# Standardized Uptake Value of 2-[$^{18}$F] Fluoro-2-Deoxy-D-Glucose in Predicting Outcome in Head and Neck Carcinomas Treated by Radiotherapy With or Without Chemotherapy

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***Purpose:*** **In patients with head and neck cancer enrolled onto a prospective study of positron emission tomography (PET), pretreatment 2-[$^{18}$F] fluoro-2-deoxy-D-glucose (FDG) uptake was evaluated as a predictor of local control and disease-free survival (DFS) after treatment by radiotherapy (RT) with or without chemotherapy.**

***Patients and Methods:*** **We studied 63 patients with carcinomas of the head and neck who had an FDG-PET scan before radical RT. Tumor FDG uptake was measured with the semiquantitative standardized uptake value (SUV). All patients but one were treated with accelerated or hyperfractionated RT schedules. Thirteen patients received concomitant cisplatin-based chemotherapy.**

***Results:*** **In 25 patients who presented with any component of treatment failure, the SUV was significantly higher than in the remaining patients without any such failure. Patients having tumors with high FDG uptake had a significantly lower 3-year local control (55% *v* 86%, *P* = .01) and DFS (42% *v* 79%, *P* = .005) compared with patients having low uptake tumors. In the multivariate analysis, the only factor that retained its significance for DFS was SUV category, whereas T category was of borderline significance. For local control, T category remained a significant factor, whereas a lower local control was observed for tumors with a high SUV compared with those with low SUV.**

***Conclusion:*** **FDG uptake, as measured by the SUV, has potential value in predicting local control and DFS in head and neck carcinomas treated by RT. High FDG uptake may be a useful parameter for identifying patients requiring more aggressive treatment approaches.**

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AS IS THE CASE FOR many cancers, indicators of patient outcome in carcinomas of the head and neck have traditionally been derived from clinical and pathologic features. These essentially include tumor size and stage, extent of lymph node involvement, and anatomic subsite.[1,2] However, despite careful evaluation of these factors, it is not possible to predict reliably the outcome of treatment in individual patients. Head and neck carcinomas are predominantly a locoregional disease, in which the success of treatment depends essentially on obtaining local and regional control. Therefore, identification of additional prognostic factors for local/regional control, particularly biologic parameters, may allow the development of individualized strategies that lead to improved results. In particular, there has been recent intense interest in tumor proliferation and its relation to local control and overall outcome.[3,4]

Tumor uptake of 2-[$^{18}$F] fluoro-2-deoxy-D-glucose (FDG), as measured by positron emission tomography (PET), has been associated with various cellular characteristics, such as cell viability[5] and proliferative activity.[6,7] Moreover, recent clinical studies of lung and breast cancers suggest that FDG uptake may have prognostic significance, in that patients with high FDG uptake had a less favorable outcome.[8,9] However, for head and neck carcinomas, the small series available in the literature are of limited usefulness regarding the question of the prognostic value of FDG uptake.[10,11] Taking advantage of an ongoing prospective study of PET scanning in head and neck cancers, this analysis was undertaken to evaluate the potential role of the standardized uptake value (SUV), a semiquantitative measurement of tumor FDG uptake, in predicting local control and disease-free survival (DFS) in patients treated by radical radiotherapy (RT), with or without chemotherapy.

## PATIENTS AND METHODS

### *Patients*

From January 1997, patients presenting with a high degree of suspicion of head and neck cancer were asked to participate in a prospective study aiming at optimizing diagnostic evaluation and posttreatment follow-up.[12] In addition to physical examination and pretreatment panendoscopy, the protocol required that magnetic reso-

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**Table 1. Patient Characteristics**

| Characteristic | | No. of Patients (N = 63) |
|---|---|---|
| Age, years | | |
| Median | 57 | |
| Range | 35-82 | |
| Sex, male/female | | 51/12 |
| Tumor location | | |
| Oral cavity | | 6 |
| Oropharynx | | 35 |
| Hypopharynx | | 8 |
| Larynx | | 14 |
| TNM classification, UICC 1997 | | |
| T1-2 | | 22 |
| T3-4 | | 41 |
| N0 | | 29 |
| N1-N3 | | 34 |
| TNM stage, UICC 1997 | | |
| II-III | | 27 |
| IV | | 36 |

Abbreviations: UICC, International Union Against Cancer; TNM, tumor, node, metastasis.

nance imaging (MRI) and FDG-PET scanning be performed before therapy and during the third, 12th, and 24th months after completion of RT. A standard head and neck examination was also planned at intervals of 1, 2, 3, and 6 months for the first, second, third, and fourth posttreatment year and then yearly. Excluded from the study were patients with other than squamous cell carcinomas, those with second primary tumors or small tumors with a high probability of local control (T1 cancers of the larynx or lip), and those with metastatic disease. All tumors were staged according to the 1997 International Union Against Cancer tumor-node-metastasis staging system.[13] Staging took into account all information provided by the different examinations, including PET scan. Patient characteristics (age, sex, tumor-node-metastasis stage, tumor location, and histology) and the results of MRI and PET-FDG scans were recorded prospectively in a dedicated database. The study was approved by a local ethics committee, and patients satisfying the inclusion criteria were enrolled after signed informed consent was obtained. Treatment consisted of either radical surgery with or without postoperative RT or radical RT with or without chemotherapy, as decided by the head and neck tumor board. Persistent or recurrent tumor was documented by at least two different examinations (MRI, PET scanning, or endoscopy). Whereas locoregional treatment failures were generally histologically confirmed, distant metastases were not.

This analysis included all patients enrolled onto the prospective study in whom radical RT was the principal local treatment and was delivered with curative intent. Patients having had major surgery to the primary tumor area were excluded, whereas patients having only neck dissection were included. With the 65 patients identified, two patients died within 3 months of therapy with unknown disease status and were consequently excluded. The characteristics of the remaining 63 patients are listed in Table 1.

### *Treatment*

In accordance with local treatment policy, four patients had radical (n = 3) or selective (n = 1) neck dissection before RT, generally for bulky neck disease. Surgery was otherwise reserved for treatment of recurrent disease. RT was started after a median interval of 5 weeks (range, 1 to 14 weeks) after PET scanning. Forty-eight patients were treated with a modified concomitant-boost accelerated RT schedule that has been previously reported.[14] Briefly, 69.9 Gy were to be delivered in 41 fractions over 38 days to clinically involved sites, whereas areas of potential microscopic involvement received 50.4 Gy in 28 fractions. Fourteen patients enrolled onto a Swiss prospective trial received hyperfractionated RT to a total dose of 74.4 Gy in 62 fractions over 44 days, including 50.4 Gy to a large volume and a 24-Gy boost. For logistic reasons one patient received monofractionated RT to a total dose of 70 Gy. The median tumor dose for all patients was 69.9 Gy (range, 69.9 to 74.4 Gy). All patients were treated with 6-MV photon beams. RT was completed to the planned dose in all patients, although acute toxicity required a temporary interruption in one patient.

Thirteen patients received concomitant chemotherapy. Chemotherapy was given to patients with stage III or IV disease who accepted this therapy and were fit enough to receive it, including those who were randomized in the chemoradiation arm of the Swiss trial. Accordingly, five patients enrolled onto the Swiss trial received cisplatin 20 mg/m$^2$ on each of 5 consecutive days (two cycles in four patients and one cycle in one patient). The remaining eight patients received two cycles of cisplatin (100 mg/m$^2$ given as a rapid intravenous infusion) followed by a continuous 96-hour intravenous infusion of fluorouracil (1,000 mg/m$^2$/d), usually during the first and fourth weeks. Three patients received one additional cycle of the same chemotherapy (one before and two after RT). During RT, the dose of fluorouracil was reduced by 20% to 40% in the second course, according to the severity of the acute mucosal reactions.

### *FDG-PET*

FDG-PET was performed with an ECAT ART (Siemens/CTI, Knoxville, TN) PET tomograph (axial field of view of 16.2 cm and resolution of 6 mm). All patients had plasma glucose checked before FDG injection, and none of them was diabetic. After a fast of 4 hours, intravenous injection of 185 MBq (5 mCi) of [$^{18}$F]fluorodeoxyglucose for 70 kg body weight was performed, and PET images were obtained 90 minutes later. The acquisition time was 16 minutes per bed position (40% transmission and 60% emission). Standard static multibed acquisition was performed, and data were stored in a single frame. The ECAT ART is a three-dimensional–only PET scanner; however, whole-body PET studies are acquired in three dimensions and rebinned online in two-dimensional mode by using the single-slice rebinning algorithm. Preinjection transmission scanning was performed with germanium-68 rod sources up to May 1999. The scanner was then upgraded to include cesium-137 single-photon sources, and scanning was performed in interleaving mode (eg, ETTEET). The standard measured attenuation correction method (with cesium-137 single-photon sources) was applied, in which the attenuation correction matrix is calculated by forward projection at appropriate angles of the resulting transmission image. The generated attenuation correction map is then used to reconstruct the emission data. The images were scatter-corrected and reconstructed by using normalized attenuation-weighted, ordered subset-expectation maximization iterative reconstruction implemented within the ECAT 7.2 software. The default parameters used in clinical routine are ordered subset-expectation maximization iterative reconstruction with two iterations and eight subsets followed by a postprocessing Gaussian filter (kernel full-width half-maximal height, 6.0 mm). The voxel size was set to 3.4 × 3.4 × 3.4 mm$^3$. The PET images were interpreted prospectively by two experienced nuclear medicine radiologists (M.A. and D.O.S.) who were

blinded to clinical and MRI findings. Interpretation of the images focused on the search for all sites of apparent increased tracer uptake in the head and neck area, as well as in the thoracic field. The degree of suspicion for malignant involvement was based on the qualitative visual interpretation of the images and the determination of the SUV, a semi-quantitative measurement of relative FDG uptake within the regions of interest (ROIs). ROIs were defined over the whole tumor volumes as displayed on the different slices. The SUV depends on the amount of injected radioactivity, the patient's weight, and the calibration factor of the camera, and it is calculated according to the following formula:

SUV = radioactivity concentration in tissue/

(Bq/g/(injected dose [Bq]/patient weight [g]).

To calculate the SUV, images were reviewed, and the slice containing the tumor was selected. Three bed positions were generally acquired. To minimize partial volume effects, the maximal SUV within the ROIs was used for further calculations. For this study, correlation with both local control and survival was based on the maximum SUV of the primary tumor, except in one patient with a T1N3 tumor, in whom only the adenopathy demonstrated increased uptake. In this case, the SUV of the lymph node was used as reference for correlation with DFS and overall survival.

### *Statistics*

Actuarial local control, DFS, and overall survival rates were calculated by the Kaplan-Meier method. Tumor persistence or recurrence at the initial primary tumor location were considered as events in determining local control rate, whereas the DFS rate additionally took into account nodal recurrences as well as distant metastases. The time interval for the above-mentioned end points was calculated from the first day of RT until the date of an event or of the last follow-up. The log-rank test was used to assess the correlation of these end points with the SUV and with the other clinical (age, T category, N category, tumor-node-metastasis stage) and therapeutic (addition of chemotherapy) variables. The confidence intervals (CIs) for survival rates were calculated by using Greenwood's formula for the SEs. The multivariate analysis was performed with the Cox proportional hazards model. Variables shown to be significant in the univariate analysis (excepted linked variables) or judged to be of obvious importance were selected for the Cox model. The Mann-Whitney *U* test was used to compare the SUV median values in different subgroups. A difference with $P < .05$ was considered significant.

## RESULTS

### *Overall Results*

At last follow-up, 38 patients were alive and 25 had died (18 from head and neck cancer, four from second cancers, one from complications of treatment, and two from intercurrent disease). The median follow-up for surviving patients was 36 months (range, 12 to 51 months). Eighteen patients presented with persistent or recurrent local or regional disease (cervical nodes) and seven with distant metastases. At 3 years, actuarial local control was 71% (95% CI, 59% to 83%), DFS was 59% (95% CI, 46% to 72%), and overall survival was 60% (95% CI, 48% to 73%).

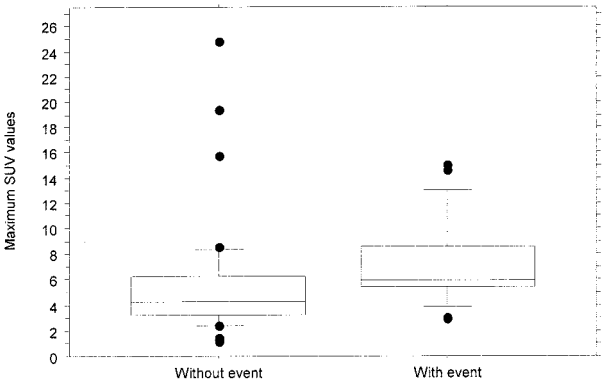


**Fig 1. Standardized uptake value (SUV) distribution according to patient disease status.**

### *Univariate Analysis*

The median value of the SUV for all patients was 5.5 (range, 1 to 24.8). In the 25 patients who presented with any component of treatment failure, the median SUV was significantly higher than the corresponding value in the remaining patients without any such failure (5.9 *v* 4.25; $P = .005$). Figure 1 displays SUV values according to patient disease status (with or without an event) at last follow-up. In the absence of an established cutoff for the SUV, the median value was used to establish two groups, one with a high ($>$ 5.5) and the other with a low ($\leq$ 5.5) SUV. In univariate analysis, patients with a high SUV had a significantly lower 3-year local control (55% *v* 86%; $P = .01$; Fig 2) and DFS

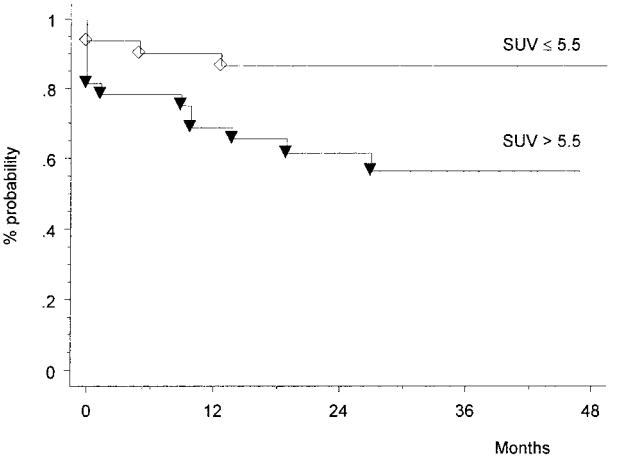


**Fig 2. Actuarial local control according to the standardized uptake value (SUV) of 2-[$^{18}$F] fluoro-2-deoxy-D-glucose.**

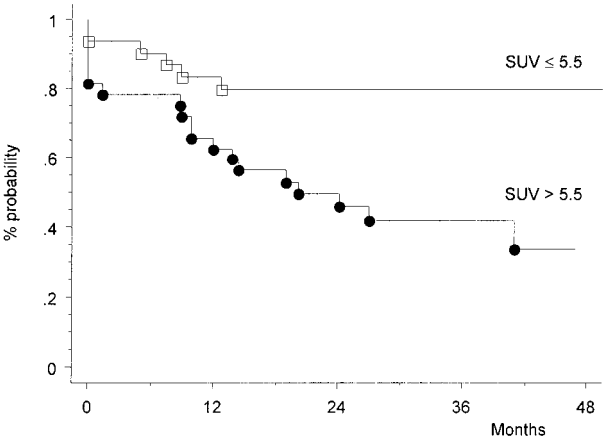


**Fig 3. Actuarial disease-free survival according to the standardized uptake value (SUV) of 2-[$^{18}$F] fluoro-2-deoxy-D-glucose.**

(42% *v* 79%; $P = .005$; Fig 3). Overall survival was also lower in the group with high SUV, but the difference was not significant (53% *v* 69%; $P = .15$). The results of the univariate analysis for local control and DFS using different clinical and therapeutic variables are given in Table 2. Besides the high SUV category, only advanced T category (T3 to T4) was found to be an adverse factor significantly influencing both local control and DFS, whereas tumor-node-metastasis stage influenced only DFS.

*Multivariate Analysis*

Factors significantly influencing local control, DFS, or both in univariate analysis were included in the Cox models. In addition, treatment strategy (with or without chemotherapy) and N category were included because of their high potential effect on these end points. For local control, only T category remained a significant adverse factor (relative risk [RR] = 0.12; $P = .04$), whereas a lower local control was observed for tumors with a high SUV compared with those with low SUV (RR = 0.41; $P = .13$). For DFS, the only factor that retained its significance was SUV category (RR = 0.37; $P = .038$), whereas T category was of borderline significance (RR = 0.42; $P = .097$). The RRs associated with these factors are listed in Table 3.

*Correlation Between SUV and Clinical Parameters*

Correlations of the SUV with clinical prognostic factors were evaluated to assess for potential linkage. T1-T2 tumors had a lower median SUV compared with T3-T4 tumors (4.1 *v* 5.9; $P = .02$). No significant difference in the median SUV was noted between cases without clinical adenopathy compared with N1 to N3 cases (4 *v* 5.5; $P = .17$). The median SUV was 4 and 5.7 in tumor-node-metastasis stage II or III and IV, respectively ($P = .012$). According to tumor location, the median SUV was 5.5 for the oral cavity, 5.7 for the oropharynx, 5.4 for the hypopharynx, and 3.9 for the larynx, with no significant differences between groups.

*Subgroup Analysis*

Taking into account the possible linkage of the SUV with the T category, essentially reflecting tumor volume, we studied the effect of the SUV in T1-T2 and T3-T4 tumors separately. For the T1-T2 tumor patients, DFS was significantly lower in the group with higher SUV (93% *v* 57%; $P = .02$). For T3-T4 tumor patients, although the group with high SUV had a lower DFS, the difference was not significant (67% *v* 38%; $P = .13$). A similar observation pertained to local control; in T1-T2 tumors, the one patient whose treatment failed locally was in the high SUV group, whereas for T3-T4 tumors, local control was 73% and 49% in patients with SUV below and above the median, respectively ($P = .17$).

## DISCUSSION

Identification of factors predictive of outcome in cancer patients treated with RT and chemotherapy is of great potential interest, because such research may allow therapy to be tailored to the characteristics of individual tumors. Despite a careful evaluation of established prognostic factors in head and neck cancer patients, it is currently

**Table 2. Univariate Analysis of Clinical and Therapeutic Factors**

| Variable | No. of Patients | % 3-Year Local Control | *P* | % 3-Year DFS | *P* |
|---|---|---|---|---|---|
| Age < 57/≥ 57 years | 33/30 | 70/72 | .91 | 63/55 | .4 |
| Sex, male/female | 51/12 | 72/67 | .61 | 59/58 | .96 |
| T category (UICC 1997), T1-2/T3-4 | 22/41 | 94/59 | .004 | 79/49 | .03 |
| N category, N0/N1-3 | 29/34 | 78/63 | .30 | 68/50 | .25 |
| TNM stage (UICC 1997), stage II-III/IV | 27/36 | 85/70 | .27 | 81/53 | .13 |
| SUV category, ≤ 5.5/> 5.5 | 31/32 | 86/55 | .01 | 79/42 | .005 |
| Chemotherapy, no/yes | 50/13 | 67/84 | .30 | 55/77 | .18 |

Abbreviations: DFS, disease-free survival; UICC, International Union Against Cancer; SUV, standardized uptake value; TNM, tumor, node, metastasis.

**Table 3. Cox Proportional Hazards Models for Local Control and DFS**

| Variable | Local Control | | | DFS | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | *P* | RR | 95% CI | *P* |
| T category (UICC 1997), T1-2/T3-4 | 0.12 | 0.01-0.95 | .04 | 0.42 | 0.15-1.17 | .097 |
| N category, N0/N1-3 | 0.74 | 0.27-2.04 | .57 | 0.76 | 0.33-1.75 | .52 |
| SUV category, ≤ 5.5/> 5.5 | 0.41 | 0.13-1.31 | .13 | 0.37 | 0.14-0.95 | .04 |
| Chemotherapy, yes/no | 0.42 | 0.09-1.85 | .25 | 0.41 | 0.12-1.38 | .15 |

Abbreviations: DFS, disease-free survival; UICC, International Union Against Cancer; SUV, standardized uptake value; CI, confidence interval.

impossible to predict reliably the outcome of treatment, even in patients within the same TN category.[15] The established heterogeneous response to RT, chemotherapy, or both is thought to be due to a complex interaction of biologic characteristics that are responsible for tumor development, growth, and invasiveness.[16] Altered glucose metabolism is one of the molecular derangements found in all stages of carcinogenesis; increased glycolysis has been observed and correlated with increased expression of the *Glut* family of glucose transporter genes.[17] Furthermore, increased expression of *Glut1* and *Glut3* was reported to be an indicator of poor prognosis in non–small-cell lung carcinomas.[18] It is thus plausible that measurement of parameters relating to glucose transport within tumor cells may be of potential value in predicting response to cancer treatment. A semiquantitative notion of tumor glucose consumption can be obtained noninvasively by FDG-PET scanning through determination of the SUV, a parameter that purports to measure tumoral FDG uptake relative to that in nontumor tissues. Recent data suggest that FDG uptake may have prognostic value in some human tumors, including lung and breast cancer, because patients with high FDG uptake were observed to have a worse outcome.[8,9] FDG uptake was also found to correlate with tumor response to chemotherapy in breast cancers.[19]

The potential value of FDG uptake in predicting outcome in head and neck cancers after nonsurgical therapy has been suggested in small series.[10,11] In 17 patients, Brun et al[10] reported that an initially low rate of glucose metabolism correlated with complete local clinical response at 5 to 6 weeks after 60- to 66-Gy hyperfractionated RT, with or without induction chemotherapy (cisplatin and fluorouracil). A similar observation was also reported by Kitagawa et al[11] in 15 patients treated with intra-arterial chemotherapy (doxorubicin, fluorouracil, and carboplatin) and concomitant monofractionated RT (30 to 40 Gy); higher pretreatment SUV correlated with more residual viable tumor cells documented histologically 4 weeks after treatment. No long-term results were provided in the last two series. In this prospective study, univariate analysis found that, beside advanced T category (T3-T4), a high tumor SUV (above the median) had a significantly negative effect on the 3-year local control and DFS. In the multivariate analysis, T category was again found to correlate significantly with local control, whereas the SUV category retained its significance regarding DFS, with an RR of 2.7 associated with high SUV (> 5.5). However, concerning local control, the RR of 2.4 associated with high SUV was not statistically significant. Although this represents the largest study addressing the relation of FDG uptake to prognosis in head and neck cancers, the small number of events may limit the interpretation of this multivariate analysis. Nonetheless, it seems plausible that FDG uptake may prove to be an independent predictive factor, because in patients presenting with any component of treatment failure, the SUV was significantly higher than that observed in patients whose treatment had not failed, suggesting that FDG uptake may be of value in predicting overall outcome. Subgroup analysis revealed that the contribution of the SUV to identifying potentially poor responders may be useful in patients with advanced primary tumors as well as in patients with early disease. In our series, the difference in DFS did not translate into a significant difference in overall survival. Patients with head and neck cancers often die of second neoplasms and intercurrent disease, making overall survival a relatively insensitive end point. Nevertheless, in a univariate analysis of 37 patients, Minn et al[20] reported a significantly lower overall survival in patients with high pretreatment FDG uptake treated with surgery, RT, or both.

FDP-PET remains an area of active research in oncology, and certain points need further clarification in subsequent studies. There is currently no consensus on the optimal methodology for the measurement of FDG uptake.[21] Regarding the SUV in particular, no diagnostic threshold has been clearly established for distinguishing uptake in malignant from that in benign tissues, and in cancer cases, no cutoff has been established for defining subgroups of differing prognoses. In the absence of an established cutoff, we chose to use the median SUV (5.5) as the basis for analysis. However, it should be emphasized that the value of 5.5 should not be considered necessarily to have any particular clinical significance. Considering the possible site

dependence of such a cutoff, additional prospective studies need to be designed and performed to establish reliable values. Regarding the prognostic value of FDG-PET, the main question concerns the possible linkage between FDG uptake intensity and the other known prognostic indicators, such as tumor extent. Minn et al[20] reported a significant association between high SUV and advanced stage in head and neck cancers. Nonetheless, current evidence suggests that intensity of FDG uptake correlates less clearly with tumor burden than it does with biologic aggressiveness. In this regard, FDG uptake has been found to be associated with cell viability[5] and particularly with cell proliferative activity.[6,7] Moreover, FDG uptake has been reported to correlate with some known radioresponsiveness factors. Thus, Clavo et al[22] demonstrated that FDG uptake is increased by hypoxia in tumor cell lines, and Furuta et al[23] reported in an animal model that a radiosensitive tumor xenograft (which exhibits the highest radiation-induced apoptosis) had a significantly lower FDG uptake compared with that of a radioresistant tumor type. Furthermore, a significant association between high FDG SUV and p53 overexpression was reported in breast cancer.[24] It remains to be determined by further research whether or not FDG uptake reliably reflects the expression of various biologic markers of tumor aggressiveness. If this notion should be confirmed, FDG-PET may come to represent a rapid, noninvasive tool for prediction of tumor response and patient outcome, allowing oncologists to better individualize therapy according to a patient's particular tumor.

In conclusion, as with other tumor locations where simple measurement of FDG SUV was found to be a predictor of patient outcome, this study provides evidence regarding the potential value of the FDG uptake, as measured by the SUV, in predicting local control and DFS in head and neck carcinomas treated by RT. If these results are confirmed by subsequent research, patients whose tumors indicate high FDG uptake should be considered for more aggressive treatment.

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