**Abstract.** Background: Apoptosis and cell proliferation in patients with adenocarcinoma of the lung have not been well described with relation to fine-needle aspiration biopsies (FNABs). To investigate the contribution of apoptosis to the growth of adenocarcinoma of the lung, both apoptosis and cell proliferation were analysed for correlation with the grade of the tumor. Patients and Methods: Fifty tumors from 50 patients with adenocarcinoma of the lung were studied. Twelve tumors were well-differentiated, 22 were moderately differentiated and 16 were poorly differentiated. The detection of DNA fragments in situ using the terminal deoxyribonucleotidyl transferase – mediated dUTP–digoxigenin nick-end labeling (TUNEL) assay was applied to investigate active cell death (apoptosis) and the MIB-1 antigen was used to investigate cell proliferation. Results: The TUNEL indices were 0.55±0.09, 0.90±0.33 and 3.1±0.99 in well-, moderately and poorly differentiated adenocarcinoma of the lung respectively. The MIB-1 antigen labeling indices were 7.1±0.12, 14.3±3.5 and 28.7±6.9, respectively, in the same order of tumor differentiation. The differences in both TUNEL and MIB-1 labeling indices were significant between well-, moderately and poorly differentiated adenocarcinoma of the lung and a positive correlation was found between the TUNEL indices and the MIB-1 indices. Conclusion: Apoptosis (cell death) and cell proliferation increases as the grade of differentiation decreases in adenocarcinoma of the lung, suggesting a rapid turn over of the tumor cells in tumors with a lower grade of differentiation.

**Correspondence to:** Alexandra Kalogeraki, MD, Ph.D., Assistant Professor of Cytopathology, University of Crete Medical School, Heraklion, Crete, Voutes P.C.71110, Greece. Tel: +30 2810394692, Fax: +30 2810394694, e-mail: kalogerakim@ yahoo.gr

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For statistical analysis, Student’s t-test was used. Apoptosis is reported to occur more frequently in colorectal adenomas with severe dysplasia (containing cells proliferating more rapidly) than in differentiated tumors, but not in poorly differentiated ones. MIB-1 nuclear-positive lung AC cells (Figure 2) were also randomly and heterogeneously distributed. MIB-1 expression was significantly greater compared with TUNEL expression in all tumors. Although TUNEL-positive cells were not necessarily localized in areas that contained many MIB-1-positive cells, there was a positive correlation between TUNEL expression and MIB-1 expression ($p<0.001$).

High values for TUNEL expression and MIB-1 expression were seen in moderately and poorly differentiated lung AC cells and were 0.90±0.33, 3.1±0.99, 14.3±3.5 and 28.7±6.9 (means±standard deviation), respectively, and both were significantly higher ($p<0.001$) compared with the values in well-differentiated lung AC (0.55±0.09 and 7.1±0.12 respectively). There were also significant differences between moderately differentiated lung AC and poorly differentiated lung AC for both TUNEL and MIB-1 expression ($p<0.05$ and $p<0.01$ respectively) (statistical analysis by Student’s $t$-test), (Table I).

**Discussion**

The significance of apoptosis and cell proliferation in cancer as biological markers, and especially as prognostic factors, has not been established. Many previous investigations conducted on this subject yielded contradictory results; some reports demonstrated that high apoptosis led to poor prognosis, some reported high apoptosis led to good prognosis and others demonstrated that apoptosis was not related to prognosis.

Apoptosis is reported to occur more frequently in colorectal adenomas with severe dysplasia (containing cells proliferating more rapidly) compared to those with mild dysplasia (4). Apoptotic cells are observed more frequently in undifferentiated carcinomas (where cells are proliferating more actively) than in differentiated tumors.

In the current study, application of the TUNEL method on FNABs specimens from patients with lung AC showed that...
apoptosis occurred more frequently in tumors with lower differentiation compared with the apoptosis found in well-differentiated tumors, a result that is in accord with the above results. There is another reported study on histological material which indicates that peripheral small-sized invasive lung AC with low apoptosis (low AI) carry an increased risk of distant metastasis (5).

Another recent study suggests that progression of lung carcinomas correlates with the increase in tumor volume, which is accompanied by an increase in apoptosis rather than an increase in cell proliferation (6).

Furthermore, we found a positive correlation between TUNEL expression and MIB-1 expression. Moderately and poorly differentiated lung adenocarcinomas had a higher proliferation rate than highly differentiated and frequent incidence of apoptosis. However, the tumor cell proliferation rate in lung AC is always higher than the rate of apoptosis. Our results are consistent with the results of previous studies on apoptosis and cell proliferation in various tumors, as gastric carcinomas, prostatic carcinomas and non-Hodgkin’s lymphomas, which demonstrated that the higher tumor malignancy is related to more active cell proliferation, as well as the higher proportion of apoptotic cells, implying that the observed increase in the number of apoptotic cells reflects the higher activities of cell division and metastasis (7-21).

In conclusion, we were able to use cytological specimens (FNABs) to study the role of cell proliferation and apoptosis in patients with lung AC. Our results show that tumors with higher rates of proliferative activity and apoptosis have a higher degree of biological aggressiveness and indicate a higher risk of distant metastasis and poorer prognosis.

References


