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REVIEW

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Prognostic factors in laryngeal squamous cell carcinoma

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Abstract

Background: The current treatment results of laryngeal squamous cell carcinoma still remain modest. Various prognostic factors have been investigated and need to be included in the management decision making.

Methods: We reviewed the pertinent literature regarding host, tumor, and treatment factors as prognostic indicators that influence outcome in patients diagnosed with laryngeal squamous cell carcinoma.

Results: Host, tumor, and treatment factors all have an important impact upon an individual patient's prognosis with laryngeal squamous cell carcinoma, whereas staging systems only take into account tumor factors. There is much work yet to be done to establish reliable, independent biomarkers that predict survival and response to treatment.

Conclusions: Optimal outcomes for an individual patient can be achieved when taking into account tumor, host, and treatment factors.

KEYWORDS

laryngeal squamous cell carcinoma, overall survival, prognostic factors

1 | INTRODUCTION

The current treatment results of laryngeal squamous cell carcinoma still remain modest with global 5-year overall incidence rates of 154 977 male cases and 22 445 female cases in 2018.[1] In 2018, there were 81 806 male deaths and 12 965 female deaths worldwide from larynx cancer. The 5-year relative survival rate for all stages of larynx cancer varies widely according to tumor site and stage. Various factors predict the outcome of malignant neoplasms of the larynx. These can be grouped into host, tumor, and treatment. Host factors include age, gender, nutritional status, physical and psychological performance status, comorbidities, and immunological response. Tumor factors include tumor site, TNM stage, grade, and the presence of a second primary

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cancer (synchronous or metachronous). Treatment factors include all available approaches to therapy and various combinations of these modalities in addition to location of treatment, that is, academic or research/teaching hospitals vs community hospitals. We reviewed the pertinent literature regarding host, tumor, and treatment factors as prognostic indicators that influence survival outcome in patients diagnosed with laryngeal squamous cell carcinoma. Host, tumor, and treatment factors all have an important impact upon an individual patient's prognosis with laryngeal squamous cell carcinoma, whereas current staging systems only take into account tumor factors.

2 | HOST FACTORS

2.1 | Age

Data in the literature are controversial concerning the effects of age on survival. Some authors state that the prognosis is better in younger patients, whereas others report it being better in the elderly. In the general head and neck cancer population, younger age has been considered as a positive prognostic factor. In a series of 1030 head and neck cancer patients, Lacy et al found that younger patients had a significantly better five-year survival rate than middle-aged or old patients.[2] Age remained a significant factor even after controlling for smoking, comorbidity, primary site, TNM stage, and nodal disease. Young patients also developed fewer recurrences and second primary tumors. In the population-based study by Misono et al comprising 10 429 patients in the Surveillance, Epidemiology, and End Results (SEER) database, better survival was observed with younger age.[3] Conversely, in a smaller Norwegian series of 1616 laryngeal squamous cell carcinoma (LSCC) patients, an increased risk for a recurrence was observed in patients who were younger than 70 years.[4]

2.2 | Gender

The site of laryngeal carcinoma differs widely according to gender. Women are more likely to have cancer of the supraglottis than of the glottis. In a review, the ratio of glottic to supraglottic tumors was 2.12:1 in men and 0.56:1 in women, which remains highly significant.[5] In a multicenter study comprising 4005 patients with head and neck cancer, women with laryngeal cancer had a reduced risk for recurrence compared with men (HR = 0.39, 95% CI: 0.24-0.74).[6] In a series of 1252 consecutive patients with LSCC who all were treated with primary radiotherapy, multivariate analyses revealed that male gender was a significant factor in predicting locoregional failure, death from cancer, and death from all causes.[7]

2.3 | Nutritional status

Malnutrition is a common problem among patients with advanced laryngeal cancer. In a retrospective study by Li et al of 473 patients with LSCC, low BMI before treatment was significantly associated with poor overall survival as an independent poor prognostic factor ($P < .001$).[8] This correlates closely with the host's immunocompetence. Patients in negative nitrogen balance have a poorer general condition and respond less well to therapy.[9] In particular patients with weight loss of more than 10% during the 6 months before surgery are a great risk for the occurrence of major postoperative complications.[10] Clearly, there are challenges with optimizing nutrition in patients diagnosed with larynx cancer and undergoing treatment. Malnourished patients should be supported with pre-treatment tube feeding nutritional support.[11] Drawing upon literature from other patient cohorts, there is evidence that high carbohydrate supplements preoperatively improve outcome in colorectal surgery.[12]

2.4 | Performance status

World Health Organization (WHO) performance status for each patient is an important factor to be included in the decision making when the type of individual LSCC treatment is considered (Table 1). In addition to smoking and drinking being prevalent among LSCC patients and affecting their performance status also comorbidities have an impact. Bøje et al studied the impact of comorbidity on treatment outcome in a series of 12 623 Danish head and neck cancer patients and found that 36% of them were affected by comorbidity at the time of diagnosis.[13] Poor general condition has been related to the risk of recurrences[14,15] and it naturally deteriorates with increasing age.[16] Anemia has been recognized as a factor contributing to decreased locoregional control after definitive RT for T1-T2N0 glottic LSCC.[17] This was supported by the study by Johansen et al in a series of 1252 Danish LSCC patients treated with primary radiotherapy.[7] Hemoglobin was found to be an independent prognostic factor. The host's general condition is usually evaluated according to different systems. Some of them are also used in oncology to measure the quality of life of cancer patients, as for example the Performance Status Scale for Head and Neck Cancer Patients,[18] the Spitzer Quality of Life

TABLE 1 WHO performance status

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Index,[19] the Functional Assessment of Cancer Therapy-Head and Neck Version,[20] and the Charlson Comorbidity Index.[21,22]

List et al suggest the use of the Functional Assessment of Cancer Therapy—Head and Neck Scale and the Performance Status for Head and Neck Cancer Patients to describe performance status and quality of life of head and neck cancer patients.[23] The patient's performance status can affect not only prognosis but also the choice of treatment.[24] Patients with decreased functional capacity may be deemed "too sick" for one treatment (eg, surgery) and thus receive an alternative (eg, radiotherapy).[24] Patients with cancer of the larynx often have other diseases and illnesses in addition to their cancer. These other conditions, which are generally referred to as comorbidities[25] have a profound effect on treatment selection and prognosis.[26]

Piccirillo and Feinstein[24] have emphasized that the American Joint Committee on Cancer (AJCC) TNM system for cancer staging is old and is constrained in its ability to provide useful prognostic information. Tumor descriptive data are conserved to four disease "stages," which are associated with a statistical gradient, but this staging process is very limited in terms of predictive utility. Information beyond the gross and microscopic extent of the cancer is needed to recommend optimal and individualized treatment regimens and to answer questions raised by our patients.

As our knowledge of tumor biology and molecular markers increases, we will be able to expand the number of significant variables available to predict tumor behavior, host resistance, and the probability of a successful outcome. The presence of comorbidity influences treatment selection and subsequent outcome.[13] Chemoradiotherapy is used less often in patients older than 70 years of age and in those with comorbidity.[27] Having a comorbidity was associated with higher rates of postoperative complications.[28] However, having a comorbidity does not impact the effectiveness of radiation therapy.[29] A meta-analysis was performed using comorbidity as a prognostic factor showed that overall survival was significantly poorer for patients with comorbidity.[29]

2.5 | Immunological response

The cellular immunologic function of laryngeal cancer patients is lower than that of healthy persons and the function of late-staged patients is lower than that of the early-staged patients.[30] Many patients with cancer of the larynx have immune deficits or abnormal immune reactions but this altered immunologic condition could depend on multiple mechanisms (alcohol abuse, viruses, malnutrition, aging, etc.). There are data to support adverse prognostic impact with immunosuppressed patients.[31]

3 | TUMOR FACTORS

3.1 | Site

The Surveillance, Epidemiology, and End Results (SEER) database tracks relative 5-year survival rates for larynx cancer in the United States. Five-year relative survival rates for patients with larynx cancer varies according to primary tumor site. Based upon data from SEER 2009-2015, 60.3% of patients diagnosed with laryngeal cancer survive 5 years.[32] The 5-year relative survival rates for localized laryngeal cancer is 77.4%, with regional involvement, the survival decreases to 44.7% at 5 years, and only 33.3% of patients with distant disease survive 5 years.[32] The 5-year relative survival rates for supraglottic cancers, according to the SEER database, is 46%. Glottic cancers have the best 5-year relative survival rate, 77%, due to a higher percentage of patients presenting with localized disease (83%). Patients with subglottic primary tumors have a 5-year relative survival rate of 53%.[32] Further, supraglottic primary tumors more often recur when compared with those with glottic primary tumors.[4,7] Supraglottic tumors are known to have higher rates of regional nodal metastasis, whereas the glottic site is a relative watershed area for lymphatic spread.

3.2 | T class

When the International Union Against Cancer published the document *TNM Classification of Malignant Tumours* in 1987[33] and the American Joint Committee on Cancer followed with the same system in 1988[34] there was agreement for the first time on the TNM classification for laryngeal cancer. It is important to recognize that the TNM laryngeal cancer classification provides a standardized group of categories for patients with laryngeal cancer, which is to say that the system allows us to *stratify* patients according to the stage of their disease at presentation.[35] We may thus share clinical observations from different parts of the world, confident in the knowledge that we are comparing similar groups of patients. The TNM system provides information on the primary tumor's anatomical location and size and on the presence of regional and distant metastases. Of course, this information is useful in predicting survival. Considerable discrepancies can occur between pretherapeutic classification and the actual extension of the tumor on pathologic analysis, particularly in the case of the larger lesions. Despite recent advances in imaging techniques (CT and MRI), the tumor's extension and especially its depth of invasion are clinically very difficult to assess.

Increasing T class and stage was noted as a risk factor for recurrence in glottic LSCC in a Danish series with 5001 LSCC patients treated with curative intent[36] and also in the series of 1252 consecutive LSCC patients by Johansen et al.[7] Local extension of the primary has an effect on treatment outcome. For example, in glottic tumors the invasion of anterior commissure has been reported to increase the risk of local failure of treatment.[37,38]

3.3 | N class

Treatment and prognosis for patients with laryngeal cancer are determined mainly by nodal status. The most significant single prognostic indicator is the presence or absence of metastatic cancer in cervical lymph nodes. This is supported both by the findings by Johansen et al[7] in a study of 1252 consecutive LSCC patients treated with

primary RT and by Lyhne et al[36] studying 5001 patients with glottic LSCC in Denmark. Contralateral or bilateral nodal involvement is more common in supraglottic primary tumors and portends a negative prognosis. Although the number, size and level of invaded nodes is clearly important, these factors are secondary to the overriding prognostic significance of extracapsular spread.[39] Errors in determining the presence and size of occult lymph node metastases have been reduced by the use of ultrasound, ultrasound-guided fine-needle aspiration biopsy, CT, MRI, and PET scans, all of which can improve the accuracy of clinical staging in advanced disease. Use of the AJCC/UICC TNM system provides prognostic information. In conclusion, the extent of cervical lymph node metastatic distribution is clearly of paramount prognostic importance.

3.4 | M class

Distant metastases in squamous cell carcinoma are usually preceded by lymph node metastases. Blood-born metastases are uncommon, but widespread dissemination to various viscera may occur in advanced stages of laryngeal cancer. The sites which appear to be most affected by distant metastatic spread are the mediastinal lymph nodes, lungs, liver, pleura, skeletal system, kidney, heart, spleen, and pancreas.[40] The cavernous sinus and temporal bones are an unusual site for metastasis. Naturally, distant metastases have been correlated with a poor prognosis.

3.5 | Histological grading of malignancy

Approximately 90% of malignant neoplasms of the larynx are squamous cell carcinomas and can be graded as well differentiated (G1), moderately differentiated (G2), or poorly differentiated (G3). The degree of a neoplasm's differentiation should not be confused with its histological grading. Factors allowing for better assessment of the histological grading of malignancies include[1]: degree of structural differentiation,[2] cellular anaplasia or pleomorphism,[3] mitotic activity index (frequency and abnormality of mitotic figures),[4] expansive or infiltrative growth,[5] inflammatory response to the tumor,[6] necrosis, and[7] lymphatic and blood vessel invasion.

Poorly differentiated cancers usually have a higher rate of metastatic disease when compared with well-differentiated cancers, but this correlation is not always valid.[41] Also, the degree of differentiation suffers from the subjectivity of interpretation by pathologists.

3.6 | Perineural invasion

The presence of perineural invasion (PNI), affecting small nerve is associated with an increased risk of local recurrence and regional nodal spread and has a negative impact upon the prognosis of patients with laryngeal cancer.[42]

3.7 | Biological markers

There are now numerous emerging technologies that promise to provide much more prognostic information on neoplasms. Among the developing technologies are: immunohistochemistry (immunohistochemical detection of proliferation markers, such as the proliferating cell nuclear antigen [PCNA] and Ki-67 [MIB 1]), molecular biology analysis (p53, c-myc and ras, EGFR, and TGF-α), nucleolus organizer regions (NORs), the determination of clonality by molecular diagnostic techniques including the polymerase chain reaction (PCR), the use of in situ hybridization (ISH), DNA ploidy by flow cytometry or image analysis, TUNEL, cell cycle regulators (including p34cdc2 or CDK1, and the D family of cyclins), among others.[41] All present biological parameters are often of "unproven" prognostic value. Considering the current situation, it is impossible to define subgroups of patients with a different biological behavior. Additional studies are needed to confirm these findings and compare the prognostic value of these and other biomarkers with other parameters in large groups of patients, with the support of sophisticated statistical analysis. Many papers complete the discussion with an inconclusive remark, such as "this marker could be of valid prognostic significance" but no acceptable marker of prognosis has been identified thus far for clinical application in patients with cancer of the larynx. The limitations of currently used biological markers in predicting tumor behavior are well recognized in laryngeal oncology. Conversely, there are many diagnostic markers that are very useful to support the histologic diagnosis (such as neuroendocrine markers, etc.). However, having emphasized the need to consider the prognostic implications of the new technologies with caution, it is worth mentioning a few of the most promising reported to date.

EGFR overexpression is established as a poor prognostic marker in LSCC.[43] However, no benefit regarding larynx preservation was observed in a randomized trial by Bonner et al where cetuximab—a monoclonal antibody targeting EGFR—was added to RT.[44]

The possibility to estimate LSCC radiosensitivity prior to treatment remains an unsolved problem and there are no clinically applicable means for this. WRAP53β has been suggested as a potential biomarker for predicting RT/CRT response in T2-T3N0 glottic LSCC.[45]

Recently, expression of sex hormone receptors, such as estrogen receptor (ER-β) and progesterone receptor (PR), was studied by Atef et al and was found significantly higher in poorly differentiated cases and cases with lymphatic invasion while androgen receptor (AR) expression was significantly lower in poorly differentiated cases and with lymphatic invasion.[46] The authors concluded, that ER-β and PR may be considered as markers for poor behavioral pattern in LSCC.

Molecular markers have been reported to have an important role in detecting occult neoplastic cells in resection margins after head and neck excision[47] Genomic, transcriptomic, and protein alterations in laryngeal cancer progression are key areas when aiming at investigation of possible targets for classification and prognostication purposes.[48]

PCR and cloning can identify a single malignant cell among 10 000 normal cells when the primary tumor contains a p53 mutation. Brennan et al studied 25 patients with p53 mutation of their head and neck carcinomas and found one or more positive margins by means of this sensitive molecular probe.[49] These findings proved to be of great value in a prognostic sense, in that the patients with negative margins by molecular analysis were observed to have a significantly increased survival. They also noted that there was a "lack of response to primary radiation therapy in patients whose tumors harbor a p53 mutation" and suggested that alternative and more aggressive therapy might be more appropriate in this instance.

There has been considerable interest in the potential prognostic value of the p53[50,51] tumor suppressor gene and analyses of its gene status (mutation) and protein status. In fact, the presence of high levels of mutant p53 has clearly been associated with diminished survival.[52] Nylander et al[52] have also reported a significant association between p53 expression and poor patient outcome specifically in patients with laryngeal squamous cell carcinoma. The authors conclude that p53 could be one of several factors of importance in predicting patient outcome.

Another potentially useful prognostic indicator is the bcl-2 gene. It has been shown by immunohistochemical studies that bcl-2 gene expression correlates significantly with poorly differentiated tumors with the presence of nodal metastasis and with increased tumor recurrence.[53]

When comparing the volume of high-quality scientific investigation concerning prognostic markers, we find a relative paucity of reports in the field of laryngeal cancer relative to other more common solid tumors (eg, lung, colon, and breast). Grénman et al reviewed the published studies of markers in cancer of the larynx and concluded that because of the complexity of cell-signaling phenomena, it is likely that valuable prognostic tools will emerge from the measurement of several factors in combination rather than from any one factor alone.[54]

The UM-A9 monoclonal antibody will bind with most squamous cell carcinoma cell culture lines, suggesting that it displays tumor specificity (as it will not bind to fibroblasts, lymphocytes, red blood cell, melanomas, or normal keratinocytes). Immunohistology has confirmed that most squamous cell carcinomas express this antigen and many tumors show high levels of the antigen at the growing edge of tumor nests and inside the tumor cells. Of the greatest importance in a prognostic sense is the finding that the disease-free survival decreases in head and neck squamous cell carcinoma patients as the intensity of A9 antigen expression increases.[55]

Increased DNA content of laryngeal cancer cells as measured by the adjusted DNA index (aDI) appears to reflect an increased proliferative capacity and a greater frequency of cervical lymph node metastasis. Wolf et al studied 94 patients with stages III and IV laryngeal carcinoma and found that a shorter time to recurrence, higher number of positive nodes, and generally worse prognosis correlates with higher levels of DNA content.[56] Milroy et al believe that the role of DNA ploidy as an independent prognostic indicator has yet to be determined.[57]

In 2014, Bradford et al published a biomarker study in a prospective cohort of patients with advanced larynx cancer treated in a phase II clinical trial.[58] Important observations from this study included the identification of tumor immunohistochemical expression of cyclin D as a strong predictor of overall and disease-specific survival (P = .0008 and 0.0147, respectively). Further, the addition of cyclin D1 expression added predictive information to a survival model using clinical stage alone. In addition, tumors that overexpressed cyclin D1 were more likely to have mutated p53. Moreover, aggressive histologic growth pattern was associated with response to induction chemotherapy.

The incidence of p16INK4a/HPV positivity in LSCC is generally low and the average of reported observations in the four meta-analyses vary between 16% and 28%.[59-62] Furthermore, there is a large geographical variation. The impact of p16INK4a in predicting treatment outcome and survival in LSCC remains controversial, but it might have a role in nonsmokers,[63] females[64] and younger LSCC patients.[65]

Clearly there is much work yet to be done to establish reliable, independent biomarkers that predict survival and response to treatment. The assessment of prognostic factors and biomarkers in patients enrolled in prospective clinical trials is necessary to limit the impact of uncontrolled variables that impact outcome and response.

3.8 | Second primary cancer

Another important factor influencing survival is the presence of other, synchronous or metachronous primary cancers, whether in the head and neck area or elsewhere, but especially in the esophagus, lung and oral cavity. Cancers of the larynx tend to have second primaries in the lung, whereas neoplasms in the oral cavity tend to have second primaries in the esophagus. The presence of a previous or synchronous cancer halves survival.[66] Patients with cancer clearly are at a higher risk of developing a second primary cancer.[67]

4 | TREATMENT FACTORS

An important factor in the management of cancer of the larynx is the determination whether the carcinoma is in situ, microinvasive or frankly invasive. "Minimal laryngeal cancer" defines carcinoma in situ and microinvasive carcinoma, and the prognosis is generally favorable. Invasive cancer of the larynx, left untreated, is inevitably a fatal disease: 90% of untreated patients die within 3 years.[68] Treatment recommendations vary by tumor site and stage as well as patient factors. Surgery and radiotherapy, either alone or in combination, are the conventional modalities for the management of squamous cell carcinoma of the larynx. Transoral laser microsurgery (TLM) and Transoral Robotic Surgery (TORS) are alternatives to open surgery in specific clinical scenarios at experienced head and neck centers. These transoral approaches are most applicable in the treatment of early malignant neoplasms of the supraglottic and glottic larynx. In squamous cell carcinoma, chemotherapy in conjunction with radiotherapy is an alternative to laryngectomy in patients with advanced larynx cancer. The

landmark VA Laryngeal Cancer Group Study, published in 1991, identified equivalent outcomes for patients with advanced larynx cancer randomized to induction chemotherapy followed by radiation alone for responders as compared to primary surgery (laryngectomy/neck dissection) and postoperative adjuvant radiation.[69] In 2003, Forastiere et al published the results of the Radiation Therapy Oncology Group 91-11 follow-up study, that compared induction cisplatin/5-FU (PF) followed by radiotherapy (RT), concomitant cisplatin/RT and RT alone for patients with advanced larynx cancer.[70] Patients with T4 primaries were excluded from this trial. The 10-year follow-up results were published in 2013 (Long-Term Results of RTOG 91-11).[71] Importantly, overall survival did not differ in any of the treatment arms.

A recent paper published by Wolf et al[72] suggested that superior survival rates could be achieved with a bioselective treatment approach that utilized a single cycle of neoadjuvant chemotherapy to select subsequent treatment. Good survival rates were also achieved in patients selected for primary surgery, and both neoadjuvant chemotherapy and primary surgery had better survival rates than with concurrent chemoradiotherapy. These data suggest that the optimal individualized treatment approach for patients with advanced laryngeal cancer has not yet been defined, and likely does include surgery.

Chen et al utilized the National Cancer Database (NCDB) to investigate clinical and demographic factors associated with improved survival in patients with advanced laryngeal cancer diagnosed between 1995 and 1998.[73] They found that total laryngectomy yielded the best survival in patients with advanced larynx cancer. The authors did note that their results differed from the prospective randomized clinical trial data, suggesting that caution is needed when applying clinical trial findings to broader care settings. Lassig et al[74] investigated the effect of treating institution (academic vs community) on outcomes in head and neck cancer. Using Kaplan-Meier analysis, they noted that the 5-year survival rate was 53.2% (95% confidence interval [CI], 45.3%-61.1%) for academic centers and 32.8% (95% CI, 22%-43.6%) for community hospitals ($P < 0.001$). The paper by Gourin et al provides support for the role of hospital volume as an important factor in achieving optimal outcomes of therapy.[75]

Delays in diagnosis is an unfortunate phenomenon among LSCC patients and this will obviously have an impact on tumor stage. Teppo et al observed professional diagnostic delay (ie, the time from the first doctor's appointment to the diagnosis) of 1 year or longer as an independent predictor of local and regional failure.[76]

The treatment of laryngeal cancer should be selected according to the best evidence with respect to site and stage of disease, patient factors, the physician's experience, and treatment centers available. Of course, the largest impact on the patient's *quality of life* is whether or not the cancer is cured. However, treatment-related toxicities and morbidity must be taken into account to optimize functional results.

5 | CONCLUSION

The TNM system is an anatomical means of classification, which takes into account neither the biological aggressiveness of the specific tumor nor the host's immunological response. It was not developed to serve as a specific guideline for the management of a particular patient, nor does the system have the ability to predict the outcome of individual patients. Whereas physicians are focused on the concept of optimal treatment, patients are interested in their prognosis, and one of the most important tasks is to assess our present ability to predict the probable outcome for an individual patient with laryngeal cancer.

The development and application of molecular biology tools to analyze biopsy material may be predictive for the biological behavior of laryngeal cancer but cannot be employed routinely at this time, but significant progress is being made and biomarkers may inform both prognosis and optimum treatment in the future.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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