Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 5, pp. 1295–1300, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.12.039

CLINICAL INVESTIGATION **Head and Neck**

PREDICTION OF OUTCOME IN HEAD-AND-NECK CANCER PATIENTS USING THE STANDARDIZED UPTAKE VALUE OF 2-[^{18}F]FLUORO-2-DEOXY-D-GLUCOSE

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Purpose: Tumor uptake of 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) may relate to outcome in cancer patients. Pretreatment FDG uptake was evaluated as a predictor of local control (LC) and disease-free survival (DFS) in patients with head-and-neck cancer managed primarily either by radiotherapy (RT) or surgery.

Patients and Methods: Tumor FDG uptake using the Standardized Uptake Value (SUV) was measured in 120 patients studied prospectively using positron emission tomography (PET). Treatment consisted of either radical RT with or without chemotherapy (73 patients) or radical surgery with or without postoperative RT (47 patients). Median follow-up of the surviving patients was 48 months.

Results: The median SUV was higher in 46 patients who failed treatment than in the remaining controlled patients (5.8 vs. 3.6, $p = 0.002$). In monovariate analysis, patients with tumors having high FDG uptake (SUV > median, 4.76) had poorer LC ($p = 0.003$) and DFS ($p = 0.005$). This difference was also observed when the RT and surgery groups were analyzed separately. In the multivariate analysis T-category ($p = 0.005$) and SUV ($p = 0.046$) remained independent adverse factors for LC, whereas N-category ($p = 0.004$), T-category ($p = 0.02$) and SUV ($p = 0.05$) were independent determinants of DFS.

Conclusion: These results suggest that pretreatment tumor FDG uptake represents an independent prognostic factor in patients with head-and-neck cancers, whatever the primary treatment modality. Tumors having high FDG uptake are at greater risk of failure and should be considered for more aggressive multimodality therapy.

FDG-PET, Head-and-neck cancer, Predictive factor.

INTRODUCTION

According to tumor stage, the treatment of head-and-neck carcinoma is based upon radical radiotherapy (RT) or surgery or both, with or without chemotherapy. While locoregional disease control can be achieved in most patients, failure above the clavicles occurs in as many as 30%–40% of cases (1, 2). Locally recurrent tumors not only threaten patients' survival but also seriously impair their quality of life, as many such patients will die with symptomatic local tumor progression. Moreover, patients with advanced disease are submitted to intensive treatment combinations, and those who are destined to relapse suffer from severe acute toxicity with little benefit (3). Despite careful evaluation of the traditional clinical factors such as tumor size/stage, lymph node involvement, and anatomic subsite, it is impossible to reliably predict the outcome after a selected treatment (4). Identification of novel pretreatment factors that potentially predict outcome is thus of great interest. Patients whose prognoses are likely to be unfavorable with current approaches might be selected for alternative strategies, either by moving away from single-modality therapy to multidisciplinary approaches, by intensifying radiochemotherapy schedules, or by adding innovative biologic agents.

There is increasing current interest in the metabolic imaging of cancers, particularly that based upon tumor uptake of 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) as measured by positron emission tomography (PET). This noninvasive imaging technique has been applied to the staging and follow-up of patients with head-and-neck carcinomas as well as other tumor types (5, 6). Furthermore, it has been suggested that tumor FDG uptake may have prognostic significance, in that patients with high FDG uptake generally have

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This work was supported by the Swiss National Science Foundation (Grant no. 31–45955.95).

Acknowledgments—The authors thank Professor John M. Kurtz, Division of Radiation Oncology, University Hospital, Geneva, Switzerland, for reviewing the manuscript.

Received Aug 20, 2003, and in revised form Dec 8, 2003. Accepted for publication Dec 10, 2003.

a less favorable outcome (7–9). However, most clinical reports have been based on limited series of patients selected for treatment either with predominantly surgical (7, 8) or nonsurgical (10) approaches. As a consequence it is unknown whether the predictive value of FDG uptake pertains to the response to specific therapies, or rather might reflect the biologic aggressiveness of the disease, independently of the chosen modality. The present study was undertaken to assess the prognostic value of the FDG uptake in unselected series of patients who took part in a prospective study of PET scanning in head-and-neck cancers whatever the treatment they received. The standardized uptake value (SUV), a semiquantitative measurement of tumor FDG uptake, was correlated with local control (LC) and disease free-survival (DFS).

PATIENTS AND METHODS

Patients

Patients enrolled in a prospective PET scanning study (11), aiming at optimizing diagnostic evaluation and post-treatment follow-up, form the basis of this analysis. Patient selection and study design were previously described (10). Briefly, participation was solicited of all patients presenting with a suspicious lesion of the head-and-neck region. The study was approved by a Geneva University Hospital ethics committee, and patients were enrolled after signed informed consent was obtained. In addition to routine pretreatment physical examination and panendoscopy, all study patients received magnetic resonance imaging and FDG-PET scanning, both before and at fixed intervals after therapy. Excluded were cancers other than squamous-cell carcinomas, second primary tumors, small lesions of the vocal cord or lip, and patients presenting with distant metastatic disease. All tumors were staged according to the 1997 Union Internationale Contre le Cancer (UICC) TNM staging system (12). Patient characteristics as well as the results of diagnostic studies were recorded prospectively in a dedicated database. Between January 1997 and December 2000, 123 patients were enrolled. Treatment was decided by the multidisciplinary head-and-neck tumor board. As the main study goal was diagnostic, intensity of FDG-PET uptake did not influence the choice of treatment modality. One patient who refused the proposed treatment and 2 patients who died within 3 months after therapy with unknown disease status were excluded, leaving 120 patients eligible for the present analysis. Patient characteristics are displayed in Table 1.

Table 1. Patient characteristics

Characteristics	RT group, $n = 73$	Surgery group, $n = 47$	Total, $n = 120$
Median age, years (range)	58.5 (35–82)	56 (36–81)	57.5 (35–82)
Sex: male/female	59/14	38/9	97/23
Tumor location			
Oral cavity	6	26	32
Oropharynx	39	7	46
Hypopharynx	11	2	13
Larynx	17	9	26
Unknown primary	0	3	3
TNM classification (UICC 1997)			
T0–2	26	30	56
T3–4	47	17	64
N0	32	22	54
N1–N3	41	25	66
TNM stage (UICC 1997)			
I–II	12	16	28
III–IV	61	31	92

Abbreviations: RT = radiation therapy; UICC = International Union Against Cancer.

Treatment

Treatment consisted of either radical RT with or without chemotherapy (RT group, 73 patients) or radical surgery with or without postoperative RT (surgery group, 47 patients). All patients in the RT group received radical locoregional RT using 6 MV photon beams, without surgery to the primary lesion. Before RT 6 patients had neck dissections for bulky neck disease, and because the SUV values used concerned mainly those of the primary tumor uptake (5 on 6 patients), those patients were classified in the RT group. Fifty-seven patients were treated with a modified concomitant-boost accelerated RT schedule that has been previously reported (13). The remainder received other hyperfractionated ($n = 14$) or monofractionated schedules ($n = 2$). The median tumor dose for all patients was 69.9 Gy (range 69.8–74.4). Nineteen patients received concomitant chemotherapy, generally with two cycles of cisplatin, with or without a continuous infusion of 5-fluorouracil.

In the 47 patients in the surgery group, various surgical approaches were used according to tumor location and extension. Local or single subsite excisions was undertaken in 35 patients and multiple subsites or organ excisions in 9. Forty-one patients (including the 3 patients with unknown primary tumors) had radical ($n = 10$), modified radical ($n = 30$), or selective ($n = 1$) neck dissections, bilateral in 18 patients. Thirty-one patients received postoperative locoregional RT (median dose, 66.4 Gy; range, 31.5–69.9 Gy), using single daily fractions in all but 2 patients.

FDG-positron emission tomography

The technique has been described previously in detail (10). In short, FDG-PET was performed using an ECAT ART (Siemens/CTI, Knoxville, TN) PET tomograph (axial field of view of 16.2 cm and resolution of 6 mm). After a fast of 4 hours and blood glucose evaluation, i.v. injection of 185 MBq (5 mCi) of ^{18}F-fluorodeoxyglucose for 70 kg body weight was performed, and whole-body PET images were obtained. The acquisition time was 16 min per bed position (40% transmission and 60% emission). The PET images were interpreted prospectively by two experienced nuclear medicine radiologists (M.A., D.O.S.) masked to clinical and magnetic resonance imaging (MRI) findings. Standard up-

take values (SUV), a semiquantitative measurement of relative FDG uptake within the regions of interest (ROIs), were calculated. The SUV was 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 maximum SUV within the ROIs was used for further calculations (here after SUV). For the present study, correlation with both local control and survival endpoints was based upon the maximum SUV of the primary tumor, except in 5 patients (3 with unknown primary tumors and 2 with T1–2 tumors), in whom only the lymph nodes demonstrated increased uptake. Consequently, for these 5 patients the SUV of the lymph node was used as reference for correlation with DFS.

Statistical analysis

The Kaplan-Meier method was used to calculate actuarial local LC, and DFS and overall survival rates. Persistent or recurrent tumor was documented at least by two different examinations (MRI, PET scanning, or endoscopy). For LC tumor persistence or recurrence at the initial primary site were considered as events, whereas for DFS nodal recurrences and distant metastases were also taken into account. The time interval for the above-mentioned endpoints was calculated from the first day of treatment until the date of an event or of the last follow-up. The log–rank test was used to assess the correlation of these endpoints with the SUV and with the other clinical (T category, N category, TNM stage), and therapeutic (treatment group) variables. The Cox proportional hazards model was used for the multivariate analysis. Variables shown to be significant or of borderline significance ($p < 0.1$) in the univariate analysis (with the exception of linked variables) were selected for the Cox model. The Mann-Whitney *U* test was used to compare the median SUV values in different subgroups. A difference with a p value of less than 0.05 was considered significant.

RESULTS

Overall results

Median follow-up for surviving patients was 48 months (range, 7–66 months). Seventy-one patients were alive at last follow-up and 49 had died (37 from head-and-neck cancer, 5 from second cancers, 1 from complications of treatment, and 6 from intercurrent disease). Forty-six patients presented with at least 1 event (32 locally or regionally persistent, or both, or recurrent disease and 20 distant metastases). At 4 years actuarial LC was 75% (95% confidence interval [CI], 67%–84%), DFS was 59% (95% CI, 50%–69%), and overall survival was 59% (95% CI, 50%–67%).

The median value of the SUV for all patients was 4.76 (range, 1–24.8). It was 5.5 and 3.4 for the RT and surgery groups, respectively ($p = 0.0013$). In the 46 patients who presented with any component of failure, the median SUV was significantly higher than the corresponding value in the remaining controlled patients (5.8 vs. 3.6, $p = 0.002$). The median value of the SUV was used to establish two groups, one with a high (> 4.76) and the other with a low (≤ 4.76) SUV when studying the whole population, although this value does not necessarily represent the best discriminative cut-off.

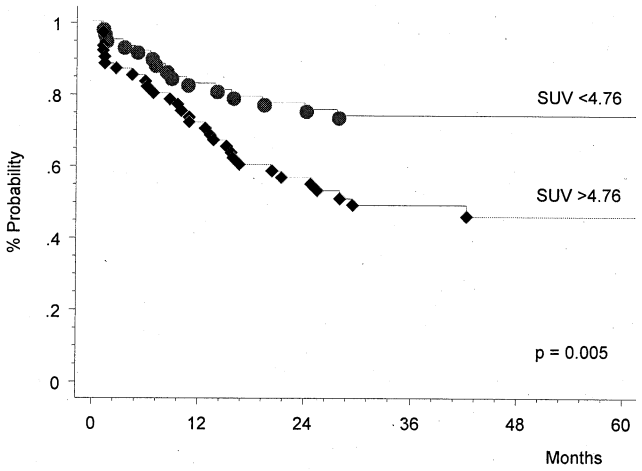

Fig. 1. Actuarial disease-free survival according to the median standardized uptake value (SUV) of 2[^{18}F]fluoro-2-deoxy-D-glucose (FDG) in the whole series.

Correlation between SUV and clinicopathologic parameters

To assess the potential linkage of the SUV with clinical prognostic factors, different correlations were evaluated. Thus, T1–2 tumors had a lower median SUV compared with T3–4 tumors (3.6 vs. 5.5, $p = 0.004$). A significant difference in the median SUV was noted between N0 compared with N1–3 cases (respectively, 3.5 vs. 5.4, $p = 0.026$). According to tumor location, the median SUV was 3.5 for oral cavity, 5.17 for oropharynx, 6 for hypopharynx, and 3.6 for larynx, with significant differences between groups ($p = 0.012$). Moreover, no significant association was found between the SUV value and the histologic grading ($p = 0.82$).

Univariate analysis

In univariate analysis, patients with a high SUV had a significantly lower 4-year local control (63% vs. 88%, $p = 0.003$). This difference was observed also when the two groups (RT and surgery) were analyzed separately with their respective median SUVs of 5.5 and 3.4. Thus for the RT group, the LC rates were 58% vs. 88% ($p = 0.01$), and for the surgery group, 64% vs. 95% ($p = 0.016$), respectively, for high and low SUV subgroups. For DFS, patients with high SUV had a significant lower 4-year rate compared with patients with low SUV (46% vs. 74%, $p = 0.005$; Fig. 1). This observation was also found when studying the two treatment groups separately, particularly for the RT group (40% vs. 79%, $p = 0.005$), while for the surgery group a

Table 2. Univariate analysis of clinical and therapeutic factors

	No. of patients*	Percent 4-year local control	*p* Value	Percent 4-year DFS	*p* Value
T category (UICC 1997)					
T1–2/T3–4	56/64	89/64	0.0006	71/50	0.004
N category					
N0/N1–3	54/66	84/69	0.06	79/44	0.0006
TNM stage (UICC 1997)					
Stage I–II/III–IV	28/92	88/72	0.07	88/51	0.001
Histological grading					
G1/G2/G3	42/32/21	79/64/79	0.2	70/44/63	0.07
SUV category					
$<4.76/\geq 4.76$	62/57	88/63	0.003	74/46	0.005
$<3.5/\geq 3.5$	43/77	95/65	0.0008	80/48	0.001
Treatment strategy					
RT group/surgery group	72/47	72/81	0.24	58/62	0.59

Abbreviations: DFS = disease-free survival; UICC = International Union Against Cancer; SUV = standardized uptake value.
* One patient with unknown local status was excluded from local control analysis.

trend was noted (51% vs. 74%, $p = 0.095$). Table 2 displays the results of the univariate analysis for LC and DFS using different clinical, pathologic and therapeutic variables. Besides the high SUV category, advanced T-category (T3–4) was found to be an adverse factor significantly influencing both local control and DFS, while advanced N and TNM stage categories influenced significantly DFS and were of borderline significance for LC. On the other hand, histologic grading was not correlated to LC or to DFS. The 4-year overall survival was also lower in the group with high SUV (≥ 4.76), but the difference was not significant (44% vs. 66%, $p = 0.14$).

The best discriminative cut-off of the SUV regarding LC and DFS was investigated within SUV subgroups defined by successive arbitrary cut-offs. The value of 3.5 was found to be the cut-off that separated the whole population into two groups with different outcome and having the highest degree of significance (data not shown). Thus for LC the 4-year rates were 65% vs. 95% ($p = 0.0008$), for DFS the rates were 48 vs. 80% ($p = 0.001$), and for overall survival the rates were 49% vs. 68% ($p = 0.11$) for the high SUV group and the low SUV group, respectively.

Multivariate analysis

Factors significantly influencing LC or DFS or both in univariate analysis as well as factors of borderline significance were included in the Cox models. Taking into account the difference in the median SUV values from one tumor subsite to another, and the imbalance in the subsite distribution within treatment groups, the multivariate analysis was done by using a stratification by tumor subsite. For LC, T category ($p = 0.005$) and SUV category remained significant adverse factors, either by considering the median value (4.76) or the best cut-off (3.5; $p = 0.046$ and 0.014, respectively). For DFS, N category was the most significant factor ($p = 0.004$), followed by T category ($p = 0.02$) and then the SUV category ($p = 0.051$ and 0.018 for the cut-off of 4.76 and 3.5, respectively). The relative risks associated with these factors are listed in Table 3.

DISCUSSION

Positron emission tomography imaging represents an area of very active research in oncology. Besides providing useful diagnostic information regarding pretreatment stag-

Table 3. Cox proportional hazards models for local control and DFS

	Local control			DFS		
	Relative risk	95% CI	*p* Value	Relative risk	95% CI	*p* Value
T category (UICC 1997)						
T1–2/T3–4	0.24	0.09–0.66	0.005	0.47	0.25–0.89	0.02
N category						
N0/N1–3	0.5	0.19–1.31	0.16	0.32	0.15–0.69	0.004
SUV category						
$<4.76/\geq 4.76$	0.39	0.16–0.98	0.046	0.52	0.27–1.00	0.051
$<3.5/\geq 3.5$	0.16	0.03–0.69	0.014	0.39	0.17–0.85	0.018

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

ing and posttreatment follow-up (5, 14), intensity of FDG uptake is emerging as a valuable predictive factor regarding treatment outcome (7, 9). In a previous analysis we have shown that high FDG uptake, as measured by the SUV, was correlated with lower LC and DFS in patients treated by radiotherapy with or without chemotherapy for head-and-neck cancers (10). In the present study, on the one hand we confirm our earlier results in a larger series with longer follow-up, and on the other hand our findings suggest that FDG uptake has similar significance in patients whose treatment was based upon surgery. Furthermore, in multivariate analysis of the entire series the SUV category was found to be an independent prognostic factor for LC and DFS, whatever the cut-off used (the median value or the best discriminative value). The original contribution of this prospective study of 120 patients is to furnish the strongest evidence yet available indicating that FDG uptake provides independent outcome information, above and beyond that yielded by more traditional clinical or therapeutic parameters. Although various endpoints were used in previous publications, our results are generally in agreement with those of the other studies dealing with head-and-neck carcinomas, both in nonsurgical (15, 16) and surgical series (8, 17).

As stressed in our previous work, certain points need further clarification in subsequent studies. The first concerns the apparent linkage between FDG uptake and tumor burden or stage. While advanced tumors generally tend to have higher FDG uptake (8, 10, 17), the same impact of the SUV value has been observed within a given tumor stage (8, 10). This suggests that FDG uptake not only reflects tumor burden/stage but also expresses, at least in part, some intrinsic biologic characteristics of the tumor. This notion is consistent with data showing an association of high FDG uptake with parameters related to tumor aggressiveness such as cell viability (18), proliferative activity (19), hypoxia (20), low apoptosis rate (21), and p53 overexpression (22). These characteristics are all potentially adverse factors in patients treated with RT or chemotherapy or both, while some of them may also impact negatively in patients treated surgically. Accumulating data thus suggest that FDG-PET may serve as a noninvasive method that can indirectly measure the expression of various biologic markers of tumor aggressiveness.

The other problems that remain to be resolved concern the methodology for measuring FDG uptake. In this regard, the advantages and disadvantages of the different methods have recently been reviewed (23). While the SUV is the most widely used measurement method, other more complex methods such as metabolic rate (MR) calculation have also been studied. Interestingly, in a series of head-and-neck patients studied using FDG-PET and treated by radical RT, Brun *et al.* (24) recently reported a correlation coefficient of 0.8 between SUV and MR; furthermore, the two methods yielded similar clinical results, in that values below the medians were in each instance correlated with superior LC and survival. Nevertheless, for a routine use, the optimal methodology remains to be defined. Moreover, when considering the SUV, there is no standard cut-off for defining subgroups of differing prognoses. This makes direct comparison of different series problematical, and standardizing the calculation method at least for each tumor location will be mandatory.

In conclusion, the present study confirms our previous results and those of the other groups, thereby strengthening the notion that pretreatment tumor FDG uptake represent an independent prognostic factor in head-and-neck carcinomas patients, whatever the primary therapy used, RT or surgery. Thus, patients with high FDG uptake should be considered at increased risk of failure and may benefit from more aggressive multimodality treatment combinations.

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