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DNA copy number variation and loss of heterozygosity in relation to recurrence of and survival from head and neck squamous cell carcinoma: a review

Yu Chen, PhD[1] and **Chu Chen, PhD**[2]

[1]Program in Epidemiology, Fred Hutchinson Cancer Research Center, Department of Epidemiology and Department of Otolaryngology: Head and NeckSurgery, University of Washington

[2]Program in Epidemiology, Fred Hutchinson Cancer Research Center, Department of Epidemiology and Department of Otolaryngology: Head and NeckSurgery, University of Washington

Abstract

Background—Genetic aberrations, such as DNA copy number variation (CNV) and loss of heterozygosity (LOH), have been implicated in head and neck squamous cell carcinoma (HNSCC) initiation and progression. This review examines CNV and LOH as predictors of HNSCC recurrence and mortality.

Methods—We searched PubMed for relevant publications and compared and discussed results from the articles.

Results—Certain CNV and LOH events have consistently been associated with HNSCC recurrence and survival. The recent high-resolution SNP arrays have the potential to identify many more genetic changes and concurrent genome-wide CNV, copy-neutral and/or allelic imbalance LOH in HNSCC that may bear on prognosis.

Conclusions—Our review confrms that outcome in HNSCC can be predicted to a considerable extent by the presence of tumor cell genetic aberrations. It points out the limitations of some methodologies that were used in the past and discusses the advantages and challenges of using genome-wide SNP arrays.

Keywords

Head and Neck Neoplasm; Gene Dosage; Loss of Heterozygosity (LOH); Prognosis; Neoplasm Recurrence; Local

Introduction

World wide, head and neck cancers (oral cavity, nasopharynx, other pharynx, esophagus, larynx and thyroid) are the second most common malignancy (over 1.2 million new cases annually) and rank second (over 770,000 deaths) as a cause of cancer death[1;2]. The major histological type for head and neck cancer is squamous cell carcinoma (HNSCC).

Corresponding author: Chu Chen, PhD. Program in Epidemiology, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N, M5-C800, Seattle, WA 98109-1024, USA. cchen@fhcrc.org; Phone: (206) 667-6644; Fax: (206) 667-2537.

About 40% of HNSCC cases arise in the oral cavity and oropharynx (oral squamous cell carcinoma (OSCC))[2]. In the US, patients with OSCC have a 5-year survival of 50–60%[3]. Those patients who survive often suffer disfigurement, loss of eating and speech function and poor quality of life[4]. Prediction of progression of HNSCC can have an important bearing on the aggressiveness of treatment of HNSCC. However, tumor characteristics such as anatomic site, thickness and grade are limited in their ability to predict prognosis and treatment response[5].

HNSCC likely results from cumulative epigenetic and genetic alterations[5–11]. Genetic alterations, including copy number variation (CNV – copy number gains or losses) and loss of heterozygosity (LOH – allelic imbalance or copy-neutral LOH), may result in inactivation of tumor-suppressor genes and activation of oncogenes[8;12;13], which in turn may lead to uncontrolled cell growth and metastasis[12–16]. Plausibly, the presence of CNV/LOH has the potential to serve as a prognostic indicator, alone or in combination with other markers, to identify HNSCC patients at high risk of recurrence and death. The purpose of this review is to summarize current knowledge with regards to CNV and LOH as they are related to the prognosis of HNSCC.

Methods

For this review, we searched the PubMed using the following keys words from MeSH database: “Head and Neck Neoplasms”, “Gene Dosage”, “Gene Amplification”, “Loss of Heterozygosity”, “Prognosis”, “Neoplasm Recurrence, Local”. The main search term combinations included “Head and Neck Neoplasms”[Mesh] AND “Gene Dosage”[Mesh] AND “Prognosis”[Mesh]; “Head and Neck Neoplasms”[Mesh] AND “Gene Dosage”[Mesh] AND “Neoplasm Recurrence, Local”[Mesh]; “Head and Neck Neoplasms”[Mesh] AND “Loss of Heterozygosity”[Mesh] AND “Prognosis”[Mesh]; “Head and Neck Neoplasms” [Mesh] AND “Loss of Heterozygosity”[Mesh] AND “Neoplasm Recurrence, Local”[Mesh]; “Head and Neck Neoplasms”[Mesh] AND “Gene Amplification”[Mesh] AND “Prognosis” [Mesh]; “Head and Neck Neoplasms”[Mesh] AND “Gene Amplification”[Mesh] AND “Neoplasm Recurrence, Local”[Mesh]. We also applied search term combinations [“Head and Neck Neoplasms”[Mesh] and comparative genomic hybridization] and [“Head and Neck Neoplasms”[Mesh] and SNP arrays] to check whether there were any additional reports on genomic aberrations and survival/recurrence that used high throughput array methods.

Results

We grouped the studies conducted over the past decades into two categories based on the methodologies used in each of the studies: low throughput/low resolution methods (fluorescent in situ hybridization (FISH) and polymerase chain reaction (PCR)-related methods) to study localized CNV/LOH occurrence; and high throughput/high resolution methods (array-related methods) to identify genome-wide CNV/LOH events. Tables 1 and 2 describe respectively the association between CNV/LOH and HNSCC survival by low throughput methods (Table 1) and high throughput methods (Table 2). Table 3 describes the association between CNV/LOH changes and HNSCC recurrence. When univariate Cox regression p-values are available, these p values are reported; if univariate Cox regression p-values are not available, the log rank test p-values are reported; if neither are available, the multivariate Cox regression p-values are reported. In Table 4, the number of studies reporting associations between presence of CNV or LOH with survival and recurrence of HNSCC is summarized based on chromosomal arms.

Localized CNV and LOH and survival

Many studies have applied PCR-based methods and FISH to detect markers which could predict survival of head and neck cancer patients (Table 1). Twelve studies that examined 11q13 found consistent amplification in this region[17–28]. Amplification of oncogene *CCND1*[18–20;23–25], *EMS1*[18;22], *bcl-1*[18;25], *Int-2*[21;26;27], *bcl-1/CCND1*[25] and *Int-2/hst*-1 co-amplification[17] located in this region were associated with shorter survival. It is possible that amplification of 11q13 plays an important role in head and neck cancer survival, given the many known oncogenes, such as *bcl-1, Int-2, hst-1, EMS1, CCND1/PRAD1*, reside in this region[8]. An increase in the copy number at 3q26-27[29], *CCNL1* (3q25-q29)[30], *EGFR* (7p12)[31;32], *BTAK* (20q13) and *E2F1* (20q11)[33]; increased c-*MYC*/*CDKN2A* (8q24.21/9p21) and *CCND1*/*CDKN2A* (11q13/9p21) ratios[28], combination of *CCND1* amplification and *p16 (CDKN2A*, 9p21) deletion[23], and loss of *DIAI* (22q13)[34] have also been shown to be associated with reduced head and neck cancer survival.

Results from close to two dozen studies indicate that many of the LOH events on certain chromosomal regions are associated with shorter survival of HNSCC patients (Table 1). All but one of these studies[35] compared paired tumor tissues and normal blood/tissues either from the same individual or from healthy controls. The regions with LOH changes that were associated with survival included 2q[36], 3p[37;38], *M6P/IGF2R* (6q25-27)[39], 8p23[40;41], 8p23-22[41], 8p21.3-11.21[42], 9p24.2-21.2[42], *p16* (9p21)[43], 10q[44], 13q[45], 14q[46], 18q[35;47]. However, some studies reported that such an association was only seen if LOH changes were detected in more than one or two chromosomal regions or genes: in more than one of the 3p13, 3p24-26, 9p21 regions[48]; 3p21 and/or 9p21[49]; in more than two loci among 3p21, 3p26, 8p, 13q, 17p[50]; *p53* (17p13) and *Rb* (13q14)[51]; or with fractional allelic loss (FAL) score > 0.4[48]. A report by Kim *et al* [8] indicated that 3p LOH was an early event during the carcinogenesis process. Our review shows that 3p LOH is also associated with survival among patients with HNSCC[49;50], OSCC[37;48] or nasopharyngeal carcinoma (NPC)[38], suggesting 3p LOH may be involved in later stages of cancer progression as well. The biological importance of the genomic aberrations present in chromosomes 3 – 13, 16 – 18, 21 – 22 (particularly on chromosomes 3, 9, 11 and 17) and in potentially-affected oncogenes and tumor-suppressor genes in OSCC or HNSCC have been nicely summarized by Scully *et al*[52].

While informative, there are some limitations to the above mentioned studies. The specimens from some of these studies were from formalin-fixed, paraffin-embedded tissues, which could have led to problems with DNA being fragmented or degraded[17;20;21;23;24;27;29–31;36;39;41;42;47;53]. Samples with mixed population of cells will have attenuated signals. Some of these studies used microdissection to collect purer cell populations to avoid signal contamination caused by bystander cell populations[25;36;37;39;41;42;47;48], while other studies did not try to isolate pure cell populations or to provide tumor content in the tissue examined[17–23;26;27;29–31;33;49–51]. Only two studies did not provide information on how the samples were processed or information on tumor contents[35;38]. Most of these studies focused on a few individual genes or microsatellite markers (range 1 to 55) located in quite limited regions of chromosomal arms or cytobands and were conducted by PCR-based methods, FISH, or Southern Blot methods that were not very sensitive[17;18;22;29;34;48]. The pros and cons of various methods used to detect CNV and LOH have been summarized by Wreesmann *et al*[7]. In general, whole genome-based detection methods, such as comparative genome hybridization (CGH) and single nucleotide polymorphism (SNP) arrays will provide broader coverage of the chromosomal aberrations with more detailed profiling[7;54;55].

Genome-wide CNV and LOH and survival

By using CGH, studies have identified some CNV and LOH that were associated with poor prognosis of HNSCC (Table 2). In OSCC, 7p gains were associated with worse survival[56]. In HNSCC, poor prognosis was associated with gains at 2q12, 3q21-29, 3q25-27, 6p21.1, 8p11, 11q13, 12q24, 14q11, 14q23, 14q24, 14q31, 14q32, 15q24, 16q22, 17q23, 17q24, 17q25, 20q13, 22q13; losses at 1p21, 2q34, 5q11, 5q12, 5q14, 5q15, 5q31, 6q14, 6q15, 8p21-22, 10p12, 12q22, 18q11.2, 21p21, 21q11, 21q21, 21q22, 22q[57–59]; and high level of gain at 11q13 (ratio > 2)[57]. In esophageal squamous cell carcinoma, gains at 5p15, 8q24-qter, 14q21, alone or all three together, predicted shorter survival[60].

Several of these studies had used fresh frozen tissue with tumor content higher than 70%[57–59]. One study used microdissected fresh frozen tumor tissues to increase their chances of obtaining high quality tumor DNA[60]. Gebhart *et al*[56] did not mention how they collected the samples or what the tumor contents were.

Localized and genome-wide CNV and LOH and recurrence

Tumor recurrence is another important indicator of patient prognosis. Using FISH and PCR-related methods, studies showed amplification at 3q26-27[29]; amplification at 11q13 region[18] including *EMS1* (22), *CCND1*[24;25;61;62], amplification and/or rearrangement of *bcl-1/CCND1*[25]; high polysomy and/or amplification at *EGFR* (7p12)[53]; copy number of *erbB-2* (17q21.1) > 1.2; of *erbB*-3 (12q13) < 0.11[63]; ratio of *c-MYC* (8q24.21)/*CDKN2A* (9p21) >2[28]; combination of *CCND1* (11q13) amplification and *CDKN2A* (*p16*, 9p21) deletion[23]; combination of CCND1 (11q13) amplification and p53 (17p13.1) LOH in stage IV patients[61] to be associated with higher risk of HNSCC/OSCC recurrence (Table 3). Two of these studies applied microdissection to enhance collection of pure cell populations[25;62]. Another two studies used tissues with tumor content higher than 70%[28;53]. Other than a few studies that specified the use of fresh frozen tissue[18;22;25;28], most either did not mention how the tissues were processed[61] or what the tumor content was[22–24;29;61].

In HNSCC/OSCC, localized LOH changes associated with recurrence were found in the following regions: LOH ≥ 2 loci on 2q[64], 3p[37], 6p[65], *M6P/IGF2R* (6q25-27) in patients who received radiotherapy[39], 8p23[40], 9p21[66], *INFα* (9p22)[67], 11q23[68], 13q[65], 3p21 and/or 9p21[49]; LOH at *p53* (17p13.1) and amplification at *CCND1* (11q13)[61]; LOH/microsatellite instabilities at *p53* (17p13.1), *INFα* (9p22) within tumor margins[69]. A fractional allelic loss score of ≥ 0.4, based on 6 SNP markers and 13 microsatellite markers, was associated with OSCC local recurrence[48].

Using fresh frozen tissue with more than 70% tumor content, two CGH studies of HNSCC found the following genomic alterations to be associated with recurrence: gains at 1q32, 1q42-43, 2p24-25, 2q12, 3q21-29, 6p21.1, 6p22-24, 7p22, 11q13, 14q23, 14q24, 14q31, 14q32, 15q24, 16q22, 17q, 20q; losses at 8p21-22, 11q23-25, 18q11.2, 18q21, 19p, 22q; and high level of gains (ratio > 1.5) at 11q13[58;59]. Compared to the low-throughput methods, these studies had a much improved resolution to detect genome-wide CNV and LOH events. However, CGH still has limited resolution (< 5 to 10Mb)[7] compared to a new set of SNP arrays with resolution of 15 – 90 kb[55]. Also, unlike the SNP array, CGH can not detect balanced chromosomal changes, such as copy-neutral LOH[55;70;70].

SNP arrays to detect genome-wide CNV and LOH

Single nucleotide polymorphism (SNP) arrays were originally designed to assess associations between single-nucleotide polymorphisms and disease risk. However, SNP arrays can also be used as efficient tools to detect CNV and LOH events in cancers by comparing information between tumor and normal reference DNA[55;71–73]. To detect LOH,

information on SNP genotype from paired tumor and normal DNA was compared to see whether heterozygous loci in the normal reference DNA samples turned into homozygous loci in the tumor DNA samples. To determine CNV, the hybridization signal intensities of corresponding SNP locus in the normal sample and in the tumor sample were compared[55;71]. So far, there have only been a few studies using SNP arrays to detect CNV and LOH in HNSCC; use of the ["Head and Neck Neoplasms"[Mesh] AND SNP array] search term identified only seven papers, and none pertained to the evaluation of HNSCC prognosis. Tong *et al*[74] identified 6q LOH in OSCC by Affymetrix HuSNP arrays, a result that was confirmed by conventional microsatellite analysis. Zhou *et al*[72] examined a cell line model for OSCC progression using a 10K SNP array and suggested that CNV and/or LOH at 3pter-3p35.3, 3p14.1-3p13, 11p, 11q14.3-11q22.2, and 11q13.5-11q14.1 might be associated with OSCC progression. Zhou *et al* also observed concurrent CNV and LOH in region 1q22-24.1 and 1q42.13 in both pre-malignant and malignant cells, but not in normal cells[72]. Frequent allelic imbalances, including losses at 3p, 8p, 9p, and gains at 8q, 11q, and 20q, were detected in advanced stage OSCC samples with the use of 10K and 100K SNP arrays[75].

The 500K Affymetrix SNP array set with 2.5 kb median physical distance and 5.8 kb average distance between SNPs (> 85% of genome within 10 kb of a SNP)[76;77] has been used to simultaneously detect LOH, overall copy number changes and allele-specific copy number changes with very high resolution in various cancers, but not yet in HNSCC[77]. By using a high resolution array such as the Affymetrix 500K SNP array set, researchers may discover genomic alterations that contribute to the various clinical phenotypes and varied disease survival. However, while this new technology holds great promise, it also presents some challenges. With the large numbers of genomic aberrations detected by the SNP arrays, concerns about data complexity, multiple-testing issues, and statistical power of the study need to be addressed.

Based on existing cumulative knowledge, survival and recurrence in patients with HNSCC are associated with genomic alterations present in a number of chromosomal regions and genes (Table 4). The most commonly reported CNV associated with survival pertain to chromosomal regions 11q (14 studies), 3q (4 studies), 7p and 22q (3 studies); LOH in 3p (5 studies), 8p and 9p (4 studies), 13q (3 studies). Most of these CNV studies focused on the examinations of specific genes that have been shown to play important roles in head and neck carcinogenesis, e.g. *CCND1, EMS1, Int-2, bcl-1* at 11q13; *CCNL1* at 3q; *EGFR* at 7p12; or *BTAK* or *E2F1* at 22q. Most LOH studies tested various micro-satellite markers at certain regions to analyze the association between LOH changes and survival. As far as recurrence is concerned, the most commonly reported CNV/LOH associated with recurrence involved CNV at 11q (11 studies); LOH at 9p (4 studies) and 17p (3 studies). CNV/LOH at other chromosomal areas, as listed in Table 4, has only been reported by one or two studies. Similar to studies with survival outcomes, these CNV studies with recurrence outcomes focused on some of the specific genes and LOH studies focused on using micro-satellite markers.

There were only two papers that combined clinical characteristics, such as tumor, node, metastasis (TNM) staging or treatment conditions, with CNV or LOH to predict survival[37;39]. Partridge *et al* found that 3p LOH was associated with poorer survival. The association was present even in patients with early stage I & II tumors[37]. Jamieson *et al* also showed that in patients who received radiotherapy (RT), 6q LOH was associated with reduced survival[39].

With the advent of SNP array technology and technologies to interrogate transcriptome and proteome, a better picture should emerge regarding the extent CNV/LOH might bear on

HNSCC survival and recurrence, the specific CNV and/or LOH that might exert such an effect, and whether certain CNV and/or LOH, alone or in combination with other parameters, such as TNM staging, transcriptome profile, proteome profile, etc., can improve the prediction of HNSCC recurrence and mortality.

Conclusions

Genomic markers, such as CNV and LOH, have been shown to be associated with disease-specific survival from and recurrence of HNSCC in a number of studies done by low throughput/lower resolution methods. However, most of these studies had some potential limitations, such as poor DNA quality or contaminated signals due to mixed cell populations present in the examined tumor samples. Also, these studies could detect either CNV or LOH, but not both, due to the limitations of their methodology. The current commercially-available SNP arrays have much improved resolution than the previously used methods and can be used to simultaneously detect CNV and LOH (allelic imbalance or copy number-neutral LOH). There have been no studies applying the high resolution SNP arrays, such as the Affymetrix 500K SNP set, to detect genomic aberrations in HNSCC or to predict HNSCC prognosis. While the SNP array approach provides an opportunity to identify potential genomic markers that could be used to better predict prognosis, there are also a number of challenges researchers need to overcome. These challenges pertain largely to the need for high quality DNA from high tumor content samples in large numbers of patients with HNSCC who have been monitored for tumor recurrence and survival.

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Table 1

Localized CNV, LOH Events and Head and Neck Cancer Prognosis

Author	Cancer type	Number of cases	Sample handling	Methods	Location of markers	Follow-up time	Clinical outcomes
Localized CNV							
Kitagawa Y, 1991[17]	ESCC	107	Tumor and adjacent normal tissues (paraffin-embedded) Tumor content: NA	Slot-Blot analysis	*Int-2/hst-1* (11q13)	Mean follow-up: 29 mo; max. follow-up: 119 mo.	5-yr survival: 22% with (28%, 30/107) vs. 43% w/o (72%, 77/107) *Int-2/hst-1* coamplification ($p < 0.001$)
Mori M, 1992[27]	ESCC	90	Tumor and paired normal tissues (paraffin-embedded) Tumor content: NA	Dot-blot hybridization	*Int-2* (11q13)	> 60 mo; max. follow-up: 66.7 mo (2000 days)	Poorer survival in cases with (25%, 5/20) vs. cases w/o (75%, 15/20) *Int-2* amplification in LN- patients (Generalized Wilcoxon test $p < 0.01$)
Meredith SD, 1995[18]	HNSCC	56	Tumor tissues (fresh frozen) Tumor content: NA	Southern Blot	11q13 (*bcl-1, PRAD1/ CCND1, hst1, EMS1, GST-pi-1*)	Mean follow-up: 17.6 mo (range 2 – 59)	Lower overall survival in cases with (39%, 22/56) vs. cases w/o (61%, 34/56) amplification (Wilcoxon rum sum test $p = 0.0024$)
Bellacosa A, 1996[19]	LSCC	51 primary	Tumor and partially paired normal tissues (fresh frozen) Tumor content: NA	Southern Blot	*CCND1* (11q13)	Median follow-up: 29 mo (range 2 – 60)	Overall survival: 75.0% (6/8) with (18%, 9/51) vs. 29% (12/42) w/o (82%, 42/51) *CCND1* amplification ($p = 0.03$)
Shinozaki H, 1996[20]	ESCC	122	Tumor and adjacent normal tissues (paraffin-embedded) Tumor content: NA	Slot blot analysis	*CCND1* (11q13)	Mean follow-up: 35 mo; max. follow-up: 144 mo	5-yr survival: 11.6% with (23%, 28/122) vs. 55.3% w/o (77%, 94/122) *CCND1* amplification (Cox-Mantel & Generalized Wilcoxon test $p < 0.001$)
Kitagawa Y, 1996[31]	ESCC	107 primary	Tumor and adjacent normal tissues (paraffin-embedded) Tumor content: NA	Southern Blot	*EGFR* (7p12)	Median follow-up: 18 mo (range 1 – 119)	5-yr survival: 7% with (12%, 13/107) vs. 43% w/o (88%, 94/107) *EGFR* amplification (Generalized Wilcoxon test $p < 0.001$)
Ikeda Y, 1996[21]	ESCC	63 primary	Tumor and adjacent normal tissues (paraffin-embedded) Tumor content: NA	Slot-blot hybridization	*c-erbB (*7p12*), Int-2 (*11q13)	> 36 mo; max. follow-up: 60 mo	5-yr survival among T1b cases: 55% with (22%, 12/54) vs. 97% w/o (54%, 29/54) *Int-2* amplification (Generalized Wilcoxon test $p < 0.05$)
Miyahara H, 1998[26]	LSCC	21 primary	Tumor and adjacent normal tissues (fresh frozen) Tumor content: NA	Southern Slot Blot hybridization	*Int-2, bcl-1* (11q13)	Follow-up range: 38 to 69 mo	5-yr survival: 56% with (43%, 9/21) vs. 92% w/o (57%, 12/21) *Int-2* amplification (Wilcoxon test $p < 0.05$)

Author	Cancer type	Number of cases	Sample handling	Methods	Location of markers	Follow-up time	Clinical outcomes
Rodrigo JP, 2000[22]	HNSCC	104 primary	Tumor (fresh frozen) and normal tissues from not paired non-cancer patients Tumor content: NA	Differential PCR	*CCND1* (11q13), *EMS1* (11q13)	≥ 36 mo	Lower disease-specific survival in cases with (20%, 21/104) vs. cases w/o (80%, 83/104) *EMS1* amplification ($p < 0.0001$)
Singh B, 2002[29]	HNSCC	50 primary and 49 non-cancerous	Tumor, pre-malignant/normal tissues (paraffin-embedded) Tumor content: NA	FISH	3q26-27	Median follow-up: 82.5 mo	3-yr cause-specific survival: 40% (20%, 10/50) with high level 3q amplification (>4X copy number) vs. 94%; 83% (44%, 22/50; 36%, 18/50) normal copy or low copy (Wilcoxon test $p = 0.001$)
Namazie A, 2002[23]	HNSCC	103	Tumor and a subset of 20 normal tissues (paraffin-embedded) Tumor content: NA	FISH	*CCND1* (11q13), *p16* (9p21)	Median follow-up: 42 mo (range: 1 – 151)	Lower 3-yr survival in cases with (30%, 31/103) vs. w/o (70%, 72/103) *CCND1* amplification ($p = 0.0042$, univariate RR: 2.38) Lower 3-yr survival in cases with (20%, 21/103) vs. w/o (80%, 82/103) *CCND1* amplification plus *p16* deletion ($p = 0.003$, univariate RR: 3.16)
Reis PP, 2002[34]	OSCC	40 primary	Tumor (fresh frozen) and normal adjacent tissues/ blood Tumor content >80%	qRT- PCR for 4 genes; FISH for 2 micro-satellites	22q13	Mean follow-up: 15.8 mo (range 2 – 48)	Overall survival: 24% for cases with (25%, 10/40) vs. 66% w/o (75%, 30/40) *DIA1* deletion ($p = 0.0018$)
Miyamoto R, 2003[24]	OSCC	41 primary	Fine-needle aspiration biopsies (paraffin-embedded) Tumor content: NA	FISH	*CCND1* (11q13)	Median follow-up: 25.4 mo (range 7.7 – 39.3)	Overall survival: 46% with (32%, 13/41) vs. 85.7 w/o (68%, 28/41) *CCND1* amplification ($p = 0.0016$)
Fujita Y, 2003[33]	ESCC	41 primary	Tumor tissues (fresh frozen) and blood DNA from a normal male Tumor content: NA	CGH and FISH	*AIB1* (20q12), *BTAK* (20q13), *DcR3* (20q13), *E2F1* (20q11)	Max. follow-up: 30 mo (900 d)	Shorter cumulative survival for cases with (39%, 16/41) vs. cases w/o (61%, 25/41) *BTAK* amplification (copy number ≥ 3) ($p < 0.01$) Shorter cumulative survival for cases with (37%, 15/41) vs. cases w/o (63%, 26/41) *E2F1* amplification (copy number ≥ 3), ($p < 0.01$)
Akervall J, 2003[28]	HNSCC	78 primary plus 2 cell lines established from two primary HNSCC	Tumor tissues (fresh frozen) Tumor content: >70%	qRT-PCR	*c-MYC* (8q24.21), *CCND1* (11q13), *CDKN2A* (9p21)	≥ 40 mo	Disease-specific survival: 55% (16/29) with (36%, 29/80) vs. 31% (16/51) w/o (64%, 51/80) *CCND1/*

Author	Cancer type	Number of cases	Sample handling	Methods	Location of markers	Follow-up time	Clinical outcomes
							CDKN2A ratio >2 (p = 0.049) Shorter disease-specific survival in cases with (n = 30) vs. cases w/o (n = 50) *c-MYC/CDKN2A* ratio >2 (p = 0.043)
Sticht C, 2005[30]	HNSCC	280 primary	Tumor (paraffin-embedded) and uvula mucosa tissue from healthy people Tumor content: NA	FISH	*CCNL1, SNO, PIK3CA, TP73L* (3q25-3q29)	Max. follow-up: 120 mo	Lower overall survival for cases with (3%, 7/216) vs. cases w/o (88%, 189/216) *CCNL1* high level amplification (> 8 signals per cell) (p = 0.0063)
Chung CH, 2006[56]	HNSCC	82 primary and 14 recurrent	Tumor tissues (formalin-fixed, paraffin-embedded) Tumor content >70%	FISH	*EGFR* (7p12)	Median follow-up: 24.5 mo; max. follow-up: 36 mo	Worse overall survival for cases with (57%, 43/75) vs. cases w/o (43%, 32/75) *EGFR* high polysomy and amplification (p < 0.01)
Sabbir MG, 2006[25]	HNSCC	79 primary and 5 dysplastic	Tumor and corresponding normal adjacent tissues/blood (fresh frozen) Tumor: microdissected	Southern Blot	*bcl-1, CCND1* (11q13), *CCND2* (12p13), *CCND3* (6p21)	Median follow-up: 44 mo (range: 12 – 78)	Lower 5-yr cumulative survival in cases with (25%, 20/79) vs. cases w/o (75%, 59/79) *CCND1* amplification (p = 0.0001) Lower 5-yr cumulative survival in cases with (54%, 43/79) vs. cases w/o (46%, 36/79) *bcl-1* and *CCND1* amplification and/or rearrangement (p = 0.00001)
Localized LOH							
Li X, 1994[50]	HNSCC	68	Tumor tissue (fresh frozen) and paired blood Tumor content: NA	PCR 43 micro-satellite markers	Each of the autosomal chromosomes	Median follow-up: 10 mo (range: 1 – 26)	Risk of dying: 31% (4/9) with (48%, 13/27) vs. 0% (0/14) w/o (52%, 14/27) LOH > 2 loci (3p21; 3p26; 8p; 13q; 17p) (X^2 test p = 0.0386)
Partridge M, 1996[37]	OSCC	48 primary	Tumor (fresh frozen) and paired normal mucosa/ blood Tumor: microdissected (tumor content > 50%)	PCR 15 micro-satellite markers	3p	Max. follow-up: 100 mo	Shorter overall survival time in cases 38 mo with (n = 34) vs. cases 27 mo w/o (n = 14) 3p LOH (p = 0.023); in cases 42 mo with (n = 14) vs. cases 102 mo w/o (n = 11) 3p LOH among stage I & II tumors (p = 0.021)
Gleich LL, 1996[51]	HNSCC	63 primary and 12 recurrent	Tumor and matched normal tissues (fresh frozen) Tumor content: NA	PCR/Southern blot 3 micro-satellite markers	*p53* (17p13) and *Rb* (13q14)	Mean follow-up: 21.2 mo (range: 12 – 44)	Died of cancer/alive with cancer: 70% with (22%, 10/46) vs. 21% w/o (78%, 36/46) *p53* (17p13) and *Rb*

Author	Cancer type	Number of cases	Sample handling	Methods	Location of markers	Follow-up time	Clinical outcomes
							(13q14) LOH (X^2 test p = 0.009)
Scholnick SB, 1996[41]	Supraglottic larynx cell carcinoma	59 primary	tumor and paired normal tissues (paraffin-embedded) Tumor: micro-dissected	PCR 3 micro-satellite markers	D8S264 (8p23), D8S552 (8p23-p22), and D8S133 (8p21)	Median follow-up: 77 mo (6.4 years)	Lower disease-specific survival in cases (n = 14) with vs. cases (n = 31) w/o D8S264 (8p23) LOH (p = 0.004) Lower disease-specific survival in cases (n = 16) with vs. cases (n = 31) w/o D8S552 (8p23-p22) LOH (p = 0.034)
Lee, DJ 1997[46]	HNSCC	73 primary	Tumor (fresh frozen) and paired blood Tumor content >70%	PCR 20 micro-satellite markers	14q	Mean follow-up: 31 mo (range: 17 – 52)	95% CI: overall survival: 0.42–0.81; 0.31–0.73 cases with (47%, 25/53) vs. 0.63–0.94; 0.57–0.89 cases w/o (53%, 28/53) 14q LOH (~12 mo; ~29 mo) (p = 0.04, univariate HR: 2.7, 95% CI: 1.0–7.0)
Ransom DT, 1998[36]	HNSCC	10 stage I/II HNSCC cases and 17 controls	tumor and normal tissues (paraffin block) Tumor: manually micro-dissected	PCR 11 micro-satellite markers	2q, 3p, 5q, 9p, and 17p	Cases: median follow-up: 15 mo (range: 8 – 23); controls: median follow-up: 68 mo (range: 30 – 138)	Shorter survival time: 15 mo with cases (75%, 6/8) vs. 68 mo w/o (20%, 3/15) 2q LOH (OR = 10.4, 95% CI: 1.15–159)
Pearlstein RP, 1998[47]	HNSCC	67 primary	Tumor and normal tissues (paraffin-embedded) Tumor: manually micro-dissected	PCR 3 micro-satellite markers	18q	Dead cases follow-up range: 0.5 – 66 mo; alive cases follow-up range: 24 – 100 mo	2-yr survival: 24% cases with (40%, 27/67) vs. 56% cases w/o (60%, 40/67) 18q LOH (unadjusted RR: 2.46, 95% CI: 1.32–4.58; p = 0.025)
Gasparotto D, 1999[44]	HNSCC	47 primary	Tumor and paired normal mucosa (fresh frozen) Tumor content >70%	PCR 7 Micro-satellite markers	10q	Maximum follow-up: 52 mo	Shorter survival time in cases with (43%, 20/47) vs. cases (57%, 27/47) w/o 10q LOH (p = 0.0051); 10q22-23 (p = 0.0009); 10q25-26 (p = 0.047)
Matsuura K, 1999[49]	HNSCC	93	Tumor tissues (fresh frozen) and paired blood Tumor content: NA	PCR 3 Micro-satellite markers	3p21, 9p21	Mean follow-up: 23 mo (range: 2 – 51)	5-yr disease-specific survival: 34.5% cases (47%, 27/57) with vs. 84.6% cases w/o (53%, 30/57) 3p21 and/or 9p21 LOH (p < 0.001)
Partridge M, 1999[48]	OSCC	48	Tumor tissues (fresh frozen) and paired blood Tumor: microdissected	6 SNP markers; 13 microsatellite markers	3p, 8p21-23, 9p13-21, 9q22, 13q14.2, *Rb* (13q14), *p53* (17p13) and *DCC* (18q21.3)	Median follow-up: 49 mo (range: 28 – 166)	Lower overall survival in cases with (n = 15) FAL score ≥ 0.4 vs. cases with (n = 16) FAL score = 0.21 – 0.39 vs. cases with (n = 17) FAL score ≤ 0.2 (p < 0.0002, univariate HR: 8.36, 5.37, 1)

Author	Cancer type	Number of cases	Sample handling	Methods	Location of markers	Follow-up time	Clinical outcomes
							Reduced survival in cases with LOH ≥ 1 loci within 3p24-26, 3p13, 9p21 (univariate p = 0.0002, HR: 4.21; p = 0.02, HR: 2.52; p = 0.01, HR: 2.65)
Lung ML, 2001[38]	NPC	47	Tumor tissues and paired blood Tumor content: NA	PCR 8 micro-satellite markers	3p, 6p, 9p, I1q and 14q	NA	Risk of dying: 57.1% cases with (24%, 5/21) vs. 7.7% cases w/o (76%, 16/21) D3S1351 (3p) LOH (X^2 test p = 0.031)
Bockmühl U, 2001[40]	HNSCC	51 primary	Tumor tissues and paired normal tissues (fresh frozen) Tumor content: >70%	7 micro-satellite polymorphisms	8p23	Median follow-up: 24.6 mo (range: 1 – 48)	Lower disease-specific survival in cases with (45%, 23/51) vs. cases w/o (55%, 28/51) 8p23 LOH (p = 0.0436)
Bazan V, 2002[43]	LSCC	64 primary	tumor and paired normal mucosa (fresh frozen) Tumor content >80%	PCR-SSCP 1 micro-satellite marker	D9S1747 (*p16*: 9p21)	Median follow-up: 53 mo (range: 11 – 102)	Shorter overall survival in cases with (25%, 16/64) vs. cases w/o (75%, 48/64) *p16* (9p21) LOH (p < 0.05)
Jamieson TA, 2003[39]	HNSCC	116 locally advanced but non-metastatic	Tumor and normal non-mucosal tissues (paraffin-embedded) Tissues: microdissected	PCR, 6 polymorphic markers	*M6P/IGF2R* (6q25-27)	Median follow-up: 76 mo (range: 2 – 128)	5-yr cause specific survival in cases treated with RT: 29% (95% CI: 5%–53%) cases with (n = 17) vs. 75% (95% CI: 54%–96%) cases w/o (n = 16) *M6P/IGF2R* (6q25-27) LOH (Cox-Mantel test p = 0.02)
Takebayas hi S, 2004[35]	HNSCC	21 paired primary/ secondary HNSCC cell lines	Cell lines	PCR 43 micro-satellite markers	18p11.21 to 18q23	Cases with vs. cases w/o 18q LOH median survival: 10.5 mo vs. 96 mo	Survival time: 10.5 mo cases with (n = 7) vs. 96 mo cases w/o (n = 4) 18q LOH at primary tumors (Wilcoxon test p = 0.0453)
Coon SW, 2004[42]	HNSCC	150 primary	Tumor (paraffin-embedded) and normal blood DNA Tumor: manually micro-dissected	PCR 3–4 micro-satellite markers per region (8 regions)	3p24.3-p14.3, 3p14.2-p13, 5q11.2-q31.3, 8p21.3-p11.21, 9p24.2-p21.2, 10p12.1-p11.22, 18q12.3-q23 and 21q21.1-q22.2	Max. follow-up: 204 mo (17 years)	Shorter survival time in cases with (n = 28) vs. cases w/o (n = 57) 8p21.3-8p11.21 LOH (p = 0.047) Shorter survival time in cases with (n = 37) vs. cases w/o (n =37) 9p24.2-9p21.2 LOH (univariate p = 0.01 after adjusting for multiple comparison)
Sabbir MG, 2006[45]	HNSCC	55 primary	Tumor tissues and matched benign tissues/blood DNA (fresh frozen)	PCR 11 polymorphic micro-satellite markers	13q	Follow-up: up to 60 mo (5 years)	Shorter 5-yr cumulative survival in cases with vs. cases w/o 13q13.1; 13q14.2; 13q21.2-22.1; 13q31.1 LOH

Author	Cancer type	Number of cases	Sample handling	Methods	Location of markers	Follow-up time	Clinical outcomes
			Tumor content: > 60%				(p = 0.00001; p = 0.0012; p = 0.05; p = 0.00001)

HNSCC: head and neck squamous cell carcinoma; OSCC: oral squamous cell carcinoma; LSCC: Laryngeal squamous cell carcinoma; ESCC: esophageal squamous cell carcinoma; NPC: nasopharyngeal carcinoma

NA: not available; LN-: lymph node negative; w/o: without; mo: months; max.: maximum

RT: radiotherapy; FAL: fractional allelic loss

PCR-SSCP: PCR-single strand conformation polymorphism; FISH: Fluorescent in situ hybridization; CGH: comparative genomic hybridization; PCR: Polymerase chain reaction

RR: relative risk; HR: hazard ratio; OR: odds ratio; CI: confidence interval

Unless indicated, p values are from log rank test

Table 2

Genome-wide CNV, LOH Events and Head and Neck Cancer Prognosis

Author	Cancer type	Number of cases	Sample handling	Methods	Location of Markers	Follow-up time	Clinical outcomes
Bockmuhl U, 2000[59]	HNSCC	113 primary	Tumor tissues (fresh frozen) Tumor content:: >70% tumor	CGH	Whole - genome	Median follow-up: 44 mo (95% CI: 40.14 – 48.76)	Shorter disease-specific survival in cases with gains at 2q12, 3q21-29, 6p21.1, 11q13, 14q23, 14q24, 14q31, 14q32, 15q24, 16q22 and losses at 8p21-22, 18q11.2 ($p < 0.05$)
Ueno T, 2002[60]	ESCC	51 primary	Tumor tissues (fresh frozen) and blood DNA Tumor: micro-dissected	CGH	Whole - genome	Max. follow-up: 45 mo	Worse overall survival in cases with (n = 19) vs. cases w/o (n = 32) 5p15 gain ($p = 0.0002$) Worse overall survival in cases with (n = 31) vs. cases w/o (n = 20) 8q24-qter gain ($p = 0.007$) Worse overall survival in cases with (n = 11) vs. cases w/o (n = 40) 14q21 gain ($p = 0.04$) Worse overall survival in case with (n = 5) vs. cases w/o (n = 11) all three changes ($p = 0.0002$)
Ashman JN, 2003[58]	HNSCC	45 primary	Tumor tissues (fresh frozen) Tumor content:: >70%	CGH	Whole - genome	Mean follow-up: 35 mo (95% CI: 28.3 – 41.7)	Disease-specific survival (mean): 45 mo in cases with (n = 34) vs. 63 mo in cases w/o (n = 11) 3q25-27 gain: ($p = 0.043$) Shorter disease-specific survival in cases with (n = 8) vs. in cases w/o (n = 37) 22q deletion ($p = 0.011$)
Gebhart E, 2004[56]	OSCC	35	Surgical tumor samples Tumor content: NA	CGH	Whole - genome	Cases with vs. cases w/o mean survival: 21.3 mo vs. 36.8 mo	Shorter survival in cases with (n = 19) vs. cases w/o (n = 16) 7p12 gain: (X^2 test $p = 0.024$)
Wreesmann VB, 2004[57]	HNSCC	82 primary	Tumor tissues and placenta reference DNA Tumor content:: >70% tumor	CGH	Whole - genome	Median follow-up: 22.5 mo	Lower disease-specific survival in cases with 11q13 amplification (high level gain (ratio > 2.0)), gains at 12q24, 14q11, 8p11, 22q13, 17q23, 17q24, 17q25, 20q13 and losses at 1p21, 2q34, 5q11, 5q12, 5q14, 5q15, 5q31, 6q14, 6q15, 6q16, 10p12, 12q22, 21p11, 21q11, 21q21, 21q22 ($p < 0.01$)

HNSCC: head and neck squamous cell carcinoma; OSCC: oral squamous cell carcinoma; ESCC: esophageal squamous cell carcinoma

NA: not available; w/o: without; mo: months; max.: maximum

CGH: comparative genomic hybridization

HR: hazard ratio; CI: confidence interval

Unless indicated, p values are from log rank test

Table 3

Localized and Genome-wide CNV, LOH Events and Head and Neck Cancer Recurrence

Author	Cancer type	Number of cases	Sample handling	Methods	Location of Markers	Follow-up time	Clinical outcomes
Localized CNV							
Meredith SD, 1995[18]	HNSCC	56	Tumor tissues (fresh frozen) Tumor content: NA	Southern Blot	11q13 (*bcl-1, PRAD1/ CCND1, hst1, EMS1, GST-pi-1*)	Mean follow-up: 17.6 mo (range 2 – 59)	Earlier recurrence or persistent disease: 82% cases with (39%, 22/56) vs. 50% cases w/o (61%, 34/56) 11q13 amplification (Fisher's exact p = 0.04)
Werkmeister R, 1996[63]	OSCC	85	Tumor tissues (fresh) and paired normal mucosa Tumor content: NA	Double-differential PCR	*erbB-1* (7p12), *erbB-2* (17q21.1), *erbB-3* (12q13)	Mean follow-up: 28 mo	3-yr disease-free survival: 25% cases with (61%, 52/85) vs. 58% cases w/o (39%, 33/85) *erbB-2* (17q21.1) amplification (copy number > 1.2) (p = 0.01) 3-yr disease-free survival: 15% cases with vs. 79% cases w/o *erbB-3* (12q13) amplification (copy number < 0.11) (p = 0.01)
Nogueira CP, 1998[61]	HNSCC	56	Tumor and paired blood Tumor content: NA	PCR, RFLP – LOH; semi-quantitative PCR - amplification	*TP53* (17p13.1), *CCND1* (11q13)	Mean follow-up: 12.5 mo; max. follow-up: 23 mo	Recurrence and/or metachronus tumors: 64.3% (9/14) cases with (33%, 18/54) vs. 22.5% (9/40) cases w/o (67%, 36/54) *CCND1* (11q13) amplification (X^2 test p = 0.007) Recurrence and/or metachronus tumors in stage 4 patients: 28.6% (4/14) cases with *CCND1* (11q13) amplification or *p53* (17p13.1) LOH and 55.6% (5/9) cases with both *CCND1* (11q13) amplification and *p53* (17p13.1) LOH vs. 0% (0/14) cases w/o *CCND1* (11q13) amplification or *p53* (17p13.1) LOH (X^2 test p = 0.027)
Rodrigo JP, 2000[22]	HNSCC	104 primary	Tumor (fresh frozen) and normal tissues from not paired non-cancer patients Tumor content: NA	Differential PCR	*CCND1* (11q13), *EMS1* (11q13)	> 36 mo	Recurrence: 100% (18/18) cases with (20%, 21/104) vs. 54% (37/69) cases w/o (80%, 83/104) *EMS1* (11q13) amplification (X^2 test p = 0.0004)
Fujii M, 2001[62]	OSCC	23 primary	Tumor tissues (paraffin-embedded) Tumor: microdissected	FISH	*CCND1* (11q13)	Mean follow-up: 53 mo (range: 24 – 83)	5-yr disease-free survival: 23.1% cases with (57%, 13/23) vs. 80.0% cases w/o (43%, 10/23) *CCND1* (11q13) amplification (p = 0.007)
Singh B, 2002[29]	HNSCC	50 primary and 49 non-cancerous	Tumor, pre-malignant/normal	FISH	3q26-27	Median follow-up: 82.5 mo	3-yr disease-free survival: 10% cases with vs. 69.3% cases w/o high level 3q26.3 amplification (>

Author	Cancer type	Number of cases	Sample handling	Methods	Location of Markers	Follow-up time	Clinical outcomes
			tissues (paraffin-embedded) Tumor content: NA				4X copy number (Wilcoxon p = 0.006) Recurrence: 90% cases with vs. 32% cases w/o high level 3q26.3 amplification (Fisher's exact test p = 0.003)
Namazie A, 2002[23]	HNSCC	103	Tumor and a subset of normal tissues (paraffin-embedded) Tumor content: NA	FISH	*CCND1* (11q13), *p16* (9p21)	Cases with vs. w/o *CCND1* (11q13) amplification) median follow-up: 38 mo vs. 40 mo; Cases with vs. w/o *p16* (9p21) amplification median follow-up 36 mo vs. 43 mo	Incidence of recurrence: 38.4% cases with vs. 19.3 cases w/o *CCND1* (11q13) amplification (univariate cox p = 0.021, RR: 3.37) Incidence of recurrence: 51.3% cases with vs. 18.7% cases w/ o*CCND1* (11q13) amplification plus *p16* (9p21) deletion (univariate cox p = 0.013, RR: 5.91)
Miyamoto R, 2003[24]	OSCC	41 primary	Fine-needle aspiration biopsies (paraffin-embedded) Tumor content: NA	FISH	*CCND1* (11q13)	Median follow-up: 25.4 mo (range 7.7 – 39.3)	Disease-free survival: 23% cases with (32%, 13/41) vs. 64% cases w/o (68%, 28/41)*CCND1* (11q13) amplification (p = 0.0052)
Akervall J, 2003[28]	HNSCC	78 primary	Tumor tissues (fresh frozen) Tumor content: >70%	Real time PCR for *c-MYC*, *CCND1*, *CDKN2A*	*c-MYC* (8q24.21), *CCND1* (11q13), *CDKN2A* (9p21)	> 40 mo	Disease-free interval: 60% (18/30) cases with (45%, 35/78) vs. 30% (18/50) cases w/o (55%, 43/78) *c-MYC/CDKN2A* (8q24.21/9p21) ratio > 2 (p = 0.014)
Chung CH, 2006[53]	HNSCC	82 primary and 14 recurrent	Tumor tissues (formalin-fixed, paraffin-embedded) Tumor content >70%	FISH	*EGFR* (7p12)	Median follow-up: 24.5 mo	Progression-free survival (time to recurrence/death): 18/20 mo in cases with vs. 25/29 mo in cases w/o *EGFR* (7p12) high polysomy and/or amplification (p < 0.05)
Sabbir MG, 2006[25]	HNSCC	84 primary	Tumor tissues and normal adjacent tissues/blood (fresh frozen) Tumor: microdissected	Southern Blot	*bcl-1*, *CCND1* (11q13)	Median follow-up: 44 mo (range: 12 – 78)	Worse disease-free survival in cases with (25%, 20/79) vs. cases w/o (75%, 59/79) *CCND1* (11q13) amplification (p = 0.00001) Worse disease-free survival in cases with (54%, 43/79) vs. cases w/o (46%, 34/79) *bcl-1* and *CCND1* (11q13) amplification and/or rearrangement (p = 0.0003)
Localized LOH							
Shibagaki I, 1994[65]	ESCC	36	Tumor and their adjacent normal tissues (fresh frozen) Tumor content: NA	PCR-RFLP 55 polymorphic markers	Every autosomal arm except 13p, 21p, and 22p	Maximum follow-up: 33.3 mo (1000 days)	Worse disease-free survival in cases with (n = 7) vs. cases w/o (n = 16) 6p LOH (p = 0.0325) Worse disease-free survival in cases with (n = 19) vs. cases w/o (n = 17) 13q LOH (p = 0.0062)

Author	Cancer type	Number of cases	Sample handling	Methods	Location of Markers	Follow-up time	Clinical outcomes
Scholnick SB, 1996[41]	Supraglottic larynx cell carcinoma	59 primary	tumor and paired normal tissues (paraffin-embedded) Tumor: micro-dissected	PCR 3 micro-satellite markers	D8S264 (8p23), D8S552 (8p23- p22), and D8S133 (8p21)	Median follow-up: 77 mo (6.4 years)	Lower disease-free survival: 2.2 yrs in cases with (n = 13) vs. > 6.4 yrs in cases w/o (n = 31) D8S264 (8p23) LOH (p = 0.028)
Partridge M, 1996[37]	OSCC	48 primary	Tumor (fresh frozen) and paired normal mucosa/ blood Tumor: microdissected (tumor content > 50%)	PCR 15 micro-satellite markers	3p	Cases with vs. cases w/o mean survival: 38 mo vs. 74 mo	Disease-free survival: 38 mo in cases with (n = 34) vs. 74 mo in cases w/o (n = 14) 3p LOH (p = 0.043)
Matsuura K, 1998[66]	HNSCC	75 primary	Tumor tissues (fresh frozen) and blood Tumor content: NA	PCR 2 microsatellite markers	7p31, 9p21	NA	Recurrence: 39% (9/23) cases with vs. 12% (5/41) cases w/o 9p21 LOH (X^2 test p = 0.012)
Lydiatt WM, 1998[67]	HNSCC	42 primary	Tumor and paired blood Tumor content: NA	PCR, southern blot; 9 microsatellite marker	9p24, 9p22-24, 9p22, 9p21-22, 9p21	Median follow-up: 47 mo (range: 24 – 51)	Recurrence: 90% (9/10) cases with vs. 10% (1/10) cases w/o *IFN-α* (9p22) LOH (X^2 test p < 0.001)
Lazar AD, 1998[68]	HNSCC	56	Tumor tissues and matched blood Tumor content: high proportion	PCR, 3 microsatellite markers	11q23	Mean follow-up: 24.2 mo	Recurrence 53.8% (7/13) cases with vs. 0% (0/8) cases w/o 11q23 LOH (X^2 test p = 0.04)
Nogueira CP, 1998[61]	HNSCC	56	Tumor and paired blood Tumor content: NA	PCR, RFLP – LOH; semi-quantitative PCR – amplification	*TP53* (17p13.1), *CCND1* (11q13)	Mean follow-up: 12.47 mo; max. follow-up: 23 mo	Recurrence: 64.3% (9/14) cases with (33%, 18/54) vs. 22.5% (9/40) cases w/o (67%, 36/54) *CCND1* (11q13) amplification (X^2 test p = 0.007) Recurrence: 71.4% (10/14) cases with (38%, 14/37) vs. 28.6% (4/14) cases w/o (62%, 23/37) *CCND1* (11q13) amplification or *p53* (17p13.1) LOH; 44.4% (4/9) cases with (24%, 9/37) 55.6% (5/9) cases w/o (76%, 28/37) both*CCND1* (11q13) amplification or *p53* (17p13.1) LOH (X^2 test p = 0.027)
Matsuura K, 1999[49]	HNSCC	93	Tumor tissues (fresh frozen) and paired blood Tumor content: NA	PCR 3 Micro-satellite markers	3p21, 9p21	Mean follow-up: 23 mo (range: 2 – 51)	Recurrence: 79% (19/24) cases with vs. 24% (8/33) cases w/o 3p21 and/or 9p21 LOH (X^2 test p < 0.0001)
Partridge M, 1999[48]	OSCC	48	Tumor tissues (fresh frozen) and paired blood Tumor: microdissected	6 SNP markers; 13 micro-satellite markers	3p, 8p21-23, 9p13-21, 9q22, 13q14.2, *Rb* (13q14), *p53* (17p13) and *DCC* (18q21.3)	Median follow-up: 49 mo (range: 28 – 166)	Higher risk of loco-regional recurrence in cases with FAL score ≥ 0.4 (n = 15) vs. in cases with FAL score = 0.21 – 0.39 (n = 16) vs. in cases with FAL score ≤ 0.2 (n = 17) (p = 0.02)

Author	Cancer type	Number of cases	Sample handling	Methods	Location of Markers	Follow-up time	Clinical outcomes
Sardi I, 2000[69]	HNC	41	Primary tumors (paraffin sections), paired margins (microdissected), blood DNA Tumor content: NA	PCR 10 micro-satellite markers	2p, 3q, 4q, 9p, 16q, 17p, 21q	Median follow-up: 13 mo (range: 5 – 21)	Disease-free survival in tumor margin: 64% (7/11) cases with (n = 11) vs. 7% (1/14) cases w/o (n = 14) *TP53* (17p13.1), *IFN-α* (9p22) LOH/micro-satellite instabilities (p = 0.0049)
Bockmühl U, 2001[40]	HNSCC	51 primary	Tumor and paired normal tissues (fresh frozen) Tumor content: >70%	7 micro-satellite polymorphic markers	8p23	Median follow-up: 24.6 mo (range: 1 – 48)	Lower disease-free survival in cases with (n = 23) vs. cases w/o (n = 28) 8p23 LOH (p = 0.016)
Yamamoto N, 2003[64]	OSCC	40 primary	Tumor and paired normal tissues (fresh frozen) Tumor content >80%	PCR 30 micro-satellite markers	2q, 3p, 21q	NA	Poorer prognosis (recurrence and metastasis): 56% (10/18) cases with (71%, 10/14) vs. 44% (8/18) cases w/o (31%, 8/26) cases w/o 2q LOH ≥ 2 loci (Fisher's exact test p = 0.021)
Jamieson TA, 2003[39]	HNSCC	116 locally advanced but non-metastatic	Tumor and normal non-mucosal tissues (paraffin-embedded) Tissues: microdissected	PCR, 6 polymorphic markers	*M6P/IGF2R* (6q25-27)	Median follow-up: 76 mo (range: 2 – 128)	5-yr relapse free survival in patients with RT: 23% (95% CI: 2%–44%) cases with (n = 17) vs. 69% (95% CI: 46%–92%) cases w/o (n = 16) *M6P/IGF2R* (6q25-27) LOH (Cox-Mantel test p = 0.02)
Genome wide CNV							
Bockmuhl U, 2000[59]	HNSCC	113 primary	Tumor tissues (fresh frozen) Tumor content:: >70% tumor	CGH	Whole - genome	Median follow-up: 44 mo (95% CI: 40.14 – 48.76)	Shorter disease-free interval in cases with gains at 1q32, 1q42-43, 2p24-25, 2q12, 3q21-29, 6p21.1, 6p22-24, 7p22, 11q13, 14q23, 14q24, 14q31, 14q32, 15q24, 16q22 gains and losses at 8p21-22, 11q23-25, 18q11.2, 18q21 (p < 0.05)
Ashman JN, 2003[58]	HNSCC	45 primary	Tumor tissues (fresh frozen) Tumor content:: >70% tumor	CGH	Whole - genome	Mean follow-up: 35 mo (95% CI: 28.3 – 41.7)	Shorter disease-free survival in cases with amplification at 11q13 (ratio > 1.5), gains at 17q and 20q; losses at 19p and 22q (p < 0.05)

HNSCC: head and neck squamous cell carcinoma; HNC: head and neck cancer; OSCC: oral squamous cell carcinoma; ESCC: esophageal squamous cell carcinoma

NA: not available; LN-: lymph node negative; w/o: without; mo: months; max.: maximum; RT: radiotherapy

FISH: Fluorescent in situ hybridization; CGH: comparative genomic hybridization; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism, SNP: Single nucleotide polymorphism

HR: hazard ratio; RR: relative risk; CI: confidence interval

FAL: fractional allelic loss

Unless indicated, p values are from log rank test

Table 4

Number of Studies Reporting Associations between Presence of CNV or LOH with Survival from or Recurrence of HNSCC

Survival															
	1p	1q	2p	2q	3p	3q	4p	4q	5p	5q	6p	6q	7p	7q	8p
CNV	1			2		4			1	1	1	1	3		2
LOH				1	5							1			4
	8q	9p	9q	10p	10q	11p	11q	12p	12q	13p	13q	14p	14q	15p	15q
CNV	2	2		1			14		2				3		1
LOH		4			1						3		1		
	16p	16q	17p	17q	18p	18q	19p	19q	20p	20q	21p	21q	22p	22q	X/Y
CNV		1		1		1				2	1	1		3	
LOH			2			2									
Recurrence															
	1p	1q	2p	2q	3p	3q	4p	4q	5p	5q	6p	6q	7p	7q	8p
CNV		1	1	1		2					1		2		1
LOH				1	2						1	1			2
	8q	9p	9q	10p	10q	11p	11q	12p	12q	13p	13q	14p	14q	15p	15q
CNV	1	2					11		1				1		1
LOH		4					1				1				
	16p	16q	17p	17q	18p	18q	19p	19q	20p	20q	21p	21q	22p	22q	X/Y
CNV		1		2		1	1			1				1	
LOH			3												