5.11. The molecular pathology of radiofrequency mucosal ablation of Barrett's esophagus

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Background: The objective of mucosa ablation techniques in Barrett's esophagus is to eradicate mutation bearing intestinalized mucosa cells and induce their replacement by normal squamocolumnar lining cells. We integrated mutational analysis into microscopic evaluation to better understand the biology of the mucosal ablative approach and to personalize the diagnosis and predict treatment efficacy.

Materials and Methods: Recut microscopic sections (4 um thick) from tissue blocks of 21 patients undergoing radiofrequency mucosal ablation (RMA) for Barrett's metaplasia and low grade dysplasia were microdissected at multiple target sites. 16 patients underwent a single RMA and 5 were treated twice with histopathology available pre and post treatment for up to a 2.5 year follow-up. A total of 51 microdissection targets were analyzed for a broad panel of 16 allelic imbalance (loss of heterozygosity [LOH]) mutational markers affecting 1p, 3p, 5q, 9p, 10q, 17p, 17q, 21q, 22q using quantitative fluorescent PCR/capillary electrophoresis. The presence, cumulative number and extent of clonal expansion (% of microdissected target cells bearing individual mutations; less than 75% = lowly expanded mutations, greater than 75% = high) was correlated with the histopathologic features.

Results: RMA induced replacement of Barrett's metaplasia by normal mucosa in 15 or 16 patients (94%). In each case, mutations that were present in the metaplastic cells were no longer detectable in postablative specimens indicating that the mutated clone and its precursors had been eradicated. In the one patient with persistent disease, all mutations that were shown to be lowly clonally expanded were eradicated but the highly expanded mutations remained. Similarly, in patients requiring two RMA procedures, highly clonally expanded mutations remained present in intestinalized cells after initial treatment. Such highly expanded mutations were seen to affect a wide range of markers and were not confined to a single genomic locus. Of note, mutational regression did not necessary take place immediate after treatment but could occur at 6-12 months.

Conclusions: RMA is shown to induce regression of mutation bearing and cause reversion of intestinalized to normal squamocolumnar cells. Regression is time dependent and can occur at 6-12 months following treatment. Intestinalized mucosal cells bearing highly clonally expanded mutations are more resistant to regression but can be eliminated by repeat treatment. Integrated microscopic/molecular analysis provides sensitive parameters with which to classify, plan RMA and monitor patient with Barrett's metaplasia on a more personalized basis.