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Поступила 2.11.2006

УДК 616.24-006.6-07

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PROGNOSTIC ROLE OF TUMOR MARKERS IN OPERABLE NON-SMALL CELL LUNG CANCER

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SUMMARY

The aim of the present study was to evaluate whether tumor markers Cyfra 21 and NSE may contribute to staging and evaluation of prognosis in patients with operable lung cancer. 432 operated patients (mean age 61±9) were involved in the study. There were 278 (bi)lobectomies, 120 pneumonectomies, 12 segmental resections and 22 explorative thoracotomies. Pathologic staging was stage I in 195, stage II in 86, and stage IIIA in 151. The relationship between the level of tumor markers and the postoperative pathologic staging was studied. Survival estimates (Kaplan Meier) were made with reference to the preoperative level of Cyfra-21, crossed with TNM stage and type of resection. Relative risk was estimated with the Cox proportional hazard model. Cyfra-21 was increased in 32% of patients, 69% of whom had squamous cell carcinoma (SCC). NSE was elevated in 57, 40% of whom had adenocarcinoma. Despite a low sensitivity, there was a correlation to tumor size and N-stage: sensitivity for both markers was highest in stages T3/T4, or N2. Elevated Cyfra-21 levels heralded a poor prognosis in patients with stage I or III disease, and following (bi)lobectomy, (mean survival 101 and 46 months respectively, p<0.005). Relative risk for death in presence of elevated Cyfra 21 level was 1.4. Low sensitivity makes that Cyfra-21 and NSE are inappropriate tools for staging of operable lung cancer. An elevated Cyfra-21 level indicates a poor prognosis.

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ПРОГНОСТИЧЕСКАЯ РОЛЬ ОНКОМАРКЕРОВ ПРИ ОПЕРАБЕЛЬНОМ НЕМЕЛКОКЛЕТОЧНОМ РАКЕ ЛЕГКИХ

РЕЗЮМЕ

Цель настоящего исследования – оценить возможность опухолевых маркеров Cyfra-21 и NSE определять патологическую стадию и давать прогноз пациентам с операбельным раком легких. Было обследовано 432 прооперированных больных (средний возраст 61±9). Выявлено 278 случаев (би)лобэктомии, 120 пневмоэктомий, 12 сегментальных резекций и 22 таракомий. Патологическая стадия: стадия I была у 195, стадия II – у 86 и IIIA – у 151 больного. Изучалась взаимосвязь между уровнем опухолевых маркеров и послеоперационных патологических стадий. Оценка выживаемости (Kaplan Meier) была сделана с ссылкой на дооперационный уровень Cyfra-21, пересекаясь со стадией TNM и типом резекции. Относительный риск оценивался моделью Cox пропорционального вредного фактора. Cyfra-21 был увеличен у 32% больных, 68% из которых имели плоскоклеточный рак (SCC). NSE повышен у 57%, 40% из которых имели аденокарциному. Несмотря на низкую чувствительность, отмечена взаимосвязь размера опухоли и N-стадии: чувствительность обоих маркеров была самой высокой на стадии T3/T4 или N2. Повышенные Cyfra-21 уровни предвещали неблагоприятный прогноз для больных на I и III стадии болезни с последующей (би)лобэктомией, (средняя выживаемость 101 и 46 месяцев соответственно, p<0,005). Относительный риск смерти при наличии повышенного уровня Cyfra-21 составил 1,4. Низкая чувствительность показывает, что Cyfra-21 и NSE не под-

ходят для определения стадии операбельного рака легких. Повышенный уровень Cyfra-21 указывает на неблагоприятный прогноз.

Early detection of non small lung cancer (NSLC) remains an unresolved issue in thoracic oncology. More than half the patients are diagnosed at an advanced stage of disease, stage III or IV [1]. About 40% of patients already have distant metastases at the time of diagnosis. Though surgery is regarded as the curative treatment, survival rates after radical operations for stages I or II do not exceed 60 and 35% respectively [2].

Given these poor long term results, adequate initial staging is of paramount importance to avoid unnecessary surgery and to define adequate multimodality treatment strategies. Traditional medical imaging does not enable accurate staging of the primary tumor (T), and is subjected to a high range of errors when attempting to stage lymph node involvement (N) [3]. The advent of positron emission tomographic scan does not completely solve these problems. While realiable for detection of occult distant metastases, the nodal staging remains subjected to errors. A negative PET-scan is credited a high diagnostic accuracy, whereas a positive PET scan is subjected to a high false positive rate [4]. Following induction chemotherapy, diagnostic accuracy for lymph node staging does not exceed 50%, and its sensitivity is below 20% in stage N2 [5, 6]. This reality is frustrating because adequate N-staging remains one of the key markers for definition of treatment strategies.

From a theoretical point of view, tumor markers identified in the peripheral blood stream could be of interest for positive diagnosis, staging, and estimation of prognosis. Recent trials performed in thoracic oncology raise serious interest for tumor markers such as cytokeratin 19-fragments (Cyfra-21) and neuron specific enolase (NSE) [7, 8]. We designed the following study to test a double hypothesis: (1) that elevated levels of tumor markers might be associated with advanced tumor or nodal stage and with pathological signs of aggressiveness such as vascular invasion, existence of tumor microemboli or additional pulmonary tumor nodules; (2) that elevated marker levels may herald a poor prognosis.

Patients and methods

Patients. We included 432 patients (353 men and 79 women; mean age 61±9) operated for lung cancer within the period from 1997 to 2001 at the authoring institution: 278 (bi)lobectomies, 120 pneumonectomies, 12 segmental resections and 22 explorative thoracotomies were performed. Pathology applied to the definitions of World Health Organization criteria. The pathologic stage of each tumor was determined according to the revised International System for Staging of Lung Cancer [9].

Preoperative staging included computed tomodensitometric scan of the chest, abdomen and brain, and fiberoptic bronchoscopy. Nuclear bone scan was performed when symptoms were present. Pet-scan was not available.

The patient distribution according to the tissue diagnosis is demonstrated in Table 1. Patients with squamous cell carcinoma (SCC) (n=241) and with adenocarcinoma (AC) (n=123) dominated. The majority of patients were stage I (n=195) and IIIa (n=151). One hundred thirty four patients were T1 and 203 were T2. Nodal staging was N0 in 228 patients, N2 in 106 patients, and a further 5 revealed to be N3.

Table 1

Morphologic characteristics of patients (n=432)

Characteristics	Number of patients	Percentage
Type		
SCC	241	56%
AC	123	28%
LCC	24	6%
NT	22	5%
BAC	18	4%
SCLC	4	1%
AJCC-Stage		
I	195	**45%**
II	86	**20%**
IIIa	151	**35%**
T stage		
T1	134	31%
T2	203	47%
T3	58	13%
T4	37	9%
N stage		
N0	228	53%
N1	93	22%
N2	106	24%
N3	5	1%

Abbreviations: SCC – squamous cell carcinoma; AC – adenocarcinoma; LCC – large cell carcinoma; NT – neuroendocrine tumor; BAC – bronchioloalveolare carcinoma; SCLC – small cell lung cancer.

Histologic markers of tumor aggressivity were noted as follows. Vascular invasion was obviated in 120 patients (28%). The tumor size exceeded 5 cm in 125 patients (29%). Emboli formed by tumor cells were found in pulmonary lymphatic microvessels in 56 patients (13%). Satellite tumor nodes in the surrounding pulmonary parenchyma were found in 30 patients (7%), which were multiple in 16 patients (4%).

Methods. Cyfra-21 and NSE blood serum levels were measured in all patients preoperatively. For that purpose venous blood was sampled, centrifuged to obtain serum and stored at -180°C till laboratory testing. The level of tumor markers was measured twice in each patient. The measurement was performed by immunoradiometric method with the use of laboratory tech nical equipment – Cis Biointernational, Gif/Yvette, France. The Cyfra-21 level of 3,3 $ng.ml^{-1}$ and the NSE level of 12,5 $ng.ml^{-1}$ were regarded as upper normal levels [8].

The relationship between the level of tumor markers (normal or elevated) and the results of postoperative pathological examination including the tumor histology, the extension according to TNM stage and AJCC classification, the tumor size above 5 cm, the presence of vascular invasion, emboli in lymphatic vessels and additional pulmonary tumor nodes was studied.

Secondly, we assessed the influence of the preoperative level of Cyfra-21, TNM stage and type of resection on long-term survival.

Statistical analysis. The comparison of qualitative data for independent samples was performed with the Chi-Square Test. The comparison of two and more variables that belong to the interval scale and obey normal distribution was performed with t-test or simple variance analysis. The variables that belong to the interval scale but do not obey normal distribution were compared with the use of the Mann-Whitney U-test or the Kruskal-Wallis H-test. The survival rate was determined according to the Kaplan-Meier method. The comparative as sessment of survival curves was performed with Log-rank test. The associated risk was assessed with the Cox model. The survival rate was determined according to the Kaplan-Meier method. The comparative assessment of survival curves was performed with Log-rank test. The associated risk was assessed with the Cox model.

Results

Rough results. The level of Cyfra-21 was found elevated in 32% of all patients and the NSE level in 13% only (table 2). The distribution of patients according to the tumor type in the elevated Cyfra-21 level group was as follows: squamous cell carcinoma predominated and accounted for 69%; adenocarcinoma was found in 22%, bronchoalveolar carcinoma in 5%, large cell carcinoma in 3%, neuroendocrine carcinoma in 1% (p=0,0007). Patients with adenocarcinoma prevailed in the group with elevated NSE level (42%). Other histological types in this group were distributed as follows: squamous cell carcinoma in 35%, bronchoalveolar carcinoma in 16%, large cell carcinoma in 7% (p=0,0001). The sensitivity of Cyfra-21 to predict squamous cell carcinoma or adenocarcinoma was 40% and 25% respectively. The NSE demonstrated the greatest sensitivity of 19% for adenocarcinoma.

Relation between markers and extent or tumor aggressivity. The sensitivity of Cyfra-21 for T stage increased together with the tumor size (table 3): 9% for T1 stage, 38% for T2 and for T3 stage, 46% for T4 stage (p=0,0001). At the same time, the sensitivity of NSE with respect to T stage was found significantly lower : 4% for T1 stage, 15% for T2 stage, 28% for T3 stage and 11% for T4 stage (p=0,0001).

The sensitivity of Cyfra-21 for N stage was also higher than that of NSE (table 3). The index for Cyfra-21 was 22% for N0 stage, 37% for N1 stage, 42% for N2 stage and 40% for N3 stage (p=0,0005). Results observed with NSE were 10% for N0 stage, 10% for N1 stage, 21% for N2 stage and 40% for N3 stage (p=0,015).

The sensitivity of tumor markers according to the AJCC stage was as follows (table 3): 20% for stage I, 36% for stage II, 43% for stage III with Cyfra-21 (p=0,0001); 8% for stage I, 14% for stage II, 18% for stage III with NSE (p=0,02). Moreover, significant difference of tumor markers' sensitivity to a and b substages was found only at stages I and II. For Cyfra-21 these values were 7% for stage Ia and 30% for stage Ib, 6% for stage IIa and 47% for stage IIb.

Table 2

Levels of positivity of tumor markers

Histology	№ patients	Elevated cyfra 21	Elevayed NSE
Total	432	139	57
Squamous cell Ca	241	95	20
adenoCa	123	31	23
Bronchoalveolar Ca	18	6	0
Large cell Ca	24	4	8
Neuroendocrine Ca	22	1	4
Small cell Ca	4	0	0

With NSE, these indexes were 3% for stage Ia and 12% for stage Ib, 7% for stage IIa and 19% for stage IIb. Besides, the sensitivity of Cyfra-21 within stage IIb subcategories was 60% for T2N1 and 33% for T3N0.

Table 4 displays an analysis of tumor marker levels with reference to histologic markers of tumor aggressiveness. The highest Cyfra-21 sensitivity (58%) was observed when the tumor size exceeded 5 cm. The sensitivity of Cyfra-21 for other characteristics did not exceed 32%. The NSE sensitivity was equally low in the case of vascular invasion and in the case of tumor size above 5 cm, comprising 30%. This index was even lower with other characteristics. The specificity of NSE for signs of tumor aggressiveness was found higher than that of Cyfra-21 and exceeded an average of 80%. Thus, it comprised 89%, 94% and 89% in the case of vascular invasion, tumor size above 5 cm and emboli in pulmonary lymphatic microvessels, respectively. The highest Cyfra-21 specificity of 84% was observed when the tumor size exceeded 5 cm.Prediction of survival. The average survival for the whole population was 81 months. We limited prognostic studies to the Cyfra-21 marker, because the cohort of patients with elevated NSE levels was too small.

The survival data according to pathological stages, type of resection and Cyfra-21 level are presented in Table 5. The survival rate was 2,5 times higher in patients with normal initial Cyfra-21 level than among the patients with elevated level.

The comparison of survival rate in each stage confirmed the adverse prognostic significance of elevated Cyfra-21 level in stage I and in stage III (figure 1 and 2). There was no significant difference in survival among patients with stage II disease; this could be the effect of a small sample size. A significant difference in survival according to preoperative Cyfra-21 level was also observed following (bi)lobectomy. There was no significant difference in survival after pneumonectomy, although a trend towards improved survival was noted with normal Cyfra-21 level.

Table 3

Sensitivity of Cyfra-21, NSE – according to N and T status

Characteristics		Cyfra-21 (%)	NSE (%)	p
T status				
T1		9	4	0,15
T2		38	15	0,0001
T3		38	28	0,24
T4		46	11	0,001
N status				
N0		22	10	0,002
N1		37	10	0,0001
N2		42	21	0,00008
N3		40	40	NS
N0	**T1**	7	**3**	**0,45**
	T2	30	**12**	**0,001**
	T3	33	22	0,31
	T4	39	13	0,19
N1	T1	6	7	0,99
	T2	60	15	0,0001
	T3	50	0	0,2
	T4	50	0	0,2
N2	T1	24	5	0,09
	T2	50	26	0,02
	T3	53	38	0,49
	T4	55	11	0,006

Table 4

Sensitivity of Cyfra-21, NSE – according to tumor aggressiveness signs'

Tumor aggressiveness signs'	Cyfra 21	NSE	P*
Angioinvasion	32	19	0,026
Tumeur>5cm	58	30	0,0001
Embols	31	26	0,68
Additional pulmonary tumor nodes	32	13	0,12

* Fisher's exact test

Table 5

The mean duration of survival (Kaplan-Meier) in groups according to pathological stages, type of intervention and Cyfra-21 level

	Cyfra N (months)	Cyfra↑ (months)	p
Global (n=432)	91	37	0,0001
Stage I (n=195)	111	52	0,0074
Stage II (n=86)	45	37	NS
Stage III (n=151)	39	21	0,0015
(Bi) lobectomy (n=278)	101	46	0,0012
Pneumonectomy (n=120)	40	32	NS

The multivariate analysis with use of the Cox model revealed that patients' postoperative mortality risk with elevated Cyfra-21 level was 1.4 times higher than in patients with normal level ($p<0,05$).

Discussion

The majority of studies dealing with Cyfra-21 and NSE conclude that these tumor markers are independent prognostic factors in patients with lung cancer [10, 11, 12].

The first hypothesis we have tested was potential correlation of positive markers to advanced stage or aggressive tumor behavior, whom conventional staging with imaging techniques had failed to identify. The study unfortunately revealed that only a low proportion of patients considered to be operable have elevated tumor markers: Cyfra-21 was elevated in 32 % of patients, and NSE in 13% only. This is in contrast to the data of other authors reporting a sensitivity of these tumor markers in the range of 48-76% for Cyfra-21 and 22%-27% for NSE in patients with newly diagnosed NSCLC [13, 14, 15, 16]. This difference can be attributed to the fact that our investigation was limited to patients with presumably operable lung cancer. Hence, patients with diagnosed IIIb – IV stages, were excluded from the study; this is probably the population with the highest positivity for markers. When looking into the tissue diagnosis in patients with elevated marker levels, we noticed that 69% of patients with elevated Cyfra-21 levels had squamous cell carcinoma. The sensitivity of this tumor marker to SCC was also higher than to other histological types. These data reflect previously published results and support the expediency of Cyfra-21 use for specifying the histological tumor type preoperatively [13, 16].

NSE is most frequently used for evaluation of neuroendocrine tumors including small cell cancer [18]. In our study the NSE sensitivity to various NSCLC subtypes was found unacceptably low. It did not exceed 19% in patients with AC. The studies of Molina et al. [15] and of Diez et al. [16] also revealed low sensitivity of this tumor marker in specifying NSCLC type. It is remarkable that the diagnosis of AC prevailed in the group of patients with elevated NSE. This observation reflects the fact that in up to one third of specimens with adenocarcinoma one may observe cell clusters with neuroendocrine vacuoles.

One of the 2 major questions addressed by this study was the ability of tumor markers to predict advanced tumor stage. Considering the fact that the blood concentration of tumor cell cytokeratin fragments (Cyfra-21) and the enolase concentration (NSE) can increase with the growth of a secreting tumor, a relationship between the disease stage and the blood level of these tumor markers can be reasonably anticipated.

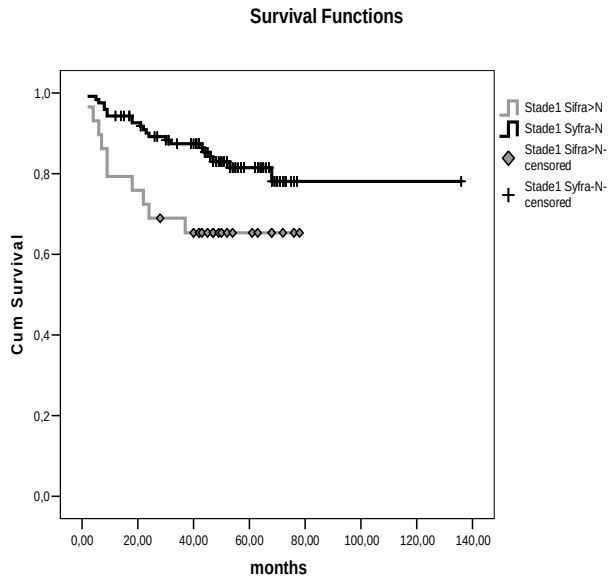

Fig. 1. Survival estimates according to preoperative Cyfra-21 level in stage 1.

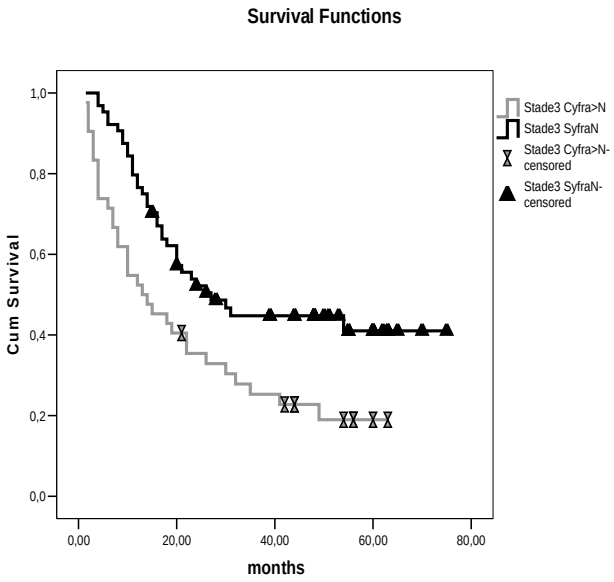

Fig. 2. Survival estimates according to preoperative Cyfra-21 level in stage 3.

The available published data relating to this issue are controversial. Lagarde et al. [19] and Molina. et al. [15] revealed a significant relationship between the NSCLC stage and CYFRA-21 level. At the same time Kasimir-Bauer et al. [20] demonstrated the lack of significant correlation between CYFRA-21 level and the tumor stage, the size and the number of lymph nodes involved.

Our results demonstrated low sensitivity of tumor markers in stage T1, but an increase of sensitivity of Cyfra-21 was noted with the increase in T-stage: it increased from 9% in stage T1 to 46% in stage T4. The sensitivity of NSE was considerably lower and did not exceed 28% in stage T3. Similarly the sensitivity of both tumor markers increased with the N-stage, but did not exceed 42% in stage N2. Comparable results were reported by Karnak et al. [13].

Sensitivity of the tumor markers was different in the substages of stage I and stage II. For instance, it was 7% for stage T1N0 and 30% for stage T2N0; for T1N1, T2N1 and T3N0 stages it was 6%, 60% and 33%, respectively. This observation confirms the anticipated increase of tumor marker concentration with the increase of T-stage. At the same time the sensitivity at T2N1 stage was found 2 times higher than at T3N0 stage – 60% and 33% respectively. This is probably explained that T3 tumors are defined by invasion of the parietal pleura or beyond and may be of smaller volume than T2 tumors. Tumor markers were not discriminative between stages IIIa and IIIb.

Appropriate identification of inoperable forms of lung cancer is one of the foundamental questions during preoperative work-up. We hypothesized that tumors with pathologic signs of aggressiveness (lymphatic tumoral emboli, angioinvasion, satellite nodules) might be accompanied by early occult metastases, and that an increased marker could be a useful indicator. This did however not apply to our observed results, which showed a rather low sensitivity of both tested tumor markers. Kasimir-Bauer et al. came to the same conclusion [20]. Though not useful on clinical grounds, we underline that sensitivity of Cyfra-21 was higher than that of NSE. The greatest Cyfra-21 sensitivity (58%) was observed with tumor size above 5 cm.

Our survival analysis demonstrates likewise to Niklinski et al [10], and Reinmuth et al. [11], that the preoperative increase of Cyfra-21 in operable lung cancer is a negative prognostic factor. Moreover, we observed the same mortality risk –1,4 as assessed with the Cox model as formerly demonstrated by J.L. Pujol et al. [8].

Comparing survival between stages, we observed that an elevated Cyfra-21 level is associated with a significantly lower survival in stages I and III. Use of Cyfra-21 may therefore be used to identify patients at high risk for tumor progression, and could be an argument in favor of induction chemotherapy.

During the period under in-vestigation, PETscan was not available at our institution. We may speculate that at least some of the patients with elevated Cyfra-21 would have shown occult metastatic disease with this diagnostic tool. The lack of significant difference of survival in stage II and after pneumonectomy is probably related to small sample sizes.

In conclusion, our study showed that tumor markers Cyfra-21 and NSE are not appropriate to detect advanced tumor stage in potentially operable patients, owing to a low sensitivity.Their level is well correlated to tumor size, but conventional medical imaging is more reliable. Markers do not solve the problem of early detection of occult N2 disease. However, an elevated Cyfra-21 level is a proven predictor of adverse prognosis, and could be an argument to select patients for neoadjuvant chemotherapy.

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Поступила 1.11.2006

УДК [615.32+613.292]:616.12-06

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ДОЗОЗАВИСИМЫЙ ЭФФЕКТ БИОЛОГИЧЕСКИ АКТИВНОЙ ДОБАВКИ К ПИЩЕ «МАГИСТР-ОЙЛ» ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИИ

Владивостокский филиал ГУ ДНЦ ФПД СО РАМН – НИИ медицинской климатологии и восстановительного лечения,
ФГУП Тихоокеанский научно-исследовательский рыбохозяйственный центр

РЕЗЮМЕ

Изучено влияние различных доз биологически активной добавки (БАД) Магистр-ойл» на состояние водно-электролитного, азотистого обменов, белковосинтезирующую и гепатобилиарную функции печени при экспериментальной кардиовазопатии у крыс. БАД «Магистр-ойл» представляет собой липидную фракцию из печени командорского кальмара *Berryteuthis magister*, содержащую10% полиненасыщенных жирных кислот (ПНЖК) и 50% алкилдиацилглицеридов. Биотропной в отношении выделительных систем организма в условиях экспериментальной кардиовазопатии является доза 1 г/кг в сутки. Негативное действие БАД «Магистр-ойл» установлено при ее введении в дозе 2 г/кг в сутки и обусловлено усугублением электролитного дисбаланса, снижени-