# Role of Fusion in Radiotherapy Treatment Planning

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**The fusion of functional imaging to traditional imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), is currently being investigated in radiotherapy treatment planning. Most studies that have been reported are in patients with lung, brain, or head and neck neoplasms. There is a potential role for either positron emission tomography (PET) or single photon emission computed tomography (SPECT) to delineate biologically active or tumor-bearing areas that otherwise would not be detected by CT or MRI. Furthermore, target volumes may be modified by using functional imaging, which can have a significant impact in the modern era of three-dimensional radiotherapy. SPECT may also be able to identify "nonfunctional" surrounding tissue and may influence radiotherapy beam arrangement.**


RADIOTHERAPY (RT) TREATMENT planning has evolved in complexity over the past 50 years. Initially, the use of visual and palpable landmarks guided the radiation oncologist to the treatment site. The external contour of the patient at the specified anatomic level was contoured, and the approximate location of the tumor and normal, surrounding organs was drawn by using surface anatomy and radiographs. The advent of the simulator changed the method of treatment planning as internal bony landmarks were used by clinicians to locate the organ of interest. Tumor and normal tissues were displayed on a single planning plane with doses displayed as isodose lines. During the past decade the radiation oncology community has entered another phase in treatment planning methodology by the use of image-guided radiotherapy. Computed tomography (CT) simulation became routine, and target volumes and normal tissues were contoured on a computer terminal. A three-dimensional image of the tumor was created as well as the surrounding critical structures. Dose volume histograms became the rule. Magnetic resonance imaging (MRI) provided better anatomic definition of the brain and could be fused with CT to determine target volumes. The birth of three-dimensional radiotherapy made it possible for treatments to be more conformal; dose escalation, while maintaining the same probability of late toxicity, became feasible. Today, we are faced with another dimension in RT treatment planning in the form of functional imaging. The "biological target volume" can be identified by using functional imaging that is then fused to the anatomical image derived from CT or MRI scans to determine a precise target volume.[1,2] Biological imaging that may be helpful to radiation oncologists include those that assess tumor hypoxia and potential doubling time. Both positron emission tomography (PET) and nuclear MRI and spectroscopy studies could be used to aid in delineating target volumes. Functional imaging may also play a role in normal tissue sparing when irradiating adjacent tumor. Single photon emission computed tomography (SPECT) perfusion imaging could be used to avoid perfused lung tissue from the irradiated volumes.[3] In this manuscript, we discuss the potential role of fusion in different disease sites as it relates to RT treatment planning and the preliminary results of this method of RT treatment delivery.

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*0001-2998/03/3303-0017$30.00/0*

*doi:10.1053/snuc.2003.127313*

## LUNG CANCER

Most of the information we have on functional imaging-based RT has been derived from patients with non-small cell lung cancer (NSCLC). PET using 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose (FDG) has been used extensively as part of the work-up to determine disease extent. With the exception of bronchoalveolar carcinoma, most NSCLC primary tumors are visualized with FDG.[4-6] Staging of mediastinal disease with CT and MRI has reported sensitivities of 52% and 48% and specificities of 69% and 64%, respectively.[7] A recent meta-analysis showed that CT and PET had sensitivities of 79% and 95% and specificities of 60% and 77%, respectively, for staging of nodal disease.[8] The same study found an accuracy of 92% for PET and 75% for CT scans. The utility of FDG-PET in detecting metastatic disease depends on the site of spread. Adrenal gland metastasis is almost always detected by PET imaging, whereas brain metastasis is not as well visualized as are metastases to other organs.[4,9] For bone metastasis, one study showed 98% were accurately staged by using PET, whereas 87% were accurately staged by using bone scan. FDG-PET identified 11 of 12 patients with bone metastasis, whereas the bone scan had only a 50% sensitivity.[4]

Studies have shown alterations in staging of NSCLC in 24 to 62% of patients when FDG-PET was used.[5,10,11] In patients who are found to have distant metastases, clinical management can be drastically altered. Tucker et al noted that the information from FDG-PET resulted in the cancellation of surgery for the primary tumor in 30% of cases; likewise, 19% permitted surgery contrary to conventional imaging results.[12] In the same study, approximately 70% of patients had a clinical management

**Table 1. Institutional Series using PET-CT Fusion for Radiotherapy Treatment Planning in Non-Small Cell Lung Carcinoma**

| Study | Institution/ No. of Patients | Proportion of Patients with Change in Management with use of PET fusion | Comments |
|---|---|---|---|
| Kiffer [17] | Austin and Repatriation Medical Center, Victoria, Australia N = 15 | 26.7% | |
| Nestle [18] | Saarland University Medical Center Germany N = 34 | 35% | Nine of 17 (53%) of patients with atelectasis had change in target volume |
| Erdi [19] | Memorial Sloan-Kettering Cancer Center, NY N = 11 | 100% | Increase in PTV in 64% of patients (Average increase of 19% in PTV)<br>Decrease in PTV in 36% of patients (Average decrease of 18% in PTV) |
| Vanuytsel [20] | University Hospital Leuven, Belgium N = 73 | 62% | Average decrease of 29% in PTV<br>Average decrease of 27% in V20 |
| Mah [21] | University of Toronto, Canada N = 30 | Not reported | 23% found to have distant metastasis 17% had increase in PTV<br>Change in PTV was variable according to physician<br>Decrease of 24–70% in PTV<br>Increase of 30–76% in PTV |
| Kalff [22] | Peter MacCallum Cancer Institute, Melbourne, Australia N = 34 | 65% | Treatment volumes increased in 15% and decreased in 21% of patients |

Abbreviations: PTV = Planning Target Volume; V20 = Volume of Lung Receiving at least 20 Gy.

change when the PET information was used. In 17% of cases chemotherapy or RT was added, whereas in 8% chemotherapy or RT was eliminated. A recent study from the Peter MacCallum Cancer Institute showed that patients selected for radical RT had a different prognosis according to type of staging studies performed. Median survival for PET-staged patients was 31 months, while for non-PET patients it was 16 months, reflecting the value of PET in avoiding radical RT for those with distant spread.[13]

The role of FDG-PET fused to CT slices on RT treatment planning for NSCLC is currently under investigation. There have been a few studies, which indicate that the results of FDG-PET may alter target volumes for RT treatment planning. The significance of change in the planning target volume (PTV), clinical target volume (CTV) or the gross tumor volume (GTV) is especially important in the modern era of three-dimensional, conformal RT for lung carcinoma.[14-16] Smaller treatment volumes can be treated with higher doses of radiation because of more sparing normal lung tissue with conformal RT. Table 1 lists some of the studies that have been performed by using PET-CT fusion.[17–22] With information from FDG-PET, these studies indicate that 26 to 100% of patients with NSCLC will have a change in radiotherapy management when compared with CT-based treatment planning alone. Approximately 15 to 64% had an increase in the PTV, whereas 21 to 36% had a decrease in PTV.

V20, the volume of lung tissue receiving at least 20 Gy, has been correlated with the development of pneumonitis.[23,24] Graham et al have previously shown a 0%, 7%, 13% and 36% incidence of ≥Grade 2 pneumonitis for V20 of <22%, 22 to 31%, 32 to 40%,and >40%tg, respectively.[24] Vanuytsel et al noted a 27% reduction in V20 when using PET-CT fusion.[20] Schmuecking et al noted up to a 17% reduction in V20 with the fusion of FDG-PET to the CT scan. Therefore, the use of PET-CT hybrid fusion may be able to spare normal tissue from a dose above the tolerance dose of the lung.[25]

One important application of PET-CT fusion is in the treatment of patients with atelectasis. It is often difficult to differentiate collapsed lung from lung cancer; hence, the appropriate target volume can be problematic when using conformal RT. Nestle et al found that 53% of cases had a change in target volume in tumor next to an atelectatic segment when PET was fused to the CT treatment planning slices.[18] Whether using the PET defined volume in patients with atelectasis is the appropriate way to define the local extent of NSCLC is a subject of controversy.[26] Quality assurance for image fusion, including the appropriate window level for a PET, requires further study. Clinical-pathologic studies related to image fusion would also be a welcome addition to the literature.

Although there is variability in the gross tumor volume according to the contouring radiation oncologist,

it seems that using the PET-CT shows less variability when compared with CT treatment planning alone.[27] A study by Caldwell et al showed a mean ratio of largest to smallest GTV of 2.31 and 1.56 among different observers for CT alone and for PET-CT, respectively. The mean coefficient of variation based on PET-CT was significantly smaller than for CT alone.

SPECT lung perfusion scans provide information in three dimensions regarding the functionality of lung tissue and might be useful in designing radiotherapy fields.[3,28] In a study from Duke University, SPECT-CT fusion was useful in detecting the 48% of patients with hypoperfused regions of the lung. In 11% of patients, the RT field angles were altered to avoid highly functional lung tissue.[29] Using SPECT-CT fusion, Seppenwoolde et al have shown a 6% gain in lung perfusion when compared with geometrically optimized CT plans in patients with one hypoperfused hemithorax.[30] For those with smaller perfusion defects, perfusion-weighted optimization resulted in the same plan as the CT scan geometrically designed plan.

## BRAIN TUMOR

The most studied PET application in oncology has been in the imaging of brain tumors. FDG-PET has the ability to help differentiate between histologically aggressive and less aggressive brain tumors, as well as to separate viable tumor from necrosis after RT.[31] FDG is transported across the blood-brain barrier by the same carrier molecules as glucose, and hence, a disturbance of the blood-brain barrier is not necessary for FDG accumulation in tumor tissue.

Both CT and MRI have been used in RT treatment planning of brain neoplasms. Because of the greater soft tissue contrast of MRI, the tumor volume can often be defined with better accuracy. A study by Thornton et al showed a 1.5-fold increase in the tumor volume when using MRI as opposed to CT.[32] Recently, Gross et al studied 18 patients with malignant gliomas (8 anaplastic astrocytomas, 1 mixed glioma, and 9 glioblastoma) by using MRI with gadolinium diethylene-triamine-pentaacetic acid (DTPA) fused with FDG-PET for RT treatment planning.[33] In 44% and 22% of cases, FDG-PET identified additional tumor volume of $<1$ mL and $>1$ to 5 mL. The median increase of the tumor volume by PET information was 7.3%, which translated to less than 10% of the volume in more than half of the patients. The authors of this study concluded that FDG-PET provided additional significant information only in a minority of patients because of the high intensity of FDG uptake in normal brain tissue. The group from Massachusetts General Hospital arrived at the same conclusion. In a study of eight malignant glioma patients, only two had additional information provided by FDG-PET over MRI.[34] There has recently been some interest in combining the FDG-PET with MRI for gamma knife radiosurgery of recurrent gliomas and metastatic lesions in improving target definition.[35]

Another agent, which has been examined in RT treatment planning using PET, is L-methyl-$^{[11C]}$methionine (MET). MET appears to have more potential in low-grade gliomas where glucose consumption as measured by FDG would be low.[36] Furthermore, MET uptake by the normal brain parenchyma is relatively low.[37] A study of 14 patients with predominantly low-grade gliomas showed that MET-PET was only helpful in outlining the GTV in 27% of cases. The MET-PET based tumor volumes were, in general, smaller than those defined with $T_2$-weighted MRI.[38]

SPECT has also been used to determine functional areas of the brain. Investigators at the University of Chicago have designed RT plans that spare "functional" areas of the brain in the treatment of brain lesions.[39] The silent areas of the brain, however, may not be entirely nonfunctional, and caution is necessary in delivering higher doses of RT to less "functional" areas on SPECT.

Iodine-123-alpha-methyl-L-tyrosine (IMT) is an amino acid, which has been shown to be actively accumulated in brain tumors and not actively accumulated in normal brain parenchyma. IMT uptake in brain tumors can be visualized with SPECT. Grosu et al studied 30 patients with non-resected glioma and found that 23% of cases had IMT tumor uptake 2 cm outside the GTV volume defined by a $T_2$-weighted MRI study.[40] In another study of 66 patients with surgically resected brain gliomas, IMT-SPECT and MRI were performed for RT treatment planning. In 29% of patients, IMT uptake was located outside the MRI postoperative changes, which led to an increase of 20% more tissue in the boost volume.[41] Findings on IMT-SPECT, therefore, may modify target volumes for resected gliomas planned with MRI studies alone.

## HEAD AND NECK CANCER

Numerous investigators have examined FDG-PET in the staging of head and neck cancer. Sensitivity rates of 88% and 81% for primary tumor and nodal metastases, respectively, have been reported.[42,43] Laubenbacher et al reported a sensitivity and specificity of 90% and 96%, respectively, for PET and 78% and 71%, respectively, for MRI in the detection of nodal metastasis.[44] One site where PET-FDG is not recommended at the present time is in the management of parotid neoplasms where clinical examination and/or MRI has a better accuracy.[45]

Limited information is available regarding the role of PET-CT fusion in the radiotherapy treatment planning of head and neck cancers. A study of 21 patients (12 oropharyngeal carcinoma and 9 nasopharyngeal carcinoma) was performed recently at Hokkaido University.[46] PET, MRI, or CT detected none of the three superficial primary tumors. The GTV volumes for primary tumors were not altered by image fusion in 89% of the cases. In

one case the GTV volume was increased by 49%, whereas in another it was decreased by 45%. Thirty-nine positive nodes were detection by PET fusion, whereas only 28 were detected by physical examination and CT/MRI. Parotid sparing became possible in 71% of patients whose upper neck areas near the parotid glands were tumor free when scanned by FDG-PET. The clinical outcome was excellent in these patients with only one recurrence at a median follow-up of 18 months when using the PET fusion defined volumes. A recent study of oropharyngeal carcinomas showed that the GTV volumes determined by PET were usually smaller compared with those obtained from CT or MRI alone.[47]

A technique for PET imaging-based hypoxia measurements using Cu (II)-diacetyl-bis-($N^4$-methylthiosemicarbazone) or Cu-(ATSM) was recently described by Chao et al at Mallinckrodt Institute of Radiology.[48] Cu-diacetyl-bis($N^4$-methylthiosemicarbazone) (ATSM) PET coregistered with CT images could be used for treatment planning to deliver higher doses of radiation to hypoxic regions, which are the more "radioresistant" portions of the target volume. Future studies are needed to examine and verify this novel approach.

An area where PET fusion can potentially improve RT treatment planning is in patients with metastatic cervical nodes with unknown primary. Many radiation oncologists treat these patients to include the nasopharynx, base of tongue, and hypopharynx in the treatment field because of the uncertainty of where the primary tumor is located. Approximately one third of primaries will be identified by using PET imaging.[49,50] The PET-CT fused images may be helpful in sparing more critical normal tissues in the vicinity of the target volume.

## OTHER TUMORS

PET-CT fusion may also be useful in other diseases, such as cervical cancer, lymphoma, and melanoma. The role of fusion in RT treatment planning in these subsites has not been fully explored. For cervical cancer, FDG-PET has been found to be a better imaging modality than CT scan in detecting lymph node metastases.[51] Measurement of tumor volume by FDG-PET has been correlated with eventual outcome.[52] There, therefore, exists a potential for identification of lymph nodes in the pelvis, which may require higher doses of RT if there are found to be PET-avid. For lymphomas, $^{67}$Ga has been shown to be inferior when compared with FDG-PET in detecting low-grade lymphomas.[53] Melanoma is another disease where FDG-PET fusion may have a role in planning, although most of the patients who will receive RT are likely to be palliative.[54]

## CONCLUSIONS

Most of the current information on the role of fusion in RT treatment planning has been in the management of lung cancers, brain tumors, and head and neck neoplasms. Although quality assurance concerns related to image manipulation and fusion remain, functional imaging may have a role in determining target volumes for RT. Biological target volumes may be identified that can then be more aggressively treated compared with functionally silent portions of the clinical target volume. SPECT imaging may also be used to help spare functioning normal tissue from the direct path of RT beams. Longer follow-up is necessary to determine whether better local control and less toxicity are achievable with the use of functional imaging-based techniques.

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