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Pet-Ct Based Radiotherapy Planning

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ABSTRACT

With the advent of advanced imaging techniques such as positron emission topography/computed topography, use of radiotherapy in the management of various cancers has become more effective and is shown to have better outcomes. PET/CT scanning is useful for evaluating tumour biological heterogeneity of malignant lesions providing comprehensive information regards the tumour's metabolism, hypoxia, and proliferation. Integration of PET/CT imaging in radiotherapy helps in assessing tumour volume to achieve effective tumour control by adjusting radiation dose. Literature is extensive on PET/CT based radiation planning and here we aim to provide a brief review of PET/CT use in different malignancies.

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Background

A multidisciplinary approach of medical, surgical, and radiation oncologists is essential for effective management of most cancers as almost 50% of patients require radiation as a part of their treatment. Major components of radiation are good immobilisation, target volume delineation, robust treatment planning and regular checks for errors. Radiotherapy aims at giving a tumoricidal dose while preserving normal tissue function and reducing radiation-induced toxicity.

Achieving a good tumour control with radiation is invariably dependant on the total dose delivered to the identified tumour volumes, use of concurrent radiosensitisers and the tumour biology. Therefore, accurate delineation of the gross tumour volume (GTV) necessitates quality imaging for appreciation of tumour extent and its locoregional spread. Normal tissue sparing can only be achieved if the tumour delineation is adequate that helps radiation oncologists to plan for conformal radiation techniques. Delineation of the regions of interest like the GTV (Gross Tumour Volume) and CTV (Clinical Target Volume) of the primary and locoregional spread is followed by dose prescription accordingly.

In the past, information from clinical examination and radiographic imaging was used to plan for radiation therapy, however in the recent years advent of modern imaging techniques has improvised tumour volume delineation. With the advances in imaging modalities such as PET scan, radiation oncologists are now comfortable in planning conformal radiation therapy techniques such as 3 D-CRT (Conformal Radiation Therapy), IMRT (Intensity Modulated Radiation Therapy, VMAT (Volumetric-Modulated Arc Therapy), and SRT (Stereotactic Radiotherapy).

Conformal techniques were reported to have a mishap of geographic miss and usually occurs when a marginal tumour area has either escaped radiation or irradiated incompletely because the total volume of the tumour was not appreciated. This can be greatly reduced with the help of appropriate imaging modalities. One such modality that has revolutionised the therapeutic approach is the FDG-PET (18F-fluorodeoxy-D-glucose - Positron Emission Tomography).

FDG-PET (18F-fluorodeoxy-D-glucose - Positron Emission Tomography) provides information based on alterations in the tissue metabolism from normal physiology differentiating tumour cells from normal tissue [1]. Evidence exists to reinforce the need for this type of functional information about tumours and their surroundings for radiotherapy treatment planning [2,3]. Many studies in the recent past have emphasized on the integration of FDG-PET with conventional CT-based radiation therapy planning to achieve better patient outcomes, modifications to patient management and improvises target volume delineation [4-11].

PET-scans are used for tumour staging, for tumour response prediction, for selection or delineation of target volumes, for response assessment to treatment, for detection of recurrence, or as an aid to evaluate changes in organ function post-treatment [12]. PET imaging is reported to reduce PTV thus attenuating the toxicity with the same radiation dose or allowing radiation dose escalation with the same toxicity [13]. According to its biological activity, the "Biological Tumour Volume" (BTV) separates the tumour. Precise BTV definition is required for escalating the radiation dose without much normal tissue injury.

FDG-PET based RT planning is extensively investigated in the lung cancer, head and neck cancers, gynaecological malignancies, and lymphomas. We aim to summarize the available evidence

on PET-CT based RT and outcomes of its use in different malignancies. This article intends to analyse the applications of PET in radiotherapy planning, stressing on its application for lung, head and neck, oesophageal, gynaecological malignancies, and lymphomas. Besides this, why use PET-CT for radiation therapy planning? How helpful is PET-CT based radiation therapy planning? Where can we use PET-CT integration with RT planning? Does it impact the survival?

Head and Neck Cancer

About 15 studies reported the sensitivity of nodal detection with PET as 87%, and specificity as 95% in head and neck cancer compared to CT/MRI that have a sensitivity of 77% and a specificity of 87%. For anatomic localization of the metastatic neck nodes, inclusion of PET was found to be superior to CT/MRI alone with 96% sensitivity and 98.5% specificity as demonstrated in the study by [14]. In the detection of suspected recurrence and residual disease in head and neck cancers, PET has played a crucial role with a sensitivity and specificity of up to 100%, as opposed to the 75% sensitivity and 80% specificity of CT/MRI [15-18].

Non-Small Cell Lung Cancer

FDG-PET is helpful for malignancy staging in the setting of radiation therapy for appropriate patient selection [19]. This is especially relevant when definitive chemo-radiation is being planned for a patient with NSCLC and may already have distant metastasis. Patients with stage III disease may have a rate of about 20 % unsuspected distant spread [20,21]. In a run-through of the literature accessible, for diagnoses of the primary lung cancer FDG-PET is reported have 91% sensitivity, 68% specificity, an 83% sensitivity and 91% specificity in mediastinal staging compared to 56– 65% sensitivity and 73–87% specificity for CT based mediastinal staging [21,22].

Oesophageal tumours

PET has higher accuracy than CT for identifying lymph node and distant metastases when used for initial staging of oesophageal cancer. This permits accurate selection of the most suitable treatment [24-26]. For detection of the primary disease in oesophagus, PET has sensitivity around 90–100% [27]. Similarly, for diagnosis of pathological lymph nodes PET-CT exhibits higher sensitivity (30–77%) and specificity (86–99%) than does CT (sensitivity 11–57%, specificity 69–99%) [28-34].

Gynaecological Malignancies

A couple of studies assessed role of FDG-PET for discerning suspicious pelvic mass on ultrasonography and found 58% to 78% sensitivity and 78% to 87% specificity [11-12]. In the face of relatively low sensitivity of FDG-PET in the diagnosis of ovarian cancer, most of the false-negative results were either invasive stage I tumours or those of low malignant potential (borderline ovarian tumours). Advanced stages of ovarian cancer display avidly increased FDG uptake and are visualized better. Nevertheless, cellular composition of tumours has a notable effect on the level of FDG uptake. Large cystic components in the abdominal or pelvic masses as well as mucinous tumours are usually not be metabolically active.

Brain Tumours

Malignant gliomas and brain metastases are the most common brain tumours and neuroimaging is crucial in clinical decision making and to as an assessment tool to evaluate response to therapy. In low-grade tumours, neuroimaging is required to evaluate recurrent disease and to monitor transformation into high-grade tumours. In high-grade and metastatic tumours, it is challenging to differentiate recurrent tumour from post-radiation necrosis.

FDG-PET has a role in identifying the grade of the tumour, assessing suspected high-grade transformation, characterising relapse with an equivocal MR and differentiating cerebral tumour from an atypical infection in immunocompromised patients having an indeterminate lesion. MRI provides superior structural detail but has poor specificity in identifying viable tumours in the brain post-treatment. 18 An area of the treated brain has diffuse background metabolic activity and usually is of lower metabolic activity than the normal untreated brain. Summary of prior reports have reported that FDG PET to be proficient in distinguishing treatment necrosis from tumour recurrence with sensitivity and specificity in the ranges of 65%-81% and 40%-94%, respectively.

F-FDG PET identifies anaplastic transformation and has prognostic value. The sensitivity and specificity of (18) F-FDG in understanding a recurrent tumour and treatment-induced changes can be improved drastically by co-registration with MRI and by delayed imaging 3-8 h after injection. F-FDG PET/CT plays a crucial role in the tumour staging and follow-up to effectively evaluate therapy response of known metastases but is not considered the modality of choice to detect brain metastases.

Radiotracers Used for Pet Based Rt Planning

[18F] Fluoro-deoxy glucose (FDG) is the tracer most often used which allows to evaluate tumour metabolism [35-38]. Of late, there is increasing interest for various specific biomarkers like the tracers used for tumour hypoxia and high mitotic activity [39-45]. Tumour hypoxia can be envisioned using various PET tracers such as [18F] Fluoromisonidazole (FMISO) [16], [18F] Fluoroazomycin (FAZA) [15] and Cu-ATSM [17] whereas [18F] Fluorothymidine (FLT) is used for imaging areas with high tumour proliferation. Human brain commonly shows intense uptake of FDG, as it metabolizes glucose exclusively, while myocardial uptake is variable in patients who have fasted. Adipose tissue shows negligible FDG uptake, but brown fat which has a role in thermogenesis can be eventfully activated in a nervous patient.

How has PET changed the treatment volumes?

A change of 30-60 % was seen in the GTV primary and 51 % in the GTV node while delineation of GTV based on PET-CT fusion as reported by Bradley et al on patients with NSCLC. In another study reported by Vila A et al, 34 % of the patients had alterations in the delineation of GTV primary. Dietl and colleagues reported that changes in radiotherapy technique due to PET occurred in 40.8% of 49 patients in a prospective study [46]. Possible reasons for noteworthy changes in target volumes in lung cancer with PET include higher pick up of nodal metastasis than that of CT and better distinction of the border between malignant tissue and atelectasis [46]. Inclusion of PET thus enables encompassing the previously unidentified regional nodal involvement which can result in 10-25 % patients having alterations in the GTV. Also, consideration for excluding large PET negative nodes or uninvolved/collapsed lung tissue drastically reduces the GTV.

Does PET-CT integration impact survival?

There is a paucity of data on whether the changes in the tumour volumes as detected by PET also have a favourable outcome in terms of survival. Improvement in the overall survival was revealed in the only RCT done by Ung et al. It is quite sensible that one expects a survival benefit due to PET-based RT planning as it permits targeting the appropriate areas with radiation.

Drawbacks of PET Integration?

Limitations of PET integration include PET/CT error, false positivity, inability to detect microscopic spread, mis-registration between anatomical and functional information. Rigid parts of the body have minimal error such as the brain. The minimal error is unpreventable in image fusion, whether a separate or combined PET/CT scanner is used. Many soft- and hardware solutions claim higher precision in image fusion, up to 1–2 mm in all directions. Various movements which are possible in the neck have the likely mis-registration amidst anatomical and functional information. This explains the need for acquisition of PET/CT in the treatment position for radiation. There is also a potential risk of incorrectly converting the intent of the treatment from radical to palliative therapy due to false-positive findings in PET. The microscopic disease cannot be detected by PET. However, estimation of the true risk of microscopic nodal disease can be done if accurate information of the gross nodal disease is known.

Conclusion

FDG PET-CT is a precious tool for refreshing the conventional radiation therapy target volumes. Detection of the BTV is very essential as it impacts the radiation therapy planning. Tumour staging, response assessment and detection of recurrence are the major applications of PET-CT. Coalescing PET with treatment planning leads to significant alterations in the tumour volumes. Generalisation of PET-CT applications in all the tumour sites is taken with a pinch of salt. Future studies are awaited to throw more light on its impact on survival and the unexplored indications in oncology highlighting its widespread role.

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