"USE OF NARROW BAND IMAGING IN ENDOSCOPIC EVALUATION OF ANGIOGENESIS IN LARYNGEAL LESIONS- A ONE YEAR OBSERVATIONAL STUDY IN DR. PRABHAKAR KORE HOSPITAL"

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Dr. ANIL. S. HARUGOP M.S., Ph.D.
Professor & Head of department
Department of Otorhinolaryngology
and Head & Neck Surgery,
J.N.Medical College,
Nehru Nagar,
Belagavi -590010

Date:

Place: Belagavi

Dr. (Mrs)N.S. MAHANTSHETTI M.D.
Principal
J.N.Medical College,
Nehru Nagar,
Belagavi -590010

Date:

Place: Belagavi

PLAGIARISM CERTIFICATE

KLE

JAWAHARLAL NEHRU MEDICAL COLLEGE

(Recognized by Medical Council of India, New Delhi)

Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)

Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 - 2471350 0831 - 2470759 www.jnmc.edu principal@jnmc.edu

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Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BE0119006.
Postgraduate Student,
2019-20 Batch,
Department of ENT,
J. N. Medical College, Belagavi.

LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	WLI	White Light Imaging
2	NBI	Narrow Band Imaging
3	H&N	Head and Neck
4	SCC	Squamous Cell Carcinoma
5	IPCL	Intraepithelial Papillary Capillary Loop
6	Dlscopy	Direct Laryngoscopy
7	Hb	Hemoglobin
8	&	And
9	RGB	Red Green Blue
10	LP	Lamina propria
11	Inf	Inferior
12	CIS	Carcinoma In situ
13	VC	Vocal cord

ABSTRACT

TITLE-"USE OF NARROW BAND IMAGING IN ENDOSCOPIC EVALUATION OF ANGIOGENESIS IN LARYNGEAL LESIONS -A ONE YEAR OBSERVATIONAL STUDY IN DR. PRABHAKAR KORE HOSPITAL"

BACKGROUND - NBI is a Biologic Endoscopy which works by evaluating biological behaviour of targeted lesions and allows a clearer distinction between malignant lesions, their precursors and also non malignant lesions. Lesions invisible on WLI are also sometimes highlighted and seen. NBI evaluates neo angiogenesis of a lesion thereby minimizing unnecessary need for biopsies and histopathological evaluation. Angiogenesis is process of forming new blood vessels. For growth of tumour cells and their metastatic growth, development of vascular network is important since cancer cells have high metabolic need and require good availability of nutrients and oxygen. [8] Therefore neoangiogenesis is key in allowing growth and spread of tumours. It's a sign of how far a tumour has progressed, and in H&N SCC, its role has been investigated.

New vessels formed through tumour angiogenesis arise from other vessels and exhibit irregular patterns and branching. Characteristic changes are variations in appearance of vessels in superficial mucosa seen as "Intraepithelial Papillary Capillary Loop" (IPCL). These are evaluated with help of NBI in order to look for angiogenesis.

OBJECTIVE- To evaluate role of narrow band imaging in diagnosis of various laryngeal lesions.

MATERIALS & METHODS- This is an observational study conducted in the Department of ENT & HNS, KLES Dr. Prabhakar Kore Hospital, Belagavi from January 2020 to December 2020. All patients with suspected laryngeal lesions, more than 18 years of age, that come to department of otolaryngology H&N surgery. underwent conventional WLI in OPD in sitting position.

- Suspicious lesions were identified on WLI by color change (leukoplakia, demarcated red lesions) & mucosal surface irregularities (growth, protrusions, and ulcer formation).
- NBI was performed immediately after WLE. All images, for purpose of studying later were computer saved.
- Histopathological co relation done, wherever required.

RESULT- 78 patients enrolled in our study out of which 76 patients got NBI done following WLI, Out of 76 patients , 45 patients (59.21%) were males and 31(40.79%) were female patients. Male: female ratio in patients with laryngeal lesions was seen to be 1.5:1. In our study it was seen that 32/76 patients (42.11%) had no underlying co morbidities or history of any habits. Amongst the underlying co morbidities, it was seen that voice abuse and history of smoking were most common (13.16% each) followed by GERD (9.21%) and voice overuse (7.89%). White light endoscopy performed for all patients revealed that vocal polyp (40.79%) were highest in number, then vocal nodules (22.37%), suspicious malignant lesion (13.16%), chronic laryngitis (11.84%) and then tubercular laryngitis (3.95%). Co relation between histopathological findings and patterns of NBI showed that. Inflammatory mucosa on HPR showed type 1 pattern in 25% patients, type II in 50% patients and type III in 25% patients. Vocal cord polyp with no dysplasia showed normal pattern in 42.86%

patients, type I in 14.29% patients and type II in 42.865 patients. All Inflammatory polyps showed type II pattern. Polyps with mild dysplasias showed type II in 70% patients and 10% each in type I . III and V. Polyps with moderate dysplasias showed 57.14% patients having type II & 42.86% with type III pattern. Mild mucosal dysplasias showed type II pattern in 66.67% patients and type III in 33.33% . Severe dysplasias showed type IV pattern in 66.67% and type III in 33.33%. Vocal nodules showed 71.43% having type I , 28.57% type II. However nodules with mild dysplasia showed type II pattern in 100% patients and type III pattern in moderate dysplasia.

CONCLUSION- Growth and progression of tumours requires "Angiogenesis". It is a hallmark of tumor progression.[9] Inflammatory lesions and pre malignant lesions also undergo angiogenesis through various mechanisms and this neoangiogenesis can help in determining their malignant potential.

NBI is a very novel kind of endoscopic techniques and is quite unique in its ability to identify the microvascularization pattern of various lesions. Narrow Band Imaging identified laryngeal lesions and their angiogenic properties with high accurancy in our study. Histopathological co-relation demonstrated that NBI correctly identified neoangiogenesis in inflammatory and precancerous lesions. Its main role is seen in such lesions only so that we can plan early detection.

KEYWORDS- WLI , NBI , Angiogenesis , Laryngeal lesions

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INTRODUCTION

Early detection of laryngeal lesions requires reliable and advanced diagnostic tools. Over years there has been advancement of lighting systems and camera system allowing better visualization of laryngeal lesions. However it is very challenging to tell difference between benign and malignant lesion in many cases.(1) Benign and malignant laryngeal lesions are diverse diagnostic entities. 2:3 is ratio of benign versus malignant lesions. (2)

Patients with head and neck malignancies tend to present very late because of multiple hidden areas in H&N. (3) Small changes that occur in epithelium during early phase of disease are usually not seen and thus not diagnosed early. If lesions are detected till they are limited to vocal folds, they have a very good prognosis.(4)

White light imaging (WLI) plays crucial role in detecting H&N cancers and surveillance evaluation post treatment. However, less than 1 cm lesions are sometimes not seen on WLI.(1) Therefore for improving detection of various cancerous or precursor lesions , early, new methods of imaging had to be developed. (5)

Biologic Endoscopy is a recent advancement. It works by evaluating biological behaviour of targeted lesions and allows a clearer distinction between malignant lesions, their precursors and also non malignant lesions. Lesions invisible on WLI are also sometimes highlighted and seen.(6) Autofluorescense, chemiluminescence, toluidine blue , contact endoscopy and Narrow band imaging (NBI) are available biological tools. Characteristics of a tumour and its precursor lesions, like neoangiogenesis, can be assessed by these novel techniques and made use of for predicting cancerous potential of various lesions.

“NBI evaluates neo angiogenesis of a lesion thereby minimizing unnecessary need for biopsies and histopathological evaluation.”

NBI provides contrast of vessels and their enhancement at surface of mucosa. Its technology uses two techniques. Firstly, different wavelength of light allow different penetration depth and secondly light of 415 & 540 nm is specifically absorbed by haemoglobin.[1]

In NBI mode, narrowband light of 400±430 nm and 525±555 nm passes through an optical filter provided by an arc lamp of xenon along with a while light filter. So RGB broadband light, each narrow bandwidth of light is sequentially illuminated. Lights' depth penetration is determined by its wavelength; wavelengths' which are short get reflected and scattered superficially, allowing accentuation of epithelial architecture.[7]Haemoglobin absorbs green and blue light maximum, allowing optimal view of superficial mucosa capillaries & vessels.

Angiogenesis is process of forming new blood vesssels. For growth of tumour cells and their metastatic growth, development of vascular network is important since cancer cells have high metabolic need and require good availability of nutrients and oxygen. [8] Therefore neoangiogenesis is key in allowing growth and spread of tumours. It's a sign of how far a tumour has progressed, and in H&N SCC, its role has been investigated.[9] Inflammatory lesions and precursor lesions of malignancy also undergo angiogenesis through various mechanisms and this neoangiogenesis can determine their malignant potential.

New vessels formed through tumour angiogenesis arise from other vessels and exhibit irregular patterns and branching. Characteristic changes are variations in appearance of vessels in superficial mucosa seen as "Intraepithelial Papillary Capillary Loop" (IPCL). These are evaluated with help of NBI in order to look for angiogenesis.[1]

OBJECTIVE

To evaluate role of narrow band imaging in diagnosis of various laryngeal lesions

REVIEW OF LITERATURE

3.1 History of Laryngoscopic examination

Laryngology has grown over the years due to the constant advancement in visualisation of the larynx through newer imaging modalities. In 1807, Phillip Bozzini tried to develop a tool for visualisation of the orifices in the human body. It was called 'Lichtleiter' and consisted of a handle that could incorporate candle along with a reflector to act as a source of light. He also used it for visualisation of the larynx, but required an extra mirror [10]

Figure 1: Lichtleiter as described by Phillip Bozzini

This was tried and tested for few years till Babington in 1829 developed and used ' glottoscope'. It was 1st time an instrument specific for laryngeal visualisation was used . The instrument had many mirrors and a spatula to tackle tongue base. Device was 1st to allow internal and enhanced view of glottis [11]

Babington's work was followed by Avery in 1844. He created a laryngeal cannula that was comparable to Bozzini's, but he used a separate artificial source of light by wearing light on his head. His ingenious invention used mirror, which was concave in nature, that was perforated allowing reflection of light into oropharynx, making it easier to see larynx. As accurate laryngeal imaging was yet to be discovered. Horace Green tried to solve problem of insufficient laryngeal vision, all his career, but with not much success. Transoral injection of caustics was used by him to try and provide treatment to various laryngeal membranes' illnesses [(12)(13)].

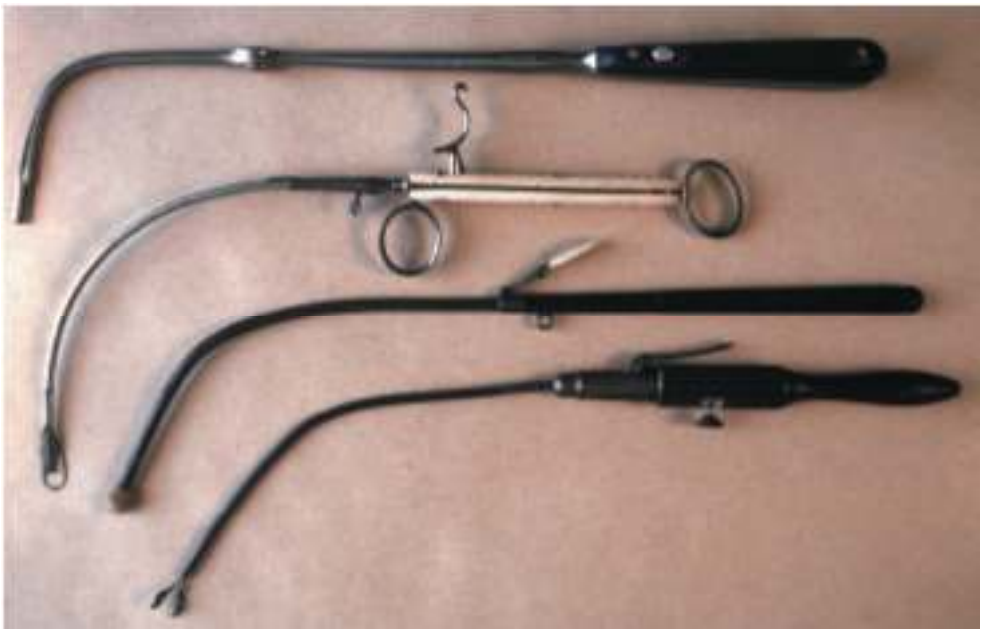


Figure 2: Evolution of laryngeal endoscopes over time

Green's most important contribution to laryngology came in 1852, when he described – Dlscopy, 1st time, and performed removal of a laryngeal tumour. He visually controlled the removal[(10)] Sunlight provided light for doing direct laryngoscopy, initially.[(14)]

Figure 3: Sir Alfred Kirstein using his autoscope

After electricity had been introduced, Kirstein utilised a light on his head, in using his first, spatula of autoscope. He then created a handpiece which could be electrified. It had a prism for providing light distally and an incandescent bulb giving illumination in proximal part. Jackson, eventually used detachable electrified light-carriers to provide distant lighting. In 1962, Broyles was first to demonstrate benefit of fiberoptic light transmission in peroral endoscopy but its use in larynx was not demonstrated.[16][17]

Around similar time,surgical microscope's extra light improved direct laryngoscopes' lighting . Since then, there has been no significant change.

Colleagues of Sawashima were 1st to disclose laryngoscopy using a flexible type of fibreoptic in 1968.[18] Flexible transnasal laryngoscopy was tolerated much better than a rigid type of transpharyngeal one, which was a significant advancement in laryngology. [10]

Biologic Endoscopy is a recent advancement. It works by evaluating the biological behaviour of targeted lesions and allows a clearer distinction between malignant lesions, their precursors and also non malignant lesions. Lesions invisible on WLI are also sometimes highlighted and seen.(6) Using autofluorescense, chemiluminescence, toluidine blue , contact endoscopy and Narrow band imaging (NBI) are available biological tools. Characteristics of a tumour and its precursor lesions, like neoangiogenesis, can be assessed by these novel techniques and made use of for predicting the cancerous potential of various lesions. NBI is a novel technique which evaluates neo angiogenesis, a process seen in malignant conditions and its precursor lesions. It thereby minimizes unnecessary need for biopsies and histopathological evaluation.

NBI had been 1st proposed in May 1999 by Dr. Kazuhiro Gono , Olympus Corporation's Department of Technology of of endoscopy in Tokyo, Japan. 2004 was when it was used clinically for 1st time.(19)

Endoscopy under white light only looks at mucosal lesions macroscopically. Biologic endoscopy procedures, on the other hand, can provide more information about a target lesion's behaviour and allow viewing of lesions that aren't apparent otherwise on WLI. (20)

3.2 NBI and Neoangiogenesis

NBI had been 1st proposed in May 1999 by Dr. Kazuhiro Gono , Olympus Corporation's Department of Technology of endoscopy in Tokyo, Japan. 2004 was when it was used clinically for 1st time. (19)

Figure 4 : Narrow Band Imaging machine

NBI is newest of biological endoscopic procedures, and it differs from others by concenterating solely on organisation of microvascularisation of the lesions and not entire lesion. Its principles were studied thoroughy and developed, and it was first used in 2004 to evaluate cancers of stomach, rectum and oesophagus.[21][22]

After identifying lesions of hypopharynx in people with oesophageal cancers, NBI's use was identified in larynx [23]. It has recently been used in pulmonary medicine to diagnose "Angiogenic squamous dysplasia", which preceeds pulmonary cancer.[24] NBI identifies dysplasias and precursors of malignancies by identifying vascular pattern and ' angiogenesis'

Tumour bed usually recruits adjacent blood arteries and endothelial cells to supply nourishment and other requirements to proliferating tissue. **Thus, "neovascularisation through angiogenesis, formation of 56 new blood vessels from pre-existing ones" is one of the hallmarks of cancer**. Serpentine, undulating, coiling, erratic flow of blood, junction enlargement, and an interrupted / nonexistent basement membrane zone are all hallmarks of these arteries formed by process of angiogenesis.[25]

More convoluted veins leads to slower flow of blood causing RBCs carrying Hb to congregate. When outer surface blood veins of .true cord run transversely rather than longitudinally, it is thought to be a feeding vessel for various tissue alterations such as cystic changes, polypoidal changes and also cancers. If they grow more tangled, it indicates that pathology has progressed. Intraepithelial papillary capillary loop (IPCL) will spiral as a result of alterations in vascular pattern caused by carcinogenetic stimuli.

For example in recurrent respiratory papillomatosis, these IPCL will take appearance of wide angled turning points, symmetrically placed loops seen as dots , in association with turning points which are narrow angled in pre-cancerous situations, & randomly organised in those which appear cancerous. [26] As with any other biological approach, diagnosing hyperkeratotic lesions is a significant problem since they might mask vascular pattern, which is underlying. However, by carefully examining pattern of vasculature, through an effect, known as umbrella effect [27], they cannot be overlooked. It assesses neoangiogenic shapes & organisation.

Therefore, since > 90% of tumors of larynx with malignant nature develop from precancerous epithelial lesions, proper cure and function-preserving therapy requires prompt. Majority of laryngeal lesions show a variety of epithelial changes

and may manifest at different levels of dysplasia – diagnostic methods are required for identifying the biological behaviour of these lesions. [28] NBI provides this assessment by selectively assessing biological behaviour of lesions.

3.3 Principles of NBI: [19][29][30]

Wave – Particle duality is a unique aspect of light. It has a wavelength, which is, in each wave, distance that is in between two peaks. Wavelength determines how deep light may penetrate into particular tissues. It is also influenced by its scattering and absorption characteristics. Between wavelengths of 400 and 700 nm, visible spectrum exists. Visually, various wavelengths are viewed as different colours. When the light has a wide bandwidth, it seems white.

Light of different wavelengths behaves differently in biological tissues. Some of light that strikes a surface is reflected, while others diffuse into it. It scatters in numerous directions and propagates three-dimensionally as it enters tissue & tiny particles come in contact with it as. Part of dispersed light is also absorbed by blood. Broad band is narrowed from RGB using an optical filter that absorbs all but two bands, one between 400 and 430nm and other between 525 and 555nm, by sliding in and out of optical axis.

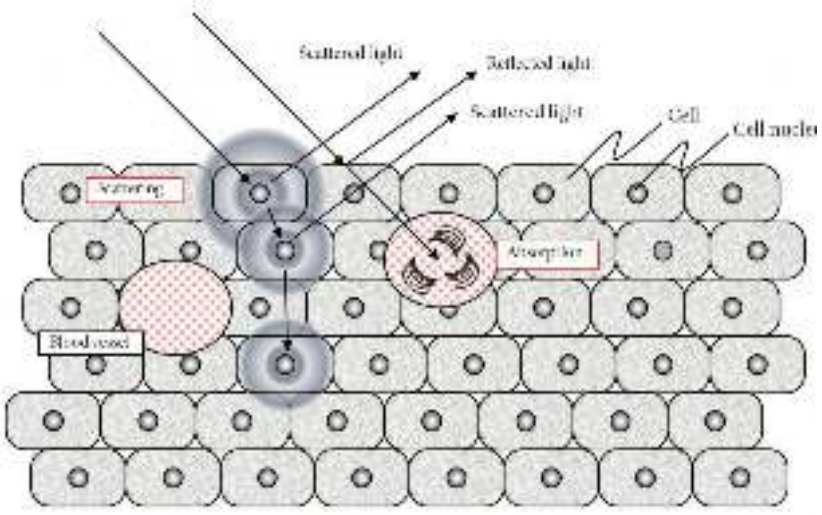


Figure 5 : Scattering and absorption in tissue

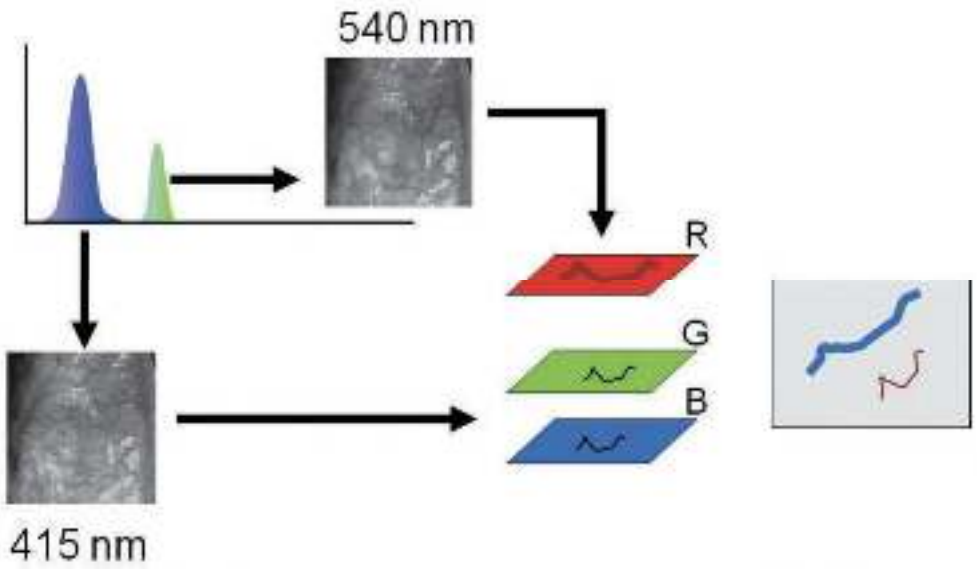


Figure 6: Colour allocation of NBI

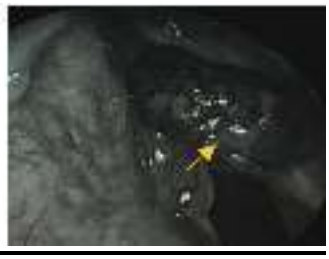
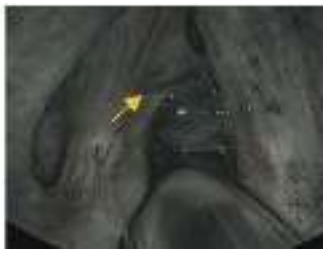
Eventual colour created is not same as traditional colour due to NBI's unique colour allocation rules. Blue filter is first band, which is centred at 415nm. Display with blue & green channel are assigned to it, it goes only upto surface mucosa & capillaries of brown colour. Display with red channel transmits another band centred at 540nm, via green filter. It allows penetration of layer underneath mucosa and displays thick conspicuous, blue BVs [(29)]

Ni et al. investigated these vascular patterns in larynx, which they called "Intraepithelial papillary capillary loop"(IPCL). A classification system was put forward, dividing appearance of vessels into five categories ranging from what appears normal to cancerous modifications [(26)]. Extent of damage of these IPCL patterns aids in determining depth of tumour invasion. [(31)]

So any alteration in pathology of epithelium of vocal cord, or it's lamina propria layer may be seen now using current evaluation methods. [(32)]

Papilloma, leukoplakia, and cancers are examples of epithelial abnormalities. Diffuse lesions, such as Reinke's edoema, or specific lesions, such as nodules, polyps,

cysts, scars, webs, varices, and ectasias, can occur within the lamina propria. Granuloma is the most frequent benign arytenoid lesion.

Type I : Thin, oblique and arborescent vessels are interconnected ICPLs are almost invisible		
Type II : Diameter of oblique and arborescent vessels is enlarged ICPLs are almost invisible		
Type III : ICPLs are obscured by white mucosa		
Type IV : ICPLs can be recognised as small dots		
Type Va : ICPLs appear as solid or hollow, with a brownish, speckled pattern and various shapes		

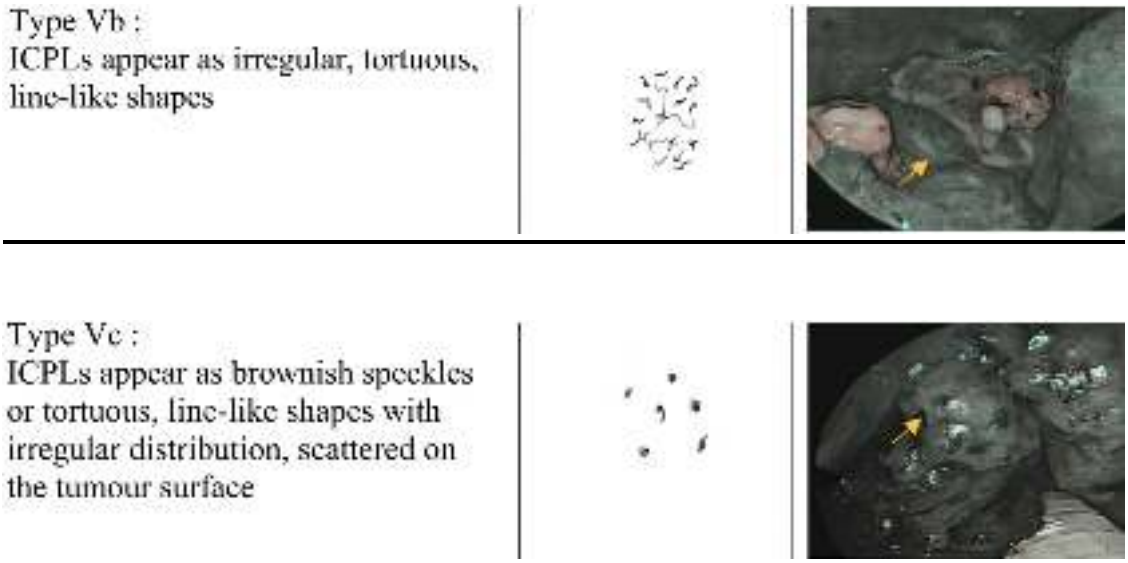


Figure 7 : Ni et al classification of vascular patterns

3.4 Anatomy of Larynx

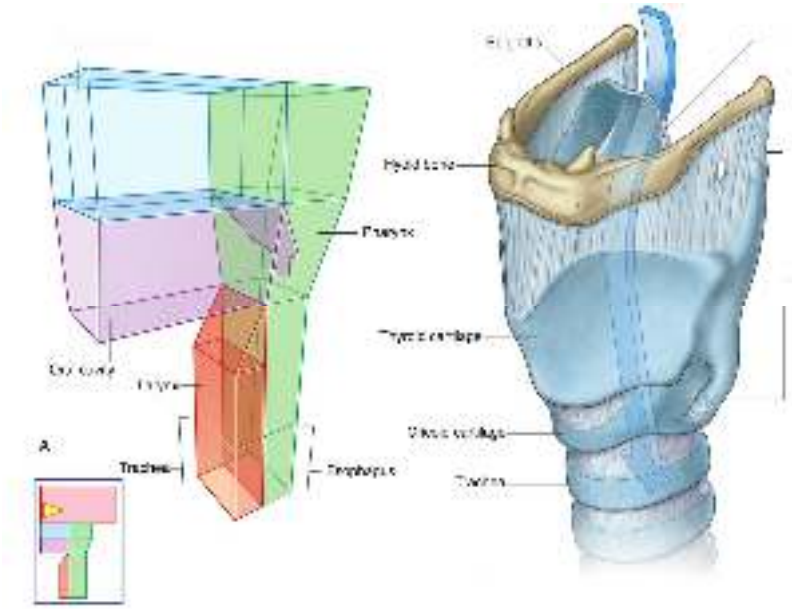


Figure 8: Structure of Larynx

Human larynx is a musculo ligamentous organ with a framework made of cartilage that forms an entry to the lower respiratory tract. In the absence of

respiration at neutral lung volume, it lies in front of 3rd to 6th cervical vertebrae and is slightly higher in women. (33)

The laryngeal cavity is connected to the trachea below and opens into the pharynx above. Larynx is sphincter that closes lower tract of respiration and is a sound-producing organ in humans.

3.4.1 Embryology of the larynx(34)

There are three stages to laryngeal growth

1. Organogenesis begins throughout embryonic phase [0-8 weeks].
2. Foetal phase [13-26 weeks], during which developed organs mature.
3. Post-natal period during which larynx descends

Larynx begins as a slit-like groove in pharynx floor during development. Epiglottis develops anterior to this slit from ventral ends of third and fourth branchial arches. Sixth branchial arches generate arytenoids laterally to this swelling. Laryngeal cartilages are formed from ventral fourth and fifth arches. Buccopharyngeal anlage gives rise to supraglottic larynx, whereas trachea pulmonary anlage gives rise to glottic (each side independently) and subglottic sections.

Lymphatics follow this pattern with areas above ventricle, draining superiorly through thyrohyoid membrane and areas below ventricle draining inferiorly through cricothyroid membrane to regional lymph nodes. **This embryology forms rationale for the vertical partial laryngectomy, and the supraglottic horizontal laryngectomy**. **However, midline development of epiglottis necessitates need for b/l dissection of neck for malignancies above glottis.**

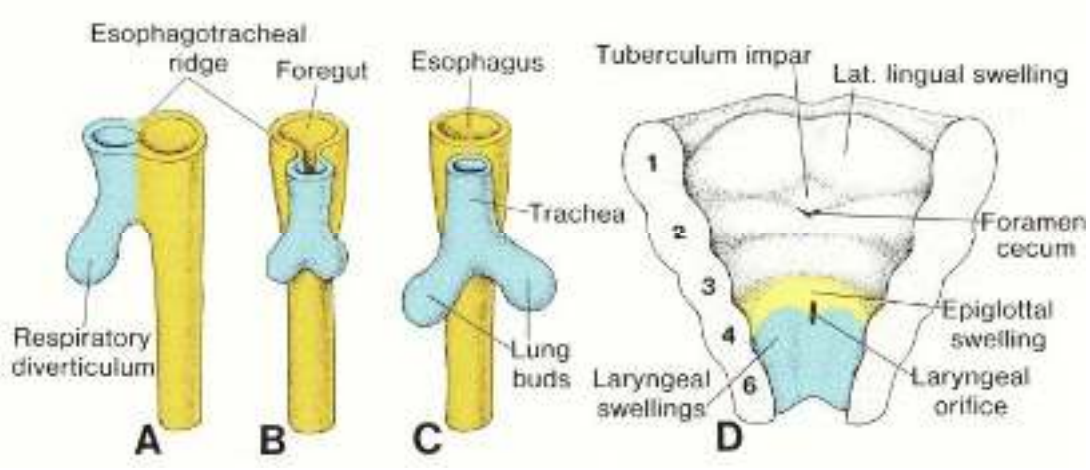


Figure 9: Embryology of Larynx

3.4.2 Cavity of the larynx [33]

Larynx's core cavity is tubular and coated with mucosa. Larynx' membrane which is fibroelastic, as well as, its cartilages, offer structural support. Just below and posterior to quadrangular membranes, into anterior aspect of pharynx, opens the larynx, superiorly. Underlying cuneiform & corniculate cartilages are marked on each side of inlet as tubercles.

Mucosal fold generates a dip (inter arytenoid notch) between two corniculate tubercles, forming its posterior boundary in midline.

Inferiorly larynx continues into trachea, lies horizontally and cricoid cartilage rings around it. Furthermore, inferior entrance never closes however its closes after epiglottis moves lower.

3.4.3 Regions of Cavity of larynx[33]

Projecting from medial wall of cavity of larynx are mucosal folds – vestibular and vocal. They divide larynx into

- Btw inlet of larynx & vestibular folds, Vestibule is present. It's laryngeal cavity's upper chamber.

- Between vestibular folds above and vocal folds below, **is laryngeal cavity's central region.**
- **Infraglottic space,** inferior most part forming larynx, lies btw inferior aperture and folds of larynx.

3.4.4 Laryngeal mucosal lining [35]

- Laryngeal mucous membrane is prone to edema and is weakly connected in other areas.
- Mucous glands are found throughout mucous lining of larynx, with a concentration on posterior portion of .epiglottis, aryepiglottic fold's lower area, & saccule.
- In supraglottis, posterior section of glottis, and subglottis, lining of mucosa is mostly, pseudostratified ciliated columnar epithelium.
- Other areas have non keratinized ssquamous type epithelium.

3.4.5 Laryngeal Folds: [36]

These are vital in voice generation & protection of human airway.

- Vestibular folds - These .are two mucosa-covered pink-colored folds. They join to epiglottis under the thyroid cartilage angle and posteriorly go upto arytenoid's antero-lateral surface. They function primarily to protect airway.
- True folds – They are vibrator of phonation. Are whitish structures that runs from central party of the thyroid cartilage's angle to arytenoid cartilage's vocal process. Muscles of phonation abduct, adduct, relax, and tension them to alter sound's pitch.
- Ventricle is space between true & false cords.

3.4.6 Structure of vocal fold

Vocal folds - flat white folds that runs between thyroid cartilage and arytenoid. The difference in pitch is due to differences in length and thickness btw men & women. Men have longer and thicker folds.

A line travelling across tip of the vocal process divides human vocal folds into two sections: Membranous portion-anteriorly, which contains ant 2/3rd, & post inter cartilaginous region, which includes post 1/3rd.

Human voice folds have a laminar structure which was explained by Hirano in 1974. Vocal fold is a laminated structure with five layers. Primary mass is created by vocalis muscle, which is coated by mucosa-epithelium & lamina propria are contained within it. Mucous lining's outermost layer is made up of -non-keratinized sstratified squamous epithelium, with no glands secreating mucosa. These cells are homogeneously arranged, have a nucleus that is spheroid in shape & ratio between nucleus & cytoplasm. Basement membrane zone secures epithelial lining tono cell containing lamina propria. Lamina also divided in 3 layers based on extracellular matrix content: superficial, middle, and deep.

3.4.7 Mucociliary layer[36]

Over epithelium is a mucociliary blanket layer. It is made up of two layers: a layer of mucin & a serous type layer. Mucinous layer consists of a, viscous, thick consistency .mucin that aids in hydration & protection of layer above it, keeping vocal fold healthy. Cilia can flow freely because above serous layer has low viscosity with high fluid. Beating of cilia is in a circular motion posteriorly and superiorly in lower airway, reaching posterior glottis. This passes through glottis' squamous epithelium until it reaches lateral to free edge of vocal cord, pushing it posteriorly until swallowed.

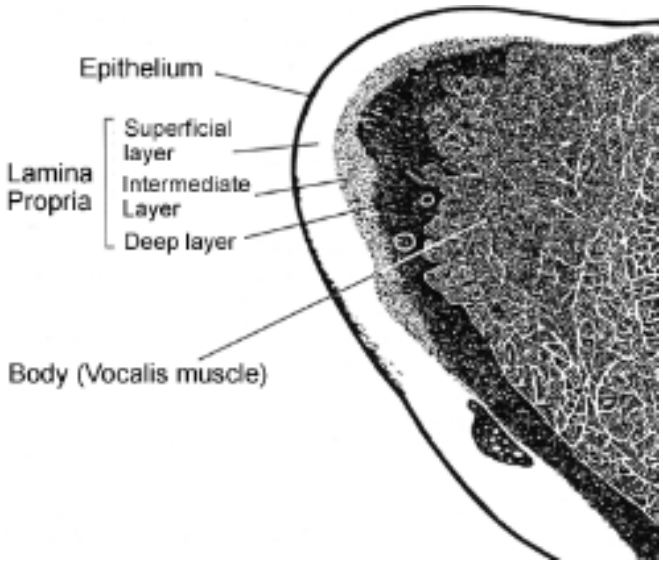


Figure 10: Zone of Basement membrane

Desmosomes, collagen IV, and VII are amongst varied components constituting zone of basement membrane.

They help anchor epithelium & LP during vocal fold vibration. "Lamina lucida, lamina densa, and zona reticularis" are three zones that make up this zone. Largest shearing stresses occur in this location during vocal fold vibration. Strength of collagen is genetically determined. This explains predisposition of some to disorders of vocal cord.

LP: [36][37]

Three layers of LP, rich in collagen & elastin, are classified as functionally relevant. The lamina propria's superficial layer (SLP), called "Reinke's space", includes a gelatin-like fibrous component, making it exceedingly loose and malleable, allowing for vibration.

Elastin is abundant in intermediate layers (ILP), while collagen fibres predominate in deep levels (DLP). **Vocal ligament is made up of the intermediate and deep layers.** Type I collagen fibrils produce support tissue that can withstand stress acting longitudinally with deformation resistance. "Elastin" gives tissue elastic

property & allows reverting to its natural shape if it becomes distorted. Cells and interstitial chemicals like hyaluronic acid, combine and form extracellular matrix-it fills gaps, resists forces which are shearing, encourages migration of cells & aids healing of any wound.

3.4.8 Histology of vocal folds[37]

"Fibroblasts, macrophages and tissue macrophages" - most common cells in LP. Fibro-blasts are uniformly distributed throughout lamina propria, maintaining its proteinaceous content and integrity.

Macrophages are found in zone of basement membrane and superficial layers of lamina propria, where they combat substances causing inflammation, at epithelial level.

Myofibroblasts- Differentiated fibroblasts, are cells for repair, that are always found in superficial lamina propria layer, mending microscopic injuries to vocal fold. As a result, any prolonged or serious injury to vocal folds is irreversible and becomes pathological.

Broyle's tendon is collagen fibres containing mass, attached to thyroid cartilage's inner side, near anterior commissure.

Bundles of elastic fibres run from anterior to posterior part of membrane component of folds of larynx, forming an in between layer called "anterior and posterior macula". These provide cushioning & shielding of ends of vocal folds from tearing force of vibration.

Due to slope up of inferior edge, near anterior commissure, fold of larynx become narrow. Here an apex is formed with. As a result, malignancies affecting anterior commissure also affect subglottis.

3.4.9 Vascular arrangement of the vocal fold: [38]

Capillaries make up surface LP, whereas venules & arterioles extend into deep layers of vocal cord's. Between arterioles and venules, there is direct connection. Muscle layer is well segregated from this arrangement. Vessels that travel down long axis of vocal cord enter from front or back. At arteriolar level, communication between vessels and their branching "anastomosis" in form of coiling, bending & serpentining is prominent. Reactive mechanisms can cause these vessels to become more conspicuous, increase in number, density, branching, and anastomosis.

3.5 Parts of larynx [36][39]

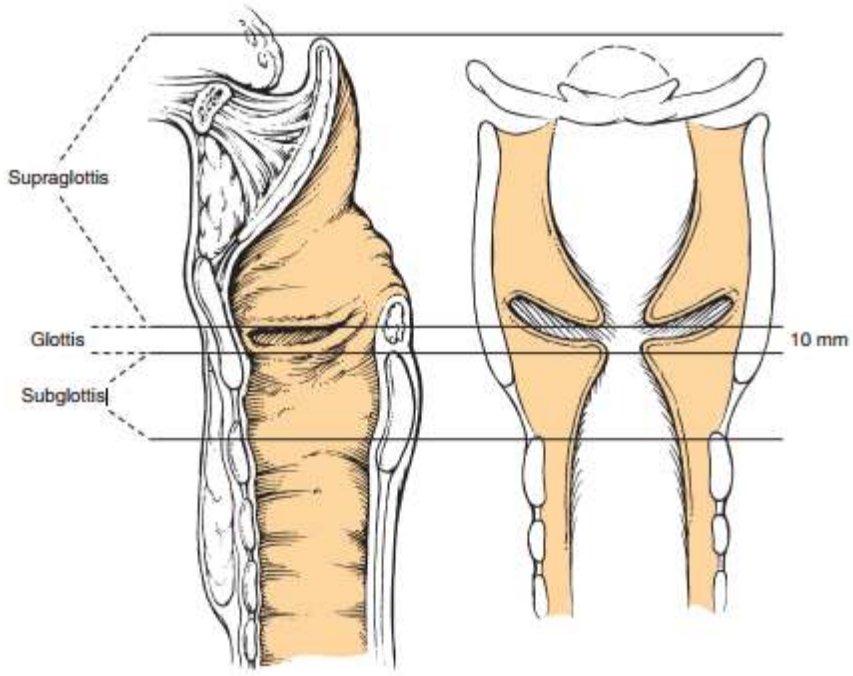


Figure 11: Divisions of Larynx

By demarcating lines, whole larynx is separated into Supra-glottis, glottis, and sub-glottis.

1. Supraglottis- Suprahyoid portion of epiglottis to demarcating line, is supraglottis, that runs along lateral margin of ventricle and meets superior surface of real cord at its connection.

2. Glottis continues 1 cm below demarcation line.

3. Subglottis is area btw inf limit of glottis & inf edge of .cricoid.

This division indicates embryological origins as well as a barrier against laryngeal cancer spread.

The pyriform sinus is an inverted pyramid that is posterolateral to the glottis. It restricted medially- fold between arytenoid & epiglottis, arytenoid, & superior cricoid, laterally by membrane between thyroid and hyoid and thyroid lamina's interior. It starts above at pharyngoepiglottic fold. Around roughly superior border of the cricoid, apex of sinus merges with inlet of oesephagus.

Within pyriform sinus, there are 32 two essential markings: anteriorly in the sinus floor, a little fold forms route of the SLN; and posteriorly in the sinus floor, a small fold marks the course of SLN.

The second, more changeable feature is the protrusion of thyroid cartilage's superior cornu into sinus. It shouldn't be mistaken for neoplasm.

3.5.1 Spaces of Larynx

Spaces in the larynx contain fat, lymphatics and vessels. They represent potential pathways of tumour spread that may have a significant bearing on treatment and prognosis.

1. Boyers pre-epiglottic space

Prior to epiglottis is pre-epiglottic Space (Of Boyer). Hyoepiglottic ligament binds it superiorly, thyroepiglottic ligament binds it inferiorly, membrane btw thyroid

and hyoid & inner surfaces of thyroid laminae bind it anteriorly, paraglottic gaps binds laterally. "**Cancer on infrahyoid part of the epiglottis can enter the preepiglottic area and acquire access."**

2. Paraglottic Space

Paraglottic area is crucial in trans-glottic & extra-laryngeal dissemination of neoplasms because of its anatomy-lateral to area both over and below vocal folds ."**Supraglottic cancer invading into this space may quickly extend extra laryngeally."**

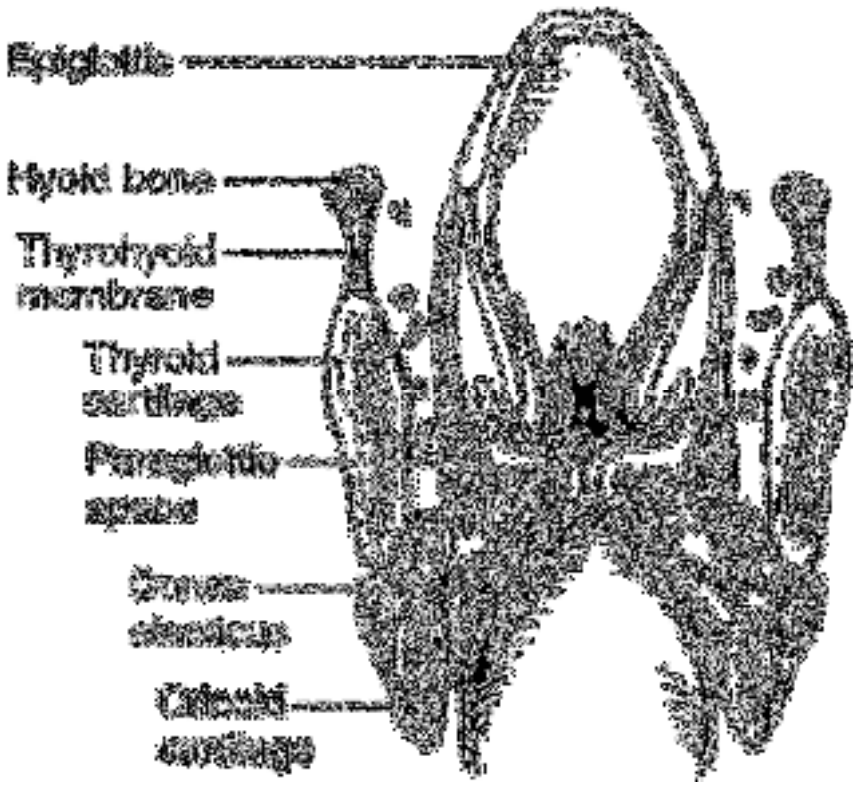


Figure 12: Cross section of Larynx

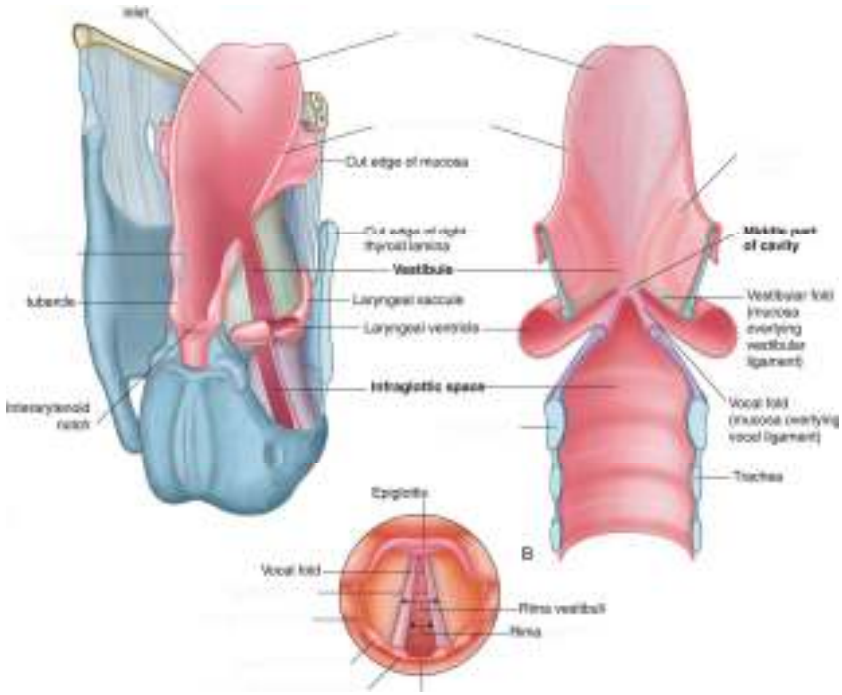


Figure 13: Spaces of Larynx

3.6 Vascular supply of larynx[36]

"Superior thyroid artery", is generally derived as branch of "external carotid artery", is frequently source of the superior laryngeal artery. Lingual and/or facial arteries can cause it in some uncommon circumstances. Directly from external carotid artery, it is seen to arise in roughly 20% of cases.

Inferior thyroid artery ascends, twists towards medial surface, and crosses behind deep ccervical, arteries & cranial nerve X on both sides of thyrocervical trunk of subclavian artery. It ascends along trachea to approach inferior pole of thyroid gland. Vessel and recurrent laryngeal nerve are quite near here; artery's inferior laryngeal branch follows nerve all the way to the larynx.

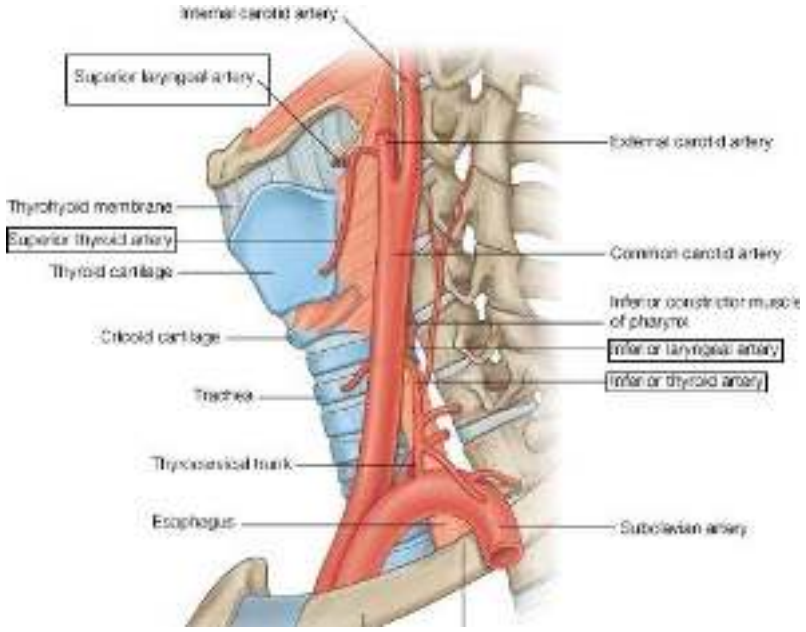


Figure 14: Vascular Supply of Larynx

3.7 Structural or neoplastic lesions of Larynx

3.7.1 Disorders of Lamina propria

3.7.1.1 Vocal fold polyps [40][41][42]

Men are more likely than women to have polyp of vocal cords, which is non malignant growth of > 3mm that develops in free edge of vocal fold. They're most common in smokers and people between ages of 30 and 50. A significant aetiological element is phonotrauma. Cigarette smoking can harm vocal cord, resulting in hyaline degeneration causing, thereby impacting closure of cords & modifications, such as increase in tension of muscles.

Patient usually report that their voice has become hoarse, that their pitch dropped, that their speech has cut out, that they have lost part of their vocal range, and that speaking is a burden.

After vocal nodules "1.0–1.7%", 2nd most common lesion of larynx seen were polyps "0.3–0.6%". Gnjatic et al investigated individuals having polyps & concluded -67.5 % patients had history of smoking with 59.0 percent reporting vocal abuse. Histological studies of polyps in the larynx has shown presence of protein " ADAM33". "**This disintegrin and metalloproteinase protein is linked to angiogenesis and tissue remodelling, and it could be a key role in development of chronic inflammation in the vocal folds**."

3.7.1.2 Nodules of vocal fold

Nodules are small (< 3mm in diameter) swellings, normally bilateral formed at mid membranous part. Their small, pointed, and white colour seen, notably in vocalists, is because they occur as a result of a trauma to cords that occurs superficially. After various hypothesis regarding nodules' occurrence, abuse of voice has been attributed. Forced speech production caused by increased stress in neck & shoulder region produces a harsh sound to voice, which is characterised as voice abuse.

3.7.1.3 Reflux Laryngitis

Both the voice cords and Sblood vessels are edematous. Pachyderma, a disorder characterised by increased mucosal tissue, edoema, and hypertrophy in arytenoids' area, is visible in the space behind the vocal cords.

3.7.1.4 Laryngeal hyperkeratosis

Chronic hyperplasia and hyperkeratosis of laryngeal mucosa, with resulting hyperkeratosis of vocal cord epithelium, causes laryngeal keratosis, an inflammatory condition of vocal cord epithelium. Cause is unknown, but it may be linked to smoking, alcohol, or acid reflux. Hoarseness is most common symptom.

Appearance is that of confluent or patchy white plaques. A white plaque that cannot be scraped off is known as leukoplakia in Greek. To rule out neoplasia or dysplastic lesions, a histological diagnosis is required. Although laryngeal hyperkeratosis appears to be a simple procedure, laryngologists know that it is prone to recurrence.

3.7.1.5 Sulcus Vocalis

A sulcus vocalis is a deep invagination of mucosa that occurs in a limited area. 'open cysts' may be used to characterise aetiology of these cysts. The reason attributed to this nomenclature is their frequent conjunction with epidermoid cysts, therefore any trauma to a cyst's neck causes its enlargement causing discharging of material within it.

3.7.1.6 Vocal fold granuloma:

This is caused by perichondritis, which can be caused by ET intubation or LERD and affects arytenoid cartilage's vocal process.

3.7.1.7 .Reinke's oedema.

It describes swelling of folds of larynx that is chronic and irreversible. Pseudomyxoma or pseudomyxomatous laryngitis, polypoidal degeneration/ polypoid hypertrophy are some other names for disorder. Chronic oedema of vocal folds causes it.

Reinke's edoema is caused by a buildup of gelatinous, mucinous material in Reinke's space, which is commonly linked to cigarette use, laryngopharyngeal reflux illness, and voice abuse.

3.7.2 Disorders of epithelium [43][44][45][46][47]

Papillomas, leukoplakia, and carcinomas are common epithelial abnormalities. Most major and extensive study has been done in this field, underlining their risk factors, the importance of early detection, and effective care.

SCC makes about 85-95 & of cancers of larynx. It's made up of stratified squamous epithelium that's gone through squamousal type of metaplasia.

As a result, premalignant lesions, such as "hyperplasia, keratosis, mild, moderate, or severe dysplasia, and carcinoma in situ (CIS)", as defined WHO, are of critical relevance. Their histological nature is not determined by their appearance. "Hyperkeratosis or parakeratosis" without atypia of cells / dysplasia can be seen in early lesions.

Loss of normal maturation and atypia of cells along with stratification characterise squamous cell dysplasia. Mild dysplasia affects just $1/3^{rd}$ of epithelium from basal surface, dysplasia of moderate nature affects $2/3^{rd}$ thickness of epithelium, and severe affects > $2/3^{rd}$ of epithelial thickness. "Carcinoma in situ (CIS)" / Intraepithelial tumour characterised by presence of carcinoma-like characteristics across epithelium without stromal or basement membrane disruption. Severe dysplasia and CIS biologically behave similarly and can thus be grouped together. Mild dysplasia has an 11 percent probability of malignant transformation, while severe dysplasia has a 30 percent risk. Average time span required in transforming between dysplasias & malignancy is determined around 3-4years, although it can be as long as ten years.

MATERIALS AND METHODS

Source of data

All cases of laryngeal lesions in ENT & HNS department in KLE Institute of Higher Education and Research Dr.PrabhakarKore Hospital during the study period of 1 year from January 2020-December 2020

Method of data collection

Study design- Observational Study

Study period- 1 year

Sample size (n)- 78

Minimum sample size formula based on prevalence is

$$n = \frac{z_\alpha{}^2 P(1-P)}{d^2}$$

percentage of prevalence is indicated by p

percentage difference in prevalenc is d

level of significance is linked to z_α. $z_\alpha = 1.96$ for 5% level of significance

With P = 44 & d = 25% of P = 11%, sample size is 78

Two patients dropped out of study. Final sample size 76

STATISTICAL ANALYSIS-

Since study is of observational study plan of analysis was as follows. For the continuous quantitative variables mean and standard deviation calculated.

In terms of rates, ratios and percentages categorical data was expressed. using Chi-square test, association between outcome, clinical and demographic characteristics tested.

Apart from above suitable tools like ANOVA, correlation, regression etc., will be used according to need.

For all tests, value of $p < 5\%$ (0.05) considered significant.

Ethical Considerations

Ethical clearance for the study was obtained from the JNMC Institutional Ethics Committee on Human Subjects Research and the reference number was MDC/DOME/308

Inclusion Criteria-

- All patients with suspected laryngeal lesions, more than 18 years of age, that comes to department of otolaryngology H&N surgery.

Exclusion Criteria-

- All those patients < 18 years age & already operated patients.

Procedure-

- All 76 patients that came to our OPD with history of laryngeal underwent conventional WLI in OPD in sitting position.
- Suspicious lesions were identified on WLI by color change (leukoplakia, demarcated red lesions) & mucosal surface irregularities (growth, protrusions, and ulcer formation).
- NBI was performed immediately after WLE. All images, for purpose of studying later were computer saved.
- Histopathological co relation done, wherever required.

RESULTS

78 patients enrolled in our study out of which 2 patients dropped out.76 patients got NBI done following WLI. Age of the patients that presented to us with history of laryngeal complaints ranged from 3rd to 7th decade of life, as seen in Table 1. 4th decade (35.53%) was the most common age of presentation followed by 5th decade (26.32%), 6th decade (23.68%) and only 14.47% patients in the 3rd decade of life, shown in graph 1. Mean age of patients presenting with laryngeal complaints to our OPD was seen to be 42 years of age.

Graph 1 : Distribution of patients by age groups

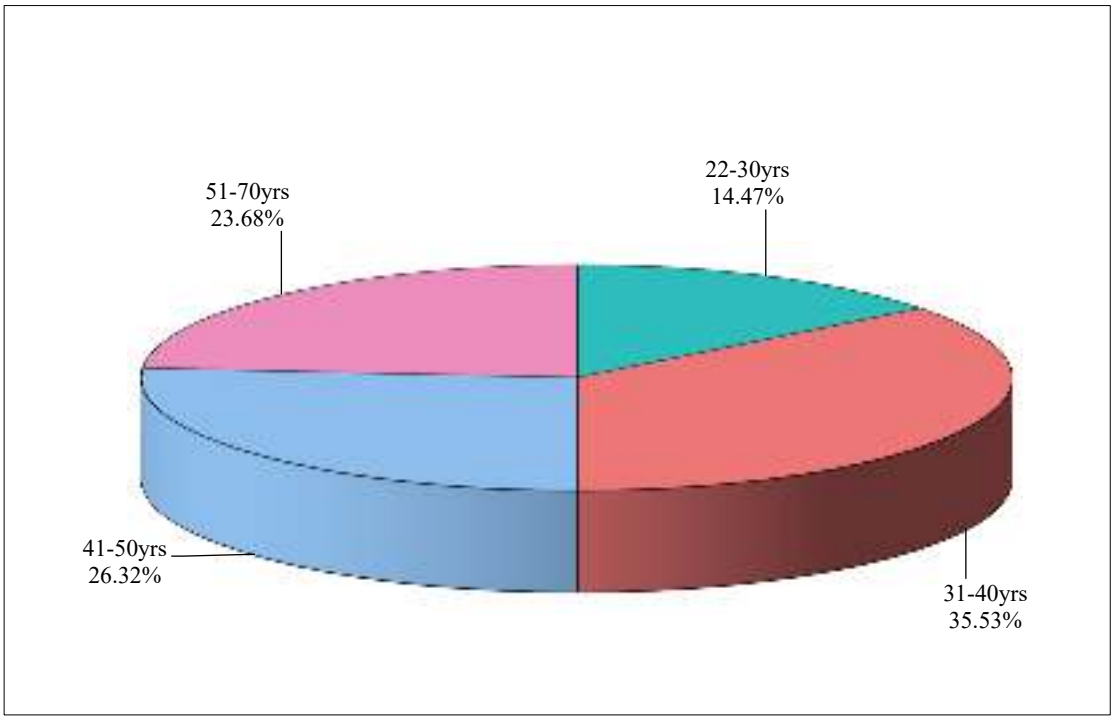


Table 1: Distribution of patients by age groups

Age groups	No of patients	% of patients
22-30yrs	11	14.47
31-40yrs	27	35.53
41-50yrs	20	26.32
51-70yrs	18	23.68
Total	76	100.00
Mean ± SD	42.92±10.96	

Out of 76 patients, 45 patients (59.21%) were males and 31(40.79%) were female patients. Male: female ratio in patients with laryngeal lesions was seen to be 1.5:1 as seen in Graph 2 and Table 2.

Graph 2 : Gender distribution of patients

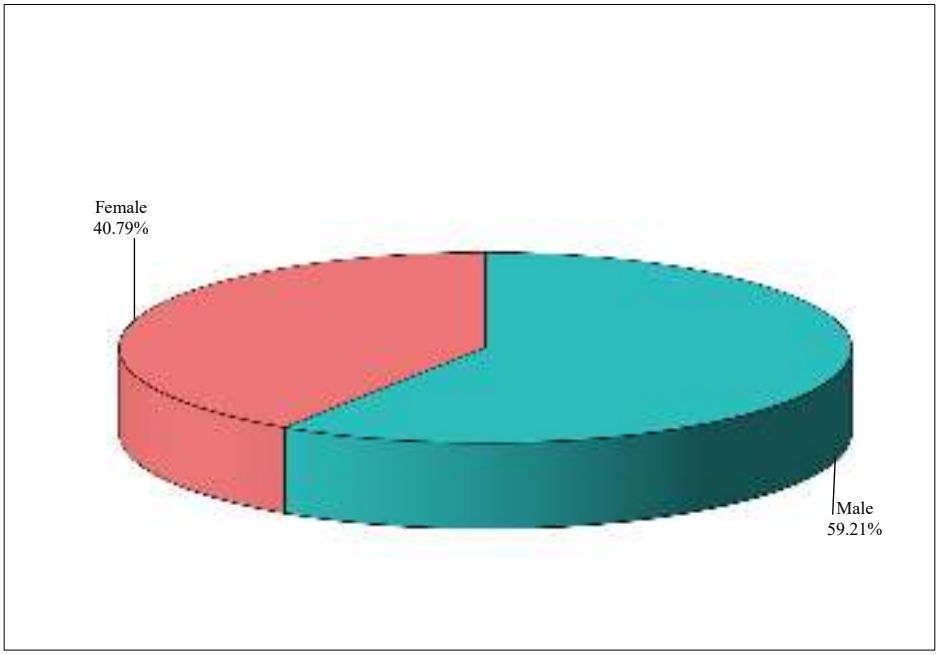


Table 2: Gender distribution of patients

Gender	No of patients	% of patients
Male	45	59.21
Female	31	40.79
Total	76	100.00

As shown in Table 3 and graph 3, In our study it was seen that 32/76 patients (42.11%) had no underlying co morbidities or history of any habits. Amongst the underlying co morbidities, it was seen that voice abuse and history of smoking were most common (13.16% each) followed by GERD (9.21%) and voice overuse (7.89%). Alcohol intake was a risk factor in 2.6% patients and smoking along with alcohol acted as a confounding factor with a total of 5.26% patients. 1.32% patients had chronic smoking along with gutka chewing and voice abuse as an underlying co morbidity. Voice overuse with GERD was seen in 2.63% patients.

Table 3: Distribution of patients by Habits/ Co morbidities

Habits/co-morbidities	No of patients	% of patients
Alcohol intake	2	2.63
Chronic smoker + Alcoholic	1	1.32
Chronic smoker with voice abuse	1	1.32
GERD	7	9.21
Smoker	10	13.16
Smoking+alcohol	4	5.26
Smoking+gutka chewer	1	1.32
Voice abuse	10	13.16
Voice overuse	6	7.89
Voice overuse+gerd	2	2.63
Nil	32	42.11
Total	76	100.00

Graph 3 : Relation between underlying comorbidity and laryngeal lesions

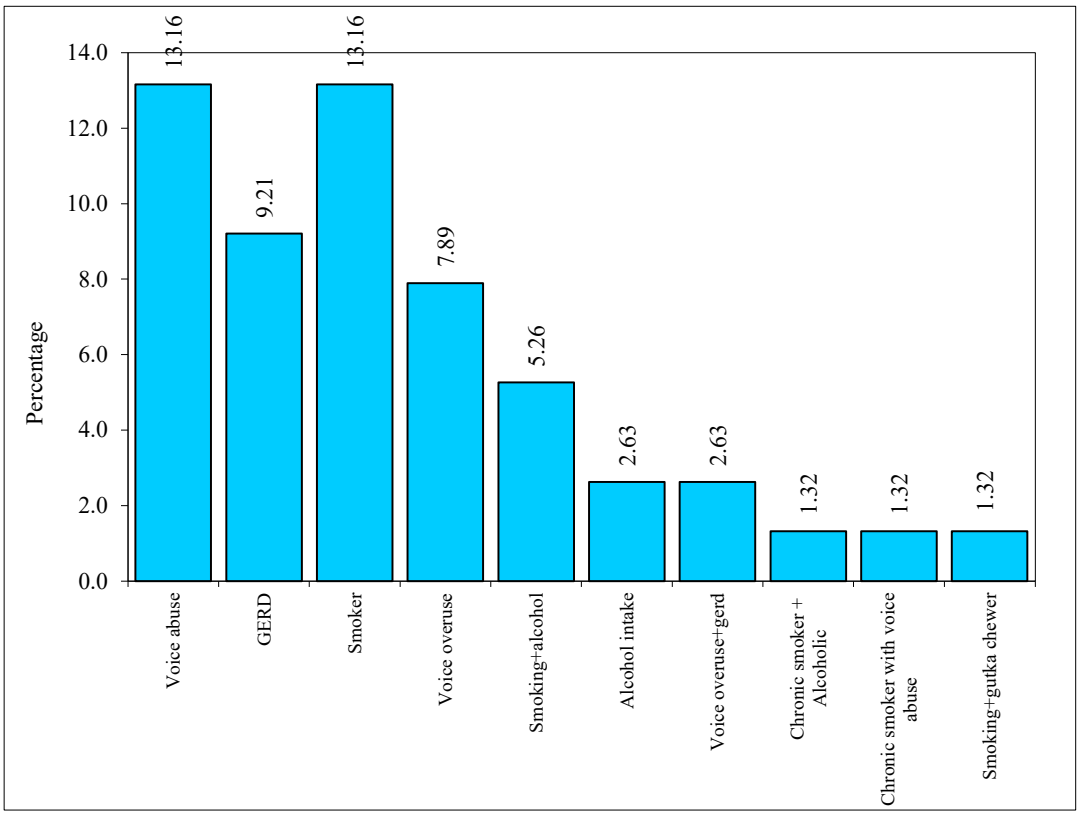
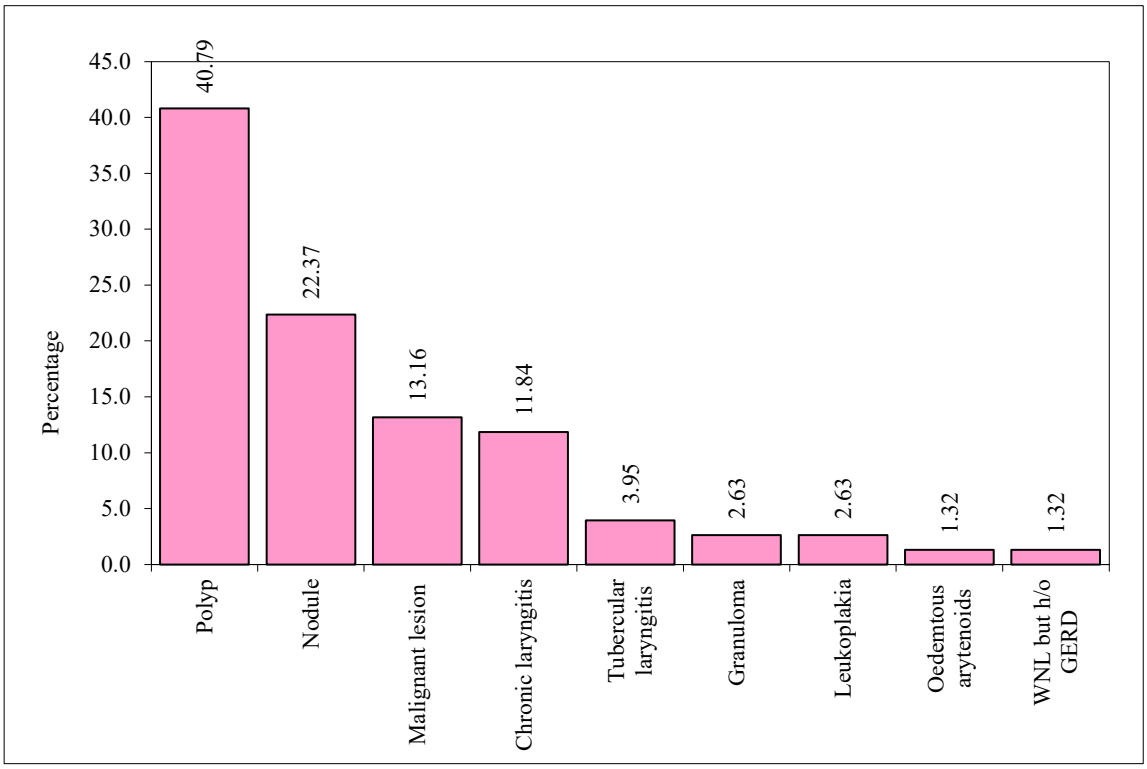


Table 4 shows white light endoscopy performed for all patients revealed that vocal polyp (40.79%) were highest in number, then vocal nodules (22.37%), suspicious malignant lesion (13.16%), chronic laryngitis (11.84%) and then tubercular laryngitis (3.95%). Only 2 patients presented with leukoplakia (2.63%), 2 patients with vocal cord granuloma (2.63%) and 1 patient with oedematous arytenoids (1.32%). In 1 patient (1.32 %) no lesion was seen on white light endoscopy.

Table 4: Distribution of patients by 70 degree Endoscopy findings

Endoscopy findings	No of patients	% of patients
Granuloma	2	2.63
Polyp	31	40.79
Nodule	17	22.37
Chronic laryngitis	9	11.84
Leukoplakia	2	2.63
Malignant lesion	10	13.16
Oedemtous arytenoids	1	1.32
Tubercular laryngitis	3	3.95
WNL but h/o GERD	1	1.32
Total	76	100.00

Graph 4 : Distribution of patients by 70 degree Endoscopy findings



In our study, graph 5 And table 5 shows Narrow Band Imaging patterns were studied, according to Ni et al classification, were categorised intointo 5 types [(26)] . It was observed that 46.05% lesions showed type II pattern, 18.42% had type I pattern. 13.16% patients had type III pattern. Type IV pattern observed in 10.53% patients and 7.89% patients showed type V pattern.

Table 5: Distribution of patients by NBI grades

NBI grades	No of patients	% of patients
Normal	3	3.95
Type 1	14	18.42
Type 2	35	46.05
Type 3	10	13.16
Type 4	8	10.53
Type 5	6	7.89
Total	76	100.00

Graph 5: Distribution of patients by NBI grades

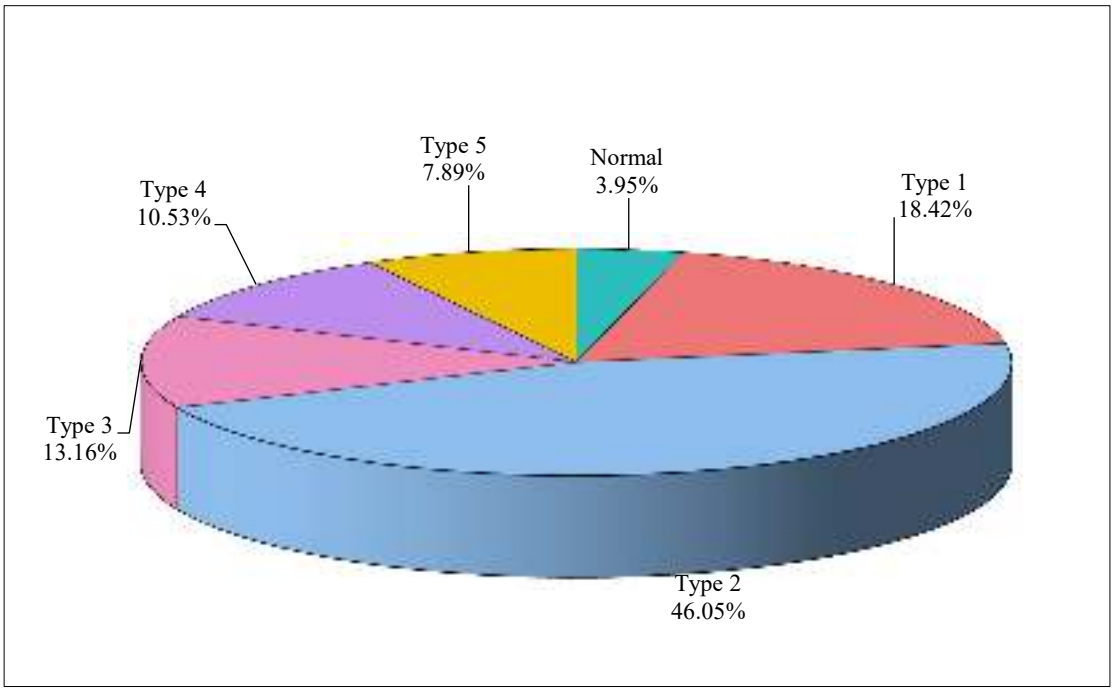
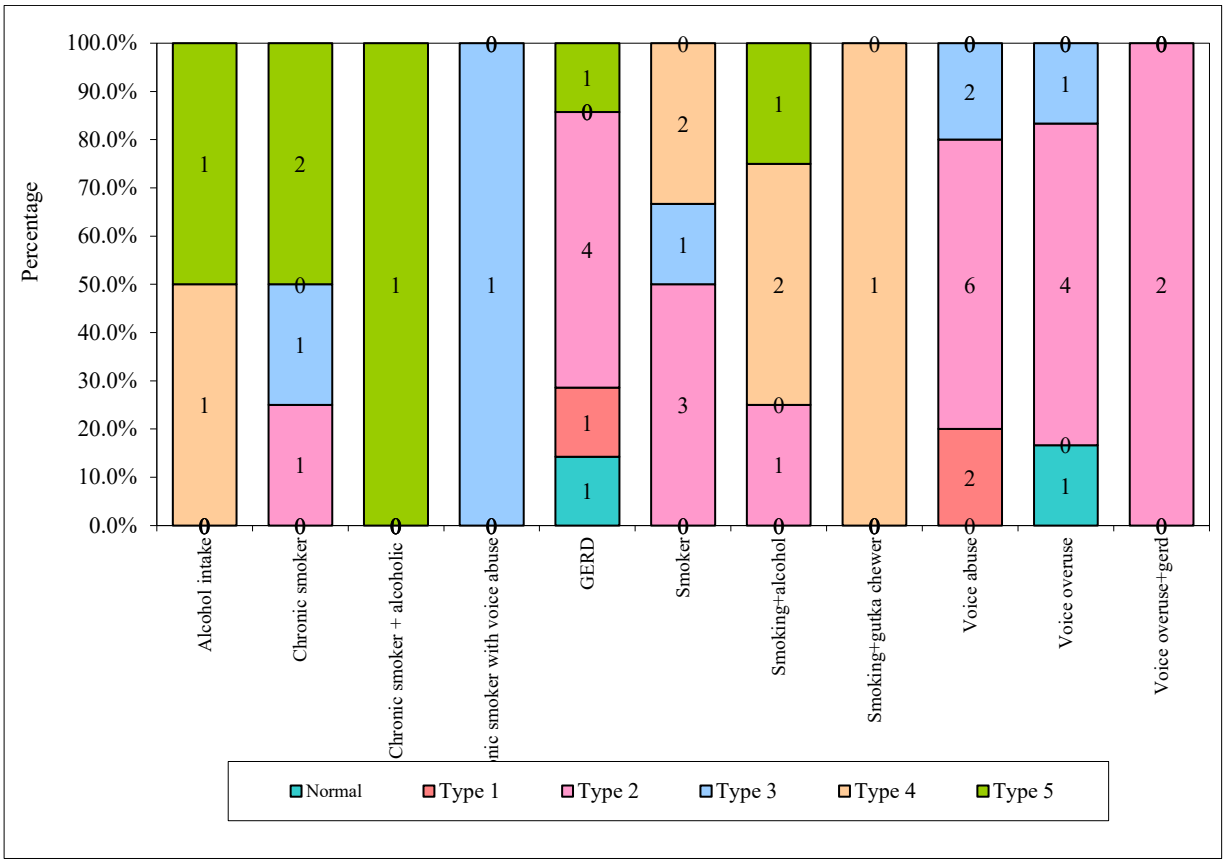


Table 6: Association between Co-morbidities and NBI grades

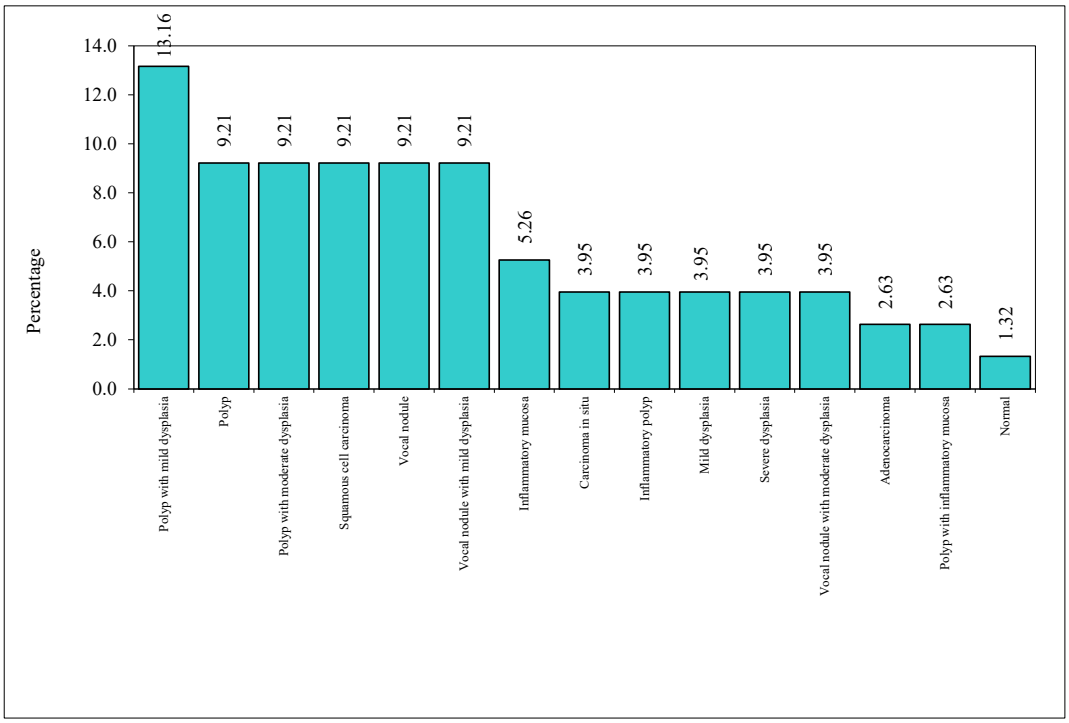
Habits/co morbidities	Normal	Type I	Type II	Type III	Type IV	Type V
Alcohol intake	-	-	-	-	1	1
Chronic smoker	-	-	4	2	2	2
Chronic smoker + alcoholic	-	-	-	-	-	1
Chronic smoker with voice abuse	-	-	-	1	-	-
GERD	1	1	4	-	-	1
Smoking+alcohol	-	-	1	-	2	1
Smoking+gutka chewer	-	-	-	-	1	-
Voice abuse	-	2	6	2	-	-
Voice overuse	1	-	4	1	-	-
Voice overuse+gerd	-	-	2	-	-	-
Nil	1	11	14	4	2	-

As seen in Table 6 and graph 6, patients having co morbidities showed higher vascular patterns on NBI. Patients having history of Alcohol intake showed Type IV and Type V pattern. In Chronic smokers 4 patients had type II , 2 patients type III , 2 patients showed type IV pattern and 1 has type V . Patient with both alcohol and smoking history showed Type IV pattern in 2 patients, type V in 2 patients and 1 patient showed type II pattern. None of the patients with voice abuse, voice overuse or GERD showed Type IV or type V pattern. Majority of these patients showed type II pattern.

Graph 6: Association between Co-morbidities and NBI grades



Graph 7 : Patient distribution by HPR (histopathological report)

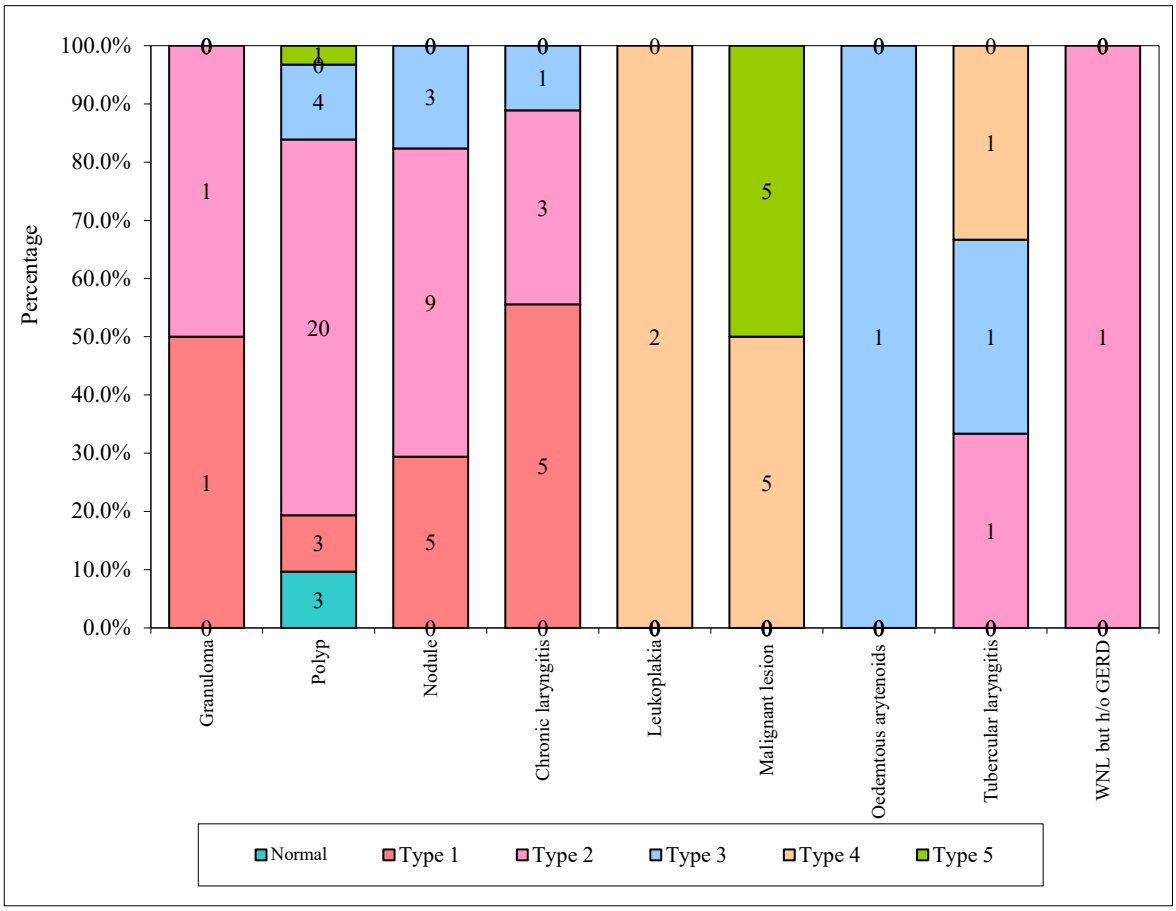


Vocal polyps were the most common lesions seen. Out of 31 patients, 20 patients showed type II pattern (64.52%), 3 patients showed normal mucosa and type I pattern respectively (9.68%), 4 patients showed type III pattern (12.90%) and only 1 patient showed type V pattern (3.23%). Out of 17 vocal nodules, 5 showed type I pattern (29.41%), 9 type II(52.94%) and only 3 showed type 3 pattern (17.65%). In patients with changes of laryngitis seen on white endoscopy – most of them showed type I pattern (5 patients), 3 patients depicted type II and only 1 patient depicted type III pattern. 50% vocal cord granuloma showed pattern of type I nature and 50% showed type II pattern. Lesions with malignant potential like leukoplakia showed type IV pattern on NBI. However in suspected malignant lesions , out of 10 patients , 5 depicted pattern of type IV nature and 5 patients depicted pattern of type V nature.

Table 7 : Association between endoscopy findings and NBI grades

Endoscopy findings	Normal	Type I no. (%)	Type II no. (%)	Type III no. (%)	Type IV no. (%)	Type V
Granuloma	-	1(50%)	1(50%)	-	-	-
Polyp	3(9.68%)	3(9.68%)	20(64.52%)	4(12.90%)	-	1(3.23%)
Nodule	-	5(29.41%)	9(52.94%)	3(17.65%)	-	-
Chronic laryngitis	-	5(55.56%)	3(33.33%)	1(11.11%)	-	-
Leukoplakia	-	-	-	-	2(100%)	-
Malignant lesion	-	-	-	-	5(50%)	5(50%)
Oedemtous arytenoids	-	-	-	1 (100%)	-	-
Tubercular laryngitis	-	-	1(33.33%)	1(33.33%)	1(33.33%)	-
WNL but h/o GERD	-	-	1(100%)	-	-	-

Graph 8 : Association between endoscopy findings and NBI grades



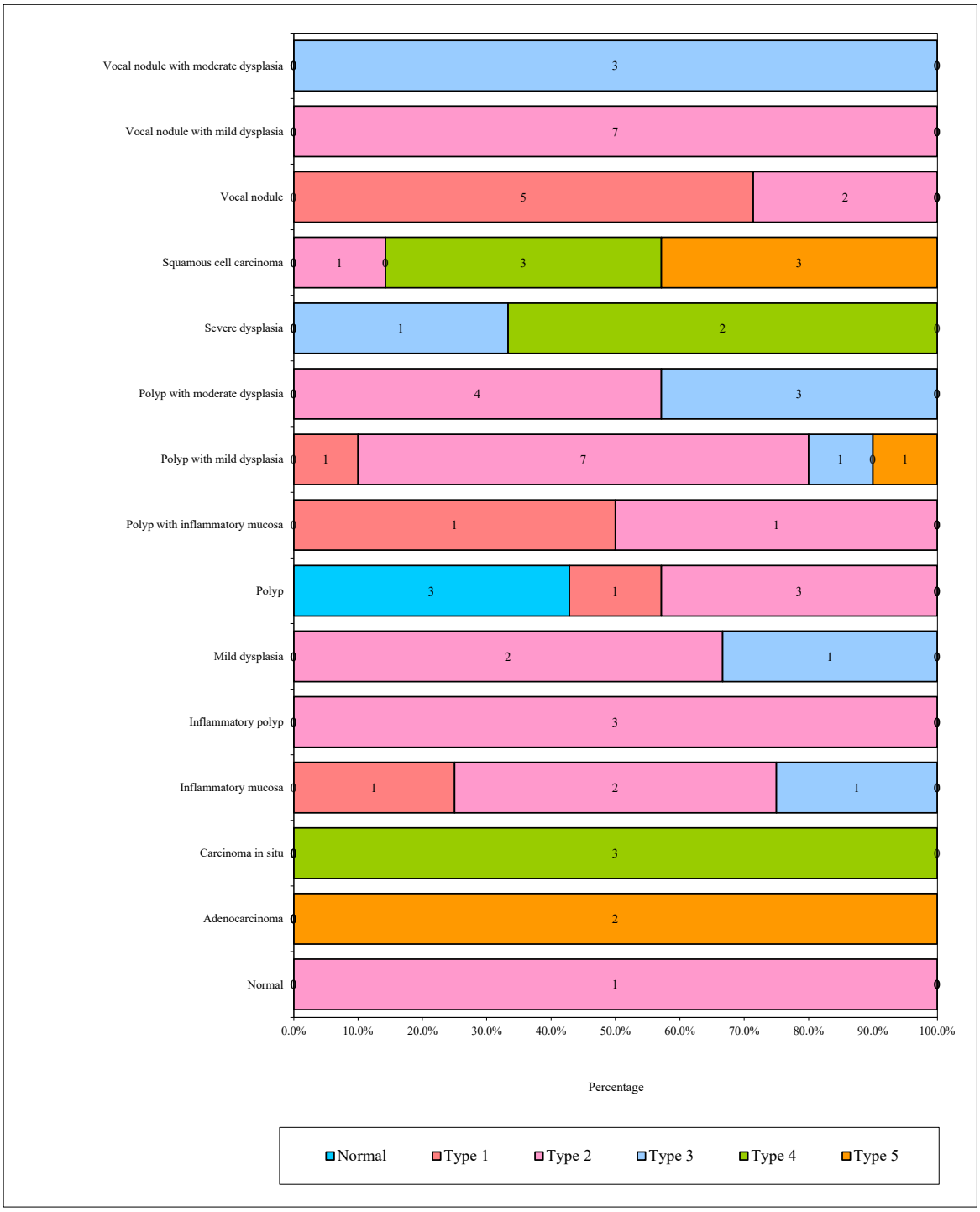
Co relation between histopathological findings and patterns of NBI shown in table 8 and graph 9 show that lesions 100% of lesions showing normal mucosa on WLI showed NBI type II. Inflammatory mucosa on HPR showed type 1 pattern in 25% patients, type II in 50% patients and type III in 25% patients. Vocal cord polyp with no dysplasia showed normal pattern in 42.86% patients, type I in 14.29% patients and type II in 42.865 patients. All Inflammatory polyps showed type II pattern. Polyps with mild dysplasias showed type II in 70% patients and 10% each in type I. III and V. Polyps with moderate dysplasias showed 57.14% patients having type II & 42.86% with type III pattern. Mild mucosal dysplasias showed type II pattern in 66.67% patients and type III in 33.33%. Severe dysplasias showed type IV

pattern in 66.67% and type III in 33.33%. Vocal nodules showed 71.43% having type I , 28.57% type II. However nodules with mild dysplasia showed type II pattern in 100% patients and type III pattern in moderate dysplasia. 100% adenocarcinomas showed type IV , 100% carcinoma in situ showed type IV pattern. 42.86% SCC showed type IV and Type V each, 14.29% showed type II.

Table 8 : Association between HPR (histo pathological report) and NBI grades

HPR(histo pathological report)	Normal	Type 1	Type 2	Type 3	Type 4	Type 5
Normal	-	-	100.00	-	-	-
Adenocarcinoma	-	-	-	-	-	100.00
Carcinoma in situ	-	-	-	-	100.00	-
Inflammatory mucosa	-	25.00	50.00	25.00	-	-
Inflammatory polyp	-	-	100.00	-	-	-
Mild dysplasia	-	-	66.67	33.33	-	-
Polyp	42.86	14.29	42.86	-	-	-
Polyp with inflammatory mucosa	-	50.00	50.00	-	-	-
Polyp with mild dysplasia	-	10.00	70.00	10.00	-	10.00
Polyp with moderate dysplasia	-	-	57.14	42.86	-	-
Severe dysplasia	-	-	0.00	33.33	66.67	0.00
Squamous cell carcinoma	-	-	14.29	0.00	42.86	42.86
Vocal nodule	-	71.43	28.57	-	-	-
Vocal nodule with mild dysplasia	-	-	100.00	-	-	-
Vocal nodule with moderate dysplasia	-	-	-	100.0	-	-
Not done	-	71.43	28.57	-	-	-

Graph 9: Association between HPR (histo pathological report) and NBI grades



DISCUSSION

In adults, majority of the blood vessels are already developed and do not undergo further cell division. However 0.01% of the cells of endothelium can and do undergo division. When there is an increased or irregular vascular growth, it contributes to many neoplastic and non-neoplastic disorders. Various diseases also manifest due to abnormal remodelling of the blood vessels.

New blood vessels emerging or their intussusception via already existing vessels causes formation of tumour vessels. This process is called as 'Tumour NeoAngiogenesis '. Sometimes precursors of endothelium are released from the wall of vessels or they get mobilised from BM and give rise to angiogenesis of a tumor. In non-neoplastic diseases, angiogenesis is proposed to occur due to inflammation and hypoxia. [25]

Structurally and functionally, vessels formed through angiogenesis are abnormal.This kind of vasculature that is formed after neoangiogenesis is very disorganized, therefore, dilated and torturous vessels are seen having multiple branching patterns and diameters. Yancopoulos et al. explained perivascular cuffs are formed as these tumour cells keep growing along & around the normal vessels

Therefore, since > 90% of tumors of larynx with malignant nature develop from precancerous epithelial lesions, proper cure and function-preserving therapy requires prompt diagnosis. Majority of laryngeal lesions show a variety of epithelial changes and may manifest at different levels of dysplasia – diagnostic methods are required for identifying the biological behaviour of these lesions. [28] NBI provides this assessment by selectively assessing the biological behaviour of lesions.

Kazuhiro Gono , in 1990 , conceived an optical technology called Narrow Band Imaging (NBI) , which works by reducing the wavelength band of WLI into a band of 415 & 540nm. The NBI light falls into spectrum of light that is ready absorbed by haemoglobin, allowing enhancement of micro BVs located on epithelium. By doing so , it provides contrastment and highlighting pattern of capillaries below epithelium compared to surrounding mucosa. “This allows in vivo analysis of microvascular architectural transformation that occurs in benign to malignant conditions”. These microvascular patterns seen are referred to as “intraepithelial papillary capillary loops”- prime determinants in clinical evaluation of lesions of epithelium. [29]

We evaluated the neoangiogenic changes in various laryngeal lesions as seen on NBI & tried understanding NBI’s role in neoangiogenesis evaluation for finding laryngeal disorders, earlier. Majority of patients that came to our OPD with laryngeal complaints belonged to 4th decade of life with mean age seen of 42 years. This age of presentation was similar to other Indian studies [48][49] Out of these patients , men were in a higher proportion and male to female ratio seen was 1.5:1. A proposed theory for laryngeal lesions higher in men is the higher prevalence of habits and co morbidities responsible for diseases of larynx in men.[50][51]

Amongst the co morbidities seen in our patients, voice abuse (13.16%) and smoking (13.16%) were most common followed by GERD (9.21%) and voice overuse (7.89%). A study done by [51]. It was observed in our study that in the presence of underlying co morbidities, higher patterns of NBI were seen indicating angiogenesis and possibility of malignant transformation. In patients with no habits or co morbidities, majority of patients showed type I () and type II pattern ( ) , only showed type III pattern and type IV pattern seen in only . However patients with

history of smoking and alcohol intake show higher types of vascular pattern. Patients with chronic smoking showed only type II pattern and above . However patients with history of alcohol intake and smoking showed only type 5 pattern on NBI. Not many studies have been done in the Indian set up to establish a co-relation between risk factors and comorbidities for laryngeal diseases and their vascular changes seen in NBI.

WLI for all patients revealed that the most common laryngeal lesion with which the patients presented was vocal polyp (40.79%) followed by vocal nodules (22.37%), suspicious malignant lesion (13.16%), chronic laryngitis (11.84%) and then tubercular laryngitis (3.95%) . Only 2 patients presented with leukoplakia (2.63%) , 2 patients with vocal cord granuloma (2.63%) and 1 patient with oedematous arytenoids(1.32%). In 1 patient (1.32 %) no lesion was seen on white light endoscopy.

A similar Indian research done by Mahesh et al., concluded that most common lesion of larynx seen was - polyps of cords “40.47%”, nodules “28.57%” laryngeal Tb “14.30%”, laryngocele “4.76%”, webs of larynx “4.76%”, cysts of epiglottis “4.76%” and hemangioma in subglottis“2.38%”. [(52)]

For all the lesions seen on white light endoscopy, Narrow band imaging patterns were studied. Majority of the patients presented with benign lesions in our study and Type II pattern was the most commonly seen(46.05%) followed by type I pattern (18.42%). Patients with lesions having malignant potential like leukoplakia - demonstrated only type IV pattern. (100%). In some patients with no evident changes seen on WLE but with underlying co morbidities , changes were seen on NBI eg- patients with history of GERD or smoking but no evident changes seen on WLI , type

II pattern was seen indicating beginning of vascular changes. All suspected malignant lesions showed only type IV and type V pattern on NBI , demonstrating the tumour neoangiogenesis with their characteristic patterns.

It was seen in our study that even in various benign lesions and suspected malignant lesions, varying degree of NBI patterns were seen. In order to understand this pattern, we co related NBI findings with histopathology. We observed that normal benign lesions with no degree of dysplasia showed normal pattern or type I pattern. As the dysplasia increased, the NBI patterns progressed. Carcinoma in situ and leukoplakia showed type IV pattern and the lesions that came as adenocarcinoma or squamous cell carcinoma, they showed type V pattern on NBI, thereby indicating malignant potential. In their study, Chang *et al*. advised that Narrow Band Imaging can easily act useful and efficient technique for diagnosis of laryngeal lesions. They observed 97.2% sensitivity & 100% specificity of NBI in evaluation of laryngeal lesions.[1]

On the basis of visible patterns of blood vessels, Turkmen et al. also classified vocal fold disorders with a good sensitivity. [53] A recent Indian study demonstrated that performing both WLI and NBI multiplies the chances of early identifying malignancies of larynx and lesions preceding it. NBI helps detection and delineation of suspicious malignant disorders, their horizontal extension, and field cancerization. This was 1st study on use of NBI in laryngeal lesions' diagnosis amongst Indian patients. Therefore we can say that early detection of laryngeal malignancies and their precursor lesions can easily be done by identifying the angiogenic patterns seen in NBI

Table: Association between endoscopy findings and NBI grades in each of co-morbidity category

Habits/co morbidities	Endoscopy	Normal	Type I	Type II	Type III	Type IV	Type V
Alcohol intake	Malignant lesion	-	-	-	-	1	1
Chronic smoker	Polyp	-	-	2	-	-	1
	Chronic laryngitis	-	-	1	1	-	-
	Malignant lesion	-	-	-	-	1	1
	Leukoplakia	-	-	-	-	1	-
Chronic smoker + alcoholic	Malignant lesion	-	-	-	-	-	1
Chronic smoker with voice abuse	Oedemtous arytenoids	-	-	-	1	-	-
GERD	Polyp	1	1	2	-	-	-
	Nodule	-	-	2	-	-	-
	Malignant lesion	-	-	-	-	-	1
Nil	Granuloma	-	1	1	-	-	-
	Polyp	1	2	8	3	-	-
	Nodule	-	3	3	-	-	-
	Chronic laryngitis	-	5	1	-	-	-
	Malignant lesion	-	-	-	-	1	-
	Tubercular laryngitis	-	-	-	1	1	-
	Wnl but h/o gerd	-	-	1	-	-	-
Smoker	Polyp	-	-	2	-	-	-
	Nodule	-	-	-	1	-	-
	Malignant lesion	-	-	-	-	1	-
	Tubercular laryngitis	-	-	1	-	-	-
Smoking+alcohol	Chronic laryngitis	-	-	1	-	-	-
	Leukoplakia	-	-	-	-	1	-
	Malignant lesion	-	-	-	-	1	1

Smoking+gutka chewer	Malignant lesion	-	-	-	-	1	-
Voice abuse	Polyp	-	-	2	-	-	-
	Nodule	-	2	4	2	-	-
Voice overuse	Polyp	1	-	4	1	-	-
Voice overuse+gerd	Polyp	-	-	2	-	-	-

CONCLUSION

- Growth and progression of tumours requires "Angiogenesis". It is a hallmark of tumor progression.[9] Inflammatory lesions and pre malignant lesions also undergo angiogenesis through various mechanisms and this neoangiogenesis can help in determining their malignant potential.
- NBI is a very novel kind of endoscopic techniques and is quite unique in its ability to identify the microvascularization pattern of various lesions. Narrow Band Imaging identified laryngeal lesions and their angiogenic properties with high accurancy in our study.
- In some patients, NBI It was able to identify changes in the superficial vasculature of lesions and over the mucosa even though WLI didn't show any significant structural lesions – indicating start of the disease process.
- Histopathological co-relation demonstrated that NBI correctly identified neoangiogenesis in inflammatory and precancerous lesions. Its main role is seen in such lesions only so that we can plan early detection.
- Malignant lesions do not necessarily need NBI as they are easily seen on even White light endoscopy. Its main role is in lesions like leukoplakia or carcinoma in situ which may show varying degrees of biological activity.
- Therefore angiogenesis is definitely a strong determinant of the disease progression and also the malignant potential of various lesions. By identifying 'neoangiogenesis 'NBI acts as an optical biopsy. It should be used as a regular diagnostic tool for early diagnosis of the various laryngeal lesions. Using NBI to evaluate angiogenesis and classifying lesions on their biological characteristics can help in avoiding the need for unnecessary biopsies in some cases and also plan

early management of neoplastic lesions avoiding their further spread and need for more extensive surgeries.

SUMMARY

- 78 patients enrolled in our study out of which 76 patients got NBI done following WLI, Out of 76 patients , 45 patients (59.21%) were males and 31(40.79%) were female patients. Male: female ratio in patients with laryngeal lesions was seen to be 1.5:1.
- In our study it was seen that 32/76 patients (42.11%) had no underlying co morbidities or history of any habits. Amongst the underlying co morbidities, it was seen that voice abuse and history of smoking were most common (13.16% each) followed by GERD (9.21%) and voice overuse (7.89%).
- White light endoscopy performed for all patients revealed that vocal polyp (40.79%) were highest in number, then vocal nodules (22.37%), suspicious malignant lesion (13.16%), chronic laryngitis (11.84%) and then tubercular laryngitis (3.95%).
- Co relation between histopathological findings and patterns of NBI showed that. Inflammatory mucosa on HPR showed type 1 pattern in 25% patients, type II in 50% patients and type III in 25% patients. Vocal cord polyp with no dysplasia showed normal pattern in 42.86%. patients, type I in 14.29% patients and type II in 42.865 patients. All Inflammatory polyps showed type II pattern. Polyps with mild dysplasias showed type II in 70% patients and 10% each in type I. III and V. Polyps with moderate dysplasias showed 57.14% patients having type II & 42.86% with type III pattern. Mild mucosal dysplasias showed type II pattern in 66.67% patients and type III in 33.33% . Severe dysplasias showed type IV pattern in 66.67% and type III in 33.33%. Vocal nodules showed 71.43% having type I ,

28.57% type II. However nodules with mild dysplasia showed type II pattern in 100% patients and type III pattern in moderate dysplasia

- Therefore NBI was able to identify changes in the superficial vasculature of lesions and over the mucosa even though WLI didn't show any significant structural lesions – indicating start of the disease process.
- Histopathological co-relation demonstrated that NBI correctly identified neoangiogenesis in inflammatory and precancerous lesions. Its main role is seen in such lesions only so that we can plan early detection.
- By identifying 'neoangiogenesis 'NBI acts as an optical biopsy. It should be used as a regular diagnostic tool for early diagnosis of the various laryngeal lesions

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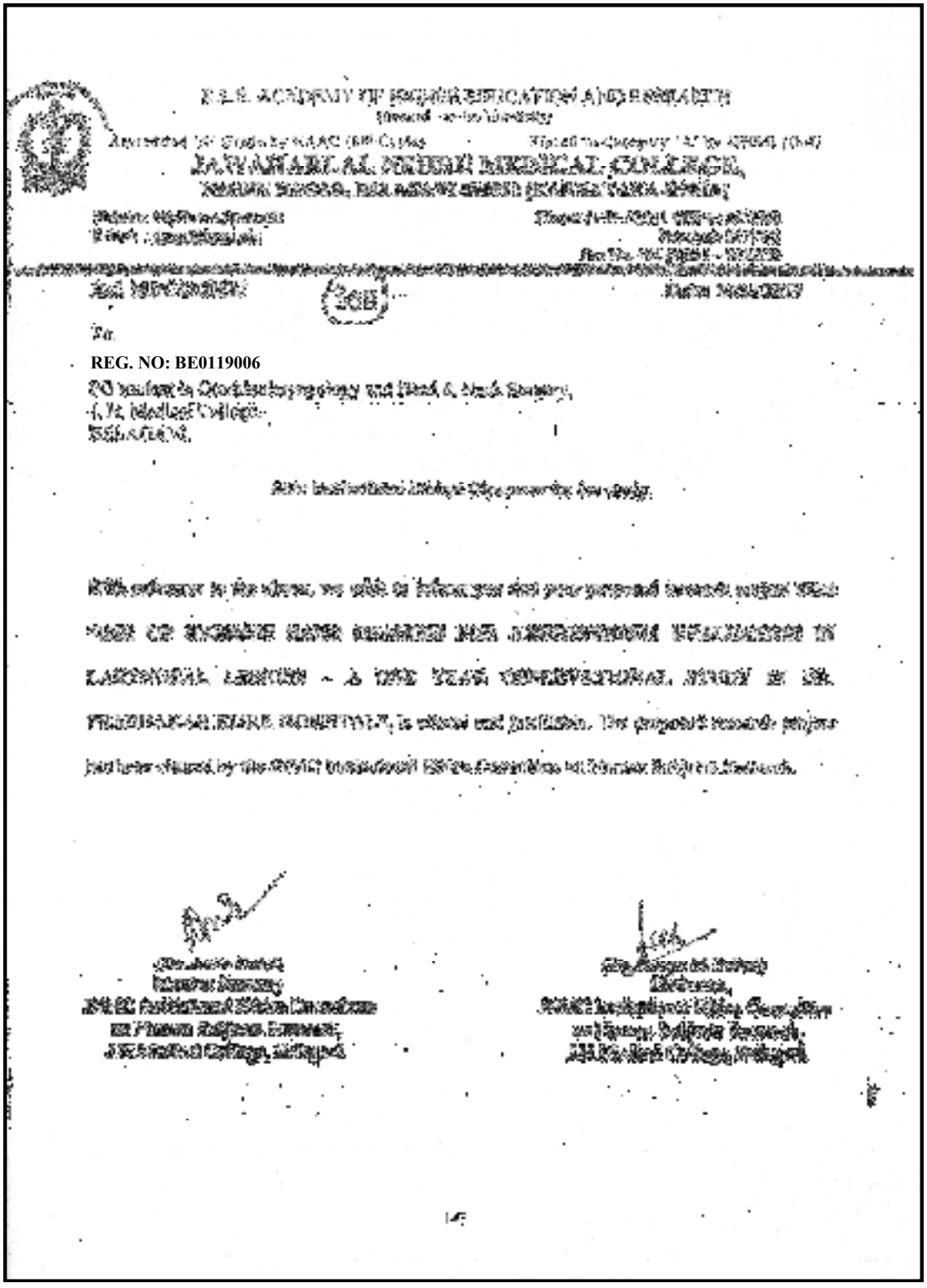
ANNEXURE I

ETHICAL CLEARANCE.



REG. NO: BE0119006

ANNEXURE II

INFORMED CONSENT

Use of narrow band imaging in endoscopic evaluation of angiogenesis in Laryngeal lesions

PRINCIPAL INVESTIGATOR: DR._____

CO-INVESTIGATOR : REG. NO: BE0119006

INTRODUCTION AND PURPOSE:

The present study is conducted among patients who are undergoing Narrow Band Imaging Evaluation in ENT & HNS department in KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum for symptoms suggesting of a laryngeal lesions

PROCEDURE:

If you agree to participate in this study, the relevant data will be collected as per the proforma and the final diagnosis will be confirmed.

After getting enrolled in the study, you will be evaluated with Narrow Band Imaging for diagnosis of laryngeal lesions.

BENEFITS:

Patient will not be eligible for any kind of monetary benefits or free services by virtue of your participation in the study.

RISKS:

Methods applied to do the study are safe.

COST OF PARTICIPATION:

The cost of the Investigation will be borne by the Study Subject.

PRIVACY AND CONFIDENTIALITY:

The results of the study may be published in journals for scientific purposes. However your identity will not be revealed. All information collected will be coded so that no one other than the investigator will know your identity.

WITHDRAWAL FROM THE STUDY:

You can withdraw from the study at any time if you wish to do so.

AUTHORIZATION TO PUBLISH THE RESULTS:

The researcher may use the information gathered from this study for presentation in scientific meetings. However your identity will not be revealed.

QUERIES AND CONTACT:

If you have any queries regarding the study, you can contact **REG. NO: BE0119006** without any hesitation on and guide Dr. _____

If you have any query about rights as a research participant you can contact Dr.Roopa M Bellad, Professor, Department of Paediatrics and Chairman, Jawaharlal Nehru Medical College Institutional Ethics Committee on human subjects research.

CONSENT SUMMARY:

I have been explained all the contents of this consent form in my local language and having understood and clarified all my queries about the study to the best of my knowledge, I hereby give my voluntary consent for participation in the study. I do sign the informed consent form in front of an eyewitness whom I recognize.

Name and Signature/ left thumb impression of the participant:

Name and Signature of the interviewer:

Name and Signature/ left thumb impression of the eyewitness (Relative):

Signature of the guide:

Date:

ANNEXURE III

PROFORMA

Use of narrow band imaging in endoscopic evaluation of angiogenesis in laryngeal lesions

Date:
O.P. No: IP No:
Name: Age:
Sex: Occupation:
Address: Phone No:

D.O.A D.O.D:

CLINICAL PROFILE:

Chief Complaint:

History of Present Illness

Past History:

Personal History:

Family History:

Physical Examination:

I) General Physical Examination -

Vital signs:

Pulse-

Blood pressure-

Respiratory Rate-

Pallor

Icterus

Clubbing

Cyanosis

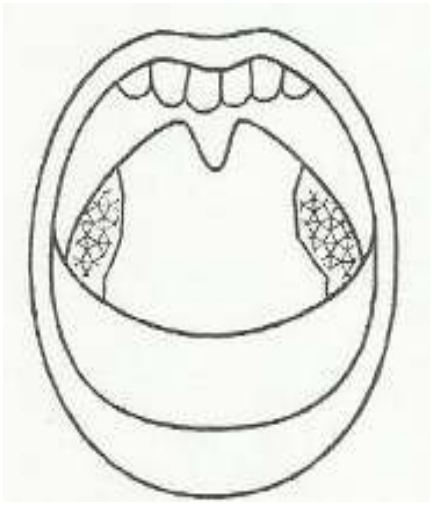
Lymphadenopathy

Oedema

II) ENT Examination

1. **THROAT EXAMINATION -**

   1.1 ORAL CAVITY and OROPHARYNX:



1.2 INDIRECT LARYNGOSCOPY-

2. NECK EXAMINATION

WHITE LIGHT ENDOSCOPY FINDINGS

NBI FINDINGS:

DIAGNOSIS

1. Type I NBI pattern

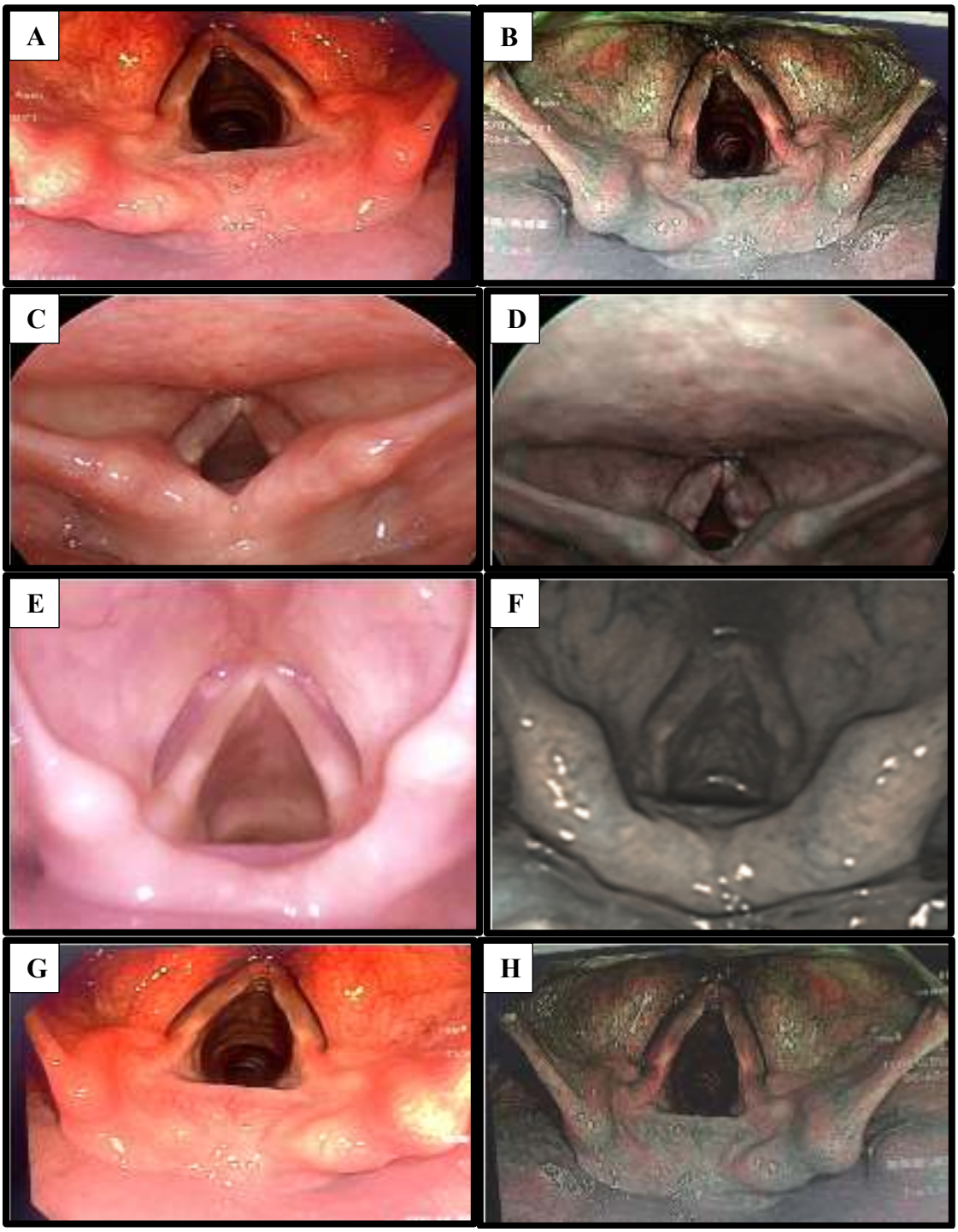


Figure A-H indicating Type 1 pattern on NBI. (A) WLI in a patient with h/o GERD revealing Chronic Laryngitis. (B) NBI showing thin, oblique vessels – Type I pattern. (C) showing vocal cord nodules in the vocal cords in patient with no co morbidities. (D) indicating Type 1 pattern. (E) showing normal vocal cords in the WLI in patient with history of voice change secondary to chronic rhinosinusitis (F) NBI image showed normal pattern with type 1 pattern in some areas. (G) WLI showing bilateral vocal cords nodule with NBI revealing type 1 pattern.

2. Type II NBI pattern

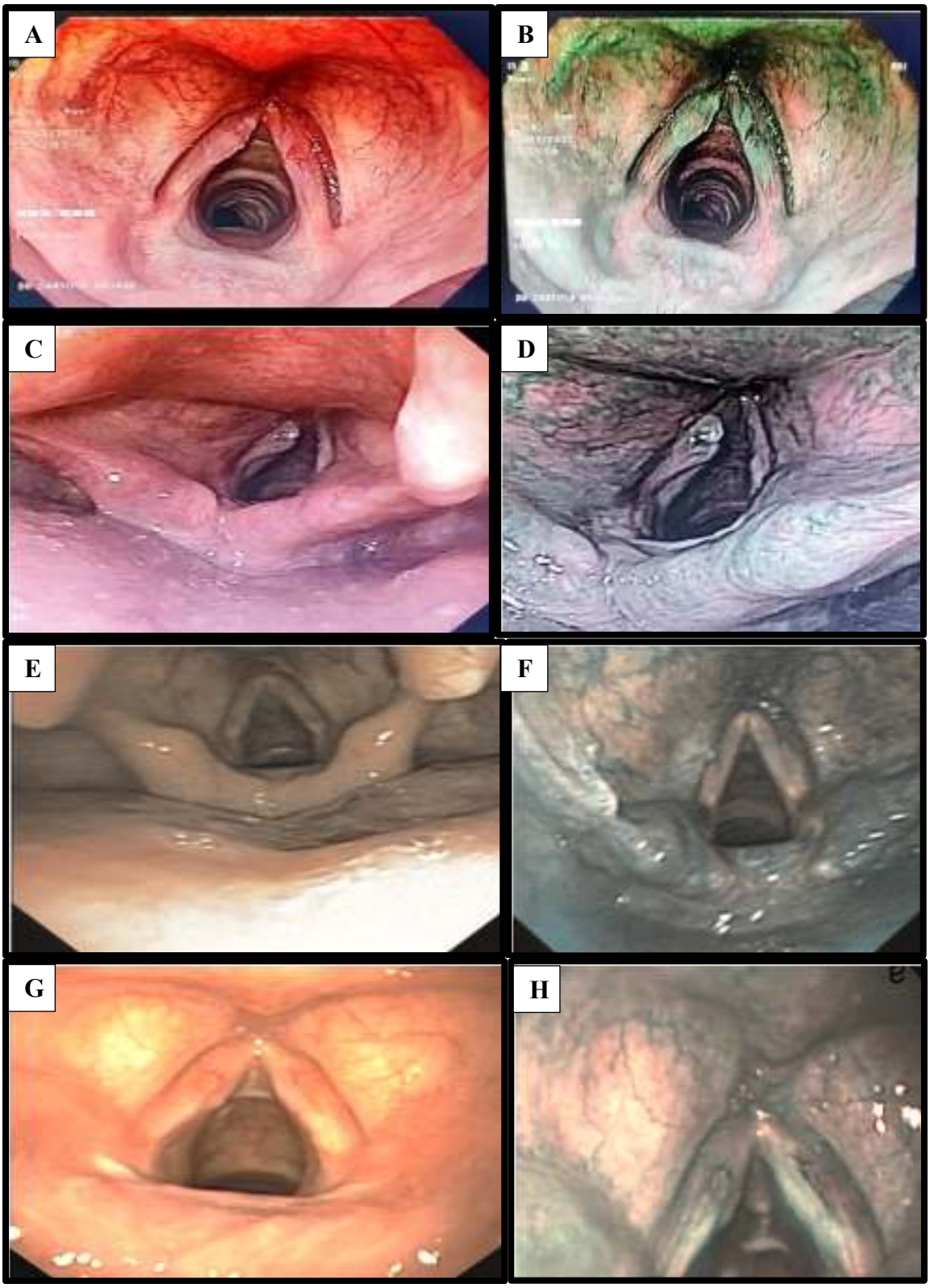


Figure A To H showing type II pattern on NBI. (A) showing intubation granuloma in patient post thyroidectomy (B) showing arborescent vessels enlarged. (C) showing right vocal cord polyp in a smoker with GERD (D) polyp is more clearly visible & showing enlarged vessels. (E) VC nodules in patient with voice overuse (F) type II pattern seen. (G) Chronic laryngitis in alcoholic (H) NBI showing arytenoids with dilated vessels

3. Type III NBI pattern

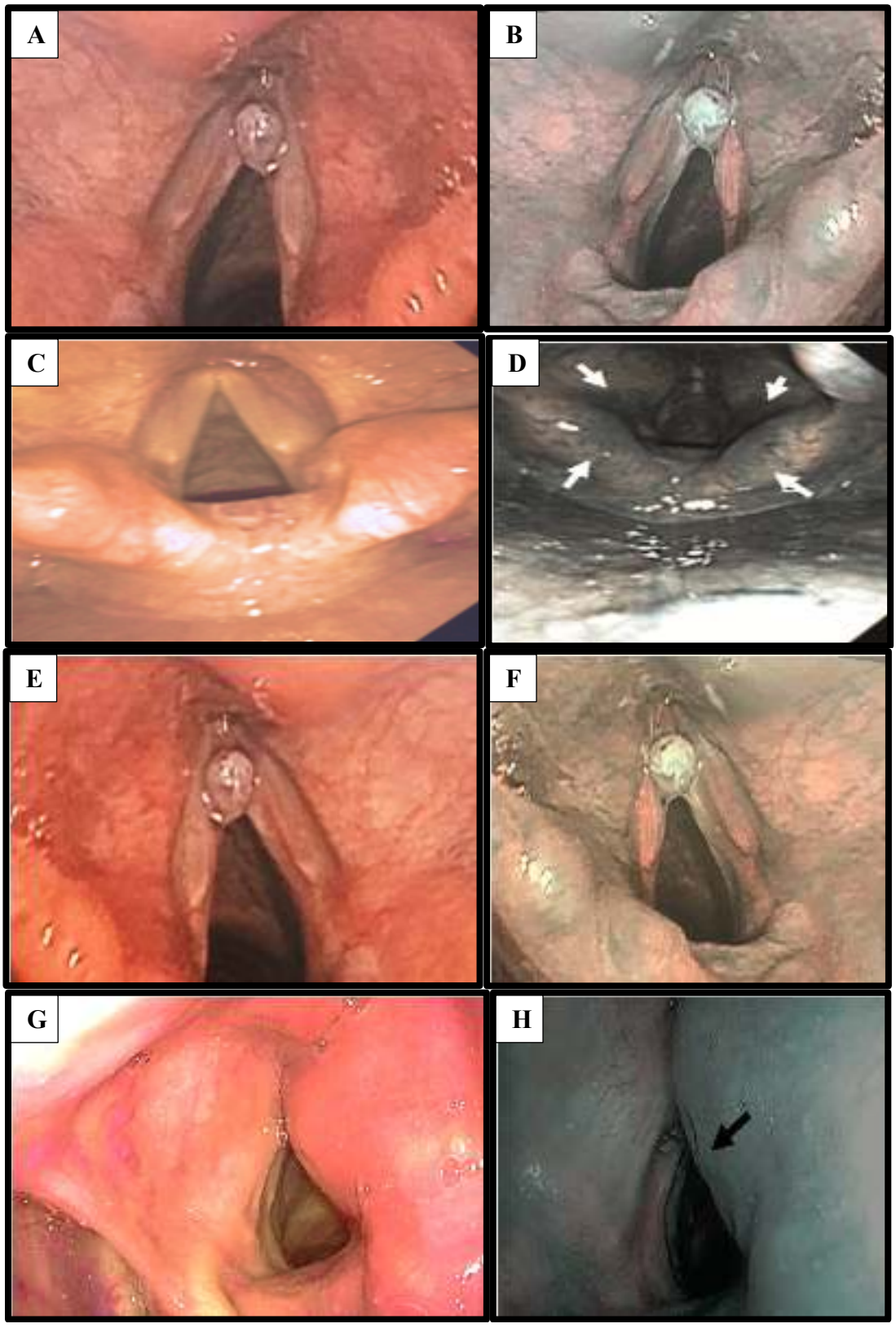


Figure A To H showing type III pattern on NBI. (A) showing vocal cord polyp in patient with voice overuse with smoking (B) showing white mucosa covering ICPLs. (C) showing VC nodules in a smoker with GERD (D) nodule is more clearly visible & showing enlarged vessels. (E) showing vocal cord polyp in patient with voice overuse with smoking (F) type III pattern seen. (G) Chronic laryngitis in smoker with alcohol intake (H) NBI showing arytenoids Type III pattern

4. Type IV NBI pattern

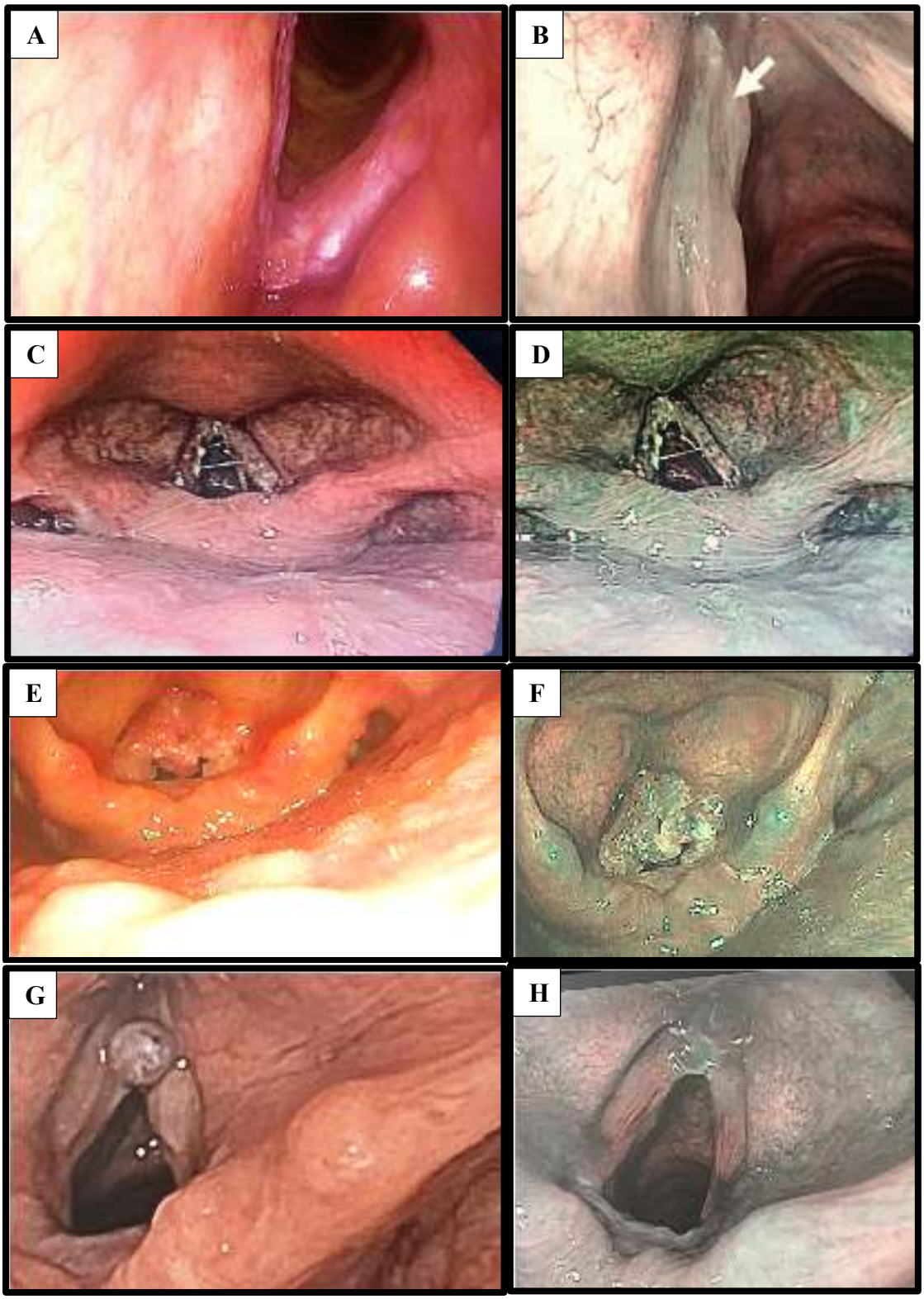


Figure A To H showing type IV pattern on NBI. (A) showing leukoplakia in patient with voice overuse (B) showing ICPLs as small dots(C) showing Tubercular laryngitis in a smoker with GERD (D) Type IV pattern. (E) WLI imaging showing a growth (F) type IV pattern seen. (G) Vocal cord polyp in smoker with alcohol intake (H) NBI showing arytenoids and anterior VCs Type IV pattern

5. Type V NBI pattern

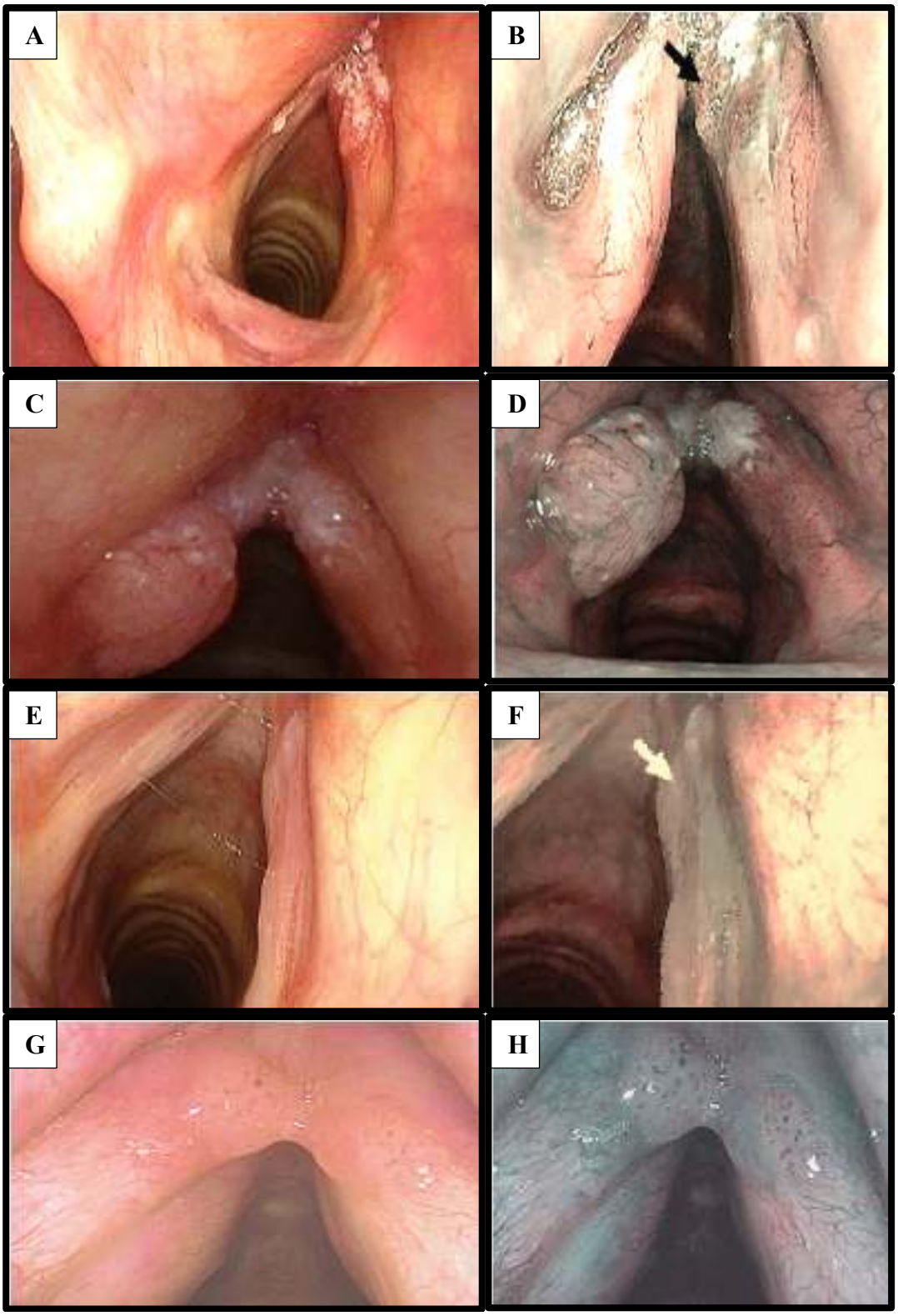


Figure ATo H showing type V pattern on NBI. (A) showing leukoplakia which is elevated in patient with smoking (B) showing ICPLs brown spots indicating vascular atypia. (C) showing a VC growth in a smoker with GERD (D) growth is more clearly visible & showing enlarged vessels with type V pattern. (E) showing? leukoplakic lesions in patient with voice overuse with smoking (F) type V pattern seen. (G) Chronic laryngitis with polyposis in smoker with gutka chewing (H) NBI showing brown speckled dots Type V pattern

ANNEXURE V - KEY TO MASTERCHART

1. VC - Vocal Nodule
2. WNL - Within Normal Limits
3. GERD - Gastro oesophageal reflux Disease

NAME	AGE	SEX	HABITS/CO MORBIDITIES	70 DEGREE	NBI GRADE	HPR
1	70	M	CHRONIC SMOKER	CHRONIC LARYNGITIS	TYPE 2	NOT DONE
2	35	F	VOICE ABUSE	VC NODULE	TYPE 2	VOCAL NODULE WITH MILD DYSPLASIA
3	40	M	NIL	WNL BUT H/O GERD	TYPE 2	NOT DONE
4	35	F	GERD	VC NODULE	TYPE 2	VOCAL NODULE WITH MILD DYSPLASIA
5	50	M	NIL	RIGHT VC POLYP	TYPE 2	POLYP
6	35	F	SMOKER	VC NODULE	TYPE 3	VOCAL NODULE WITH MODERATE DYSPLASIA
7	37	F	NIL	LEFT VC POLYP	TYPE 2	POLYP
8	42	M	NIL	VC NODULE	TYPE 2	VOCAL NODULE WITH MILD DYSPLASIA
9	51	F	NIL	RIGHT VC GRANULOMA	TYPE 2	NORMAL
10	44	F	CHRONIC SMOKER	LEFT VC POLYP	TYPE 5	POLYP WITH MILD DYSPLASIA
11	67	M	CHRONIC SMOKER + ALCOHOLIC	MALIGNANT LESION IN THE PYRIFORM SINUS	TYPE 5	SQUAMOUS CELL CARCINOMA
12	29	F	CHRONIC SMOKER	CHRONIC LARYNGITIS	TYPE 3	MILD DYSPLASIA
13	52	M	GERD	RIGHT VC POLYP	TYPE 2	POLYP WITH MILD DYSPLASIA
14	50	M	VOICE ABUSE	VC NODULE	TYPE 3	VOCAL NODULE WITH MODERATE DYSPLASIA
15	33	M	VOICE ABUSE	RIGHT VC POLYP	TYPE 2	POLYP WITH MODERATE DYSPLASIA
16	39	F	VOICE ABUSE	LEFT VC POLYP	TYPE 2	POLYP WITH MILD DYSPLASIA
17	40	F	NIL	LEFT VC POLYP	TYPE 2	POLYP WITH MODERATE DYSPLASIA
18	59	M	CHRONIC SMOKER WITH VOICE ABUSE	OEDEMTOUS ARYTENOIDS	TYPE 3	SEVERE DYSPLASIA
19	30	M	VOICE OVERUSE	RIGHT VC POLYP	TYPE 2	POLYP WITH MODERATE DYSPLASIA
20	53	M	SMOKING+ALCOHOL	MALIGNANT LESION IN LEFT VC	TYPE 4	CARCINOMA IN SITU
21	37	M	NIL	LEFT VC POLYP	TYPE2	POLYP WITH MILD DYSPLASIA
22	58	M	CHRONIC SMOKER	MALIGNANT LESION IN RIGHT VC	TYPE 5	ADENOCARCINOMA
23	46	M	SMOKER	RIGHT VC POLYP	TYPE 2	POLYP WITH INFLAMMATORY MUCOSA
24	51	M	ALCOHOL INTAKE	MALIGNANT LESION IN LEFT VC	TYPE 4	SQUAMOUS CELL CARCINOMA
25	25	F	NIL	LEFT VC POLYP	TYPE 3	POLYP WITH MODERATE DYSPLASIA
26	33	F	NIL	CHRONIC LARYNGITIS	TYPE 2	MILD DYSPLASIA
27	48	M	GERD	MALIGNANT LESION IN RIGHT CORD	TYPE 5	SQUAMOUS CELL CARCINOMA
28	30	F	VOICE OVERUSE+GERD	RIGHT VC POLYP	TYPE 2	POLYP WITH MILD DYSPLASIA
29	65	M	SMOKER	MALIGNANT LESION IN RIGHT VC	TYPE 4	SQUAMOUS CELL CARCINOMA
30	50	F	VOICE ABUSE	VC NODULE	TYPE 2	VOCAL NODULE
31	62	M	NIL	MALIGNANT LESION IN RIGHT VC	TYPE 4	CARCINOMA IN SITU
32	40	F	NIL	RIGHT VC POLYP	TYPE 2	INFLAMMATORY MUCOSA
33	33	M	NIL	CHRONIC LARYNGITIS	TYPE 1	NOT DONE
34	49	M	ALCOHOL INTAKE	EPIGLOTTIC MALIGNANT LESION	TYPE 5	ADENOCARCINOMA
35	45	F	NIL	LEFT VC POLYP	TYPE 1	POLYP WITH MILD DYSPLASIA
36	37	M	VOICE ABUSE	VC NODULE	TYPE 2	VOCAL NODULE WITH MILD DYSPLASIA
37	40	M	VOICE ABUSE	VC NODULE	TYPE 1	VOCAL NODULE
38	30	M	NIL	LEFT VC GRANULOMA	TYPE 1	INFLAMMATORY MUCOSA
39	38	M	VOICE OVERUSE	LEFT VC POLYP	TYPE 2	POLYP WITH MODERATE DYSPLASIA
40	27	M	NIL	CHRONIC LARYNGITIS	TYPE 1	NOT DONE
41	30	F	SMOKING+ALCOHOL	MALIGNANT LESION IN LEFT VC	TYPE 5	SQUAMOUS CELL CARCINOMA

42	41	F	NIL	LEFT VC POLYP	TYPE 2	SQUAMOUS CELL CARCINOMA
43	55	M	SMOKING+GUTKA CHEWER	MALIGNANT LESION SEEN IN VALLECULA	TYPE 4	SQUAMOUS CELL CARCINOMA
44	37	F	GERD	RIGHT VC POLYP	TYPE 1	POLYP WITH INFLAMMATORY MUCOSA
45	45	M	VOICE ABUSE	VC NODULE	TYPE2	VOCAL NODULE WITH MILD DYSPLASIA
46	46	M	NIL	VC NODULE	TYPE2	VOCAL NODULE WITH MILD DYSPLASIA
47	40	M	NIL	LEFT VC POLYP	TYPE 1	VOCAL POLYP
48	52	M	NIL	CHRONIC LARYNGITIS	TYPE 1	NOT DONE
49	37	M	VOICE OVERUSE	LEFT VC POLYP	TYPE 2	POLYP
50	50	M	NIL	TUBERCULAR LARYNGITIS	TYPE 3	INFLAMMATORY MUCOSA
51	43	M	NIL	VC NODULE	TYPE 1	VOCAL NODULE
52	45	F	GERD	RIGHT VC POLYP	NORMAL	VOCAL POLYP
53	46	F	NIL	VC NODULE	TYPE 2	VOCAL NODULE
54	29	F	NIL	LEFT VC POLYP	TYPE 2	POLYP WITH MILD DYSPLASIA
55	33	M	VOICE OVERUSE	LEFT VC POLYP	TYPE 3	POLYP WITH MODERATE DYSPLASIA
56	39	M	VOICE OVERUSE+GERD	LEFT VC POLYP	TYPE 2	INFLAMMATORY POLYP
57	50	F	NIL	CHRONIC LARYNGITIS	TYPE 1	NOT DONE
58	56	M	SMOKER	LEUKOPLAKIA	TYPE 4	CARCINOMA IN SITU
59	36	F	NIL	RIGHT VC POLYP	TYPE 3	POLYP WITH GRADE 1 DYSPLASIA
60	34	F	VOICE ABUSE	VC NODULE	TYPE 1	VOCAL NODULE
61	41	M	NIL	VC NODULE	TYPE 1	VOCAL NODULE
62	50	F	NIL	TUBERCULAR LARYNGITIS	TYPE 4	SEVERE DYSPLASIA
63	38	F	NIL	VC NODULE	TYPE 1	VOCAL NODULE
64	24	F	VOICE OVERUSE	LEFT VC POLYP	NORMAL	VOCAL POLYP
65	31	F	SMOKING+ALCOHOL	CHRONIC LARYNGITIS	TYPE 2	INFLAMMATORY MUCOS
66	55	F	NIL	LEFT VC POLYP	TYPE 3	POLYP WITH MODERATE DYSPLASIA
67	22	M	VOICE ABUSE	VC NODULE	TYPE 3	VOCAL NODULE WITH MODERATE DYSPLASIA
68	62	M	SMOKER	TUBERCULAR LARYNGITIS	TYPE 2	MILD DYSPLASIA
69	34	M	NIL	LEFT VC POLYP	NORMAL	POLYP
70	40	F	GERD	VC NODULE	TYPE 2	VOCAL NODULE WITH MILD DYSPLASIA
71	61	M	SMOKING+ALCOHOL	LEUKOPLAKIA	TYPE 4	SEVERE DYSPLASIA
72	57	M	SMOKER	RIGHT VC POLYP	TYPE 2	INFLAMMATORY POLYP
73	54	M	NIL	CHRONIC LARYNGITIS	TYPE 1	NOT DONE
74	24	M	VOICE OVERUSE	RIGHT VC POLYP	TYPE 2	INFLAMMATORY POLYP
75	50	F	NIL	RIGHT VC POLYP	TYPE 2	POLYP WITH MILD DYSPLASIA
76	40	M	GERD	RIGHT VC POLYP	TYPE 2	POLYP WITH MILD DYSPLASIA
77			GREEN- CHRONIC LARYNGTIS			
78			YELLOW-VC POLYP			
79			BLUE-VC NODULE			
80			ORANGE-TUBERCULAR LARYNGITIS			
81			GREY-LEUKOPLAKIA			
82			PINK-MALIGNANT LESION			