files of salivary ACC and to correlate the profile with PNI. These studies showed 53 genes as being two-fold or more differentially expressed in PNI cancer cell groups as compared to non-PNI cancer cell controls. Out of the 53 genes found consistently differentially expressed, 38 were up-regulated and 15 down-regulated. These findings substantiated many genes previously reported for ACC (Frierson et al. 2002; Patel et al. 2006), but also revealed several novel genes that appeared to be associated with initiation and progression of PNI, included among which were MCAM (CD146), AREG, MGEA6, CARD12, PMP22, TRAG-3, MMP-7, NTF-4, APOC1, MAGEA2 , MAGEA4, MAGEA6, and MAGEA9 (Chen et al. 2007).

Initial attempts to use gene profiling to classify salivary gland neoplasms have shown differences between ACCs and other types of malignant tumors. Hierarchical clustering analysis revealed that the latter group, including salivary duct carcinoma (SDC), mucoepidermoid carcinoma (MEC), and acinic cell carcinoma (ACI), share overlapping gene expression patterns. Thirteen known genes were differentially expressed in MEC and ACI, 37 in SDC, and 59 in ACCs. Highly expressed genes included the genes for immunoglobulin J chain and chemokine HCC-1 in MEC, transcriptional factor IIF and SON DNA-binding protein in ACI, and von Hippel Lindau gene (VHL) in SDC. Underexpressed genes included the genes for the D13S824E locus in MEC, SKAP 55 protein in ACI, and KIAA0074 and prostate carcinoma tumor antigen in SDC. Interestingly, a distinctively different pattern within the ACIs was noted based on their site of origin. According to the heat map of clustering within ACI cases, 11 known genes were found to discriminate between ACI cases from major salivary gland (ACI-major) and ACI from minor salivary gland (ACI-minor). In particular, the expression of keratin 5 and keratin 13 was markedly lower in ACI-major than in ACI-minor (Maruya et al. 2004).

In a like fashion gene expression profiles have been studied in a variety of salivary gland carcinomas, including MEC, ACI, and SDC. These studies showed a total of 162 deregulated genes. However, only 5 genes were overexpressed in all carcinomas, including fibronectin 1 (FN1), tissue metalloproteinase inhibitor 1 (TIMP1), biglycan (BGN), tenascin-C (HXB), and insulin-like growth factor binding protein 5 (IGFBP5), whereas 16 genes were underexpressed. Interestingly, diversity in gene expression between the carcinoma types was identified by hierarchical clustering. Each carcinoma entity was clustered together, but MEC, SDC, and ACI were separated from each other. Significance analysis of microarrays identified 27 genes expressed differently between the groups. In MEC, overexpressed genes included those of cell proliferation (IL-6 and SFN) and cell adhesion (SEMA3F and COL6A3), whereas many underexpressed genes were related to DNA modification (NTHL1 and RBBP4). Apoptosis-related genes CASP10 and MMP11 were overexpressed in SDC, in accordance with the typical tumor necrosis seen in this entity. An intermediate filament protein of basal epithelial cells, cytokeratin 14 (KRT14) was clearly differently expressed among the three types of carcinoma (Leivo et al. 2005).

Although molecular genomic and proteomic profiles are beginning to impact our consideration of many neoplasms, except for breast, the surgical pathologists are still guided in large part by histological grade and evidence of invasion, particularly when evaluating salivary gland tumors. Histologi-

Table 7.2. Grading of salivary gland tumors.

Low-grade
Acinic cell carcinoma
Basal cell adenocarcinoma
Clear cell carcinoma
Cystadenocarcinoma
Epithelial-myoepithelial carcinoma
Mucinous adenocarcinoma
Polymorphous low-grade adenocarcinoma
Low-grade, intermediate-grade, and high-grade
Adenocarcinoma, NOS
Mucoepidermoid carcinoma*
Squamous cell carcinoma
Intermediate-grade and high-grade
Myoepithelial carcinoma
High-grade
Anaplastic small cell carcinoma
Carcinosarcoma
Large cell undifferentiated carcinoma
Small cell undifferentiated carcinoma
Salivary duct carcinoma

*Some investigators consider mucoepidermoid carcinoma to be of only two grades: low-grade and high-grade (Spiro et al. 1978).