의학석사 학위논문

수술적 절제를 받은 소세포 폐암의 질감 분석을 이용한 영상 예후 예측인자

Prognostic Value of Computed Tomography Texture Features in Patients with Small Cell Lung Cancer Treated by Surgical Resection

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이 논문을 의학석사 학위 논문으로 제출함

2018 년 2 월

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국문요약

서론

소세포 폐암 (small-cell lung cancer, SCLC) 은 전체 폐암의 13 %를 차지하고, 비소세포 폐암 (non-small-cell lung cancer, NSCLC) 과는 다른 생물학적, 임상적 특징을 가지며, 이에 따라서 치료 방법 및 병기 설정에 차이가 있었다.

최근 IASLC (International Association for the Study of Lung Cancer) 에서는 8 판 개정안에서 SCLC 의 병기 설정을 기존의 limited stage 와 extensive stage 로 나누던 방법에서, 종양의 크기와 임파선 전이, 원격 전이를 바탕으로 TNM classification 으로 수정하자는 제안이 있으며, ASCO (American Society of Clinical Oncology) 에서는 TNM stage 를 기준으로 stage I 혹은 stage II 로 판단되는 early-stage 의 SCLC 에서 기존의 치료법 (전신적 약물 치료 및 방사선 치료) 보다 수술적 절제 (surgical resection) 가 우선시 된다는 가이드라인을 발표하였다. 그러나 여전히 SCLC 의 예후 인자에 대한 연구가 부족하며, 수술적 절제의 역할에 대한 clinical evidence 가 잘 알려지지 않았다.

최근 종양간 다양성 (intratumoral diversity) 에 다한 연구의 일환으로 질감분석 (texture analysis) 이 이용되고 있으며, 이에 따른 연구 결과 NSCLC 에서 몇 가지 질감분석 특징이 예후와 관련이 있다는 보고가 있었다.

이에 본 연구는 수술적 절제를 시행한 SCLC 환자에서의 영상 검사를 통한 질감분석으로 예후를 예측할 수 있는 지표가 있는지 조사하고자 한다.

본론

본 연구는 후향적 연구로 2010 년 1 월부터 2016 년 12 월까지 본원에서 SCLC 로 진단받은 1224 명의 환자를 대상으로 하며, 그 중 수술적 절제를 받은 104 명의 환자 중 질감분석에 적합한 환자 40 명을 선정하였다. CT 영상은 6 종류의 CT 스캐너를 이용하였으며, contrast enhanced image 를 시행하였다. 질감분석은 PACS 를 바탕으로 in-house software program 을 이용하였으며, 질감분석에 사용된 특징은 다음과 같다: (a) mean, (b) standard deviation (SD), (c) skewness, (d) kurtosis, (e) the 10th, 25th, 50th, 75th, 90th and 95th percentile values, (f) gray-level co-occurrence matrix (GLCM) inverse difference moment (IDM) and (g) GLCM contrast.

Cox 회귀 분석을 통해 생존 분석을 시행하였으며, 단일변량 및 다변량 분석을 시행하였고 C-index 로 검정하였다.

결론

40 명의 환자 중 16 명의 환자에서 재발하였으며, 18 명이 관찰기간 중 사망하였다. 전체 생존기간은 평균 1294.4 일 (95% 신뢰구간, 1009.1-1579.7 일) 이며, 재발하기 전 까지 기간은 평균 808.9 일 (95% 신뢰구간, 619.7-998.0 일) 이다.

질감 분석을 하였을 때 90 percentile 값이 생존기간과 유의한 상관관계가 있었으며 (p = 0.013), C-index 는 0.896 이었다.

따라서 90 percentile 값이 전체 생존기간과 유의한 상관관계가 있으며, 예후를 예측하는 인자로 이용 가능할 것으로 보인다.

영문요약

Purpose

To assess whether the CT texture features can predict prognosis in patients with small cell lung cancer (SCLC) who underwent surgical resection for curative intent.

Materials and methods

The institutional review board approved this retrospective study with a waiver of patients' informed consent. From January 2010 to December 2016, 40 patients (M = 34, F = 6, mean age = 68.3) with early stage SCLC (stage Ia = 17, stage Ib = 11, stage IIa = 8, stage IIb = 3, stage III = 1) who underwent curative resection at our institution were included. The median follow-up period was 834.0 days. CT texture parameters of primary tumors were obtained by using an in-house software from contrast-enhanced preoperative CT. Significant prognostic predictors of overall survival and disease-free survival among clinical and CT texture parameters were determined by Cox regression model.

Results

A total of 16 patients showed recurrence and 18 patients died during the follow-up period. The median overall survival was 1294.4 days. In univariate analysis, there was no significant predictor of disease-free survival. In case of overall survival, univariate analysis revealed that 90 percentile value and GLCM maximum probability were significantly associated with survival (p = 0.013 and 0.044, respectively). In multivariate analysis, the 90 percentile value was the sole independent predictor of overall survival in patients with SCLC. The C-index for the developed model was 0.896.

Conclusion

The 90 percentile value can have a potential prognostic value in patients with SCLC who underwent surgical resection although the prognosis of early SCLC is variable.

차 례

표 목차 및 그림 목차

Introduction

Small cell lung cancer (SCLC) accounts for approximately 13% of all newly diagnosed cases of lung cancer worldwide (1). Compared to non-small cell lung cancer (NSCLC), SCLC has different biological and clinical characters. SCLC is characterized by rapid growth, early metastasis, and initial good response to chemotherapy and radiotherapy (1, 2). Therefore, the management and staging of SCLC differ from those of NSCLC.

Recently, there was a major change in the staging system and management strategy. Union for International Cancer Control TNM Classification of Malignant Tumors 7th edition (2009) suggested using the tumor, node, and metastasis (TNM) classification for staging SCLCs, as the staging system gives more information about the prognosis and therapeutic approach (3), comparing to previous staging system dividing into two categories; limited and extensive stage. The 8th edition of International Association for the Study of Lung Cancer (IASLC, 2016) also recommends the use of the TNM classification for staging SCLC, with a demonstrated prognostic value (4).

Patients with SCLC have been typically treated with systemic chemotherapy with or without radiotherapy for decades (5). Recently, American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommended that surgical resection for selected SCLC patients provide the best local control compared with chemotherapy and radiotherapy (6-8). Yet, there are no randomized controlled trials comparing chemoradiotherapy to chemoradiotherapy with surgical resection.

Not only the staging system and treatment strategy, but also there are other possible prognostic factors such as good performance status, female sex, younger age, which were significantly associated with survival (3). Other laboratory tests level have also been suggested as a prognostic values, but the results were variable in studies (9-11).

Intratumoral diversity including histology, gene expression, genotype, metastatic and proliferative potential play an important role in cancer's development, progression, and its therapeutic response, as well as patients' prognoses (12). To assess the histologic and genetic heterogeneity, however, it is always necessary to do tissue samplings, which is invasive, time-consuming and limited representation for the entire tumor. Texture analysis refers to the appearance, structure and arrangement of the parts of an object within the image (13, 14), which enables to assess tumor heterogeneity via imaging. It is already known that computed tomography (CT) texture analysis of some tumors provides prognostic or predictive values for variable cancers (15-20).

There are studies about texture analysis of lung cancer images. One has been shown that the texture analysis is a predictive value of patients' prognosis and there is a tendency that more heterogeneous tumors on imaging are to be more aggressive and to be associated with poorer outcomes (21). There are other studies showed that CT texture features are potential prognostic biomarkers in NSCLC patients (22-24). Although the texture analysis features are recognized as biomarkers that may predict prognosis of NSCLC, texture analysis associated with survival outcome of SCLC has not been described yet, to our knowledge.

Thus, the purpose of this study was to assess whether the CT texture features can predict prognosis in patients with SCLC who underwent surgical resection for curative intent.

Methods and Materials

This retrospective study was approved by the institutional review board of Asan Medical Center (approval number 2016-0300), which waived the requirement for patients' informed consent.

Patients

A search of our hospital's electronic medical record system between January 2010 and December 2016 revealed 1224 patients who were pathologically confirmed SCLC, of whom 104 patients underwent surgical resection for curative intent. Among them, 64 patients were excluded from the study because of the following reasons (Fig 1): (a) patients with preoperative CT inappropriate for texture analysis (n = 25) or with non-enhanced CT (n = 5); (b) patients who have synchronous NSCLC (n = 33); (c) patients who had missed metastasis in the brain (n = 1).

Clinical data including age and sex of patients, smoking history, clinical tumor stage, histologic diagnosis, date of baseline CT, date of recurrence occurred on the CT, location of recurrent tumor, patient survival status and survival duration were collected from our electronic medical record system. The pathologic stage of SCLCs was derived from the Tumor, Node, and Metastasis (TNM) staging classification system, as per the American Joint Committee on Cancer (AJCC), 7th edition.

Time of diagnosis was defined as the date of operation for surgical resection. Patients were followed till death or last observation date recorded in the electronic medical record. Stage of the disease was assessed at the time of diagnosis.

CT image acquisition

CT images were scanned with one of the six scanners: Somatom Sensation 16 (Siemens Healthcare), Somatom Plus (Siemens Healthcare), Somatom Definition Flash (Siemens Healthcare), LightSpeed QX/I (GE Healthcare), LightSpeed Ultra (GE Healthcare), or

HiSpeed (GE Healthcare). The imaging parameters included 120 kVp and 100-200 mAs with dose modulation. All imaging data were obtained with a slice thickness of 1 mm, collimation of 0.75 mm and reconstruction with sharp kernel.

All CT scans were performed with contrast media; intravenously administration of 90-120 mL iopromide 300 (300 mg I/mL Ultravist, Bayer Pharma, Berlin, Germany) at a rate of 2.5 mL/s using an automatic power injector and the CT scanning was performed with a 50-second delay.

CT texture analysis

Our in-house software program was implemented using dedicated C++ language with Microsoft Foundation Classes (Microsoft, Redmond, WA) (25-27). Lesion segmentation of primary lung cancers was conducted manually in the lung window setting (width, 1500 HU; level, -700 HU), and regions of interest (ROI) were drawn along the boundary of the whole tumor volume (Fig 2). Artifacts such as air, dense calcification, vessels, metal, and streak artifacts were excluded from the ROI. Concomitant atelectasis or adjacent structure invasion was separated from the primary tumor using the difference in contrast. Once the whole tumor was segmented, various texture features were automatically calculated and extracted. The analyzed CT texture features included (a) mean, (b) standard deviation (SD), (c) skewness, which is a measure of the degree of asymmetry of a distribution, (d) kurtosis, (e) the 10th, 25th, 50th, 75th, 90th and 95th percentile values (nth percentile gray-level intensity of a cumulative histogram), (f) gray-level co-occurrence matrix (GLCM) inverse difference moment (IDM) and (g) GLCM contrast and et cetera (14).

Statistical Analysis

Disease free survival (DFS) was calculated from the date of surgery to the earliest among the followings; date of recurrence (including local recurrence and/or distant recurrence), the date of the last follow-up without evidence of disease, or the date of death from any cause. Overall survival (OS) was calculated from the date of surgery to the date of death, the date the patient was last known to be alive, or the date of the most recent follow-up. The date of last known to be alive was assessed with medical record. The last date of data collection was 16 September 2017.

Univariate Cox proportional hazard regression analysis was performed to analyze the impact on DFS and OS of the patients by clinical and pathological variables (including sex, age, smoking history, pathologic tumor stage, and histologic diagnosis) and CT texture features as described above. The quantitative CT texture features were dichotomized by cutoff value, which were set by performing receiver operating characteristic (ROC) analysis. The cutoff value with the largest sum of sensitivity and specificity on the ROC analysis was chosen as the optimal cutoff value. The qualitative variables with p-values less than 0.05 were used as input variables for multivariate analyses. The quantitative variables determined by ROC analysis were entered as input variables for multivariate analyses. Multivariate analyses were performed using the backward elimination method. Kaplan-Meier survival analysis was used to significant variables in multivariate analysis.

The C-index was used to evaluate the discriminative power of Cox proportional hazard models. The C-index is defined as the probability of concordance given that the pairs considered are usable in which at least one had an event. The C-index takes values from 0.5 to 1.0, with 0.5 indicating no predictive discrimination and 1.0 indicating perfect discrimination. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, Ill, USA) and R software (Version 3.2.1; R foundation, Vienna, Austria). A p-value of less than 0.05 was considered to indicate a significant difference.

Result

Patients

The characteristics of all patients and tumors are described in Table 1. Among 40 patients (mean age, 68.3±2.02; range, 37-78 years), 34 patients were male (mean age, 67.8±2.00; range, 48-78 years) and 6 patients were female (mean age, 66.3±1.89; range, 37-72). 37 patients were current smoker or ex-smoker, mean amount of smoking was 40.1±9.26 pack-years (range 0.7-150 pack-years). Followings are pathologic stage of the patients: stage Ia = 17, stage Ib = 11, stage IIa = 8, stabe IIb = 3, stage III = 1.

Among 40 patients, a total of 16 patients showed recurrence of the SCLC and 18 patients died during the follow-up period. The locations of the recurrent tumor were variable among the patients; LN recurrence of SCLC occurred in 5 patients, local recurrence on the surgical resection site in 2 patients, pleural seeding in 1 patient, trachea in 1 patient, and extra-thoracic recurrence in 7 patients (4 in brain, 2 in adrenal gland, and 2 in liver). The OS was 1294.4 days (95% confidence interval [CI], 1009.1-1579.7 days), and the DFS was 808.9 days (95% CI, 619.7-998.0 days).

CT Texture Features and Survival Analysis

In univariate analysis, there were no significant differences in OS or DFS with regard to the pathologic tumor stage (p = 0.277, p = 0.589). Other clinical factors including sex, age, amount of smoking were not significantly associated with OS (p = 0.425, p = 0.221, p = 0.451, respectively) or DFS (p = 0.948, p = 0.904, p = 0.826, respectively).

Regarding to OS, univariate analysis revealed that 90th percentile value and GLCM maximum probability were significantly associated with survival (p = 0.013 and 0.044, respectively). Subsequent multivariate Cox proportional hazards regression analysis revealed that 90th percentile value was independent predictors of OS of SCLC treated with surgical resection (Fig 3, p = 0.0065, hazard ratios = 0.2809). The C-index for the developed model was 0.896. Parameters of CT texture features were dichotomized based on their optimal cutoff values obtained from ROC curve analysis (Fig 3, Fig 4). The optimal cutoff value for 90th percentile value was 92.5. Kaplan-Meier survival analysis revealed that higher 90th percentile value showed significantly worse overall survival for the patients with SCLC who underwent surgical resection (Fig 5).

Discussion

Our study showed that the prognosis of SCLC was variable and the CT texture feature of 90th percentile value may be useful for predicting OS of SCLC with surgical resection. SCLC patients with higher 90th percentile value showed significantly worse OS than whom showing lower value.

Over the decades, SCLC still remains a disease with a high mortality rate and a low cure rate, even for the patients with limited stage (28). In spite of their initial responses to therapy, the majority with SCLC develops local recurrence (29). Recently, the paradigm of the management of SCLC has been changed, several guidelines recommend surgical resection for the early staged, locally limited SCLC patients (6-8). Nonetheless, only a few can be the candidate for surgical resection (4). In the previous report, median survival for patients with limited stage is about 15-20 months (30). However, OS of our study population's is 1294.4 days, which corresponds well with median survival of a group with stage I and II who underwent surgical resection was 30.8 months (31).

There are a few prognostic values in SCLC except clinical and pathological TNM staging (4). IASLC revealed that T and N descriptors are significantly associated to the survival of SCLC patients (4). However, in our study there was no significant correlation between TNM staging and OS or DFS. And the other clinical factors including age, sex, and smoking history did not show significant association to OS or DFS, even though previous studies revealed that factors including female sex and younger age were significantly associated with survival (3). It is probably due to the small number comparing to the previous studies. And the fact that this study is designed for the patients who underwent surgical resection, not for the full-scale SCLC population also contributes to the biased results. Despite this kind of selection bias, we narrowed the target patients to see the prognostic factors of the patients who have resectable SCLC.

CT texture parameters in this study were chosen according to the previous studies. In the texture analysis, the histogram of an image defined as the count of how many pixels in the image possess a given grey-level value. The percentile is one of the derivative parameters from the histogram. The percentile gives the highest grey-level value under which a given percentage of the pixels in the image are contained (13). In our study, the 90th percentile value was significantly associated with OS ($p = 0.013$). Subsequent multivariate Cox proportional hazards regression analysis revealed that 90th percentile value was independent predictors of OS of SCLC treated with surgical resection.

Interestingly, the 90th percentile based on CT texture analysis also showed significant association with OS of esophageal squamous cancer (32). Furthermore, in gastric cancers, the higher percentiles such as 75th and 90th percentiles in the CT texture analysis could distinguish poorly differentiated gastric cancers from others (33). In the study of glioma, histogram analysis of apparent diffusion coefficient (ADC) maps was a useful tool for grading gliomas; low percentile values could be used to differentiate high-grade from low-grade gliomas and the high percentile values may be useful for discriminating between grade III and grade IV gliomas (20).

Previous study reported that enhancement of all lung cancers helps differentiating malignancy from benign tumor, and enhancement reflects the vascularity of the nodule (34). Moreover, the degree of enhancement of lung nodule was significantly associated to the amount of central vascular staining and enhancement seems to be an indicator of malignancy (35). Since the higher percentile value indicates the higher CT attenuation value zone within the ROI, these results can be explained that the increased permeability of dysfunctional neo-vessels is associated with lesion attenuation or enhancement and this imaging feature can imply poor prognosis (33). Therefore, CT texture features can have a potential prognostic value in patients with SCLC who underwent surgical resection. In addition, CT texture feature may provide alternative or additional treatment options in addition to the surgical resection for the patients who would be expected to have poorer OS. Nevertheless, there was no predictor of survival in the architectural and cytologic features of SCLC in the pathologic study by this time (36).

Our study had some limitations. First, even though not all the patients who were indicated to surgical resection were underwent surgical resection, there were 104 patients underwent surgical resection among the 1224 patients who were diagnosed as SCLC in our institution. It is far larger number compared to the other studies. In Shepherd et al., only 1,806 patients out of 68,611 patients who diagnosed as SCLC underwent surgical resection with or without other treatment (3). In another study in England, only 465 patients were treated surgically out of 45,848 patients who were diagnosed as SCLC (37). It would be contributed to the change of guideline, recently. Second, the ROIs were manually drawn on CT without reference to pathologic specimens by 1 reader. Thus, interobserver variability of tumor segmentation or replication of texture parameters was not evaluated. However, there is some evidence that first-order statistical features are relatively unaffected by segmentation methods (11). Third, the number (n = 40) of this study was too small to analysis survival duration or other outcome. It would be contributed to the recent change of guidelines, which recommend surgical resection for the early SCLC, rather than chemoradiotherapy alone (6-8). Fourth, we assessed contrast-enhanced CT for texture analysis, which could be easily affected by the patients' cardiac output, blood volume, and body mass.

In conclusion, the 90th percentile value can have a potential prognostic value in patients with SCLC who underwent surgical resection although the prognosis of early SCLC is variable.

Table 1. Characteristics of the patients.

Characteristic	Number of patients (n=40)
Age, years*	68.3 (37-78)
Gender	
Male	34
Female	6
Smoking status, pack year**	40.1 (0.7-150)
Current or ex-smoker (pack-year)	37
Non-smoker	3
Clinical stage	
Stage Ia	17
Stage Ib	11
Stage IIA	8
Stage IIb	3
Stage IIIa	1
Recurrence	16
LN recurrence	5
Local recurrence	2
Pleural seeding	1
Trachea	1
Extra-thoracic recurrence	7
Death	18

* Data are median age, and range in parentheses

** Data are median smoking duration, and range in parentheses

Figure 1. Flowchart of the study population.

SCLC = small cell lung cancer; NSCLC = non-small cell lung cancer.

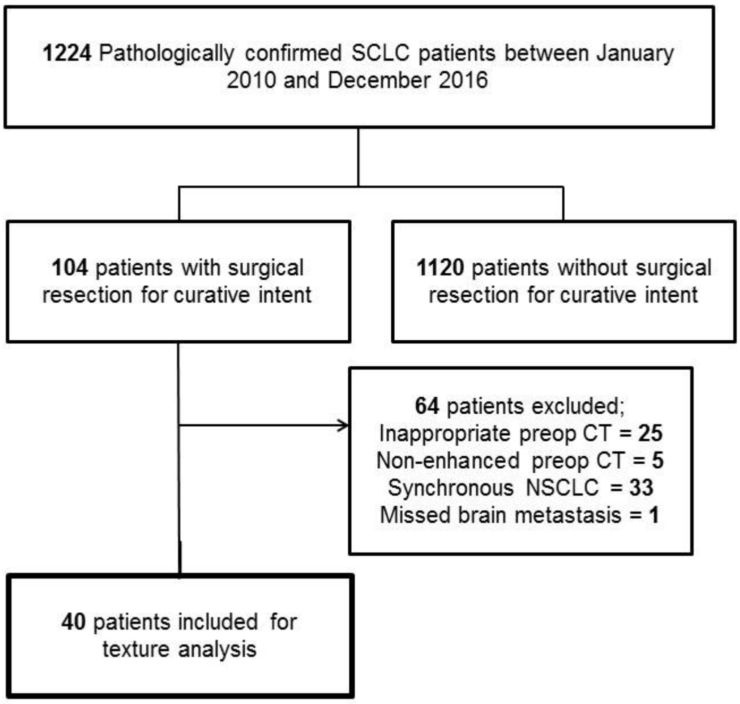


Figure 2. Texture analysis using an in-house software.

Lesion segmentation for primary lung cancer was conducted manually in the lung window setting (width, 1500 HU; level, -700 HU) and ROI was drawn along the boundary of the whole tumor volume using in-house software program. After lesion segmentation, texture features were automatically extracted.

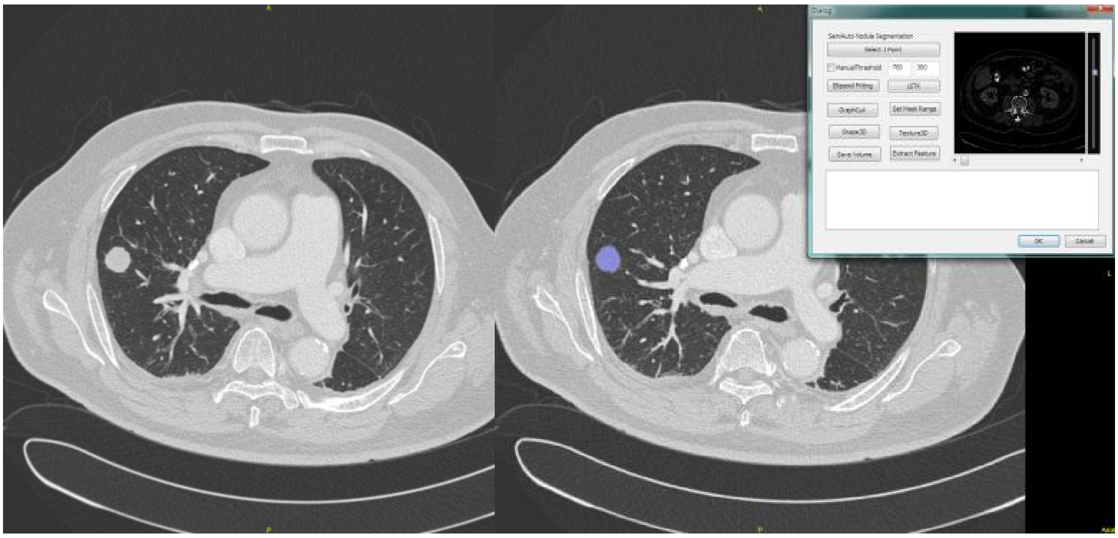


Figure 3. ROC curve of the 90th percentile value.

The optimal cutoff value for 90th percentile value derived from ROC curve. The optimal cutoff value for 90th percentile value was 92.5.

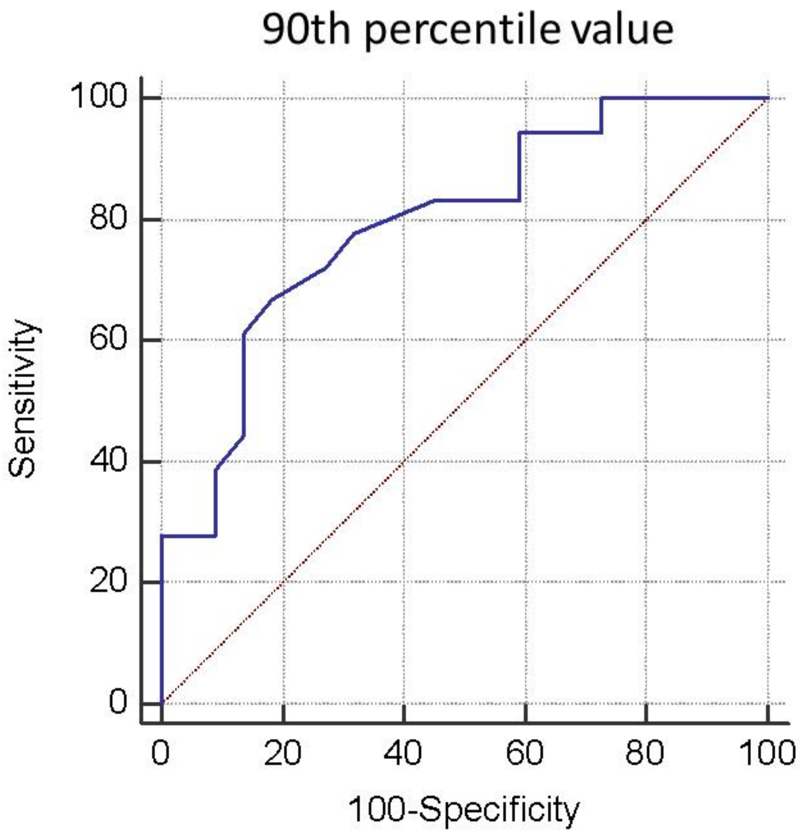


Figure 4. A 64-year-old male patient with SCLC.

This patient's CT texture analysis showed higher 90th percentile value than cutoff value (90th percentile value: 149). (A) CT scan at the time of diagnosis shows a nodule in right lower lobe in lung setting and mediastinal setting. (B) CT scan shows recurrent tumor in the left adrenal gland. Recurrence occurred in 256 days and the overall survival was 426 days.

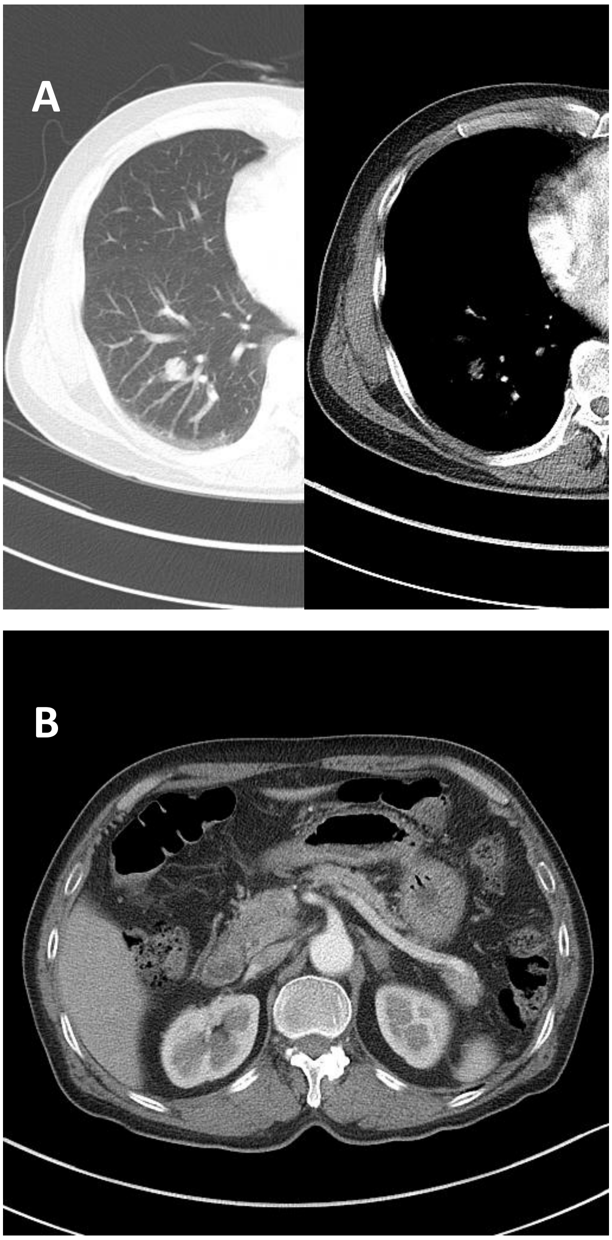
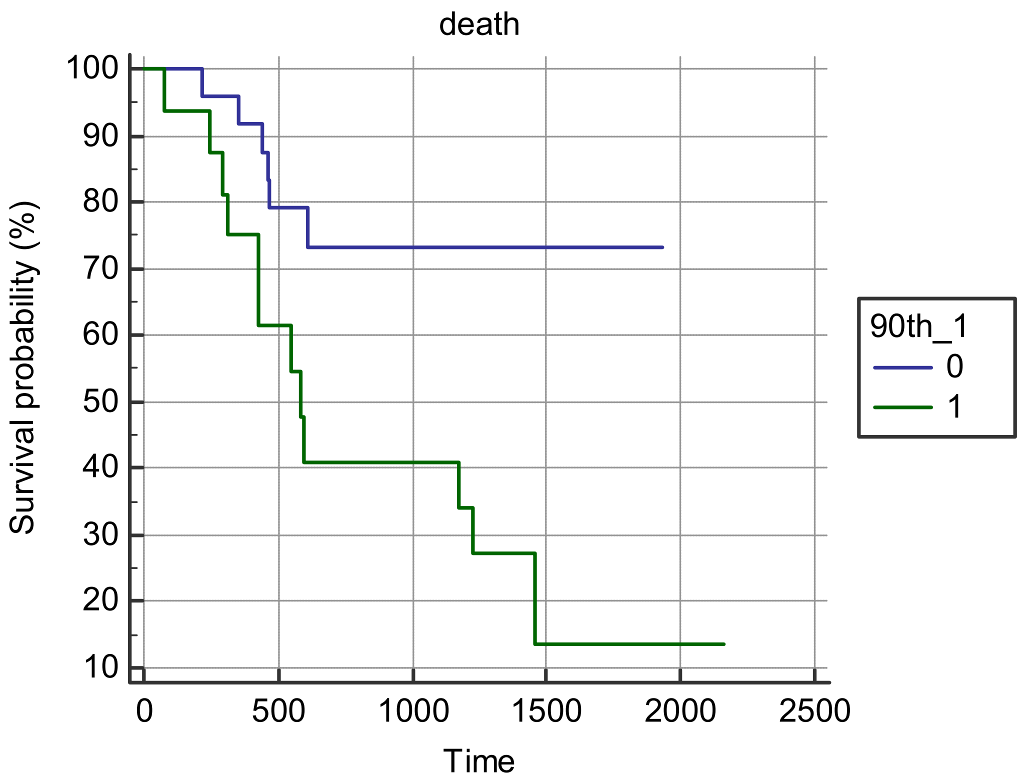


Figure 5. Kaplan-Meier survival analysis.

Kaplan-Meier survival analysis revealed that higher 90th percentile value showed significantly worse overall survival for the patients with SCLC who underwent surgical resection.



Supplementary information: CT texture features used in the texture analysis.

CT texture parameters in this study were automatically calculated.

First-order statistics describe the distribution of voxel intensities within the CT image through commonly used and basic metrics. Let ***X*** denote the three dimensional image matrix with ***N*** voxels and the first order histogram with discrete intensity levels. The following first order statistics were extracted:

1. **Mean:**

$$mean = \frac{1}{N}\sum_{i}^{N}\mathbf{X}(i)$$

2. **Standard deviation:**

$$standard\ deviation = \left(\frac{1}{N-1}\sum_{i=1}^{N}(\mathbf{X}(i)-\bar{X})^2\right)^{1/2}$$

3. **Skewness:**

$$skewness = \frac{\frac{1}{N}\sum_{i=1}^{N}(\mathbf{X}(i)-\bar{X})^3}{\left(\sqrt{\frac{1}{N}\sum_{i=1}^{N}(\mathbf{X}(i)-\bar{X})^2}\right)^3}$$

Where $\bar{X}$ is the mean of ***X***

4. **Kurtosis:**

$$kurtosis = \frac{\frac{1}{N}\sum_{i=1}^{N}(\mathbf{X}(i)-\bar{X})^4}{\left(\sqrt{\frac{1}{N}\sum_{i=1}^{N}(\mathbf{X}(i)-\bar{X})^2}\right)^2}$$

Where $\bar{X}$ is the mean of ***X***

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