

BACKGROUND & OBJECTIVES

HPV oncoproteins E6 and E7 interferes with crucial cellular mechanisms such as cell regulation and apoptosis. E6 oncoprotein disrupts the p53 pathway while E7 oncoprotein inactivate R.

P16 activates Rb-dependent cell cycle arrest; in cells with functional Rb, elevated p16 is a potent inhibitor of cellular proliferation. HPV positive tumors which are characterized by loss of Rb function secondary to E7 oncoprotein activity, have high levels of p16. As a consequence, HPV positive OSCC is characterized by overexpression of p16 and low Rb.

In many patients with OSCC, HPV is not the only carcinogen and often superimposed carcinogens (smoking, alcohol) play an important role in tumor initiation and progression.

The objective of this study is to explore the patterns of Rb expression in p16 positive and negative OSCC, in relation to patient's smoking history.

DESIGN

Rb expression was evaluated by immunohistochemistry in 66 cases of p16 positive OSCC and 36 p16 negative OSCC. Smoking history was available in all cases and patients were divided in (current) smokers, remote smokers (quit smoking at least 3 year prior to diagnosis) and nonsmokers.

Rb staining was scored as **low** if nuclear staining was present in 20% or less of the tumor cells nuclei and **high** if more than 20% of the tumor cells were positive.

RESULTS

Of the 66 patients with p16 positive OCC, low Rb was present in 60% or more of cases (59% in nonsmokers, 73% is remote smokers and 62% in smokers). The remainder patients showed high Rb expression.

Among the 36 cases of p16 negative OSCC, 100% of smokers showed high Rb expression, while in the nonsmokers and remote smokers groups, only 20% of patients showed high Rb expression.

	Smoking status, nr. cases	Rb high	Rb low
P16 positive	Smokers = 13	5 (38%)	8 (62%)
	Remote smokers = 29	8 (27%)	21 (73%)
	Nonsmokers = 24	10 (41%)	12 (59%)
P16 negative	Smokers = 24	24 (100%)	0
	Remote smokers = 5	1 (20%)	4 (80%)
	Nonsmokers = 7	2 (28%)	5 (72%)

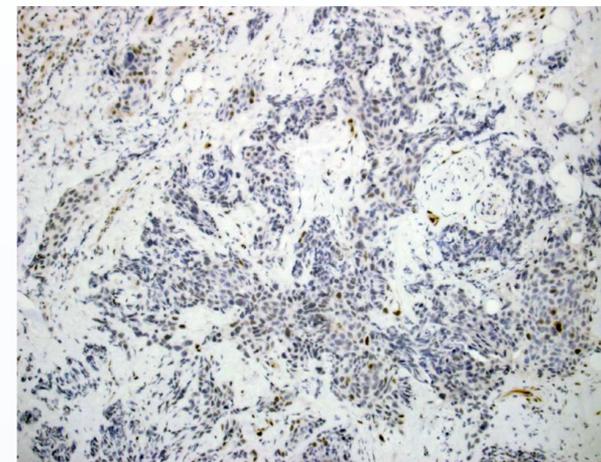


Figure 1: OSCC, low Rb expression (200X)

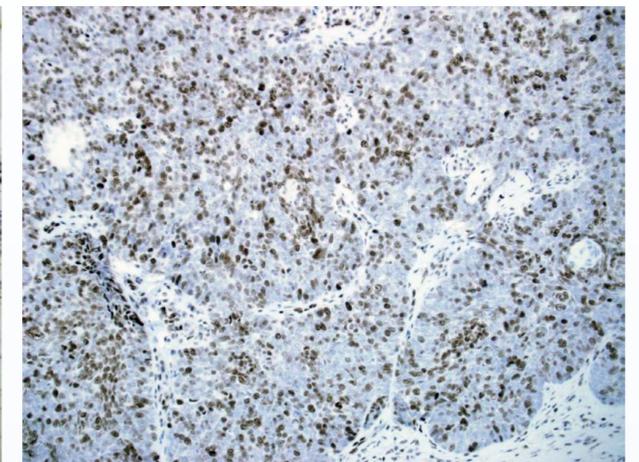


Figure 2: OSCC, high Rb expression (200X)

CONCLUSION

Low Rb expression in p16 positive OSCC is in agreement with HPV E7 oncoprotein effect on the p16/Rb axis. However, approximately 30% of the p16 positive patients had high Rb expression, irrespective of their smoking history. This may be due to differences in the degree of inhibition by E7 oncoprotein, making the HPV action on the host cell more important than patient's smoking history.

High Rb expression in p16 negative OSCC supports the hypothesis that cell proliferation in HPV negative tumors may involve loss or silencing of the p16 tumor suppressor via a pathway independent of Rb activity.

REFERENCES

1. Witkiewicz A, Knudsen K, Dicker A, Knudsen E - *The meaning of p16 staining in tumors. Functional significance, clinical associations and future developments* Cell Cycle 10:15, 2497-2503, August 1, 2011
2. Lowry D, Munger K *Prognostic implications of HPV in oropharyngeal cancer* N Engl J Med 2010, July1, 363(1), 82-4