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Comparative Analysis of External and Internal Radiotherapy-Dependent Plans in Patients with Gynecological Cancer

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Abstract. *Background/Aim: Radiotherapy plays a key role in the treatment of gynecological cancer. Modern radiotherapy techniques with external beams (e-RT) are applied in a broad spectrum of gynecological cancer cases. However, high radiation doses, affecting normal tissue adjacent to cancer, represent the main disadvantage of e-RT regimens. For this reason, brachytherapy (BT), an internal beam-based technique (i-RT), is suggested following e-RT. Our purpose was to compare e-RT plans using volumetric-modulated arc therapy (VMAT) with those using 3D conformal techniques (3D-CRT) and compare BT plans guided by 3D or 2D imaging based on the potential corresponding toxicity levels. Materials and Methods: In this preliminary, non-randomized comparative retrospective study, 15 females suffering gynecological cancer were enrolled. Modern e-RT and i-RT (BT) techniques were applied. Results: Concerning e-RT, D95/D99/rectum 2cc/bladder 2cc and small intestine 2cc were measured and compared; in i-RT, rectum 2cc/bladder 2cc were measured and compared. The median dose to the planning target volume in VMAT was 97.4 Gy compared with 92.9 Gy in 3D-CRT. The rectum received almost 5 Gy less in VMAT compared to 3D-CRT (median of 43.5 Gy vs. 48.6 Gy; p=0.001). In the bladder, dose differences were minimal, while the small intestine received 47.6 Gy in VMAT (p=0.001). Regarding 3D-BT, the rectum received 63.1 Gy compared with 49.9 Gy (p=0.009) in 2D-BT. Concerning the bladder, mean 2D-BT and 3D-BT doses were 71.9 and 65 Gy, respectively, differing non-significantly. Conclusion: VMAT was found to be superior to 3D-CRT, especially in dose distribution, volume coverage and protection of critical organs. Similarly, 3D-BT should be preferred over 2D-BT due to critical advantages.*

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Gynecological cancer, including the reproductive system and breast, represents a leading cause of mortality in females worldwide compared only with lung cancer (1). Persistent infection with high-risk human papillomavirus is responsible for the majority of cervico-vaginal carcinomas (2). Concerning gynecological cancer frequency, ovarian, endometrial, cervical, vaginal, and vulvar carcinomas are the prominent histological types. Rare gynecological cancer types are derived from the fallopian tubes and placenta, directly related to pregnancy (3). Treatment for gynecological cancer depends on several factors, including the tumor type, stage and location, and general health of the patient. In many cases, a single therapeutic approach is sufficient to treat it, while in others, a combination of surgery, radiotherapy (RT) and chemotherapy offers the best therapeutic effect (4).

In particular, RT combined with chemotherapy plays a decisive role in the treatment of gynecological cancer, especially in inoperable stages. There are two main RT categories, external (e-RT) and internal (i-RT). The i-RT method is also known as brachytherapy (BT) (5). More specifically, during e-RT, radiation is delivered from the outside environment into the organs. Modern e-RT techniques are particularly important for the treatment of gynecological cancer. RT techniques such as intensity-modulated radiation therapy and volumetric-modulated arc therapy (VMAT) are designed and applied in such a way that the incident radiation is perfectly targeted to the tumor, without particularly burdening the adjacent healthy tissues (6). According to their design, intensity-modulated radiation therapy and VMAT create an uneven distribution of the dose in the target volume (compared to older techniques, such as 3D conformal RT (3D-CRT), as some areas are irradiated with higher intensity radiation than others. Interestingly, image-guided RT plays a key role in the precision with which radiation is delivered to the target tumor (7).

In contrast to e-RT, BT regimens provide radiation doses from the inside through the intra-abdominal and intra-tissue placement of radioactive sources (radioisotopes) in the diseased organ (8). The aim of the placement of these sources is to administer a high dose of radiation locally to the tumor, with the help of personalized applicators which are surgically placed in or near the target tumor. It is essentially the absolute 'compliant' RT method due to the fact that the sources used in BT deliver their maximum dose to the core of malignant tumors, thereby also providing protection to the adjacent normal tissues and organs. BT is an essential component of gynecological cancer radiotherapy, as Tandertup *et al*. point out (9). High dose-rate BT uses high activity sources (^{192}Ir), allowing the dose to be delivered in a short period of time (of the order of a few minutes to an hour) in an optimal way. It can be applied up to a total of six times, with one or two applications per week (10). In some cases, e-RT is unable to deliver a high radiation density (high dose in a small volume) in specific treatment positions. The introduction of computerized tomography (CT)- and magnetic resonance imaging (MRI)-compatible applicators has improved the accuracy of computerized-based treatment RT plans (11).

Image-guided BT is based on 3D or even 4D imaging (CT/MRI) and is used in specialized centers; it is one of the most critical developments of recent years, allowing easier identification of the target tumor and the organs at risk (OARs) (12). This innovative change radically upgraded treatment that in several centers was previously based on 2D planning (orthogonal projection), which had adverse effects on organs such as the rectum and bladder (13). Development and implementation of computer-based treatment planning has limited side-effects while at the same time increasing local disease control and patient survival [International Commission on Radiation Units and Measurements (ICRU) 38 (14) and ICRU 89 (15)].

In the current retrospective clinical study, our aim was to compare the value of VMAT and 3D conformal techniques and also to evaluate the BT plans guided by 3D or 2D imaging based on the corresponding RT-dependent toxicity levels in a group of females suffering from gynecological cancer.

Materials and Methods

Study group. The current research study took place at the Radiotherapeutic Oncology Center of the private HYGEIA hospital located in Maroussi, Attica, Greece. The research was carried out after approval by the HYGEIA Hospital Scientific Council. The Ethics Committee of Medical School, University of Patras consented also to the application of this research protocol according to the World Medical Association Declaration of Helsinki (Research Protocol ID 2880-14/10/2020). The enrolled patients were informed about the subject of the research, and the maintenance of privacy and protection of their personal data according to the EU General Data Protection Regulation 2016/679 guidelines. The study was carried out covered a period of 2.5 years (June 2020-February 2023). Fifteen female patients with stage II or more gynecological cancer according to the Federation International of Gynecology and Obstetrics Guidelines (either operated or non-operated cases) were enrolled in this RT-based protocol. In order to be included, patients had to have undergone e-RT with VMAT technique, followed by three-dimensional BT with an ^{192}Ir source (key criterion).

The current research protocol was based on a team effort including a Radiation Therapist-Oncologist who performed the BT and supervised the patients throughout their treatment regimen, a Medical Physicist who prepared all the treatment plans for each patient, and a Radiation Therapist who performed the RT and was also responsible for 3D imaging after the applicators were inserted during the BT procedure.

RT methods. The study group receiving e-RT with VMAT technique and 3D imaging-guided BT were investigated. After the planning CT scan, the Radiation Oncologist planned the target tumor (PTV) and OARs in the treatment planning system. In these patients, after 45 Gy e-RT irradiation to the whole pelvis, a midline block 4 cm in width and 8-10 cm in height was used. Then the plans created for this reason by the Medical Physicist for the specific treatments were compared with other plans they had created in the planning system, for the needs of the research, related to the presumed e-RT with 3D-CRT and BT that would have been based on 2D imaging. In this way, comparison and further analysis of the dosimetric differences resulting from the above were performed. In fact, each patient received 45 Gy to 55.8 Gy in total. Essentially, one or two plans were designed for the VMAT technique [depending on whether the patient would follow one or two treatment phases (first phase with/without boost)], one or two for 3D-CRT (one or two phases, depending on whether there was a boost) and after the end of external treatments from a plan for 3D-BT and 2D-BT, respectively.

Regarding the e-RT plans (3D-CRT and VMAT) a comparison was made of the percentage of the dose reaching 95% of the target volume (D95), D99 and the minimum dose received by 2 cm^3 (D2cc) by OARs (rectum, bladder, and small intestine). Regarding

Table I. *Radiotherapy (RT) methods and mean doses for the corresponding critical organs.*

	RT method (n=15)					
	e-RT, Gy			i-RT, Gy		
Organ	VMAT	3D-CRT	*p*-Value	3D-BT	2D-BT	*p*-Value
Rectum	43.5 Gy	48.6 Gy	**0.001**	63.1 Gy	49.9 Gy	0.009
Bladder	50.8 Gy	50.9 Gy	NS	71.9 Gy	65 Gy	NS
Small intestine	47.7 Gy	50.7 Gy	**0.001**			

2D/3D: Two/three dimensional; BT: brachytherapy; CRT: conformal radiotherapy; e-RT: external radiotherapy, i-RT: internal radiotherapy; VMAT: volumetric-modulated arc therapy. Significant *p*-values are shown in bold.

the BT procedure, after the insertion of the special applicators by the Radiotherapist-Oncologist, the vagina was filled with gauze to firmly secure the applicator and increase the distance between the radiation source and the rectum. Then orthogonal X-ray images were taken by the researcher to confirm the applicator was inserted correctly (2D imaging). The patient was transferred to the CT scanner to obtain 3D images for the treatment. This allowed the specific images to be taken. This also enabled the calculation of the dose that the target tumor finally received and also the dose received by the OARs depending on the BT plan (based on 2D or 3D imaging). The definition of the high risk-clinical target volume (HR-CTV) during the creation of the plan was made through point A (usually within the para-cervical triangle – which meant 2 cm lateral to the center of the uterine canal and 2 cm above the vaginal mucosa, at the level of the uterus), and point A varied according to the disease to be treated.

Following completion of the CT scan obtaining 3D images of the applicator and the surrounding areas, and the contour of the target tumors and OARs (rectum, bladder), the respective BT plan was extracted using the Oncentra Brachy (Elekta Solutions, Stockholm, Sweden) treatment planning system. This represents the main treatment planning tool for high-dose rate modality.

Immediately after, the procedure was optimized by manually adding or removing stop positions and adjusting dwell times at each given source position. The system graphics optimizer was used to optimize the dose distribution by adjusting the isodose lines. Dose–volume histogram parameters were calculated for the target tumor (HR-CTV), rectum (D2cc) and bladder (D2cc).

Statistical analysis. Statistical processing of data was done using SPSS 26 software (IBM, Armonk, NY, USA). Due to the relatively small sample size (n=15), normality testing was not meaningful and non-parametric procedures were applied. The minimum value of the statistical significance level was set at 5%. Because the significance (p-value) does not tell us anything about the importance of an effect, the effect size was used, which is an objective and standardized measure of the size of the observed effect. The larger the effect size, the more significant the effect. The effect size, *i.e.*, the practical significance of the result, was calculated based on Cohen's criteria (low if less than 0.5, medium if it between 0.5-0.8 and large if greater than 0.8). For descriptive statistical analysis, continuous variables are expressed as the mean with standard deviation, or median and interquartile range (IQR), while discrete values are given as the absolute number. To compare two observations from the same individuals, the Wilcoxon signed-rank test was applied. In order to have a more accurate assessment of the statistical significance, the Monte-Carlo simulation method was used. This is a method that allows relatively reliable conclusions when the data sample is small.

Results

The research sample consisted of 15 women with a mean age of 63.2±12.5 years and a median age of 61 (IQR=55-68) years. Regarding diagnosis, nine cases were diagnosed as squamous cell carcinoma, four as endometrial adenocarcinoma, and two as cervical adenocarcinoma. Two patients presented with regional infiltration of lymph nodes, three patients with pelvic, two with para-aortic, and one presented with infiltration of both pelvic and para-aortic lymph nodes; the remaining seven did not have lymph node infiltration. Results and statistical significance are presented in Table I.

In the e-RT based treatment regimen, patients received a mean total radiation dose of 49.5±3.8 Gy and median total dose of 50.4 (IQR=50-50.4) Gy. In the BT regimen, they received a mean total radiation dose of 23.1±6.2 Gy and median of 28 (IQR=14-28) Gy. These were patients who received more than 78 Gy total doses. For e-RT, the median D95 of the PTV of the VMAT and 3D-CRT treatment plans were estimated to be 97.4 (IQR=95.5-98) Gy and 92 .9 (IQR=91.7-95) Gy, respectively ($p<0.001$). The median D99 of the PTV were estimated to be 84 (IQR=78-91.2) Gy and 78 (IQR=76.5-89) Gy; respectively, with the Monte-Carlo confidence interval guaranteeing with 99% confidence that the true p-value was 0.027. The effect size was calculated to be 0.56, therefore the clinical significance of the result is medium to low.

Regarding the OARs, the median doses received by the rectum in the VMAT and the 3D-CRT techniques were estimated to be 43.5 (IQR=37.1-49.1) Gy and 48.6 (IQR=45.3-51.2) Gy, respectively, with the Monte-Carlo confidence interval guaranteeing with 99% confidence that the true *p*-value was less than 0.001. The effect size was calculated to be 0.88, consequently the clinical significance of the result is high.

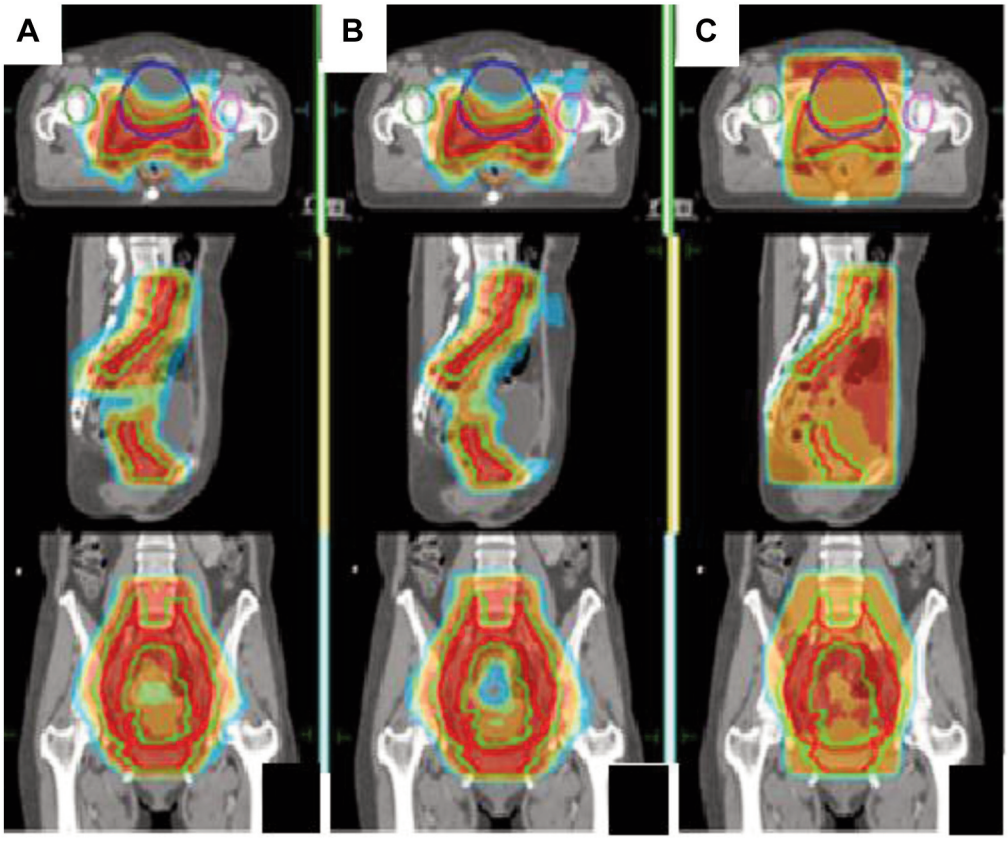

Figure 1. *Comparison of dose distribution in postoperative treatment plans of a patient with cervical cancer treated with (A) volumetric-modulated arc therapy (VMAT), (B) intensity-modulated radiation therapy (IMRT) and (C) 3D-conformal radiotherapy (CRT) techniques. VMAT and IMRT increased the protection of the bladder, rectum and small intestine compared with 3D-CRT. VMAT achieved a better dose conformity (encircled anatomic areas: Red=clinical target volume, green=planning target volume, blue=bladder, orange=rectum).*

The mean doses received by the bladder in VMAT and 3D-CRT were estimated to be 50.8±4.1 Gy and 50.9±4.6 Gy, respectively. The non-parametric Wilcoxon test indicated that there was no statistically significant difference between the VMAT and 3D-CRT techniques in the doses received by the bladder (Z=–0.284, p=0.776). The median doses received by the small bowel were calculated to be 47.7 (IQR=45.1-49.7) Gy and 50.7 (IQR=49.3-52.2) Gy, respectively. The non-parametric Wilcoxon test indicated that dose received by the small intestine was statistically significantly higher with the 3D-CRT technique (Z=–3.408, p<0.001). The effect size was calculated to be 0.88, therefore the clinical significance of the result is high.

Concerning BT, the mean and median D95 values to the PTV in 3D-BT were estimated to be 90.7±4.5 Gy and 89.5 (IQR=86.2-94.5) Gy, respectively, while the D99 values were 88.8±4.9 Gy and 87.8 (IQR=84.3-92.7) Gy, respectively. The median doses received by the rectum in 3D-BT and 2D-BT were estimated to be 63.1 (IQR=58.7-70.6) Gy and 49.9 (IQR=46-66.1) Gy, respectively. The non-parametric Wilcoxon test indicated that the dose received by the rectum was statistically significantly higher with 3D-BT (Z=–2.613, p=0.009). The effect size was calculated equal to 0.67 so the clinical significance of the result is moderate. The median doses received by the bladder with the 3D-BT and 2D-BT techniques were calculated to be 71.9 (IQR=60.4-78.2) Gy and 65 (IQR=51-75.7) Gy, respectively. The non-parametric Wilcoxon test indicated that there was no statistically significant difference in the doses received by the bladder between the two techniques. Representative images of the corresponding RT methods are presented in Figure 1.

Discussion

VMAT and 3D-CRT are the main techniques used in e-RT, but they differ in how radiation is delivered and how they shape the radiation dose distribution (16). As seen from the results, VMAT offers many advantages over 3D-CRT. More specifically, VMAT provides exact dose compliance. In fact, VMAT allows for an extremely uniform dose distribution. It can shape the

radiation dose to match the shape of the tumor more precisely. This means that the tumor receives a higher dose while minimizing exposure to radiation of surrounding healthy tissues, reducing the risk of side-effects (17, 18). Therefore, as can be extrapolated from our results, the target volume coverage provided by VMAT was better than that of 3D-CRT and should be considered as the technique to be used for e-RT. VMAT also demonstrated a reduced treatment time. It is quite a bit faster than 3D-CRT. VMAT emits radiation from multiple angles while continuously adjusting the intensity of the radiation beam. Through this feature, the radiation time is reduced, which increases the likelihood that the patient will stay still on the treatment table, and therefore the treatment will be carried out with the best possible therapeutic result (19). Additionally, VMAT allows enhanced dose scaling, which potentially improves local control and treatment outcomes. The ability in VMAT to optimize radiation beam angles and intensity also reduces the exposure of adjacent healthy structures to radiation, which can lead to fewer side-effects and complications (20, 21).

In conjunction with the virtues referred to above, VMAT is also characterized by flexibility and adaptability. VMAT can adapt to changes in tumor size, shape, and location during treatment, especially with the help of the image-guided RT technique, which uses medical imaging to help provide precise and accurate radiation treatment, even in areas that may move (22). According to our research results, the OARs (rectum, bladder, and small intestine) received less radiation in VMAT compared to that delivered in 3D-CRT. This particular finding, combined with superior dose compliance in VMAT, as can be seen in research carried out by Dröge *et al*. often results in reduced acute and long-term side-effects compared to 3D-CRT (23), making it a more tolerable treatment option. Patients who undergo RT with the VMAT technique complain less about side-effects, such as frequent or other dysuria symptoms, irregular bowel movements or diarrhea. These side-effects are referred to as post-abdominal cystitis and proctitis (24). Additionally, VMAT provides a better patient experience. Shorter treatment times, reduced side-effects and improved accuracy contribute to a better overall patient experience and can lead to increased satisfaction and compliance with treatment protocols (25).

As far as BT is concerned, especially that based on CT or even MRI, 3D (or 4D) is widely used today in specialized Radiation Oncology Centers to treat gynecological cancer. The goal through this treatment is to improve coverage of the target tumor and reduce toxicity to OARs. 2D-BT was mainly used in the past and especially in public hospitals which either did not have the equipment or the relevant applicators compatible with CT/MRI (26). For this reason, imaging after the insertion of the respective applicator was traditionally done by taking X-rays at 0˚ and 90˚, based on which the corresponding BT plan was designed. However, this technique has its limitations. There are not many studies in the literature highlighting the differences in dosimetry between 3D-BT and 2D-BT. A study presented similarity in the dose received by the rectum in both planning methods but, on the other hand, pointed out that patients experienced side-effects in the rectum, and mainly in BT based on 2D imaging (27). According to the European Society for Gynaecological Therapeutic Radiology and Oncological, there are specific dose tolerances of OARs. In another study, Ling *et al*. investigated the maximum doses that the bladder and rectum received using CT and found that the percentage of radiation received by the bladder modeled on the basis of the 3D design was almost twice as high as that for the reference ICRU points during the 2D design (28). However, some studies showed no statistically significant differences in the doses received by OARs between the two planning methods. In two of them, Jamema *et al*. reported no significant difference between mean values in dose–volume histograms and ICRU benchmarks, especially the ICRU 38 recommendations (14, 29). In our RT analysis, we also observed no statistically significant dose differences comparing the two BT methods. Concerning the doses received by the OARs, there are several factors that modify these. One factor critical in RT-based therapeutic regimens in a variety of malignancies (*e.g*. of the prostate) is the reconstruction of ICRU points in the design system, a process which can be directly affected by metal and applicator noise (metal artifacts) (30). Another factor is the different techniques used at different centers when applying a rectal catheter. More specifically, there are cases where the rectal catheter is placed inside the vagina. Regarding the differences observed in the dose received by the rectum, these are explained by the fact that in 2D-BT, the planning system does not measure the D2cc of the rectum, which is very close to the irradiated area, but counts one point (ICRU point), that is, it is a spot dose. The definition of this point may vary in some cases because the rectum may be less full or empty of gas and thus change its position during imaging. This particular ICRU point is further away from the center of radiation (around the center of the rectal marker placed), which explains the smaller values received by the rectum based on the 2D imaging design.

In contrast to the 2D-based technique, 3D design offers optimal dose delivery. 3D imaging helps ensure that the prescribed radiation dose is accurately delivered to the tumor, as is observed in head and neck carcinomas (31). This minimizes the risk of underdosing, which can lead to treatment failure, or overdosing, which can damage healthy tissues. In addition, with 3D imaging, treatment plans can be tailored to the specific size, shape, and location of the tumor, which is impossible in 2D-BT, where the radiation area is calculated based on point A. This personalization helps maximize the effectiveness of treatment and reduce damage to healthy tissues. The improved precision and customization that 3D imaging offers in BT can lead to better treatment outcomes, with higher tumor control rates and lower complication rates (32-34). Due to the inability of many

centers to perform BT based on 4D imaging for various reasons, performing BT based on 3D imaging is a useful tool and an equally efficient substitute (35). Certainly, it is a huge development considering that in the recent past, BT-dependent plans were based on orthogonal projection and spot dose (36).

In conclusion, while VMAT appears to have many advantages, particularly in dose distribution, tumor coverage and OAR protection, it is important to note that the choice between VMAT and 3D-CRT may depend on where the tumor is located, how large or small the tumor is, and the individual needs of the patient. In some cases, 3D-CRT may still be an appropriate treatment option, particularly for simpler treatment scenarios or in patients with large lesions in the region where the radiation field will be more extensive. This statement is supported by the results of this research, in which there was no significant statistical difference in the dose received by the bladder between e-RT treatment plans with VMAT and those with 3D-CRT. This may also be due to the larger radiation field, as the research sample concerned patients with International Federation of Obstetrics and Gynecology stage II or more gynecological cancer. Decisions about which e-RT method to use should be made in consultation with Radiation Oncologists and based on the individual circumstances of the patient.

Concerning the i-RT methods, BT based on 3D imaging should be preferred over that based on 2D. The CT-based design allows for more realistic, accurate tumor identification and enables optimization of the dose to the target tumor and OARs. Each institution must continually review its resources and assess the need to provide new equipment (*e.g.*, new CT- and MRI-compatible applicators) with a focus on more advanced patient treatment. Further research on guided BT, especially in Greece, is necessary, particularly since the international literature has shown that the best therapeutic results and the greatest chances for local control of gynecological cancer are achieved by the combination of e-RT with modern techniques and BT-guided by 3D imaging.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

PV, ET, KS: Design of the study and article writing; GA, DP, and DS: academic advisors; NG, GK, KK, SM and DK: collection and management of references and published data. All Authors read and approved the final article.

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