

# PET Imaging During Radiotherapy of Head and Neck Cancer

**T**he worldwide incidence of head and neck cancer is estimated at approximately 643,000 (1). In the United States, approximately 53,640 new head and neck cancers will be diagnosed in 2013, with 11,520 deaths expected (2). The treatment choice for head and neck cancer depends on the primary site and surgical resectability; however, with an increasing effort of preservation of organ function the use of definitive radiation therapy alone or in combination with chemotherapy has been increasing, particularly in oropharyngeal cancers. PET/CT with  $^{18}\text{F}$ -FDG has an established role in initial staging and after completion of radiotherapy to evaluate for the need for salvage surgery. According to guidelines of the National Comprehensive Cancer Network (NCCN), salvage surgery is not necessary

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if the posttherapy  $^{18}\text{F}$ -FDG PET/CT scan result (obtained at least 12 wk after treatment completion) is negative for residual disease and residual nodes are less than 1 cm, whereas surgery is recommended with a positive  $^{18}\text{F}$ -FDG PET/CT scan result and residual nodes larger than 1 cm (3). There are, however, limited data on  $^{18}\text{F}$ -FDG PET in monitoring treatment response to chemoradiation during treatment, which could allow the early identification of nonresponders who may be candidates for adaptive treatment

strategies. Brun et al. imaged 47 head and neck cancer patients with  $^{18}\text{F}$ -FDG PET at baseline and after a median of 24 Gy of radiation therapy and found a significantly higher rate of complete remission and better 5-y overall survival in patients with tumors that showed a lower metabolic rate on the mid-therapy scan (4). In a more recent study, Hentschel et al. imaged 37 head and neck cancer patients, one group after 10, 30, and 50 Gy of radiation and another group after 20, 40, and 60 Gy of a total of 72 Gy (5). Patients with a rapid drop in  $^{18}\text{F}$ -FDG uptake in tumors showed significantly better disease-free survival. Imaging at 10–20 Gy (1–2 wk into radiation therapy) was found to be the best time point for using  $^{18}\text{F}$ -FDG PET to monitor patients during therapy (5). The performance of  $^{18}\text{F}$ -FDG PET was, however, significantly lower in predicting disease-free survival in 2 additional studies when  $^{18}\text{F}$ -FDG PET was performed later, after 40 or 47 Gy of radiation, and images were analyzed only visually for the presence or absence of residual uptake in tumors (6,7). It has also been questioned whether the changes in standardized uptake value (SUV) early after radiation therapy fully reflect the changes in the biology of head and neck cancer. In a preclinical study that used autoradiography and PET imaging 11 d after radiation therapy, the maximum SUV (SUV<sub>max</sub>) remained constant, although the tumor  $^{18}\text{F}$ -FDG accumulation on autoradiography decreased in viable tumor areas (8).

Because both radiation therapy and chemotherapy decrease proliferation rates in responding tumors, imaging the changes in cell proliferation may provide a more accurate evaluation of the treatment effects. Among several radiolabeled nucleoside analogs developed for imaging cell proliferation,

3'-deoxy-3'- $^{18}\text{F}$ -fluorothymidine ( $^{18}\text{F}$ -FLT), a thymidine analog that is not incorporated into DNA, is most widely studied. The intracellular trapping of  $^{18}\text{F}$ -FLT is a function of the enzymatic activity of thymidine kinase 1, a key enzyme in DNA synthesis with high activity during the proliferative S phase of the cell cycle and low activity in the quiescent G0/G1 phase (9). Untreated head and neck squamous cell cancers are readily detectable with  $^{18}\text{F}$ -FLT PET, with high tumor-to-background ratios, although the SUV with  $^{18}\text{F}$ -FLT tends to be generally lower than with  $^{18}\text{F}$ -FDG (10–14). Comparison studies of  $^{18}\text{F}$ -FLT and  $^{18}\text{F}$ -FDG by Hoshikawa et al. showed similar detectability and false-positive rates in primary tumors and cervical nodal metastases for  $^{18}\text{F}$ -FLT and  $^{18}\text{F}$ -FDG (11,12). The pretherapy staging of head and neck cancer with  $^{18}\text{F}$ -FLT PET appears limited by the nontumoral uptake in reactive cervical nodes due to proliferation of reactive B-lymphocytes (15).

Previous studies have shown a significant drop in  $^{18}\text{F}$ -FLT uptake in squamous cell head and neck cancer early after initiation of radiotherapy (14,16). However, the correlation between the change in  $^{18}\text{F}$ -FLT uptake in head and neck cancer and disease-free survival was only recently reported in 2 studies published in *The Journal of Nuclear Medicine* (6,17). Hoeben et al. imaged 48 patients with stage III or IV head and neck cancer at 3 time points, first at baseline (pretherapy), after 5–12 daily fractions of radiotherapy (corresponding to 10–24 Gy), and in a subgroup of 29 patients also after 15–19 daily fractions (corresponding to 30–38 Gy) (17). Although 98% of patients had complete clinical response at the end of treatment, the 3-y disease-free survival was only 79%. There was a significantly better disease-free survival in patients who showed a 45% or more

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drop in SUVmax (and  $\geq 41\%$  on gross tumor volume delineated with  $^{18}\text{F}$ -FLT) on the early mid-therapy scan. However, the change in SUVmax between the baseline and late mid-therapy scan was not predictive of treatment outcome. Patients undergoing radiotherapy alone had a better outcome if the baseline SUVmax in the primary tumor was lower ( $\leq 6.6$ ), whereas in the combined chemoradiation therapy group a higher baseline SUV tended to correlate with better outcome, possibly reflecting the better efficacy of chemotherapy in tumor tissue with a higher rate of cellular proliferation. The other recent study on the utility of  $^{18}\text{F}$ -FLT PET during radiation therapy was reported by Kishino et al. in the October 2012 issue of *The Journal of Nuclear Medicine* (6). Different from the study by Hoebe et al., the follow-up  $^{18}\text{F}$ -FLT PET scans in the study by Kishino et al. (6) were obtained at a later time point during treatment (median of 40 Gy of radiotherapy). The image analysis also differed in the study by Kishino et al., which dichotomized the results as positive or negative based on visual assessment of residual uptake rather than the change in SUV. This study found that during radiotherapy  $^{18}\text{F}$ -FLT uptake in the tumor disappeared faster than  $^{18}\text{F}$ -FDG; however, the residual  $^{18}\text{F}$ -FLT uptake after 40 Gy of therapy still only showed a positive predictive value of 35% (17% for  $^{18}\text{F}$ -FDG). The negative predictive value of absence of uptake was similar for  $^{18}\text{F}$ -FLT and  $^{18}\text{F}$ -FDG (97% and 100%, respectively), although many more lesions showed visual disappearance of  $^{18}\text{F}$ -FLT accumulation at 40 Gy. The presence of residual  $^{18}\text{F}$ -FLT or  $^{18}\text{F}$ -FDG uptake after 40 Gy of radiation did not correlate with local control of disease over a median follow-up of 39 mo.

Several preliminary conclusions can be drawn from these studies. (1) Head and neck cancer treatment monitoring during radiotherapy with PET, either with  $^{18}\text{F}$ -FDG or  $^{18}\text{F}$ -FLT, is more effective if done earlier during therapy rather than later, probably at around 20 Gy ( $\sim 2$  wk with the conventional fractionation of 2 Gy/d). This may be at least partly explained by the inability

of PET scans obtained later during the course of therapy to identify microscopic residual disease that is ultimately responsible for tumor recurrence. As shown by Kasamon et al. in lymphoma, the late PET scan may not be able to differentiate the tumors with the higher rate of cell kill from tumors with slower cell kill (18), leading to a false-negative late PET scan because microscopic residual disease will be below the detectability of the PET imaging system. In early responding tumors on the other hand, the rapid cell kill will lead to a rapid and significant drop in uptake of  $^{18}\text{F}$ -FLT and  $^{18}\text{F}$ -FDG early after initiation of radiotherapy. Another potential issue is the development of postradiation inflammatory changes, which will become more profound later in the therapy and may confound the interpretation of PET images. (2) Accurate quantitation of uptake in addition to visual assessment appears to improve the predictive value of PET in monitoring response to radiation therapy in head and neck cancer. This requires careful standardization of PET acquisition and image analysis for larger multicenter studies that can validate the utility of PET in monitoring response to radiation therapy in head and neck cancers. (3) Comparison data of  $^{18}\text{F}$ -FLT and  $^{18}\text{F}$ -FDG PET imaging during radiotherapy of head and neck cancer is limited. Compared with  $^{18}\text{F}$ -FDG, the more rapid change in  $^{18}\text{F}$ -FLT uptake during therapy may suggest that  $^{18}\text{F}$ -FLT better reflects the change in tumor biology with radiation; however, outcome data demonstrating the superiority of  $^{18}\text{F}$ -FLT to  $^{18}\text{F}$ -FDG in this setting are still lacking. It may be prudent to incorporate  $^{18}\text{F}$ -FDG PET in future clinical trials evaluating the utility of  $^{18}\text{F}$ -FLT PET during radiotherapy to monitor treatment response in head and neck cancers.

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