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## Evaluation of the treatment of non-small cell lung cancer with brain metastasis and the role of risk score as a survival predictor

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### Abstract

**Objective:** The modality of treatment for patients with brain metastasis from non-small cell lung cancer (NSCLC) has not yet been established. Among these patients, few survive longer than 3 years. However, a small group of these patients demonstrate a better prognosis. The objective of this study is to clarify the efficacy of treatment and evaluate factors affecting long-term patient survival. **Methods:** We retrospectively reviewed the medical charts of 70 patients found to have brain metastasis from NSCLC in Fukuoka University Hospital between 1994 and 2002. These patients were grouped according to therapy received for the brain and lung and separated into two groups, as follows: LBR, lung and brain resection; LR, lung resection without brain resection. We also evaluated these groups for a set of several factors. Risk score was calculated with reference to the data from multivariate analysis, which can estimate survival. **Results:** The number of patients who underwent lung surgery plus brain surgery was 41. In this LBR, the 1- and 3-year survival rates after treatment of brain were 66.4 and 22.9%, respectively. We found that a therapeutic strategy including surgery for primary lung and brain can afford patients an extended survival time compared to the survivals of other LR group. The 3-year survival of patients with high carcinoembryonic antigen (CEA) was 0 vs. 39.6% among patients normal for CEA. Some factors, including histological type, nodal metastasis, serum LDH and CEA, were associated with survival. The multivariate Cox model identified both adenocarcinoma histological subtype, node status and high serum CEA as independent prognostic factors, whereas serum LDH was not found to be significant. Risk score was determined in our study to estimate prognosis according to the multivariate data. From this equation, previously we can expect 1- or 3-year survival of each patient with brain metastasis from NSCLC, refer to the risk score. **Conclusions:** Stringent selection, i.e. low-risk score (adenocarcinoma, node-negative and normal level of CEA) of candidates for surgical treatment for primary lung and brain metastasis from NSCLC may be an acceptable and valuable approach.

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**Keywords:** Metastatic brain tumor; NSCLC; Prognosis; Risk score

### 1. Introduction

Non-small cell lung cancer (NSCLC) after complete resection has not allowed to complete survive. In many patients, lung cancer easily metastasizes in the brain or bone [1,2]. Approximately 20% of patients with lung cancer develop a brain metastasis [3]. Long survival of NSCLC patients with brain metastasis is rare, though in some cases such patients do demonstrate a long-term survival rate (10 years) after treatment for brain metastasis [4]. Previously,

almost all patients with brain metastasis received whole brain radiotherapy (WBRT), though this treatment modality often results in neurological toxicity. A recent study showed that gamma knife surgery (GKS) for NSCLC with brain metastasis affords effective local tumor control in approximately 84% of patients [5]. The standard of care for patients with solitary brain metastasis in NSCLC may involve select consideration for surgical resection. It has not been established which treatment strategy (surgery or GKS) has the most significant positive influence on survival and affords effective local control in patients presenting with metachronous or synchronous brain tumor from NSCLC. The treatment modality for patients with NSCLC suffering

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brain metastasis remains somewhat controversial due to the heterogeneity characteristic of this disease. It is important for predicting the survival or control of quality of life. The aim of this study is to investigate the clinical evaluation of patients at the time of presentation of brain metastasis from NSCLC and attempt to clarify factors affecting prognosis. Significance and indication for surgical resection for primary or brain metastasis are also discussed.

## 2. Materials and methods

We reviewed the clinical records and follow-up data of histologically proven NSCLC patients seen at Fukuoka University Hospital from January 1994 to December 2002. Of these 640 patients who underwent pulmonary surgical resection for NSCLC, at first, we retrospectively selected 94 whose brain metastases at the time of presentation were confirmed by the presence of lesions on magnetic resonance imaging or computed tomography. The specimen from lung was examined by the bronchoscopic biopsy or needle aspiration cytology. Patients were excluded if they had exhibited rare histological results. Our inclusion criteria for the resection of the brain were as follows: location of the metastasis is surgically accessible, include the margin criterion of free brain used herein, tumor size less than 3 cm, and distinct negativity for cancer in other distant regions. Gamma knife radio-surgery (GKS) was indicated for patients after brain surgery if relapse. Brain resection was thought to be done completely in all cases, because of free margin of the brain. These patients with brain metastasis related to the lung cancer finally selected were 70 and separated into two groups as follows: LBR, lung and brain resection; LR, lung resection without brain resection. Of these patients, 42 metachronous, 28 synchronous were subject to lobectomy or bilobectomy with mediastinal lymphadenectomy. The patients were considered to be potentially cured by the surgical approach except the brain. Forty-one of these patients underwent combined resection of the lung and brain. The therapeutic modalities for brain metastasis were GKS in 28 cases, brain surgery plus GKS in four cases, surgery only for brain metastasis in 25 cases, brain surgery plus WBRT in eight cases, and brain surgery plus both GKS and WBRT in four cases. Serum levels of lactate dehydrogenase (LDH) (upper limit of normal values; 400 IU/l), serum alkaline phosphatase (Al-p) (upper limit of normal values; 350 IU/l), serum carcinoembryonic antigen (CEA) (upper limit of normal values; 4.0 ng/ml) were recorded. After confirmation of brain metastasis, Kaplan–Meier survival curves were calculated. Risk score was determined in our study to estimate prognosis at 1- or 3-year survival. The risk score was calculated by method of Markmann et al. [6].

### 2.1. Statistical analysis

All statistical analyses were performed with the StatView 5.0.1 software package (SAS Institute Inc.). Survival rates were calculated by the Kaplan–Meier method and survival curves

Table 1

Clinical characteristics of 70 patients with brain metastasis from NSCLC (LBR, lung and brain resection; LR, lung resection without brain resection)

	LBR	LR
Patients number	41	29
Gender (male/female)	32/9	19/10
Age	59.14 ± 9.42	67.65 ± 7.52
Histology (AD/SQ/other)	26/13/2	18/8/3
Number of brain meta (1/2–4)	40/1	25/4
<i>At brain metastasis</i>		
CEA (ng/ml)	16.83 ± 28.26	21.04 ± 15.60
LDH (IU/l)	381.30 ± 101.99	405.00 ± 165.83
Al-p (IU/l)	201.96 ± 271.12	271.12 ± 42.96

were compared using a log-rank test. Statistical comparisons were made using the  $\chi^2$ -test. For multivariate analysis, a Cox's proportional hazards regression model was used to evaluate variables that were significant predictors of survival by SPSS.

## 3. Results

### 3.1. Patient population

A summary of the 70 patients is shown in Table 1. The mean age of the patients was 61.9 ± 6.7 years. Of the 70 patients with brain metastasis from NSCLC, there were 41 in LBR, 29 in LR. Histological distribution of tumor types included 44 adenocarcinomas, 21 squamous cell carcinomas, and 5 large cell carcinomas. Sixty-four patients (91.4%) had neurological symptoms and 37 patients (52.8%) had respiratory symptoms. Of these patients who developed brain metastases, 42 were metachronous and the others were synchronous. There was no significant difference in distribution among the two groups. Serum CEA level at proven brain metastasis was 16.83 ± 28.26 ng/ml in the LBR group, 21.04 ± 15.06 ng/ml in the LR group. Serum LDH level at proven brain metastasis was 381.30 ± 101.99 IU/l in the LBR group, 405.00 ± 165.60 IU/l in the LR group. There were also no significant differences

Table 2

Profile of patients with brain metastasis who underwent lung surgery (LBR, lung and brain resection; LR, lung resection without brain resection)

	LBR	LR	P-value
Operation (lobe/bil or pneumo)	29/13	26/3	NS
Pathological T (T 1/2/3)	4/21/16	1/15/13	NS
Pathological N (N0/1/2)	13/8/20	13/3/13	NS
Meta-/synchronous	23/18	19/10	NS
Adjuvant to brain (WBRT/GKS/both)	8/4/4	0/28/0	NS
<i>Metachronous</i>			
DFI (days)	432.43 ± 392.65	459.23 ± 457.84	NS
MST from primary surgery (days)	954.00 ± 321.28	639.00 ± 66.95	NS

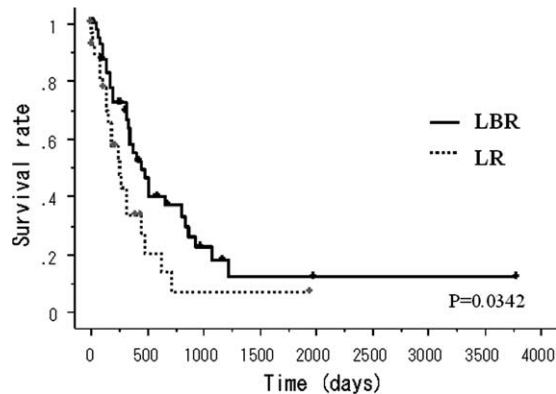


Fig. 1. Kaplan–Meier survival curves for the modalities used for brain metastasis: LBR, lung and brain resection; LR, lung resection without brain resection.

observed in serum level of CEA or LDH among the groups. Serum AI-p showed similar data among groups.

The characteristic factors in two groups are compared in Table 2. Of the 70 open thoracotomies, 55 were lobectomy and 15 were bilobectomy or pneumonectomy. Of these patients, 5 were pathologic T1, 36 were T2, and 29 were T3. Twenty-six patients were pathological N0, 11 were N1, and 33 were N2. In metachronous cases, the mean time development of cerebral metastasis (disease-free interval) was  $432.43 \pm 392.65$  days in LBR and  $459.23 \pm 457.84$  days in PR. There were no statistical differences between the two groups in terms of surgical technique or pathological factors including node, T factor, metachronous or synchronous.

### 3.2. Survival analysis

To show the relationship between the respective groups and prognosis. Actual survival rates of patients are shown in Fig. 1. Overall survival rates at 1 year and 3 years were as follows: LBR, 66.4 and 21.9%; LR, 33.2

and 6.6%, respectively. The LBR group had better prognoses than the other groups. There was a significant difference in survival rate of LBR group vs. LR ( $P = 0.0342$ ). Between metachnous and synchronous, there were no significant difference in survival but tended toward significance ( $P = 0.0987$ ). As shown in Fig. 2a, histologic types of adenocarcinoma showed survival rates of 63.6% at 1 year and 18.8% at 3 years. Other types of non-adenocarcinoma showed survival rates of 23.7% at 1 year and 12.6% at 3 years. There was a significant difference between these two groups ( $P = 0.0159$ ). When comparing the survival curves observed in patients who underwent pulmonary resection, Fig. 2b shows the node status and survival curves; the 1-year survival rate of patients with nodal involvement was 41.4 vs. 59.3% among patients negative for nodal involvement. The 3-year survival rates were 7.8 and 34.9%, respectively. Statistically significant differences were also seen between cases with and without lymph node invasion ( $P = 0.0208$ ). Fig. 3a shows Kaplan–Meier survival plots generated from curves stratified by LDH status at the time of diagnosis of brain metastasis, the 1-year survival of patients with high LDH was 18.6%; that of patients with normal LDH was 73.2%. The 3-year survival of patients with high LDH was 0%; that of patients with normal LDH was 21.0%. These results were significantly associated with survival ( $P < 0.001$ ). We further analyzed the survival rates of the patients for correlations with the level of serum CEA at the time of diagnosis of brain metastasis. Fig. 3b shows the serum CEA and survival curves, where the 1-year survival rates of patients with high CEA was 33.6 vs. 85.9% among patients with normal CEA. The 3-year survival rates were 0 and 39.6%, respectively. Statistically significant differences were also seen between patients with high and those with normal levels of CEA ( $P < 0.001$ ).

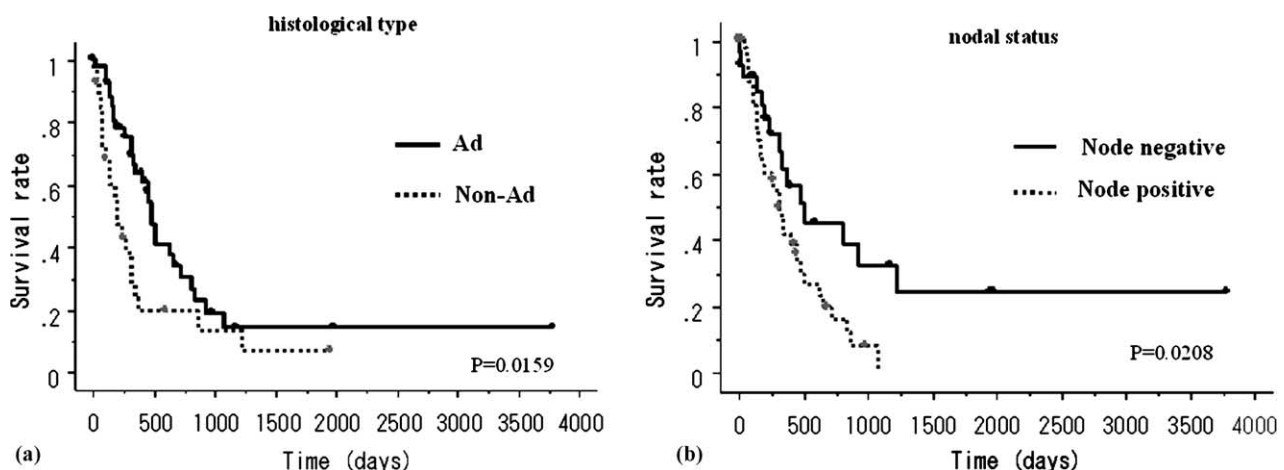


Fig. 2. (a) Kaplan–Meier survival curve for patients with brain metastasis according to histological subtype (adenocarcinoma vs. non-adenocarcinoma). (b) Kaplan–Meier survival curve for patients with brain metastasis according to node status (node-negative vs. node involvement).

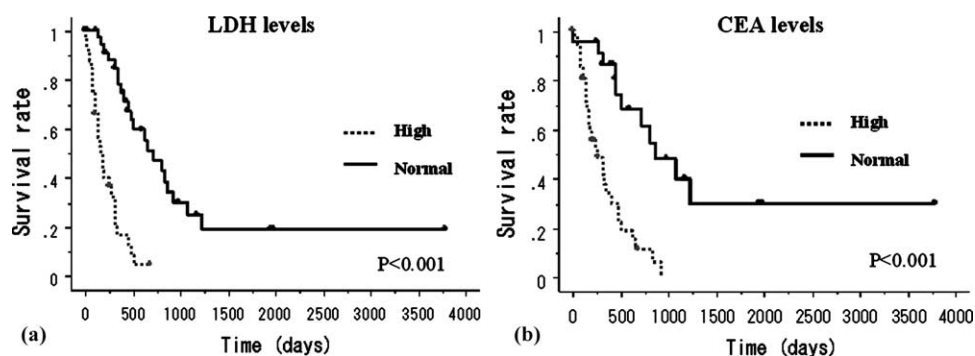


Fig. 3. (a) Kaplan–Meier survival curve for patients with brain metastasis according to LDH level at progress of brain metastasis. (b) Kaplan–Meier survival curve for patients with brain metastasis according to CEA level at progress of brain metastasis.

Multivariate analysis was performed to evaluate the respective prognostic roles of these tissue factors. All variables that significantly affected survival in analysis were used to draw up a Cox proportional hazard model (Table 3). After stepwise multivariate analysis, adenocarcinoma ( $P = 0.0035$ ) and high CEA ( $P = 0.0103$ ) maintained their independent prognostic effects on overall survival. Node status was also an independent factor ( $P = 0.0366$ ) but high LDH was not significant ( $P = 0.3093$ ). From these Cox proportional hazards analysis, risk score was determined in our study to estimate prognosis. The risk score was calculated by method of Markmann et al. [6]. Briefly as follows, estimate 1-year survival after brain metastasis from NSCLC and  $R$  is shown: estimated survival =  $0.492 \times \exp^{(R-2.670)}$ , where 0.492 is the mean 1-year survival for the patient group and  $R$  is the patient risk score calculated by  $R = (1.861 \times \text{CEA status} + 1.397 \times \text{node status} + 2.349 \times \text{histological type})$ . Three categorical variables are definite as follows: CEA status = 1 if high and 0 if normal, node status = 1 if involvement and 0 if without, histological type = 1 if non-adenocarcinoma and 0 if adenocarcinoma. The mean overall risk score for the group is 2.670. From this equation, the relationship between risk score and predicted survival at 1-year is shown in Fig. 4a. And also predicted survival at 3-year is shown in Fig. 4b. This figure can be used to predict the individual patients survival with brain metastasis from NSCLC. For the example, previously patient is expected 1-year survival of 27.9% and 3-year survival of 3.53% if the risk score is 3.25.

#### 4. Discussion

Because lung cancer with brain metastasis is still a major contributory factor to overall cancer mortality, in our study, we divided patients into two groups which included surgical resection for primary cancer or metastases of the brain. In these groups, patients undergoing combined lung and brain surgery proved to have a longer survival in comparison with

patients in the other groups after diagnosis of metastases. Surgical resection of single brain metastasis in patients with NSCLC may improve survival compared with that of conservative management [7,8]. Our data also conflict with that in previous reports. No significant differences were observed between the patients with synchronous and metachronous (data not shown). In the subgroup of synchronous primary lung and brain metastases, therapeutic modality of the resection was indicated for brain metastasis at first. The surgical treatment for brain metastasis can expect the remission of the neurological symptoms in a short time. Furthermore, the LR is surgically suitable for candidate, if the resection of brain metastasis was defined as complete. GKS is usually indicated as the NSCLC suffering from brain metastasis who expect short life or not single. Brain surgery is generally selected for patients who had a single metastasis and considered the primary site can control. With regard to node status, the patients with pathological node-negative disease showed significantly longer survival than those with nodal involvement. The 5-year survival after definite brain metastasis was 25% in the node-negative group in our study. These data suggested that node negativity predicts good control. Further, a surgical approach may be positively indicated for patients with brain metastases from NSCLC who are node-negative. Mussi et al. reported that the 5-year survival of 14 patients with N0 and metachronous single brain metastasis who had undergone lobectomy was 29% [9]. The results in this paper

Table 3  
Prognostic significance of variables related to survival tested by multivariate analysis in patients with brain metastasis from NSCLC (Ad, adenocarcinoma)

Factors	Parameter estimate	Odds ratio (95% C.I)	P-value
Non-Adeno vs. Adeno	2.349	10.442 (2.167–50.303)	0.0035
Node involvement	1.397	4.044 (1.091–14.987)	0.0366
High CEA at BM	1.861	6.472 (1.551–26.634)	0.0103
High LDH at BM	0.508	1.663 (0.624–4.430)	0.3093

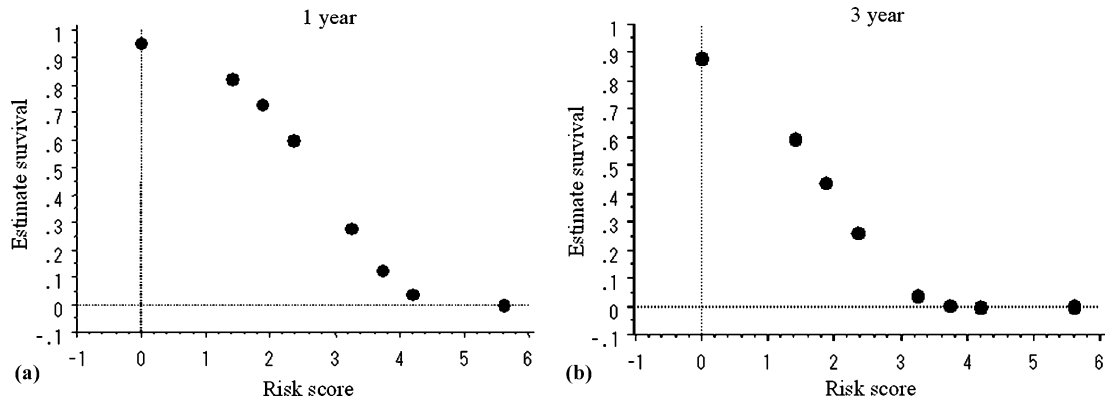


Fig. 4. Relation of risk score and estimate survival at 1- or 3-year after brain metastasis.

were similar to ours. But another large study showed that nodal status did not correlate with survival by univariate analysis. In that study, however, N0-1 and N2-3 cases were compared and, furthermore, not all with surgery [10]. Analysis of histological results showed significant differences in survival, as shown in Fig. 2a. Ohta et al. reported that complete resection on patients with adenocarcinoma with brain metastasis had significant prognostic impact on both overall survival and disease-free survival, but survival after brain surgery alone was not found significant [11]. Adenocarcinoma was predominant in each of our groups, though the differences among them in terms of survival after treatment of brain metastasis were not found to be significant. Recently, Amin et al. reported that 94% of 35 cases of primary lung adenocarcinoma with a micropapillary component showed development of metastases and in nine of these cases (25.7%), metastasis occurred in the brain [12]. In metastatic adenocarcinomas in which the primary tumors were mainly lung cancers (51.3%), a consistent tendency for E-cadherin expression and proliferation potential in metastatic brain tumors were noted [13]. CEA is well known to express on cancer cells and to be especially associated with adenocarcinoma. Recently, Buccheri and Ferrigno developed a new role for the old CEA test [14]. In their series, the CEA test was among the most accurate methods for predicting an early postoperative recurrence; CEA level higher than 10 ng/ml was associated with a 67% probability of tumor relapse. Another author showed data indicating that patients with high CEA had a 5-year survival rate of 49% compared with a 72% 5-year survival rate for patients with normal CEA and that persistently high CEA level after surgery in clinical stage I is an especially strong indicator of a very poor prognosis [15]. We analyzed the serum CEA as a prognostic marker at the time of presentation of NSCLC with brain metastasis. Patients whose CEA level was within the normal range had long survival compared to that of patients with high levels of CEA. Other serum markers have been reported as prognostic predictors in patients with brain metastasis. A high serum neuron-specific enolase (NSE) level was shown to be an

independent determinant of a poor outcome in patients with previously untreated NSCLC and brain metastases at the time of presentation [10]. Other data indicate that serum assay of NSE is also a useful marker in NSCLC. Bubb et al. reported that biomarker analysis of Ki-67, p53, and bcl-2 in NSCLC had a strong correlation to brain metastasis [16]. Another author found that patients with brain relapse had significantly higher expression of p53 and urokinase plasminogen activator [17]. Recently, our group presented that expression of interleukin 13 receptor alpha2 (IL-13Ralpha2) was rare or weak in cases of pulmonary adenocarcinomas with brain metastasis [18]. This finding suggested that immune evasion might play an important role in metastasis to the brain from NSCLC. Furthermore, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF) are angiogenic factors well known to serve as independent prognostic factors for SCLC survival. Coexistence of these factors showed a correlation to poor survival in our recent report [19]. Interestingly, VEGF isoform A (VEGF-A) expression by Mel57 human melanoma cells led to tumor progression in an angiogenesis-independent fashion in a murine brain metastasis model [20]. These data indicated that another subset of angiogenic factors might also be associated with progression to the brain. It is known that the elevation of LDH is reflected in the rapid production and consumption of neutrophils in patients with unresectable lung cancer [21]. Elevation of LDH may correlate to insufficient host immune severance. Serum lactate dehydrogenase (LDH) is a biochemical parameter that is elevated in the majority of cases of extensive-stage small-cell lung cancer [22]. Another study reported that patients with brain metastasis from NSCLC also proved to have a shorter survival relative to high serum LDH level [10]. However, LDH was not shown to be a significant independent factor in that multivariate analysis. Our data has demonstrated that LDH level was a significant survival factor in patients presenting high serum levels of LDH on presenting with brain metastasis, although LDH level was not shown to be a significant independent factor in multivariate analysis.

Additionally, the observation at the LR before occurring metastasis in metachronous group, serum LDH correlated the prognosis after presenting brain metastasis (data not shown). Our data indicated that the serum level of LDH might predict the possibility of recurrence after LR.

Risk score was determined in our study to estimate prognosis according to the multivariate data. From this equation, previously we can expect 1- or 3-year survival of each patient with brain metastasis from NSCLC refers to the risk score. The patients with high risk score may not indicated surgery to the primary resection. But if the patients previously calculated and showed the low-risk score, surgery to the lung may have an important role for the survival.

## 5. Conclusion

Although NSCLC with brain metastasis is staging in stage IV, some of these patients have a chance of better local control and improved survival rate. Our results suggest that particularly patients identified as node-negative, in whom a normal level of CEA or adenocarcinoma has been confirmed may be classified as sub-stage IV.

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