Review Article

Indian Journal of Genetics and Molecular Research
Volume 13 Number 1, January - June 2024
DOI: http://dx.doi.org/10.21088/ijgmr.2319.4782.13124.3

Oral and Liver Cancers: Paradigm in Diagnostic Methodologies

Shuchi[1], Tanu Alen[2], Neha Sharma[3], Sneha Kandpal[4], Ankita Singh[5], Narotam Sharma[6], Shraddha Singh[7]

How to cite this article:

Shuchi, Tanu Alen, Neha Sharma *et al*. Oral and Liver Cancers: Paradigm in Diagnostic Methodologies. Ind J Genet Mol Res. 2024; 13(1):29–43.

Abstract

Early detection of oral cancer is essential for patient survival, and auxiliary techniques should be considered when conducting an objective clinical examination. Non-invasive techniques such as liquid biopsy and brush biopsy are being used, and downstream molecular approaches require harmonization and standardization. Safety precautions are being revised. Cervical cancer is common in low-income areas due to advanced stages of Human Papilloma Virus (HPV) infection and lack of treatment, poor prognosis, and diagnosis. Control strategies such as Pap smear screening and HPV vaccinations have been used to reduce the exponential increase in new cases. However, the preventative efficacy of HPV vaccines is only advantageous to those who have not been exposed to the virus. Further study is needed to determine how aberrant alternative splicing affects cervical cancer. Pap smear testing is an effective, convenient, affordable, and secure method for identifying precancerous cervical epithelial lesions. Hepatocellular carcinoma (HCC) is the third most prevalent cancer related cause of death worldwide, with sorafenib, chemotherapy, immunotherapy, oncolytic viral therapy, and novel target therapy available treatments. The X-Ray cross-complementing (XRCC) genes are essential elements of the DNA repair pathway and have been investigated in relation to a variety of human malignancies. Studies from Northern and Southern India have reported genetic polymorphisms in the DNA repair genes with respect to a variety of cancer risks, including prostate, breast, oral, and oesophageal cancers. This review provides a insight on various Biomarkers of malignancies with respected to Oral and Liver cancers emphasizing on their diagnosis and the need of non-invasive techniques.

Keywords: Hepatocellular Carcinoma; Malignancies; Biopsy; Biomarkers of Cancer; Hyperplasia.

Author Affiliation: [1,4]M.Sc Student, [2]Assistant Professor, Amity Institute of Biotechnology, Amity University, Noida 201301, Uttar Pradesh, [3]Assistant Professor, Department of Biosciences and Biotechnology, Banasthali Vidyapith, Rajasthan 304022, [5]Junior Scientist and Quality Manager, [6]Scientist & Head Laboratories, DNA Labs-A Centre for Applied Sciences, Dehradun 248001, Uttarakhand, [7]M.Sc Student, Microbiology, DBS PG College, Dehradun 248001, Uttarakhand, India.

Corresponding Author: Narotam Sharma, Scientist & Head Laboratories, DNA Labs-A Centre for Applied Sciences, Dehradun 248001, Uttarakhand, India.

E-mail: Sharmanarotam5@gmail.com

Received on: 22.05.2024 **Accepted on:** 30.06.2024

INTRODUCTION

Malignancies may regard as a group of diseases characterized by abnormal cells growth caused by multiple changes in gene expression that leads to the dysregulated balance of cell proliferation and ultimate cell death, this may ultimately evolve into a population of cells that can then invade tissues and metastasize to distant sites, causing significant morbidity and, if untreated, results in the death of the host. Malignancies often termed cancer were first described by *Hippocrates*, the Greek physician who lived during 460–370 BC. He coined the term carcinoma. In Greek *karcinos* means "crab". This is

because tumours often have a central cell mass with extensions radiating outward that mimic the shape of a Crab.[1] The formation and spread of cancer are complex processes that are not fully known. Whether it is triggered by any internal stimuli (e.g., inherited mutations, hormones, or immune conditions) or environmental/acquired factors (e.g., tobacco, diet, radiation, or viral infections), a cancer results from the accumulation of multiple mutations within the malignant cells.[1] The causes of cancer are so diverse, complicated, and only partially understood. Many things are known to increase the risk of cancer, including dietary factors, certain infections, lack of physical activity, obesity, and environmental pollutants.[2] Cancer often couldn't be detected in the early stage, resulting in late treatment and sometimes death. Genetical changes in genes also contribute to malignancies. These genes are used as a biomarker for the early detection of malignancies, such as - EGFR, KRAS for lung cancer, BRCA1, BRCA2 for breast cancer, TGS p53 for Oral cancer, etc. According to a journal published in the American Cancer Society, Cancer is rising as a leading cause of death partly reflecting marked declines in mortality rates of stroke and coronary heart disease, relative to cancer, in many countries. This claim was done based on estimates from the World Health Organization (WHO) in 2019, in which cancer is deemed as the first or second leading cause of death before the age of 70 years in 112 out of 183 countries and it also ranks third or fourth in a further 23 countries.[3] According to the Centres for Disease control prevention [CDC], cancer records the second highest reason for deaths worldwide, with more than 90% of deaths being caused by cancer cell metastasis.[7] This is mainly because malignant tumours can expel tumour cells that infect nearby tissue and get within the lymphatic and circulatory systems. Circulating tumour cells (CTCs) have a significant role in the development of cancer metastases and have a favourable prognostic value in the early diagnosis of cancer.[7] A malignant neoplasia that develops on the lip or oral cavity is called oral cancer. The International Agency for Research on Cancer's (IARC) most recent studies show that the annual incidence of oral cancer which includes lips, tongue, gingiva, mouth floor, parotid, and salivary glands, is occurring greatly around the globe.[11,13] It can be challenging to distinguish potentially malignant oral epithelial lesions (PMOELs) with a higher risk of transformation from those with a lower risk; dysplasia is thought to be the best predictor of potential malignant transformation.[29,30] The clinical oral examination, which involves visual inspection and digital probing of the mouth cavity, serves as the starting point for the diagnostic procedure as the most typical clinical symptoms of oral mucosal carcinoma.[31,32] Adenocarcinoma (AC) and squamous cell carcinoma (SCC) are the two histological kinds of cervical cancer, which are malignant tumors of the cervix.[51] Human papillomavirus (HPV) infection is the most frequent cause of cervical cancer.[53] The most common subtypes of human papillomavirus (HPV), which account for 70% of instances of cervical cancer, are HR HPV 16 and 18.[51,53] In India, a successful human papillomavirus (HPV) HPV 16 and HPV 18 subtypes vaccination program is anticipated to reduce cervical cancer cases by 75%.[67] Smoking was found to be significantly linked with high-risk human papillomavirus (HR HPV) DNA positive, but not with the viral human papillomavirus (HPV) 16 E7 oncoprotein in human papillomavirus (HPV) induced carcinogenesis.[68] The chemical components of tobacco, such as benzyl pyrenes, polycyclic aromatics, and tobacco based nitrosamines, as well as tar based vaginal sanitizers, may influence the onset of cancer, including cervical cancer.[71] The goal of cervical cancer diagnosis or screening is to reduce or eradicate the high death rate and the number of new occurrences of cervical cancer brought on by chronic human papillomavirus (HPV) infection. The primary screening test for detecting precancerous cervical intraepithelial neoplasia and the early stage of invasive cervical cancer is the Pap smear test, which can detect early cervical epithelial alterations).[116] The E6 and E7 gene products of human papillomavirus (HPV) target several cellular processes, with the inactivation of tumour suppressor proteins pRB and p53 respectively.[121,122,124] The adiposity and insulin dysregulation has been associated with the progression of nonalcoholic fatty liver disease (NAFLD) to cirrhosis and hepatocellular carcinoma (HCC), indicating a dynamic process influenced by a variety of variables.[151,152,153] The prevention of cirrhosis development and hepatic decompensation requires early identification and therapy. It is challenging to estimate the prevalence of HCC in patients with AIH, although research has shown that malignancy can develop because of both the underlying liver disease and the prolonged immunosuppression used in treatment.[155, 157]

Malignancies and Cancers

The malignant cell is an uncontrolled cell growth as shown in Fig. 1. Malignancies may regard as a group of diseases characterized by abnormal

cells growth caused by multiple changes in gene expression that leads to the dysregulated balance of cell proliferation and ultimate cell death, this may ultimately evolve into a population of cells that can then invade tissues and metastasize to distant sites, causing significant morbidity and, if untreated, results in the death of the host. Blood-borne metastasis is initiated by malignant cells that are transported through the circulation from the primary tumour to vital distant organs, and it is directly responsible for most cancer related deaths.[7]

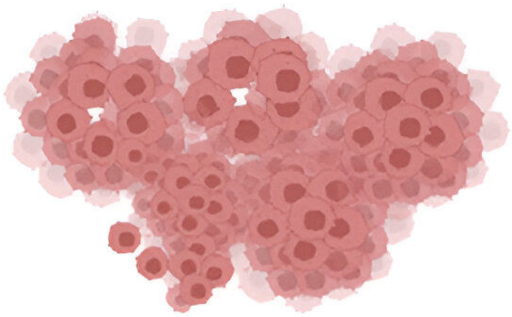

Fig. 1: The Image of a Cluster of Malignant Cells

For the development of primary tumours, blood is needed that is supplied through the process of angiogenesis. The new blood vessels formed due to angiogenesis can also provide an escape route to malignancy cells, by which these cells can leave the tumour and enter the body's blood circulatory systems. These malignancy cells can also enter the blood circulatory system via the lymphatic system. These malignancy cells need to survive in the blood circulatory system until they are arrested in a new organ; here, they might charge from the blood circulatory system to the other surrounding tissue. The likelihood of reducing cancer mortality depends on the early diagnosis of tumours. Blood based screening test for malignancies has recently been investigated through multiple approaches, with a recent outcome forming around the high utility of methylated DNA as a cancer marker.[8] Pan Seer detects five common types of cancer in 88% (95% CI: 80–93%) of post-diagnosis patients with a specificity of 96% (95% CI: 93–98%). Pan Seer detects cancer in 95% (95% CI: 89–98%) of asymptomatic individuals later diagnosed with malignancies, demonstrating that cancer can be non-invasively detected up to four years before the current standard of care.[8] Many cancers related to the female genital tract or reproductive system had been detected as the most common malignancy of the female, and its incidence is rising in parallel with the mounting prevalence of obesity. Urine, a prototype non-invasive sample, is gaining attention for biomarker discovery for the detection of malignancies in urinary tract cancer as it is easily accessible and can be collected repeatedly and in quantity. Identification of urinary biomarkers for malignancies detection relies on the excretion of systemic biomarkers by the kidneys or urinary contamination by biomarkers shed from the uterus.[9] X-Ray cross-complementing/XRCC (subtypes: XRCC1, XRCC2, XRCC3) gene deficiency delays the re-joining of SSB (Single strand DNA binding protein) that induces mutations which, as a result, elevated levels of sister chromatid exchanges, i.e., a hallmark of genomic instability and could also influence malignancies rate in the patients.[10] It is also associated with different types of malignancies. The CA125 is elevated in the serum of most women with cancer, but pre-operative serum levels of CA125 are below the conventional cut-off of 35 U/ml in roughly 50% of clinically detected stage I cases and in most of the women with occult cancers identified at prophylactic surgery.[4,5] B-HCG has also been suggested as a biological marker of prognostic significance in colonic adenocarcinoma.[6] A biopsy is one of the most common orthodox methods of collecting malignancies samples from the patient. This is a painful procedure as if an entire tumour is collected as a sample rather than a tissue infected by malignancies. This procedure helps in analysing if the sample collected is malignant or not, so based on this observation patient is informed about their health condition.

The appealing designation of liquid biopsy, as well as the promise of a patient friendly, minimally invasive method with implications for cancer detection, monitoring, and treatment, sparked a flurry of excitement in the scientific community, as well as in patient advocacy and the media as this technique minimize the pain a patient suffers when a biopsy sample is collected. As stated earlier, the orthodox method of tissue biopsy is done by collecting damaged malignant tissue through minor surgery, which is a painful procedure. Sometimes, it also advances the spreading of malignancies in surrounding cells. This happens as sometimes after the biopsy the sample collected area becomes highly active in metastasis resulting in the increase of the malignant cell number.

Types of Cancer

i. ***Carcinoma:*** This cancer originates from the epithelial tissue lines or skin that cover the internal organs such as the lung, colon,

pancreatic, and ovarian.

ii. ***Sarcoma:*** This cancer originates from the mesenchymal tissue that starts in bone, soft tissue cancers, osteosarcoma, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.

iii. ***Leukemia:*** This cancer originates from the blood forming tissue such as bone marrow and it produces many abnormal blood cells that enter the blood/leukemia. lymphoblastic [Acute lymphoblastic leukemia (ALL) and Chronic lymphoblastic leukemia (CLL)] leukemias and myelogenous [Acute myelogenous leukemia (AML) and Chronic myelogenous leukemia (CML)] leukemias are the subtypes of leukemia.

iv. ***Lymphoma:*** This cancer originates from the cells of the immune system/lymphoma i.e., T-cell lymphomas, B-cell lymphomas, Hodgkin lymphomas, and non-Hodgkin lymphoma.

Types of Tumours

i. ***Malignant tumour:*** A tumour that grows only locally and does not spread by invading/ metastasizing is referred to as a malignant tumour as shown in Fig. 2.

ii. ***Benign tumour:*** Tumours that grow by invading the neighboring cells and tissues,

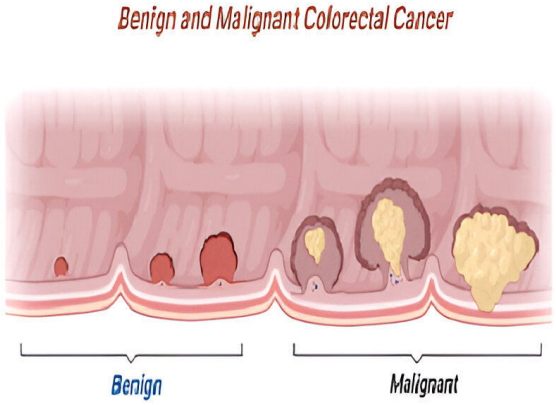

Fig. 2: The Image Showing the Benign and Malignant Tumour

then enter the blood vessels and lastly metastasize in different sites are referred to as benign tumours as shown in Fig. 2.

Normal Cells to Tumour Formation

i. ***Hyperplasia:*** The term "hyperplasia" describes tissue growth caused by an excessive rate of cell division, which results in a higher than usual cell count as shown in Fig. 3 (B). However, the hyperplasia process may be reversible, and cell structure and the regular arrangement of cells inside the tissue continue to be normal. A normal tissue reaction to a grating stimulation can be hyperplasia.

ii. ***Dysplasia***: Loss of normal tissue organization and cell structure is a hallmark of dysplasia, an aberrant kind of uncontrolled cell growth as shown in Fig. 3 (C). Such cells frequently return to their normal behavior, but sometimes they develop cancer over time. Areas of dysplasia should be constantly watched by a medical practitioner because they have the potential to develop into malignant growths. They require therapy on occasion.

iii. ***Carcinoma in situ:*** The term "carcinoma in situ" is occasionally used to describe the most severe forms of dysplasia. Carcinoma in situ is a term for an unchecked cell proliferation

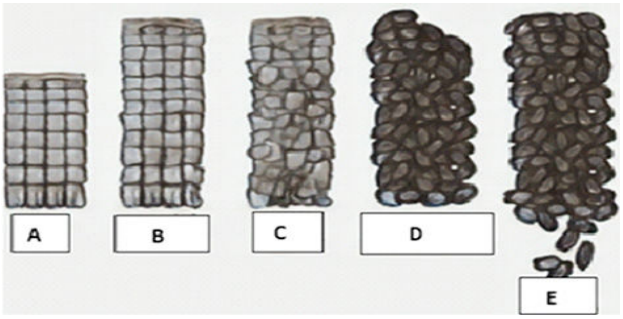

Fig. 3: The Image Represents **A:** Normal Cells; **B:** Hyperplasia; **C:** Mild Dysplasia **D:** Carcinoma In Situ; **E:** Cancer

that remains in the original area as shown in Fig. 3 (C). In Latin, in situ means "in place." However, because carcinoma in situ has the potential to spread and become invasive, it is often surgically removed whenever possible.

Oral Cancer

A malignant neoplasia that develops on the lip or oral cavity is called oral cancer as shown in Fig. 4. It is typically referred to as squamous cell carcinoma (OSCC) since 90% of malignancies in the dental area histologically begins in squamous cells. For dental surgery in particular, oral cancer is a vitally relevant worldwide public health issue. It is among the top 10 cancer incidence rankings.[11] In most ethnic groups, men are two to three times

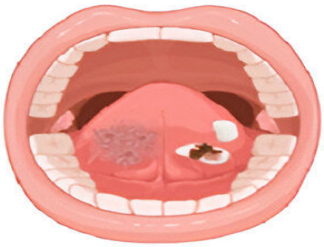

Fig. 4: The Image Represents the Lesion in the Oral Mucosa

more likely to develop oral cancer than women. The International Agency for Research on Cancer's (IARC) most recent studies show that the annual incidence of oral cancer which includes lips, tongue, gingiva, mouth floor, parotid, and salivary glands, is occurring greatly around the globe.[11]

Malignant Lesions

Clinically questionable oral mucosal lesions such as leukoplakia, erythroplakia, submucosal fibrosis, and lichen planus are examples of potentially malignant oral epithelial lesions (PMOELs), a category of oral illnesses and diseases that can exist prior to the beginning of Oral cancers are squamous cell carcinomas (OSCC). Nonetheless, the majority of PMOELs do not develop into malignancy.[13]

Leukoplakia

Leukoplakia is a white area of oral mucosa that cannot be removed and is recognized clinically or histopathologically as such. Being a clinical term without a connection to histology, leukoplakia does not indicate the presence or absence of any stage of epithelial dysplasia. The alveolar mucosa, buccal mucosa, palate, tongue, and floor of the mouth are the areas where these lesions typically develop most frequently.[12] An idiopathic condition is leukoplakia. Clinically speaking, oral leukoplakias can be divided into two categories: homogeneous lesions and nonhomogeneous lesions.[14,15] More frequent and mostly benign, homogeneous leukoplakias are flat and uniform in appearance with a few tiny superficial fractures. Nonhomogeneous leukoplakias can have many features, including flat and specked, white, and red in hue (erythroleukoplakia), nodular, exophytic, or papillary/verrucous.[14,15]

Erythroplakia

Erythroplakia typically manifests as a crimson, well-defined lesion with a velvety texture that is far less common. Erythroleukoplakia, speckled erythroplakia, and leukoerythroplakia are terms used to describe lesions with red and white patches. The soft palate, ventral tongue, mouth floor, and tonsillar pillars are the most typical locations for this lesion, and most individuals only have one lesion.[12]

Oral Lichen Planus

Oral Lichen Planus or OLP is a long-term inflammatory condition with an immunological basis that typically affects middle aged individuals, especially women between the ages of 30 and 60. Although it typically affects the skin, it can also involve other mucosal surfaces, such as the oral mucosa. It is primarily a chronic condition.[17,18] The potential for the development of oral lichen planus progressing into oral squamous cell carcinoma is currently being explored,[16] with reported transformation rates varying from 0% to 12.5%. Clinical or histological traits cannot be used to foretell potential malignant change.[18] The probability of malignant transformation is highest in erosive OLP, followed by atrophic OLP, and lowest in reticular OLP.[17]

Submucosal fibrosis

A chronic fibrotic lesion of the oral mucosa is called submucosal fibrosis. It is most likely a sign of an over healing wound reacting to ongoing mechanical or chemical assaults on the mucosal lining. It is generally acknowledged that this lesion has cancerous potential.[19,21] The loss of fibro-elasticity in the afflicted tissue that results in palpable fibrous bands that can impede tongue motion and restrict mouth opening is a hallmark of submucosal fibrosis.[20] The buccal mucosa, followed by the tongue, lip, palate, and gingiva, is the area of this ailment that is most frequently affected; a predominance in males has been seen. Initially thought to be idiopathic, submucosal fibrosis is now thought to have a multifactorial aetiology that includes iron, zinc, and vitamin deficits as well as the capsaicin found in chilies.[22,23]

Chronic Inflammation

Oral cancer has been linked to chronic mucosal irritation as an etiological component. As a result of the related chronic inflammation, mediators such as cytokines are released, which causes oxidative stress and consequent DNA damage in cells, which results in the carcinogenic process.[24] The parts of the oral mucosa that come into touch with teeth

or dental implants are typically impacted, and malignancies associated with chronic inflammation are most frequently found at the lateral edge of the tongue.[24] Chronic mucosal trauma is known to both initiate and advance oral cancer since it can result in lesions on healthy mucosa or exacerbate already present lesions.[24,25]

Oral Bacteria and Cancer

Patients with oral cancer frequently exhibit very poor oral hygiene. Oral cancer development is influenced by biological interactions between Fusobacterium nucleatum and Porphyromonas gingivalis, two bacteria found in oral biofilms, and epithelial cells.[26]

Diagnosis

It can be challenging to distinguish PMOELs with a higher risk of transformation from those with a lower risk; dysplasia is thought to be the best predictor of potential malignant transformation.[29,30] Before taking a biopsy, it is impossible to determine whether dysplastic alterations are present because the presence or absence of dysplasia is not directly correlated with a particular clinical appearance of the lesion.[29] A so called carcinoma-in-situ, or intraepithelial carcinoma, is obvious when dysplasia alterations are significant and cover the full thickness and stratum of the epithelium.[29] Oropharyngeal and oral cancers associated with HPV (mostly HPV type 16) have been more common in recent years, mostly in younger persons. Many clinical and scientific research have focused more and more on the oncogenic impact of the oral microbiome, mucosal inflammation, and oral mucosal trauma from teeth and prosthetic devices. Actinic ultraviolet radiation (UV), primarily UV-B, also contributes to lip cancer. Moreover, due to a deficiency in DNA repair pathways, hereditary diseases such as xeroderma pigmentosum, Fanconi's anemia, and ataxia telangiectasia indicate elevated risk.[12] The clinical oral examination, which involves visual inspection and digital probing of the mouth cavity, serves as the starting point for the diagnostic procedure as the most typical clinical symptoms of oral mucosal carcinoma.[31,32] Early on, the tumour may have no symptoms at all, but it may be obvious as a noticeable deviation in (Table 1) from the usual surface and texture of the mucosal lining.

Table 1: Common Signs and Symptoms of Oral Cancer

1	Constant mouth soreness and pain.
2	Modification in the mucosa appearance.
3	Modification in mucosa accordant.
4	Constant white or red or a mixture of both patches in the mouth.
5	Plague or any kind of raised patch in the oral area.
6	Bump or lump growth in the mucosa.
7	A generalized bleeding region within the mucosa.

Suspecting lesions need to be evaluated further. According to the American Dental Association's most recent evidence based protocol, any mucosal lesion that persists for two weeks or longer after the removal of any potential local irritants (broken teeth, ill fitting dental prosthetic devices, and appliances, dental plaque, etc.) must be biopsied for histological examination. This recommendation was originally made by the World Health Organization and the National Institute of Dental and Craniofacial Research.[33] Although a biopsy is still the gold standard, there are several drawbacks that determine patients from consenting to the treatment. These drawbacks include fear, tension, pain, and the possibility of damaging good tissues, as well as the possibility of infection, discomfort, temporary incapacity, and aesthetic concerns.[35]

Toluidine Blue Staining

Toluidine blue staining is a simple, inexpensive, and non-invasive technique used as an aid in the diagnosis of malignant and pre-malignant lesions of the oral cavity.[37] Its application is very easy and fast: a 1% aqueous solution is applied for 30 s on the area of the suspect lesion and after the application of 1% acetic acid to remove salivary and bacterial pellicle; the staining pattern is then evaluated.[36] When toluidine blue staining data are combined with information from a clinical examination, the sensitivity can be increased to 100%,[38] notably for malignant lesions, but it remains lower for premalignant lesions.[36] However, because mucosal ulcerations of any kind (traumatic, inflammatory, or pre-neoplastic) tend to bind toluidine blue, their specificity is still restricted.[38] Additionally, it has been discovered that toluidine blue positivity is associated with a worse prognosis because positive lesions tend to enlarge and lead to cancer more frequently than negative lesions.[39]

Autofluorescence Imaging

Autofluorescence imaging provides details about the lesion's nature, aiding in diagnosis and making it easier to identify lesions that require biopsy.[40] In recent decades, several gadgets have

been commercialized. Autofluorescence imaging is justified by the idea that changes in the mucosa's fluorescence are brought on by dysplasia and malignancy. Because of the disturbance in the distribution of the components that induce autofluorescence in healthy tissues,[42] the disease results in a loss of green fluorescence, giving the mucosa an appearance of darkness as opposed to the normal mucosa's light green fluorescence.[41] Since benign conditions like inflammatory diseases can cause changes in tissue autofluorescence that are comparable to those caused by malignant and pre-malignant conditions, the main disadvantage of this technique is its low specificity (estimated 58%). However, the benefits of this technique include its high sensitivity (estimated 91%) and non-invasiveness.[43]

Salivary Biomarkers

In the past ten years, research has discovered biomarkers in biological fluids,[44] such as saliva, that may increase early identification and find a premalignant or malignant tumour that is asymptomatic or undetectable. Indicators of pathological processes and carcinogenesis, such as viruses, cytokines (IL-1b, IL-8, TNF-), protein receptors (CD44)[45-47]and DNA and RNA markers that are overexpressed in a carcinogenic process,[45,49] have been found in more than 100 biomarkers in human saliva.[48,45] Additional study is still needed to determine whether these testing methods are a reliable tool for physicians to assess the possibility and/or presence of malignant transformation of the oral mucosa and raise the sensitivity and specificity of these testing methods.[45,50]

Tissue Biopsy

A tissue biopsy is a procedure that uses surgery or specialized tools to remove lymph nodes or soft tissues from the mouth cavity. For diagnosing oral cancer, a traditional tissue biopsy is the most reliable method. There are multiple techniques for taking a tissue sample, including surgical biopsy, punch biopsy, lymph node biopsy, brush biopsy, and needle aspiration biopsy. These techniques use a variety of instruments, including a scalpel, circular blade, hollow needle, and other implements.[73] For pathological analysis, tissue from the surgical biopsy is cut into frozen sections (FS)[74,75] and stained with hematoxylin and eosin (H&E).[76,77] The current gold standard for tumour assessment during surgery is this.

Liquid Biopsy

When liquid biopsies are used as a screening tool, all cells have the potential to be analyzed for markers that match the disease; in oncology, fluid samples are analyzed to find mutations in cancer. A liquid biopsy is a quick, simple method that allows early detection and helps early diagnosis with low risk, minimal pain, a short recovery time, and a low cost.[73] Because saliva analysis for oral cancer biopsy can potentially discover biomarkers for oral carcinoma, it can be used as a screening technique for an early diagnosis of oral and oropharyngeal cancer.[73]

Liver Cancer

The aggressive tumour is known as liver cancer, as shown in Fig. 8, which develops in the liver, and typically takes place alongside cirrhosis and chronic liver disease. Males get liver cancer at a rate that is more than twice as high as females do worldwide. East and Southeast Asia and Middle and Western Africa have the greatest incidence of liver cancer, whereas South-Central and Western Asia and Northern and Eastern Europe have the lowest rates.[125]

Hepatocellular carcinoma (HCC), also known as primary liver cancer, is the third greatest cause of cancer related death globally and is the fifth most prevalent disease in men and the seventh most common cancer in women.[125,126] The inter disciplinary approach to treating liver cancer today allows for the selection of multiple treatment choices based on the patient's unique medical history, tumour stage, degree of underlying liver disease, and general state of health. The interdisciplinary approach to treating liver cancer today allows for the selection of multiple treatment choices based on the patient's unique medical history, tumour stage, degree of underlying liver

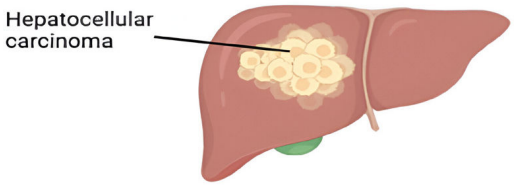

Fig. 8: The Image Represents Liver Cancer

disease, and general state of health.[127] Sorafenib, chemotherapy, immunotherapy, oncolytic viral therapy, and new target therapy are utilized

to treat hepatocellular carcinoma (HCC). Adjuvant therapy, locoregional therapy, liver transplantation, and surgical resection are used to treat early stage cancer, while TACE is used to treat intermediate stage cancer.[127]

The National Comprehensive Cancer Network [NCCN] in the United States, the European Association for the Study of the Liver European Organization for Research and Treatment of Cancer [EASLEORTC] in Europe, and the Asian Oncology Summit 2009 [AOS] in Asia all have different management guidelines for liver cancer that are heterogeneous.[125-129]

Stages in Liver Cancer

There are numeral staging methods that have been developed to determine the prognosis of HCC, including the frequently used tumour node metastasis (TNM), Okuda, and Barcelona Clinic Liver Cancer (BCLC) systems, as well as the Cancer of the Liver Italian Programme (CLIP), score.[130-136] The variety of these staging methods reflects the heterogeneity of HCC as well as regional preferences and differences in respectability or transplant eligibility.

TNM

The number of tumours and the presence and degree of vascular invasion within the tumour are the two most significant prognostic markers according to the 2010 revision of the TNM staging system for hepatocellular carcinoma (HCC).[136] The TNM staging approach embraced the underlying liver fibrosis score as a clinically meaningful prognostic factor rather than using the existence of liver cirrhosis or tumour grade to determine the final tumour stage.[127]

Okuda

The number of ascites, serum albumin levels, and bilirubin levels are used by Okuda and colleagues to determine the severity of cirrhosis, as well as the tumour size.[130] Patients with Okuda stages I, II, and III who were left untreated had respective survival rates of 8.3, 2.0, and 0.7 mo. The Okuda method's limited utility as a clinical grading system is due to the exclusion of pathologic criteria including vascular invasion and the presence or absence of nodal metastases, as well as the fact that patients staged using this system typically had unresectable hepatocellular carcinoma (HCC).

CLIP

To assess the prognosis of patients with liver cancer, the CLIP score, which ranges from 0 to 6, includes an index of the degree of liver cirrhosis i.e., Child-Pugh. Stage, tumour form and extension, AFP serum levels, and portal vein thrombosis[137-139] have demonstrated the value of the CLIP scoring system in stratifying patients with advanced hepatocellular carcinoma (HCC).

BCLC

The BCLC staging method establishes clinical stages based on the size of the primary tumour, the degree of vascular invasion and extrahepatic metastasis caused by the tumour, the performance status of the individual, and the level of baseline liver function (Child-Pugh stage). This technique, which is better grounded in clinical practice, enables the application of the proper treatment approach to each BCLC stage. Stage 0 is the early stage. Stage A is the stage in which patients have tumours that are amenable to potentially curative treatment such as surgical resection, liver transplantation, or local ablation. Stage B or intermediate stage is where patients have multinodular tumours, which are treated by TACE. However, Stage C or advanced stage patients have tumours with vascular invasion and have extra hepatically spread, sorafenib treatment is provided to those patients. Lastly, Stage D patients with the lowest performance status, cirrhosis, are treated with supportive care.[127,140]

Hepatitis C and Hepatitis B Virus

The most frequent cause of liver infection today is chronic hepatitis C virus (HCV). Hepatic failure can result from chronic hepatitis C virus (HCV) infection, which can worsen liver function[145] as shown in Fig. 9. The progression of liver injury can range from stable liver function to abrupt decompensated hepatic failure, and it is unpredictable.[146] The most important factor that greatly contributes to carcinogenesis is the ongoing inflammation and death of hepatocytes. Poorly

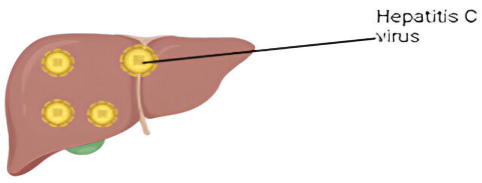

Fig. 9: The image represents HCV action on the Liver

differentiated hepatocytes multiply and transform into dysplastic nodules and hepatocellular carcinoma (HCC) because of cell turnover. Once hepatocellular carcinoma (HCC) is identified, the level of liver inflammation in hepatitis C virus (HCV) patients also predicts their prognosis. Currently, there are 6 main genotypes of hepatitis C virus (HCV) i.e., HCV 1, HCV 2, HCV 3, HCV 4, HCV 5, and HCV 6. According to Morgan et al.[147], treating HCV significantly decreased the likelihood of developing HCC.

The most common cause of hepatocellular carcinoma (HCC) worldwide, chronic hepatitis B (CHB), is expected to affect 240 million people.[148] Patients with hepatitis B virus (HBV), as shown in Fig. 10, have a 2% to 5% risk of developing hepatocellular carcinoma (HCC), and it can happen even in the absence of cirrhosis. Male sex, getting older, and specific genetic variants are all factors that raise the risk of hepatocellular carcinoma (HCC).[145] Hepatocellular carcinoma (HCC) screening is crucial in these patients because of the link between Hepatitis B Virus (HBV) and hepatocellular carcinoma (HCC). Hepatitis B e antigen and Hepatitis B surface antigen loss are the goals of current antiviral therapy, which also aims to lower viral load and suppress Hepatitis B Virus (HBV) replication. An elevated risk of developing hepatocellular carcinoma (HCC) has been linked to the presence of certain antigens. The conclusion of a 35-study meta-analysis by Lok et al.[149] provides more evidence in favor of the treatment of immune-active Chronic Hepatitis B (CHB) for an overall decrease in hepatocellular carcinoma (HCC).[149,150]

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver (NAFL), as shown in Fig. 11, and nonalcoholic steatohepatitis (NASH) are subtypes of nonalcoholic fatty liver disease (NAFLD). Hepatic steatosis is present in Nonalcoholic fatty liver (NAFL) but there is no indication of inflammation, whereas in nonalcoholic steatohepatitis (NASH), hepatic steatosis is linked to hepatic inflammation that is histologically identical to alcoholic steatohepatitis.[151] The purpose of nonalcoholic fatty liver disease (NAFLD) management is to change one's lifestyle to counteract elements that would otherwise cause the condition to advance.[145] In patients with nonalcoholic fatty liver disease (NAFLD), hepatocellular carcinoma can sometimes manifest without cirrhosis, making the condition more challenging. The adiposity and insulin dysregulation has been associated with the progression of nonalcoholic fatty liver disease (NAFLD) to cirrhosis and hepatocellular carcinoma (HCC), indicating a dynamic process influenced by a variety of variables.[152,153] Non-alcoholic fatty liver disease (NAFLD) treatment options are scarce.

Autoimmune Hepatitis

Hypergammaglobulinemia, interface hepatitis evident on histology, persistent liver inflammation, and the development of autoantibodies like antinuclear antibodies, anti-smooth muscle antibodies, and liver/kidney microsomal antibodies are the four main characteristics of autoimmune hepatitis.[154-156] The prevention of cirrhosis development and hepatic decompensation requires early identification and therapy. It is challenging to estimate the prevalence of HCC in patients with Autoimmune Hepatitis (AIH), although research has shown that malignancy can develop as a result of both the underlying liver disease and the prolonged immunosuppression used in treatment.[155,157] The following main risk factors for HCC in Autoimmune Hepatitis (AIH) are immunosuppression for at least three years, male sex, and cirrhosis for at least 10 years with decompensation shown as portal hypertension.[145] A late diagnosis is made in most liver cancer or hepatocellular carcinoma (HCC) patients. The most conventional method for diagnosing and screening hepatocellular carcinoma (HCC) has been a combination of ultrasound imaging (US), computer tomography imaging (CT), magnetic resonance imaging (MRI), and measurement of serum alpha-fetoprotein (AFP) levels.[141] Glypican-3 (GPC3), Dickkopf-1 (DKK1), and circulating miRNAs have all recently been proposed as potential biomarkers for early HCC diagnosis.[142-144]

DISCUSSION AND CONCLUSION

The diagnosis of malignancies in the early stage could make the wonder in the field of cancer diagnosis. There are many methods that have suggested that there is a chance of future malignancies in the patient but not many cancers can be detected through this method. The use of biopsy for the detection of malignancies is the most orthodox and most used method for malignancy detection, but it is also seen that this method many times prolonged the cancer growth in the patient and is a very painful procedure. The latest method of liquid biopsy is less painful, and many clinical trials are ongoing on this for the diagnosis. Future systems should have the following qualities: (i) low cost, (ii) portability and compactness, (iii) quicker diagnosis, (iv) comfort (no biopsy), and (v) excellent sensitivity and accuracy.

For precision and high-quality results, it should be investigated how different methodologies might be combined. In order to improve the healthcare related to skin cancer, clinicians, researchers, and practitioners should go forward in developing a standard protocol and knowledge sharing database.

Conflict of Interest: None

REFERENCES

1. A. Forner, J.M. Llovet, J. Bruix, Hepatocellular carcinoma, Lancet 379 (2012) 1245e1255
2. A.G. Ostor, Natural history of cervical intraepithelial neoplasia: a critical review, Int J Gynecol Pathol 12(2) (1993),186–192.
3. Anand, P., A.B. Kunnumakkara, et al, September 2008. Cancer is a preventable disease that requires major lifestyle changes. Pharm. Res., 25(9):2097-116.
4. Ansari M, Mehdi G, Arif SH, Ansari H, Khan T. Smear patterns and spectrum of premalignant and malignant cervical epithelial lesions in postmenopausal Indian women: A hospital-based study. Diagn Cytopathol 2012;40:976-83.
5. Arakeri, G.; Brennan, P.A. Oral submucous fibrosis: An overview of the aetiology, pathogenesis, classification, and principles of management. Br. J. Oral Maxillofac. Surg. 2013, 51, 587–593. [CrossRef] [PubMed]
6. Ashok Shian et al, The Role of Diagnosis and Treatment of Underlying Liver Disease for the Prognosis of Primary Liver Cancer 2017; DOI: 10.1177/1073274817729240
7. Awan, K. Ecacy of Autofluorescence Imaging as an Adjunctive Technique for Examination and Detection of Oral Potentially Malignant Disorders: A Systematic Review. J. Contemp. Dent. Pract. 2015, 16, 744–749. [CrossRef] [PubMed]
8. Awan, K.H.; Morgan, P.R.; Warnakulasuriya, S. Evaluation of an autofluorescence based imaging system (VELscope) in the detection of oral potentially malignant disorders and benign keratoses. Oral Oncol.2011, 47, 274–277. [CrossRef] [PubMed]
9. Bahr, W.; Stoll, P. Intraoperative histological evaluation of tumor resection borders without prolonging surgery. Int. J. Oral Maxillofac. Surg. 1992, 21, 90–91. [CrossRef]
10. Bal MS, Goyal R, Suri AK, Mohi MK. Detection of abnormal cervical cytology in papanicolaou smears. J Cytol 2012;29:45-7.
11. Bisognin A, Pizzini S, Perilli L, Esposito G, Mocellin S, Nitti D, et al. An integrative framework identifies alternative splicing events in colorectal cancer development. Mol Oncol 8: 129-141, 2014.
12. Brennan, M.; Migliorati, C.A.; Lockhart, P.B.;Wray, D.; et al. Management of oral epithelial dysplasia: A review. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol. 2007, 103, S19.e1–S19.e12. [CrossRef]
13. British Columbia Oral Cancer Prevention Program, BC Cancer Agency; College of Dental Surgeons of British Columbia. Practice, C. Guideline for the early detection of oral cancer in British Columbia 2008. J. Can. Dent. Assoc.2008, 74, 245.
14. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX and de Sanjosé S: Cervical human papillomavirus prevalence in 5 continents: Meta-analysis of 1 million women with normal cytological findings. J Infect Dis 202: 1789-1799, 2010.
15. Buchakjian, M.R.; Tasche, K.K.; Robinson, R.A.; Pagedar, N.A.; Sperry, S.M. Association of Main Specimen and Tumor Bed Margin Status With Local Recurrence and Survival in Oral Cancer Surgery. JAMA Otolaryngol. Head Neck Surg. 2016, 142, 1191–1198. [CrossRef] [PubMed]
16. Calin GA, Dumitru CD, et al: Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA 99: 15524-15529, 2002.
17. Campo E, Palacin A, Benasco C, Quesada E, Cardesa A. Human chorionic gonadotrophin in colorectal carcinoma, an immunohistochemical study. Cancer 1985; 59:1611-16.
18. Capparé, P.; Teté, G.; Romanos, G.E.; Nagni, M.; Sannino, G.; Gherlone, E.F. The 'All-on-four' protocol in HIV-positive patients: A prospective, longitudinal 7-year clinical study. Int. J. Oral Implantol. 2019, 12, 501–510.
19. César Rivera Review Article Essentials of oral cancer 2015
20. Chainani-Wu, N.; Madden, E.; et al. Toluidine blue aids in detection of dysplasia and carcinoma in suspicious oral lesions. Oral Dis. 2015, 21, 879–885. [CrossRef]
21. Chalasani N, Younossi Z, Lavine JE, et al. American Association for the Study of Liver Diseases. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American association for the study of liver diseases, American college of gastroenterology, and the American gastroenterological association. Hepatology. 2012;55(6):2005-2023
22. Chatterjee S, Chattopadhyay A, Samanta L and Panigrahi P: HPV and cervical cancer epidemiology-current status of HPV vaccination in India. Asian Pac J Cancer Prev 17: 3663-3673, 2016.
23. Chatzistamatiou K, Katsamagas T, Zafrakas M, et al. Smoking and genital human papilloma virus infection in women attending cervical cancer screening in Greece. World J Obstet Gynecol 2: 53-61, 2013
24. Chun-Yu Liu et al. Treatment of Liver Cancer: Cold Spring Harb Perspect Med 2015;5:a021535

25. CLIP. 2000. Prospective validation of the CLIP score: A new prognostic system for patients with cirrhosis and hepatocellular carcinoma. The Cancer of the Liver Italian Program (CLIP) Investigators
26. Cohen PA, Jhingran A, Oaknin A and Denny L: Cervical cancer. Lancet 393: 169-182, 2019.
27. Crespi, R.; Capparè, P.; Romanos, G.E.; Mariani, E.; Benasciutti, E.; Gherlone, E. Corticocancellous porcine bone in the healing of human extraction sockets: Combining histomorphometry with osteoblast gene expression profiles in vivo. Int. J. Oral Maxillofac. Implant. 2011, 26, 866–872.
28. Czaja AJ. Diagnosis and management of autoimmune hepatitis: current status and future directions. Gut Liver. 2016;10(2):177-203.
29. Deng Y, et al: miR-376c inhibits cervical cancer cell proliferation and invasion by targeting BMI1. Int J Exp Pathol 97: 257-265, 2016.
30. Denny L, de Sanjose S, Mutebi M, et al. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. Lancet 2017; 389: 861–70.
31. DeVeld, D.C.; Skurichina, M.; Witjes, M.J.; Duin, R.P.; Sterenborg, H.J.C.M.; Roodenburg, J.L. Autofluorescence and di use reflectance spectroscopy for oral oncology. Lasers Surg. Med. 2005, 36, 356–364. [CrossRef]
32. Dong J, et al: MicroRNA-217 functions as a tumor suppressor in cervical cancer cells through targeting Rho-associated protein kinase 1. Oncoly Lett 16: 5535-5542, 2018.
33. E.L. Franco, J. Cuzick, A. Hildesheim and S. de Sanjose, Chapter 20: Issues in planning cervical cancer screening in the era of HPV vaccination, Vaccine 24(Suppl 3) (2006), S171–S177.
34. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. 2010. AJCC cancer staging manual, 7th ed. (ed. Edge SB, et al.), p. 175. Springer, New York.
35. F. Mantovani and L. Banks, The human papillomavirus E6 protein and its contribution to malignant progression, Oncogene 20(54) (2001), 7874–7887.
36. Faustino NA and Cooper TA: Pre-mRNA splicing and human disease. Genes Dev 17: 419-437, 2003.
37. Fehri E, Ennaifer E, Ardhaoui M, Ouerhani K, Laassili T, Bel Haj Rhouma R, Guizani I and Boubaker S: Expression of Toll-like receptor 9 increases with progression of cervical neoplasia in Tunisian women-a comparative analysis of condyloma, cervical intraepithelial neoplasia and invasive carcinoma. Asian Pac J Cancer Prev 15: 6145-6150, 2014
38. Felekkis K, Touvana E, et al: microRNAs: A newly described class of encoded molecules that play a role in health and disease. Hippokratia 14: 236-240, 2010.
39. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. 2010. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127: 2893–2917.
40. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-E386, 2015.
41. Fong ZV, Tanabe KK. 2014. The clinical management of hepatocellular carcinoma in the United States, Europe, and Asia: A comprehensive and evidence-based comparison and review. Cancer 120: 2824–2838
42. Ford, P.; Farah, C. Early detection and diagnosis of oral cancer: Strategies for improvement. J. Cancer Policy 2013, 1, e2–e7. [CrossRef]
43. Franzmann, E.J.; Donovan, M.J. Effective early detection of oral cancer using a simple and inexpensive point of care device in oral rinses. Expert Rev. Mol. Diagn. 2018, 18, 837–844. [CrossRef]
44. Fujiki H: Gist of Dr. Katsusaburo Yamagiwa's papers entitled 'Experimental study on the pathogenesis of epithelial tumors' (I to VI reports). Cancer Sci 105: 143-149, 2014.
45. FUTURE II Study Group: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 356: 1915-1927, 2007.
46. Ghebre RG, Grover S, Xu MJ, Chuang LT and Simonds H: Cervical cancer control in HIV-infected women: Past, present and future. Gynecol Oncol Rep 21: 101-108, 2017.
47. Gherlone, E.F.; Capparè, P.; Tecco, S.; Polizzi, E.; Pantaleo, G.; Gastaldi, G.; Grusovin, M.G. A Prospective Longitudinal Study on Implant Prosthetic Rehabilitation in Controlled HIV-Positive Patients with 1-YearFollow-up: The Role of CD4+ Level, Smoking Habits, and Oral Hygiene. Clin. Implant. Dent. Relat. Res. 2015, 18, 955–964. [CrossRef]
48. Glucksmann, A.; Walter, L.; Cherry, C.P. The role of serial biopsies in the treatment of oral cancer. Clin. Radiol. 1967, 18, 310–312. [CrossRef]
49. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al; Alliance for Cervical Cancer Prevention Cost Working Group: Cost-effectiveness of cervical-cancer screening in five developing countries. N Engl J Med 353: 2158-2168, 2005.
50. Golfetto L, Alves EV, Martins TR, et al. PCR-RFLP assay as an option for primary HPV test. Braz J Med Biol Res 51: e7098, 2018.
51. Goodson WH III, Lowe L, Carpenter DO, Gilbertson M et al: Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: The challenge ahead. Carcinogenesis 36 (Suppl 1): S254-S296, 2015.

52. Gopal S, Achenbach CJ, Yanik EL, Dittmer DP, Eron JJ and Engels EA: Moving forward in HIV-associated cancer. J Clin Oncol 32: 876-880, 2014

53. Goss PE, Lee BL, Badovinac-Crnjevic T, Strasser-Weippl K, et al: Planning cancer control in Latin America and the Caribbean. Lancet Oncol 14: 391-436, 2013.

54. Guanghuan Yang et al A Systematic Review of Oral Biopsies, Sample Types, and Detection Techniques Applied in Relation to Oral Cancer Detection 2022

55. H. zur Hausen, Papillomaviruses and cancer: from basic studies to clinical application, Nat Rev Cancer 2(5) (2002),342–350.

56. Hadi Esmaeilsabzali et al Detection and isolation of circulating tumor cells: Principles and methods 2013;1063–1084.

57. Haim, S. Oral leukoplakia. Harefuah 1981, 101, 35–37. [CrossRef] [PubMed]

58. Haverkos HW: Multifactorial etiology of cervical cancer: A hypothesis. MedGenMed 7: 57, 2005.

59. Herrero R, González P and Markowitz LE: Present status of human papillomavirus vaccine development and implementation. Lancet Oncol 16: e206-e216, 2015.

60. Hrad V, Abebe Y, Ali SH, Velgersdyk J, Al Hallak M, Imam M. Risk and surveillance of cancers in primary biliary tract disease [Published online June 19, 2016]. Gastroenterol Res Pract. 2016;2016:3432640.

61. Huitzil-Melendez FD, Capanu M, O'Reilly EM, Duffy A, Gansukh B, Saltz LL, Abou-Alfa GK. 2010. Advanced hepatocellular carcinoma: Which staging systems best predict prognosis? J Clin Oncol 28: 2889–2895.

62. Hyuna Sung et al Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries 2021; 71:209–249

63. J. Zhou, L. Yu, X. Gao, J. Hu, J. Wang, et al., Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma, J. Clin. Oncol. 29 (2011) 4781e4788.

64. Jacobson G, Chuang L and Pankow M: Improving quality of care and timely access to radiation therapy for patients with invasive cervical cancer at the National Cancer Institute Paraguay. Gynecol Oncol Rep 25: 82-86, 2018

65. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. 2011. Global cancer statistics.CACancer J Clin 61: 69–90.

66. Jit M, Brisson M, Portnoy A and Hutubessy R: Cost-effectiveness of female human papillomavirus vaccination in 179 countries: A PRIME modelling study. Lancet Glob Health 2: e406-e414, 2014.

67. Joseph, B. Oral Cancer: Prevention and Detection. Med. Princ. Pract. 2002, 11 (Suppl. 1), 32–35. [CrossRef]

68. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, et al: A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 372: 711-723, 2015.

69. K. Munger, J.R. Basile, S. Duensing, A. Eichten, S.L. Gonzalez, M. Grace et al., Biological activities and molecular targets of the human papillomavirus E7 oncoprotein, Oncogene 20(54) (2001), 7888–7898.

70. Kailas D. Datkhile, Madhavi N. Patil Assessment of role of genetic polymorphisms in XRCC1, XRCC2 and XRCC3 genes in cervical cancer susceptibility from a rural population: a hospital based case-control study from Maharashtra, India DOI: 10.18203/2320-6012.ijrms20183658 2018

71. Karki R, Pandya D, Elston RC and Ferlini C: Defining 'mutation' and 'polymorphism' in the era of personal genomics. BMC Med Genomics 8: 37-37, 2015

72. Kaur, J.; Jacobs, R.; Huang, Y.; Salvo, N.; Politis, C. Salivary biomarkers for oral cancer and pre-cancer screening: A review. Clin Oral Investig. 2018, 22, 633–640. [CrossRef]

73. Kelechi Njoku1 et al, Urinary Biomarkers and Their Potential for the Non-Invasive Detection of Endometrial Cancer 2020

74. Kim SU, Park SK, Yoo KY, Yoon KS, Choi JY, Seo JS, et al. XRCC1 genetic polymorphism and breast cancer risk. Pharmacogenetics and Genomics. 2002;12(4):335-8

75. Kocjan BJ, Bzhalava D, Forslund O, Dillner J and Poljak M: Molecular methods for identification and characterization of novel papillomaviruses. Clin Microbiol Infect 21: 808-816, 2015.

76. Korneev KV, Atretkhany KN, Drutskaya MS, Grivennikov SI, Kuprash DV and Nedospasov SA: TLR-signaling and proin- flammatory cytokines as drivers of tumorigenesis. Cytokine 89: 127-135, 2017.

77. Kunckler M, Schumacher F, Kenfack B, Catarino R, et al. Cervical cancer screening in a low-resource setting: A pilot study on an HPV-based screen-and-treat approach. Cancer Med 6: 1752-1761, 2017.

78. Levin A, Wang SA, Levin C, Tsu V and Hutubessy R: Costs of introducing and delivering HPV vaccines in low and lower middle income countries: Inputs for GAVI policy on introduction grant support to countries 2014.

79. Li, Y.-N.; Lu, R.; Zhang, J.; Zhou,G. Inter-and intra-observer agreement on the judgment of toluidine blue staining for screening of oral potentially malignant disorders and oral cancer. Clin. Oral Investig. 2018, 23, 1709–1714.[CrossRef]

80. Lingen, M.W.; Kalmar, J.R.; Karrison, T.; Speight, P.M. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol. 2008, 44, 10–22. [CrossRef] [PubMed]

81. Liu B, Tian Y, Li F, Zhao Z, Jiang X, Zhai C, Han X and Zhang L: Tumor-suppressing roles of miR-214 and miR-218 in breast cancer. Oncol Rep 35: 3178-3184, 2016.
82. Liu F, Dai M, Xu Q, Zhu X, Zhou Y, et al: SRSF10-mediated IL1RAP alternative splicing regulates cervical cancer oncogenesis via mIL1RAP-NF-κB-CD47 axis. Oncogene 37: 2394-2409, 2018.
83. Liu, J.L.; Walsh, T.; Kerr, A.R.; et al. Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. Cochrane Database Syst. Rev. 2012, 29. [CrossRef]
84. Lohse AW, Mieli-Vergani G. Autoimmune hepatitis. J Hepatol. 2011;55(1):171-182.
85. Lok AS, McMahon BJ, Brown RS Jr, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. Hepatology. 2016;63(1):284-306.
86. Lousada-Fernandez, F.; Rapado-Gonzalez, O.; Lopez-Cedrun, et al. Liquid Biopsy in Oral Cancer. Int. J. Mol. Sci. 2018, 19, 1704. [CrossRef]
87. Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, Lok AS. 2005. Prognosis of hepatocellular carcinoma: Comparison of 7 staging systems in an American cohort. Hepatology 41: 707–716
88. Mathonnet G, Labuda D, Meloche C, Wambach T, Krajinovic M, Sinnett D. Variable continental distribution of polymorphisms in the coding regions of DNA-repair genes. J Human Genetics. 2003;48(12):659.
89. Mattheij I, Pollock AM and Brhlikova P: Do cervical cancer data justify HPV vaccination in India? Epidemiological data sources and comprehensiveness. J R Soc Med 105: 250-262, 2012.
90. Maymone, M.B.; Greer, R.O.; Kesecker, J.; et al. Premalignant and Malignant Mucosal lesions: Clinical and Pathological Findings Part II. Premalignant and malignant mucosal lesions. J. Am. Acad. Dermatol. 2018, 81, 59–71. [CrossRef]
91. Maymone, M.B.; Greer, R.O.; Kesecker, J.; Sahitya, P.C.; et al. Premalignant and Malignant Mucosal lesions: Clinical and Pathological Findings Part II. Premalignant and malignant mucosal lesions. J. Am. Acad. Dermatol. 2018, 81, 59–71. [CrossRef]
92. Mehta AM, Mooij M, Brankovic I, Ouburg S, Morre SA and Jordanova ES: Cervical carcinogenesis and immune response gene polymorphisms: A review. J Immunol Res 2017: 8913860, 2017.
93. Min Yu, et al, Circulating tumor cells: approaches to isolation and characterization 2021
94. Mishra GA, Pimple SA and Shastri SS: Prevention of cervix cancer in India. Oncology 91 (Suppl 1): S1-S7, 2016.
95. Morassi, M.L.; Trimarchi, M.; Nicolai, P.; Gregorini, G.; Maroldi, R.; Specks, U.; Facchetti, F. Cocaina, ANCA egranulomatosi diWegener [Cocaine, ANCA, andWegener's granulomatosis]. Pathologica 2001, 93, 581–583. (In Italian) [PubMed]
96. Moretti, M.; Lissoni, A.; Gastaldi, G.; Arrigoni, G.; Doglioni, C.; Abati, S. Expression of hexokinase ii in oral keratotic lesions with or without inflammation. Front. Physiol. 2019, 10. [CrossRef]
97. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Int Med. 2013;158(5 pt 1):329-337
98. National Cancer Registry Programme of India. Three-year report of population based cancer registries: 2012–14. Bangalore: National Centre for Disease Informatics & Research, 2016.
99. Neville, B.W.; Day, T.A. Oral Cancer and Precancerous Lesions. CA Cancer J. Clin. 2002, 52, 195–215. [CrossRef]
100. Nicolas Wentzensen and Magnus von Knebel Doeberitz Biomarkers in cervical cancer screening.2007
101. Obade, A.Y.; Pandarathodiyil, A.K.; Oo, A.L.; Warnakulasuriya, S.; Ramanathan, A. Application of optical coherence tomography to study the structural features of oral mucosa in biopsy tissues of oral dysplasia and carcinomas. Clin. Oral Investig. 2021, 25, 5411–5419. [CrossRef] [PubMed]
102. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K. 1985. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 56: 918 –928
103. Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. Gynecol Oncol 2006; 100:20–26. The diagnostic tools appear only to be sensitive in detecting ovarian cancer at an advanced stage, while three of four tumors with early-stage disease in this series had normal screening tests prior to the diagnosis. [PubMed: 16188302]
104. Olson, M.A.; Rogers, R.S.; Bruce, A.J. Oral lichen planus. Clin. Dermatol. 2016, 34, 495–504. [CrossRef]
105. Omar, E. Current concepts and future of noninvasive procedures for diagnosing oral squamous cell carcinoma—A systematic review. Head Face Med. 2015, 11, 6. [CrossRef] [PubMed]
106. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30(12): 2212-2219
107. Pachouri SS, Sobti RC, Kaur P and Singh J. Contrasting impact of DNA repair gene XRCC1

polymorphisms Arg399Gln and Arg194Trp on the risk of lung cancer in North Indian population. DNA Cell Biol. 2007;26:186-91.

108. Park JY, Lee SY, Jeon HS, Bae NC, Chae SC, Joo S, et al. Polymorphism of the DNA repair gene XRCC1 and risk of primary lung cancer. Cancer Epidemiology and Prevention Biomarkers. 2002;11(1):23-7.
109. Patel MM, Pandya AN, Modi J. Cervical pap smear study and its utility in cancer screening, to specify the strategy for cervical cancer control. Natl J Community Med 2011; 2:49-51.
110. Pentenero, M.; Val, M.; Rosso, S.; Gandolfo, S. Microbiopsy a first-level diagnostic test to rule out oral dysplasia or carcinoma in general dental practice. Oral Dis. 2018, 24, 109–111. [CrossRef]
111. Piemonte, E.D.; Lazos, J.P.; Brunotto,M. Relationship between chronic trauma of the oralmucosa, oral potentially malignant disorders and oral cancer. J. Oral Pathol. Med. 2010, 39, 513–517. [CrossRef] [PubMed]
112. Poon D, Anderson BO, Chen LT, Tanaka K, Lau WY, Van Cutsem E, Singh H, Chow WC, Ooi LL, Chow P, et al. 2009. Management of hepatocellular carcinoma in Asia: Consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 10: 1111–1118.
113. Popov VB, Lim JK. Treatment of nonalcoholic fatty liver disease: the role of medical, surgical, and endoscopic weight loss. J Clin Tran Hepatol. 2015;3(3):230-238.
114. Pushp Lata Sachan, Meenakshi Singh et al. A Study on Cervical Cancer Screening Using Pap Smear Test and Clinical Correlation PMCID: PMC5996593 2018
115. Q. Shen, J. Fan, X.R. Yang, Y. Tan, W. Zhao, et al., Serum DKK1 as a protein biomarker for the diagnosis of hepatocellular carcinoma: a large-scale, multicentre study, Lancet Oncol. 13 (2012) 817e826.
116. Reibel, J. Prognosis of Oral Pre-malignant Lesions: Significance of Clinical, Histopathological, and Molecular Biological Characteristics. Crit. Rev. Oral Biol. Med. 2003, 14, 47–62. [CrossRef]
117. Rengaswamy Sankaranarayanan, Partha Basu, Prabhdeep Kaur, Rajesh Bhaskar, Gurinder Bir Singh et al. Review: Current status of human papillomavirus vaccination in India's cervical cancer prevention efforts Lancet Oncol 2019; 20: e637–44
118. Rethman, M.P.; Carpenter,W.; Cohen, E.E.; Epstein, J.; Evans, C.A; et al. Evidence-Based Clinical Recommendations Regarding Screening for Oral Squamous Cell Carcinomas. J. Am. Dent. Assoc. 2010, 141, 509–520. [CrossRef]
119. Rinella ME. Nonalcoholic fatty liver disease. JAMA. 2015; 313(22):2263-2273
120. Rodney Hull et al. Review Cervical cancer in low and middle-income countries 20: 2058-2074, 2020.
121. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: A WHO systematic analysis. Lancet Glob Health 2: e323-e333, 2014.
122. Scarinci IC, Garcia FAR, Kobetz E, Partridge EE, et al: Cervical cancer prevention: New tools and old barriers. Cancer 116: 2531-2542, 2010.
123. Schiller JT, Castellsagué X and Garland SM: A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 30: F123-F138, 2012.
124. Senapathy JG, Umadevi P and Kannika PS: The present scenario of cervical cancer control and HPV epidemiology in India: An outline. Asian Pac J Cancer Prev 12: 1107-1115, 2011.
125. Sharma, M.; Shetty, S.S.; Radhakrishnan, R. Oral Submucous Fibrosis as an Over healing Wound: Implications in Malignant Transformation. Recent Pat. Anticancer Drug Discov. 2018, 13, 272–291. [CrossRef] [PubMed]
126. Silvio Abati et al, Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis 2020.
127. Stamm S, Ben-Ari S, Rafalska I, Tang Y, Zhang Z, Toiber D, Thanaraj TA and Soreq H: Function of alternative splicing. Gene 344: 1-20, 2005.
128. Swaminathan R, Selvakumaran R, Vinodha J, et al. Education and cancer incidence in a rural population in south India. Cancer Epidemiol 2009; 33: 89–93.
129. Swanson M, Ueda S, Chen LM, Huchko MJ, Nakisige C and Namugga J: Evidence-based improvisation: Facing the challenges of cervical cancer care in Uganda. Gynecol Oncol Rep 24: 30-35, 2018.
130. Tarek Abdel-Fatah et al, Clinicopathological and functional significance of XRCC1 expression in ovarian cancer 2013.
131. Tazi J, Bakkour N and Stamm S: Alternative splicing and disease. Biochim Biophys Acta 1792: 14-26, 2009.
132. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261-283.
133. Thacker J, Zdzienicka MZ. The mammalian XRCC genes: their roles in DNA repair and genetic stability. DNA Repair (Amst). 2003;2:655-72.
134. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
135. Ueno S, Tanabe G, Sako K, Hiwaki T, Hokotate H, Fukukura Y, Baba Y, Imamura Y, Aikou T. 2001. Discrimination value of the new western prognostic system (CLIP score) for hepatocellular carcinoma in 662 Japanese patients. Cancer of the Liver Italian Program. Hepatology 34:529–534.
136. Urban-Wojciuk Z, Khan MM, Oyler BL, Fåhraeus R, Marek-Trzonkowska N, Nita-Lazar A, Hupp TR and Goodlett DR: The role of TLRs in anti-cancer immunity and tumor rejection. Front Immunol 10: 2388, 2019.

137. Van Der Waal, I. Oral potentially malignant disorders: Is malignant transformation predictable and preventable? Med. Oral Patol. Oral Cir. Bucal 2014, 19, e386–e390. [CrossRef]

138. Van Haaften-Day C, Shen Y, Xu F, et al. OVX1, macrophage-colony stimulating factor, and CA-125-II as tumor markers for epithelial ovarian carcinoma: a critical appraisal. Cancer 2001; 92:2837–2844. [PubMed: 11753957]

139. Vettriselvi V, Vijayalakshmi K, Solomon FD, Paul VP. XRCC1 and XPD Gene Polymorphisms in a South Indian Population. Asian Pacific J Cancer Prev. 2007;8:283-6.

140. Vidal AE, Boiteux S, Hickson ID, Radicella JP. XRCC1 coordinates the initial and late stages of DNA abasic site repair through protein-protein interactions. EMBO J. 2001;20:6530-9.

141. Villa, A.; Villa, C.; Abati, S. Oral cancer and oral erythroplakia: An update and implication for clinicians. Aust. Dent. J. 2011, 56, 253–256. [CrossRef]

142. Villa, A.; Villa, C.; Abati, S. Oral cancer and oral erythroplakia: An update and implication for clinicians. Aust. Dent. J. 2011, 56, 253–256. [CrossRef]

143. Waggoner SE: Cervical cancer. Lancet 361: 2217-2225, 2003.

144. Walsh, T.; Liu, J.L.; Brocklehurst, P.; Glenny, A.M.; et al. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. Cochrane Database Syst. Rev. 2013. [CrossRef] [PubMed]

145. Wang Y and Luo T: LINC00673 rs11655237 polymorphism is associated with increased risk of cervical cancer in a Chinese population. Cancer Control 25: 1073274818803942, 2018.

146. Wang Z, Sheng L, Yang Y, et al. The management of autoimmune hepatitis patients with decompensated cirrhosis: real-world experience and a comprehensive review. Clin Rev Allerg Immunol.2017;52(3):424-435.

147. Warnakulasuriya, S.; Johnson, N.W.; Van DerWaal, I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J. Oral Pathol. Med. 2007, 36, 575–580. [CrossRef]

148. Whitmore, S.E.; Lamont, R.J. Oral Bacteria and Cancer. PLOS Pathog. 2014, 10, e1003933. [CrossRef]

149. Wirth TC, Manns MP. The impact of the revolution in hepatitis C treatment on hepatocellular carcinoma. Ann Oncol. 2016;27(8):1467-1474.

150. World Health Organization: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. World Health Organization, 2013. https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/. Accessed March 16, 2019.

151. X.B. Man, L. Tang, B.H. Zhang, S.J. Li, X.H. Qiu, et al., Upregulation of Glypican-3 expression in hepatocellular carcinoma but downregulation in cholangiocarcinoma indicates its differential diagnosis value in primary liver cancers, Liver Int. 25 (2005) 962e966.

152. Xingdong Chen et al, Non-invasive early detection of cancer four years before conventional diagnosis using a blood test 2020

153. Yang X, Cheng Y and Li C: The role of TLRs in cervical cancer with HPV infection: A review. Signal Transduct Target Ther 2: 17055, 2017.

154. Yang Y, Liu Y, Li G, Li L, Geng P and Song H: microRNA-214 suppresses the growth of cervical cancer cells by targeting EZH2. Oncol Lett 16: 5679-5686, 2018.

155. Zhang B, et al: microRNAs as oncogenes and tumor suppressors. Dev Biol 302: 1-12, 2007

156. Zhang, L.; Williams, M.; Poh, C.F.; et al. Toluidine Blue Staining Identifies High-Risk Primary Oral Premalignant Lesions with Poor Outcome. Cancer Res. 2005, 65, 8017–8021. [CrossRef]

157. Zhang, L.; Williams, M.; Poh, C.F.; et al. Toluidine Blue Staining Identifies High-Risk Primary Oral Premalignant Lesions with Poor Outcome. Cancer Res. 2005, 65, 8017–8021. [CrossRef]