의학석사 학위논문

CT 질감 분석에서 얻은 종양의 비균질성: 호지킨 림프종의 예후 인자

Tumor heterogeneity from CT texture analysis is a prognostic factor of Hodgkin lymphoma

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박미연

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이 논문을 의학석사 학위 논문으로 제출함

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영문요약

Purpose

To find the factors showing significant correlation with prognosis by analyzing computed tomography (CT) imaging markers of the patients diagnosed as Hodgkin lymphoma, and to find the factors, which show the additional correlation when analyzed with tumor burden, a known prognostic factor.

Materials and methods

Between January 2007 and December 2016, a total of 134 patients (78 males, mean age = 37.3 years) who were diagnosed as Hodgkin lymphoma with appropriate CT scans and positron emission tomography-computed tomography (PET-CT) scans. The median interval between diagnosis and the last follow-up date was 53 months (30.5 - 74.25 months). CT texture parameters of Hodgkin lymphoma were obtained by using an in-house software based on plug-in package for ImageJ. Univariate and multivariable Cox regression analysis were used to investigate the association between the prognosis, and several clinical and CT texture parameters.

Results

A total of 43 patients showed resistance to the treatment, relapse or death. In univariate and multivariable logistic regression analysis of clinical parameters in all patients, age and the number of involved sites were significantly associated with prognosis (HR, 1.02, P=0.03; HR, 1.82, P=0.03, respectively). In the 99 patients with thoracic involvement, the univariate and multivariable logistic regression analysis revealed that the number of involved sites and energy, the sum of squared value of gray-level co-occurrence matrix (GLCM) in each pixel, were independently associated with the prognosis (HR, 1.66, P=0.002; HR, 0.90, P=0.02, respectively). The Kaplan-Meier curve using these two predictive factors were significantly different (P<0.05).

Conclusion

Among the CT texture parameters, energy shows significant correlation with outcome in the patients with Hodgkin lymphoma. This can mean that increased heterogeneity of tumors is associated with worse prognosis.

Key words

Texture analysis; Hodgkin lymphoma; prognosis; heterogeneity

차 례

표 목차 및 그림 목차

Introduction

Patients with Hodgkin lymphoma are usually treated with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and radiotherapy. Hodgkin lymphoma is known to have the best outcome after treatment [1-4]. Complete response rate is approximately 80-90 %. However, about 15 % of the patients with limited stage, and 35-40 % of the patients with advanced stage are refractory to therapy or relapse after therapy within years [3, 5]. For these patients, additional treatment such as high-dose chemotherapy after autologous stem cell transplantation can help to improve the prognosis [4, 6].

Previous studies have suggested that the tumor burden is the best prognostic factor for predicting the risk of relapse and treatment response of Hodgkin lymphoma [3, 5, 7-10]. However, it is difficult to measure the exact tumor burden, so there is a limit to clinical applications. Although there are other well-known clinical prognostic factors, they are only indirect indicators [11-15].

To diagnose Hodgkin disease and evaluate its progress, the pre-treatment and post-treatment computed tomography (CT) studies are generally performed. However, there are few studies about the role of quantitative CT imaging markers on tumor morphology extracted from CT images, as prognostic factors [16]. If we find out the radiologic prognostic factor before treatment, it would be a great benefit for the patients because we can decide the adequate treatment plan and prepare for the deteriorating condition of the patients in advance.

The purpose of this study is to find the factors showing significant correlation with prognosis by analyzing CT imaging markers of the patients diagnosed as Hodgkin lymphoma.

Materials and Methods

Study population

This study was approved by the institutional review board of our institution (approval number: 2018-0658) which waived the requirement for informed consent due to the retrospective nature of this study.

Between January 2007 and December 2016, a total of 192 patients who were diagnosed with Hodgkin lymphoma were found. Among them, 58 patients were excluded; 17 patients only with postoperative or postprocedural CT images, possibly resulting in erroneous measurement; 16 patients due to follow-up loss before completing a chemotherapeutic cycle; 15 patients due to inadequate or insufficient CT studies (poor CT image quality or incomplete coverage of involved lesions); 6 patients without follow-up after completing a chemotherapeutic cycle, thus making us unable to assess the response or relapse; 2 patients with recurred lymphoma; 1 patient without PET study; 1 patient without demonstrable lymphoma involvement on CT scan.

All patients were pathologically confirmed to have Hodgkin lymphoma. They were ≥15 years of age at the time of diagnosis, without any previous treatment or history of malignancy. They had been treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) therapy regimens with or without radiation. Ann Arbor staging classification system was used for staging. Response criteria were based on standard guidelines [2, 4]. Electronic medical records and CT images were thoroughly reviewed.

Clinical data

From thorough review of electronic medical records, clinical and pathologic data were obtained including patient demographics, B symptom, hemoglobin, leukocyte count, percentage of lymphocyte, albumin level, bulky mass, clinical stage, extranodal involvement,

bone marrow involvement, number of involved sites, histologic types, and international prognostic score (IPS).

Image acquisition

All patients underwent a CT examination of involved sites, using 16- or 64-MDCT scanners (LightSpeed 16 or Optima CT660, GE Healthcare, Milwaukee, WI, USA; Somatom Sensation 16, Siemens Medical Systems, Erlangen, Germany). The typical imaging variables included the following: 120 kV tube voltage; 100-200 mAs effective tube current with dose modulation; axial scan mode; 128×0.6 mm detector collimation; and 3-5 mm axial and coronal reconstructed section thickness. Neck CT images were obtained at 70 seconds after the intravenous administration of 140 ml iopamidol (Isovue-370; Bracco Diagnostics, Princeton, NJ, USA) at a rate of 2.5 ml/seconds. Chest CT images were obtained after injection of 100 mL iopromide 300 (300mgI/mL Ultravist, Bayer Pharma, Berlin, Germany) at a rate of 2.5mL/sec using a power injector, with a 50 second delay following contrast medium injection. Abdomen and pelvis CT images were obtained after injectino of 150 mL of iopromide (Ultravist 370; Bayer Pharma, Berlin, Germany) at a rate of 3 ml/s using an automatic injector, with a 75 second delay following contrast medium injection. The radiological images were reviewed using a picture archiving and communication system (PACS).

Quantitative CT analysis

Digital Imaging and Communications in Medicine data of the CT images were loaded to the ImageJ (Bethesda, Maryland; http://rsbweb.nih.gov/ij/) for lesion segmentation. Every lymphomatous lesion needed for quantitative CT analysis was semi-automatically outlined in consensus by two expert radiologists, who were blind to the clinical information about the patients in each scan slice, matching with PET-CT scan at the time of diagnosis. Tumor

volume, mean attenuation (HU), standard deviation, modal value (most frequently appearing HU), median attenuation, skewness (symmetry of the pixel distribution), kurtosis (sharpness of the peak of the pixel distribution), entropy (complexity of the pixel distribution), uniformity, energy (sum of the squared value of GLCMs, homogeneity of the attenuation), variance (sum of the squared value of standard deviations), root mean square (energy/number of pixel), and coefficient of variance (standard deviation/mean) of involved lesions were obtained. These parameters are derived using the CT attenuation values (HU), and if the attenuation values of pixels are plotted, these values could be derived automatically using ImageJ software [17-19].

Tumor volume was calculated from the sum of the volumes of all the slices, using the areas of the lesion in the each slice and the slice thickness. The volume of the involved bone marrow was calculated from the volume of the hematopoietically active tissue using Wickramasinghe's formula (hematopoietic marrow volume = 20 mL/kg body weight). A variable fraction of the so-calculated total volume of marrow was considered for tumor burden according to the microscopic characteristics of the lymphoid infiltration: diffuse (50%), focal (10%) or nodular (5%). Finally, the calculated tumor burden was normalized to body surface area, and this relative tumor burden (rTB). This technical procedures have been detailed carefully in previous studies [5, 7, 9, 10, 20, 21].

Statistical analysis

Continuous variables were expressed as the means ± standard deviations, and categorical variables as numbers and percentages. Outcome variables were divided into patients with complete response, and patients showing refractory diseases, relapse and death.

Univariate and multivariate Cox regression analysis with forward conditional method were used to analyze the independent prognostic factors of clinical variables and CT texture features on tumor response. The factors showing significant difference were dichotomized by

cutoff value, which were set by performing receiver operating characteristics (ROC) analysis. Kaplan-Meier survival analysis was used to significant variables in multivariate analysis.

Statistical analysis was performed using SPSS statistical software (SPSS Inc., version 21.0, Chicago, IL, USA). A *P*-value of less than 0.05 was considered to indicate a significant difference.

Results

Patients' characteristics

The characteristics of total 134 patients are described in Table 1. The mean age of included patients was 37.3 years, and the median interval between diagnosis and the last follow-up date was 53 months (30.5 - 74.25 months). Followings are clinical stage of the included patients: stage I = 9, stage II = 48, stage III = 25, stage IV = 52.

The patients who were died or showed recurrence or showed resistance to the treatment were 43 patients (32 %): 15, late relapse more than 6 months after chemotherapy; 21, early relapse less than 6 months after chemotherapy; 2, resistant to the treatment; 5 died patients. When comparing the complete response group to the adverse event group, age, body mass index (BMI), number of involved sites, clinical stage, and extranodal involvement were significantly different between two groups (*P* value = 0.02, 0.03, 0.005, 0.04, and 0.04, respectively).

Clinical predictors of adverse outcomes

The results of univariate and multivariable logistic regression analysis of clinical parameters were described in Table 2. In univariate analysis, age (HR, 1.02; *P*=0.02), number of involved sites (HR, 1.65; *P*=0.001), and advanced stage (HR, 2.03; *P*=0.03) were significantly correlated with adverse outcomes. In multivariable analysis using age, BMI, number of involved sites, advanced stage, and extranodal involvement, age (HR, 1.02; *P*=0.03) and number of involved sites (HR, 1.82; *P*=0.03) were independently associated with adverse events.

The statistically significant factors were dichotomized based on their optimal values obtained from ROC curve analysis. The optimal cut-off values were 30 years for age, and 2 for the number of involved sites. Kaplan-Meier survival analysis revealed that older patients

(more than 30 years old), and the patients with more than 2 involved sites showed worse outcome (P=0.036 and P< 0.001, respectively) (Fig 1, Fig 2).

CT texture analysis of thoracic involvement

Due to different reconstruction algorithm and scan timing among neck, chest and abdomen CTs, the texture analysis is difficult to evaluate. Thus, we performed subgroup analysis using the chest CT scans of the patients with thoracic involvement (Table 3). A total of 99 patients showed thoracic involvement. Of them, 57 patients had anterior mediastinal involvement. In the univariate analysis, age (HR, 1.03; P=0.01), number of involved sites (HR, 1.60; P=0.004), energy (HR, 0.90; P=0.03), and advanced stage (HR, 2.46; P=0.03) were significantly associated with adverse outcome. In a multivariable analysis using age, number of involved sites, median HU, energy and advanced stage, the number of involved sites (HR, 1.66; P=0.002) and energy (HR, 0.90; P=0.02) were independently associated with adverse events.

The statistically significant factors were dichotomized based on their optimal values obtained from ROC curve analysis. The optimal cut-off values were 2 for the number of involved sites and 1 x 10^8 for energy. Kaplan-Meier survival analysis revealed that the patients with more than 2 involved sites and the patients with lower energy showed worse outcome (P< 0.001 and P=0.049, respectively) (Fig 3, Fig 4).

Discussion

This study investigated several clinical and radiologic prognostic factors of Hodgkin lymphoma. In a total of 134 patients, age and number of involved sites were revealed as significant prognostic factors among the clinical parameters. For texture analysis, we select the patients who show thoracic involvement, because of the different protocols of neck, chest, and abdomen CT scans. In the 99 patients with thoracic involvement, the number of involved sites was significantly associated with prognosis among the clinical parameters, and energy, i.e. the sum of squared value of GLCM of each pixel, was significantly associated with prognosis among CT texture parameters. The patients with more number of involved sites and lower energy value tend to show worse outcome. The energy value reflects the homogeneity of pixel distribution. In other words, the tumors with lower energy value look more heterogeneous. Therefore, the result from this study can mean that increased heterogeneity of tumors is associated with worse prognosis. It is generally known that the prognosis of the patients is worse as the tumor heterogeneity becomes higher in the histopathologic and genomic aspects. Thus, this study is meaningful in that the heterogeneity in the radiologic aspect, especially CT, can predict the patients' prognosis.

Age, BMI, stage, and extranodal involvement were significantly different between the patients with complete remission and the patients with adverse outcome, though they were not showed as significant prognostic factors. Relative tumor burden, previously known as significant prognostic factor, did not show significant correlation with prognosis [3, 5, 7-12, 20].

Among the patients with abdominal involvement or cervical involvement, the CT texture parameters were not significantly associated with patient outcome, unlike thoracic involvement. The lymphomatous lesions in the thorax are mainly anterior mediastinal masses or conglomerated lymph nodes, but the lesions in the abdomen and neck are predominantly enlarged lymph nodes, which were smaller than thoracic lesions. When outlining each lesion, it is thought that these abdominal and cervical lesions are more vulnerable to partial volume artifact because of their small sizes. Therefore, accurate texture analysis seems to be more

difficult.

This study has some limitations. First, it is a retrospective study performed at a single medical institution, and has limited number of patients. The sampling error can occur in this study. In this study, the ratio of adverse outcome was very high (32.1 %): 22.8 % in the early stage, 39.0 % in the advanced stage. Although including all the excluded patients (n=192), the ratio of adverse outcome was higher (36.5 %). Perhaps our medical center, as a tertiary hospital, seemed to include more people with poor general conditions and people with higher stages, i.e. patients with stage IV were most common, so there is a limitation to generalizing to the entire population. In addition, the problem of artifacts can result in the error of CT texture analysis such as beam hardening artifact and partial volume artifact. These artifacts can aggravate tumor heterogeneity and interfere with accurate measurement of tumor textures on CT. Moreover, several unmeasurable extranodal lesions such as lymphangitic metastasis or splenomegaly cannot be evaluated correctly. These can be the reason why relative tumor burden does not show significant correlation with prognosis, unlike previous papers.

In conclusion, among the CT texture parameters, energy shows significant correlation with outcome in the patients with Hodgkin lymphoma. This can mean that more portion of low attenuation within the tumors, such as necrosis, tends to show worse prognosis. In the future, it will be necessary to perform more accurate texture analysis using larger data.

Tables

Table 1. Patient characteristics and comparison of complete response with adverse outcome

	Complete response (n=91)	**Adverse outcome (n=43)**	***P*-value**
Age, years	36.4 ± 15.7	43.8 ± 18.4	0.02
Male sex	51 (56 %)	27 (62.8 %)	0.46
BMI, kg/m^2	22.9 ± 4.0	21.6 ± 2.6	0.03
Hemoglobin, g/dL	12.7 ± 2.2	12.3 ± 2.0	0.30
Leukocytes, $10^3/\mu L$	9.4 ± 4.4	9.1 ± 5.6	0.79
Lymphocyte, %	21.8 ± 10.6	21.5 ± 13.1	0.89
Serum albumin, g/dL	3.7 ± 0.6	3.7 ± 0.6	0.78
Number of involved sites	1.5 ± 0.7	2.0 ± 1.0	0.005
IPS score	1.8 ± 1.2	2.1 ± 1.1	0.17
CT volume, cm^3	172.6 ± 248.6	194.2 ± 244.0	0.64
rTB, cm^3/m^2	109.6± 149.1	134.1± 156.3	0.38
Last follow-up, days	2090.8 ± 997.3	1864.7 ± 1071.1	0.23
B symptoms	30 (33 %)	18 (41.9 %)	0.32
Bulky mass	12 (13.2 %)	4 (9.3 %)	
Stage			0.04
Early (IA/IB/IIA/IIB)	44 (48.4 %)	13 (30.2 %)	
Advanced (III/IV)	47 (51.6 %)	30 (69.8 %)	
Extranodal involvement	38 (41.8 %)	26 (60.5 %)	0.04
BM involvement	8 (8.8 %)	4 (9.4 %)	0.92

Note. Data are demonstrated as numbers and percentages in parenthesis or mean ± standard deviation. BMI, body mass index; IPS, international prognostic score; CT, computed tomography; rTB, relative tumor burden; BM, bone marrow.

Table 2. Predictors of adverse outcomes in patients with Hodgkin lymphoma

	Univariate		**Multivariable**	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age	1.02 (1.00 – 1.04)	0.02	1.02 (1.00 – 1.04)	0.03
Male sex	0.79 (0.43 – 1.47)	0.46		
BMI	0.93 (0.86 – 1.01)	0.08		
Hemoglobin	0.93 (0.81 – 1.07)	0.32		
Leukocytes	1.00 (1.00 – 1.00)	0.58		
Lymphocyte	1.00 (0.97 – 1.02)	0.78		
Serum albumin	0.92 (0.55 – 1.55)	0.77		
Number of involved sites	1.65 (1.21 – 2.24)	0.001	1.82 (1.07 – 3.09)	0.03
IPS score	1.16 (0.91 – 1.48)	0.23		
CT volume	1.00 (1.00 – 1.00)	0.49		
rTB	1.00 (1.00 – 1.00)	0.31		
B symptom	1.18 (0.65 – 2.17)	0.59		
Bulky mass	0.85 (0.31 – 2.39)	0.76		
Advanced Stage	2.03 (1.06 – 3.89)	0.03		
Extranodal involvement	1.79 (0.97 – 3.30)	0.06		
BM involvement	0.99 (0.36 – 2.79)	0.99		

Note. BMI, body mass index; IPS, international prognostic score; CT, computed tomography; rTB, relative tumor burden; BM, bone marrow; CI, confidence interval; HR, hazard ratio.

Table 3. Predictors of adverse outcomes with thoracic involvement (n=99)

	Complete response (n=64)	**Adverse outcome (n=35)**	***P*-value**	**Univariate**		**Multivariable**	
				HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age, years	33.0 ± 14.5	42.5 ± 18.9	0.01	1.03 (1.01 – 1.04)	0.01		
Male sex	36 (56.2 %)	19 (54.3 %)	0.85	0.99 (0.51 – 1.92)	0.97		
BMI, kg/m^2	22.2 ± 4.1	21.4 ± 2.9	0.30	0.96 (0.87 – 1.05)	0.33		
Hemoglobin, g/dL	12.4 ± 2.1	12.0 ± 2.1	0.37	0.94 (0.81 – 1.10)	0.45		
Leukocytes, $10^3/\mu L$	10.4 ± 4.5	9.1 ± 5.9	0.22	1.00 (1.00 – 1.00)	0.11		
Lymphocyte, %	19.6 ± 9.8	20.9 ± 13.9	0.59	1.01 (0.98 – 1.04)	0.56		
Serum albumin, g/dL	3.6 ± 0.6	3.7 ± 0.6	0.71	1.09 (0.62 – 1.94)	0.76		
Number of involved sites	1.6 ± 0.8	2.1 ± 1.1	0.01	1.60 (1.16 – 2.22)	0.004	1.66 (1.20 – 2.29)	0.002
IPS score	2.0 ± 1.2	2.1 ± 1.1	0.47	1.10 (0.83 – 1.44)	0.52		
CT volume, cm^3	156.9 ± 250.0	73.4 ± 94.2	0.06	1.00 (1.00 – 1.00)	0.09		
Anterior mediastinal mass	41 (64.1 %)	16 (45.7 %)	0.08	0.56 (0.29 – 1.10)	0.09		
Mean HU	65.9 ± 15.9	71.3 ± 13.7	0.09	1.02 (1.00 – 1.04)	0.15		
Standard deviation of HU	42.4 ± 24.4	41.3 ± 13.7	0.81	1.00 (0.98 –1.01)	0.68		
Modal HU	69.3 ± 17.9	72.4 ± 17.8	0.39	1.01 (0.99 – 1.03)	0.51		
Median HU	68.1 ± 15.2	79.5 ± 46.4	0.07	1.01 (1.00 – 1.01)	0.06		
Skewness	-1.4 ± 2.0	-1.2 ± 1.9	0.59	1.05 (0.86 – 1.29)	0.61		
Kurtosis	20.6 ± 33.9	24.9 ± 46.3	0.61	1.00 (1.00 –1.01)	0.43		

Table 3. continued

Entropy	5.6 ± 0.8	5.7 ± 0.9	0.45	1.08 (0.71 – 1.64)	0.72		
Uniformity	0.03 ± 0.02	0.02 ± 0.02	0.80	1.78 (0.00 – 81.6 x10^7)	0.96		
Energy, 10^8	7.4 ± 10.9	2.8 ± 4.3	0.003	0.90 (0.82 – 0.99)	0.03	0.90 (0.81 – 0.98)	0.02
Variance	2385.2 ± 5194.9	1888.8 ± 1423.7	0.58	1.00 (1.00 – 1.00)	0.58		
RMS	80.7 ± 21.5	83.1 ± 16.0	0.58	1.00 (0.99 – 1.02)	0.75		
CV	0.8 ± 1.0	0.6 ± 0.2	0.32	0.46 (0.11 – 1.95)	0.29		
rTB, cm3/m2	139.3 ± 167.2	140.5 ± 164.7	0.97	1.00 (1.00 – 1.00)	0.83		
B symptom	23 (35.9 %)	14 (40 %)	0.69	1.01 (0.54 –2.07)	0.88		
Bulky mass	11 (17.2 %)	4 (11.4 %)	0.45	0.80 (0.28 – 2.26)	0.67		
Advanced stage	38 (59.4 %)	28 (80 %)	0.04	2.46 (1.07 – 5.63)	0.03		
Extranodal involvement	29 (45.3 %)	22 (62.9 %)	0.10	1.77 (0.89 – 3.52)	0.10		
BM involvement	5 (7.8 %)	3 (8.6 %)	0.90	1.03 (0.32 – 3.37)	0.96		

Note. BMI, body mass index; IPS, international prognostic score; CT, computed tomography; HU, Hounsfield unit; RMS, root mean square (energy/number of pixels); CV, coefficient of variance (standard deviation/mean); rTB, relative tumor burden; BM, bone marrow; CI, confidence interval; HR, hazard ratio.

Figures

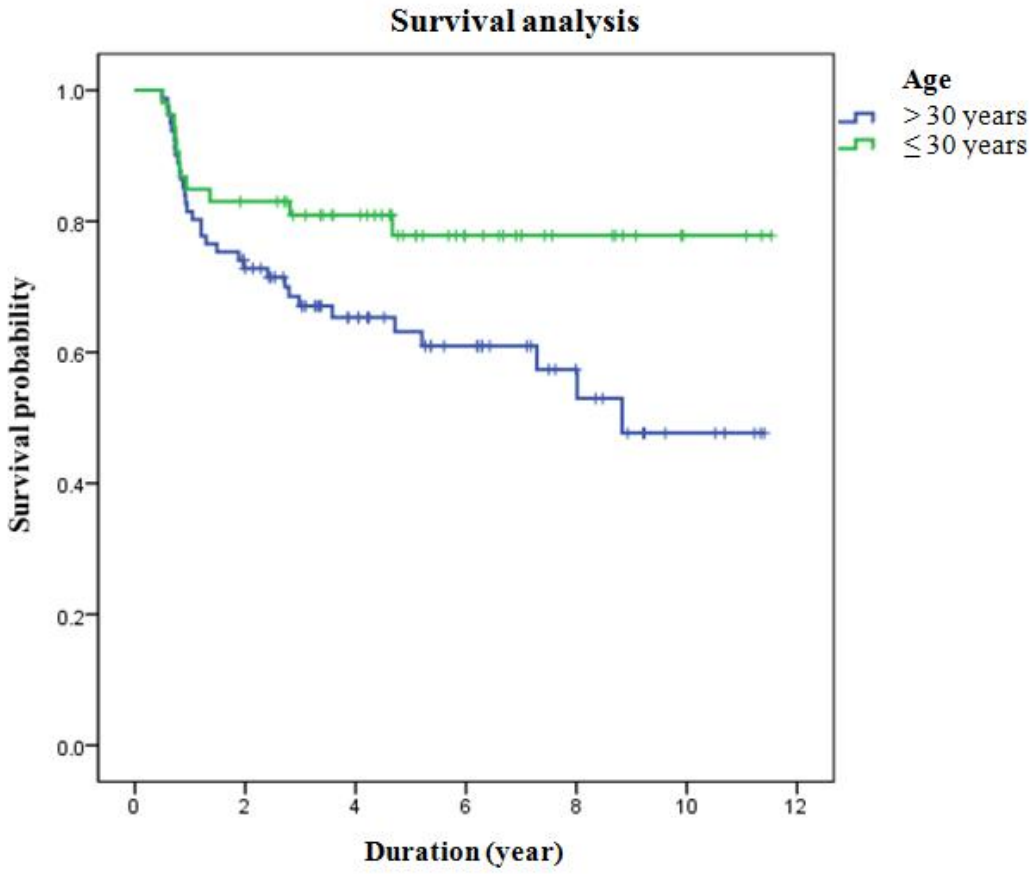

Figure 1. Kaplan-Meier survival analysis of age in all included patients (n = 134).

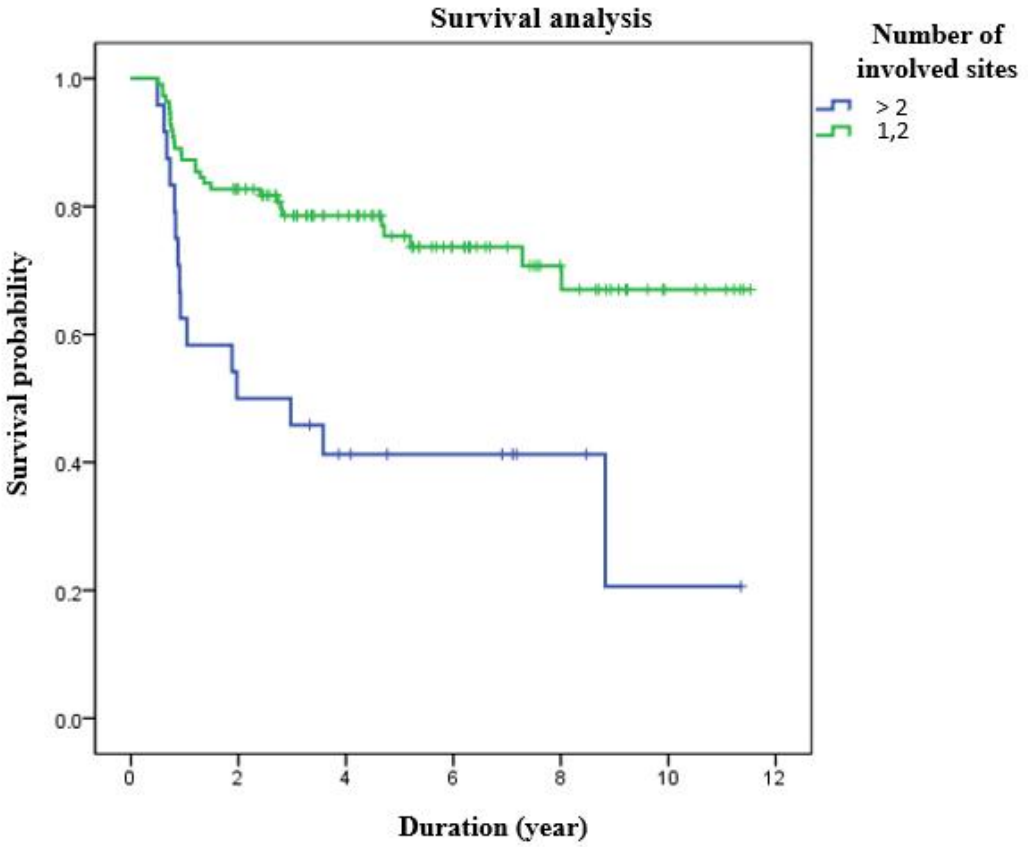

Figure 2. Kaplan-Meier survival analysis of the number of involved sites in all included patients (n = 134).

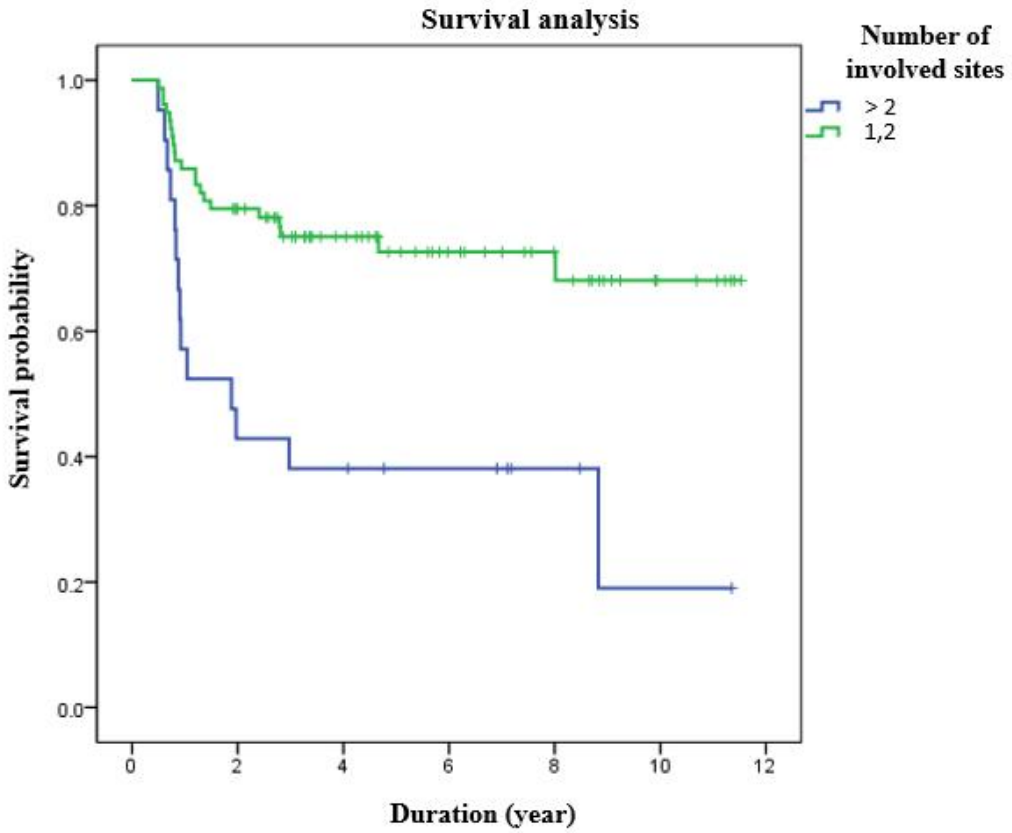

Figure 3. Kaplan-Meier survival analysis of the number of involved sites in the patients with thoracic involvement (n = 99).

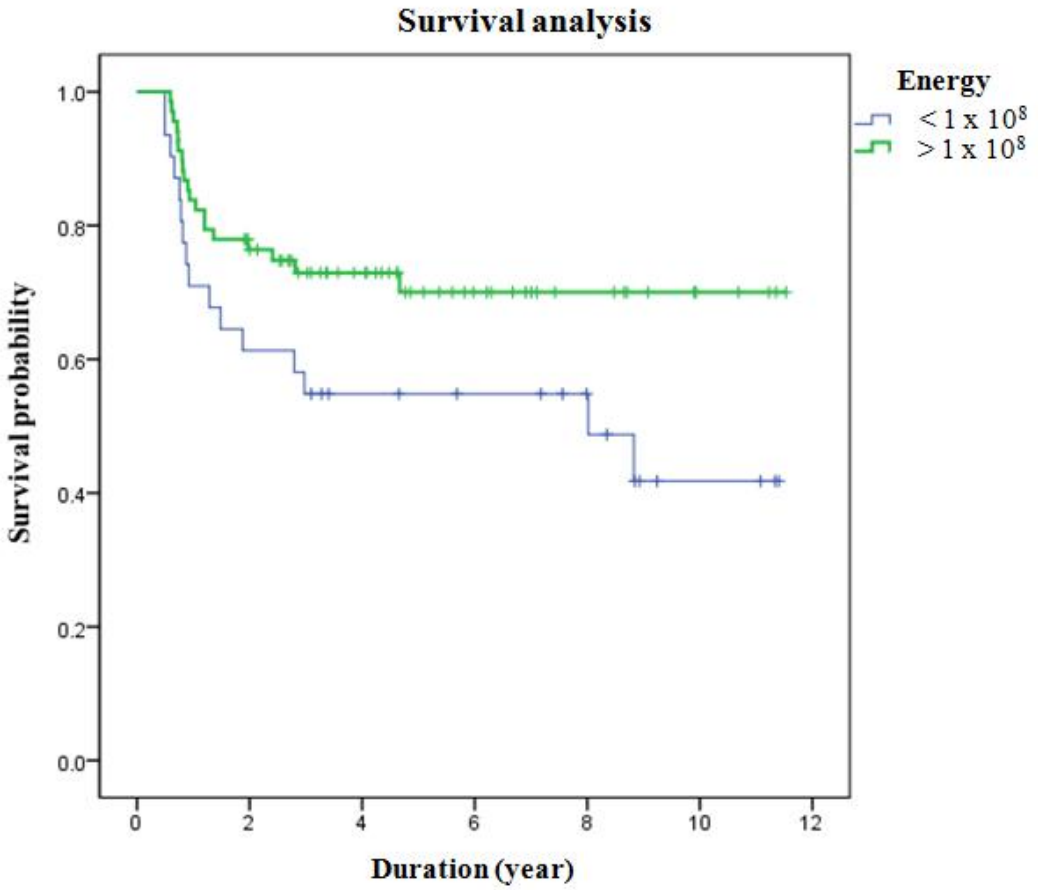

Figure 4. Kaplan-Meier survival analysis of the energy in the patients with thoracic involvement (n = 99)

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CT 질감 분석에서 얻은 종양의 비균질성: 호지킨 림프종의 예후 인자

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서론

호지킨 림프종 (Hodgkin lymphoma) 은 일반적으로 복합항암요법 (adriamycin, bleomycin, vinblastine, dacarbazine)과 방사선 요법으로 치료하게 된다. 일반적으로, 호지킨 림프종은 완전 관해가 대략 80-90 % 정도로 치료에 반응이 좋은 질병으로 알려져 있다. 그러나 낮은 병기 (stage I, II) 의 환자 중 15 %, 높은 병기 (stage III, IV) 의 환자 중 35-40 % 에서는 치료에 반응하지 않거나, 치료 후 수년 이내에 재발하게 된다.

이전 연구들에서는 종양의 부피 (tumor burden) 가 호지킨 림프종의 재발 위험도나 치료 반응을 평가하는데 있어 가장 좋은 예후인자라고 제시하고 있다. 그러나, 실제 정확한 종양의 부피를 측정하는 것은 어렵기 때문에 임상적 적용이 어려운 상황이다. 다른 잘 알려진 임상적 예후인자들 또한 간접적인 지표에 불과하다.

만약 치료 전 CT 를 이용하여 영상의학적 예후인자를 발견해낼 수 있다면, 미리 적절한 치료 계획을 세우고 환자 상태의 악화에 대해 대비할 수 있다는 점에서 큰 이득이 될 것이다.

따라서 본 연구는 호지킨 림프종 환자에서 정량적 CT 인자들을 분석하여 예후와 유의한 연관관계가 있는 영상의학적 인자가 있는지 조사하고자 한다.

본론

본 연구는 후향적 연구로 2007 년 1 월부터 2016 년 12 월까지 본원에서 호지킨 림프종으로 진단 및 치료를 받은 192 명의 환자를 대상으로 하였으며, 그 중 예후를 평가하기 어렵거나 분석에 적합한 CT 가 없거나 종양의 여부를 확인할 수 있는 PET-CT 가 없는 경우를 제외하고 134 명의 환자를 선정하였다. CT 영상은 3-5 mm 절편 두께를 가지는 조영 증강된 영상을 사용하였으며, 영상질감분석은 PACS 를 바탕으로, Image J 에 기반을 둔 in-house software 를 이용하여 시행하였다. 질감 분석에 사용된 특징은 volume, mean attenuation, modal attenuation, median attenuation, standard deviation, skewness, kurtosis, entropy, uniformity, energy, variance, root mean square, coefficient of variance 이다.

종양의 부피는 이전 연구들과 마찬가지로 모든 영상마다 종양이 있는 부위를 반자동으로 그려 절편 두께를 곱한 후, 그 값을 모두 더하였다. 골수 조직 침범의 경우 침범된 현미경적 특징에 따라 다양한 방법으로 구하였다. 이렇게 구해진 부피를 체표면적으로 나누어 상대적 종양 부피 (relative tumor burden) 를 구하였다.

단변량, 다변량 Cox 비례 위험 모형을 이용하여 임상적 요인들과 CT 질감 분석 요인들 중에 치료 반응과 유의한 연관관계가 있는 요인들이 무엇이 있는지 분석하였고, 유의하게 나온 변수들에 대해 cutoff value 를 구하여 이분화 시킨 후, Kaplan-Meier survival analysis 를 시행하였다.

결론

포함된 134 명의 평균 연령은 37.3 세였고, 진단과 마지막 추적 관찰 사이의 기간 중간값은 53 개월 (30.5-74.25 개월) 이었다. 치료에 반응이 없거나 재발한 사람들, 사망한 사람들은 총 43 명 (32 %) 이었다.

전체 환자를 대상으로 임상적 요인들에 대해 단변량 및 다변량 Cox 비례 위험 모형 분석을 시행하였을 때, 나이 (HR, 1.02; P=0.03) 와 병변이 침범한 장기의 수

(HR, 1.82; *P*=0.03) 가 독립적으로 예후와 유의한 연관관계를 보였다. 30 세보다 나이가 많은 경우, 3 개 이상의 장기를 침범한 경우에 Kaplan-Meier survival analysis 상에서 유의하게 나쁜 예후를 보였다 (*P*=0.036, *P*< 0.001).

질감 분석에 앞서, CT 마다 protocol 이 제각기 다르기 때문에, 정확한 질감 분석을 하기 위해 thoracic involvement 가 있는 99 명의 환자 군을 대상으로 통계 분석을 시행하였다. 99 명 환자들의 임상적 요인들과 정량적 CT 요인들에 대해서 Cox 회귀 분석을 시행하였을 때, 침범한 장기의 수 (HR, 1.66; *P*=0.002) 와 energy (HR, 0.90; *P*=0.02) 가 예후와 유의한 연관관계를 보였다. 침범한 장기의 수가 3 개 이상인 경우, energy 값이 1×10^8 보다 작은 경우 Kaplan-Meier survival analysis 에서 유의하게 나쁜 예후를 보였다 (*P*< 0.001, *P*=0.049).

결론적으로, CT 질감 분석 요인들 중에서 energy가 호지킨 림프종 환자들의 예후와 유의한 상관관계를 보였다. Energy는 종양의 균질성 (homogeneity) 를 반영하는 지표로, energy 값이 낮다는 것은 종양이 균질하지 않게 보인다는 뜻이 된다. 즉, 종양이 heterogeneous하게 보일 수록, 나쁜 예후를 보인다는 것을 의미할 수 있다. 앞으로, 더 큰 규모의 환자 군을 대상으로 정확한 질감 분석을 시행하는 것이 필요할 것이다.