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Review Article

HPV Causes Head and Neck Cancer

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Abstract

Human papillomavirus (HPV) - associated head ANd neck epithelial cell cancer (HNSCC) is an entity with distinctive clinical and molecular characteristics, that primarily arises from the palatine tonsils and base of the tongue. Nowadays, bodily cavity cancers ar increasing in incidence despite declining prevalence of smoking and in direct opposition to a decreasing incidence of all different HNSCC. a scourge of HPV-associated bodily cavity cancers appears to account for these incidence trends. HPV-positive malignancies represent 5-20% of all HNSCC and 40-90% of these arising from the cavity. HPV-16 is out and away the foremost common unsound HPV genotype detected in bodily cavity epithelial cell cancer (SCC). HPV-associated HNSCC have a strikingly higher prognosis with improved responsiveness to the treatment choices together with therapy and chemo-radiotherapy and favorable survival rates. so the treatment choice for HPV- associated bodily cavity cancer is changing into a important issue. Novel studies concerning HPV-associated bodily cavity cancer have contributed to our raised understanding of this new entity. Multiple clinical trials ar presently afoot to see whether or not a number of these patients are often satisfactorily managed with a de-escalated treatment approach. However, information ar presently poor to vary treatment ways for HPV-associated bodily cavity cancer.

Keywords

Human papillomavirus, Head and neck cancer, bodily cavity cancer, carcinoma, epithelial cell cancer

Introduction

Head and neck epithelial cell cancer (HNSCC) is that the fifth commonest non-skin cancer worldwide, with associate degree annual incidence of 600,000 cases and concerning sixty,000 cases within the us and Europe [1]. Despite microscopic anatomy homogeneity, HNSCC ar a very heterogeneous cluster of tumors each from molecular [2-4] and clinical points of read [5]. the most clinical nonuniformity issue is that the web site of origin, that conjointly correlates with the precise risk factors [2,5,6]. The best-established risk factors for HNSCC ar tobacco and alcoholic abuse [6]. Overall incidence of HNSCC has fallen within the last 3 decades; but the incidence of bodily cavity cancer, chiefly faucial tonsil and base of tongue, has been increasing each in us and Europe [7-12]. speculative human papillomavirus (HPV) infection, whose role within the carcinogenesis of cervical cancer has been well established and extensively studied [6], is currently a well-recognized [13,14] and rising risk issue for HNSCC [2]. a plague of HPV-associated bodily cavity cancers looks to account for these incidence trends of HNSCC. This rise in incidence is usually occurring in people aged between 40-55 years, while not history of tobacco and alcohol consumption, and is related to persistent HPV infection [2,7].

HPV ar tiny DNA (DNA) viruses that ar cosmopolitan in vertebrates. The papillomavirus order includes early and late genes that cipher early proteins E1-E7 and late proteins L1-L2. the first proteins ar nonfunctional proteins concerned in replication and transcription of the order (E1-E5) or in host cell tumoral transformation (E6 and E7), whereas L1 and L2 ar the structural capsid proteins of the particle. The HPV E6 and E7 oncogenes cipher proteins consisting of roughly 151 and ninety eight amino acids, severally. These genes ar mostly answerable for the onset and persistence of the malignant method in each head and neck and anogenital cancers [17]. At the molecular level, the flexibility of E6 and E7 proteins to remodel cells relates partially to their interaction with 2 intracellular proteins, p53 and malignant neoplasm (Rb), severally. Integration of HPV into the host order disrupts or deletes the E2 infective agent sequence, resulting in hyperbolic expression of the E6 and E7 genes. The hyperbolic expression of E6 and E7, in turn, inactivates growth suppressor macromolecule p53 and also the atomic number 37 pathway, leading to hyperbolic proliferation and genomic instability [15,18].

In the traditional cell, the p53 macromolecule could be a negative regulator of cell growth, dominant cell cycle transit from G0/G1 to S section, and conjointly operates as a growth suppressor macromolecule by halting cell growth once body injury and permitting DNA repair enzymes to function [17,19,20]. E7 macromolecule sensitizes wild-type p53-containing cells to necrobiosis, however exerts associate degree anti-apoptotic impact in cells with mutated p53 [17,21,22]. speculative HPV oncoprotein E7 promotes oncogenesis by obstruction the activity of the atomic number 37 macromolecule and increasing the transcriptional activity of E2F transcription factors, resulting in aberrant p16 macromolecule over expression.

The atomic number 37 macromolecule inhibits the impact of positive growth regulation and halts cell growth or induces cell necrobiosis in response to DNA injury [17,23]. one in all the functions of atomic number 37 is to bind and render inactive the E2F transcription issue. E2F controls DNA synthesis and cyclin operate and promotes the S section of cell athletics. E7 interacts with atomic number 37 macromolecule via associate degree E2F/Rb macromolecule advanced. once E7 binds to atomic number 37 macromolecule, E2F is free and permits cyclin A to push cell athletics [17]. The interaction of E7 with atomic number 37 might allow cells with broken DNA to bypass the G1 growth arrest unremarkably elicited by wild-type p53 [24]. These processes permit ungoverned cell growth within the presence of genomic instability that will cause malignant modification.

The molecular profiles of HPV positive tumors ar distinct from those of HPV negative cancers. The absence of genetic or epigenetic alterations within the p53 and pRb pathways in HPV positive head and neck cancers is in sharp distinction to what's ascertained in HPV negative head and neck cancer. within the typical HPV negative epithelial cell carcinomas, p53 mutations ar terribly frequent, together with small levels of

p16 and hyperbolic levels of pRb. in contrast, HPV positive carcinomas ar related to wild-type p53, down regulation of pRb, and upregulation of p16. These variations in organic phenomenon recommend that HPV positive and HPV negative head and neck cancers [17]. Recent studies rumored that genetic options ar totally different between HPV-positive and HPV-negative SCC. for instance, EGFR sequence copy range gains gift solely in HPV-negative SCC, and such tumors show worse prognosis than HPV-positive /EGFR gain- negative tumors. As EGFR could be a therapeutic target, such molecular characteristics would possibly influence the therapeutic strategy for SCC within the future.It is well-established that HPV confers a survival advantage in bodily cavity SCC [25-29]; but Lim et al. found no important distinction in survival obsessed with if HPV was integrated or not [15].

A growing range of analysis papers concerning HPV-associated HNSCC are revealed in recent years. These novel studies have contributed to our hyperbolic understanding of this new entity. Multiple clinical trials ar presently afoot to work out whether or not a number of these patients will be satisfactorily managed with a de-escalated treatment approach. However, knowledge ar presently scant to vary treatment methods for HPV-associated bodily cavity cancer. the current review highlights the HPV- associated HNSCC by the sunshine of the novel publications.

Determination of HPV standing and identification

Although the management of bodily cavity SCC has not needed the analysis of HPV standing however, HPV-testing is that the customary care in several establishments. The HPV-induced bodily cavity cancer constitutes a brand new growth entity with improved prognosis; but heterogeneous results ar obtained from the clinical studies with regard to the clinical and biological behavior among-HPV positive patients [30-32]. this might result to variations between infective agent load and or infective agent organic phenomenon [32], and highlights the necessity for assessing the presence of HPV within the growth [2].

Histologically HPV-positive HNSCCs square measure poorly differentiated with a basaloid morphology and lack of organic process [16]. However, associate degreeatomy} criteria square measure too little and unreliable in creating an HPV designation. Immune-histochemical testing and/or HPV DNA/RNA testing square measure needed and commonplace of care. A helpful proxy for HPV- associated HNSCC is p16 assay (IHC) once used for cavity primary tumors. However, p16 IHC isn't helpful as AN HPV surrogate for alternative anatomic sites, wherever HPV-associated tumors square measure rare, leading to a high false-positive rate for line of work HPV-associated tumors.
Numerous HPV biomarkers exist, as well as detection of HPV deoxyribonucleic acid in tumors and serological markers indicative of additive microorganism exposure (antibodies to HPV16 L1, the virus' capsid protein) or expressed oncoproteins (antibodies to HPV16 E6 and E7 proteins [33,34]. additionally, p16 overexpression within the neoplasm has been used as AN indirect biomarker of HPV, as expression of the E7 oncoprotein suppresses pRb and will increase the amount of p16 macromolecule via a feedback mechanism [33]. Currently, there's no agreement on the foremost applicable methodology to discover HPV in HNSCC. The HPV testing strategies square measure principally supported detective work HPV-DNA in cancer tissues either with in place interbreeding (ISH) or enzyme chain reaction (PCR) or each [35].

Clinical options of HPV-Associated Head and Neck Cancer

Patients with HPV-positive HNSCC tend to bemiddle-aged man, non-smokers, non-drinkers or delicate to moderate drinkers, and have higher|the next} socioeconomic standing and better performance standing than patients with HPV-unrelated HNSCC [2,35-37]. Usually, the patients with HPV-induced HNSCC have the next range of sexual partners and a lot of sexual perversion partners [38]. Open-mouthed petting was found to be related to the event of oral HPV infection [39]. even so, HPV-induced bodily cavity malignant neoplastic disease happens each among exposed and non-exposed to tobacco/alcohol, with coffin nail smoking being a systematically associated risk issue for oral HPV infection and a suspected modifier of the explanation of HPV-induced HNSCC [2]. Distinct molecular profiles separate them from HPV-negative cancers and show several similarities with HPV- positive cervical epithelial cell cancer. there's proof that HPV- positive HNSCC may be a sexually transmitted sickness. Current literature has shown that, the chance factors of HNSCC square measure astonishingly the same as those of cervical cancer and cervical intraepithelial pathological process (CIN), as well as the amount of sexual partners, younger age initially sexual issues, apply of sexual perversion, history of venereal warts and younger age [33,40,41].
As mentioned earlier HPV-associated HNSCC principally develops from cavity. The palatine tonsils and base of the tongue square measure a lot of oft concerned than alternative bodily cavity subsites [2,42].

Prognosis of HPV-Associated Carcinomas

Fakhry and colleagues established in 2008 that HPV- positive tumors have a strikingly higher prognosis with improved responsiveness to each therapy and chemo-radiotherapy and favorable survival rates [25]. during this study, cardinal patients with bodily cavity or cartilaginous structure cancer were prospectively treated with 2 cycles of paclitaxel and carboplatin induction therapy, followed by concomitant chemo-radiotherapy exploitation weekly paclitaxel. Oncogenic HPV was detected in four-hundredth of patients. The patients with HPV-positive tumors had higher response rates ANd an improved biennial overall survival of ninety fifth compared with sixty two of patients with HPV-negative tumors. once the study by Fakhry and colleagues, several studies evaluated the impact of HPV in prognosis, and their results steered that the patients with HPV-positive HNSCC, notably those with bodily cavity primary, treated by actinotherapy, chemo- actinotherapy, and surgery or combined modality medical care, have higher outcome than those with HPV-uninduced cancer [28,43]. In these studies steered that the HPV-positive SCC patients were calculable to own up to AN eightieth reduction in risk of sickness failure compared to HPV-negative patients. to boot, retrospective analyses of deposit neoplasm specimens from patients listed in phase II clinical trial and III trials, that received a lot of specific treatment regimens [26,28]; and meta-analyses [44,45] confirmed that HPV-positive HNSCC may be a separate life entity which these patients have considerably higher prognosis than patients with HPV-unrelated tumors. In these studies, the survival profit was most predominant or restricted in patients with AN bodily cavity primary neoplasm. the explanation why patients with HPV positive HNSCC have higher prognosis than those with HPV-unrelated cancer remains to be explained; but their younger age at designation, higher performance standing, lower tobacco smoking or alcohol drinking habit or distinct biology of the HPV- positive cancers might result in have higher prognosis [2]. there's sturdy proof that coffin nail smoking might modify the clinical behavior of HPV-positive SCC, adversely poignant the prognosis of those neoplasms [46]. Recently, a algorithmic partitioning analysis showed that the mixture of neoplasm HPV standing, smoking and TN class (T: the scale of the first (primary) neoplasm and N: close (regional) liquid body substance nodes that square measure involved) segregates patients with stage III and IV bodily cavity SCCs into three teams with totally different prognoses: patients with HPV-induced SCCs were thought-about to be at low risk, with the exception of smokers with advanced nodal class, World Health Organization were thought-about to be at intermediate risk; patients with HPV(-) SCCs were thought-about to be at high risk, with the exception of non- smok-

ers with tumors of stage T2 or T3, World Health Organization were thought-about to be at intermediate risk [47]

Current Management of HPV-Associated Head and Neck Cancer

Treatment for patients with HPV associated cavum cancer presently is that the same as for those with HPV negative cavum cancers, except within the context of a clinical test. though testing for HPV positivism provides prognostic info, there area unit depleted knowledge to change medical care based mostly upon HPV standing [16].

Despite the absence of proof from randomised, controlled trials to support a reduction of treatment intensity, in HPV- positive cavum carcinomas, some investigators argue that intensive concomitant chemo-radiation regimens might represent overtreatment [13,48]. Since the patients with HPV-positive cavum malignant neoplastic disease tend to be younger and have prolonged survival, associate degree aggressive multimodal medical care might end in severe acute and late term toxicities. during this context, most efforts area unit targeted toward reduction of treatment intensity in HPV-positive cavum epithelial cell carcinomas with the intent to scale back toxicity and thereby improve the long-run quality of life, whereas maintaining effectiveness. suggested treatment reduction is achieved by reducing the entire dose of radiation therapy in an exceedingly coincident chemo-radiotherapy setting, by mistreatment radiation therapy and EGFR inhibitors, as well as cetuximab, rather than noble metal based mostly chemo- radiation therapy or radiation therapy alone rather than chemo-radiotherapy, and first surgery +/− de-intensified adjuvant treatment rather than up-front chemo-radiotherapy [2].

Ongoing clinical studies area unit assessing the roles of de-intensification of radiation therapy and/or therapy during this population. Among these (Eastern Cooperative medicine cluster [ECOG] 1308) multicenter study evaluated eighty patients with stage III or marsh plant HPV associated cavum cancer received induction therapy with 3 cycles of cisplatin, paclitaxel, and cetuximab [49]. Lower dose of {radiation medical care|radiotherapy|radiation|actinotherapy|irradiation|therapy} was given to sixty two patients World Health Organization had a primary web site clinical complete response once induction therapy as fifty four Gy in twenty seven fractions, a pair of Gy/fraction. the opposite fifteen patients had typical dose radiation therapy as sixty nine.3 Gy in three fractions. The patients World Health Organization got
69.3 Gy had clinical partial response or stable malady once induction medical care. In each teams, radiation treatment was given in conjunction with weekly cetuximab. during this study, the patients World Health Organization had a whole response to the initial induction medical care, the biennial progression free survival was eightieth [49]. identical cluster had similar leads to ECOG trial E2399 [50]. In E2399 the biennial progression-free survival for HPV-positive patients was eighty four once paclitaxel carboplatin induction followed by radiation therapy with weekly paclitaxel. but during this study typical dose of radiation therapy as seventy Gy/2 Gy per fraction was used.

Treatment de-intensification is also achieved by the dose reduction or elimination of therapy or replacement of therapy with a targeted agent for HPV-associated cases. for instance, the continuing RTOG 1333 (NRG HN-002) trial compares a radiation therapy-alone program versus radiotherapy and reduced-dose cisplatin in regionally advanced HPV-associated malady in non-/light smokers (≤ ten pack-years) [51]. within the therapy arm of this trial, cisplatin is delivered weekly throughout half dozen weeks of radiation therapy at forty mg/ money supply (total = 240 mg/m2), a decrease from the historical commonplace of one hundred mg/ money supply each three weeks for three cycles (total = three hundred mg/m2).

Another approach is that the replacement of cisplatin with cetuximab, associate degree FDA-approved anti-EGFR antibody with radio sensitizing properties [52]. in an exceedingly randomised trial examination radiation therapy alone to radiation therapy with coincident cetuximab in stage III/IV head and neck cancer, it absolutely was shown that combined medical care improved OS [53]. The survival profit was greatest among patients with cavum primary cancers, low growth stage, high nodal stage, and younger age. These factors area unit related to HPV-positive cases. Secondary analyses of this trial urged that the addition of cetuximab to radiation therapy compared with radiation therapy alone in p16-positive (HPV-associated) cavum malignant neoplastic disease improved daft regional management and overall survival [54].

every three weeks for two doses with seventy Gy of radiation for 987 patients with stage III/IV p16-positive cavum malignant neoplastic disease [55]. This trial has completed accumulation, and initial results area unit expected to be declared at intervals future few years. The results of the trial area unit essential to our understanding of the role of cetuximab within the treatment of HPV- associated cavum malignant neoplastic disease.

Two additional phase II current trials; ECOG 3311 (NCT01898494) and NRG HN-002 (NCT02254278) are measure the reduction of treatment intensity in HPV-positive cavum carcinomas. extra knowledge and longer follow-up are going to be needed from these and alternative trials before lower-dose radiation treatment, substitution of radiation dose by induction therapy, use of probably less unhealthful medication, use of minimally invasive surgery, or radiation therapy alone is thought of a customary approach for HPV-positive patients. To date, the HPV-positive cavum malignant neoplastic disease patients ought to be treated with commonplace treatment of alternative cavum malignant neoplastic disease patients.

Conclusions

HPV-associated HNSCC is associate degree entity with distinctive clinical and molecular characteristics, that chiefly arises from the palatine tonsils and base of the tongue. HPV-16 is out and away the foremost common risky HPV genotype detected in cavum SCC. Patients with HPV-positive HNSCC tend to be old adult male, non-smokers, non-drinkers or delicate to moderate drinkers, and have a {better|the next} socioeconomic standing and better performance standing than patients with HPV-unrelated HNSCC. Treatment for patients with HPV-associated cavum cancer presently is that the same as for those with HPV negative cavum cancers, except within the context of a clinical test. it's probably that the patients with HPV-positive HNSCC are going to be treated with de-escalated therapies within the future. supported the randomised trials, over time, ancient cytotoxic therapy is also replaced by targeted agents like cetuximab, including reduced-dose radiation treatment. the long run commonplace treatment of HPV-associated SCC of the bodily cavity is vague, unfinished the results of current trials.

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