

## Review

# Biomarkers and Imagistic Methods for Early Diagnosis and Prognostic of Laryngeal Cancer

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## REZUMAT

### *Metode imagistice și biomarkeri cu rol în diagnosticul precoce al cancerului laringian*

Carcinomul scuamos laringian este cel mai frecvent întâlnit tip de cancer din sfera capului și gâtului și reprezintă 1-2% din totalul cancerelor, la nivel mondial înregistrându-se aproximativ 540 000 cazuri noi anual și aproximativ 270 000 de decese, rata de mortalitate fiind aproape 50%. Principalii factori de risc în apariția cancerului cavității orale, orofaringelui și hipofaringelui sunt consumul de alcool și fumatul. Virusul papilomatozei umane (HPV) a fost de asemenea un factor înscriminat. Toți acești factori duc la modificări citologice și structurale ale epiteliului laringian. În ciuda tuturor posibilităților terapeutice pentru stadiile avansate ale acestei patologii (radioterapie, chirurgie, terapie sistemică) 40-60% din pacienți au recurențe locale. Noile metode de diagnostic ce țin de biologia moleculară prin intermediul profilului molecular au deschis calea spre noi posibilități terapeutice iar terapia țintită începe să câștige din ce în ce mai mult teren.

**Cuvinte cheie:** cancer laringe, biomarkeri, recidivă tumorală, calitatea vieții

## ABSTRACT

Laryngeal squamous cell carcinoma is the most common type of cancer of the head and neck area and represents 1-2% of the global malignancies that occur worldwide. There are approximately 540,000 new cases every year and about 271,000 deaths, which shows the mortality rate to be easily over 50%. The main risk factors for cancers of the oral cavity, larynx, oropharynx, and hypopharynx are tobacco and alcohol use. The human papillomavirus (HPV) has also been proved to be a cause of oropharyngeal cancer. All these factors may determine cytological and structural changes in the laryngeal epithelium. Despite all the possibilities of treatment for locally advanced disease (various combinations of radiotherapy, surgery, and systemic therapy), 40% to 60% of the patients will develop recurrence. The better understanding of the molecular biology of the

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disease through molecular profiling has opened new treatment possibilities that are starting to be explored and the role of targeted therapy is gaining interest.

**Key words:** larynx cancer, biomarkers, recidiva, quality of life

## INTRODUCTION

For years, intermediate and advanced staged tumors were approached with total laryngectomy and post-operative RT until 1991, when the Veterans Administration Larynx Study and other subsequent organ preservation trials established the role of chemo radiation in the upfront treatment of intermediate laryngeal cancers (stage III and early IV a).

Surgical management of the larynx and hypopharyngeal malignancies have become increasingly challenging as surgical organ preservation strategies are applied. Failures of these protocols are often accompanied by post radiation sequels, which enhance post-surgical complications when a salvaging laryngectomy/laryngopharyngectomy is undertaken.

That is why, having a prognosis scale for this type of cancer would be a great help for the surgeons who would be able to easier decide which surgical technique to use, or if medical treatment is to be taken into consideration in order to preserve the larynx function and to reduce the risk of recurrences. There is currently no prediction scale of laryngeal cancer and no biological markers that are accurate enough to assess this type of cancer.

### Relevant Biomarkers and imagistic methods

There are some studies that have demonstrated correlations between markers of systemic inflammation and the evolution of some types of malignant tumors.

Very recent studies (Kacan et al, 2014, Kemal et al, 2014) try and manage to a large extent to achieve a correlation between the change ratio neutrophil / lymphocyte and increased risk of tumor recurrence, increased tumor aggressiveness, worse prognosis and increased risk of metastasis in various types of malignancies.

Biological prognostic factors that are presently used in the immunohistochemical studies in the vast majority of malignant pathological examinations are:

- P53 Oncogene is a protein encoded by the oncosuppressor gene P53 and is located on the

short arm of chromosome 17; this protein "monitors" cell cycle, "preventing" cancer appearance. It is present in all normal cells. Alteration of the normal structure of the p53 protein results in a mutant p53 protein that is expressed but does not have the oncosuppressor function, which leads to inefficient tumor suppression. P53 gene mutations have been proved to show poor prognostic, higher tumor aggressiveness and early metastasis. Its detection during the stage of dysplasia may raise some important questions regarding which medical protocol is to be implemented.

The association with other factors of poor prognosis during an early stage can help the doctor in deciding for a more aggressive therapeutic approach.

- COX2 (Cyclooxygenase 2) - increases prostaglandin synthesis and cell proliferation, promotes angiogenesis, increased invasion and inhibition of apoptosis.
- Fox P3 (forkhead transcription factor) - is a marker that is found in tumor cells and has a fairly direct relationship with cancer of the head and neck area. It is associated with poor prognosis and it seems that in combination with a modified marker COX-2 their prognostic values are more important than the individual.
- D1-Cyclin seems to have an oncogenic role in laryngeal cancer, but unknown prognostic value.
- PCNA (proliferation cell nuclear antigen) - is a nuclear protein from the cyclin family, whose level of synthesis correlates directly with the rate of proliferation and DNA synthesis and quantify tumor progression and proliferation.
- Ki-67 - is a nuclear protein that is elevated in active phases of the cell cycle, and is absent in G0. It provides information on cells that are in cycle but not on the duration of the cycle. It is important to note that cells that are Ki-67 positive are more sensitive to radiation and chemotherapy.

Associations of P53, Ki-67 and PCNA appear to have a higher prognostic value than of that of each

marker individually.

- EGFR (Epidermal growth factor) is a membrane receptor that controls proliferation, apoptosis, angiogenesis, cell adhesion and motility. It is an important factor in tumor angiogenesis.

Its overexpression in malignant tumors is correlated with disease progression, lower chance of response to radio and chemotherapy and decreased survival time.

- VEGF (Vascular endothelial growth factor) shows proliferation, differentiation and migration of endothelial cells from existing blood and lymphatic vessels. Its detection is an important factor for the prognosis of early metastasis.
- SOX 2 is a new factor studied as a prognostic factor in the pathology of malignant tumors of the head and neck and appears to have a role in early detection of the tumor but not in its prognosis.
- TIMP-1 (tissue inhibitor of metalloproteinase - The one) - although it is a known factor in the prognosis of malignant diseases there are very few studies and its role is still unknown regarding larynx cancer.

Another type of high-impact investigations especially useful in early diagnosis and also have prognostic value are imagistic investigations.

Endoscopic investigations - and especially Narrow band imaging (NBI) is a new imaging technique that detects specific tumor neoangiogenesis. It is considered a significant improvement in the possibility of detecting early mucosal lesion of the upper aerodigestive tract. Early detection of mucosal neoplastic lesions is important for patients survival. The studies show, especially in patients previously treated by means of curative radiotherapy or chemoradiotherapy, that early detection rate of recurrent disease is quite low. Studies show that the accuracy, sensitivity, specificity, and positive and negative predictive value of the method are very high (88%, 92%, 76%, 96%, and 91%, resp.).

CT and MRI examinations are very important for clinical staging of laryngeal cancer. Studies show that CT has an accuracy of 70% and MRI has an accuracy of 80%.

PET CT scan is a non-invasive procedure using tracers labeled with positron emitters such as fluorine -18. Its specificity and positive predictive value and negative predictive value regarding tumor

recurrence of about 91%, 81%, 64% and 96% makes it an investigation with a high degree of prognostic for tumor recurrence. In addition, PET has an increasing role in therapy response assessment after chemoradiotherapy. This post-therapy evaluation to identify which patient will benefit from neck dissection is considered an indication by National Comprehensive Cancer Network and Society of Nuclear Medicine guidelines.

Molecular profiling is yet another investigation which is used on increasingly larger scale. It establishes a targeted therapy and helps oncologists to skip some steps in therapy induction, and also has scientific value in discovering the functioning mechanisms of oncogene.

## CONCLUSIONS

Squamous cell carcinoma of the larynx is a heterogeneous disease at both anatomical and molecular level. There is a need for multidisciplinary team to adequately manage and monitor the outcome. There is an important improvement in technology (radiation technique, chemotherapy, imaging, surgery techniques) and all this has improved the outcome of the patients. Although there are multimodal treatment options, including surgery, RT, chemotherapy, 40% to 60% of the patients with locally advanced larynx carcinoma will relapse. There are multiple ongoing clinical trials that raise important questions about treatment sequences and the importance of function preservation of the organ. The better understanding of the molecular biology of the disease through molecular profiling has opened new treatment possibilities that are beginning to be explored and the role of targeted therapy is starting to win ground.

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