



VOICE DISORDERS

LARYNGEAL ATYPIA AND EARLY CANCER

Laryngeal Atypia and Early Cancer: Highlights

Vocal Fold Atypia

Vocal fold atypia often appear as whitish or reddish lesions on the vocal fold surface, and are comprised of abnormal-looking cells that are not cancerous. Thought to be a prequel to cancer, atypia are usually considered as pre-cancerous or pre-malignant.

Early Vocal Fold Cancer

Early vocal fold cancer also appear as whitish or reddish lesions, but have abnormal-looking cells that have invaded the boundary of the top layer of the vocal fold.

Early cancer may affect one or both vocal folds and are often referred to as T1 or T2 type vocal fold cancers that have not spread to neck lymph nodes or elsewhere in the body.

Symptoms Do Not Distinguish Vocal Fold Atypia from Early Cancer

Because voice symptoms are similar for both atypia and early cancer, symptoms alone do not distinguish between vocal fold atypia and early cancer. Medical consultation is necessary.

Smokers Are Vulnerable

Smoking is the single greatest risk factor for developing vocal fold atypia and cancer. Risk increases with the number of cigarettes smoked and years spent smoking. A scratchy, low voice in a smoker should not simply be dismissed as "smoker's laryngitis" since vocal fold cancer – a potentially life threatening disease – might be present.

Disease Trends

Vocal fold atypia can and often do recur. Early cancer can lead to advanced cancer which can be life-threatening.

Treatment Perspective

Early diagnosis and complete excision of the affected area result in excellent cure rates.

Understanding Laryngeal Atypia and Early Cancer

Perspective on Cancer

Cancer anywhere in the body has common characteristics. Cancer develops when cells designed to perform useful functions undergo changes that are ultimately harmful to the body. Such changes include:

- Uncontrolled growth
- A tendency to invade nearby tissues

In advanced cases cancer cells spread throughout the body causing death. As with all cancers, vocal fold cancer can be life threatening if left untreated.

Vocal Fold Atypia and Early Cancer – Distinct but Related

There is a subtle transition from vocal fold atypia to early cancer. Determining the difference between the two conditions usually requires very careful microscopic examination of the tissues.

Working Definitions

- **Vocal fold atypia:** Early cell changes that often lead to cancer.
Atypia (without cells not of normal type): One of the early changes that occurs in cells that will eventually become cancerous is that they begin to look different (atypical) from normal surrounding cells. These atypical cells are less organized in their pattern. In vocal fold atypia, the surface layer of vocal fold cells (epithelium) fails to show an orderly pattern of maturation (**dysplasia**).
Atypia is a "prequel" to cancer – pre-malignant. As with atypia anywhere in the body, vocal fold atypia (or dysplasia) can lead to vocal fold cancer, thus the need to identify and remove atypia promptly.
- **Early vocal fold cancer:** When abnormal-looking cells have invaded the deepest layer of the epithelium cover, the lesion is identified as an early cancer.

Key Information

Early vocal fold (or glottic) cancer refers to stage T1a or T1b and early T2 cancers.

- **T1a:** Early cancer that is confined to one vocal fold
- **T1b:** Early cancer that is confined to the vocal folds and involves both vocal folds
- **T2a:** Early cancer in one vocal fold that either:
 1. invades the supraglottis and/or subglottis, or
 2. causes impaired mobility of the vocal fold
- **T2a:** Early cancer in both vocal folds that either:
 1. invades the supraglottis and/or subglottis, or
 2. causes impaired mobility of the vocal fold

Criteria for Staging Vocal Fold Cancers

- the size of the cancer
- how it has affected the mobility of the involved vocal fold

Location of Vocal Fold Atypia and Early Cancer

Vocal fold cancer and atypia usually affect the surface cells (**epithelium**) of the vocal fold. The surface cells have typical features and are referred to as squamous cells. Vocal fold cancer is frequently squamous cell cancer, although other cell type cancers can

occur.

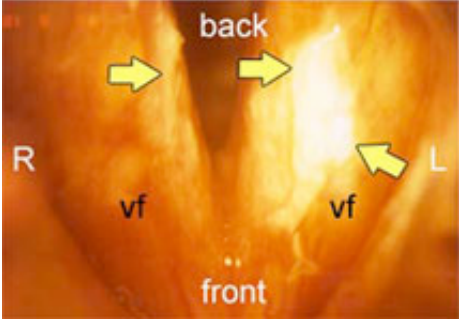
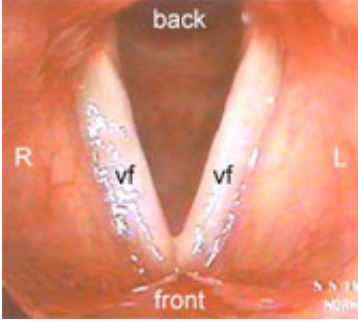
The Atypia - Cancer Spectrum

Vocal fold cancers are thought to start out as pre-malignant vocal fold atypia. In fact, vocal fold atypia may be present for many years before transforming into cancer. The reason why this transition occurs is still unknown.

Red Flag

Early Detection Is Key

Uncertainty surrounding the transition of atypia into a cancerous lesion underscores the importance of seeking medical care for the condition as early as possible.

Atypia on left Vocal Fold	Normal Vocal Folds
	
A "close-up" view showing atypia lesions [indicated by arrows] on the left and right vocal fold (vf). The lesion on the right is smaller.	Normal vocal folds with no lesions on surface.

What are the causal risk factors of atypia or early stage cancer?

Smoking – the Most Significant Risk Factor of Atypia and Early Stage Cancer

- Vocal fold atypia and cancer usually present in men over the age of 45 who have smoked significantly. Risk for atypia or cancer is higher as the number of cigarettes smoked and the number of years spent smoking increases.
- Non-smokers rarely develop vocal fold atypia or vocal fold cancer.
- Interestingly, physicians' knowledge about the risk of smoking is based on the observation that vocal fold atypia/cancer was relatively uncommon prior to the introduction of mass-produced cigarettes around 1910.

Other Risk Factors

Although smoking is the main cause of atypia/cancer, other risk factors do exist.

- Viral infection of vocal folds, such as **recurrent respiratory papillomatosis (RRP)** and **verruccous vulgaris**, may be precursors to atypia/cancer. *(For more information, see RRP-Papillomatosis.)*
- The backflow of stomach fluids to the voice box/laryngeal area (**reflux laryngitis**) leads to inflammation and risk for cancer. Unlike the surface lining cells of the stomach, the surface lining of the voice box is highly sensitive to the acidity of stomach fluids. *(For more information, see Reflux Laryngitis.)*

Symptoms of Laryngeal Atypia and Early Cancer

Symptoms of Laryngeal Atypia and Early Cancer

Key Perspectives

- Vocal fold atypia and cancer can cause a wide range of symptoms that will affect a person's ability to speak and, in some cases, breathe.
- Because symptoms are similar for both atypia and cancer, symptoms alone can never be used to distinguish between vocal fold atypia and early cancer.
- Since many different abnormalities of the vocal folds can cause similar symptoms, a complete and full medical workup is important.

Voice-Related Symptoms

- Atypia and early cancer lesions reduce the ability of vocal folds to vibrate during speaking and singing. This results in voice complaints frequently described by patients as:
 - Gradual and progressive hoarseness
 - Rough, irregular quality to voice
 - Inability to project voice
 - Effortful phonation
 - Voice fatigue, especially at the end of the day
- **Hoarseness:** Hoarseness, common in both vocal fold atypia and early cancer, starts gradually and is usually progressive, changing little over months or years. Often friends, or family members, first detect a change in voice quality, rather than patients (who hear their own voices daily).
- **Common cold can spur symptoms:** Hoarseness and other symptoms may present just after a cold. The common cold does not cause the cancer, but rather causes a sudden worsening of voice quality.

Breathing Symptoms or "Airway Symptoms"

Breathing symptoms are rare but can occur in patients with vocal fold atypia and early cancer. When a lesion mushrooms outwards – rather than burrowing deep into the vocal fold – the passage of air through the voice box can be blocked. Breathing symptoms might also be caused by another problem present at the same time.

- **Difficult breathing (dyspnea):** A patient's labored breathing may be first noticed by a family member while the patient is sleeping. Dyspnea may also occur during physical exercise – even during a simple activity such as walking up stairs – when airflow demands are greater.
- **Noisy breathing (stridor):** Stridor results from a narrowing of the opening between the vocal folds (glottis).

Red Flag

- Noisy breathing (stridor) is a sign of obstruction or narrowing of the laryngeal or tracheal parts of the airway.
- Stridor is a sign of difficulty passing air.
- Any breathing difficulty needs immediate medical attention.

Inadequate Breath Support

Patients may have difficulty maintaining adequate breath support – often described by patients as a feeling that their voice

trails off due to "lack of air behind it." This feeling may be due to a lesion blocking the smooth flow of air into the windpipe or because much more air is required to drive the vocal folds into vibration.

Coughing Up Blood

In rare instances when the lesion surface becomes eroded or irritated, it may bleed, causing patients to cough up small amounts of blood. This condition is known as hemoptysis.

Smoking's Effect on Symptoms

Smoking is the single greatest risk factor for developing vocal-fold atypia and cancer. However, individuals who have smoked for many years often have a low, rough, scratchy quality to their voice – frequently referred to as "smoker's laryngitis." Unfortunately, smoker's laryngitis makes it harder to detect hoarseness due to vocal fold atypia or cancer in smokers.

Red Flag

A scratchy, low voice in a smoker should not be simply dismissed as "smoker's laryngitis," since vocal fold cancer, a potentially life-threatening disease, might be present.

Diagnosis of Laryngeal Atypia and Early Cancer

Minimal Role of Radio-Imaging

Interestingly, **radiographic imaging** (CT scan, MRI, X-ray) is usually not useful in the detection of vocal fold atypia or early cancer, because these imaging techniques do not currently provide enough detail and resolution of these early lesions. However, radiographic imaging can be helpful in detecting the spread of cancer to other body locations such as the lungs, head, and neck.

Typical Findings of Vocal Fold Atypia and Early Cancer

Finding	Description	Likely Diagnosis
White Lesions (keratosis or leukoplakia)	A white, rough, irregular lesion on the surface of the vocal folds	95% Atypia
Red Lesions (erythroplakia)	A reddish, rough, irregular lesion on the surface of the vocal folds	Carcinoma in-situ
Papular Red Lesions	Reddish lesions with small "bubbles" on surface	Carcinoma in-situ
Exophytic Lesions	Irregular lesions that stick outwards from the vocal folds	Usually advanced cancer

Classifying Atypia and Early Cancer

The three main aspects of early vocal fold cancer that are helpful in determining treatment plans are:

- Location of lesion
- Effect on vocal fold (arytenoids) mobility
- Effect on mucosal vibration

If the lesion is cancerous, the first two characteristics will determine the stage of disease.

Location and Depth of the Lesion

- **One-sided or both vocal folds affected:** The most important issue with regard to the location of early vocal fold cancer is whether it is present on one or both vocal folds. The number of vocal folds involved has greater impact than the size of the lesion on the treatment outcomes for early cancer.
- **Spread to anterior commissure tendon:** One specific aspect of spread pertinent to treatment is whether a lesion has traveled into the anterior commissure tendon (**Broyle's ligament**). This ligament forms a bridge between the vocal folds. In general, bilateral cancers do spread onto this tendon as they pass over onto the second vocal fold. If this tendon is involved, physicians must determine whether further spread (for example, into the thyroid cartilage) has occurred.
- **Cancer spread determines treatment plans:** The extent of cancer spread determines the treatment plan for a patient. Fortunately, through advances in microsurgical techniques and radiation therapy (XRT), early cancer lesions that have spread to different points within the larynx can be treated with 90 to 95 percent effectiveness.

Effect of a Lesion on Vocal Fold Mobility

Not surprisingly, a lesion that invades a vocal fold deeply or spreads to the **cricoarytenoid joint** can prevent vocal fold

movement. *(For more information, see Anatomy & Physiology of Voice Production.)*

Effect on Ability of Vocal Folds to Vibrate

Even if restricted to the top layers of the vocal folds, atypia and early cancer result in poor vocal fold vibratory function, hence voice disorder. This is not surprising given that the vocal fold mucosa – which is composed of the epithelium and superficial lamina propria – is a key player in vocal fold vibration. Abnormalities in vocal fold vibration result in hoarseness and other voice symptoms.

Additionally, swelling that often accompanies early cancer hinders vocal fold vibration.

Diagnosis by Microscopic Analysis

The only true method to determine whether a lesion is atypia or cancerous is to excise all or part of the growth and perform a microscopic analysis of the lesion's cellular characteristics. Visual examination of the lesions on the surface does not allow a definitive diagnosis.

Treatment of Laryngeal Atypia and Early Cancer

Dual Purpose: Diagnosis and Treatment

The overall management of atypia and early cancer is similar, each requiring the precise removal of all or part of the involved vocal fold tissue for microscopic examination [**excisional biopsy**]. Often the entire lesion is removed during excisional biopsy. If the entire lesion is removed – with an edge of normal tissue surrounding the abnormal tissue – no further treatment (chemotherapy or radiation therapy) is necessary.

Key Information

Voice Preservation and Cancer Treatment Possible

Unlike cancers in most other parts of the body, early vocal fold cancers do not always require removal of a significant amount of normal tissue when surgically treating lesions. Excision of the early cancer and preservation of normal tissue result in better voice outcomes.

90 to 95 Percent Cure Rate for Early-Stage Cancer

Early diagnosis and complete excision result in excellent cure rates.

Microscopic Analysis of Cellular Features – Histopathological Analysis

After excision of a lesion, a microscopic analysis of the lesion's cell features will be performed to determine:

- Whether or not the lesion is cancerous
- Whether or not the resection successfully removed the entire lesion along with a non-cancerous surrounding margin

Perspective on Surgical and Radiation Therapy for Early Cancer

- **General rule for surgical excision:** As a general rule, any vocal fold lesion that has not penetrated through the **basement membrane** of the **vocal fold epithelium** is treated via surgical excision. By definition, atypia never invades lower than this point, although cancer may.
- **Normal vocal fold "untouched" in surgical excision:** Surgical excision may result in a better vocal outcome than radiation therapy (XRT) because the normal vocal fold is not touched in surgical excision, while both vocal folds are affected in radiation therapy.
- **Radiation therapy is single-use:** Use of radiation therapy in the treatment of early cancer may be undesirable, since XRT is a single-use cancer treatment and would be considered unnecessary for minimal microscopic disease. The excisional biopsy that is necessary to establish the diagnosis may be adequate treatment for a small lesion.

Key Information

- Treatment for vocal fold early cancer must be individualized.
- Decisions regarding the use of radiation therapy or surgery will depend upon the nature of the lesion (size, depth, location), a patient's vocal needs, the experience of the surgeon and radiation therapist, and other pertinent medical factors.

What are the complications of treatment for vocal fold atypia/cancer?

Both radiation therapy and phonosurgical excision can cause a number of complications. Patients should discuss treatment and possible complications of treatment with their physician.

In Brief: Complications Associated with Phonosurgery

Complication	What Happens	Why It Occurs	Treatment
Hemorrhage	Bleeding; coughing up blood	Re-bleeding after surgery	If uncontrolled, need for surgical intervention
Airway obstruction	Blocked airway causing breathing difficulties	Can result from swelling, although rare	<ul style="list-style-type: none"> Establish temporary airway Remove excess tissue causing the blocked airway
Granuloma formation (<i>For more information, see Vocal Fold Granuloma</i>)	Inflammation-response growths on vocal folds over irritated areas	Usually occurs with reflux	<ul style="list-style-type: none"> Anti-reflux therapy Voice rest Surgical excision when necessary
Vocal fold scarring	Scar tissue formation in vocal folds	Scar-response to surgical excision	No definitive treatment at present
Excess hoarseness and dysphonia	Voice symptoms greater than expected after surgery	Lack of breath support, aerodynamic inefficiency	<ul style="list-style-type: none"> Voice therapy Medialization procedures

In Brief: Complications Associated With Radiation Therapy (XRT)

Radiation therapy can cause side effects and complications that affect voice outcomes. The area affected by XRT side effects or complications is larger than that affected by phonosurgery because XRT treatment affects a broader area and does not distinguish between normal and cancerous cells. Current efforts increasingly try to target XRT to the cancerous lesion.

Complication	What Happens	Why It Occurs	Treatment
Fibrosis of the normal vocal fold epithelium	Fibrous tissue formation, resulting in loss of vocal fold pliability	Radiation therapy does not distinguish between normal and cancerous areas; also results from injury and inflammation	If reflux present, anti-reflux treatment
Vocal fold dryness (<i>laryngitis sicca</i>), which produces hoarseness	Dry mucous membranes, decreasing ability of vocal folds to vibrate	Destruction of mucous glands from radiation, which affects both cancer cells and normal cells	No reliable, definitive treatment at present

In Brief: Serious Complications Associated with Radiation Therapy (XRT)

Rare	Very Rare
<ul style="list-style-type: none"> Chondroradionecrosis of the thyroid cartilage Arytenoid fixation <p>Note: Both complications can drastically limit vocal fold function, impairing voice</p>	Additional primary cancers over a period of years

Peri-Operative Care

- **Anti-reflux therapy:** After surgery, treatment for backflow of stomach fluids to the voice box area (**laryngopharyngeal reflux**) will be provided, since reflux frequently occurs post-surgery. The exposure of "raw" surgical wounds within the larynx to acidic stomach fluids that have backflowed to the area could significantly hamper healing and recovery and increase risk for complications. (*For more information, see Reflux Laryngitis.*)
- **Antibiotics:** As with most surgical procedures, preventive antibiotic treatment may be provided to minimize the risk of post-surgical infections.
- **Analgesics:** Reduction of pain after surgery helps recovery to proceed as quickly and painlessly as possible.
- **Voice rest:** Complete voice rest is usually advised for about two weeks, with modified voice use advised for two additional weeks, in order to optimize healing and the recovery of voice function.
- **Voice therapy:** Often, both preoperative and postoperative voice therapy are recommended to help patients recuperate from surgery and rehabilitate voice after surgery. (*For more information, see Voice Therapy.*)

Red Flag

Atypia Frequently Recurs

- Although removal of atypia typically precludes the later development of cancer, atypical epithelium frequently recurs and requires repeat endoscopic excisions.
- New phonosurgical developments in resection and reconstruction have facilitated improved voice outcomes despite repeated surgical removal of atypia.

Vocal Fold Reconstruction After Phonosurgical Management

Once the voice box has healed from removal of the lesion, vocal fold reconstruction can be done if/when necessary. Vocal fold reconstruction may involve medialization to help bring the vocal edge(s) to the middle, resulting in better glottic closure and allowing vocal fold vibration during sound production.

Monitoring for Lesion Recurrence

For both atypia and early cancer, follow-up monitoring after surgery is important to detect whether atypia has recurred (as it frequently does) or whether another primary cancer lesion has developed. Since a cancerous lesion poses more of a health risk than atypia, follow-up schedules for cancer are usually more rigorous.

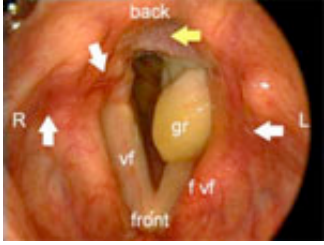
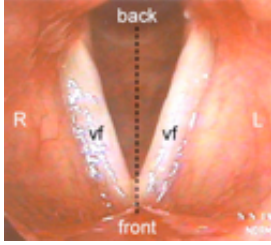
The table below highlights a typical follow-up schedule for patients whose lesions have been successfully removed. This timeline can be varied depending on the specific clinical characteristics and needs of an individual patient.

Follow-Up by Severity

Atypia (Less Severe)	Carcinoma in situ	Early Cancer (More Severe)
Follow-up care is individualized based on: <ul style="list-style-type: none">• severity of atypia• response to surgical excision• patient and surgeon preference• logistic and geographic limitations	Monthly follow-up similar to early cancer schedule	<ul style="list-style-type: none">• First year: every month• Second year: every other month• Third year: every third month• Fourth year: every fourth month• Fifth year and indefinitely: every 6-12 months

Images of Vocal Fold Granuloma

Comparison of Vocal Fold With Granuloma and Reflux Laryngitis Versus Normal Vocal Folds

Vocal Fold Granuloma	Normal Vocal Folds
 <p>A granulo (gr) is detected as a yellowish growth covering the right arytenoid process. Irritation from reflux of stomach fluids into the voice box is also detected with redness and swelling in vocal folds (vf) and false vocal folds (f vf) and pachyderma or thickening of tissue in the back of vocal folds.</p>	 <p>In contrast, a normal voice box (larynx) does not have any growths, and does not exhibit redness, swelling, or any thickening of the surface cover.</p>

This diagram can be found in Vocal Fold Granuloma: Understanding the Disorder.

Laryngeal Atypia and Early Cancer: Vocabulary

Vocal Fold Atypia

Non-cancerous but irregular cells in vocal fold epithelium; often leads to cancer; often recurs after removal

Vocal Fold Early Cancer

Cancer of vocal fold epithelium that is confined to the vocal folds and has not spread

Vocal Fold Epithelium

Surface lining of vocal folds composed of squamous cells

 **Advisory Note**

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