Acta Oncologica, 2010; 49: 201–208

informa
healthcare

ORIGINAL ARTICLE

Measurement of tumor volume by PET to evaluate prognosis in patients with head and neck cancer treated by chemo-radiation therapy

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Abstract

Purpose. To evaluate the prognostic value of the metabolic tumor volume measured on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging and other clinical factors in patients treated for locally advanced head-and-neck cancer (HNC) at a single institution. *Materials and methods.* Between June 2005 and August 2008, 59 patients with HNC that underwent pretreatment FDG-PET studies received neoadjuvant chemotherapy and radiation therapy. Metabolically active tumor regions were delineated on the pretreatment PET scans by a fixed SUV of 2.5. We evaluated the relationship of the 18F-fluorodeoxyglucose-PET maximum standardized uptake value (SUV) and the metabolic tumor volume (MTV) with the progression-free survival (PFS) and overall survival (OS). *Results*. The MTV and lymph node metastasis were predictive of the PFS and OS. The lymph node status did not correlate with the MTV. A higher MTV of 9.3 cm^3 was significantly associated with an increased risk of recurrence (2.19-fold, $p = 0.006$) and death (1.62-fold, $p = 0.051$). Separation of patients with tumor volumes ≤ 9.3 cm^3 and no lymph node disease vs. any other combination was strongly predictive of the PFS and the OS. *Conclusions*. MTV and lymph node status were prognostic values associated with survival. Quantitative measurement of tumor volume separates patients with a good prognosis from those with a poorer prognosis. A subset of patients with relatively small tumors and no lymph node involvement did very well.

Squamous cell carcinoma (SCC) of the head and neck is a histologically distinct but clinically a heterogeneous entity including multiple anatomical sites of origin with different natural history and clinical behavior. Due to these characteristics, it is difficult to accurately predict the efficacy of treatments and the prognosis of patients using conventional clinical/pathological criteria. An increase in the biological knowledge of head and neck cancer in terms of parameters, such as tumor aggressiveness, would help to determine optimal management and evaluate prognosis [1,2]. Differential tumor uptake of FDG compared with normal tissues correlates with biological factors such as cell viability and proliferative activity [3–5]. As a result, FDG-PET provides a non-invasive functional imaging procedure reflecting the functional and biological metabolism of head and neck tumors. The results from recent studies of cancers of the head and neck indicate that high FDG uptake in the primary tumor, typically characterized as a standardized uptake value (SUV) greater than the median, predicts a poorer patient outcome [6–10].

Crude surrogates such as volumetric staging have been demonstrated to correlate inversely with the duration of survival in patients with head and neck cancer [11]. Accordingly, it has been demonstrated that the gross tumor volume (GTV) determined by MRI predicts overall survival as well as local tumor control [12]. Until recently, it has been difficult to quantify the tumor burden directly and systematically. FDG-PET allows us to systematically measure

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(Received 22 June 2009; accepted 24 October 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/02841860903440270

the tumor burden; it may be a more direct and reliable method of quantifying the tumor burden because it incorporates functional criteria. However, only a few studies have investigated whether the tumor burden is associated with the volume of tumor tissue demonstrating increased FDG uptake on the PET, or the metabolic tumor volume (MTV); this may be a potential novel prognostic factor for HNC.

The aim of this study was to evaluate the possible usefulness of the tumor burden as characterized by the metabolic tumor volume (MTV) and metabolically active areas, measured by the maximum standardized uptake value (SUV), in predicting response to treatment, progression free survival and overall survival.

Materials and methods

Patients

We conducted a retrospective review of the medical records of all patients with head and neck cancer and 59 patients with HNC that underwent pretreatment FDG-PET studies between June 2005 and August 2008 at Pusan National University Hospital. The principal eligibility criteria were histologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, stage III or IV disease, without distant metastases.

The patients received neoadjuvant chemotherapy (cisplatin with docetaxel or S-1 or 5-FU) followed by definitive radiation therapy. The patients had received no prior chemotherapy, radiation therapy or surgery.

Treatment schedule

Every case was discussed at a multidisciplinary team (i.e., a surgeon, a medical oncologist, and a radiotherapist) meeting and neoadjuvant chemotherapy (cisplatin with docetaxel or S-1 or 5-FU) followed by definitive radiation therapy was restricted to the patients that wanted to preserve organ function or unresectable patients. The neoadjuvant chemotherapy regimen was repeated every 21 days for a maximum of three cycles, but the regimen was expected to be adjusted or cut in cases with disease progression, unacceptable toxicity or patient refusal. Radiation therapy was planned after three cycles of chemotherapy for all patients who achieved a PR or CR after two cycles of chemotherapy. If the response to the drug regimen did not meet the above criteria, after two cycles of chemotherapy, early radiotherapy was then performed. Radiation therapy was started within four weeks of the last cycle of chemotherapy, and it was administered five days per week. It was given in daily fractions of 1.8 Grays (Gy), and the total dose to the primary tumor site was 70.2 Gy.

PET protocol and measurement of tumor volume

Patients were imaged using a Gemini positron emission/computed tomography (PET/CT) scanner (Philips, Milpitas, CA, USA). Each patient fasted for at least eight hours before imaging. After ensuring that the blood glucose levels were $<$180 mg/dL, patients were injected with 296~444 MBq (8.0~12.0 mCi) of FDG. The patients then underwent PET/CT imaging after a tracer uptake time of 45 to 60 min. Frontal and lateral x-ray projection images were acquired as localizers to select the field of view, and CT data were collected in the helical acquisition mode. PET data covering the same field of view were acquired in the three-dimensional mode, for 3–5 min of acquisition time per bed position. The PET data were then reconstructed with an ordered set expectation maximization algorithm, using the CT images for attenuation correction. A whole-body spiral CT was performed with 120 kVp, 130 mAs (current-time product), 0.5 mm/s table feed, and a pitch of 0.9. Subsequently, a PET emission scan in a three-dimensional mode was acquired.

Each tumor thus identified by the user was then segmented automatically in three dimensions by software using the following procedure. First, the voxel of maximum intensity along the selected projection line was used as the starting point for a region growing procedure. The algorithm then found the voxel of local maximum intensity within a specified radius (default value of 1 cm) of the starting voxel. The region growing algorithm then defined the segmented volume as all voxels connected to the local maximum intensity voxel that had intensity greater than a specified fraction of the maximum intensity. The threshold intensity value used in this study was a fixed SUV of 2.5, which was identified as a reasonable choice in several prior studies [13–16]. After all hypermetabolic tumor foci were segmented, the software calculated the MTV, defined as the total volume of primary tumors in the body in cubic centimeters, as well as the maximum and average SUV within the MTV. The SUV is a semiquantitative measure of radiotracer uptake and is calculated according to the following formula: SUV = tissue radioactivity concentration [nCi/mL]/[injected dose(mCi)/patient weight (g)].

Statistical analysis

Data was analyzed with the SPSS Windows 15.0 software. The correlation of metabolic tumor

volume and lymph node grade was assessed by the analysis of variance (ANOVA). The volume was also computed in patients with and without lymph node disease and compared using the t-test. Correlation of tumor volume and stage was computed similarly. Linear regression was employed for the correlation of tumor volume by PET and CT. The SUVmax and PET tumor volume were also compared using a regression analysis. Time to event was calculated as the time interval from the date of diagnosis to the date of death or the first finding on clinical or imaging exam that suggested local, regional, or distant disease recurrence and led to additional confirmatory testing (e.g., biopsy or additional imaging). The Cox proportional hazards model was used to evaluate prognostic variables for multivariate prediction of progression free survival (PFS, with event defined as relapse at any site or death) and overall survival (OS, with event defined as any death); tests were based on the likelihood-ratio statistic. Prognostic factors analyzed included stage, lymph node status, PET MTV, and maximum SUV. We analyzed MTV and maximum SUV as continuous variables, whereas we analyzed stage and lymph node status as categorical variables in the Cox proportional hazards model. Disease-free and overall survival curves were estimated using the Kaplan-Meier method.

Results

Patient characteristics

Patient characteristics including gender, age at diagnosis, primary site, American Joint Committee on Cancer stage, lymph node status at diagnosis, and type of neoadjuvant chemotherapy for the 59 patients are summarized in Tables I and II. The median age of the patients was 65 (range: 47–81 years), and there were more men in the group (56 male and 3 female patients). The primary tumor sites were the larynx in 38 patients (64.4%), the hypopharynx in eight patients (13.6%), and the oropharynx in 13 patients (22.0%). There were 26 patients (44.1%) with stage III tumors and 33 patients (65.9%) with stage IV tumors. Eighteen patients (31.5%) had N2 or N3 nodal disease before the start of neoadjuvant chemotherapy.

MTV and other correlations with the tumor burden

The mean CT tumor volume was 33.5 cm^3 (range, 2.1–182.6) and the mean metabolic tumor volume was 23.5 cm^3 (range, 1.2–170.8) for all patients. The average SUVmax was 8.9 (range, 1.4–78.0). The metabolic tumor volume correlated with the T-stage was statistically significant by both the ANOVA and the t-test ($p = 0.016$, $p = 0.014$). The CT volume was larger than the MTV because it encompassed all of the visualized disease; whereas we assigned a fixed SUV of 2.5 for the semiautomated delineation of the MTV. The CT volume was highly correlated with the MTV. The correlation coefficient was 0.77 ($p < 0.001$). We plotted the metabolic tumor volume on the PET studies versus the primary tumor SUVmax and, as shown in Figure 1, there was no association.

Table I. Patient and disease characteristics at baseline.

	Patients	
Characteristics	No	%
Total patients	59	
Sex		
Male	56	94.9
Female	3	5.1
Age (years)		
Median	65	
Range	47-81	
Primary tumor site		
Larynx	38	64.4
Hypopharynx	8	13.6
Oropharynx	**13**	22
Stage at time of diagnosis		
III	**26**	44.1
IVa	21	35.6
IVb	12	20.3
Neoadjuvant chemotherapy type		
Docetaxel/Cisplatin	**43**	72.9
TS-1/Cisplatin	**13**	22.0
5-FU/Cisplatin	3	5.0

Prognostic value

Tumor-specific characteristics were analyzed for their association with the metabolic tumor volume and SUVmax. Correlation of the grading of the lymph node site with the volume was not significant ($p = 0.064$) by ANOVA. The primary tumor volumes for patients with and without lymph node disease were 23.8 ± 11.8 cm^3 and 30.8 ± 12.1 cm^3, respectively; this difference was not significant ($p = 0.311$) by the t-test. The metabolic tumor volume correla-

Table II. Primary tumor and lymph node staging.

Lymph	Primary tumor status			
Node status	T1	T2	T3	T4
N0	–	–	10	9
N1	4	8	3	7
N2	2	3	5	6
N3	–	1	1	–

Table III. Cox Proportional-hazards modeling parameters for progression free survival from head and neck cancer in all patients

	Coefficient	SE	Coefficient/SE	P	Exp(B)
Stage	0.492	0.375	1.719	0.190	1.635
Lymph node metastasis	0.242	0.228	1.331	0.028	1.274
SUVmax	0.018	0.011	2.658	0.103	1.018
PET MTV	0.010	0.004	4.783	0.029	1.010

MTV, metabolic tumor volume; SE, standard error; Exp (Coefficient), hazard ratio; PET, positron emission tomography; SUVmax, maximal standardized uptake value.

Table IV. Cox proportional-hazards modeling parameters for survival from head and neck cancer in all patients

	Coefficient	SE	Coefficient/SE	P	Exp(B)
Stage	-0.251	0.531	0.223	0.637	0.877
Lymph node metastasis	0.221	0.584	1.143	0.046	1.247
SUVmax	0.014	0.025	0.328	0.567	1.014
PET MTV	0.011	0.007	2.600	0.052	1.011

MTV, metabolic tumor volume; SE, standard error; Exp (Coefficient), hazard ratio; PET, positron emission tomography; SUVmax, maximal standardized uptake value.

tion with stage was statistically significant by the t-test ($p = 0.277$). For the 26 patients with Stage III disease, the volume was 14.5 ± 10.2 cm^3, whereas for the 33 patients with Stage IV disease the volume was 27.5 ± 7.3 cm^3. The primary tumor SUVmax was not associated with the lymph node metastasis by both ANOVA ($p = 0.992$) and the t-test ($p = 0.176$). Furthermore, the primary tumor SUVmax was not associated with stage by the t-test ($p = 0.176$).

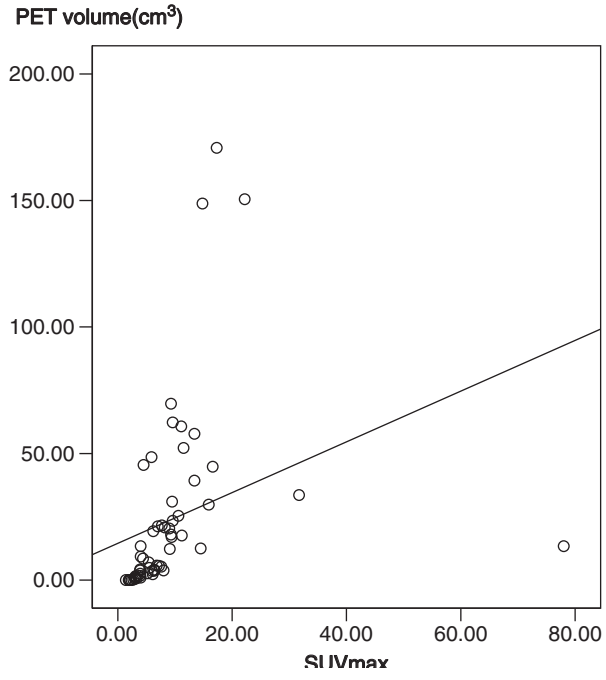

Figure 1. Head and neck tumor volume from an F-18 fluorodeoxyglucose-positron emission tomography (PET) study versus the maximal standardized uptake value (SUVmax) in the primary tumor (correlation coefficient [R2] =0.087).
Y= 14.512+1.003*R2, R2=0.087.

The overall response rate of neoadjuvant chemotherapy was 80.3% and all 59 patients received radiotherapy or chemoradiotherapy. The final response rate to treatment was 83.1%. A lower metabolic tumor volume at diagnosis was predictive of a treatment response ($p = 0.026$). However, the primary tumor SUVmax at diagnosis was not predictive of a treatment response ($p = 0.151$). The median time to disease progression was 9.0 months among the 16 patients with relapse. We analyzed the association between the progression free survival and the primary tumor SUVmax, metabolic tumor volume, stage and lymph node status using the Cox proportional-hazards model and observed that the metabolic tumor volume and lymph node status were significant predictors of disease progression of head and neck cancer (Table III). We also analyzed the association between overall survival and these factors, and observed that the lymph node status was a significant predictor of patient death ($p = 0.046$). The association between the overall survival and metabolic tumor volume was marginally confirmed ($p = 0.052$) (Table IV).

To further analyze the correlations of the metabolic tumor volume, a cut-off point was determined by generation of histograms of the tumor volumes for patients with and without recurrence and death. The two risk groups identified were patients with a tumor volume ≤ 9.3 cm^3 and patients with tumor volume from > 9.3cm^3. A higher MTV of 9.3 cm^3 was significantly associated with an increased risk of recurrence (2.19-fold, $p = 0.006$) and death (1.62-fold, $p = 0.051$). The Kaplan-Meier progression-free

survival curves and overall survival curves for the two tumor volume groups are shown in Figures 2 and 3.

Both metabolic tumor volume and lymph node status were predictive of recurrence and death, but not correlated with each other; a Kaplan-Meier analysis of the combination of these factors was performed. The two risk groups were patients with small tumor volumes ($V \leqslant 9.3$ cm^3) and no lymph node disease (n = 11 [Group I]) and patients with larger volumes, lymph node involvement, or both (n = 46 [Group II]). The Kaplan-Meier progression-free survival curves and overall survival curves for the two risk groups are shown in Figures 4 (p = 0.019) and 5 (p = 0.037).

Discussion

PET/CT is an increasingly popular imaging modality that incorporates both anatomic localization and functional information and has the potential of being a valuable tool for risk stratification in patients with head and neck cancer [17]. Recent studies have evaluated the ability of FDG-PET to predict outcomes. The prognostic value of FDG-PET for HNC remains controversial. Some studies on lung and head and neck cancers have suggested that a higher SUV is correlated with a worse prognosis [18–22]. Other studies have demonstrated that patients that had a primary tumor SUV greater than the median tended to have poorer local control and disease-free survival [23–28]. In contrast to some of the prior studies, we observed that the primary tumor SUVmax was not related to response to treatment, progression free survival or overall survival. Greven et al. [29] and Vernon et al. [30] also failed to confirm the maximum SUV as a predictor of outcome. Therefore, other metabolic tumor parameters besides SUV require investigation.

The tumor burden might be an important prognostic value. Plataniotis GA et al. and Knegjens et al. found that in patients with a larger tumor volume in advanced HNC, measured by CT or MRI, there was a correlation with inferior local control and overall survival [31]. Our study differs from this prior study in that our tumor volumes were derived from FDG-PET scans, which may be a more direct and reliable method for quantifying tumor burden, because it incorporates functional criteria.

La et al. [32] found that only tumor volume (as measured on PET), but not the SUV, was associated with progression free survival and overall survival in patients with head and neck cancer. These results are similar to our findings that the metabolic tumor

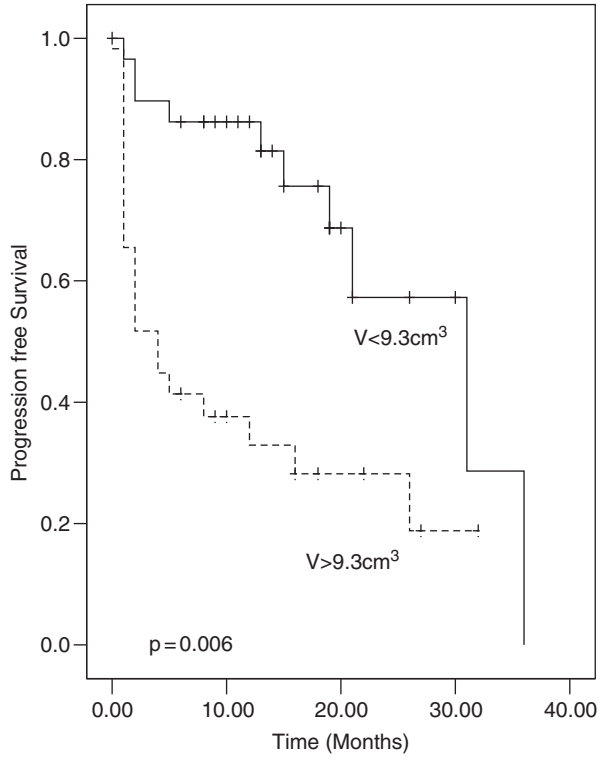

Figure 2. Progression free survival for two tumor volume subgroupings: tumor volume $\leqslant$ 9.3 cm^3, tumor volume $>$ 9.3 cm^3, as labeled (p = 0.006).

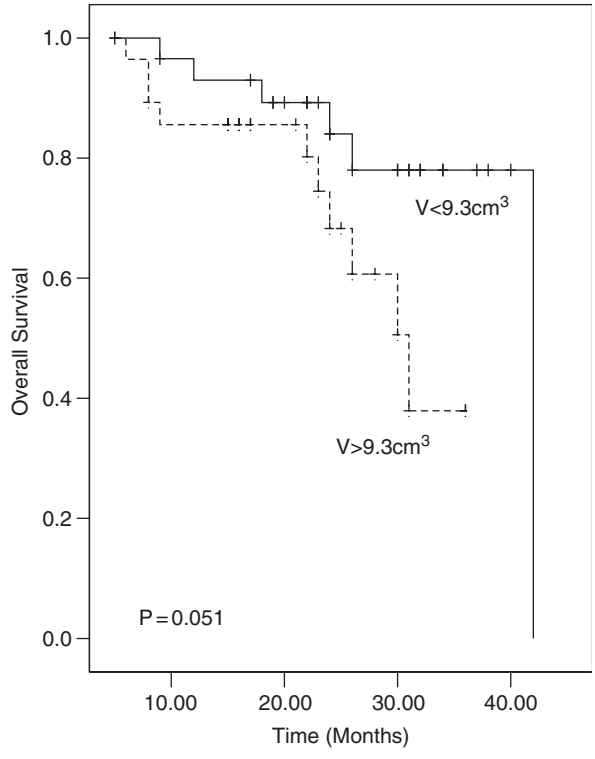

Figure 3. Overall survival for two tumor volume subgroupings: tumor volume $\leqslant$ 9.3 cm^3, tumor volume $>$ 9.3 cm^3, as labeled (p = 0.051).

volume was a more accurate predictor than the SUVmax with regard to response to treatment and the progression free survival. The significance of being able to stratify patients according to their MTV at diagnosis into two distinct outcome groups suggests that its specific value is significant and that the MTV might be a novel quantitative biomarker for predicting which patients will have a worse outcome before treatment is initiated. Similar results have been reported in lung cancer and lymphoma where the MTV was shown to be highly prognostic for disease progression and death, independent of other established prognostics factors [33,34]. In our study, the association between overall survival and metabolic tumor volume was marginally confirmed ($p = 0.052$). This may have been because of the small sample size and short term follow up period.

In addition, the results of this study showed that the lymph node status was strongly correlated with recurrence and overall survival. Previously a report [35] demonstrated that the lymph node status was significantly related to the disease-free and overall survival. Interestingly, although both volume and lymph node status are predictive of survival, they are not correlated with each other in patients with head and neck cancer. Thus, it is reasonable to suspect that they are independent predictors of survival that may be even more effective when combined. As shown in Figures 4 and 5, a subset of patients with relatively small tumors and no lymph node involvement had a good prognosis.

This observed powerful effect of metabolic tumor volume and lymph node status, and the absence of a correlation between them, may have a reasonable explanation that reflects the inherent biologic characteristics of the tumors [36]. The patients with large tumors fare more poorly than those with small tumors, and patients with lymph node spread also have a worse prognosis. Perhaps the group with the most favorable prognosis has tumors with cells that divide slowly and are of a type that does not readily spread beyond the primary tumor. Patients that do less well may have more aggressive tumors that spread to lymph nodes early, before the tumor becomes large. Thus, patients with small tumors that are free of lymph node involvement at the time of diagnosis do remarkably well after treatment; perhaps these patients can be reassured at the time of initial treatment that they have an excellent prognosis. Perhaps more importantly, the other patients that are predicted to do poorly may be candidates for more aggressive initial treatment.

In conclusion, the results of this study showed that the maximum SUV of the primary tumor was not associated with survival. However, the MTV and

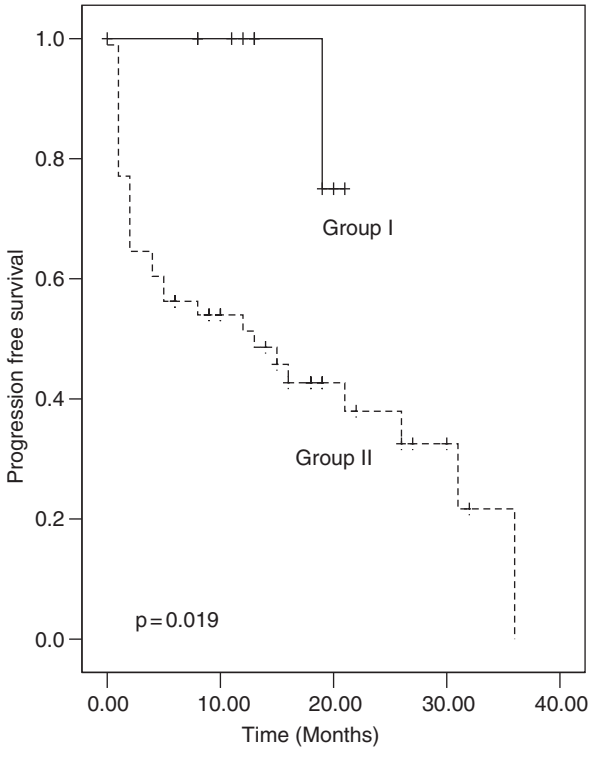

Figure 4. Progression free survival for two risk subgroupings: small volumes ($\leqslant 9.3$ cm^3) and no lymph node involvement [Group I], larger volume and lymph node involvement [Group II], as labeled ($p = 0.019$).

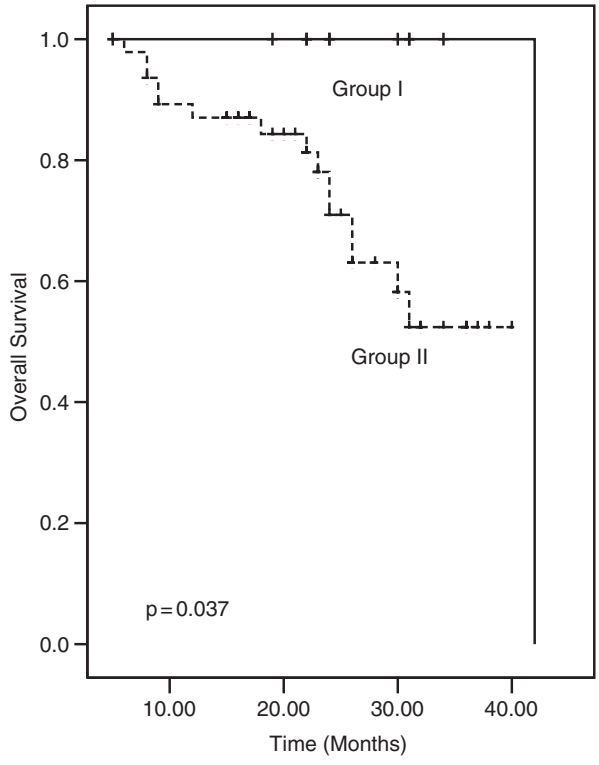

Figure 5. Overall survival for two risk subgroupings: small volumes ($\leqslant 9.3$ cm^3) and no lymph node involvement [Group I], larger volume and lymph node involvement [Group II], as labeled ($p = 0.037$).

lymph node status were associated with survival. The quantitative measurement of the tumor volume was used to separate patients with a good prognosis from those with a poorer prognosis. A subset of patients with relatively small tumors and no lymph node involvement did remarkably well. Additional large-scale studies are needed to confirm our findings.

Acknowledgment

This study was supported by a grant from the National R & D Program for Cancer Control, Ministry for Health, Welfare and Family Affairs, Republic of Korea (09299599).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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