Original Article

DNA repair capacity correlates with standardized uptake values from ^{18}F-fluorodeoxyglucose positron emission tomography/CT in patients with advanced non−small-cell lung cancer

Xin (Eric) Jiang [a,b], Ting Xu [a,**], Qingyi Wei [c,*], Peng Li [d], Daniel R. Gomez [a], Laurence E. Court [e], Zhongxing Liao [a]

[a] *Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA*
[b] *Duke University, Durham, NC 27708, USA*
[c] *Duke Cancer Institute, Duke University Medical Center, Durham, NC 27710, USA*
[d] *Department of Medical Oncology, Henan Cancer Hospital, Zhengzhou, Henan 450008, China*
[e] *Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA*

Abstract

Objective: The DNA repair capacity (DRC) of tumor cells is an important contributor to resistance to radiation and platinum-based drugs. Because DRC may be affected by tumor cell metabolism, we measured DRC in lymphocytes from patients with non−small-cell lung cancer (NSCLC) and compared the findings with the maximum standardized uptake value (SUV_{max}) on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) after (chemo)radiation therapy.

Methods: This study included 151 patients with stage IA-IV NSCLC who had FDG PET at a single institution and donated blood samples before chemotherapy. We assessed the correlation of DRC, measured in peripheral T lymphocytes by a host-cell reactivation assay with SUV_{max} and their associations with overall survival (OS) time by hazards ratios calculated with a Cox proportional hazards regression model.

Results: SUV_{max} of the primary tumor at diagnosis was inversely associated with lymphocyte DRC ($r = -0.175$, $P = 0.032$), particularly among patients with advanced disease ($r = -0.218$, $P = 0.015$). However, ΔSUV_{max} of primary tumor was not significantly associated with DRC ($r = 0.005$, $P = 0.968$). SUV_{max} of regional lymph nodes at diagnosis ($r = -0.307$, $P = 0.0008$) and after (chemo)radiation treatment ($r = -0.329$, $P = 0.034$) and SUV_{max} of the primary tumor after (chemo)radiation treatment ($r = -0.253$, $P = 0.045$) were also inversely associated with OS time.

Conclusion: DRC was inversely associated with primary tumor SUV_{max} before treatment but not with ΔSUV_{max} after (chemo)radiation.

 * Corresponding author. Duke Cancer Institute, Duke University Medical Center, Durham, NC 27710, USA.
 ** Corresponding author. Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Main Building Y3.5327, 1515 Holcombe Blvd, Houston, TX 77030, USA.
  E-mail addresses: txu@mdanderson.org (T. Xu), qingyi.wei@duke.edu (Q. Wei).

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Introduction

Treatment for non−small-cell lung cancer (NSCLC) includes chemotherapy, radiotherapy, and surgery, in various combinations. However, the recommended treatment for unresectable tumors is often concurrent chemoradiotherapy.[1]

Glucose uptake by tumors, measured with the radiotracer ^{18}F-fluorodeoxyglucose on positron emission tomography (FDG PET), provides an assessment of the metabolic activity of tumors *in vivo*. Cancers such as NSCLC can be detected by elevated glucose uptake on PET images.[2] This uptake can be quantified on PET images as standardized uptake values (SUVs), which are directly proportional to the proliferative activity of the tumor.[3] Changes in SUV for primary tumors and peripheral lymph nodes before and after treatment can be useful for assessing whether a tumor has responded to therapy.

Exposure of tumors to radiation generates double-strand breaks in cellular DNA, which are lethal, if they cannot be adequately repaired.[4] Thus, a poor response to radiotherapy could reflect efficient DNA repair capacity (DRC) of tumor cells. The SUV, which also represents tumor cell activity, could be affected by the DRC as well. In this study, we evaluated potential correlations between DRC, measured in peripheral lymphocytes with a host-cell reactivation assay, but presumably inherited as a host factor, and the maximum SUV (SUV_{max}) of the primary tumor and regional lymph nodes on PET scans obtained before and after radiation, with or without concurrent chemotherapy, for unresectable NSCLC.

Materials and methods

Patient selection criteria

Patients were selected from a database of patients who had received radiation ≥60 Gy delivered by intensity-modulated radiation therapy (IMRT) or passively scattered proton therapy (PSPT), with or without chemotherapy, as definitive treatment for stage IA-IV NSCLC from January 2002 through April 2009 in the Department of Radiation Oncology at MD Anderson Cancer Center. The 151 selected patients all had PET scans of primary tumors and regional lymph nodes before treatment; some had PET scans after treatment, and all had information on DRC available through the same database.

SUV measurement

Primary tumor and regional lymph node SUV measurements were obtained as described previously.[5] The maximum values were calculated as SUV = tissue radioactivity concentration (mCi/ml)/[injected dose (mCi)/body weight (kg)]. All measured SUVs were described as SUV_{max}, which was obtained from the maximum tumor uptake in a 1-pixel region of interest. Use of SUV_{max} is an effective way of reducing partial volume effects[6] and standardizing data collection. Changes between pretreatment SUV (SUV_{pre}) and post-treatment SUV (SUV_{post}) were calculated as $\Delta SUV = SUV_{post} - SUV_{pre}$. In patients who had chemotherapy, the SUV_{pre} data were derived from PET images obtained before the start of chemotherapy. SUV_{post} data were derived from PET images obtained at the closest time after radiation therapy (RT) had been completed.

DRC measurement

Blood samples (20 ml) had been collected in 2 green top heparin vacutainer tubes. Peripheral lymphocytes were then isolated within one day using Ficoll approach and cryopreserved in liquid nitrogen. At least 6×10^6 lymphocytes were thawed and cultured in duplicates for 3 days before transfection. 250 ng plasmid was used for each transfection. Finally, DRC was measured in peripheral lymphocytes with a host-cell reactivation assay.[7,8] The assay used benzo(a)pyrene diol epoxide (BPDE), an ultimate metabolite of polycyclic aromatic hydrocarbon in tobacco smoke, to damage non-replicating recombinant plasmids containing a chloramphenicol acetyltransferase (CAT) reporter gene, which had been transfected in parallel with undamaged plasmids by the diethylaminoethyl-dextran method[9] into cultured T-lymphocytes stimulated by phytohemagglutinin.

Cultures were then incubated for 40 hours after transfection to allow the repair and expression of the CAT reporter.

Because unrepaired DNA adducts can block CAT transcription, measurable CAT activity in the transfected cells was proportional to the ability of the cells to remove BPDE-induced DNA adducts from the plasmids. CAT activity was measured by adding chloramphenicol and [^{3}H] acetyl coenzyme A and measuring the production of [^{3}H] monoacetylated and [^{3}H] diacetylated chloramphenicols with a scintillation counter. Finally, DRC was calculated as a ratio of the radioactivity (cpm) of cells transfected with BPDE-treated plasmids to the radioactivity of cells transfected with untreated plasmids, as a measure of treated versus baseline CAT expression levels.

Statistical analysis

Data were analyzed with SAS version 9.3 (SAS Institute, Cary, NC, USA). We used one-way frequency procedures for discrete variables and univariate analysis of the distributions of continuous variables such as age, DRC, and SUV. Student's *t* tests were used to compare differences in continuous variables between two groups for each categorized discrete variable. Spearman's rank correlation coefficients and Pearson correlation coefficients were used to express correlations between SUV and DRC or overall survival (OS) time. We used the Cox proportional hazards model to evaluate potential effects of DRC and SUV on OS, calculated as hazard ratios (*HR*s) with corresponding 95% confidence intervals (*CI*s). Survival time was calculated from the date of diagnosis until the date of death or last follow-up. All *HR*s were adjusted for age, gender, race and stage. Kaplan−Meier analysis was used to visualize the effect of SUV on the cumulative probability of OS, and log-rank tests were used to compare differences in survival time of the various groups. All reported *P* values were two-sided, with *P* < 0.05 as the significance level.

Results

Characteristics of the 151 patients in this analysis are shown in Table 1. The dataset consisted of 72 men and 79 women, with a median age of 62 years (range, 29−87 years); 57.6% (87/151) were <65 years old. One hundred and ten patients (72.8%) were non-Hispanic white. Eighty-six patients (57.0%) had adenocarcinoma, followed by squamous cell carcinoma (32/151, 21.2%), and others including not-otherwise-

specified NSCLC. Most patients (125/151, 82.8%) had advanced disease (stage III−IV according to the 7th edition of the American Joint Committee on Cancer staging criteria), and 90.1% (136/151) received concurrent chemoradiation. Dates of diagnosis ranged from September 2001 through July 2008, and 116 patients (76.8%) had died during the 10-year follow-up period (Table 1).

The distribution of continuous variables and the correlations between SUV characteristics, DRC, and OS time are shown in Table 2. The median DRC was 8.5% (range 3.6%−17.5%). No difference in DRC mean (±SD) values was found for patients with early versus advanced stage disease [(8.3 ± 2.7)% *vs.* (8.8 ± 2.8)%, *P* = 0.825]. The median OS time was 20.2 months (range 3.0−122.7 months). The median OS time was 32.5 months for those with early disease and 17.9 months for advanced disease; corresponding mean OS time was significantly different [(45.7 ± 6.7) months *vs.* (37.5 ± 3.9) months; *P* = 0.047]. Median primary tumor SUV$_{max}$ at diagnosis was 13.8 for all patients (range 2.4−52.8) and mean values were not significantly different by stage (stage I−II *vs.* stage III−IV: 16.4 *vs.* 15.0; *P* = 0.426). The median primary tumor SUV$_{max}$ after RT (available for 63 patients) was 6.0 (range 0.0−25.0). The mean SUV$_{max}$ of the primary tumor after RT was 5.8 for early stage patients and 7.4 for advanced stage patients separately (*P* = 0.328). The mean value of

Table 1
Characteristics of the study population.

Parameter	*n* (%)	Deaths (%)
All patients	151 (100.0)	116 (76.8)
Age, years		
<65	87 (57.6)	64 (55.2)
≥65	64 (42.4)	52 (44.8)
Gender		
Male	72 (47.7)	57 (49.1)
Female	79 (52.3)	59 (50.9)
Ethnicity		
Non-Hispanic white	110 (72.8)	84 (72.4)
Black	35 (23.2)	27 (23.3)
Hispanic	6 (4.0)	5 (4.3)
Tumor histology		
Adenocarcinoma	86 (57.0)	69 (59.5)
Squamous	32 (21.2)	28 (24.1)
Others	33 (21.8)	19 (16.4)
Disease stage		
I-II	26 (17.2)	17 (14.7)
III-IV	125 (82.8)	99 (85.3)
Chemotherapy		
Yes	136 (90.1)	104 (89.7)
No	15 (9.9)	12 (10.3)
Radiation treatment		
Yes	151 (100.0)	116 (100.0)
No	0 (0.0)	0 (0.0)

Table 2
Continuous variables and correlation analysis of SUV with DNA repair capacity and overall survival time.

Parameter	n	Median	Range	DNA repair capacity		Overall survival time	
				Correlation (r)	P	Correlation (r)	P
Age	151	62.0	29.0—82.6	—	—	—	—
DNA repair capacity, %							
All patients	151	8.5	3.6—17.5	—	—	−0.012	0.880
Early-stage (I-II)	26	7.8	5.2—16.9	—	—	−0.115	0.575
Advanced-stage (III-IV)	125	8.6	3.6—17.5	—	—	0.026	0.772
Overall survival time, months							
All patients	151	20.2	3.0—122.7	—	—	—	—
Early-stage (I-II)	26	32.5	10.5—97.7	—	—	—	—
Advanced-stage (III-IV)	125	17.9	3.0—122.7	—	—	—	—
SUV_{max} of primary tumor at diagnosis							
All patients	151	13.8	2.4—52.8	−0.175	0.032	−0.069	0.398
Early-stage (I-II)	26	15.5	2.6—40.2	0.259	0.201	−0.098	0.634
Advanced-stage (III-IV)	125	13.4	2.4—52.8	−0.218	0.015	−0.085	0.347
SUV_{max} of primary tumor after RT							
Total	63	6.0	0.0—25.0	−0.233	0.066	−0.253	0.045
Early-stage (I-II)	16	6.4	0.0—12.2	−0.100	0.712	−0.217	0.420
Advanced-stage (III-IV)	47	6.0	0.0—25.0	−0.319	0.029	−0.245	0.097
ΔSUV_{max} of primary tumor							
Total	63	−6.6	−25.9 to 7.2	0.005	0.968	−0.097	0.451
Early-stage (I-II)	16	−6.7	−23.0 to −0.6	−0.126	0.641	−0.541	0.030
Advanced-stage (III-IV)	47	−6.5	−25.9 to 7.2	0.023	0.877	0.022	0.884
SUV_{max} of regional lymph nodes at diagnosis							
Total	116	4.5	0.0—51.0	−0.044	0.637	−0.307	0.0008
Early-stage (I-II)	21	0.0	0.0—20.0	−0.240	0.294	−0.073	0.754
Advanced-stage (III-IV)	95	5.0	0.0—51.0	−0.041	0.691	−0.275	0.007
SUV_{max} of regional lymph nodes after RT							
Total	42	0.0	0.0—22.2	−0.164	0.298	−0.329	0.034
Early-stage (I-II)	11	0.0	0.0—13.7	−0.104	0.761	−0.491	0.125
Advanced-stage (III-IV)	31	2.8	0.0—22.2	−0.135	0.468	−0.232	0.210
ΔSUV_{max} of regional lymph nodes							
Total	42	0.0	−16.0 to 10.6	−0.093	0.556	0.108	0.494
Early-stage (I-II)	11	0.0	−6.3 to 10.6	0.813	0.002	0.000	1.000
Advanced-stage (III-IV)	31	−0.2	−16.0 to 10.1	−0.212	0.253	0.091	0.628

SUV: standardized uptake value; SUV_{max}: maximum standardized uptake value; RT: radiation therapy; ΔSUV_{max}: changes from pretreatment SUV_{max} to post-treatment SUV_{max}, calculated as $\Delta SUV_{max} = postSUV_{max} - preSUV_{max}$; —: not applicable.

ΔSUV_{max} of primary tumor was −9.8 for early stage and −7.6 for advanced stage patients ($P = 0.316$). The range of reduction in primary tumor SUV_{max} was 20%—100% for 50 patients (79.4%), but 2 patients had no change and 5 patients had increases of 4%—189%. The median SUV_{max} of the regional lymph nodes at diagnosis was 4.5 for all patients (range 0.0—51.0). It was significantly different between stage groups with mean values of 2.8 and 6.9 for early and advanced stage separately ($P = 0.021$). The median SUV_{max} of the regional lymph nodes after radiation therapy was 0 for all patients (range of 0.0—22.2). The mean values of SUV_{max} were not significantly different between stage groups (stage I—II vs. stage III—IV: 2.9 vs. 3.6, $P = 0.695$). The reduction in SUV_{max} for the regional lymph nodes ranged from 6% to 100% for 20 of the 42 patients for whom this information was available; another 14 patients had no SUV_{max}

detected at diagnosis or after radiation therapy, and 8 patients showed increases in SUV_{max} ranging from 14% to 151%. The difference in mean regional-node ΔSUV_{max} between stage groups was not significant at $P = 0.286$ (stage I—II vs. stage III—IV: −0.39 vs. −2.42).

We further assessed correlations between the SUV_{max} and DRC expressed as Spearman's rank correlation coefficients (Table 2). The SUV_{max} of the primary tumor at diagnosis correlated significantly with a decrease in DRC ($r = −0.175$, $P = 0.032$) in all 151 patients, and this association was more pronounced for the 125 patients with advanced disease ($r = −0.218$, $P = 0.015$) than for the 26 patients with early disease ($r = 0.259$, $P = 0.201$). The SUV_{max} of the primary tumor after radiation therapy marginally correlated with a decrease in DRC ($r = −0.233$, $P = 0.066$) in the 63 patients for whom this

information was available; similarly, the association was significant for 47 patients with advanced disease ($r = -0.319$, $P = 0.029$) but not for the 16 patients with early disease ($r = -0.100$, $P = 0.712$). Notably, in 11 patients with early disease, ΔSUV_{max} of the regional lymph nodes correlated significantly with DRC ($r = 0.813$, $P = 0.002$). Scatter plots shown in Fig. 1 also showed similar trends of correlation between DRC and SUV_{max} of the primary tumor at diagnosis according to disease stage.

Primary tumor SUV_{max} after treatment and SUV_{max} of regional lymph nodes at diagnosis and after treatment were also found to correlate with a decrease in OS time ($r = -0.253$, $P = 0.045$; $r = -0.307$, $P = 0.0008$ and $r = -0.329$,

$P = 0.034$). The ΔSUV_{max} of the primary tumor for the 16 patients with early-stage disease also correlated with OS time ($r = -0.541$, $P = 0.030$), as did SUV_{max} of regional lymph nodes at diagnosis for the 95 patients with advanced-stage disease ($r = -0.275$, $P = 0.007$).

Finally, we performed survival analysis using a Cox proportional hazards regression model to evaluate the potential influence of DRC and SUV on OS, calculated as *HR*s and corresponding 95% *CI*s. Crude *HR*s and *HR*s adjusted for age, gender, race and stage (Table 3) confirmed the correlation analysis findings in that every unit increase in SUV_{max} of the primary tumor after treatment led to a 9% increase in *HR* for poor OS, and every unit increase in the SUV_{max} of the regional

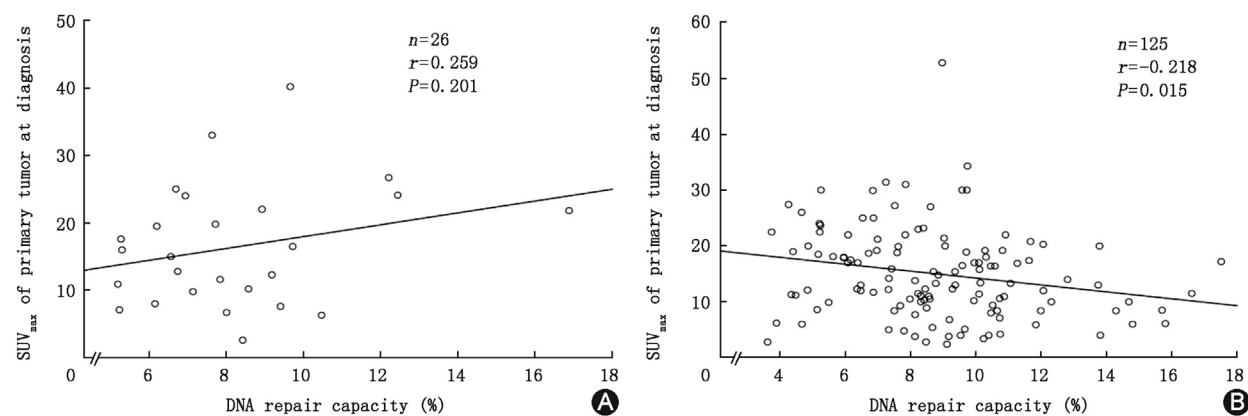Fig. 1. Correlations between DNA repair capacity (DRC) and maximum standardized uptake value (SUV_{max}) on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) of the primary tumor at diagnosis for stage I-II (A) and stage III-IV (B).

Table 3
Associations between SUV and overall survival.

Parameter	Crude *HR* (95% *CI*)	Adjusted *HR*[a] (95% *CI*)
DNA Repair Capacity, % (continuous)	1.03 (0.97−1.10)	1.02 (0.96−1.09)
Dichotomized (≥ 8.5 *vs.* <8.5)	0.90 (0.62−1.29)	0.92 (0.63−1.33)
SUV_{max} of primary tumor at diagnosis	1.00 (0.98−1.02)	1.00 (0.98−1.02)
Dichotomized (≤ 13.8 *vs.* >13.8)	1.05 (1.02−1.12)[b]	1.08 (0.75−1.57)
SUV_{max} of primary tumor after RT	1.06 (1.00−1.05)[b]	1.09 (1.03−1.16)[b]
Dichotomized (≤ 6.0 *vs.* >6.0)	1.13 (0.73−1.75)	1.17 (0.75−1.82)
ΔSUV_{max} of primary tumor	1.02 (0.98−1.07)	1.02 (0.98−1.07)
Dichotomized (≤ -6.6 *vs.* >-6.6)	0.93 (0.59−1.46)	0.92 (0.59−1.45)
SUV_{max} of regional lymph nodes at diagnosis	1.03 (1.00−1.05)[b]	1.03 (1.00−1.05)[b]
Dichotomized (≤ 4.5 *vs.* >4.5)	1.71 (1.13−2.60)[b]	1.66 (1.06−2.60)[b]
SUV_{max} of regional lymph nodes after RT	1.07 (1.01−1.14)[b]	1.06 (0.99−1.15)
Dichotomized (0 *vs.* >0)	2.92 (1.36−6.25)[b]	4.03 (1.50−10.83)[b]
ΔSUV_{max} of regional lymph nodes	0.96 (0.89−1.04)	0.94 (0.86−1.01)
Dichotomized (≤ 0 *vs.* >0)	1.66 (0.77−3.57)	1.49 (0.68−3.31)

SUV: standardized uptake value; SUV_{max}: maximum standardized uptake value; ΔSUV_{max}: percentage changes from pretreatment SUV_{max} to posttreatment SUV_{max}, calculated as $\Delta SUV_{max} = postSUV_{max} - preSUV_{max}$; *HR*: hazard ratio; *CI*: confidence interval; RT: radiation therapy.
[a] Adjusted for age, sex, race and stage.
[b] $P < 0.05$.

lymph nodes at diagnosis led to a 3% increase in *HR* for poor OS. Further, when the SUV_{max} of the regional nodes at diagnosis and the SUV_{max} of the regional nodes after RT were dichotomized at their median values, the adjusted *HR*s were 1.66 (95% *CI*: 1.06−2.60) and 4.03 (95% *CI*: 1.50−10.83) (Table 3). Kaplan−Meier curves of OS according to the SUV_{max} of regional nodes at diagnosis (Fig. 2A and B) indicate a significant difference for patients with advanced disease ($P = 0.017$) but not for those with early-stage disease ($P = 0.532$); on the other hand, OS according to the SUV_{max} of the regional nodes after radiation was significantly different for the 11 patients with early-stage disease ($P = 0.033$) and was borderline different for the 31 patients with advanced-stage disease ($P = 0.060$) (Fig. 2C and D).

Discussion

We previously reported that large decreases in SUV_{max} after definitive radiation were associated with better survival for 49 patients with locally advanced

(stage III) NSCLC; more specifically, having a high post-treatment SUV_{max} (in either the primary tumor or the lymph nodes) was associated with higher risks of death and disease recurrence.[5] In another study of 84 patients with stage III NSCLC treated with concurrent chemotherapy and high-dose proton therapy, we found that SUV_{max} after treatment predicted local recurrence-free survival and that SUV_{max} both before and after treatment predicted distant metastasis-free survival, progression-free survival, and OS.[10] In the present analysis of a larger number of patients (151), most (82.8%) of whom had stage III−IV disease, OS was significantly associated with SUV_{max} of the primary tumor after treatment and with SUV_{max} of the regional lymph nodes, both at diagnosis and after treatment.

FDG-PET is useful for visualizing cellular metabolism. Compared with normal cells, tumor cells usually show higher glucose metabolism,[11] which is important for deoxynucleoside triphosphate (dNTP) and DNA synthesis. Elevated uptake of FDG as seen on PET scans may be biologically correlated with
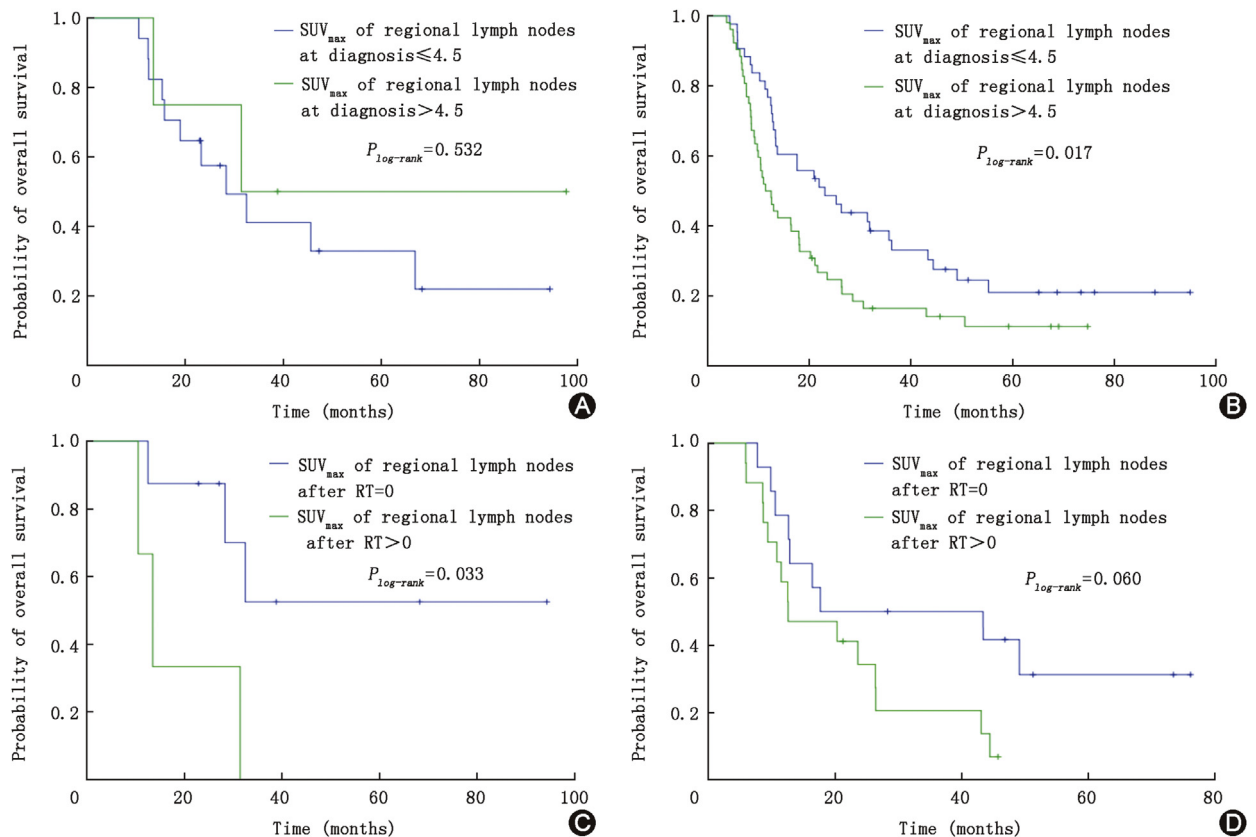

Fig. 2. Kaplan−Meier curves of overall survival according to the SUV_{max} of regional lymph nodes at diagnosis for stage I-II (A) and III-IV (B) and after RT for stage I-II (C) and III-IV (D). SUV_{max}: maximum standardized uptake value; RT: radiation therapy.

tumor metastatic potential, aggressiveness, proliferation or hypoxia, and angiogenesis.[12−14] Therapy with ionizing radiation controls cell growth via DNA damage, mainly DNA double-strand breaks. In the present study, the DRC we measured reflected nucleotide excision repair, not double-strand break repairs, and thus was not correlated with the effects of radiation treatment. However, DRC measured in peripheral blood lymphocytes was significantly inversely associated with SUV_{max} of the primary tumor at diagnosis in patients with stage III−IV disease. Genomic stability reflects a balance between DNA damage and repair; a cell's nucleotide excision repair capacity is essential to this process. In tumor cells, this balance is broken, leading to their uncontrolled growth. From a biological standpoint, it is plausible that tumor cells with poor DRC would show elevated metabolism, increased proliferation, and high SUV_{max}. We reported previously that optimal DRC in peripheral lymphocytes was associated with poor survival in 591 patients with NSCLC after platinum-based chemotherapy.[7] FDG uptake could reflect levels of proteins involved in chemo-resistance within tumor cells, and thus SUV_{max} could be useful for assessing the effectiveness of platinum-based chemotherapy.[15]

To our knowledge, very few studies have investigated the correlation between DNA repair and SUV_{max}. A Japanese research group investigated the relationship between the expression level of ERCC1 (a core protein in nucleotide excision repair) and SUV_{max} in 38 patients with thymoma and reported a statistically significant correlation (Spearman $r = 0.554$).[16] However, the finding from a Korean research group did not support that correlation in 313 NSCLC patients.[17] Therefore, more rigorous investigation of potential relationships between FDG uptake and DRC is warranted.

In conclusion, our findings from the present study confirmed that SUV_{max}, especially that of primary tumors after radiation treatment and that of regional lymph nodes before and after radiation treatment, was significantly associated with OS in patients with NSCLC. SUV_{max} of primary tumors before treatment was significantly inversely associated with cellular DRC, as evaluated in peripheral lymphocytes. Therefore, assessing the DRC in surrogate tissues may provide guidance for the choice of chemotherapeutic agents or other treatment modalities in the future.

Conflicts of interest

None.

Acknowledgements

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