Summary of the study
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Oral cancer poses a major health problem in many parts of the world including India where at least 56,000 new cases are thought to occur each year, resulting in about 100,000 individuals suffering from the disease at any given time. Radiotherapy is the primary mode of treatment for head and neck cancers. The practice of radiotherapy is confounded by high rates of local recurrence, occurring in about 25% of patients treated with a curative intent. Further 20% of the treated patients show residual disease. Radiotherapy being a local treatment, the most valid assessment for predicting the response depends on loco regional status. Development of predictive markers is therefore essential to estimate the overall benefit of getting cured by the treatment. Tissue kinetics is dependant on the balance between cell proliferation and cell death, which in turn depends on blood vessels for the supply of essential nutrients and oxygen. In tumors, the tissue kinetics shift more towards proliferation and some tumors induces growth of new blood vessels, which favours further proliferation. Thus the basis of anticancer treatment is therefore aimed at promoting cell death. The levels of cell death and proliferation regulatory proteins and the extent of tumor vasculature influences the cellular response to treatment. Therefore analysis of pre-treatment levels of cell death, proliferation and vascularisation in relation to the expression of cell death regulatory molecules p53, bcl-2 and bax during tumor progression, treatment response, tumor relapse and follow-up status.
Summary of results

A. Tumor progression

1. The expression of p53 protein showed gradual increase with increasing histological abnormality.
2. The expression of bcl-2 protein showed increased expression similar to p53 with increasing histological abnormality.
3. Cyclin D1 protein showed overall increase in the expression with increasing histological abnormality.
4. Bax protein showed a decreased expression with increasing histological abnormality.
5. Extent of apoptosis was low in malignant lesions with increasing histological abnormality.
6. Angiogenesis increased with increasing histological abnormality.

B. Invasive (malignant) lesions with relation to clinical staging and treatment response.

Over 90% cases report to the hospital with invasive cancers (malignant lesions). The treatment outcome is poor in about 45% of these cases and thus only malignant lesions were included for this part of the study.

1. There was no correlation between p53 expression and histological grades of the invasive lesions. However lowest levels were observed in poorly differentiated carcinoma.
2. Similarly apoptosis also failed to correlate with the histological grades of the invasive lesions. Apoptosis was also generally low level in poorly differentiated carcinoma.
3. Expression of bcl-2 was significantly associated with the expression of p53 protein.

4. Clinical staging based on tumor size, nodes and metastasis were not found to correlate with various grades of invasive lesions.

5. High levels of p53 protein and T status showed significant association with poor response to treatment.

6. Disease relapse was also found to correlate with high p53 levels as well as poor angiogenic status.

7. Mutant p53 protein detected by ELISA was found to correlate with follow-up status.

8. Multiple regression analysis to assess the prognostic value of p53, angiogenesis and apoptosis showed that these factors together were significantly associated with follow-up status.

C. Predictive assay

The rationale behind such a design is based on functional relation between vasculature, apoptosis and proliferation. The vasculature can provide proliferative advantage to the tumor or favour apoptosis influenced by host or treatment. If there is a host influence on the tumor, this could induce apoptosis in cells around the vasculature indicating apoptotic sensitivity of the tumor cells. Similarly if cell proliferation is deregulated, it could provide survival advantage by quick repopulation of tumor cells after treatment. Considering these facts, the apoptotic cells and proliferative cells were counted only in vascular area. Our results show that presence of de novo apoptotic cells near the vasculature showed good response to treatment, while presence of highly proliferative cells or absence of apoptotic cells was also associated with poor response or disease relapse.
Conclusion

Treatment failure is a consequence of poor response or disease relapse. The biological mediators of treatment include p53 protein, angiogenic status and apoptosis. Presence mutant p53 protein was associated with poor response to treatment as well as favouring disease relapse. Presence of apoptotic cells near the vasculature was suggestive of better response to treatment, while the absence of apoptotic cells with or without high proliferation around vasculature resulted in poor treatment outcome. This predictive assay can thus be used to develop tailored treatment modalities for individual patients who are at high risk of developing recurrent diseases. Such an approach would significantly help the management of this common cancer.