The Effect of Oral Contrast Agent on Tomotherapy Plans for Esophageal Carcinoma

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ABSTRACT

Background: The use of Contrast Agents (CAs) in radiotherapy enhances target volume contouring accuracy, but may influence dosimetric outcomes for the Planning Target Volume (PTV) and Organs-at-Risk (OARs).

Objective: This study aimed to investigate the dosimetric effects of Oral Contrast Agent (OCA) in Helical Tomotherapy (HT) treatment plans for patients with Esophageal Cancer (EC).

Material and Methods: In this experimental study, a total of 15 patients (8 females, 7 males; mean age 59.35±8.42 years) underwent two Computed Tomography (CT) scans: non-Contrast-Enhanced CT (non-CECT) and CECT. The original HT plans were performed on CECT images using the Precision Treatment Planning System (TPS), and then original plans were transferred into non-CECT images using the patient QA plan module. Dosimetric parameters, including Homogeneity Index (HI), Conformity Index (CI), D_x, V_x, and gamma index were compared between two plans.

Results: Dosimetric evaluation showed an increase in PTV dose metrics in CECT images, with significant differences in D_{98}, D_{95}, and D_{min}. Also, a significant difference was observed in HI (0.03±0.01 to 0.05±0.02) and CI (0.85±0.06 to 0.80±0.08) indices. Notably, the use of OCA led to reduced mean radiation doses to the OARs (heart, lungs, and spinal cord) demonstrating a statistically significant decrease in mean lung dose (-0.14±0.25 Gy).

Conclusion: Our findings demonstrate that the use of OCAs in Helical Tomotherapy Plans significantly enhances dosimetric outcomes by improving target volume coverage and reducing radiation exposure to critical organs.

Keywords

Esophageal Neoplasms; Contrast Media; Radiation Dosage; Radiotherapy Planning; Helical Tomotherapy

Introduction

Esophageal Cancer (EC), a major global health challenge, is recognized as a particularly aggressive type of cancer. Recent studies indicate that EC ranks as the 11th most frequently diagnosed cancer and the 7th leading cause of cancer-related mortality worldwide in 2022 [1]. Many patients are diagnosed at advanced stages of EC due to the nonspecific nature of its symptoms [2, 3]. Only

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20% of patients are eligible for the complete surgical resection of malignant tissue, while 80% typically receive radiation therapy when the disease progresses to intermediate or advanced stages [4].

The management of EC often requires sophisticated radiation therapy techniques, such as Helical Tomotherapy (HT) [5]. This approach utilizes the precision of Computed Tomography (CT) imaging to deliver targeted radiation doses while minimizing damage to adjacent healthy tissues. A crucial component of treatment planning in HT involves the use of Oral Contrast Agents (OCAs), which enhance the visibility of anatomical structures during CT scans. Contrast Agents (CAs) improve the differentiation of various structures, thereby enhancing the clarity of Planning Target Volumes (PTV) and Organs-at-Risk (OARs) [6,7]. The introduction of CAs alters the X-ray attenuation in tissues, subsequently affecting Hounsfield Unit (HU) values, which correspond to changes in electron density [8]. Therefore, when dose calculations are based on Contrast-Enhanced CT (CECT), there is a risk of dosimetric discrepancies since the actual treatment occurs without the presence of contrast. The influence of these OCAs on dose calculations continues to be a significant area of interest and concern in radiation oncology [7,9-11].

Some studies have documented the dosimetric effects of OCAs on radiation therapy plans [6,12,13]. Research has shown that using CECT images can lead to either underestimation or overestimation of radiation doses delivered to both PTV and OARs. For example, treatment plans developed from contrasted images often result in lower doses compared to those based on non-contrasted images [14]. This discrepancy occurs because the presence of contrast material alters the calculated electron density, which is essential for accurate dose distribution modeling. Studies have demonstrated that the differences in dose between treatment plans with and without contrast are statistically significant, although they remain within clinically acceptable limits. Discrepancies have been noted not only in target volumes but also in critical OARs [6,13,15]. For instance, research by Elawadi et al. [16] indicated that the dosimetric variations induced by CAs were statistically significant, yet clinically negligible concerning dose calculations. Recently, Demir et al. [17] investigated the impact of CAs on imaging for neoadjuvant treatment of rectal cancer, finding no significant differences in Three-Dimensional Conformal Radiation Therapy (3D-CRT) plans between contrast and non-contrast CT scans, apart from a slight increase in small bowel dose in HT.

In the treatment of EC, the unique capabilities of HT allow for targeted irradiation while protecting critical structures, such as the heart and lungs. However, the success of HT is dependent on precise treatment planning, highlighting the importance of OCAs. While the utilization of OCA in treatment planning is well-established, their specific dosimetric effects within HT for patients with EC remain largely unexamined. Current research on the impact of contrast materials in treatment plans is limited for EC. This study seeks to address this subject by examining the influence of OCAs on HT plans for this patient population. Although the use of OCAs is not novel, their application in HT specifically for EC represents a new area of exploration. The significance of this study is highlighted by the increasing preference for HT, which provides superior dose conformity to the target and improved protection of OAR compared to other techniques, including 3D-CRT, Intensity-Modulated Radiation Therapy (IMRT), and Volumetric-Modulated Arc Therapy (VMAT) [18-20]. Thus, to the best of our knowledge, the innovation of this research lies on the detailed evaluation and quantification of the dosimetric effects of CECT within the context of HT for EC, an area that has not been previously addressed. To date, only a few studies

have explored the impact of injectable and oral computed tomography contrast media on dose calculations in helical tomotherapy specifically for rectal cancer, although they focused on rectal cancer rather than EC [17,21]. Understanding the relationship between contrast-enhanced imaging and HT is essential for accurate dose calculations [22].

Despite the potential benefits of rotational dose transfer methods like HT, there is a limited body of research examining the impact of OCAs on treatment planning for EC patients [23]. Given the aforementioned considerations, this study aimed to evaluate the dosimetric impact of OCAs on the radiotherapy treatment planning for EC using the HT technique.

Material and Methods

Patient Population

This experimental study included 15 patients diagnosed with EC who were referred to the radiotherapy department at Imam Khomeini Hospital in Ardabil between October 2023 and November 2024. The cohort consisted of 8 females and 7 males, with a mean age of 59.35±8.42 years. Patients were excluded from the study if they met any of the following criteria: a) had allergic reactions to the OCA, b) had a history of renal disease, or c) experienced gastrointestinal disorders [7].

Target Volume and OAR Delineation

Each patient underwent two CT scans, one with CA and one without, using identical positioning and coordinate parameters. The initial CT scan was performed without oral contrast, followed by the administration of the contrast material. Both enhanced and unenhanced CT scans adhered to a consistent scanning protocol, ensuring that images were captured under uniform conditions. Further alignment was achieved using three lead spot markers or tattoo markers placed on the skin. The slice thickness for all scans was set to 3 mm.

In our study, oral iohexol contrast media were utilized, specifically Omnipaque at a concentration of 300 mg/mL (GE Healthcare, Princeton, NJ). Iodinated CAs, including iohexol, exhibit minimal plasma protein binding (around 1%) and are predominantly eliminated through the urine via glomerular filtration. Before imaging, the CT scan technologists addressed two key considerations regarding the use of OCAs with patients: (1) patients, who were unable to swallow liquid substances, were excluded from the study to prevent the risk of aspiration or other complications related to vomiting. (2) Patients with known allergies to the compounds used in the study, such as iodine, were also excluded.

After completing the non-CECT imaging, patients consumed the prepared OCA (50 ml of Omnipaque mixed in 1 liter of water) through a straw while remaining in the same supine position on the CT couch. Prior to the start of the scan, they were instructed via the audio communication system to hold a significant volume of the prepared contrast (approximately 20 to 30 ml) in their mouths. Once the imaging conditions were set, patients were asked to swallow the CA immediately before the exposure began. Due to the rapid transit of the OCA through the esophagus, the interval between the completion of OCA consumption and the initiation of the CECT scan is approximately 5 seconds. This timing ensures that the CECT scan captures images while the OCA is still present in the targeted area. No intravenous CAs were used in this study. After the scan, patients were advised to hydrate and consume plenty of fluids to facilitate the prompt elimination of the oral contrast from their bodies.

The elimination half-life (clearance) in individuals with normal kidney function is approximately 120 to 150 minutes [24]. Therefore, considering that the initial treatment session for EC patients typically occurs one day after the CT imaging, ensuring that any remnants of the CA would no longer be present

by the time treatment begins. Additionally, the duration of esophageal tomotherapy treatment typically involves around 30 fractions, without any contrast material.

To accurately evaluate the impact of the CA on dose calculations and HU measurements for OARs and PTV, patient positioning and imaging parameters, including kilovoltage (kV) and milliampere-seconds (mAs), were kept constant across both scans. After importing the CECT and non-CECT images in Digital Imaging and Communications in Medicine (DICOM) format into the Treatment Planning System (TPS), the radiation oncologist performed the necessary contouring according to ICRU-83 protocol [25]. The Gross Tumor Volume (GTV) was delineated first, followed by the application of a 3 mm isotropic margin to define the Clinical Target Volume (CTV). The CTV was then expanded by 5 mm laterally, anteriorly, and posteriorly, and by 7 mm superiorly and inferiorly to create the PTV. The bilateral lungs, heart, and spinal cord were identified as the OARs requiring delineation.

Treatment Planning

This article outlines a comprehensive workflow for radiotherapy treatment planning utilizing CT imaging and Tomotherapy technology at Imam Khomeini Hospital in Ardabil. The process began with the acquisition of CT images without the use of oral contrast. Subsequently, a second scan was conducted after the patients ingested oral contrast while in a supine position. This second scan took place within five seconds of swallowing the contrast, capitalizing on its swift transit through the esophagus and its brief presence in the tumor region. The images, formatted in DICOM, were imported into the TPS, where the radiation oncologist delineated the target volumes, including the PTV, GTV, and CTV, along with critical structures such as the spinal cord, lungs, and heart. For treatment planning, a Tomotherapy device equipped with a 6 MV linear accelerator and a binary system featuring 64 leaves (with a leaf opening and closing speed of 300 milliseconds) was employed.

The procedure included verifying contours, adjusting laser alignments, specifically, centering the green laser on the PTV and aligning the red lasers with patient markers, and configuring parameters such as field width (2.5 cm), pitch (0.43), modulation factor (2), and high computational resolution. The treatment plan was calculated and refined through an iterative process, checking Dose-Volume Histogram (DVH) curves in accordance with the Timmerman protocol [26] to ensure that critical organs remained within dose limits while the target volumes received the prescribed dose of 60 Gy over 30 sessions. Once the plan received approval, it was replicated onto non-CECT images without modifying beam weights, Monitor Units (MU), prescribed doses, or leaf movements. A Quality Assurance (QA) plan was established to compare the two plans by aligning the centers of the GTV and extracting parameters for evaluation. For each patient, a medical physicist created an HT treatment plan using CECT. The TPS, specifically ACCURAY Precision iDMSTM v2.0.1.0 build 2.0.1.0 [00800], was utilized for all plan designs. The prescribed radiation dose to the PTV was set at 60 Gy in 30 fractions, ensuring that 98% of the target volume was covered by the 100% isodose line. To achieve an optimal treatment plan, it is essential that the dose to OARs does not exceed established limits. According to institutional criteria based on the Timmerman protocol [26], the maximum allowable doses for OARs are as follows: heart V_{25}<25%, V_{30}<40%, mean heart dose <30 Gy; spinal cord D_{max}<45 Gy; bilateral lung V_5<55%, V_{20}<25%, V_{30}<15%, and D_{mean}<15 Gy. HT plans developed using CECT were applied to non-CECT scans without altering beam intensity, MU, or prescribed radiation dose. To evaluate the impact of the OCA on dose calculations, dosimetric parameters for the PTV and OARs were compared

between the two planning methods.

Dosimetric Indices

The HI serves as a dimensionless metric for quantifying the uniformity of dose distribution across the target volume. It is calculated using the following formula, where a HI value closer to zero indicates a more homogeneous dose distribution, with zero being the optimal value [27].

$$HI = \frac{D_2 - D_{98}}{D_P} \times 100 \qquad (1)$$

In this formula, D_2 represents the minimum dose received by 2% of the target volume (the maximum dose), while D_{98} denotes the minimum dose received by 98% of the target volume (the minimum dose). D_p represents the prescribed dose [28]. The CI measures how well the high-dose area aligns with the intended target volume. This index is employed during the treatment plan optimization process to ensure that the treated volume fully encompasses the PTV, with an ideal value of one. The CI is calculated as follows [29, 30]:

$$CI = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}} \qquad (2)$$

where, TV_{RI} denotes the target volume encompassed by the reference isodose, TV represents the overall target volume, and VRI signifies the volume of the reference isodose. Additionally, after completing treatment plans on CECT and non-CECT images and obtaining 3D dose distributions, other dosimetric parameters for the target and surrounding healthy tissues were extracted. These parameters included $D_{2\%}$, $D_{5\%}$, $D_{95\%}$, $D_{98\%}$, Dmin, Dmean, and D_{max} indexes, as well as various V_x metrics such as V_{100}, V_{95}, and V_{90}. For vital organs, the doses received by these tissues at different volumes were obtained using the D_x index from D_{min}, D_{mean}, and D_{max} values derived from the planning software.

Statistical Analysis

To statistically compare the data obtained from the two plans, with and without the OCA, the normality of the data was assessed using the Kolmogorov-Smirnov test. The paired t-test was applied to data exhibiting a normal distribution, while the Wilcoxon signed-rank test was used for non-normally distributed data. A P-value<0.05 was considered statistically significant. Statistical significance was defined as a P-value of less than 0.05. Levels of significance are indicated as follows: *P<0.05, **P<0.01, ***P<0.001, and ****P<0.0001. The gamma passing rate reflects the percentage of points that meet the requirement of a gamma index value below 1. To determine this metric, we used two acceptance criteria for evaluating the plans, utilizing a 20% threshold: 2%-2 mm criteria, and 3%-3 mm criteria.

Results

HU Enhancement for OARs and PTV

The administration of the OCA resulted in changes to the HU values for OARs and the PTV, with variations ranging from 1 to 43 HU. These changes were categorized into three groups: minimum, mean, and maximum. The minimum HU changes were 7 HU for both the heart and spinal cord, and 4 HU for the bilateral lungs. The mean HU changes were 18 HU for the heart, 22 HU for the spinal cord, and 10 HU for the lungs. The maximum HU alterations reached 43 HU for the heart, 12 HU for the spinal cord, and 1 HU for the lungs. The most significant increase was noted in the maximum HU for the heart. Due to the high concentration of OCA in the PTV region, the corresponding HU changes were pronounced: the minimum HU increased by 236 units, the mean HU by 428 units, and the maximum HU by 896 units.

Dose Indicators for PTV

Table 1 presents the Mean Difference (MD) results for the PTV. The dosimetric parameters showed a slight increase overall, with

Table 1: Dose metrics for Planning Target Volume (PTV) were evaluated under two conditions: before and after Oral Contrast Agent (OCA) administration. Findings presented as Mean±SD (Standard Deviation)

Parameters	Mean values		Mean difference	*P*-value
	Pre-contrast	Post-contrast		
D_{98} (Gy)	59.41±1.22	60.13±0.14	0.72±1.2	*0.030
D_{95}(Gy)	59.50±2.09	60.38±0.22	0.87±1.9	*0.025
D_{90} (Gy)	60.29±0.69	60.62±0.27	0.33±0.62	0.058
D_{80} (Gy)	60.71±0.61	60.80±0.32	0.09±0.53	0.524
D_{50} (Gy)	61.13±0.68	61.17±0.35	0.05±0.66	0.784
D_{5} (Gy)	62.02±0.48	61.98±0.41	-0.04±0.48	0.751
D_{2} (Gy)	62.46±0.79	62.13±0.48	-0.32±0.8	0.141
D_{min} (Gy)	56.69±0.48	57.64±0.57	0.96±0.77	***0.0003
D_{mean} (Gy)	61.04±0.73	61.17±0.34	0.13±0.74	0.934
D_{max} (Gy)	63.34±0.84	63.21±0.56	-0.14±0.52	0.328
V_{100} (cm^3)	158.75	158.54	-0.22±11.18	0.609
V_{95} (cm^3)	165.20	162.01	-3.19±8.98	0.266
V_{90} (cm^3)	167.12	162.89	-3.23±9.33	0.232
HI	0.05±0.02	0.03±0.01	-0.017±0.02	***0.0006
CI	0.8±0.08	0.85±0.06	0.05±0.03	***0.0001

D_{max}: Maximum dose, D_{mean}: Mean dose of volume, D_{min}: Minimum dose, D_p: Prescribed dose, D_X: Dose attained x% of the volume, V_X: Volume that received x% dose, HI: Homogeneity index, CI: Conformity index. The statistical significance levels are presented using the following notation, *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

exceptions noted for D_{max}, D_5, and D_2. Statistically significant differences were identified in certain dose metrics, including D_{98} (MD 0.724 Gy±1.2, 95% CI [0.056 to 1.392]), D_{95} (MD 0.88 Gy±1.95, 95% CI [-0.20535 to 1.96401]), and D_{min} (MD 0.95 Gy±0.77, 95% CI [0.529 to 1.383]).

In this study, we evaluated the dose falloff at varying distances from the target volume, extending up to 5 mm in 1 mm increments. To achieve this, we incorporated margins of 1 to 5 mm around the PTV and calculated the absorbed dose within each of these adjusted volumes. This analysis was performed for both series of images (CECT and non-CECT), and the results were statistically compared to determine the significance of the observed changes in dose falloff. Figure 1 presents the dose falloff results at different distances from the PTV. Notably, the changes in dose falloff are significant up to 4 mm from the edge of the PTV. This phenomenon can be attributed to the presence of contrast material at the target site during CECT imaging, which is characterized by high energy absorption and enhanced attenuation of X-rays. As a result, the absorption of radiant energy at the target and extending approximately 4 mm from its edges demonstrates significant differences when compared to the non-CECT mode. However, no statistically significant distinctions were observed for the other evaluated PTV parameters. Analysis of the HI and CI indices indicated that treatment plans developed using CECT provided a more uniform dose distribution within the PTV.

Table 1 shows that the evaluation of the 3D dose distribution using gamma index criteria of 2%-2 mm and 3%-3 mm confirmed

that all patients met both criteria. The local gamma passing rate for the 2%-2 mm criterion was 97.96%, while for the 3%-3 mm criterion, it was 99.44%. These differences were statistically significant. The DVH curve for a patient is illustrated in Figure 2, comparing scenarios with and without contrast administration. Figure 3 demonstrates the distribution of the PTV dose across the two treatment plans.

As shown in Figure 4, the isodose curves at

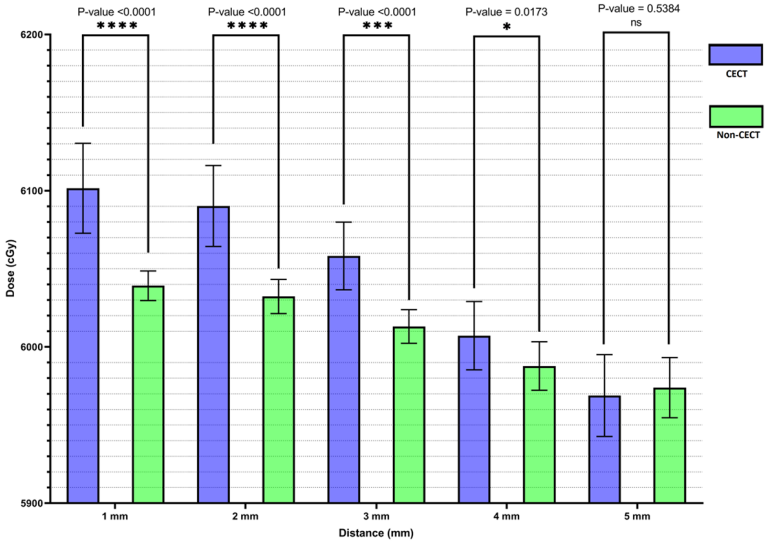

Figure 1: The results of dose falloff were evaluated at different distances from the edges of the Planning Target Volume (PTV), measured in 1 mm increments up to 5 mm. This assessment was based on absorbed dose calculations for both Contrast-Enhanced Computed Tomography (CECT) and non-CECT Helical Tomotherapy (HT) plans. The statistical significance levels are presented using the following notation, *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

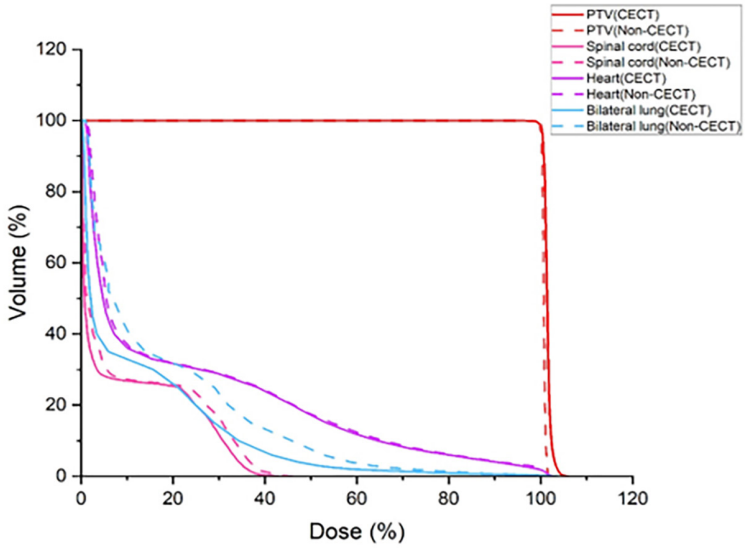

Figure 2: Comparative analysis of Dose-Volume Histogram (DVH) between Non-Contrast-Enhanced Computed Tomography (non-CECT) and CECT-based Helical Tomotherapy (HT) plans

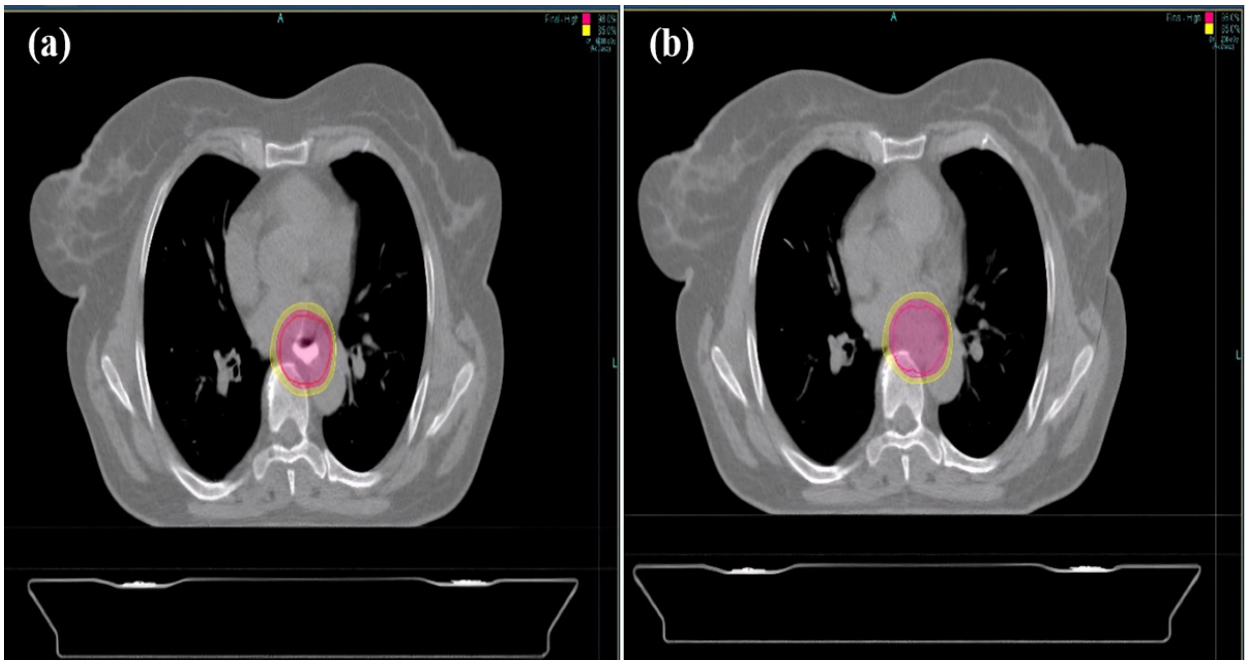

Figure 3: (**a**) Demonstrates the isodoses of 98 and 85 and volume of Planning Target Volume (PTV) for Contrast-Enhanced Computed Tomography (CECT). (**b**) Illustrates the isodoses of 98 and 85 and PTV volume in non-CECT. The PTV volume is depicted by the red curve, while the pink and yellow curves illustrate isodose 98 and isodose 85, respectively.

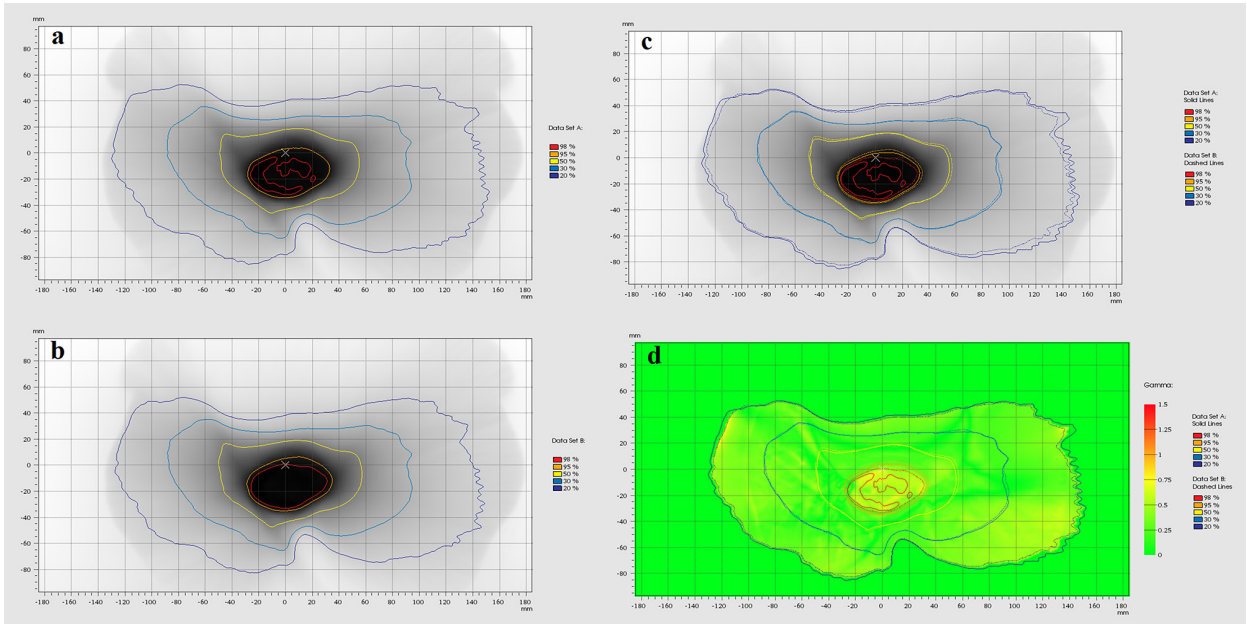

Figure 4: (**a**) The isodose curves derived from the treatment plan based on non-contrast images, (**b**) the isodose curves from the treatment plan utilizing contrast images, serving as a reference plan, (**c**) comparison of the isodose curves from the two plans (one with contrast and one without), and (**d**) the gamma pass rate distribution map.

higher levels (98% and 95%) in the contrast images encompass a larger volume compared to those in the non-contrast images. Conversely, lower isodoses, such as 20%, exhibit the opposite trend. This suggests that the average dose received by the target in the contrast-enhanced plan is greater than that in the non-contrast plan, while the average dose received by the OARs in the non-contrast plan is higher than in the contrast-enhanced images. The gamma pass rate distribution map, evaluated using gamma criteria of 3%-3 mm in Global mode, indicates a greater number of rejection points within the target area, suggesting discrepancies in dose delivery accuracy when comparing plans with and without contrast.

Dose Indicators for OARs

Table 2 provides details on the dosimetric parameters for OARs. The results indicate that the use of OCA led to a reduction in the mean radiation dose received by the heart and bilateral lungs. Additionally, D_5 and D_{max} values for the spinal cord were lower in the treatment plans utilizing CECT. The mean dose absorbed by the lungs (MD -0.14 Gy±0.253, 95% CI [-0.2844 to -0.00355]) showed statistically significant differences.

Discussion

For radiotherapy planning for esophageal carcinoma, our study introduces a novel exploration into a crucial element of treatment optimization. While prior research has investigated various applications of oral contrast media in the diagnosis and management of EC, the specific effects of these agents on Tomotherapy treatment plans have not been thoroughly analyzed. Our study is one of the first to examine how OCAs influence dose distribution in HT treatment plans for esophageal carcinoma. This distinctive focus is particularly relevant considering the growing adoption of advanced radiation delivery techniques, such as Tomotherapy, in the treatment of EC.

The findings of this study indicate that

Table 2: Dose metrics for Organs-at-Risk (OARs) were evaluated under two conditions: before and after Oral Contrast Agent (OCA) administration. Findings presented as mean±SD (Standard Deviation)

Parameters		Mean values		Mean difference	*P*-value
		Pre-contrast	Post-contrast		
Bilateral lung	V_5 (cm^3)	1889.18±1005.64	1852.62±967.21	-36.57±76.78	0.086
	V_{20} (cm^3)	713.46±1207.51	706.85±1206.17	-6.61±20.51	0.154
	V_{25} (cm^3)	216.81±122.54	213.37±124.19	-3.44±9.09	0.458
	V_{30} (cm^3)	124.10±79.65	121.69±76.83	-2.41±12.75	0.107
	D_{mean} (Gy)	9.71±3.09	9.57±3.13	-0.14±0.25	*0.045
Heart	V_{20} (cm^3)	180.10±86.06	179.04±55.85	-1.06±83.95	0.961
	V_{25} (cm^3)	124.64±64.17	122.85±42.77	-1.79±65.30	0.917
	V_{30} (cm^3)	93.75±48.39	92.03±33.55	-1.72±49.85	0.972
	V_{35} (cm^3)	79.51±32.83	79.45±28.49	-0.06±9.60	0.067
	D_{mean} (Gy)	15.75±6.51	15.54±5.45	-0.21±2.50	0.758
Spinal cord	D_5 (Gy)	16.41±4.18	15.15±3.66	- 0.27±0.88	0.073
	D_{max} (Gy)	19.39±4.75	19.24±4.30	- 0.15±1.70	0.737

V_X: Volume that received x% dose, D_{mean}: Mean dose of volume, D_X: Dose attained x% of the volume, D_{max}: Maximum dose. The statistical significance levels are presented using the following notation, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001

treatment planning using HT with CECT resulted in a more uniform dose distribution within the PTV and improved alignment between the prescribed and delivered doses. Goddu et al. [31] demonstrated that the homogeneity and conformity of the dose within the PTV were superior with the HT technique compared to 3D-CRT in breast cancer patients. The increase in dose associated with the use of OCA was most pronounced in D_{98} (0.72 Gy, Δ%: 1.21), D_{95} (0.88 Gy, Δ%: 1.46), and D_{min} (0.96 Gy, Δ%: 1.66), all of which were statistically significant. Despite these significant differences, the changes were deemed clinically acceptable. The volumes receiving 100%, 95%, and 90% of the prescribed dose were reduced by 0.22 cm^3, 3.19 cm^3, and 3.23 cm^3, respectively.

In the CECT plans, the mean radiation dose to OARs decreased, with reductions of (0.21±2.5 Gy, Δ%: 1.35) for the heart and (0.14±0.25 Gy, Δ%: 1.5) for the bilateral lungs. The most reduction was observed in D_5 for the spinal cord, which decreased by (0.27±0.88 Gy, Δ%: 1.66). Joseph et al. [14] investigated the effects of OCA on 13 rectal cancer patients treated with 3D-CRT, IMRT, and HT, reporting increases in D_{98} (0.008 Gy, 95% CI [-0.18 to 0.2]) and D_{95} (0.077 Gy, 95% CI [-0.04 to 0.19]) in HT plans with OCA. This aligns with our findings for D_{98} and D_{95} in the PTV, with the key distinction being that the changes observed in our study were within a range of 2%.

Li et al. [12] examined the effect of intravenous contrast on dose calculations in radiation treatment planning for EC, studying a cohort of 22 patients who underwent CECT scans. The research evaluated variations in dose distribution across different scenarios to quantify the impact of contrast enhancement. The results indicated that in scenarios with contrast enhancement, the mean dose variation for the PTV was less than 1.0%, while variations for the total lung and spinal cord were under 0.5%. However, when the HU value of the bloodstream exceeded 245, the average variation for heart V_{40} surpassed 1.0%. In extreme non-physiological scenarios, the PTV dose variation remained below 1.0%, yet dose calculations for organs at risk exceeded 2.0%. The study concluded that while intravenous contrast does not significantly affect dose calculations for the PTV, lung, and spinal cord, it can influence dose accuracy for the heart, particularly at elevated HU values.

Jabbari et al. [13] investigated the effects of intravenous contrast media on dose calculations in 3D-CRT for lower esophageal and rectal cancers. This study included 17 patients with lower esophageal tumors and 12 patients with rectal cancers, comparing treatment plans based on CT scans with and without intravenous contrast. In the lower esophageal region, the use of contrast resulted in an average increase in MUs of 1.28% for 6 MV photon beams and 0.75% for 15 MV photon beams, with these differences being statistically significant, indicating a considerable effect of contrast media on this anatomical area. Conversely, no statistically significant differences were noted in the rectal region, suggesting that the use of contrast media had a minimal impact on dose calculations for rectal cancers.

Research on the impact of CAs on treatment planning dose calculations in EC patients has been limited. To our knowledge, this study is the first to examine the effect of OCA on these patients using the HT method. Nevertheless, our results are consistent with findings from other studies. For example, Jabbari et al. [13] reported that the use of CAs reduced the mean dose to the lungs by 0.25±0.64 Gy and to the spinal cord by 1.5±4.14 Gy, corroborating our results. Zhu et al. [11] found that the dose difference between CECT and non-CECT plans in pancreatic cancer patients using tomotherapy and VMAT was negligible, not exceeding 1%. Jing et al. [6] reported a slight but statistically significant increase in dosages for both the PTV and OARs among 33 rectal cancer patients treated with VMAT. Their findings suggested that OCA had a more

substantial impact compared to intravenous CAs. Other studies have shown that the influence of CAs on dose calculations in treatment plans is generally less than 2%, with modifications not clinically affecting dose outcomes [6,11,32].

We employed local dose comparison gamma indices for analysis, as local gamma is more sensitive to dose variations than global gamma. The results indicated that 97.96% of patients met the 2%-2 mm criteria, while 99.44% met the 3%-3 mm criteria (Figure 4). In line with Elawadi et al. [16], who evaluated the gamma index between plans with and without contrast in 226 patients with various cancers, 94% of their plans met the 2%-2 mm criteria, and all plans met the 3%-3 mm criteria. Montero-Oleas et al. [7] reported a gamma passing rate of 95.2% for IMRT plans using a 2%-2 mm criterion. Similarly, Joseph et al. [14] assessed the dosimetric effects of small bowel oral contrast on conventional radiation therapy, IMRT, and HT treatment plans, concluding that the use of OCAs during CT simulation had no clinically significant impact on dose calculations.

Heydarheydari et al. [10] examined the differences in dose calculations caused by CAs in treatment planning for pelvic cancers, finding no statistically significant differences in radiation doses to the target volume and OARs between pre- and post-contrast plans, except for the bladder in the prostate region. Izmirli et al. [33] studied the effects of various concentrations of CAs on dose calculations in TPSs for radiotherapy. They prepared mixtures of Iopromide and water at concentrations ranging from 0% to 10% and utilized Cobalt-60 and 10 MV linear accelerator devices for calculations. Their findings indicated that higher concentrations of CAs resulted in increased dose values at maximum dose depth (D_{max}) and at a depth of 5 cm, with notable differences observed for Cobalt-60 compared to linear accelerators.

Jing et al. [6] also examined the influence of OCAs on dose calculations in VMAT plans for rectal cancer, finding that OCAs significantly increased the mean and maximum densities of the bowels, leading to actual doses for the PTV being higher than planned. They concluded that OCAs could cause underestimation of doses in treatment planning, particularly when significant volumes of enhanced intestine are near the PTV, necessitating careful consideration in clinical practice.

Demir et al. [17] in 2024 assessed the impact of CAs used for imaging on neoadjuvant rectal cancer treatment, noting that while CAs are used during treatment simulation, patients are treated without them. Their study investigated whether CT scans taken with contrast are sufficient for clinical application, randomly selecting eighteen patients who had undergone neoadjuvant treatment for rectal cancer. They performed two different CT scans for each patient, delineating contours on non-contrast CT images using image fusion with contrast CT images. All plans were generated in Eclipse TPS and Accuray Precision TPS, comparing plans with and without CAs. Their findings indicated no significant differences in either the PTV or the maximum and mean values of critical organs. However, they noted a significant increase in average post-contrast doses for the small bowel only in helical therapy.

In a similar study, Tabatabayi et al. [21] evaluated the impact of CECT on treatment planning for rectal cancer using HT. The study included patients with rectal tumors who underwent both CECT and non-CECT imaging. Target volumes, GTV, CTV, and PTV, were delineated by a radiation oncologist, utilizing IMRT techniques with Simultaneous Integrated Boost (SIB) to optimize dose delivery while minimizing exposure to OARs. The results indicated that CECT significantly improved HU values, enhancing visibility and accuracy in target volume delineation. While dosimetric evaluations showed minimal differences between CECT and non-CECT plans, certain indices such as Dmax, Dmin, HI, and CI exhibited significant changes that could

influence clinical outcomes.

In general, we encounter two primary challenges when utilizing CAs in radiotherapy: the first pertains to the artifacts generated by CAs in CT images, and the second concerns radiotherapy treatment planning when patients undergo multiple sessions without these agents present in the treatment room. A review of various studies indicates that dual-source CT single-energy spectral imaging technology can effectively eliminate CA artifacts, thereby enhancing dose calculation accuracy in treatment planning [34-36]. However, this procedure is still under investigation and is not yet routinely implemented at our institution due to the absence of the necessary equipment.

There are also strategies for managing treatment planning with CAs, such as employing override density or density correction options on CECT images [6,14]. Nevertheless, the primary focus of our study was not to address the effects of override density on treatment planning improvements in CECT images, nor to implement or compare mitigation strategies. Instead, we concentrated solely on the dosimetric effects and the absence of oral contrast media, without delving into the elimination or reduction of contrast media effects in tomotherapy plans, showing that exploring this issue could be a valuable topic for future research.

One limitation of this study is the relatively small sample size, which inherently restricts the statistical power and generalizability of the findings. This limitation partly arose from challenges in recruiting a larger cohort of EC patients who met all inclusion criteria and were suitable for both non-CECT and CECT imaging for HT planning. Despite this limitation, previous dosimetric studies evaluating radiotherapy techniques for various cancers have published findings based on fewer than 20 patients [10,13,17,21,34]. Additionally, the inherent variability in tumor location, stage, and patient anatomy introduces potential confounding factors that, despite being addressed through consistent imaging protocols and careful delineation, could influence the observed dosimetric effects. Future research involving larger, multi-center cohorts is essential to validate these findings across a broader patient spectrum and to explore potential correlations between specific anatomical features and the impact of OCAs on dose calculations.

Another limitation of our study is the inability to assess changes in radiobiological parameters, such as differential DVH file, TCP (Tumor Control Probability), and NTCP (Normal Tissue Complication Probability), which is due to the unavailability of this data in version 2.0.1.0 of the ACCURAY Precision TPS system. Future research could potentially calculate these indices using mathematical formulas and relationships through various models, such as the Lyman-Kutcher-Burman (LKB) and Relative-Seriality (RS) models, utilizing BioSuite software. This approach would enable a thorough evaluation of the radiobiological effects and toxicity associated with the use of OCA in HT treatment plans for patients with EC.

There are several issues regarding pretreatment imaging and the implementation of IGRT in HT. The first challenge arises from the presence of contrast material in the Digitally Reconstructed Radiograph (DRR) images generated by the TPS, whereas this material is absent in the daily scans (KVCT or MVCT) performed with the tomotherapy device. The second challenge pertains to patient movement, which can alter the position of the treatment isocenter. To remove the influence of the CA from the original CT images, we recommend applying density overrides or corrections before generating the DRR images. The concern regarding patient movement and setup errors can be mitigated post-image acquisition by aligning it with the DRR image through appropriate adjustments. Several studies have assessed the dosimetric implications of isocenter displacement in this context.

Chow [37] examined variations in Kilovoltage Cone-Beam Computed Tomography (kV-CBCT) dosimetry resulting from changes in isocenter positions in head-and-neck, lung-breast, and pelvic Rando phantoms using BEAMnrc MC simulations. They calculated the relative dose at the isocenter, maximum dose, and mean dose for each isocenter shift across the three phantoms. When the isocenter was positioned away from the center of the head-and-neck phantom, the maximum and mean imaging doses varied by 14% and 15% in the anterior-posterior direction, and by 9% and 7% in the left-right direction. For the lung-breast phantom, these dosimetric variations were slightly greater, ranging from 17% to 19%. In the pelvic phantom, the maximum and mean imaging doses varied between 9% and 22%. The typical imaging dose for soft tissue per kV-CBCT acquisition was found to be between 2–8 cGy. In another study, Chow et al. investigated the impact of patient dose due to kV-CBCT in prostate IMRT [38]. They analyzed vertical and horizontal dose profiles crossing the femur heads and isocenter, both with and without the kV-CBCT dose, which accounted for 2% of the prescribed dose.

Conclusion

The use of OCA does not significantly affect the dose calculations for the OARs and the PTV. Furthermore, the application of OCA leads to a reduction in radiation exposure to critical organs, thereby enhancing their preservation. The combination of HT techniques and OCA resulted in a more uniform dose distribution within the target volume, improving the alignment between areas of high dose gradients and the target. These findings indicate that CECT images can be safely integrated into radiotherapy treatment plans without concerns regarding dose-related discrepancies.

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Authors' Contribution

Z. Abdi Vadig was responsible for writing the original draft, performing formal data analysis, data collection, validation, and contributing to the conception and design of the study. H. Zamani contributed to writing the original draft. AA. Kani was involved in the conception and design of the study as well as writing, reviewing, and editing the manuscript. S. Keramat Jou participated in treatment planning and data collection. M. Molazadeh contributed to conceptualization, data curation, project administration, supervision, validation, and writing, reviewing, and editing the manuscript. All authors read, revised, and approved the final version of the manuscript.

Ethical Approval

The Research Ethics Committees of Vice-Chancellor in Research Affairs - Tabriz University of Medical Sciences approved the study protocol (Ethic code: IR.TBZMED.REC.1403.014).

Informed Consent

All participants meticulously reviewed the informed consent form and confirmed their full understanding of the objectives, methods (including the performance of both contrast-enhanced and non-contrast CT imaging), potential benefits, and risks, thereby declaring their consent to participate in the study. Furthermore, they acknowledged and respected their right to receive their routine treatment without disruption and the right to withdraw from the study at any stage.

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Conflict of Interest

None

Data Availability Statement

All data generated or analyzed during this study are included in this published article. Also, the data that support the findings of this study are available from the corresponding authors upon reasonable request.

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