Original Article

The Impact of Positron Emission Tomography/Computed Tomography Addition to Contrast-Enhanced Computed Tomography Findings during Radiation Treatment Planning of Locally Advanced Carcinoma Esophagus

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Abstract

Introduction: Does metabolic imaging help in better definition of target during radiation treatment planning by bringing about changes in dimensions of the primary tumor in terms of diameter, length, and picking up new skip lesions or nodal stations which in turn prevents geographic misses by including more ^{18}F-fluorodeoxyglucose avid regions not visible on conventional imaging? **Materials and Methods:** We compared the length and radial dimensions of the primary tumor as well as changes brought about due to addition of new nodal stations, involved structures, and skip lesions in 50 patients of carcinoma esophagus treated between 2011 and 2013, as seen on contrast-enhanced computed tomography (CT) thorax and positron emission tomography (PET)/CT and drew conclusions regarding the technical changes brought about in treatment planning by the additional input of PET/CT. **Results and Conclusions:** PET-CT tremendously changes treatment plans by expanding the gross tumor volume and including regions which might otherwise have been missed on purely CT-based plans. Of the 50 patients, it changed the contouring and treatment planning of 35 patients and did not impact the remaining 15. Whether this translates into better long-term controls requires further validation by randomized controlled trials, which was not our present objective.

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography, carcinoma esophagus, contrast-enhanced computed tomography thorax, radiation planning and contouring guidelines, target volume delineation

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Introduction

The holy grail of radiation oncology planning would be to find the imaging modality that very clearly and crisply defines the target volume to be irradiated, including any subclinical disease or micrometastatic spread. However, despite the leaps and bounds by which technology has taken over, this still remains elusive with every imaging modality offering some cons alongside the pros. Then, the next best option becomes co-registration of multiple images to get the maximum idea about the tumor volume and try to supplement one with the other, to minimize their drawbacks and capitalize on the benefits that each has to offer.

In oncological imaging, the goals are lesion detection and localization including anatomical correlation with structures such as vessels lesion characterization, proper staging, and treatment success. Some of these goals require precise anatomical imaging, whereas others demand molecular techniques. ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) are complementary, additive, and synergistic and the employment of the two is imperative in oncological clinical practice. As with most neoplasms, the gold standard for diagnosis in

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carcinoma esophagus remains histopathological confirmation. However, imaging modalities such as CT scans and PET/CT scans help determine the extent of the local tumor; invasion of mediastinal structures such as tracheobronchial tree, aorta, azygous veins, prevertebral muscles, and pleura; involvement of supraclavicular, mediastinal, or upper abdominal lymph nodes; and distant metastases which in turn help in assignment of the TNM status.

The definition of the gross tumor volume (GTV) is the single most important step in planning treatment, and all other steps depend on it. If the tumor is not well imaged and the GTV is wrong, then the entire treatment process may be futile. Based on controlled animal experiments, the steepness of dose-response curves for tumor control suggests that up to 8% change in tumor control can be measured per 100 cGy change in delivered dose near the 50% control level. This implies that if a significant portion of the GTV receives a lesser dose, local control might not be achieved.[1] To be cured by radiation therapy, the tumor must be entirely contained within a volume of tissue treated to a tumoricidal dose. The target, as drawn by a radiation oncologist at the time of planning, forms the basis for all subsequent steps, including beam planning, dose optimization, dose evaluation, dose delivery, and image verification. The radiation oncologist uses information from diagnostic images, simulation images, clinical examination and reports, knowledge of cancer biology, and his/her experience to determine the appropriate target to treat. This information is coalesced and ultimately used to generate a target drawn manually in three-dimensional (3D) on CT simulation images. The International Commission of Radiation Units and Measurements (ICRU) 24 report recommends that radiation planning and delivery should strive for an overall dose and spatial accuracy of 5% and 5 mm, respectively.[2]

The greatest advantage of PET is that the metabolic information obtained precedes morphological changes. PET can reveal targets that are not well visualized by CT/magnetic resonance (MR) structural imaging. These targets may be remote from the primary tumor, such as unsuspected lymph node or distant metastases, or they may be additional neoplastic regions adjacent to the tumor volume defined by CT/MR imaging. PET makes it less likely that treatment will be given to "equivocal" regions on CT/MR which do not actually contain tumor.

In terms of its diagnostic ability, FDG-PET reaches sufficient sensitivity (67%) and good specificity (97%) in the detection of metastatic disease and is superior in this regard to CT and other available diagnostic tools.[3] For locoregional lymph node staging, it offers a sufficient specificity of 84% but a low sensitivity of 51%.[4,5]

Materials and Methods

Previously untreated, histologically confirmed esophageal neoplasms with no tracheoesophageal/tracheobronchial fistula in patients between 20 and 80 years of age with a Karnofsky's Performance Scale ≧60% and minimum weight ≧30 kg; males and nonpregnant, nonnursing females with no contraindication to injection of contrast or to radiotherapy (RT) to be taken up for any form of radiation first, be it definitive concurrent chemoradiation therapy, palliative external beam RT, radical RT, or neoadjuvant RT with concurrent chemotherapy were selected and included in the study. Fifty patients were enrolled over a period of 2 years between January 2011 and 2013.

After obtaining a written informed consent and conducting a detailed clinical evaluation, patients were subjected to both CT and PET/CT scans within 2 weeks of each other to prevent temporal differences in findings. Standardized protocols were followed from patient preparation onward to scan acquisition and data analysis. The scans were interpreted by qualified Radiologists and Nuclear Medicine Specialists after providing them with full clinical details of each case. TNM Classification, the American Joint Commission on Cancer 7th Ed-2010[6] was used for staging the disease.

A visual fusion of both data-sets of PET and CT images was made by co-registering matched slices simultaneously on two computer screens at the time of planning in the transaction process system (TPS) and comparing all significant findings. The generation of the first plan (contouring and treatment planning) was done after taking cognizance of all investigation findings (barium swallow, UGIE, contrast-enhanced CT [CECT], PET-CT, HPER, or any other investigation such as MR imaging, bone scan and endoscopic ultrasonography, if available with the patient). All patients were treated as per this first plan (per institutional protocol and guidelines). A second proxy plan was prepared using every investigation sans the information from PET scan, and this was compared with the first plan in terms of differences in target volume (GTV/clinical target volume [CTV]/planning target volume [PTV]), length and radial margins, addition of new nodal station (NNS) or structure, changes in doses to organs at risk (OARs) and other technical changes such as beam number geometry, energy, orientation, and weightage if any.

The final GTV was contoured taking the longest possible length and radial margins on imaging including the gross primary lesion, involved nodes, and involved adjacent structures. The CTV and PTV were similarly marked as per guidelines. The standard protocols of 3D-conformal RT (CRT) for radiation dose prescription, planning, and delivery of the treatment were used. The study did not explore the technical aspects or effects of decreased tumor volumes as per PET findings whenever there was a decrease in tumor dimensions, as it was deemed imperative at the beginning of the study to err on the higher side to minimize geographical misses.

Criteria of positron emission tomography impact

The following criteria [Table 1] were used to decide whether the addition of PET findings affected the radiation planning of the patient, and if so, whether the impact was a major one or a minor one.

A master-chart was compiled to analyze the following aspects of the study:

1. Difference between PET CT and CECT in localization and mapping of the extent of tumor, regional lymph node involvement
2. Change in GTV length and diameter, target volume delineation, and/or doses to OARs, and technical
3. Changes such as changes in beam number, geometry, energy, orientation, and weightage during treatment planning if any as a result of FDG PET/CT findings.

The proportion of different types of impact (major, minor, or none) as defined in the table was measured. In case of more than one subgroup of impact, the higher group was taken as the final impact (e.g., the same patient may have A1 and B2 changes, but the final impact would be A).

Statistical tests

- The entire statistical analysis was performed using IBM SPSS version 20 (International Business Administration Corporation, Armonk, New York, USA)
- Comparison of variables between the two groups was done by two-tailed Student's *t*-test or nonparametric tests (Mann–Whitney U test)
- Correlation between different parameters was assessed using the Spearman's/Pearson's correlation test. 5% probability level (allowing an α error of 5%), was considered as statistically significant, i.e., $P < 0.05$.

Table 1: Positron emission tomography impact criteria

Impact	Group	Definition
Major	A	Major change during radiotherapy planning on TPS
	A-1	GTV length↑by ≥10 mm
	A-2	Radial margin↑by ≥5 mm
	A-3	↑or↓in dose to OAR by 5% or more
	A-4	Addition of new nodal station or involved structure to GTV
	A-5	Technical adjustments due to major changes (beam number, geometry, energy, orientation, and weightage)
Minor	B	Minor change during radiotherapy planning on TPS
	B-1	GTV length↑by <10 mm
	B-2	Radial margin↑by <5 mm
	B-3	↑or↓in dose to OAR by <5%
	B-4	Technical adjustments due to minor changes (beam number, geometry, energy, orientation, and weightage)
None	C	Initial management plan (Rx) was followed irrespective of PET findings
	C-1	No significant additional finding (s) on PET
	C-2	No technical change despite some additional findings

↑: Increase, ↓: Decrease, GTV: Gross tumor volume, TPS: Treatment planning system, PET: Positron emission tomography, OAR: Organs at risk

Results

The average length and diameter of the primary lesion on CT scan were 63.3 mm and 20.3 mm, respectively. The average length and diameter of the primary disease on PET/CT scan was 67.8 mm and 19.7 mm, respectively. The average length was greater in PET/CT than CECT, but the average radial margin was lesser on PET/CT in comparison to CECT [Table 2 and Figure 1].

Of 50 patients, the length of the primary lesion increased by ≥10 mm in 18 (36%) patients and by <10 mm in 9 (18%) of patients. The overall frequency of increase in PET length was 27 (54%). The length of the primary lesion decreased by ≥10 mm in 10 (20%) patients and by <10 mm in 11 (22%) patients. PET length matched the CT length in 2 (4%) of patients [Table 3]. The maximum diameter of the primary lesion was increased by ≥5 mm in 10 (20%) patients. It, however, decreased by 5 mm in 3 (6%), by >5 mm in 8 (16%) and by <5 mm in 19 (38%) patients. The PET diameter matched the CT diameter in 5 (10%) patients. The overall frequency of decrease in maximum diameter was 30 (60%) [Table 3].

NNS or a new involved structure was picked up by PET scan in 22 (44%) patients. PET brought about a change in dose to OARs in 27 (54%) patients [Table 4]. It increased the dose to OARs (such as thyroid, spinal cord, heart, lung, kidney, and liver) by more than or <5% in 26 (52%) patients and decreased the dose to OARs by >5% in 1 (2%) patient [Table 4].

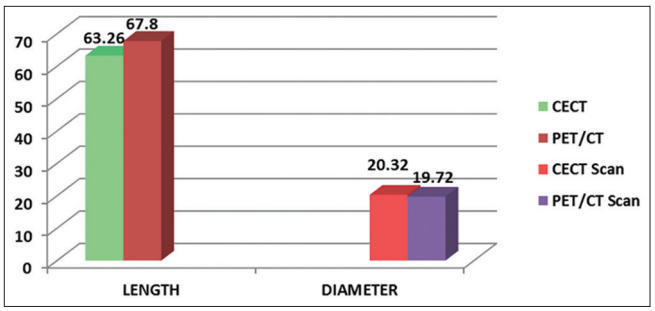

Figure 1: Tumor dimensions

Table 2: Average and range of contrast-enhanced computed tomography and positron emission tomography tumor dimensions

Parameter	Range	Minimum	Maximum	Mean	SD	*P*	
CT length (mm)	117.00	13.00	130.00	63.26	23.29	Significant 2 tailed	0.113
PET length (mm)	89.00	29.00	118.00	67.80	20.52	Wilcoxon's	0.179
CT diameter (mm)	38.00	6.00	44.00	20.32	8.78	Significant 2 tailed	0.508
PET diameter (mm)	35.00	5.00	40.00	19.72	8.89	Wilcoxon's	0.224

CT: Computed tomography, PET: Positron emission tomography, SD: Standard deviation

Overall PET brought about technical changes in treatment plan such as beam number, geometry, orientation, and weightage in 13 (26%) of patients and no technical change in the remaining 37 (15 + 22) or 74% of patients [Table 4]. As shown in Tables 2-5 and Figures 1 and 2, the total number of changes exceeds 50 due to more than one kind of impact on radiation treatment planning per patient (e.g. the same patient may have A1 and A2 changes, but the final impact would be on only one planning).

- Absolute GTV change = A1 + A2 + B1 + B2 + A4 would be a spurious reading beyond 100. Hence, a Net GTV was calculated. Net GTV Change (accounting for multiple GTV changes in each patient) =68%
- Change in dose to OARs (A3 + B3) =54%
- Technical changes due to PET/CT besides GTV = 26%
- Net Impact of PET (accounting for multiple changes in each patient and including GTV, OARs dose, and other technical changes) = Minor + major Impact = 70%.

A comparison of our study with similar studies in the past has been tabulated below which show similar results [Table 6].

Table 3: Length and diameter changes on positron emission tomography/computed tomography

Length	Frequency (%)	Diameter	Frequency (%)
<10 mm↓	11 (22.0)	<5 mm↓	19 (38.0)
>10 mm↓	9 (18.0)	>5 mm↓	8 (16.0)
10 mm↓	1 (2.0)	5 mm↓	3 (6.0)
<10 mm↑	9 (18.0)	<5 mm↑	5 (10.0)
>10 mm↑	17 (34.0)	>5 mm↑	9 (18.0)
10 mm↑	1 (2.0)	5 mm↑	1 (2.0)
None	2 (4.0)	None	5 (10.0)

↑: Increase, ↓: Decrease

Table 4: New nodal stations or structure, technical change, and OARs dose change

	Frequency (%)
NNS or structure	
Yes	22 (44.0)
No	28 (56.0)
Technical change	
Yes	13 (26.0)
No	37 (74.0)
OARs dose change	
<5%↑	9 (18.0)
>5%↑	17 (34.0)
<5%↓	-
>5%↓	1 (2.0)
None	23 (46.0)

↑: Increase, ↓: Decrease, NNS: New nodal stations, OARs: Organs at risk

Table 5: Master chart - impact of positron emission tomography on radiotherapy planning (reference: Table 1)

Group	Frequency (%)
A	30 (60.0)
B	5 (10.0)
C (C1 + C2)	15 (30.0)
A1	18 (36.0)
A2	10 (20.0)
A3	18 (36.0)
A4	22 (44.0)
A5	13 (26.0)
B1	9 (18.0)
B2	5 (10.0)
B3	9 (18.0)
B4	22 (44.0)
C1	6 (12.0)
C2	9 (18.0)
No impact (C)	15 (30.0)
Total impact (A + B)	35 (70.0)

Discussion

CT has had a major impact on radiation therapy planning, and the process of scanning patients for the purposes of radiation therapy planning is referred to as CT simulation. When scanned with the patient in radiation treatment position, CT provides the anatomy, geometry, spatial information, and electron density information required for all aspects of radiation therapy planning.[14] For localization of tumor and normal tissues and marking RT boundaries, CT provides 3D-anatomic information based on morphology and physical abnormalities with excellent spatial and good low-contrast resolution. CT also provides the geometry and spatial accuracy required for precise conformal planning and dose calculations. Furthermore, the linear relationship between CT numbers or Hounsfield units (HUs) and relative electron densities provides tissue heterogeneity information necessary for accurate therapeutic dose calculations. It helped the evolution of target localization from simple 2D-portal designs relative to bony landmarks on radiographic simulation films to direct defining of soft-tissue targets on 3D-CT datasets. Unfortunately, the sensitivity and specificity of CT for distinguishing between normal and neoplastic tissues is limited in certain clinical structures. Many solid tumors, for which dose escalation techniques with 3D-CRT and intensity-modulated RT (IMRT) can be theoretically effective, develop within soft tissues and are often surrounded by normal soft tissues of similar overlapping density

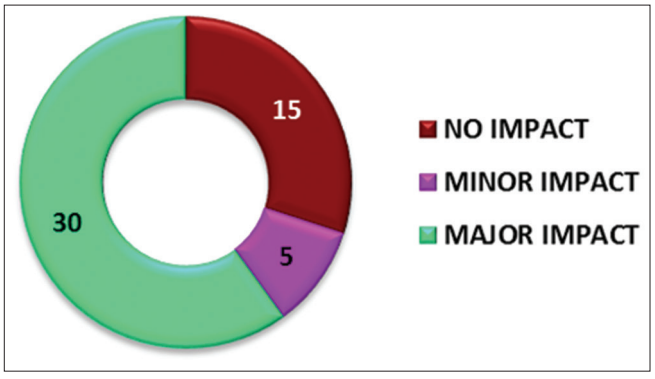

Figure 2: Positron emission tomography impact on radiation planning

Table 6: Comparison of study result with literature

Study	Year	*n*	Analysis-method	Results
Coulombe *et al*.[7]	2010-11	106	Systematic review	Length Change: 75%-86% GTV Change: 59%-100%
Vrieze *et al*.[8]	2004	14	Visual segmentation without PET/CT software fusion	PTV ↑: 21%; PTV ↓: 21% GTV↑: 43%; GTV↓: 57%
Moureau-Zabotto *et al*.[9]	2005	34	Visual segmentation with PET/CT software fusion	GTV ↑: 21% GTV ↓: 35%
Leong *et al*.[10]	2006	21	Visual segmentation; with PET/CT software fusion	GTV Change: 86% GTV↑: 69%
Schreurs *et al*.[11]	2010	28	Target volume delineation	Change: 61%
Stahl *et al*.[12]	2005	40	FDG PET versus CT discordance	Clinically relevant in 50%
Vesprini *et al*.[13]	2008	10	Inter- and intra-observer variability	FDG-PET significantly decreased both
Our study	2011-13	50	Prospective analysis of PET impact; visual Segmentation with PET/CT software fusion	PET Impact: 70% Net GTV Change: 68% GTV Length ↑: 56% GTV Radial Margin ↑: 28% NNS or structure: 44% OARs dose change: 54% Technical change: 26%

↑: Increase, ↓: Decrease, PET: Positron emission tomography, CT: Computed tomography, OARs: Organs at risk, NNS: New nodal stations, GTV: Gross tumor volume

residing within a limited range of approximately –150–100 HU for CT. This makes the distinction between the boundaries of a tumor and surrounding normal tissue difficult. This is a major source of uncertainty in the localization of the GTV and also significant intra- and inter-observer variability when using CT images. Without pathologic confirmation, it is unclear with any imaging modality that the image-based volumes defined by radiation oncologists correspond to the true GTV. Unfortunately, there is no explicit allowance for physician uncertainty in the ICRU definition of the GTV, CTV, or PTV. The current process of 3D-CRT and IMRT assumes that the GTV or CTV is correct without questions and no margin is added to explicitly account for its uncertainty. Some have recommended the incorporation of interobserver variation and physician uncertainty in a separate margin while others have proposed standardization in methods of target outlining. There is currently no consensus on this issue, and as such, this uncertainty is generally ignored in clinical practice. For certain clinical scenarios, the uncertainty in the size, shape, and location of the GTV based on CT may be the largest contributor to geometric uncertainty in the entire process of radiation planning and delivery.[15] Interobserver variability alone in GTV definition has also been shown to exceed the margins used to generate the PTV for a number of tumor sites.[16]

Furthermore, since the microscopic extension of the tumor around the GTV cannot be determined by CT, the volume treated is much greater than the GTV. On the other hand, precise and accurate localization of RT targeted to GTV is critical for optimizing the therapeutic ratio. By measuring the metabolically active tumor volume, PET on its own provides functional data that can be used to improve tumor coverage, including the involved lymph nodes, and thus reduce normal tissue exposure. Feasibility studies have shown that a PET/CT scan may provide valuable information for accurate staging and decision making in the field of RT, changing treatment strategies in about 25% of patients. Treatment changes include prevention of inappropriate RT, changes in radiation dose or target volume, and changes in treatment intent regarding curative or palliative radiation therapy. Data from a CT may be used for volume planning and delineating tumor margins; whereas, PET by differentiating viable from nonviable and aggressive from nonaggressive lesions can provide additional information to help adjust doses and spare normal structures.

With CT only, malignant regions are detected by change in either size or CT number relative to their surroundings, and accuracy is limited particularly when fibrosis and other benign processes of similar CT numbers are present. This poor contrast between malignant and nonmalignant regions can lead to uncertainty and high observer variability in localization of GTV. The longitudinal extent of esophageal tumors is difficult to accurately define on CT imaging, and this problem is compounded by the rising incidence of adenocarcinoma of the distal esophagus and gastroesophageal junction where the distal extent of the tumor (often in the cardia of the stomach) can at times be impossible to visualize on CT. Measures routinely employed for diagnostic CT scans such as administration of water or other oral contrast, intravenous anticholinergic agents to reduce peristalsis, and volumetric scanning in the supine and prone positions are not practical in RT planning CTs which are usually performed without the use of contrast agents.

CT is regarded as a low-contrast modality with most soft tissues having similar X-ray attenuation properties. As such CT values for all tissues, excluding lung and bone, are distributed over a narrow range of values of CT numbers.[17] PET images

are high contrast images, with most normal tissues exhibiting a low-intensity value as illustrated in the body histogram of PET intensity values for the same patient. The exceptions are bladder, brain, and occasionally myocardium and kidneys. Neoplastic tissues register values that are typically an order of magnitude higher and are clearly separated from nonmalignant processes. Unlike the seconds to subsecond acquisition times of CT, PET images are acquired over minutes. Furthermore, PET images can be acquired in true 3D-volumetric mode, rather than 2D at a time as in single-slice CT. PET can more accurately define the proximal and distal limits of the primary tumor GTV than CT as readily identifiable uppermost and lowermost axial CT slices containing FDG-avid tumor. Furthermore, PET allows the longitudinal extent of the tumor to be more clearly defined and is particularly useful for determining the distal extent of tumors that extend to the gastroesophageal junction and proximal stomach, where visualization with CT alone is often difficult. In contrast to the longitudinal extent of the GTV, the radial extent, which is defined by the outer wall of the esophagus, is usually clearly visible with CT alone due to its better spatial resolution. When used for initial staging of esophageal cancer, PET is more accurate than CT for detecting lymph node and distant metastases, thereby allowing more accurate selection of the most appropriate treatment.

PET/CT has limited accuracy in the identification of the primary tumor in esophageal carcinomas because a variety of benign conditions of the esophagus, such as Barrett's esophagus, also lead to high FDG uptake, giving it a false-negative rate of 20%. Early T1 lesions may be reported as a false negative. Since the T-stage depends on the depth of tumor invasion, only T3 (tumor invasion up to adventitia) or T4 lesions (tumor invasion into adjacent structures) can be confirmed with a degree of accuracy depending on the maintenance or obscuring of surrounding fat planes. For lesser T stages, exact depth cannot be demarcated either morphologically or metabolically on the resolution offered by axial slices. Furthermore, Barrett's esophagus, hiatus hernias, reflux, infective or radiation-induced esophagitis, postoperative anastomotic inflammation, sarcoidal or anthracosilicosis-associated lymphadenopathy may all give false positive results. In addition, focal areas of brown fat, asymmetric uptake in the vocal cords, and vessel atherosclerosis may lead to false-positive results, although these areas are generally better differentiated from areas of esophageal uptake on PET/CT, rather than on PET images.[18]

Early stage (Tis, T1) disease, small volume tumors ($T \leq 2$) or those that are not FDG-avid, signet ring cell adenocarcinomas and some poorly differentiated adenocarcinomas of the GE junction and peritumoral lymph nodes may all be a false negative.[19] Fortunately, FDG-nonavidity is uncommon with esophageal cancer (4%). In addition, involved nodes that are <7 mm in diameter are unlikely to be reliably detected by the current PET technology. Even with zero background signal, the spatial resolution or rather the clinical detection limit for PET, typically 4–6 mm, is substantially larger than the submillimeter resolution for CT.

Currently, due to the lack of PET-based Radiation-Treatment Planning System (R-TPS), qualitative or visual assessment of a PET or PET-CT dataset is the most common method of image segmentation used for clinical radiation targeting. However, this is subject to large uncertainties due to differences in observer expertise in image interpretation, systematic bias, experience of observers, and nonstandardization of the window, and level display parameters.

Conclusions

Metabolic/functional imaging is increasingly proving to be a robust tool in the armamentarium of the radiation oncologist to improve target delineation and hence design radiobiologically, technically, and oncologically sound radiation fields during treatment planning for optimal target coverage. As much as possible, inputs from such investigations must be sought and analyzed scientifically to generate better protocols for patients in future. As a caveat, long-term outcomes of such plannings must be recorded to not just help fine tune the method, but to validate its superiority over conventional planning.

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Conflicts of interest

There are no conflicts of interest.

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