

“Measuring” Prognosis in Small Cell Lung Carcinoma: A Theory or an Attainable Possibility?

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Introduction

Small cell lung cancer (SCLC) or oat cell carcinoma (OCC) represents 13% of all lung cancers diagnosed in the United States [1]. It is characterized by the presence of flat neoplastic cells with scant cytoplasm, thought to originate from bronchial cells of neuroendocrine function (Feyrter cells) [1-3]. A limited stage and an extensive stage disease are recognized, depending on the absence or presence of metastases. In limited stage disease a combined therapeutic approach consisting of chemotherapy and chest radiotherapy results in a median survival of approximately 18-24 months, although 45-75% of patients have a complete response. In extensive stage disease, combination chemotherapy results in a 15-30% complete response, but the majority of patients relapse. Overall, the median five years survival in SCCL/OCC is only 5% [4,5].

During the course of more than 45 years in cytopathology, one of us (S.T.) has noticed that on sputum or bronchial cytologic preparations resistance of tumor cells' nuclear membrane to externally applied pressure is a good indicator of patient's prognosis. In particular, resistance to pressure and life expectancy were inversely analogous. More specifically, high resistance to pressure indicates a <12 months survival, moderate resistance a >12months and <24 months survival, and low resistance a ≥24 months survival.

The purpose of the present study was to investigate this correlation in a sample of patients.

Material and Methods

A hundred and thirty two consecutive sputum or bronchial cytologic preparations diagnostic of SCLC/OCC were included in the study. All patients had been diagnosed and managed in the same institution, General Hospital “Sotiria”. The cytologic smears were routinely prepared, stained with Papanicolaou stain, and coverslips were fixed with Canada's balsam. A properly modified, small-dimension, cylindrical needle or a surgical probe were used to apply pressure (Figure 1. More specifically, with the preparation under microscopic observation, neoplastic cells measuring approximately 10µm were identified and pressure was applied on the coverslip overlying them (Figure 2).

Each cytologic preparation was arbitrarily categorized depending on the resistance of its neoplastic cells to pressure as low resistance (LR), moderate resistance (MR) and high resistance (HR). In particular, as LR were considered those preparations where nuclear membranes of the neoplastic cells collapsed easily after application of pressure that was, however, more than this required for breaking pulmonary macrophages (dust cells) (Figure 3 & 4), while in HR no collapse could be produced before breaking of the coverslips. The rest of the preparations were considered as MR. All tests were performed blindly by two investigators independently (S.T. and K.T) and questionable cases were examined by both investigators simultaneously. Survival was calculated through the medical files and personal communication,

and three survival groups were formed: <12 months, > 12 months and <24 months, and ≥24 months. Statistical significance was tested with Fisher's exact test, for <0.05.

Results

Overall, 102 cases (77.3%) were categorized as HR, 23 cases (17.4%) as MR, and 7 cases (5.3%) as LR. The survival was known in 26 patients. Twelve belonged to the HR group, 8 to the MR group, and 6 in the LR group. In the LR group survival was ≥24 months in 5/6 patients (83.3%), for the MR group survival was >12 months in 6/8 patients (75%), and for the HR group the survival was <12 months in 10/12 of the patients (83.3%) (Table 1, Chart 1). The difference in survival



Figure 1: Cylindrical needle (left) and surgical probe (right) used to apply pressure on the cytopathologic slides.



Figure 2: The procedure. Application of pressure on the coverslip under microscopic observation.

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among the three groups was statistically very significant (<0.0002).

Discussion

We suggest that there is a correlation between the physical characteristics of the nuclear membrane of the neoplastic cells in SCLC/OCC and patients' survival. In particular, decreased resistance of the nuclear membrane to pressure indicates a better prognosis and longer survival, while a rigid nuclear membrane is associated with a dismal prognosis, with an even less than 6 months survival.

The method described herein is technically simple, as it is applied on routinely prepared sputum cytologic smears. Its only specification is the use of Canada's balsam for the fixation of the coverslips, as it retains the plasticity of the neoplastic cells that "flow" in it, in contrast to resins that "fix" the cells making them rigid. The most critical drawback is the subjectivity of the characterization that could possibly be made objective thorough the implementation of a properly designed devise, i.e. a needle mounted with a gauge meter.

The biologic basis of the association between nuclear membrane resistance and SCLC/OCC prognosis is not clear. A possible explanation could involve the nuclear lamina of the neoplastic cells which is composed of intermediate filaments and membrane associated proteins. The nuclear lamina provides structural and

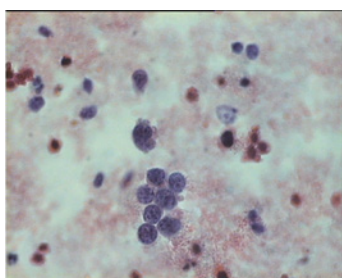


Figure 3: Photomicrograph showing SCLC cells before pressure application (Papanicolaou stain, original magnification x400).

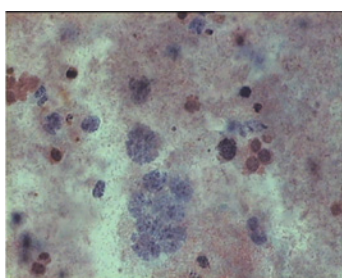


Figure 4: Photomicrograph showing destruction of the nuclear membrane of SCLC cells after pressure was applied (Papanicolaou stain, original magnification x400).

Resistance	Survival in months			Total
	<12	>12-24<	≥24	
LR	0	1	5	6
MR	2	4	2	8
HR	10	2	0	12
Total	12	7	8	26

$P=0.0002$

LR=Low resistance, MR=Medium resistance, HR=High resistance.

Table 1: Resistance to pressure and survival in 26 patients with small cell lung cancer.

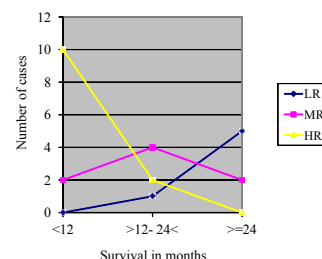


Chart 1: Resistance to pressure and survival in 26 patients with small cell lung cancer.

mechanical support and also participates in important cellular events such as DNA replication and cell division [6]. Biologically, the nuclear lamina consists of lamins and nuclear lamin-associated membrane proteins. The lamins are type V intermediate filaments which could be subcategorized as A-type (lamin A, C) or B-type (lamin B1, B2) [6-8]. Broers et al. [9] have shown immunohistochemically that lamin A was not at all or partly expressed in SCLC, while lamin B was unanimously expressed [9,10]. The presence or not of lamin A could be a potential mechanism which affects the durability of the nuclear membrane in SCLC neoplastic cells and, consequently, the patient's survival.

In the sample used for this study the accuracy of this method in predicting survival of a SCLC patient was very high, however the number of patients is limited and does not permit drawing results. Further investigation could prove or refute our observation.

As far as we are concerned, the nuclear membrane resistance of the neoplastic population in SCLC can be associated with the patients' life expectancy and may contribute as a prognostic factor for the evolution of the disease. Additionally, the former statement if proven will bear a new opportunity in the anti-cancer therapy with treatment properly modified in order to succeed higher susceptibility of the nuclear membrane and, therefore, more efficient results.

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