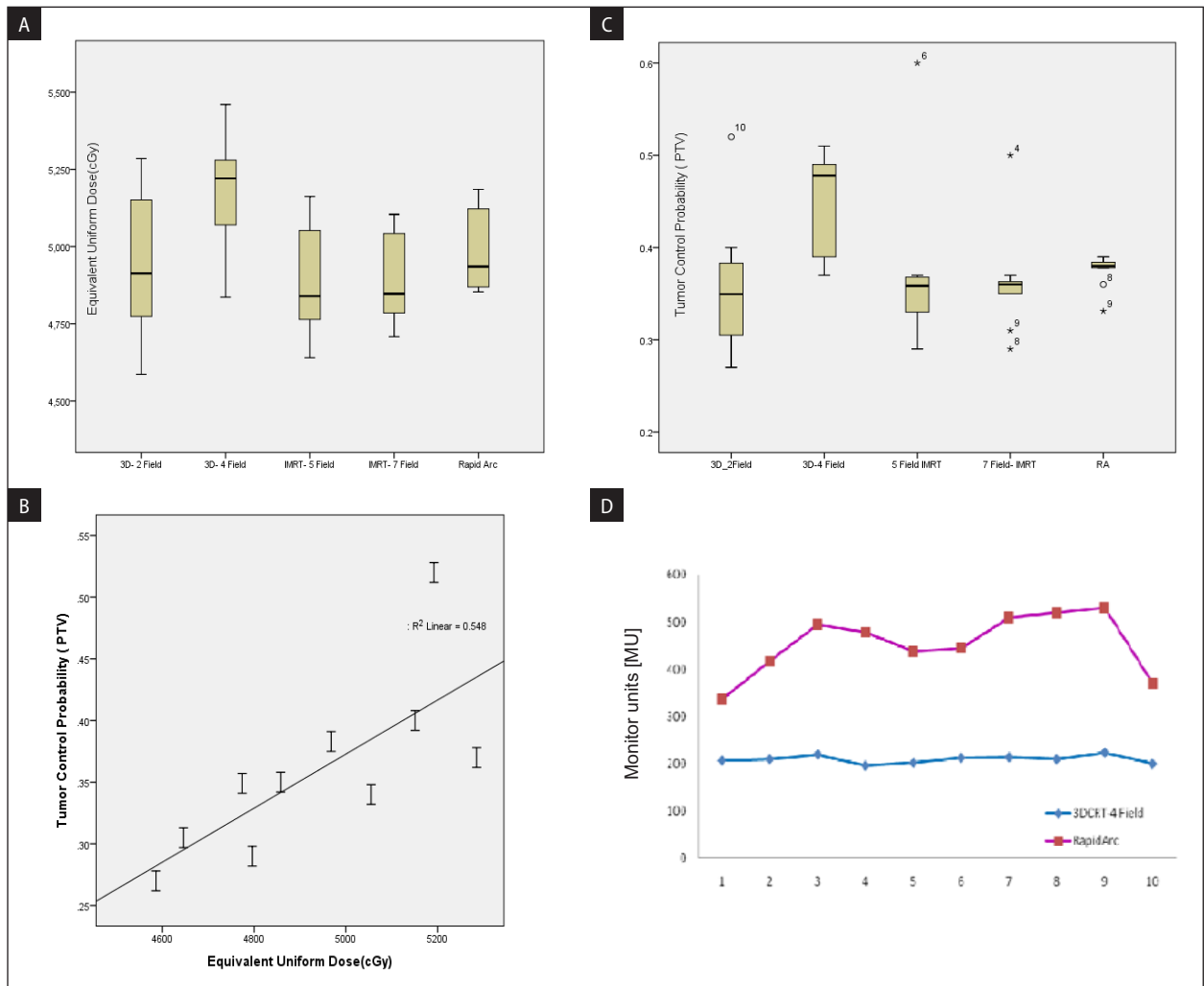
Figure 3 The normal tissue complication probability (NTCP), equivalent uniform dose (EUD) and effective volume of liver for five treatment planning techniques

Figure 4. The normal tissue complication probability (NTCP), equivalent uniform dose (EUD) and effective volume of spinal cord for five treatment planning techniques

Figure 5. Comparison of tumor control probability (TCP), equivalent uniform dose (EUD) and monitor units (MU) of five different planning techniques for planned target volume (PTV). **A.** EUD comparision with 5 planning techniques. **B.** TCP for comparision with 5 planning techniques. **C.** TCP comparision with EUD. **D.** MU comparison for 3D-CRT- 4 filed and Rapid Arc

that of Rapid Arc, which also adds to the higher likelihood of tumor control. The tumor control probability increases in direct proportion to the equivalent uniform dose (EUD). Compared to the Rapid Arc, the EUD and TCP of the 4-field 3D-CRT are unquestionably higher.

The radiobiological indexes such as EUD, NTCP and effective volume (e_{ff}) for normal structures for all three different treatment planning techniques are shown in Figure 6. The behavior of 4-field 3D-CRT treatment planning techniques is very well significant to that of Rapid Arc [18] technique.

Discussion

Therapy planning needs to be refined in order to treat esophageal cancer safely and successful-

ly. Four unique anatomical segments make up the esophagus. The desired volume is bigger despite the comparatively small lung volume in the cervical region. In the thoracic area, the lung volume is bigger. The bottom portions have a small target volume but are adjacent to the heart, liver, and kidneys.

TCP for each possible course of treatment is shown in Figure 6 in a remarkably similar manner. Principally, DVH attributes were used to assess the clinical efficacy of the treatment plan. The radiobiological evaluation of the DVH, however, has a bigger impact on the treatment plan's quality. Since it more accurately predicts tumor control and challenges with normal tissue than other traditional techniques, the radiobiological model should be taken into consideration when choosing the best
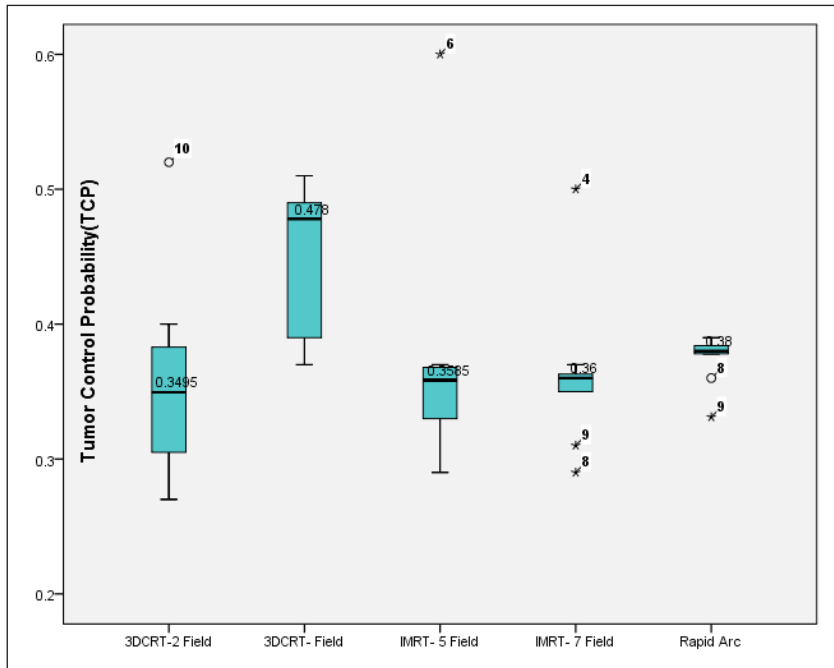
Figure 6. Tumor control probability (TCP) comparisons in 2-field three-dimentional conformal radiation therapy (3D-CRT), 4-field 3D-CRT, 5-field intensity modulated radiation therapy (IMRT), 7-field IMRT and Rapid Arc

radiotherapy treatment planning for esophageal cancer. There have not yet been any comparisons of the 2-field 3D-CRT, 5-field IMRT, 7-field IMRT, and Rapid Arc with, 4-field 3D-CRT utilizing radiobiological assessment.

The NTCP of OAR of 4-field 3D-CRT is statistically significant with Rapid Arc treatment planning techniques. It is clear that the NTCP of 4-field 3D-CRT plays equally good with IMRT and Rapid Arc techniques.

The MU for 4-field 3D-CRTare substantially lower than those for Rapid Arc techniques, and as shown in Figure 5D, the body integral dosage increases by a factor of 100 as a result of the dramatic increase in MU units. Since 4-field 3D-CRT's EUD differs significantly from Rapid Arc's, it achieves stronger tumor control than Rapid Arc. The PTV volume has a constant response for the tumour control probability, which indicates that, regardless of tumour volume, the control probability is constant, as illustrated in Figure 9B. Figure 9A illustrates this relationship between the PTV volume and the equivalent uniform dosage, which is linear, meaning that as the tumour volume increased, the equivalent uniform dose dropped.

Conclusion

In this research, the correlation between NTCP, TCP, and the EUD of 2-field 3D-CRT, 4-field 3D-CRT, 5-field IMRT, 7-field IMRT, and Rapid Arc from the Niemierko Model were investigated and quantified from the output of python software using the DVH text file from the commercial TPS and compared. The 4-field 3D-CRT treatment plans greatly and significantly reduce dosage to organs at risk as well as integral dose of normal tissue and increase the chance of tumor control compared to the five RT planning strategies. The normal tissue compilation probability is approximately 10% more in the 4-field 3D-CRT technique compared to Rapid Arc, but normal tissue integral dose is approximately 100% more in Rapid Arc techniques. It can be concluded that 3D-CRT — 4-field planning procedures are statistically superior to employ precise treatment, reliable clinical data connected to radiobiological parameters decides accurate biological plan evaluation because the choice of radiological parameter may overestimate or underestimate the NTCP-TCP values.
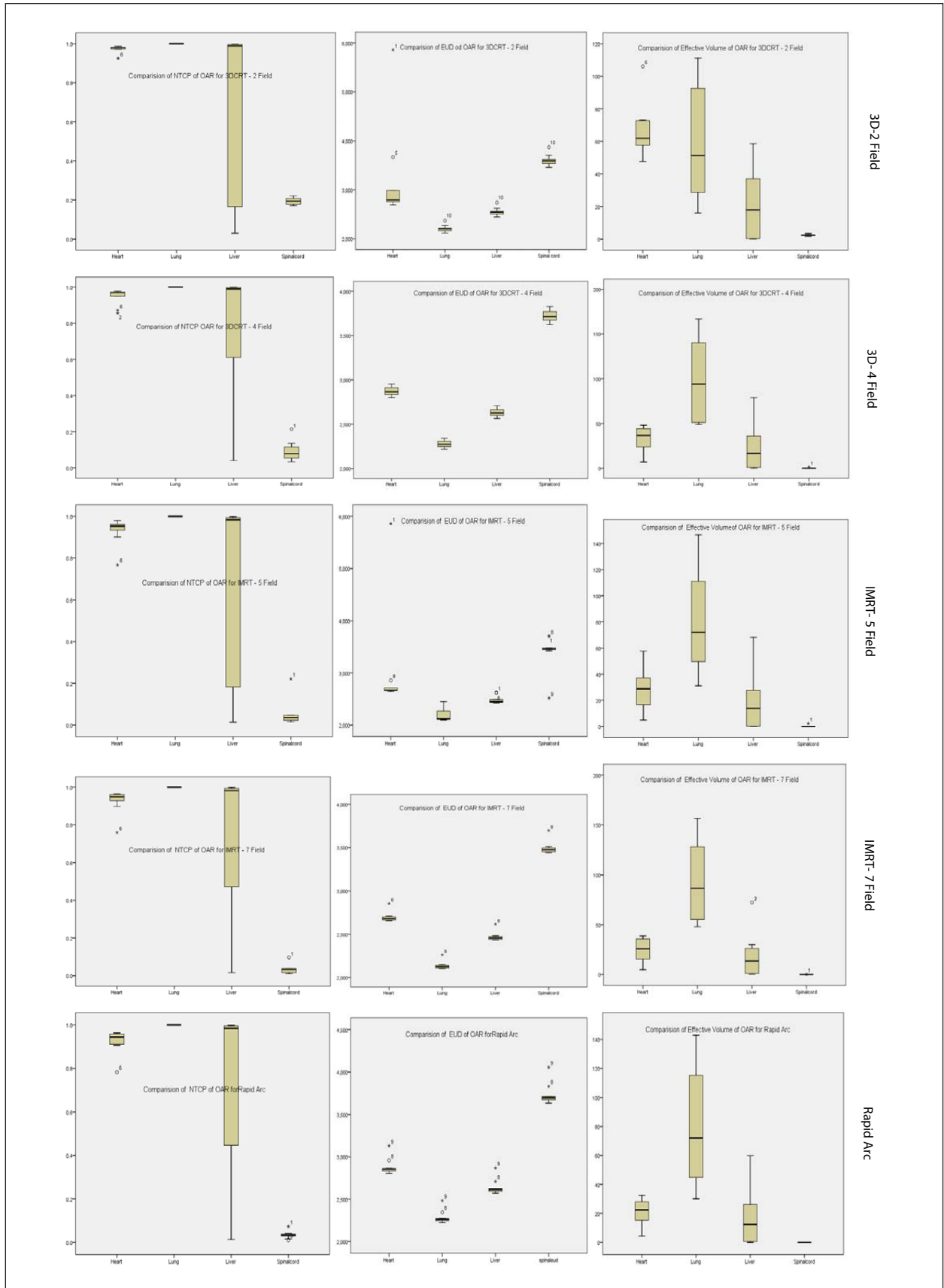
Figure 7. Comparisons of the normal tissue complication probability (NTCP)/equivalent uniform dose (EUD)/effective volume for organ at risk (OAR) for all treatment techniques
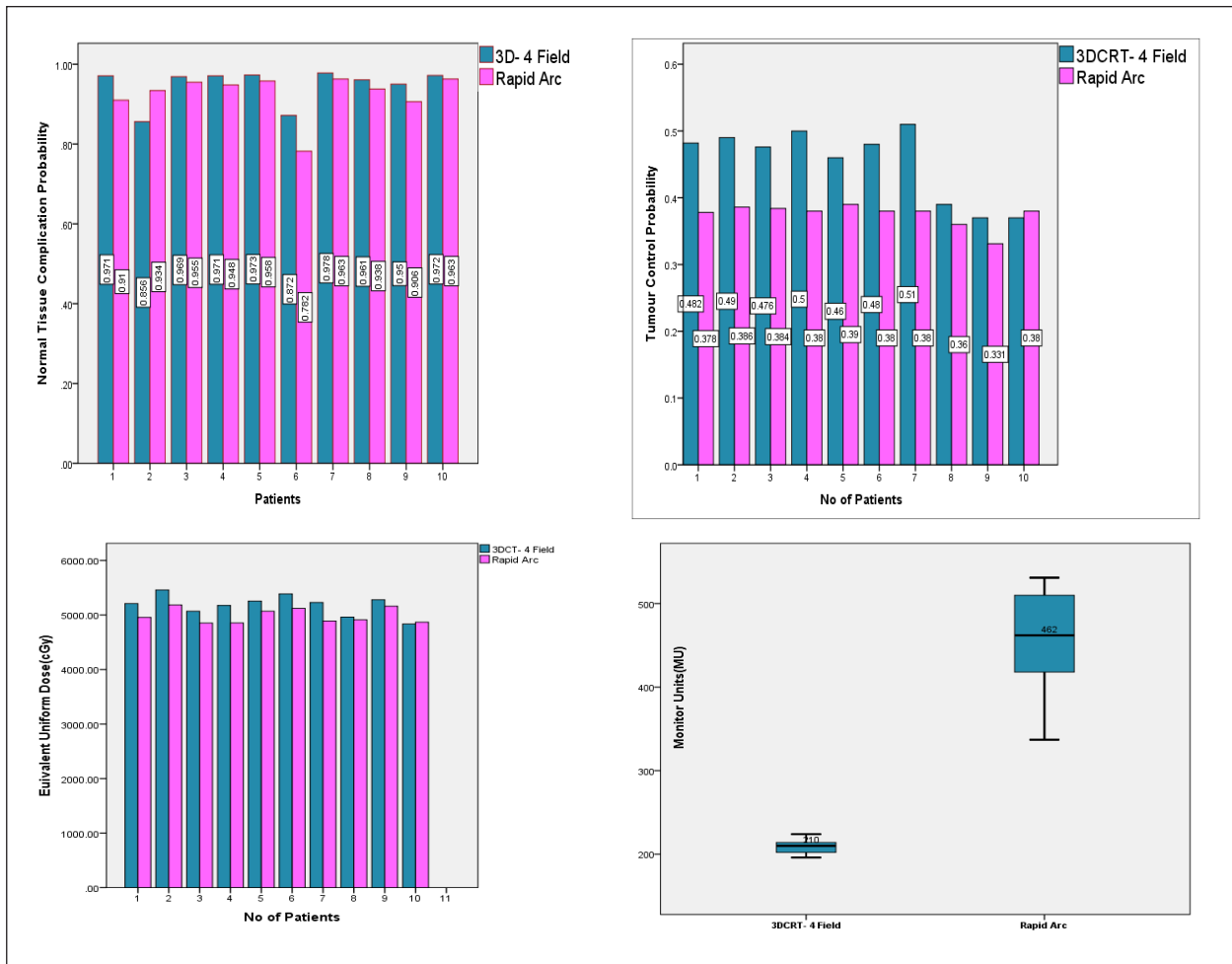
Figure 8. Comparison of 4-field three-dimensional conformal radiation therapy (3D-CRT) and Rapid Arc with the normal tissue complication probability (NTCP), tumor control probability (TCP), equivalent uniform dose (EUD) and monitor units (MU)
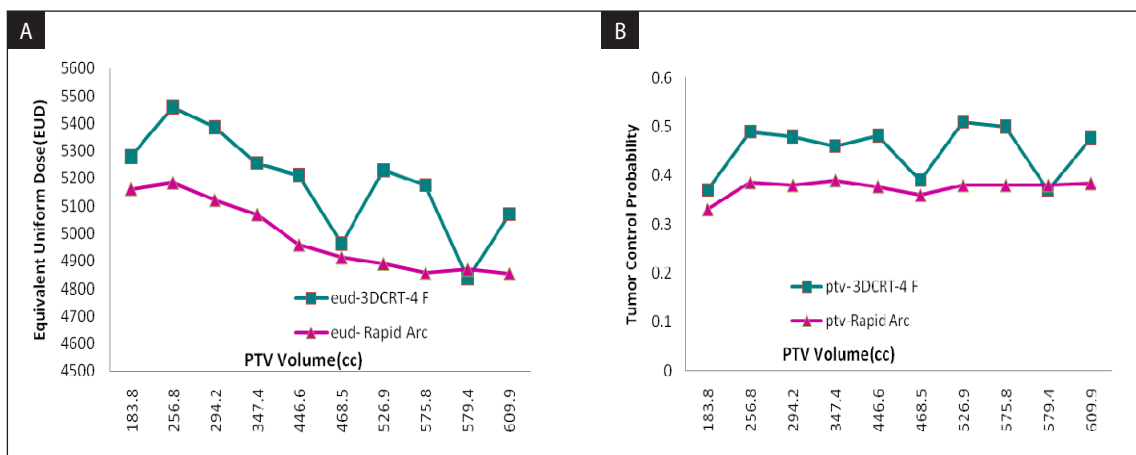
Figure 9. Equivalent uniform dose (EUD) and tumor control probability (TCP) response from planned target volume (PTV) for 4-field three-dimensional conformal radiation therapy (3D-CRT) and Rapid Arc

Conflict of interest

None declared.

Financial disclosure

None declared.

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