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HEAD AND NECK SQUAMOUS CELL CARCINOMA: A MOLECULAR LANDSCAPE

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ABSTRACT

HNSCC represents about 6% of all cancer. The general 5 year survival rate for patients with HNSCC cancer is among the lowest of the major cancer types and has not enhanced drastically amid the last decade. The pathological staging, specifically the nodal stage, is the most essential component in HNSCC. The absence of progress in head and neck oncology underlines the significance of molecular studies to characterize alterations that may associate with tumor. The molecular alterations that saw in HNSCC are essentially because of oncogene activation and tumor suppressor gene inactivation, prompting deregulation of cell expansion. Propels in the understanding of the molecular basis of HNSCC will help in the identification of new molecular markers that could be utilized for a more precise diagnosis and evaluation of prognosis and may open the path for novel ways to deal with treatment and counteractive action. The genetic modifications seen in head and neck cancer are because of oncogene activation (gain of function transformations) and tumor suppressor gene inactivation (loss of function mutations), prompting deregulation of cell multiplication and death. These genetic changes incorporate gene amplification and overexpression of oncogenes, for example, **myc, erbB-2, EGFR** and **cyclinD1** and transformations, deletion and hyper methylation prompting p16 and TP53 tumor suppressor gene inactivation. Furthermore, loss of heterozygosity in a several chromosomal regions is also found, proposing that other tumor suppressor gene not yet recognized which are involved in the tumorigenic procedure of head and neck cancer. The temporal sequence of the genetic modifications amid HNSCC development and progression has not yet been characterized and

their prognostic and diagnostic significance is still dubious. Progresses in the comprehension of the molecular basis of head and neck cancer ought to help in the identification of new markers that could be utilized for the prognosis, diagnosis and treatment of the cancer.

KEYWORDS: HNSCC, Loss of heterozygosity, Cyclin D1, TP53 tumor suppressor gene.

INTRODUCTION

HNSCC is a heterogeneous however to a great extent preventable disease with complex molecular variations. It emerges from a premalignant progenitor cells followed by cumulative genetic changes and phenotypic progression to invasive cancer.[1-3] These genetic modifications result in inactivation of multiple tumor suppressor gene and initiation of proto oncogenes, including p16ink4A, p53, cyclin D1, p14ARF, FHIT, RASSF1A, EGFR and Rb. Intramucosal migration and clonal expansion of transformed cells with formation of irregular genetic fields appear to be responsible of local recurrences and development of second primary tumors.[4-5]

A most critical prognostic variables in HNSCC is the presence of lymph node metastases. Patients with confirmed nodal involvement have only 5-year survival rate. The combined effort of early diagnosis and close patient monitoring after surgery or radio chemotherapy impacts disease progression and outcome predication in patients with HNSCC.[6-9] Early stage (I and II) patients have a 65% to 90% chance of cure with local treatment, however patients with more advanced disease have a more than 50% risk of recurrence. Lymph node metastases is the most important indicators of identification of HNSCC. Given the highly disfigurative nature of HNSCC surgical treatment and normally repeated exposure to high dose radiation, identification of primary HNSCC tumors with enhanced metastatic potential by molecular means can help clinicians in customizing appropriate treatment, particularly in cases that have no obvious nodal involvement.[10-13]

Genetic alterations and progression of squamous dysplasia to invasive carcinoma

It is generally acknowledged that HNSCC emerges from a typical premalignant progenitor cell followed by outgrowth of clonal population connected with combined genetic modifications and phenotypic progression to intrusive cancer.[14] Genetic changes result in inactivation of tumor suppressor gene and activation of proto oncogenes by deletions, point transformations, promoter methylation, and gene amplification. Microsatellite marker investigation has permitted the depiction of a genetic progression model for HNSCC in view

of the recurrence of these genetic modifications in pre invasive lesions and invasive tumors (Figure:1). Loss of chromosomal region 9p21 is found in 80% of cases, hence representing the most well-known genetic change seen in squamous dysplasia and HNSCC.[15]

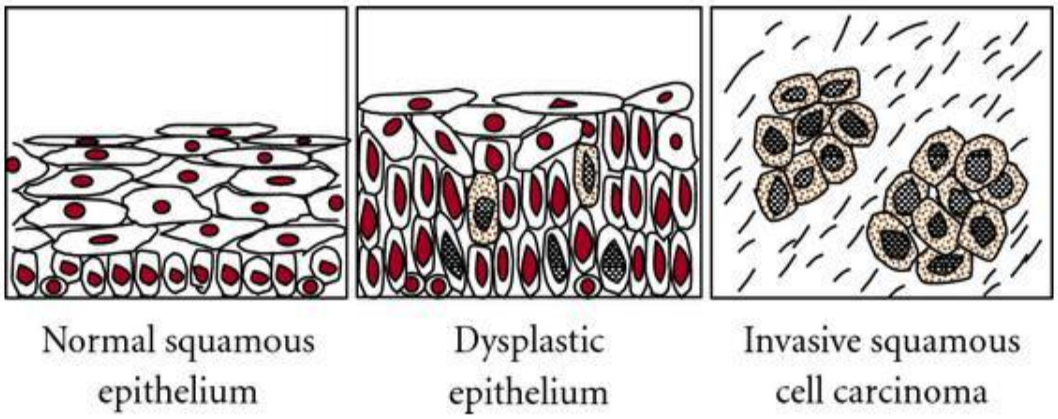

Figure: 1 ING proteins expression in the malignant development of HNSCC

Loss of heterozygosity (LOH) of 9p21 has all the earmarks of being an early event in squamous neoplasia of the head and neck and has been found in pre neoplastic lesions, including 30% of instances of squamous hyperplasia.[16] The CDKN2A gene locus found in chromosome 9p21 encodes two unique transcripts, p16 and $p14^{ARF}$, which are in charge of G cell cycle regulation and MDM2 mediated degradation of p53. P16 is regularly inactivated in HNSCC through homozygous deletion, by promoter methylation and less usually by point mutations. Loss of chromosome region 3p is another common early genetic event in squamous dysplasia and invasive HNSCC. The particular locus responsible for the tumor suppressor phenotype of 3p remains uncharacterized yet scientist have distinguished four distinct regions of allelic loss.[17]

These regions incorporate 3p14, 3p21, 3p22, 3p24 and 3p26. 3p14 consist of fragile histidine triad gene (FIHT), a putative tumor suppressor gene, which has been observed to be inactivated by exonic deletions in numerous tumor types including a small percentage of HNSCC. RSSF1A is another tumor silencer gene mapped to 3p21 and observed to be inactivated by hyper methylation in a little subset of HNSCC. Much debate stays with respect to the gene present in 3p and their significance and possible roles in HNSCC carcinogenesis. LOH of 17p and point mutation of the p53 are seen in around half of HNSCC cases.[18]

The vast majority of these transformations seem to happen late in the progression from epithelial dysplasia to invasive carcinoma. Amplification of 11q13 and overexpression of cyclin D1 is seen in 30–60% of HNSCC cases and has been connected with an expanded rate of lymph node metastases and general poor prognosis (figure:2). Cyclin D1 incites phosphorylation of Rb, accordingly empowering progression from G^1 to S stage. Both amplification of cyclin D1 and inactivation of p16 result in increased phosphorylation of Rb and progression in the cell cycle from G to S stage. Amplification and overexpression of cyclin D1 has been portrayed in up to 40% of instances of oral squamous dysplasia.[19]

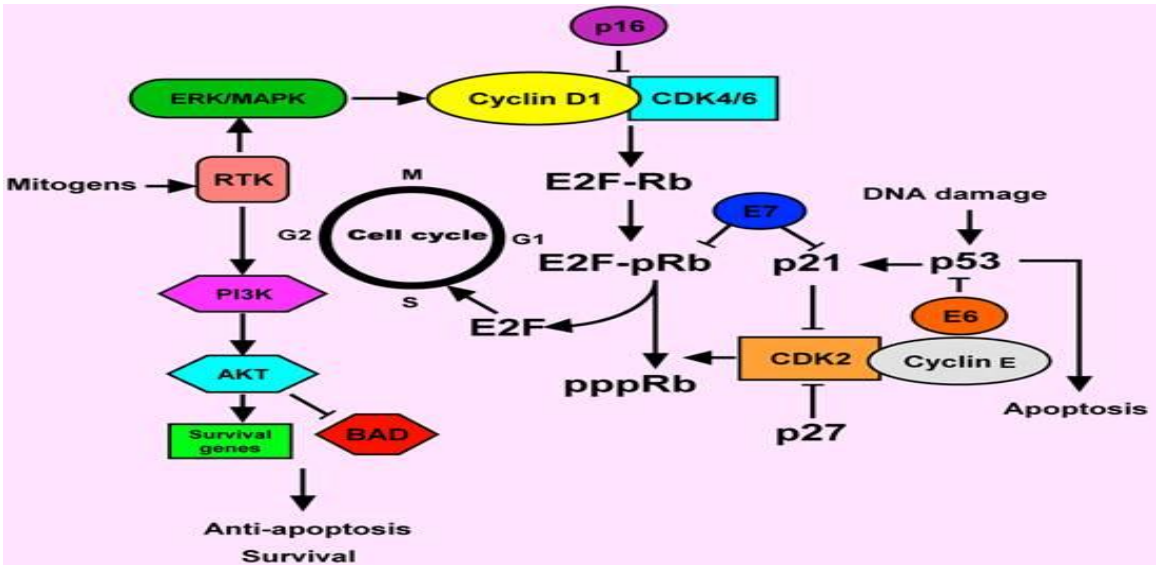

Figure: 2 Cell cycle deregulation in HNSCC.

Chromosomal Mutations in HNSCC

A standout amongst the most morphologically apparent features of neoplasia is chromosomal changes and modifications and these have been well depicted in HNSCC. Flow cytometric investigation of both dysplastic and malignant lesions demonstrates the normal dearrangement of chromosomal ploidy.[20] Clinically precancerous lesions show rates of 46% diploidy, 37% tetraploidy and 17% aneuploidy, while malignant lesions show 10% diploidy and 90% aneuploidy. Notwithstanding deletions and duplications (CNV), a discriminating component of carcinogenesis is allelic loss or loss-of-heterozygosity (LOH).

The main chromosomal aberrations in premalignant lesions are losses of 3p, 9p, 5p, and 17p. Essentially, CDKN2A encoding p16 is restricted to the most ordinarily influenced 9p21-22 locus, which demonstrates LOH in 46–71% of premalignant lesions and 72% of carcinoma and is firmly connected with progression to cancer and metastasis.[21]

Allelic loss of 3p is available in 80% HNSCC, with PCR and hybrid clone studies recommending three discrete ranges at 3p13-p14, 3p21.2-p21.3 and 3p25 are connected with tobacco-related disease and nodal status. The FHIT gene encoding a typical epithelial tumor silencer is found at locus 3p14.2. Expression of FHIT is suppressed in 65% of HNSCC and is connected with more terrible survival. Locus 3p21.31 contains various tumor-suppressor gene (LIMD1, LTF, CDC25A, SCOTIN, RASSF1a, and CACNA2D2) of which changes to LTF and RASSF1A were connected with essentially more awful result in oral cavity disease. 3p25 contains the gene locus for hOGG1 and von Hippel-Lindau tumor silencer gene. hOGG1 is an essential segment of the base excision DNA repair pathway and shows LOH in 60% of HNSCC and is under expressed in 49%(table:1). This mechanism is imperative in the repair of ionizing radiation and common oxidative and tobacco-related DNA injuries. Unrepaired tobacco-impelled benzopyrene lesions usually result G: T transversion transformations.[22] Repair of the oxidative lesion 8-oxoG likewise depends on this pathway, which can bring about a stable G: C to 8oxo G:A missense substitution when encountered by the DNA polymerase. Together these substitutions involve 54% of the most widely recognized inactivating p53 point mutations in HNSCC. This transformation design, which has additionally been emphatically connected to smoking-induced lung cancer, is corresponded with smoking introduction related HNSCC.[23]

Table 1:- Frequent molecular abnormalities in HNSCC.

LOH 9p	70-80%
LOH 3p	60-70%
LOH 17p	50-70%
LOH 11q	30%
LOH 13q	30%
Inactivation of $p16^{INKA}$	80%
Inactivation of FHIT and RASSF1A p53 mutation	50-80%
Cyclin D1 amplification	30%

Recent treatment modalities of HNSCC

Treatment of HNSCC currently considers multimodal treatment of combining surgery with radio chemotherapy. Particularly in advanced tumor stages, where surgical resection is not achievable, radio-chemotherapy is an established treatment.[24] Pre-therapeutic tumor staging in HNSCC must consider tumor spread, recognition of lymph node metastases and evaluation of a potential vascular penetration, either by the tumor itself or by suspicious lymph nodes. Usually after clinical and endoscopic investigation, imaging is performed and contributes to staging, treatment planning and patient follow up. Current treatment strategy are supportive

of therapeutic procedures that combine chemotherapeutic agents with anti angiogenic substances like Cetuximab. In this setting, clinical and image guided assessment of tumor volume and its limitation and additionally evaluation of cervical lymph node spread and angio-invasion are key for improving treatment options. Close post therapeutic patient monitoring is equally important for improved patient outcome. It ought to be performed in the first two years after diagnosis of HNSCC to distinguish and treat potential tumor recurrence in the initial stage.[25]

Computed tomography for determination and differential diagnosis of HNSCC

The most generally applied cross-sectional imaging methodology for preoperative evaluation and post therapeutic follow-up of HNSCC is multi detector-computed tomography (MD-CT). The foundation of multi detector innovation has brought about enhanced spatial resolution in z-axis with fractional volume effect becoming unimportant. Two x-ray tubes coupled to a detector framework in one gantry, at an edge of 90°, empower quick and multidimensional coverage of the volume of interest.[26] Particularly patients with advanced tumor stages and decreased consistence because of dyspnea and swallowing issue, benefit from the increased velocity of CT investigations. Short CT scan times and lessened motion artifacts enhance the indicative yield of CT. Though MD-CT offers restricted slice collimation up to 0.6 mm and multi planar reproductions, two variables which are ideally suited for imaging of hard structures, MRI is the best decision for imaging delicate tissue lesions. MD-CT gives lessened scan time combined with short patient exposure time and is consequently appropriate for entire body staging and avoidance of distant metastases in oncologic cases.[27]

Positron emission tomography-computed tomography for nodal staging in HNSCC

PET-CT is a noninvasive imaging methodology that combines the functional information of PET with the morphological information of CT and uses this data for the imaging of tumors with increased glucose metabolism. CT and MRI are established diagnostic procedures for pre-and post-remedial imaging of HNSCC. Yet, they cannot supplant the metabolic information of PET, which can portray a lymph node regardless of its morphology.[28] While contrast enhanced CT and MRI are established imaging modalities for the T classification of HNSCC and empower appraisal of the primary tumor and its expansion along with the clinical and endoscopic findings, PET permits refinement of potential lymph node metastases, contingent upon their size and FDG activity. Cystic-necrotic lymph node metastases, which occur frequently in tumor of the tonsils, can be determined with a precision

up to 92% with 18F-FDG PET-CT. Despite size and degree of the primary tumor, the localization of lymph node metastases and information on unilateral or bilateral spread is key for operation planning and definition of radiation field. 18F-FDG PET-CT is a practical imaging technique with morphological input and in this way represents a roadmap for tumor treatment.[29]

Tumor hypoxia imaging: impact of non-FDG PET tracer on therapy planning in HNSCC

Hypoxia imaging of HNSCC is exceptionally conclusive for planning the therapeutic approach. Devoted hypoxia tracer empower determination of tumor and lymph hub metastases oxygenation before and amid treatment so as to assess their radio and chemo sensitivity.[30] Tumor cell hypoxia depends on a course of molecular procedures that trigger cell and metabolic changes in the tissue. These lead to an intense and chronic hypo perfusion additionally hypo oxygenation of tumor tissue, which causes a stimulation of tumor angiogenesis which may induce resistance to radio and chemotherapy. This outcomes in prompting of cell proliferation with increased aggressiveness of the tumor and metastatic potential.[31]

Since hypoxia represent a negative prognostic component for tumor progression and imperviousness to treatment, hypoxia imaging, particularly in advanced HNSCC, plays an essential role for treatment and monitoring. Throughout the treatment, the level of tumor oxygenation in HNSCC changes. The degree of hypoxia as a prescient component, impacts the survival time of patients. PET-CT empowers analysis of tumor hypoxia over the span of treatment and hence the optimization of chemotherapy and radiotherapy can be accomplished.[32] The invasive estimation of hypoxia is performed by embedding Eppendorf electrodes in tumor tissue, PET empowers non-invasive evaluation of tumor perfusion and the hypoxia index with hypoxia tracers and in this manner is less invasive for the patient. Additionally, immunohistochemical examination of tissue after biopsy in order to differentiate tumor and scar tissue are obtrusive and dependent on adequate biopsy sample sizes.[33]

Magnetic Resonance Imaging (MRI) on the evaluation of loco regional spread of HNSCC

For the precise assessment of the tumor degree, MRI requires a streamlining of spatial resolution while maintaining adequate signal to noise ratio and minimizing output time with a

specific end goal to maintain a strategic distance from motion artefacts.[34] This contention between those 3 parameters with conflicting requirement can be determined by applying latest MR-techniques, ideally using high-field MRI frameworks with field strength of 3 Tesla, committed multi-component recipient loops and utilization of parallel acquisition methods. This technique permits a significant reduction of information obtaining by amendment of the full high resolution information set with the coil sensitivity profiles of the signal recipient coil components. In a latest investigation, the technical prerequisites for optimal picture in radiation treatment planning were characterized as 0.4x0.4 mm cut thickness.[35]

Closing Remarks

Propelled HNSCC are hard to oversee regardless of the vast treatment stockpile as of now accessible. The multidisciplinary effort to increase disease free survival and reduce typical tissue toxicity is remunerated with better loco regional control and sometimes less reactions. In any case, loco regional recurrence is still one of the fundamental explanations behind treatment failure. The most recent treatment strategy consolidated with adjuvant or targeted treatments succeeded in expanding loco regional control in advance HNSCC patients. The drawback, is the increased rate of sign and symptoms. Moreover, general survival in this patient group has not seen any significant change in the course of the last decades. While there are promising results with targeted treatments including monoclonal antibodies and with chronotherapy, the ideal treatment for advanced HNSCC patients is yet to be set up. Energizing advances are happening in the comprehension of the molecular pathogenesis of last stage HNSCC. Exhaustive modeling can uncover high-hazard predicators of late stage HNSCC offering molecular markers for early identification in body fluids, for example, blood and saliva with the goal to enhance screening precision and cost effectiveness of diagnostic testing. HPV testing is turning out to be a piece of a molecular staging system for HNSCC. An extending collection of strong diagnostic biomarkers that foresee the probability of nearby tumor recurrence is bound to be stimulus for alteration of the current AJCC-UICC staging system to mirror these vital advances.

Conflicts of Interest Statement

The Authors declare no conflicts of interest.

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