6. Krag DN, Meijer SJ, Weaver DL, et al. Minimal-access surgery for staging of malignant melanoma. *Arch Surg* 1995;130:654–658.
7. Albertini JJ, Cruse CW, Rapaport D, et al. Intraoperative radiolymphoscintigraphy improves sentinel node identification in patients with melanoma. *Ann Surg* 1996;223: 217–224.
8. Thompson JF, McCarthy WH, Bosch CMJ. Sentinel node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. *Melanoma Res* 1995;5: 255–260.
9. Reintgen D, Albertini J, Miliotes G, et al. The accurate staging and modern day treatment of malignant melanoma. *Cancer Res Ther Control* 1995;4:183–197.
10. Ross MI, Reintgen D, Balch CM. Selective lymphadenectomy: emerging role for lymphatic mapping and sentinel node biopsy in the management of early stage melanoma. *Semin Surg Oncol* 1993;9:219–223.
11. Larson D, Weinstein M, Goldberg I, et al. Edema of the arm as a function of the extent of axillary surgery in patients with Stage I-II carcinoma of the breast treated with primary radiotherapy. *Int J Radiat Oncol Biol Phys* 1986;12:1575–1582.
12. Kissin MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphedema after the treatment of breast cancer. *Br J Surg* 1986;73:580–584.
13. Veronesi U, Rilke F, Luini A, et al. Distribution of axillary node metastases by level of invasion. An analysis of 539 cases. *Cancer* 1987;59:682–687.
14. Rosen PP, Lesser ML, Kinne DW, Beattie EJ. Discontinuous or "skip" metastases in breast carcinoma. Analysis of 1228 axillary dissections. *Ann Surg* 1983;197:276–283.
15. Lloyd LR, Waits RK Jr, Schroder D, Hawasli A, Rizzo P, Rizzo J. Axillary dissection for breast carcinoma. The myth of skip metastasis. *Am Surg* 1989;55:381–384.
16. Boova RS, Bonanni R, Rosato FE. Patterns of axillary nodal involvement in breast cancer. Predictability of level one dissection. *Ann Surg* 1982;196:642–644.
17. Toma S, Leonessa F, Romanini A, et al. Predictive value of some clinical and pathological parameters on upper level axillary lymph node involvement in breast cancer. *Anticancer Res* 1991;11:1439–1443.
18. Danforth DN Jr, Findlay PA, McDonald HD, et al. Complete axillary lymph node dissection for stage I–II carcinoma of the breast. *J Clin Oncol* 1986;4:655–662.
19. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;220:391–401.
20. Giuliano AE, Dale PS, Turner RR, et al. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg* 1995;222:394–401.
21. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patients with breast cancer. *JAMA* 1996;276:1818–1822.
22. McCarthy WH, Thompson JF, Uren RF. Commentary. Minimal access surgery for staging of malignant melanoma. *Arch Surg* 1995;130:659–660.
23. Gulec SA, Moffat FL, Carroll RG. The expanding clinical role of intraoperative gamma probes. In: Freeman LM, ed. *Nuclear medicine annual.* Philadelphia: Lippincott-Raven; 1997:209–237.
24. Strand SE, Persson BRR. Quantitative lymphoscintigraphy: basic concepts for optimal uptake of radiocolloids in the parasternal lymph nodes of rabbits. *J Nucl Med* 1979;20:1038–1046.
25. Senofsky GM, Moffat FL, Davis K, et al. Total axillary lymphadenectomy in the management of breast cancer. *Arch Surg* 1991;126:1336–1342.
26. Hung JC, Wiseman GA, Wahner HW, Mullan BP, Taggart TR, Dunn WL. Filtered technetium-99m sulfur colloid evaluated for lymphoscintigraphy. *J Nucl Med* 1995; 36:1895–1901.
27. Alazraki NP, Eshima D, Eshima LA, et al. Lymphoscintigraphy, the sentinel node concept, and the intraoperative gamma probe in melanoma, breast cancer, and other potential cancers. *Semin Nucl Med* 1997;27:55–67.

Carbon-11-Methionine Uptake in Squamous Cell Head and Neck Cancer

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The purpose of this study was to investigate whether uptake of L-methyl-[^{11}C]-methionine in a tumor is related to the survival of patients with squamous cell cancer of the head and neck. **Methods:** Thirty-nine patients (median age 64 yr) with newly diagnosed squamous cell carcinoma of the head and neck entered a PET study with [^{11}C]-methionine before therapy. Tumor [^{11}C]-methionine uptake was measured as standardized uptake values (SUVs), and the PET results were compared with the clinical follow-up data of the patients. **Results:** All except one of the malignant lesions within the field of view were visible by [^{11}C]-methionine PET. The median tumor SUV was 9.0 (range 4.0–18.8). The median follow-up time for patients still alive is currently 44 mo (range 14–66 mo). No difference in survival was found between patients with tumor SUV equal to or larger than the median and those with tumor SUV smaller than the median. **Conclusion:** Carbon-11-methionine PET imaging is effective in squamous cell head and neck cancer. The amount of [^{11}C]-methionine uptake does not predict the clinical outcome.

Key Words: PET; carbon-11-methionine; head and neck cancer

J Nucl Med 1998; 39:1393–1397

The optimal treatment for most carcinomas of the head and neck is combined radiotherapy and surgery, although an early-stage cancer may be cured with radiotherapy or surgery alone. The tumor stage at diagnosis is of important prognostic value (*1*), but the role of factors related to aggressive clinical behavior and decreased radiocurability of a malignant tumor, e.g., intrinsic radioresistance, still remains unknown. There are also preliminary molecular and immunohistochemical studies showing that increased risk for locoregional relapse (*2*) or aggressive behavior (*3*) of squamous cell carcinoma may be predicted by using biochemical or genetic markers. However, these methods also have limitations. A reliable method for assessing the aggressive clinical behavior of cancer would assist the clinician in planning cancer therapy.

PET imaging with L-methyl-[^{11}C]-methionine is useful in the detection and delineation of both cerebral and extracranial human cancer (*4–7*). Methionine is an essential amino acid, and its transport is regulated by two different transport mechanisms, system A and system L (*8*). High tumor uptake reflects the increased transport of methionine from the blood into cancer cells.

There is some evidence that tumor [^{11}C]-methionine uptake may be related to the biological aggressiveness of cancer, although the results have been contradictory. Carbon-11-methionine accumulation seemed to be associated with the histological grading of brain (*4*), lung (*5*) and uterine cancer (*6*) but not lymphoma (*9*). A correlation was found between high [^{11}C]-methionine uptake and the high percentage of dividing cells in breast cancer (*7*) and in non-small cell lung cancer (*10*), suggesting that [^{11}C]-methionine PET could be used for evaluating the proliferative activity of a tumor.

The tumor stage remains perhaps the only independent prognostic factor in head and neck cancer. However, tumors with a similar clinical stage may respond to radiotherapy at different rates. There exists a great variation in the radioresponse of individual tumors and, because of heterogeneity, also within a single tumor (*11*). A reliable method for predicting the radiocurability of a tumor would be valuable. Proliferative characteristics do not seem to have any significant relationship to the histopathological grading of head and neck cancer (*11*),

Received Aug. 5, 1997; revision accepted Nov. 6, 1997.
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TABLE 1
Patient Characteristics

Characteristics	Number
Men	33
Women	6
Age (yr)	
≤64	22
>64	17
WHO performance status	
0–1	27
≥2	12
Primary site	
Oral cavity	15
Pharynx	10
Larynx	7
Paranasal sinuses	4
Parotid gland	1
Unknown	2
Primary tumor size	
T1	5
T2	7
T3	10
T4	15
Tx	2
Lymph nodes	
N0	16
N1	11
N2	10
N3	2
Histological grade	
G1	13
G2	16
G3	8
Gx	2
UICC stage	
I	4
II	5
III	8
IV	22

WHO = World Health Organization; UICC = International Union Against Cancer.

and the prognosis for head and neck cancer does not depend on histological grading or proliferative activity (*12*). Thus, more accurate predictive methods are warranted for clinical use. Metabolical activity of cancer tissue in vivo has been suggested to be related to the behavior of the disease, and recently tumor fluorodeoxyglucose (FDG) uptake was found to be a prognostic factor for head and neck cancer (*13*). Our purpose was to evaluate whether tumor [^{11}C]-methionine uptake is related to the survival of patients with squamous cell cancer of the head and neck.

MATERIALS AND METHODS

Patients

Between March 1989 and May 1995, a [^{11}C]-methionine PET study was completed for 39 patients (6 women, 33 men; age range 36–79 yr; median age 64 yr) who had been referred to the University Central Hospital of Turku for treatment of squamous cell head and neck cancer. A written informed consent was obtained from all of the patients. The study protocol was approved by the ethical board of the hospital.

All 39 patients had previously untreated cancer with histological confirmation. Staging was performed according to the International Union Against Cancer primary tumor, regional nodes and metastasis system (*14*), and consisted of a clinical examination with endoscopy, chest radiograph, ultrasonography, CT (26 patients) and MRI (CT and MRI, 5 patients) when feasible (Table 1). Tumor diameter was at least 2 cm, except in 2 patients who had primary tumors with a diameter of 1.5 cm. Curative cancer therapy was planned and combination treatment was chosen according to the type, location and stage of the disease. Decisions were not affected by the PET results.

Patients had a [^{11}C]-methionine PET study prior to therapy. The time interval between the PET study and the onset of therapy varied from 1–41 days, with a median of 8 days. After the PET study, 25 patients were treated with preoperative radiotherapy using a linear accelerator with 4 MV or 6 MV photons to the total tumor dose of 60–64 Gy and surgery to the primary site and/or the regional lymph nodes, whereas 9 patients received definitive radiotherapy to the tumor dose of 65–72 Gy. Nine of the 34 patients received accelerated hyperfractionated radiotherapy with two daily fractions of 1.6 Gy (*1,15*), while other patients were treated with conventional radiotherapy. Two patients with large hypopharyngeal tumors also received intracavitary radiotherapy. One patient underwent only radical surgery, whereas radiotherapy had to be interrupted in 4 patients because of their worsening physical condition. All 26 patients who underwent surgery had negative surgical margins, and the surgical procedures were considered radical. Of the 39 patients, 35 (90%) completed curative cancer therapy.

PET Imaging

An ECAT type 931/08-12 scanner (Siemens/CTI, Inc., Knoxville, TN) was used for the PET studies. The device produces 15 simultaneous, contiguous slices with a slice thickness of 6.7 mm, and the final in-plane resolution in reconstructed and Hann-filtered images is 8.0 mm FWHM. According to phantom studies, the measured radioactivity concentration is sufficiently stable for objects larger than 13–14 mm in diameter. Partial volume correction was not performed because the size of the tumors was considered to be large enough. Carbon-11-methionine was synthesized as previously described (*16,17*).

TABLE 2
Clinical Factors and Tumor Uptake of Carbon-11-Methionine in 39 Patients with Untreated Squamous Cell Head and Neck Cancer

	SUV <9.0 n = 18	SUV ≥9.0 n = 21
Age (yr)		
≤64	12	10
>64	6	11
WHO performance status		
0–1	10	17
≥2	8	4
Lymph node positive	11	12
Lymph node negative	7	9
Histological grade		
G1	5	8
G2	8	8
G3	4	4
Gx	0	2
UICC stage		
I–III	7	10
IV	11	11
Alive with no disease	4	10
Alive with disease	4	1
Dead of disease	10	10
Therapy interrupted	2	2

SUV = standard uptake value; WHO = World Health Organization; UICC = International Union Against Cancer.

TABLE 3
Pretreatment Tumor Carbon-11-Methionine Uptake (SUV) and Response to Therapy in 39 Patients with Head and Neck Cancer

Patient no.	SUV		Therapy	Response		Follow up (mo)
	<9.0	≥9.0		Clinical	Pathological	
1		12.3	Th. int	PD	Not op.	DOD at 11 mo
2		12.5	rad. RT	PR	Not op.	DOD at 3.7 mo
3	8.9		RT + OP	PR	POS	DOD at 16 mo
4	8.7		rad. RT	CR	Not op.	DOd at 27.3 mo
5	5.8		Th. int	PD	Not op.	DOD at 0.2 mo
6	8.4		RT + OP	PR	POS	DOD at 20 mo
7		9.8	RT + OP	PR	POS	NED at 66 mo
8		15.2	rad. RT	PR	Not op.	DOD at 8 mo
9	6.5		RT + OP	CR	NEG	DOD at 45 mo
10	4.4		rad. RT	PR	Not op.	REC at 45 mo
11		9.0	RT + OP	PR	POS	NED at 65 mo
12		10.2	RT + OP	PR	NEG	NED at 65 mo
13	8.2		RT + OP	PR	POS	DOD at 7.5 mo
14	8.4		Th. int.	PD	Not op.	DOD at 2 mo
15		9.0	rad. op	CR	POS	NED at 63 mo
16		18.8	RT + OP	PR	POS	NED at 61.5 mo
17	6.2		RT + OP	PR	POS	DOD at 8 mo
18	8.8		RT + OP	PR	POS	DOD at 13.7 mo
19	6.7		RT + OP	PR	POS	NED at 56 mo
20		11.7	rad. RT	CR	Not op.	DOD at 7.3 mo
21	8.1		rad. RT	PR	Not op.	DOD at 6 mo
22		11.5	RT + OP	CR	POS	DOD at 30 mo
23		11.4	rad. RT	CR	Not op.	NED at 45 mo
24	4.6		rad. RT	CR	Not op.	REC at 20.7 mo AWD at 45 mo
25		10.6	RT + OP	CR	POS	DOD at 23.7 mo
26	6.3		RT + OP	CR	POS	REC at 30.2 mo
26	6.3		RT + OP	CR	POS	REC at 30.2 mo AWD at 44 mo
27		9.0	RT + OP	CR	POS	DOD at 9 mo
28		11.5	RT + OP	PR	POS	NED at 27 mo
29		9.9	RT + OP	PR	POS	REC at 5 mo AWD at 25 mo
30	7.3		RT + OP	PR	POS	NED at 22 mo
31		12.4	RT + OP	PR	POS	DOD at 10 mo
32	7.4		RT + OP	PR	POS	NED at 21 mo
33	8.4		RT + OP	PR	POS	REC at 15 mo AWD at 19 mo
34		10.0	rad. RT	PR	Not op.	DOD at 9 mo
35		9.2	RT + OP	PR	NEG	NED at 19 mo
36	4.0		rad. RT	CR	Not op.	NED at 19 mo
37		10.8	RT + OP	PR	NEG	DOD at 10.1 mo
38		10.4	RT + OP	PR	POS	NED at 14 mo
39		9.1	RT + OP	PR	POS	NED at 14 mo

SUV = standardized uptake value; Th. int. = therapy interrupted; rad. RT = radical radiotherapy; RT + OP = preoperative radiotherapy and surgery to the primary site ± neck dissection; rad. OP = radical operation; PD = progressive disease; Not op. = not operated; PR = partial response; CR = complete response; DOD = dead of disease; NED = no evidence of disease; REC = recurrent; AWD = alive with disease; POS = positive pathological findings; NEG = negative pathological findings.

A 10-min transmission scan for attenuation correction was performed with a removable ^{68}Ge ring source (total counts 15–30 × 10^6 per plane). Carbon-11-methionine bolus (range 110–480 MBq; mean 320 MBq) was injected intravenously, and dynamic scanning was performed for 40 min. Clinical information was available for the investigators for the image interpretation. The regions of interest (ROI) were placed manually on the tumor areas with the highest radioactivity concentration in the last frame. The average radioactivity concentration in a ROI at 35–40 min postinjection, corrected for calibration and decay, was used for the analysis. Tumor [^{11}C]-methionine accumulation was measured as standardized uptake values (SUVs), i.e., radioactivity concentration in the ROI (Bq per cc) divided by the injected dose (Bq) divided by the body weight (g). The SUV method was chosen because of its simplicity and applicability to clinical studies, and because of its close correlation with kinetic parameters, as described by Leskinen-Kallio et al. (*18*).

Data Analysis

Follow-up was calculated from the time of the PET study, and the median follow-up time for patients still alive was 44 mo (range 14–66 mo). The cumulative survival was estimated with the product-limit method of Kaplan-Meier, and the survival between groups was compared with the log-rank test. Comparison of non-normal distributions was done using Kruskal-Wallis analysis of variance.

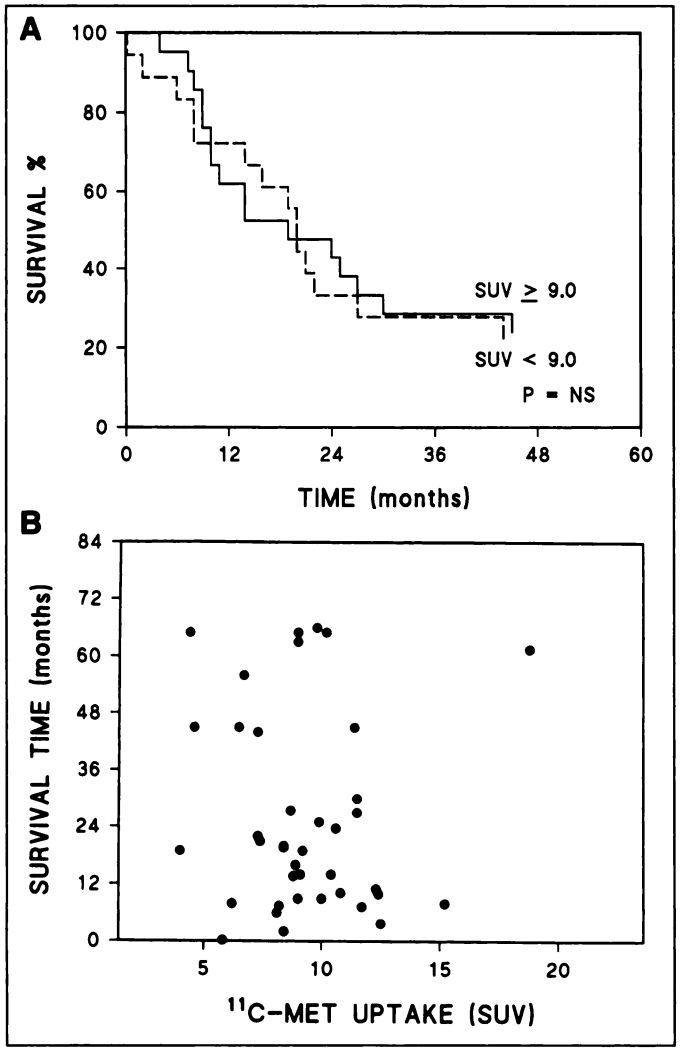

FIGURE 1. (A) Kaplan-Meier and (B) scattergram showing lack of association with tumor [^{11}C]-methionine standardized uptake value (SUV) and survival time of 39 patients with squamous cell head and neck cancer.

RESULTS

All malignant lesions within the field of view were visible by [^{11}C]-methionine PET except one. A supraglottic laryngeal cancer with a diameter of 1.5 cm was not clearly detectable because of the large metastasis in the neighboring lymph node. On the other hand, one carcinoma (2.2 × 1.2 cm) of the lower gum that was not visible by CT or MRI was clearly detected by PET. The overall sensitivity of PET for detecting primary tumors was 97% (36/37; Table 1).

The tumor SUVs ranged from 4.0–18.8 with a median of 9.0. The patients were divided into two groups according to the median tumor SUV (Table 2). When comparing clinical prognostic factors like the histological grade and stage of cancer, the two groups did not differ markedly from each other, although the performance status tended to be better in the group of patients with a tumor SUV ≥9.0. Ten patients in each group died of cancer. A tumor SUV lower than the median tended to be related to recurrent disease in the 19 patients that were still alive. Four out of 8 patients with a tumor SUV < 9.0 were alive without disease, while cancer had recurred in 4 patients. Ten out of 11 patients with a tumor SUV ≥9.0 were alive with no evidence of disease, whereas only 1 patient had a recurrency (Table 3). No difference in survival was found between the two groups of patients (p = ns) (Fig. 1A and B). When comparing Stage III and IV tumors separately, no correlation was found

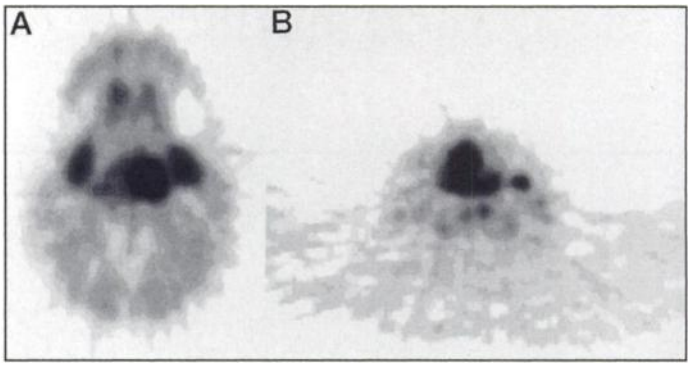

FIGURE 2. Carbon-11-methionine PET images of 2 patients with advanced (International Union Against Cancer Stage T3N1) laryngeal cancer. (A) Moderately differentiated squamous cell cancer in supraglottic area with neighboring neck metastasis and tumor standardized uptake value (SUV) of 10.2. Sublingual and right submandibular salivary glands are also visible. Patient was alive without disease at 65 mo after diagnosis. (B) Well-differentiated squamous cell cancer in glottic area with tumor SUV of 10.0. Patient died of cancer 9 mo after diagnosis.

between tumor SUVs and survival times. Tumor [^{11}C]-methionine uptake was not related to final patient outcome for primary squamous cell head and neck cancer (Fig. 2). No correlation was found between tumor [^{11}C]-methionine uptake and the histological grading of squamous cell head and neck cancer (p = ns) (Fig. 3). However, the tumor stage at diagnosis was a prognostic factor (Fig. 4).

DISCUSSION

After a fairly long patient follow-up (median 44 mo), we found no correlation between tumor [^{11}C]-methionine uptake and final clinical outcome. Since most head and neck cancer recurs within the first 2 yr after diagnosis, the follow-up of this study was sufficient for survival analysis.

Carbon-11-methionine PET is effective in imaging various types of cancer, although most human studies have been performed with brain tumors. Derlon et al. (*4*) reported that [^{11}C]-methionine uptake in cerebral gliomas was not related to the length of survival.

Methionine is an essential amino acid that is mostly used for protein synthesis but is also used for polyamine synthesis, for trans-sulfuration and transmethylation reactions. The overall transmethylation rate is significantly increased in cancer. Al-

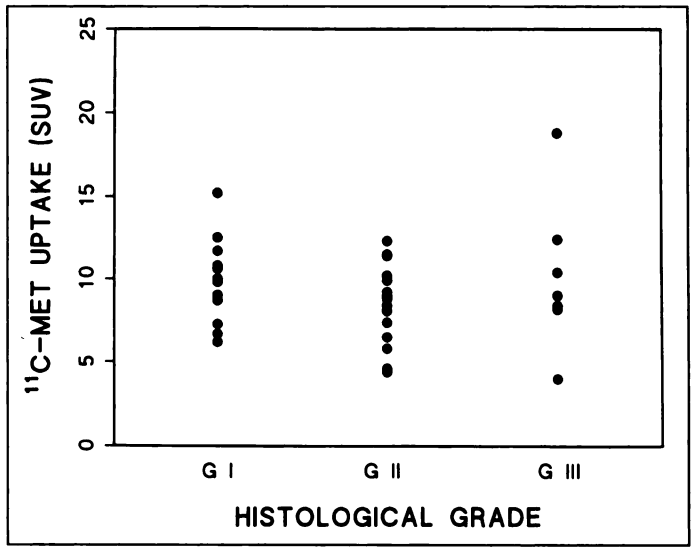

FIGURE 3. Tumor [^{11}C]-methionine standardized uptake value (SUV) and histological grading in squamous cell head and neck cancer.

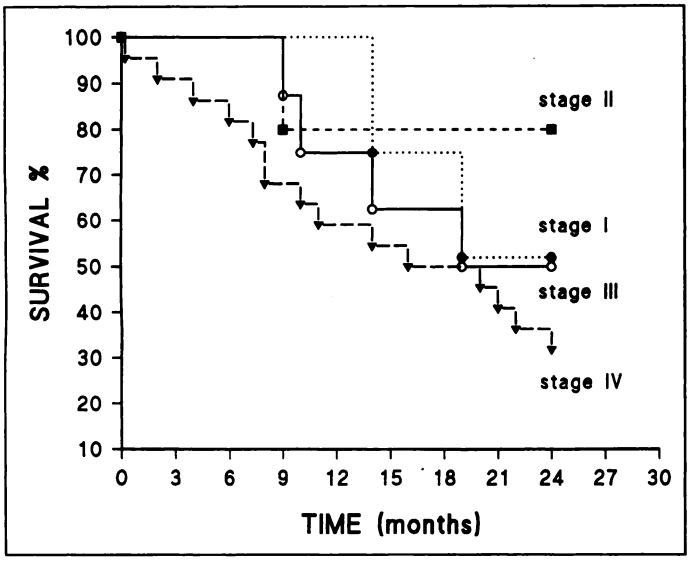

FIGURE 4. Correlation between tumor stage and survival time of 39 patients with head and neck cancer.

though the need for nutrients is markedly increased in actively proliferating tissues, tumor [^{11}C]-methionine uptake does not directly describe the proliferative activity of cancer. Carbon-11-methionine uptake may be associated with the clinical course, which is dependent on proliferative activity as well as other factors. Carbon-11-methionine uptake reflects more amino acid transport than incorporation into proteins during the first 30 min after injection. More specific PET tracers are needed for basic studies on cancer biology. For imaging head and neck cancer, L-1-[^{11}C]-tyrosine (TYR) has been used (*19*). Since tumor TYR uptake may be related to protein synthesis rate, it would be useful to know whether there is an association with tumor TYR uptake and the prognosis for head and neck cancer.

In contrast to the present results, increased glucose metabolism of cancer as measured by ^{18}F-FDG PET correlated significantly with the final patient outcome for head and neck cancer. High tumor FDG uptake was associated with a low grade of differentiation, high mitotic counts and poor prognosis in 37 untreated patients with squamous cell cancer of the head and neck, which suggests that FDG PET may predict survival in head and neck cancer (*13*). This is in line with early studies on carbohydrate metabolism that showed the anaerobic glycolytic rate in well-differentiated, slowly growing cancer is much lower than in poorly differentiated, rapidly growing cancer.

Würker et al. (*20*) found that [^{11}C]-methionine uptake in low-grade gliomas decreased prominently after local radiotherapy in those patients who had increased initial tumor uptake. They suggested that the rate of methionine incorporation might be a marker of tumor tissue radiation sensitivity. In contrast, preirradiation SUV did not predict the response to radiotherapy in 15 patients with head and neck cancer (*21*). The results of this study with ^{11}C-methionine were similar.

CONCLUSION

Pretreatment [^{11}C]-methionine uptake in squamous cell head and neck cancer had no association with the final clinical outcome. Carbon-11-methionine PET can be used to image malignant tumors and monitor therapy. It may find important applications in differentiating malignant from benign tumors or differentiating recurrent cancer from normal post-therapeutic changes.

ACKNOWLEDGMENTS

We thank professors Eeva Nordman and Uno Wegelius for their continuing support. We also thank the personnel of the Turku PET Centre for cooperation. The study was supported financially by grants from the South-Western Finland Cancer Foundation.

REFERENCES

1. Wang CC. Radiation therapy for head and neck neoplasms: indications, techniques, and results, 3rd ed. New York: Wiley; 1997:1–13:63–78.
2. Brennan J, Mao L, Hruban R, et al. Molecular assessment of histopathological staging in squamous-cell carcinoma of the head and neck. *N Engl J Med* 1995;332:429–435.
3. Clayman G, Ta-Jen L, El-Naggar A, Goepfert H. HER-2/neu oncogene as a regulator of aggressive phenotypic behavior in head and neck squamous cell carcinoma. In: Society of Head, Neck Surgeons and American Society of Head and Neck Surgery, eds. *Proceedings of the 4th international conference on head and neck cancer.* Madison, WI: Omnipress; 1996:493–501.
4. Derlon J-M, Bourdet C, Bustany P, et al. Carbon-11-methionine uptake in gliomas. *Neurosurgery* 1989;25:720–728.
5. Fujiwara T, Matsuzawa T, Kubota K, et al. Relationship between histologic type of primary lung cancer and [^{11}C]-L-methionine uptake with PET. *J Nucl Med* 1989;30:33–37.
6. Lapela M, Leskinen-Kallio S, Varpula M, et al. Imaging of uterine cancer by [^{11}C]-methionine and PET. *J Nucl Med* 1994;35:1618–1623.
7. Leskinen-Kallio S, Någren K, Lehikoinen P, et al. Uptake of ^{11}C-methionine in breast cancer studied by PET. An association with the size of S-phase fraction. *Br J Cancer* 1991;64:1121–1124.
8. Bonadonna R, Saccomani M, Cobelli C, DeFronzo R. Effect of insulin on system A amino acid transport in human skeletal muscle. *J Clin Invest* 1993;91:514–521.
9. Leskinen-Kallio S, Ruotsalainen U, Någren K, Teräs M, Joensuu H. Uptake of [^{11}C]-methionine and FDG in non-Hodgkin's lymphoma: a PET study. *J Nucl Med* 1991;32:1211–1218.
10. Miyazawa H, Arai T, Hara T. PET imaging of nonsmall-cell lung carcinoma with [^{11}C]-methionine: relationship between radioactivity uptake and flow-cytometric parameters. *J Nucl Med* 1993;34:1886–1891.
11. Peters L, Brock W, Johnson T, Meyn R, Tofilon P, Milas L. Potential methods for predicting tumor radiocurability. *Int J Radiat Oncol Biol Phys* 1986;12:459–467.
12. Syms M, Eibling D, McCoy P, et al. Flow cytometric analysis of primary and metastatic squamous cell carcinoma of the oral cavity and oropharynx. *Laryngoscope* 1995;105:149–155.
13. Minn H, Lapela M, Klemi P, et al. Prediction of survival with ^{18}F-FDG and PET in head and neck cancer. *J Nucl Med* 1997;38:1907–1911.
14. International Union Against Cancer (UICC). *Primary tumor, regional nodes and metastasis (TNM) atlas classification of malignant tumors*, 3rd ed. Berlin-Heidelberg: Springer-Verlag; 1992.
15. Valavaara R, Aitasalo K, Minn H, et al. Hyperfractionated radiotherapy in head and neck carcinoma with special reference to high dose preoperative treatment. *Radiother Oncol* 1996;40(suppl 1):S97.
16. Långström B, Lundqvist H. The preparation of ^{11}C-methyl iodide and its use in the synthesis of ^{11}C-methyl-L-methionine. *Int J Appl Radiat Isot* 1976;27:357–363.
17. Någren K. Quality control aspects in the preparation of [^{11}C]-methionine. In: Mazoyer BM, Heiss WD, Comar D, eds. *PET studies on amino acid metabolism and protein synthesis*, 1st ed. Dordrecht: Kluwer Academic Publishers; 1993:81–87.
18. Leskinen-Kallio S, Huovinen R, Någren K, et al. Carbon-11-methionine quantitation in cancer PET studies. *J Comput Assist Tomogr* 1992;16:468–474.
19. Braams J, Pruim J, Nikkels P, Roodenburg J, Vaalburg W, Vermey A. Nodal spread of squamous cell carcinoma of the oral cavity detected with PET-tyrosine, MRI and CT. *J Nucl Med* 1996;37:897–901.
20. Würker M, Herholz K, Voges J, et al. Glucose consumption and methionine uptake in low-grade gliomas after ^{125}I brachytherapy. *Eur J Nucl Med* 1996;23:583–586.
21. Lindholm P, Leskinen-Kallio S, Grenman R, et al. Evaluation of response to radiotherapy in head and neck cancer by PET and [^{11}C]-methionine. *Int J Radiat Oncol Biol Phys* 1995;32:787–794.