

Comparative Study of DNA Repair and Cell Proliferation Markers in High Grade Neuroendocrine Carcinoma of the Uterine Cervix and Small Cell Carcinoma of the Lung

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Background

- The optimal treatment for high grade neuroendocrine carcinoma of the uterine cervix (cNEC) remains undetermined.
- Most patients are treated with chemotherapy regimens used for small cell lung cancer (SCLC) because of both tumors' histological similarity and aggressive behavior.
- DNA replication and DNA damage repair processes could play a role in determining the tumors' behavior and responses to treatment.
- We hypothesized that significant differences in the expression profile of the key enzymes involved in these processes exist between cNEC and SCLC.
- Such differences could potentially identify valuable prognostic markers and new therapeutic targets in these highly lethal malignancies.

Methods

- Cases were identified by searching our institutional database.
- No pre-selection criteria other than the primary pathological diagnosis were used.
- Unpaired t-test analysis was performed and two-tailed *P* values were calculated to compare the means of the two groups (cNEC and SCLC).

By using immunohistochemical methods, the rate of expression in the primary tumor specimens was determined for the following enzymes:

- Ki-67
- Thymidine kinase (TK)
- Replication protein A (RPA)
- Thymidylate synthetase (TS)
- DNA excision repair protein (ERCC-1)
- Proliferating cell nuclear antigen (PCNA)

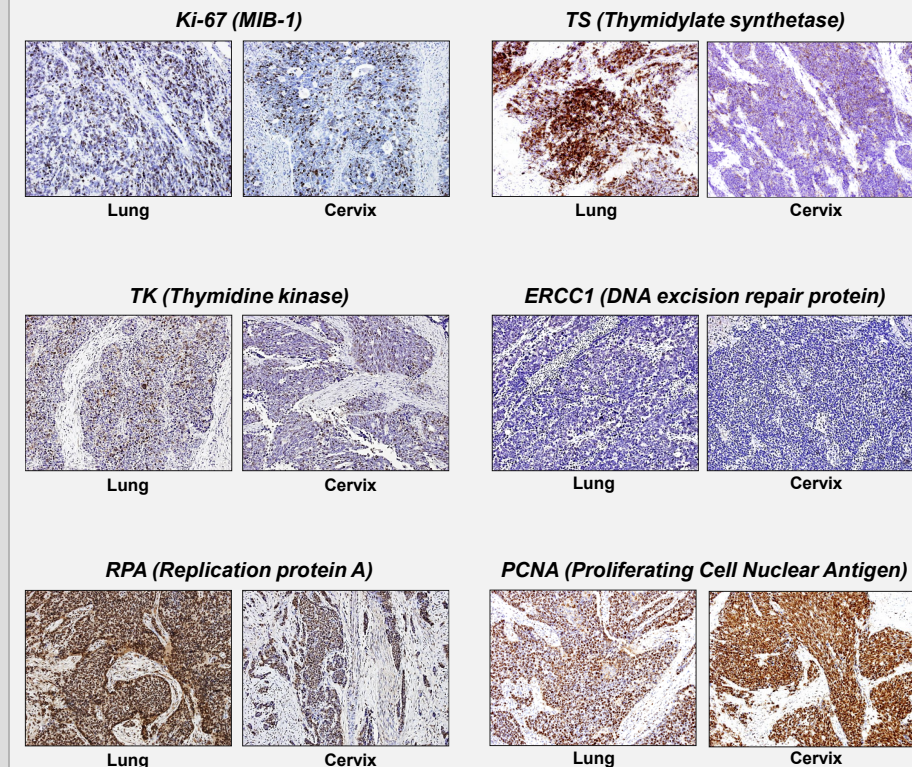
Conclusion

- This is the first comparative study of expression of the cell proliferation and DNA damage repair markers in cNEC and SCLC.
- RPA and Ki-67 are both expressed at significantly higher levels in SCLC than in cNEC.
- The mean expression rate, although not statistically significant, possibly due to the small sample size, was higher in SCLC than in cNEC for majority of analyzed markers (with the exception of TK and PCNA).
- Further studies are needed to determine possible correlation between these markers and clinical outcomes, including survival, as well as response to different modes of treatment.

Results

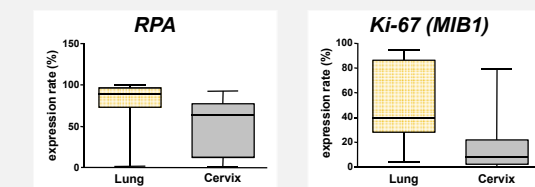
Patients' Characteristics:

- 20 patients with cNEC; 15 patients with SCLC
- All patients were seen at our institution in 1977-2010



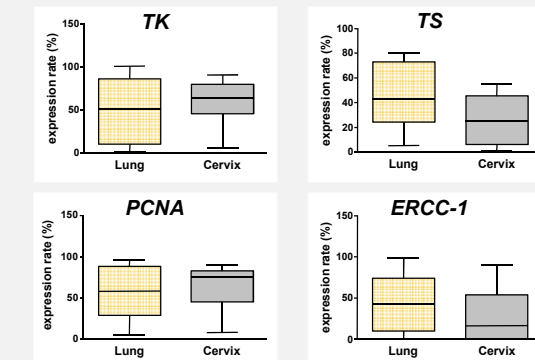
RPA and Ki-67

- RPA and Ki-67 were expressed at significantly higher levels in SCLC than in cNEC ($P=0.04$ and 0.002 , respectively)



TK, TS, PCNA and ERCC-1

- No significant difference in the expression of TK, TS, PCNA or ERCC-1 was found between the two groups.



The mean percent of positive cells and standard error of the mean for SCLC vs. cNEC:

- 74.7% (9.4) and 48.3% (7.7) for RPA
- 45.0% (11.3) and 25.3% (6.7) for TS
- 49.9% (8.4) and 16.9% (5.3) for Ki-67
- 56.6% (7.9) and 64.5% (5.9) for PCNA
- 49.7% (10.8) and 58.4% (6.4) for TK
- 43.5% (9.3) and 29.9% (7.8) for ERCC-1

Eight patients (53.3%) with SCLC expressed very high levels of RPA (>80% cells positive), vs. only 2 patients (10%) with cNEC.

High levels of Ki-67 expression (>80% cells positive) were observed in 4 pts (26.6%) with SCLC; none of the patients with cNEC had such high levels.