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Review Article

Evaluation of prognostic factors of head and neck squamous cell carcinomas in Iranian patients: A narrative review

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) represents the largest proportion of head and neck cancers (HNCs). Despite new treatment modalities, the 5-year survival rate has not improved much. Identifying the factors affecting the prognosis and survival of patients is the first step in trying to improve the prognosis of these patients. The aim of this review was to investigate prognostic factors of HNSCC in Iran.

Methods: A web-based search of all original articles conducted in Iran until October 2022 on prognostic factors of HNSCC was done using English and Persian language databases such as Google Scholar, PubMed, IranMedex, etc. The data were categorized according to clinical, histopathological and treatment parameters.

Results: A total of 7 articles related to the aim of this study were found. Age and regular periodic follow-ups were common prognostic factors in three studies. The results about factors such as the tumor staging and treatment method were contradictory among different studies. It seems that some factors such as gender, microscopic grading, and patient and professional delay in cancer management have no effect on the prognosis of this group of patients. Conclusions on some factors, such as P53 and EGFR expression and body mass index, also seem to require further investigation.

Conclusion: Age and regular periodic follow-ups are among the common prognostic factors that have been mentioned in different studies. In order to improve the survival of HNSCC patients, diagnosis at lower ages and early stages of the tumor along with periodic evaluations after cancer treatment, seems necessary.

Keywords: Squamous cell carcinoma of head and neck, head and neck neoplasms, prognosis

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Introduction

Head and neck squamous cell carcinomas (HNSCCs) originate from the mucosa of the larynx, pharynx, and oral cavity; HNSCCs are among the largest proportion of malignancies of the HN area. HNSCCs are the sixth cancers throughout the world with high recurrence and metastasis.[1]

Despite advances in diagnostic processes and tools, squamous cell carcinomas (SCCs) have been associated with increased mortality and poor prognosis. The 5-year survival rate (5-Y SR) of HNSCC varies between 25 and 60%. In order to ameliorate the survival and prognosis, the first step is identifying factors affecting them. Many histopathological and clinical factors have been studied to predict the prognosis of SCC. Research on prognostic factors has been a constant challenge in the field of cancer studies. These factors include but are not limited to, clinical stage, histopathologic grade, site, general health status, age, sex, treatment methods, ethnic group, comorbidities, alcohol consumption and smoking, metastasis to lymph nodes, presence of human papilloma virus (HPV), and genetic factors. Interaction between these factors will finally determine the HNSCC patient prognosis.[2,3] Knowing these prognostic factors will help in deciding on the treatment plan.[4] Differences in the 5-Y SR of patients with HNSCCs have been observed in different countries. According to some studies, geographical and socio-economic differences affect the 5-Y SR and prognosis of SCC.[5] Therefore, this review aimed to evaluate the prognostic factors of HNSCC in Iran.

Methods

This review approved by the ethical committee of our university (IR.BUMS.REC.1399.234). The articles searched in international databases, including ISI, Scopus, PubMed, and Google Scholar, and Persian databases, including IranMedex, IranDoc and SID.

The following keywords were used for searching the articles:

"Mouth", "pharynx", "larynx", "squamous cell carcinoma", "neoplasms", "head and neck neoplasms", "squamous cell carcinoma of head and neck", "prognosis", "survival", "Iran"

The articles published up to October 2022 were retrieved. The evaluation of the articles was done firstly by examining the title, then the abstract and finally the full text. This review included the articles that had information on survival and prognostic factors of Iranians affected by HNSCCs. We excluded the articles that had insufficient information on the prognostic factors of HNSCCs; studies that examined non-Iranian patients were also excluded.

Results

Seven articles were retrieved. Table 1 summarizes these articles.

Survival Rate

The reported 5-Y SR for oral SCC (OSCC) were 40.24%,[11] 49.4%,[9] and 50%.[8]

The reported 5-Y SR for laryngeal cancer (LC) was 47.28% [10]

The reported overall survival (OS) and disease-free survival (DFS) for HNSCC (including laryngeal SCC [LSCC], OSCC, hypopharyngeal SCC, etc.) was 61.2% and 52.4%, respectively.[10]

Prognostic factors

Clinical parameters

a. Age

In OSCC, age had a significant relationship with SR ,i.e., with increase in age, the SR decreased.[9,11]

In LC, age also had a significant relation with the SR, i.e., with increase in age, the SR decreased.[10]

b. Gender

In OSCC, gender had no significant relation with 5-Y SR; in laryngeal cancer, gender had no also significant relation with 5-Y SR.[10]

c. Regular periodic follow-up

In OSCC, this factor had a significant relationship with SR, and SR was improved by it.[11]

In LC, regular follow-ups had a significant relation with SR, and SR was improved by them.[10]

d. Staging

In HNSCC, tumor stage (T-stage) showed a significant relationship with OS; patients with higher T-stage had lower OS.[7]

In HNSCC, no3 de stage (N-stage) showed a significant relationship with DFS; patients with higher N-stage had lower DFS.[7]

e. Tumor site

In HNSCC, patients with LSCC had higher event-free survival (EFS) and OS than patients with HNSCC of other sites (non-laryngeal tumors) although the difference was significant only in EFS.[7]

f. Body mass index (BMI)

In HNSCC, BMI showed a significant relationship with DFS; patients with normal BMI had higher DFS than patients with abnormal BMI.[7]

g. Delay in cancer management

Patient delay: In OSCC, there was not significant association between patient delay > 4 weeks and SR. In LC, there was not also significant association between patient delay > 4 weeks and SR.[10]

Physician delay: In OSCC, there was not significant association between physician delay > 4 weeks and SR. In LC, there was not also significant association between physician delay > 4 weeks and SR.[10]

Histopathological parameters

a. Grading

In OSCC, there was not significant association between grading and SR.[8,9,11] In LC, there was not also significant association between grading and SR.[10]

b. Expression of biomarkers

In OSCC, the EGFR was identified as a prognostic factor. The survival time for lower EGFR score was higher

Table 1. Retrieved studies along with relevant prognostic factors

Author, year	Location of squamous cell carcinoma	Number of cases	Studied prognostic factor
Khademi, 2002[6]	Head and neck (larynx and tongue)	53	p53, c-erbB expression
Novin, 2015[7]	Head and neck (non-nasopharyngeal)	119	Age, gender, staging, treatment modality, tumor site, and body mass index
Seyedmajidi, 2017[3]	Mouth	30	AEG-1 expression
Baghai Naini, 2017[8]	Mouth	38	EGFR expression
Jafari, 2018[9]	Mouth	174	Age, gender, treatment modality, grading, and staging
Gholizadeh, 2018[10]	larynx	136	Age, gender, regular periodic follow-up, patient delay, professional delay, grading, and treatment modality
Gholizadeh, 2019[11]	Mouth	82	Age, gender, regular periodic follow-up, patient delay, professional delay, grading, and treatment modality

than that of higher EGFR score; this means that EGFR overexpression is related to poor prognosis.[8]

In HNSCC (including laryngeal SCC and tongue SCC), c-erbB expression had no relationship with histologic grading or nodal involvement. P53 expression had also no relation with grading. There was a significant association between p53 overexpression and nodal metastasis.[6]

In OSCC, expression of AEG-1 was not correlated with tumor grading, tumor staging, lymph node metastasis, or distant metastasis.[3]

Treatment modality

In Jafari and colleagues' study on OSCC, 5-Y SR showed a significant relationship with treatment method (surgery or chemotherapy); patients with surgery or chemotherapy as treatment method had higher 5-Y SR[9]; contrariwise in Gholizadeh and colleagues' study on OSCC, treatment modality had no significant relation with SR.[11] In LC, treatment modality had no significant relation with SR.[10] In Novin and colleagues' study on HNSCC (including LSCC, OSCC, hypopharyngeal SCC, etc), treatment methods had no significant relation with SR, i.e., surgical treatment resulted in similar prognosis as non-surgical treatment.[7]

Discussion

In this review, the prognostic factors in HNSCCs in Iran were investigated. Age and regular periodic follow-ups were prognostic factors common between studies. Regarding factors like staging and treatment method, the results were inconsistent among the studies. Conclusions on some factors, such as P53 and EGFR expression, seem to require further investigation.

In a review, Kumarasamy et al identified the expression of specific miRNAs that were associated with the prognosis of HNSCCs. The expression of miRNA has not been assessed in studies conducted in Iran.[12]

In Seminerio and colleagues' study, stromal infiltration of FoxP3 + regulatory T cells, tumor staging, and histologic grading were associated with prognosis, i.e., high infiltration of these inflammatory cells, early tumor stage and well-differentiated tumors were correlated with better SR.[13] This result was consistent with Novin and colleagues' study[7] and inconsistent with Jafari and colleagues' study in its findings on tumor staging.[9] The reason for the latter inconsistency may be related to the target population as in Jafari and colleagues' study,[9] the samples were limited to OSCCs. The result was inconsistent with Gholizadeh and colleagues' studies[10,11] in terms of microscopic grading. The reason for this inconsistency of the results can be due to different sample sizes in these studies and also the possibility of considering different proportions of tumors with well-, moderately-, and poorly-differentiation. In a systematic review by Cho et al, increase in circulating T regulatory cells was stated as a prognostic factor for SR in patients with OSCC.[14]

In Cadoni and colleagues' study,[15] the 5-Y SR was 60.6% for HNSCCs (49% in OSCCs, 54.8% in the oropharyngeal SCCs, 50% in the hypopharyngeal SCCs and 63.4% in LSCCs). The OS reported for head and neck cancers (HNCs) and for oral cancers in the above study is consistent with the rate reported in the studies of our review,[7-9 11] although the survival rate reported in Gholizadeh and colleagues' study[10] was much lower than in the above study; many prognostic factors can contribute to this difference in survival. In the above study,[15] older age and advanced tumor stage were unfavorable prognostic factors associated with poor OS. This result was consistent with Novin and colleagues' study [7] and inconsistent with Jafari and colleagues' study in terms of tumor staging.[9] The reason for the latter inconsistency may be related to the different treatment modalities used in the two studies. In the above study,[15] alcohol consumption was a prognostic factor for differences in recurrence and OS among HNC sites. In the study of Novin et al,[7] the location of the primary tumor, unlike Cadoni and colleagues' study, had no effect on prognosis and survival.

In a systematic review by Rivera et al, 41 biomarkers, mostly proteins, were identified as potential prognostic biomarkers in OSCCs. These biomarkers need to be validated by further studies.[16]

In a systematic review by de Kort et al, increase in the number of lymph nodes removed during surgery of HNSCC (generally ≥ 18 lymph nodes) was correlated with better OS and was proposed as a prognostic factor for HNSCCs.[17] In a systematic review by Moumoulidis et al, nodal volume was recommended as a strong prognostic factor.[18]

In a systematic review by de Morais et al,[19] no meaningful difference was found between the prognosis of OSCC in young and older patients. This finding is in contrast with Jafari and colleagues',[9] and Gholizadeh and colleagues'[10,11] studies. The reason for this difference (effect of age on prognosis of OSCC patients) may be related to differences in sample sizes and other risk factors between Jafari and colleagues', and Gholizadeh and colleagues' studies and De Morais and colleagues' review. De Morais and colleagues' conclusion is in accordance with Novin and colleagues' study.[7]

Overall, the list of factors involved in the prognosis of HNSCCs is very extensive and it is constantly being updated.

Strengths and limitations

One of the strengths was the inclusion all existing studies in this field in Iran; it addressed not only the factors that had a significant relationship with prognosis, but also the factors that did not. One of the limitations was the small number of studies conducted in Iran. Also, there was no logical balance in the types of cancers studied in different

regions; for example, the studies were mainly related to oral cancers. Also, some factors were studied in only one study, which means that further investigation is necessary in these areas.

Conclusion

Age and regular periodic follow-up are among the common prognostic factors mentioned in different studies. Therefore, diagnosis of HNSCCs at an early age and stage using up-to-date diagnostic tools and periodic screening, as well as the design and implementation of monitoring systems for cancer patients to have regular periodic follow-ups after they receive the appropriate treatment are necessary to increase the survival rate of these patients.

Authors' Contribution

Conceptualization: Hamid Abbaszadeh, Mahdieh Rajabi-Moghaddam.
Data curation: Hamid Abbaszadeh, Mahdieh Rajabi-Moghaddam.
Investigation: Hamid Abbaszadeh, Mahdieh Rajabi-Moghaddam.
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Methodology: Hamid Abbaszadeh, Mahdieh Rajabi-Moghaddam.
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Validation: Hamid Abbaszadeh, Mahdieh Rajabi-Moghaddam.
Visualization: Hamid Abbaszadeh, Mahdieh Rajabi-Moghaddam.
Writing–original draft: Hamid Abbaszadeh, Mahdieh Rajabi-Moghaddam.
Writing–review & editing: Hamid Abbaszadeh, Mahdieh Rajabi-Moghaddam.

Competing Interests

The authors had no competing interests

Data Availability Statement

All data related to the study is within the text.

Ethical Approval

Ethical approval was obtained from Birjand University of Medical Sciences (IR.BUMS.REC.1399.234).

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