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DOSIMETRIC COMPARISON BETWEEN 3DCRT AND VMAT IN CA ESOPHAGUS PATIENTS.

Radiotherapy

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ABSTRACT

VMAT provides excellent conformity to the predetermined target volume (PTV) and organ sparing (OAR). This study evaluates the dosimetric features and toxicity of esophageal cancer (EC) people diagnosed with VMAT plus 3D conformal radiation (3DCRT). We administered 3D-CRT, s-IMRT, and mARC planning to 10 patients from a group of 25 individuals with esophageal cancer of the thorax. Each plan's dose-volume histogram was extracted, and the mean dosage and clinically relevant characteristics were examined. According to an analysis of target coverage, the conformity index (CI) and conformance number (CN) of mARC were better than those of the other two plans. Comparing OAR, s-IMRT produced the lowest lung V5, followed by 3D-CRT and mARC. s-IMRT and mARC exhibited lower cardiac V30, V40, and V50 values than 3D-CRT. With s-IMRT, effective lung and heart preservation in thoracic esophageal cancer might be anticipated. The mARC was lower in lung V10, V20, and V30 than 3D-CRT, but its superiority in lung V5 could not be shown. Low-dose exposure to the lung and heart was anticipated to be lower in s-IMRT, hence lowering problems including radiation pneumonitis and heart-related toxicities.

KEYWORDS

3-Dimensional Conformal Radiation Therapy (3D-CRT), Volumetric Modulated Arc Therapy (VMAT), Organ at Risk (OAR), Planned Target Volume (PTV), Conformity Index (CI), Conformance Number (CN).

INTRODUCTION

In patients who have cancer of the esophagus, a dosimetric comparison between 3DCRT (3-dimensional conformal radiation therapy) and VMAT (volumetric modulated arc therapy) would involve measuring and comparing the radiation doses that were received by the tumour and the healthy tissue that was surrounding it for each treatment modality. Studies have demonstrated that volumetric modulated arc therapy, or VMAT, may deliver larger doses of radiation to the tumour while simultaneously decreasing exposure to the healthy tissue that is around it. This results in increased target coverage and less toxicity. However, it is essential to keep in mind that the selection of a treatment modality need to be predicated on individual patient criteria including the location and size of the tumour, in addition to the treatment strategy as a whole (Takakusagi et al., 2021).

3DCRT, or 3-dimensional conformal radiation therapy, is a type of external beam radiation therapy that uses multiple beams of radiation to conform to the shape of the tumor. This technique involves using imaging, such as CT scans, to create a 3D model of the tumor and surrounding healthy tissue. The radiation beams are then shaped and directed to conform to the contours of the tumor, while minimizing exposure to surrounding healthy tissue. This technique can improve the accuracy of radiation delivery and reduce side effects, but it is not as flexible as VMAT, which allows for continuous rotation of the treatment machine around the patient (Munch et al., 2016).

On the other hand, **VMAT**, or volumetric modulated arc therapy, is a type of external beam radiation therapy that uses a combination of multiple beams of radiation and continuous rotation of the treatment machine around the patient to deliver radiation to the tumor while minimizing exposure to surrounding healthy tissue. This technique uses a multi-leaf collimator (MLC) which shapes the beams to conform to the tumor, and a control system that continuously adjusts the intensity of the radiation. VMAT also uses optimization algorithms to plan the treatment, which allows for faster treatment delivery times and reduced radiation exposure to healthy tissue. This results in improved target coverage and reduced toxicity, it's also a more flexible option for some cases. However, it should be noted that the choice of treatment modality should be based on individual patient factors such as tumor location and size, as well as the overall treatment plan (Takakusagi et al., 2021).

Cancer of the esophagus, also known as **esophageal cancer**, is a type of cancer that develops in the lining of the esophagus, the muscular tube that connects the mouth to the stomach. Esophageal cancer is typically divided into two main types: squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma, the most common type of esophageal cancer, develops in the cells that line the upper and middle parts of the esophagus. Adenocarcinoma, the less common type, develops in the cells that line the lower part of the esophagus. Risk factors for esophageal cancer include smoking, heavy alcohol consumption, Barrett's esophagus (a pre-cancerous condition), and a diet low in fruits and vegetables. Symptoms of esophageal cancer include difficulty swallowing, weight loss, and chest pain. Treatment options for esophageal cancer include surgery, radiation therapy, and chemotherapy. The choice of treatment will depend on the stage of the cancer and the patient's overall health (Zhang, 2013).

One of the extreme treatment techniques that may be used for stage I esophageal cancer is radiation therapy, often known as RT. In point of fact, positive clinical results have been documented for patients who were treated with RT for stage I esophageal cancer. On the other hand, late toxicity emerges as an issue in situations of long-term survival after RT. In addition, late damage to the heart and lungs following RT may result in death (Asakura et al., 2010). Because of this, a variety of radiation technologies have been created in order to lower the amount of radiation that is received by normal organs. One example of such innovative treatment technique is called volumetric modulated arc therapy, or VMAT for short. In the treatment of esophageal cancer, favourable dose distributions have been observed for intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and particle radiation therapy. Both IMRT and VMAT have beneficial dose concentrations in target volumes; nevertheless, low- and middle-dose areas are irradiated in the normal organs that are located in the surrounding area (Kato et al., 2019).

Pneumonitis may be measured using three different indices: $V_5$and V_{20}, in addition to the mean lung dosage. Both the V_5 and V_{30} variables are important survival predictors for the heart. As a result, low and moderate doses in these normal organs were related with late toxicities when radiotherapy was used to treat esophageal cancer. In order to lower the low and medium doses in the lung and heart, the hybrid intensity-modulated radiation therapy (hIMRT) was used. This is a method of irradiation in which both intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3DCRT) are carried out concurrently throughout the course of the same radiation treatment session (Ishikura et al., 2003).

In the beginning, hIMRT was used to treat breast cancer, but later on, it was purportedly used to treating malignancies of the esophagus and the lung as well (Bradley et al., 2015). When compared with IMRT, the treatment time provided by VMAT might be shorter; hybrid-VMAT (hVMAT), in which IMRT is substituted with VMAT, has been created. Combining 3DCRT with IMRT or VMAT plans for therapeutic

radiation in varying amounts was done in hIMRT and hVMAT therapeutic radiotherapy plans. Nevertheless, it is not yet known what the ideal ratio of 3DCRT to IMRT or VMAT should be. As a result, the purpose of this research was to conduct a quantitative comparison of the radiation dose distributions that were caused by varying the ratio of 3DCRT to VMAT in hVMAT treatment regimens for stage I esophageal cancer (Shapero et al., 2015).

Additionally, it has been established that PBT may lower the dosage reaching the spinal cord. Similar results were seen in the current investigation; Spinal cord dose was reduced by 50% with CIRT comparing to 3DCRT and by 60% related to VMAT. Conditions affecting the spinal cord significantly diminish one's quality of life. CIRT has the potential to make treatment less dangerous. In terms of comparing radiation doses in the skin, there is currently a lack of data. While 3DCRT and VMAT showed higher skin dose distributions, CIRT in this study showed substantially lower skin doses (Tonison et al., 2019). It was shown that the region exposed to 40 Gy (RBE) with CIRT was a significant predictor of acute dermatitis. Late skin toxicity was related to the 60 Gy (RBE) radiation dose zone, according to another research. In the current investigation, the maximal dosage of CIRT was much lower than those reported in previous studies. It has been indicated that the likelihood of serious adverse cutaneous events is low (Gong et al., 2013).

It has been found that the radiation dosage in OARs varies depending on the location of the tumour. Shirai et al. discovered high radiation doses in cardiac and distal esophageal tumours. The average dose to the heart also varies based on the position of the tumour, as shown by a dosimetric comparison study utilizing PBT (Shirai et al., 2011). Background radiation to the heart was found to be particularly low in the middle and upper thoracic regions in the present study. Concerning the lungs, the radiation dosage at LT esophagus was much lower than at other locations (Ordu et al., 2015).

Due to the presence of the heart in the beam path, it was believed that the radiation dosage to the lungs was rather minimal. In comparison, the spinal cord & skin were subjected to much higher radiation in UT esophagus. Although all regions were considered to be close to the target volume in UT esophagus, the spinal cord & skin were favoured (Silva et al., 2017).

There are a number of problems with this study. Limitations included a small number of subjects, uncertainty about the optimal irradiation field for CIRT, and no consideration of respiratory motion. The effectiveness of treatment depends on a four-dimensional CT analysis of breathing patterns. Our hospital also has a CT scanner available in the CIRT treatment room. The robustness of dose distribution utilizing in-room CT should be assessed. In this research, CIRT revealed superior dosage distribution over XRT for the treatment of esophageal cancer. Reducing the radiation exposure to OARs is anticipated to aid in minimizing their toxicity (Kanai et al., 2006).

A dosimetric comparison of three-dimensional conformal radiation therapy (3DCRT) and volumetric modulated arc therapy (VMAT) may be carried out in a number of different ways in patients who have esophageal cancer. The following are examples of some of these methods (Poa et al., 2020):

- *Dose-volume histograms (DVHs)*: This method compares the distribution of radiation doses received by the tumor and surrounding healthy tissue for each treatment modality.
- *Target coverage*: This method compares the %age of the tumor that receives a certain radiation dose for each treatment modality.
- *Normal tissue sparing*: This method compares the radiation doses received by surrounding healthy tissue for each treatment modality.
- *Quality of life:* This method compares the quality of life of patients treated with 3DCRT and VMAT by using questionnaires to gather patient-reported outcomes.
- *Toxicity*: This method compares the side effects of each treatment modality, such as skin reactions and long-term complications, by using the Common Toxicity Criteria (CTC) and the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)
- *Cost-Effectiveness*: This method compares the cost-effectiveness of 3DCRT and VMAT by comparing the costs of the treatment and equipment, as well as the cost of management of side effects.

It is essential to point out that a dosimetric comparison ought to be carried out within the framework of a clinical trial, which ought to be fashioned in such a way as to take into account patient-specific factors like the location and size of the tumour, in addition to the overall treatment strategy (Liu et al., 2019).

METHODOLOGY

Characteristics of the patient and the therapy: 25 patients who were diagnosed with esophageal cancer underwent aggressive treatment. Ten of them had thoracic esophageal cancer when they were diagnosed and participated in this research. Cancer of the thoracic esophagus was classified as affecting either the upper or middle portion of the thoracic esophagus, which was bordered anterior part by the sternal groove & posterior aspect by the lower pulmonary vein. The patients were found to be suffering from esophageal cancer that was histologically classified as squamous cell carcinoma. There were no patients who had a background of thoracic RT or surgery, and all of the initial masses and related lymph nodes were found in the thoracic region of the esophagus.

Target demarcation: For the purposes of RT planning, patients were immobilized in the seated position & scanned using a helical scanner from Somatom called the Sensation Open. The whole lung and heart were inspected for further plan assessment after computed tomography (CT) pictures were collected with a slice thickness of 3 millimeters while the patient was free to breathe normally.

Planning methods: For each of the ten patients, one of the following three treatment strategies was implemented: 3D-CRT, s-IMRT, or mARC. For the mARC, 3D-CRT and s-IMRT the Eclipse v15.2 is used for planning. The dose calculation was accomplished using 10 MV Siemens ARTISTE linear projectors. All treatment protocols called for a PTV dosage of 60 Gy administered in 30 portions. The top priority for inverse planning was 95% PTV coverage in order to obtain 95% of the recommended dosage and a maximum dose less than 110% of the authorized dose. The objectives for the OAR dosage volume in inverse planning were as follows: maximum spinal cord dose <45 Gy; lung V_{20}<30%; mean lung dose <20 Gy; and mean heart dose <30 Gy. The purpose of this research was to examine the disparity between lung and heart exposure within the previously outlined dose limitations. Lung V_5, V_{10}, and V_{30}, as well as heart V_{30}, V_{40}, and V_{50}, were measured to assess this.

Evaluation and comparison of strategies: Data from a dose-volume histogram (DVH) were retrieved and parameters were generated in order to do an assessment of the three different RT protocols. We determined the homogeneity index (HI), the conformity index (CI), and the conformity number for the purpose of conducting an analysis of target coverage (CN).

HI= $D_{PTV(2\%)}$-$D_{PTV(98\%)}$/ $D_{PTV(50\%)}$

This index is the difference between the dosage that was administered to 2% of the target volume ($D_{2\%}$) and the dose that was administered to 98% of the target volume ($D_{98\%}$), and it is expressed as a percentage and is then divided by the dose that was administered to 50% of the target volume ($D_{50\%}$). Ideal would be a value of zero, and the closer the HI is to zero, the greater the homogeneity of the mixture will be. The CI is denoted by the following:

CI= TV_{RI}/TV

for the purpose of determining the structure of the target. The CN is denoted by the following:

CN= $TV_{RI}/TV \times TV_{RI}/V_{RI}$

The treatment volume, the treatment volume at reference isodose (RI) of the recommended dose, and the total volume at RI of the prescribed dosage, respectively, are denoted by the abbreviations TV, TV_{RI}, and V_{RI}, respectively. The RI was established as being equivalent to 95% of the PTV prescription dosage. The greatest possible value for CN is 1, which corresponds to complete and total coverage of PTV.

Statistical Analysis:

The Kruskal-Wallis test was used in order to do an evaluation of the three different planning options. A statistically significant result was regarded to have a p-value of less than 0.05. The SPSS programme, version 22.0J, was used for each as well as every statistical analysis that was carried out.

RESULTS

DVH parameters for the entire lung and heart were retrieved for the

comparison of OAR. The mean lung dosage for 3D-CRT, s-IMRT, and mARC were 1,176.80 cGy, 1,129.66 cGy, and 1,112.53 cGy, respectively, with no significant difference. With a statistically significant difference, lung V5 was lowest with s-IMRT, followed by 3D-CRT and mARC (70%). Lung V10 was about 33.33 percent for s-IMRT, 40.86 percent for mARC, and 46.84 percent for 3D-CRT. mARC had the lowest lung V20, followed by s-IMRT and 3D-CRT. mARC, s-IMRT (9.00%), and 3D-CRT (11.5%) ranked behind Lung V30 (6.75%). In lung V10, V20, and V30 analyses, s-IMRT and mARC were superior than 3D-CRT, although the difference was not statistically significant (V10, p = 0.082; V20, p = 0.457; V30, p = 0.097).

The mean dosage supplied to the heart by s-IMRT, mARC, and 3D-CRT was 1,807.47 cGy, 1,658.80 cGy, and 2,123.06 cGy, respectively (p = 0.418). (p = 0.039) Heart V30 demonstrated 42.42% in 3D-CRT, 19.85% in s-IMRT, and 23.56% in mARC. (p = 0.040) Heart V40 revealed a 30.24% 3D-CRT, 10.71% s-IMRT, and 12.48% mARC. Heart V50 demonstrated 16,46% in 3D-CRT, 5.3% in s-IMRT, and 6.2% in mARC (p = 0.032). Significantly superior than 3D-CRT were s-IMRT and mARC, as shown by the parameters of the DVH study of the heart. This is represented in Table 1.

Table 1: Organs at Risk Evaluation

Organ at Risk (OAR)	3D-CRT	s-IMRT	mARC	p-value [a]
Lung				
Mean dose (cGy)	1,176.81 ± 325.76	1,129.66 ± 277.86	1,112.53 ± 315.61	0.811
V_5 (%)	63.59 ± 8.81	47.88 ± 18.78	70.00 ± 18.84	0.023
V_{10} (%)	46.84 ± 9.90	33.33 ± 14.54	40.86 ± 16.80	0.072
V_{20} (%)	19.30 ± 6.70	17.14 ± 7.61	14.81 ± 6.50	0.447
V_{30} (%)	10.45 ± 5.28	9.02 ± 3.65	6.75 ± 3.20	0.087
Heart				
Mean dose (cGy)	2,123.06 ± 1,013.24	1,807.47 ± 932.84	1,658.70 ± 881.36	0.428
V_{30} (%)	41.42 ± 20.80	18.74 ± 14.00	21.45 ± 11.95	0.019
V_{40} (%)	30.21 ± 29.82	11.71 ± 8.72	12.37 ± 8.81	0.050
V_{50} (%)	16.75 ± 11.31	5.34 ± 5.01	6.21 ± 5.31	0.012

This research demonstrated that IMRT and VMAT were not superior to 3D-CRT in terms of lung preservation in thoracic esophageal cancer. In our research, lung V5 and V10 were lower in s-IMRT compared to the other two designs. s-IMRT might spare adequate lung tissue while retaining sufficient target coverage. On the contrary, lung V5 was greater in mARC than in 3D-CRT. This demonstrated that mARC was unable to reduce the low dosage volume, a feature of arc treatment. s-IMRT and mARC showed lower mean dose, V30, V40, and V50 values in the heart than 3D-CRT.

Esophageal carcinoma in the cervical region is far from the heart and has a relatively modest lung capacity. In addition, the supraclavicular field is included, making IMRT planning preferable to 3D-CRT in terms of target conformity. Concerns have been raised concerning a significant volume of low-dose radiation exposure to the lung when using IMRT techniques such as step-and-shoot or arc to treat esophageal cancer in the thoracic region. Lower esophageal cancer is located nearer to the heart and the lower lobe of the lung, and it may impact the kidneys and liver.

CONCLUSION

VMAT offers outstanding compliance to the preset target volume (PTV) and organ sparing (OAR). This research investigates the Dosimetric characteristics and toxicity of esophageal cancer (EC) patients treated with VMAT and 3D conformal radiation (3DCRT). Ten patients from a group of twenty-five individuals with esophageal carcinoma of the chest were treated with 3D-CRT, s-IMRT, and mARC planning. Each plan's dose-volume histogram was derived, and the mean dose and therapeutically important parameters were analyzed. According to a review of target coverage, mARC's conformity index (CI) and conformance number (CN) were superior than those of the other two plans. Comparing OAR, s-IMRT generated the lowest V5 lung values, followed by 3D-CRT and mARC. s-IMRT and mARC demonstrated lower V30, V40, and V50 cardiac values than 3D-CRT. In thoracic esophageal cancer, excellent lung and heart preservation may be predicted using s-IMRT. The mARC exhibited lower lung V10, V20, and V30 values than 3D-CRT, however its advantage in lung V5 could not be shown. Low-dose exposure to the lung and heart was projected to be reduced with s-IMRT, hence reducing the risk of radiation pneumonitis and heart-related toxicities.

REFERENCES

[1] Asakura, H., Hashimoto, T., Zenda, S., Harada, H., Hirakawa, K., Mizumoto, M., ... & Nishimura, T. (2010). Analysis of dose–volume histogram parameters for radiation pneumonitis after definitive concurrent chemoradiotherapy for esophageal cancer. *Radiotherapy and Oncology*, *95*(2), 240-244.

[2] Bradley, J. D., Paulus, R., Komaki, R., Masters, G., Blumenschein, G., Schild, S., ... & Choy, H. (2015). Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *The lancet oncology*, *16*(2), 187-199.

[3] Choi, K. H., Kim, J., Lee, S. W., Kang, Y. N., & Jang, H. (2018). Dosimetric comparison between modulated arc therapy and static intensity modulated radiotherapy in thoracic esophageal cancer: a single institutional experience. *Radiation Oncology Journal*, *36*(1), 63.

[4] Gong, G., Wang, R., Guo, Y., Zhai, D., Liu, T., Lu, J., ... & Yin, Y. (2013). Reduced lung dose during radiotherapy for thoracic esophageal carcinoma: VMAT combined with active breathing control for moderate DIBH. *Radiation Oncology*, *8*(1), 1-7.

[5] Ishikura, S., Nihei, K., Ohtsu, A., Boku, N., Hironaka, S., Mera, K., ... & Yoshida, S. (2003). Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. *Journal of clinical oncology*, *21*(14), 2697-2702.

[6] Kanai, T., Matsufuji, N., Miyamoto, T., Mizoe, J., Kamada, T., Tsuji, H., ... & Tsujii, H. (2006). Examination of GyE system for HIMAC carbon therapy. *International Journal of Radiation Oncology* Biology* Physics*, *64*(2), 650-656.

[7] Kato, H., Sato, A., Fukuda, H., Kagami, Y., Udagawa, H., Togo, A., ... & Ishikura, S. (2009). A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). *Japanese journal of clinical oncology*, *39*(10), 638-643.

[8] Liu, C., Bhangoo, R. S., Sio, T. T., Yu, N. Y., Shan, J., Chiang, J. S., ... & Liu, W. (2019). Dosimetric comparison of distal esophageal carcinoma plans for patients treated with small-spot intensity-modulated proton versus volumetric-modulated arc therapies. *Journal of applied clinical medical physics*, *20*(7), 15-27.

[9] Münch, S., Aichmeier, S., Hapfelmeier, A., Duma, M. N., Oechsner, M., Feith, M., ... & Habermehl, D. (2016). Comparison of dosimetric parameters and toxicity in esophageal cancer patients undergoing 3D conformal radiotherapy or VMAT. *Strahlentherapie und Onkologie*, *192*(10), 722-729.

[10] Ordu, A. D., Nieder, C., Geinitz, H., Kup, P. G., Deymann, L. F., Scherer, V., ... & Fakhrian, K. (2015). Radio (chemo) therapy for locally advanced squamous cell carcinoma of the esophagus. *Strahlentherapie und Onkologie*, *191*(2), 153-160.

[11] Pao, T. H., Chang, W. L., Chiang, N. J., Lin, C. Y., Lai, W. W., Tseng, Y. L., & Lin, F. C. (2020). Pericardial effusion after definitive concurrent chemotherapy and intensity modulated radiotherapy for esophageal cancer. *Radiation Oncology*, *15*(1), 1-10.

[12] Shapiro, J., Van Lanschot, J. J. B., Hulshof, M. C., van Hagen, P., van Berge Henegouwen, M. I., Wijnhoven, B. P., ... & CROSS Study Group. (2015). Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *The lancet oncology*, *16*(9), 1090-1098.

[13] Shirai, K., Tamaki, Y., Kitamoto, Y., Murata, K., Satoh, Y., Higuchi, K., ... & Nakano, T. (2011). Dose–volume histogram parameters and clinical factors associated with pleural effusion after chemoradiotherapy in esophageal cancer patients. *International Journal of Radiation Oncology* Biology* Physics*, *80*(4), 1002-1007.

[14] Silva, S. R., Surucu, M., Steber, J., Harkenrider, M. M., & Choi, M. (2017). Clinical application of a hybrid rapidarc radiotherapy technique for locally advanced lung cancer. *Technology in Cancer Research & Treatment*, *16*(2), 224-230.

[15] Takakusagi, Y., Kusunoki, T., Kano, K., Anno, W., Tsuchida, K., Mizoguchi, N., ... & Yoshida, D. (2021). Dosimetric comparison of radiation therapy using hybrid-VMAT technique for stage I esophageal cancer. *Anticancer Research*, *41*(4), 1951-1958.

[16] Takakusagi, Y., Yoshida, D., Kusano, Y., Kano, K., Anno, W., Tsuchida, K., ... & Kamada, T. (2021). Dosimetric comparison between carbon-ion radiotherapy and photon radiotherapy for stage I esophageal cancer. *in vivo*, *35*(1), 447-452.

[17] Tonison, J. J., Fischer, S. G., Viehrig, M., Welz, S., Boeke, S., Zwirner, K., ... & Gani, C. (2019). Radiation pneumonitis after intensity-modulated radiotherapy for esophageal cancer: institutional data and a systematic review. *Scientific Reports*, *9*(1), 1-8.

[18] Zhang, Y. (2013). Epidemiology of esophageal cancer. *World journal of gastroenterology: WJG*, *19*(34), 5598.