OTP, CD44, and Ki-67: A prognostic marker panel for relapse free survival in patients with surgically resected pulmonary carcinoid

L. Moonen[1], J. L. Derks[2], M. A. den Bakker[3], L. M. Hillen[1], R. J. van Suylen[4], J. H. von der Thüsen[5], L. M. V. Lap[1], B. J. C. A. Marijnissen[1], R. A. Damhuis[6], K. M. Smits[1], E. C. van den Broek[7], W. A. Buikhuisen[8], PALGA group, A. M. C. Dingemans[2,9], E. J. M. Speel[1,5]*

[1] Department of Pathology, GROW School for Oncology and Reproduction, Maastricht University Medical Centre, Maastricht, The Netherlands
[2] Department of Pulmonary Diseases, GROW School for Oncology and Reproduction, Maastricht University Medical Centre, Maastricht, The Netherlands
[3] Department of Pathology, Maasstad Hospital, Rotterdam, the Netherlands
[4] Pathology-DNA, location Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands
[5] Department of Pathology and Clinical Bioinformatics, Erasmus MC, Rotterdam, the Netherlands
[6] Department Research, Comprehensive Cancer Association, Utrecht, the Netherlands
[7] PALGA foundation, Houten, the Netherlands
[8] Department of Thoracic Oncology, Netherlands Cancer Institute Amsterdam, The Netherlands
[9] Department of pulmonology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Abstract

Introduction

Although most patients with pulmonary carcinoid (PC) can be cured by surgery, relapse may occur until 15 years after resection in up to 10% of patients. This is unpredictable at the outset, necessitating extensive follow-up (FU). We sought to determine whether an immunohistochemical marker panel (OTP, CD44, Ki-67) could provide better indication for relapse-free survival (RFS) and increase uniformity among pathologists regarding carcinoid classification.

Methods

All surgically resected PC (2003-2012) were identified in the Dutch cancer/pathology registry, and a matched relapse vs. non-relapse cohort (ratio 1:2, N=161) was created. Cases were revised by four pathologists and additionally for IHC-markers. The marker panel was applied to the complete population-based cohort (N=536) to investigate the negative predictive value (NPV) of relapse.

Results

Median FU was 86.7 months. WHO classification among pathologists revealed poor overall agreement (mitotic count:0.380, necrosis:0.476) compared with IHC markers (Ki-67: 0.917,

OTP: 0.984, CD44: 0.976). The mean NPV of all pathologists increased from 0.74 (WHO) to 0.85 (IHC marker panel). IHC risk stratification of the complete cohort, regardless of subtype, showed a statistically significant difference in RFS between high-risk (n=222) and low-risk (n=314) patients, with an NPV of 95.9%.

Conclusion

In conclusion, our results support the use of biomarker-driven FU management for PC patients as the OTP/CD44/KI-67 marker panel can reliably predict which patients will probably not develop relapse over time and may benefit from a more limited post-operative follow-up. Furthermore, IHC marker assessment by pathologists for PC stratification is superior to traditional WHO typing.