ORIGINAL ARTICLE

PET/CT Image Fusion for Lung Cancer Radiotherapy

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Abstract

Purpose: The main goal of radiotherapy is to deliver a lethal radiation dose to tumor tissue while minimizing the dose to healthy tissues. Treatment planning in radiotherapy requires precise determination of the treatment volume and specification of the radiation dose to both the tumor and healthy tissues. To define the treatment volume in radiotherapy, margins are considered around the tumor tissue, which may include a portion of normal tissue. Fusion of PET-CT images with CT images in the three-dimensional conformal radiotherapy for lung cancer may improve treatment by more accurately and precisely determining the Gross Tumor Volume (GTV). This study aimed to compare the treatment volumes and dosimetric parameters between conventional treatment planning (using CT images only) and treatment planning using PET-CT image fusion in 3D-conformal radiotherapy for lung cancer.

Materials and Methods: All lung cancer patients who were referred to our Radiotherapy center over two years were examined. PET-CT images and simulation CT scans of 15 patients with non-metastatic lung cancer were analyzed. All patients were treated using the 3D-conformal radiotherapy method. The treatment planning and image fusion were performed using the ISOGRAY treatment planning software. The volumetric as well as dosimetric parameters, such as mean dose, maximum dose in the target volume, and other dose-volume parameters in organs at risk such as lung tissue including V5, V13, and V20 were compared between the two groups (including the conventional treatment planning group (only using CT data) and the treatment planning using the PET-CT image fusion group).

Results: A total of 23 lung cancer patients were included during the study period; of these, eight patients were excluded due to having metastatic lung cancer. The variation in Gross Tumor Volume (GTV) among the different patients was significantly high. The fusion of PET images with CT scans increased the GTV in 11 patients (on average by 48±89.7%) and decreased it in 5 cases (46.4±98.0%). According to the results (considering all patients), no statistically significant difference was noted in the Contoured Tumor Volume (CTV) between the conventional method (based on CT images only) and the method based on the fused images with PET-CT images (P-value > 0.05). There was no statistically significant difference in maximum dose at healthy tissues/Organs At Risk (OARs), including the ipsilateral lung, contralateral lung, skin, and spinal cord, between treatment planning based on CT images and based on fusion with PET-CT data (P-value > 0.05). The mean dose in the lung (in involved side %43±.16.66) decreased (on average by %41±21.00) after fusion with PET-CT images (P-value > 0.05).

Conclusion: The use of PET-CT data in radiotherapy treatment planning for lung cancer patients undergoing adaptive 3D radiotherapy can have an improving and impactful role. The fusion of PET-CT images with CT data had a significant effect on the tumor volume definition, resulting in changes in the gross tumor volume in most patients. It is recommended to utilize data from both anatomical (CT) and functional (PET) imaging modalities for a better assessment and definition of tumor volume, as each modality has its advantages and limitations. However, by combining them, the tumor volume can be determined with greater precision and accuracy. Additionally, improving the precision in defining tumor volume can reduce the radiation dose received by healthy tissues/organs at risk.

Keywords: Three-Dimensional Conformal Radiotherapy; Lung Cancer; Computed Tomography Scan; Positron Emission Tomography; Image Fusion; Treatment Volume.

DOI:

1. Introduction

Cancer is a significant global concern, making accurate tumor diagnosis and staging essential in its management [1]. Lung cancer is the most common cancer among both men and women in the European Union, and it has been the second leading cause of cancer death in 2024 [2]. More than 40% of cancer patients receive External Beam Radiation Therapy (EBRT) during their treatment [1].

The main goal of three-Dimensional Conformal radiotherapy (3D-CRT) is to maximize the dose delivered to the tumor while minimizing damage to healthy tissues. Accurately determining the tumor volume is crucial before beginning any dose delivery or dose escalation strategy. While CT is commonly used for 3D-CRT planning, as you can see in Figure 1, the patient under treatment, it cannot accurately identify the boundaries between malignant tumors and normal tissues. Additionally, CT does not effectively determine lymph node involvement, as it provides only anatomical information [3]. Variability among observers in localizing the Gross Tumor Volume (GTV) can result in missing the tumor's precise location, which may cause the intended target margin to exceed the actual value or lead to unnecessary irradiation of normal tissues. Using PET images may effectively improve GTV localization; FDG-PET is a glucose analog that is metabolically trapped in cells, resulting in increased FDG uptake by malignant cells [4].

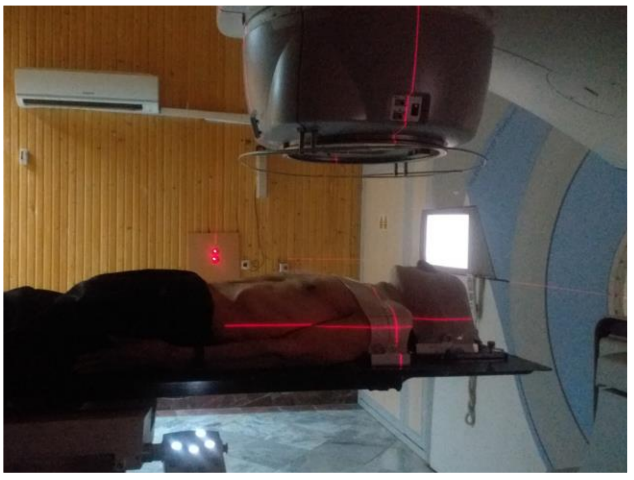

Figure 1. The patient's position during the treatment is similar to that of the CT simulator

Determining the Gross Tumor Volume (GTV) using PET-CT data may offer greater accuracy than conventional CT imaging [5]. This improved accuracy can help reduce the margin needed for target detection and minimize radiotoxicity to surrounding healthy tissues [6]. However, visual estimation of tumor volume through contouring is a subjective issue, which can lead to interobserver variability [7].

The use of FDG-PET in radiotherapy planning could minimize variability among observers in tumor definition [4]. Considering the critical need for precise target volume definition and reduction of radiation exposure to nearby organs at risk, this study investigates the effect of PET image fusion on CT data in the treatment planning of lung cancer radiotherapy. It also evaluates whether this fusion can determine GTV differently from CT alone and improve treatment planning. In Iran, PET image fusion is not routinely performed in treatment planning, or if it is performed, it has not been studied. In this study, we investigate the effectiveness of this fusion and determine whether it can be beneficial in the treatment process.

2. Materials and Methods

In this descriptive-analytical study, 16 patients with non-metastatic lung cancer who had undergone PET/CT scans and were then referred to the radiotherapy center were included in the study. PET/CT images prescribed by the oncologist were taken from the patients, and treatment planning was done using ISOGRAY software for all patients. The treatment volumes, including GTV, were determined, and dosimetric parameters after dose calculations in the treatment plan were obtained. Volumetric and dosimetric parameters were then compared between the two methods, including treatment planning without (just based on CT data) and with PET-CT images fusion. CT images were acquired using a Philips Brilliance 16-slice CT simulator, with patients positioned according to a predetermined treatment plan and supported by immobilization devices. The PET/CT machine (Siemens, with 16 slices and a 3-ring system) was used for PET/CT scans. All patients fasted for at least 8 hours before the scan. The PET scan was performed intravenously with a dose of 3 to 5 mCi of FDG per 10 kg of body weight. After that, the patient rested for 60 minutes to allow the uptake process to take place, then was placed on the scanning table and placed in a supine position with the arms above the head as you can see in Figure 2. First, a CT scan was performed, followed by a 3D PET scan. The patients remained still during the scan.

Figure 2. Patients' position for the PET/CT scan

2.1. Image Registration

Image registration is the process of merging corresponding anatomical points in two different image series, and preserves the distance between all points in an image. One image was considered a moving dataset and the other a static dataset. The CT simulator image is the static image, and the moving image includes any other image that is input into the treatment planning software, such as SPECT, MRI, and PET [8]. Image registration, also known as image fusion, is available in radiotherapy treatment planning software. In Figure 3 you can see the fused images. The static image or the CT simulator image already exists, while the moving image (the PET) needs to be added. Since merging anatomical and functional images is challenging, the CT data (from PET-CT images) were initially decoded, resulting in two anatomical images with common points. The treatment planning software had two adjustment modes, manual and automatic, but in the present study, manual adjustment was used for greater accuracy. The primary limitation of fusing images in this way is that soft tissue cannot be regarded as a fixed point, as the patient may experience weight fluctuations during treatment. Consequently, the points chosen in the two images must be comparable and dependable. Additionally, points should be selected from various areas to achieve accurate fusion, including the cervical vertebrae, spinal vertebrae, and ribs. After the CT images are fused, we need to add the PET image. The system will then select the same points for the PET as we had selected, and finally, the fusion is performed (Figure 3).

2.2. Target Volume Delineation

The target volumes, including GTV, CTV, and PTV, have been specified in the ICRU-62 report by the International Commission on Radiation Units and Measurements [9]. The GTV is the main tumor mass that the visual observer can see, but the CTV and PTV are the margins that we assign to it. The radiation oncologist created two contours for each patient: the first contour was GTV-CT, and the second contour was GTV-PET. CTV was defined with a 10 mm margin and PTV with a 15 mm margin from GTV. Organs at risk included the skin, spinal cord, intact lung, and involved lung, which were identified. Since only two of the 16 patients had a left lung tumor, the heart was not considered an organ at risk. The dose was administered so that the maximum dose uniformly reached the PTV while the minimum dose reached the organ at risk. The administered dose, 45 Gy in 25

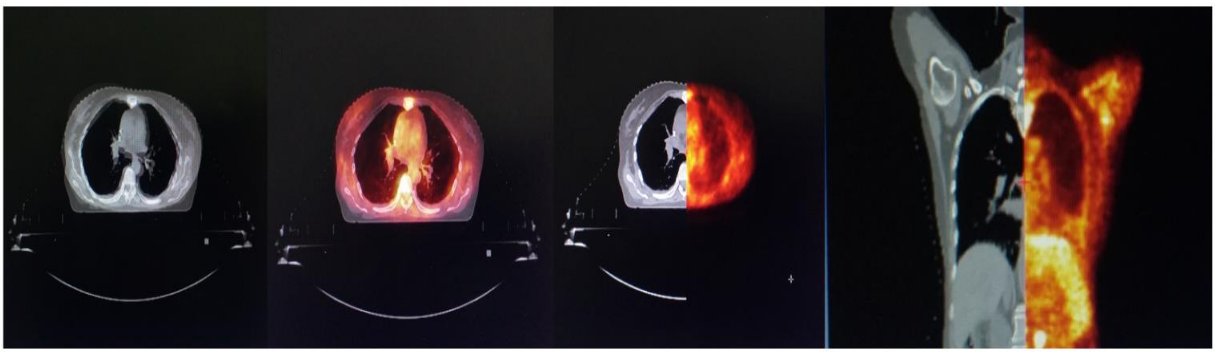

Figure 3. Fusion of PET-CT data with CT simulator image; from left to right: (a) fusion CT simulator image with CT (from PET-CT) images, (b) fusion PET image on CT simulator data, (c) and (d) PET and CT concordance image

fractions, was such that the PTV received more than 95% of the dose to ensure that the required dose reached the tumor, while the dose should not exceed 107% to avoid the formation of hot spots. We used 10 MeV energy and three fields: Anterior-Posterior (AP), Posterior-Anterior (PA), and lateral in both treatment plans, one before and one after image fusion. Cumulative dose-volume histograms were generated to compare the doses received by organs at risk and Gross Tumor Volume (GTV) in the two treatment plans (Figure 2).

2.3. Statistical Analysis

GTV(PET), CTV(PET), and PTV(PET) were compared with GTV(CT), CTV(CT), and PTV(CT), respectively, by the Mann-Whitney rank test. A p-value<0.05 was considered statistically significant. Data were calculated as mean ± standard deviation and 95% confidence interval. The Kolmogorov-Smirnov test was used to test the normality of the data. Data related to organs at risk were used in some cases due to normal distribution using a paired t-test and in others due to non-normal distribution using a Mann-Whitney. The tests were performed using SPSS software version 26, manufactured by IBM Corp, USA [10].

3. Results

In this study, 16 patients participated, including patients with non-metastatic lung cancer. The age and gender of the patients were not considered because the aim was to combine images and their effect on volumetric parameters and healthy tissues. The volumetric parameters under study were GTV, CTV, and PTV. The oncologist and the center's physicist performed the tumor mass volume contour, incorporating contours from both CT and PET images. Treatment design was based on both contours, and finally, a Dose-Volume Histogram (DVH) was obtained for both plans. DVH curves were used to examine the doses delivered to the target volume and healthy tissues. The volumetric parameters before fusion were named GTV-CT, CTV-CT, and PTV-CT, and after fusion were named GTV-PET, CTV-PET, and PTV-PET. This was just a naming convention to compare the two treatment plans (one before fusion and the other after fusion of PET images). In this study, organs at risk (including the lung, healthy lung, skin, and spinal cord) were considered. After contouring on two series of images, the tumor GTV size on PET-fused images decreased by an average of 89.7 ± 48 (cm^3 (in 11 patients (about 69% of patients))). It increased by an average of 98.0 ± 46.4(cm^3) in 5 patients (about 31% of patients). In no patient did the contouring results based on the two image series show the same tumor volume size in the two contoured image series. However, the results of the statistical analysis did not show a significant difference between the two groups. There was a large difference between the minimum and maximum values of tumor volume in the studied patients, which could be due to the nature of the tumor (in terms of speed and growth characteristics), which varies from person to person. Therefore, the volumetric data had a non-normal distribution, and for the statistical analysis of the volumetric parameters, the Mann-Whitney U test with a 95% confidence interval was used. The maximum GTV-CT volume was 357.1 cm^3, and the minimum was 3.5 cm^3. Statistical results in comparing the studied volumes, including p-values related to comparing the volumetric parameters obtained in contouring based on CT images and with PET fusion, were obtained in GTV 0.20, CTV 0.52, and PTV 0.73. In comparing the volume contoured with the CT image in conventional treatment and contoured with the PET fused image, the P value was greater than 0.05. Therefore, the results of the comparative volume tests showed that the difference between the means in the two groups was not significant. Due to the short time in the study, the number of patients was not optimal to obtain more accurate results because the patients who had non-metastatic lung cancer and the oncologist had prescribed PET for treatment were included in the study. These conditions reduced the number of patients studied.

The images shown are an example of contouring for a study patient for GTV contouring based on CT images and also based on fusion with PET images; by comparing the two images, the difference in the contoured volume of GTV in these two images can be seen. According to Figure 4, for a sample, the volume of GTV-PET is larger than that of GTV-CT. The PTV was considered to include the GTV plus a margin (20 mm); this data set was used to create a comparative treatment plan for each patient, but was not used for treatment. The average maximum dose to the skin,

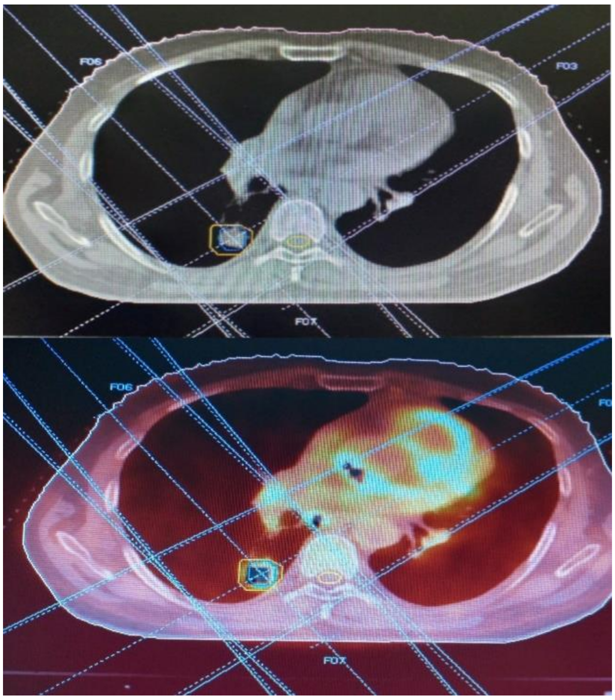

Figure 4. Comparison of GTV contoured using CT data only (a) and using the fused PET data (b) for one of the patients in the present study. (Orange border contoured with PET and blue border contoured with CT)

spinal cord, healthy lung, and involved lung was obtained before and after PET fusion. There was no difference in the mean maximum dose received by the skin, spinal cord, contralateral lung, and ipsilateral lung before and after PET fusion, and the p-values were obtained for the affected lung (0.85), intact lung (0.17), skin (0.20), and spinal cord (0.84). As one can see, there is no difference in the comparison of the maximum dose to organs at risk with CT and PET. No significant difference was found when comparing the mean dose of the lung with/without PET. Additionally, no difference in the dosimetric parameters of the lung involved was found in V5, V13, and V20.

4. Discussion

PET fusion on CT simulator image in radiotherapy planning, in most cases, increased the GTV volume in PET, which was not statistically significant, but was of high importance in terms of volume determination. It was expected that the OAR dose would increase due to the increase in GTV volume in PET, but the dose change was not statistically significant. The mean dose to the lung in the PET contour decreased, indicating that increasing the accuracy of tumor volume determination leads to a decrease in the mean dose to the lung. In cases where the tumor volume was found to be larger in CT than in PET, it may have been due to atelectasis or tumor necrosis, although these cases were not investigated. In the case of tumor necrosis, PET is considered to have a smaller volume due to the lack of uptake points, while CT also considers necrosis as a volume, which may have contributed to the lower volume in PET. However, in most cases, the GTV volume was observed to be larger in PET. GTV contouring in conventional radiotherapy has been based on anatomical imaging methods such as CT and, more recently, MRI. Since most solid tumors are soft tissue masses, their differentiation from surrounding soft tissue using CT is limited because of the low inherent contrast between soft tissues on CT scans. As a result, there may be significant inter-observer disagreement in GTV contouring for many organs, such as the prostate, bladder, and lung.

Contouring the GTV for lung tumors is particularly difficult with structural or anatomical imaging methods; even for peripheral lesions, determining tumor volume depends on the scales considered by the oncologist. The definition of GTV assumes that it is the volume of the mass that the oncologist has seen with her own eyes. Still, as is known, other factors can cause differences in opinion among different people [10]. In a study [11], tumor volume contouring was initially performed based on CT images without knowledge of PET data to minimize bias in the study. Since patients were randomly selected without prior selection, the data obtained regarding treatment volumes had a non-normal distribution; in some patients, the tumor mass had a very large volume, and in other patients, a very small volume of the tumor mass was observed. Different individuals may have some differences in determining the tumor mass volume, which will lead to differences in tumor mass volume; some of these individuals may also rely more on data obtained from PET. As we mentioned earlier, due to the small number of samples, we were unable to reach a meaningful difference, but we can certainly emphasize that the combination of structural and functional images and the data obtained from combining both types of images can be of the greatest help in correct and accurate tumor diagnosis. In treatment planning for 3D-CRT radiotherapy, the GTV must be determined and mapped accurately, and the radiation dose to the treatment volume must be well defined. Otherwise, the dose to healthy organs may increase, or the desired and uniform dose may not reach the tumor mass. The addition of functional imaging, such as PET, helps to accurately define the target volume based on tumor uptake. The results of the present study, as well as other studies in this field, indicate that fusing PET images with CT simulators can have a significant impact on radiotherapy planning [10-12]. In the present study, the difference in tumor volume based on the two methods studied, including the conventional method and the method using nuclear medicine image fusion, was not statistically significant. Although the volume changes were not statistically significant, at least in some of them, the spatial pattern of the volume attributed to the tumor was somewhat different, which is clinically valuable and, in other words, can provide an accurate determination of the tumor mass volume.

PET scanning using FDG is very useful in distinguishing tumors from atelectasis [13]. Atelectasis is the collapse of a part of the lung, which leads to insufficient oxygen absorption, and this causes that part to appear like a mass on CT images and be considered a tumor, but in PET images, due to the lack of absorption, it can easily be excluded as a tumor volume [14]. PET-FDG results help oncologists reach a common conclusion, as a result of which their disagreements regarding the determination of the tumor mass volume are eliminated or significantly reduced [13]. In the present study, scanning using FDG in the PET method was able to help in the exact location of the tumor by accurately and correctly determining the tumor border. In other words, it can be said that the data obtained from PET could have a relatively significant impact on the accurate diagnosis of the tumor, because in 11 cases the target volume was obtained using PET image fusion larger than the conventional method, and in 5 cases the target volume defined based on PET images was smaller than the conventional method, i.e. based on CT images, indicating that there was an increase or decrease in the volume compared to the conventional method. In some cases, the tumor may be necrotic, in which case the necrotic areas may not be considered in the PET images due to the lack of absorption points, thus causing the volume obtained using PET to be smaller than the volume defined using CT. However, it seems that the simultaneous use of anatomical images (CT images) and nuclear medicine images (PET-FDG) using the fusion or integration process can play a better role in correctly determining the tumor mass volume, and as a result, by reducing human error in correctly and accurately determining the tumor volume, it can reduce disagreement between experts. In the present study, PET scanning increased tumor volume (showed larger) in 68.75% of cases and reduced tumor mass volume in 31.25% of cases compared to CT. As mentioned, the size of the mass varied greatly among patients, with the largest mass (357.10) and the smallest mass (3.50) having a significant difference. We initially believed that performing fusion with PET images would likely increase the GTV in all cases, but the results changed our expectations. A study conducted by Bidyut Mandel *et al.* in 2023 revealed that accurately distinguishing the boundary between lung parenchyma and tumors is challenging. As a result, treatment planning based on CT scans may lead to incorrect target determinations. This could result in insufficient dose coverage within the target volume or potentially cause additional harm to surrounding healthy tissue [11]. In 2016, Hanna Al-Mohsina *et al.* conducted a study on the effect of PET fusion on target volume in radiotherapy planning. Of the 18 patients who underwent PET scans, in 10 of them, the scan significantly changed the GTV determination. PET also helped to determine the tumor in areas of atelectasis in 4 patients and reduced the GTV in them. PET significantly increased the GTV in 3 patients, and overall, the PET/CT fusion data helped to define the tumor [10]. As in our study, fusion had a potential impact on tumor area determination. Jacob Trotter *et al.* (2023) conducted a study on PET imaging tracers and PET/CT fusion methods and showed that image fusion or fusion is superior to visual fusion in improving tumor volume estimation. Visual fusion means that the oncologist views two images separately and visually obtains information from both images. This study also reported that image fusion reduces inter-expert disagreement in tumor volume estimation. When two oncologists independently determined GTVs for the same patient, their results were statistically significantly consistent with the data recorded on PET and CT. Although this difference was not statistically significant, and there is no absolute standard for measuring the accuracy of tumor volume estimation, the improved agreement indicates greater accuracy in tumor volume estimation, which is important in treatment planning [13]. A 2021 study by Qiu Lin *et al.* examined the use of PET/CT fusion imaging in radiotherapy for thyroid cancer. The study included patients with metastatic and non-metastatic cancer, and the volumes obtained did not differ between the two groups. The size of the thyroid tumor volume by PET was significantly different from the volume obtained in conventional treatment [15]. This study suggests that PET fusion in radiotherapy treatment may have different results in different organs. A study on the role of PET/CT fusion in radiotherapy for nasopharyngeal cancer was conducted in 2022 by Hongjia Li *et al*. In this study, they found that PET fusion on CT of radiotherapy treatment was unable to detect metastases in the skull base, intracranial, and liver, so it was limited for these organs [16]. This study showed that PET fusion is superior in accurate tumor detection. It is expected that to achieve more accurate results, we would have to expand the number of samples, but due to time constraints in conducting the study, we settled on this number. The results of the study suggest that:

- The radiation oncologist should have a solid understanding of PET imaging, including its limitations and challenges.
- Successful innovative protocols require collaboration among radiation oncologists, nuclear medicine physicians, and medical physicists.
- Given the high cost of PET imaging, it should be prescribed primarily for organs that are difficult to assess using CT for radiotherapy planning.
- Minimize the time interval between PET and CT imaging as much as possible to ensure accurate treatment volume.
- Image fusion is relatively time-consuming but is much more accurate than a visual assessment of two separate images. Therefore, image fusion can reduce errors caused by visual assessment, reduce observer variability, and also provide a more accurate volume of the tumor.

5. Conclusion

The use of PET-CT data in planning radiotherapy for lung cancer patients undergoing 3D-CRT radiotherapy is crucial. Combining PET-CT images with CT data significantly influenced the assessment of tumor volume and changed the volume of the tumor mass in most patients (11 out of 16). It is suggested to use information from both anatomical (CT) and functional (PET) imaging modalities to better determine tumor volume because each of these modalities has advantages and limitations, but by integrating them, tumor volume can be determined more accurately. Also, increasing the accuracy of determining tumor volume can reduce the radiation dose to healthy tissues/organs at risk.

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