ORIGINAL ARTICLE

NON-SURGICAL TREATMENT PROGNOSIS FOR LARYNGEAL CANCER BASED ON AMERICAN JOINT COMMITTEE ON CANCER STAGING AND T AND N INTEGER SCORE

Mohammad Hasan larizadeh[1]✉, Ahmad Naghibzadeh-Tahami[2], Hadi Eslami[3]

[1]Clinical Research Development Unit, Shafa Hospital, Kerman University of Medical Sciences, Kerman-Iran
[2]Social Determinants of Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman-Iran
[3]Department of Otolaryngology, Head and Neck Surgery, Kerman University of Medical Sciences, Kerman-Iran

Background: The American Joint Committee on Cancer (AJCC) system is the most acceptable staging method. In this study, an attempt has been made to evaluate the survival rate of laryngeal cancer based on the AJCC and T and N integer scores (TANIS). **Methods**: In this prospective cohort study, from March 2004 to March 2021, laryngeal cancer patients who were considered for non-surgical treatment were included. Radiation alone was considered for T1-T2 lesions without nodal involvement. Sequential or concomitant chemoradiation (based on physician choice) was considered for locoregionally advanced patients (T3/T4 or node positive). The 2-year, 5-year and 10-year overall survival (OS) and progression-free survival (PFS) rates were estimated using Kaplan-Meier method. Cox -Regression method was used for covariates analysis. **Results:** The 2-year, 5-year and 10-year overall survival (OS) rates in all patients were estimated to be 82%, 70% and 41%, respectively. The 2-year, 5-year and 10-year progression-free survival (PFS) rates in all patients were estimated to be 78%, 59% and 41%, respectively. The 5-year OS rates for stages I, II, III, IVa, and IVb were 83, 84, 51, 12, and 19 percent, respectively. The 5-year OS rates for TANIS 1, 2, and 3 were 85, 62 and 53 percent, respectively. Based on multivariate analysis, the group stage (p=0.001), TANIS group (p=0.003) and tumour subsite. (p=0.006) were independently effective in survival rates. **Conclusion:** TANIS-3 can simply predict the prognosis of non-surgically treated laryngeal cancers. The separation of different prognostic groups by TANIS is better than the AJCC system. More extensive studies are necessary to confirm this.

Keywords: Chemotherapy; Head and neck neoplasm; Laryngeal neoplasm; Radiotherapy

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INTRODUCTION

Laryngeal cancer accounts for about one-third of head and neck cancers and 1–2.5% of all cancers.[1] It is approximately the 20th most common cancer worldwide, with more than 150,000 new cases diagnosed annually.[2]

Laryngeal cancer is the most common squamous cell carcinoma of the head and neck in Iran, consisting 36% of all kinds of cancers in this part of the body.[3] The age-standardized rate of laryngeal cancer among Iranian men is 2.62 per 100,000 and among Iranian women is 0.46 per 100,000.[4] The survival rate in various studies is very different. The overall 5-year survival rate has been estimated to be fewer than 50% in studies conducted in Iran.[5] There are multiple factors (patient, disease, and treatment factors) that affect the prognosis of patients with head and neck cancers. The tumour stage is one of the most important prognostic factors.[6] Currently, the TNM staging system which is introduced by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC) is the most common staging method in various types of cancer.[7] The numerical suffixes after the letter T and N describe the local extent of the primary tumour and involvement of regional lymph nodes, respectively. The numerical suffix of the letter M indicates the presence or absence of distant metastasis.[8] The group staging resulting from the combination of T, N, and M was formed for greater convenience (Table-1).[9] This combination is based on the estimated prognosis, and there are no prospective studies comparing the prognostic value of different T, N, and M combinations.[8] The prognostic value of the system is limited, especially in stage IV, which contains patients with relatively unfavourable prognoses (for example, T_4N_0) and very advanced cases (for example, T_4N_3). An optimal staging system should have high predictive power and hazard discrimination.[10] For facilitation of staging, group staging resulting from the combination of T and N was proposed. Several other group staging protocols have been suggested for head and neck carcinoma (HNC), in which the combination of T, N, and M has been based on a presumed prognosis.[11] For the first time in 1993, Jones *et*

al. proposed the T and N integer score (TANIS) for HNC. Assuming that the predictive role of T and N is the same in survival, they introduced a score system numbered from one to seven by adding the numeric suffix T and N (TANIS -7) (Table-1). They compared the prognostic value of TNM staging with TANIS in the patients with head and neck cancer who had undergone concurrent or sequential radiotherapy and chemotherapy. TANIS was the best predictor for complete response to radiation and survival outcome.[11] Then, TANIS-3, in which all integer values were classified into 3 groups, was proposed (Table-1).[12]

In the present prospective study, the aim was to determine the 5-year survival rate of laryngeal cancer patients based on TANIS and the TNM stage and to compare these 2 staging systems to separate prognostic groups. For this purpose, from 2004–2021 patients who underwent non-surgical treatment were included. This is the first study which has evaluated TANIS in laryngeal cancer, exclusively.

MATERIAL AND METHODS

This research was approved by the Ethics Committee of the Kerman University of Medical Sciences (code: IR-KMU-REC-1401-236).

From March 2004 to March 2021, the data of laryngeal cancer patients who were referred to the radiation oncology ward of Kerman University of Medical Sciences were recorded prospectively. Non-surgical treatment was considered for the patients according to physicians' or patients' choice. These patients were enrolled in the study consecutively based on the census method and no randomization was done. Normal haematological, renal and hepatic function, Eastern Cooperating Oncology Group performance status of 0–1 and signed informed consent were required. The exclusion criteria included evidence of other synchronous tumours, surgery other than biopsy evidence of distant metastasis, the ambiguity of the stage, intolerance of the study protocol, incomplete treatment for any reason, lack of proper follow-up and any treatment outside the study design. CT scan with contrast and chest X-ray were performed for all patients. A more extensive study was performed to rule out metastasis in the case of clinical suspicion. Clinical staging was performed using the findings of physical examination, laryngoscopy and CT scan based on version 8 of AJCC staging system and TANIS-3 grouping score.

Radiation alone was considered for stage I and II (T1 and T2 lesions without nodal involvement). Concomitant chemoradiation or sequential chemoradiation was considered for loco-regionally advanced patients (T3/T4 or node positive).

Sequential treatment consisted of 3 cycles of induction chemotherapy with cisplatin (100 mg/m^2, on the first day), docetaxel (75 mg/m^2, on the first day), and 5-fu (750 mg/m^2, for 3 days) repeated every 3 weeks. After induction chemotherapy, those with a complete response received radiation therapy alone, and the rest received concomitant chemoradiation (carboplatin, weekly, AUC 1.5). For radiotherapy, a total dose of 66 to 70 Gy was used by conventional method and 3D technique in all patients. Neck dissection after treatment was considered for extensive (N_2 and N_3) or residual disease in nodes, whenever it was possible. After treatment, all the patients were followed and examined every 3 months to evaluate the treatment response and disease progression. Imaging was performed whenever necessary based on clinical findings (depending on the signs and symptoms, chest and abdominal CT scan, bone scan and neck CT scan were performed to confirm visceral metastasis, bone metastasis and locoregional recurrence, respectively).

Considering the better prognosis of younger patients, patients were divided into 2 age groups: less than 61 years old and 61 years old or older. The variables of age group, gender, T-stage, N-stage, group stage, TANIS group, tumour subsite and treatment modality (concomitant chemoradiation versus sequential modality) were considered for analysis. Patients who received radiotherapy alone were not included in the multivariate analysis.

The 2-year, 5-year and 10-year overall survival and progression-free survival rates were estimated using Kaplan-Meier method. The time between the first visit and the last follow-up was calculated for overall survival. Also, the time between the first visit and the first progression date (loco-regional or distant) was calculated for progression-free survival.

Log- Rank test was used to analyze the treatment results based on various factors. Cox-Regression method was used for multivariate analysis. A *p*-value ≤ 0.05 was considered a statistically significant difference.

RESULTS

Out of 560 patients, 538 met the study inclusion criteria. The patients' characteristics are shown in table-2. The mean age of the patients was 57.2 years (from 30 to 90 years, standard deviation [SD]±10.9) The mean follow-up time was 29.3 months (from 6 to 140 months, SD±36.1). Radiotherapy alone, sequential chemoradiation and concomitant chemoradiation were assigned for 43.1% (n=232), 33.9% (n=182) and 23% (n=124) patients, respectively. Thirty-one patients (5.7%) underwent salvage surgery (node dissection and/or laryngectomy) due to primary treatment failure or locoregional recurrence. Due to high-grade treatment toxicity, the treatment was not completed in 8 patients. These patients were excluded from the survival analysis.

The 2-year, 5-year and 10-year overall survival (OS) rates in all patients were estimated to be 82%, 70%

and 41%, respectively. The 2-year, 5-year and 10-year progression-free survival (PFS) rates in all patients were estimated to be 78%, 59% and 41%, respectively. Based on log-rank test, T-stage (p<0.005), N-stage (p<0.005), the group stage (p<0.005), TANIS group (p<0.005) and tumour subsite (p=0.001) had a statically significant relationship with OS. The relationship between gender (p=0.8), age group (p-0.6) and treatment modality (p=0.06) with OS was not significant. Also, the relationship between T-stage (p<0.005), N-stage (p<0.005), the group stage (p<0.005), TANIS group (p<0.005) and tumour subsite (p=0.01) with PFS was significant. The relationship between gender (p=0.5), treatment modality (p=0.07) and age group (p-0.8) with PFS was not significant.

The 5-year OS rates for stages I, II, III, Iva, and IVb were 83%, 84%, 51%, 12%, and 19%, respectively. The 5-year OS rates for TANIS 1, 2, and 3 were 85%, 62%, and 53%, respectively (p=0.001). The 5-year PFS rates for stages I, II, III, Iva, and IVb were 83%, 77%, 47%, 12%, and 19%, respectively. The 5-year PFS rates for TANIS 1, 2, and 3 were 76%, 46%, and 35%, respectively.

Based on multivariate analysis with Cox-Regression method, group stage (p=0.001), TANIS group (p=0.003) and tumour subsite (p=0.006), were independently effective in survival rates. While, the relationship between T-stage, N-stage, gender, age group and treatment modality with OS was not significant. The survival of the glottic sub-site was better than other subsites.

As shown in the survival and progression-free survival curves, TANIS grouping was more efficient than the group stage in differentiating the patients based on prognosis.

Table-1: Various staging systems.

Factors		The numbers (%)
Age	<61 years:	346 (64.3)
	>61 years:	192 (35.7)
Gender	Male:	487 (90.5)
	Female:	51 (9.5)
Subsite	Glottis:	267 (49.6)
	Supraglottic:	189 (35.1)
	Infraglottic:	34 96.3)
	Unknown:	48 (8.9)
T stage	T1:	53 (9.9)
	T2:	215 (40)
	T3:	263 (48.9)
	T4a:	3 (0.6)
	T4b:	4 (0.7)
N stage	N0:	462 (85.9)
	N1:	50 (9.3)
	N2:	19 (3.5)
	N3:	7 (1.3)
Group stage	I:	47 (8.7)
	II:	185 (34.4)
	III:	279 (51.9)
	IVa:	17 (3.2)
	IVb:	10 (1.9)
TANIS-3	1:	238 (44.2)
	2:	251 (46.7)
	3:	49 (9.1)

Table-2: Distribution of the patients according to various factors

Staging system	Groups
AJCC (version 8th, 2017)	I: T1N0 II: T2N0 III: T3N0, T1N1, T2N1, T3N1 IVa: T1-T3N2, T4aN0-N2 IVb:N3, T4b
TANIS-7	1: T1N0 (T+N=1) 2: T1N1, T2N0 (T+N=2) 3: T1 N2, T2N1, T3N0 (T+N= 3) 4: T1N3, T2N2, T3N1, T4N0 (T+N=4) 5: T2N3, T3N2, T4N1(T+N=5) 6: T3N3, T4N2(T+N=6) 7: T4N3 (T+N=7)
TANIS-3	1: T1N0, T1N1, T1N2, T2N0, T2N1, T3N0(T+N=1 to 3) 2: T1N3, T2N2, T3N1, T4N0 (T+N =4) 3: T2N3, T3N2, T3N3, T4N1, T4N2,T4N3 (T+N= 5 to 7)

Table-3: The mean overall survival (OS) and progression free survival (PFS) based on stage.

Group	The mean OS (range- SD)	The mean PFS (range- SD)
All patients	91.3(84.3-98.2, 3.5)	79.5 (72.5-86.4, 3.5)
Group stage	*p*-value <0.005	*p*-value <0.005
I	120.9 (109.9–132,5.6)	109.5(97.6–121.5, 6.1)
II	94.3 (81.8–106.7, 6.3)	93.5 (80.2–106.8, 6.7)
III	79.7 (71.1–88.3, 4.3)	67.9 (59.5–76.2, 4.2)
IVa	32.5 (14.3–50.7, 9.2)	22.4 (9.4–35.4, 6.6)
IVb	48.1 (0.2-96, 24.4)	40.6 (10–82.7, 40.6)
TANIS	*p*-value <0.005	*p*-value <0.005
1	117 (106.7–127.3,5.2)	108.5 (97.8–119.1, 5.4)
2	79.4 (70.3–88.6, 4.6)	67.3(58.4–76.2,4.5)
3	62.7 (43.5–82, 9.8)	50.1 (33.1–67.1, 8.6)

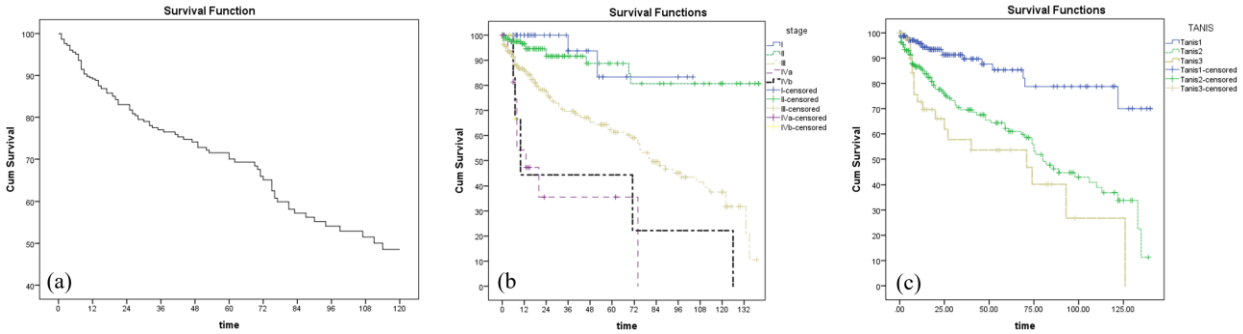

Figure 1. Overall survival curves for all patients (a) and based on group stage (b) and TANIS (c).

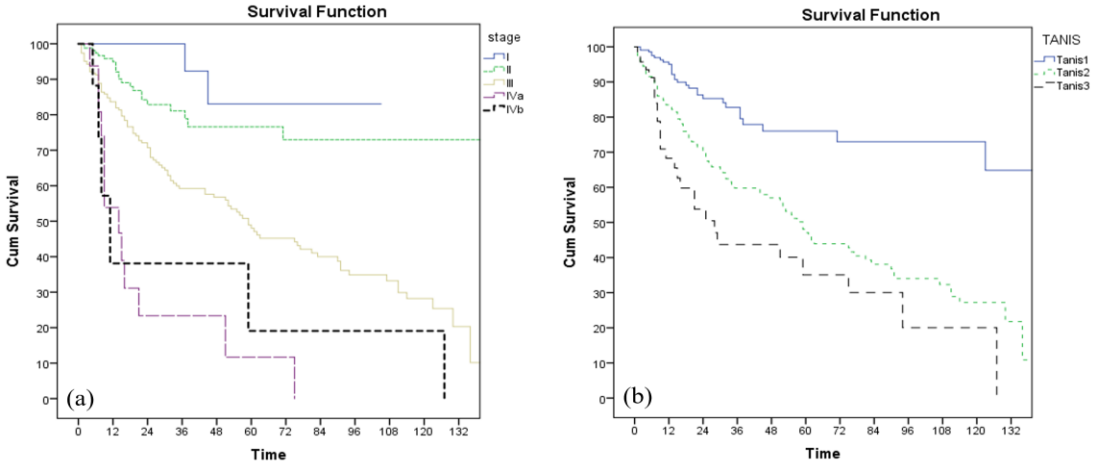

Figure-2: Progression-free survival curves according to group stage (a) and TANIS (b).

DISCUSSION

The 5-year OS was estimated to be 70% which is consistent with the results of other non- surgical studies.[5] The TNM staging system was first described by Pierre Denoix between the years 1943 and 1952.[8] The TNM system is the most commonly used staging system in the world due to its simple design. However, some disadvantages and limitations in its application have been raised.[9,10] This staging is mainly based on the anatomical extent and does not involve other prognostic factors such as biological and molecular characteristics.[9] In the eighth version of AJCC, other prognostic factors such as the human papilloma virus

and depth of invasion are added for oropharyngeal and oral cancer.[14] However, in the other head and neck cancers, non-anatomical factors have not yet been included in the staging. Lack of sufficient power in predicting the prognosis and inability to properly differentiate the groups are the other disadvantages.[15] For example, it is difficult to believe that a T4N2 patient has the same prognosis as a T1N2 patient (both are classified as IVa). The four stages formed by the combination of T, N, and M are not based on randomized studies and are based on consensus.[11] In addition to the AJCC/UICC system, other staging systems based on TNM have been proposed for head and neck cancers. Three studies have been performed to evaluate the TANIS system in head and neck cancers. The first study was conducted by Jones *et al*. In this study, they compared the prognostic performance of T, N, AJCC group staging and TANIS-7 stage according to the radiation response and survival rate. Eighty-six patients with loco-regionally advanced HNC were enrolled to receive concomitant or sequential chemoradiation. TANIS had more predictive power than the other systems in determining survival and response to radiation therapy.[11] In another study, a total of 186 oral cancer patients who had undergone primary surgery with or without chemoradiation were enrolled. A comparison of survival curves showed that the TANIS system could separate different groups according to prognosis better than TNM staging.[12] In the third study, 164 patients with oral and oropharyngeal cancer were studied retrospectively. Cox regression analysis showed that both TANIS-7 and TNM systems had a significant correlation with the survival rate, but TANIS had a higher correlation with survival.[13] In one study, the combination of TANIS 1 by 2, as well as the combination of TANIS 5, 6 and 7 together, resulted in better discrimination of 2-year disease-free survival.[12] Therefore, in the present study, TANIS-3 which is a more integrated system than TANIS-7 was used. Cox regression analysis showed that both AJCC group staging and TANIS system had a statistically significant correlation with overall survival and progression-free survival. However, survival curves showed that the separation of different prognostic groups by TANIS is better than the AJCC system. Specially, there was poor discrimination of survival curves for stages I and II. In HNC, the heterogeneity of the patients, as well as different treatment modalities and staging methods, makes it difficult to interpret prognostic results. Therefore, it is difficult to design an optimal staging in these cancers.[15] Our study is a prospective study that included only laryngeal cancer patients who received non-surgical treatment. The advantage of the present study compared to the previous studies is that treatment methods and tumour location as confounding factors do not affect the results. A newer version of the AJCC system was also used in this study.

One limitation of this study is an unequal number of patients in various groups (51.9 % were in stage III, and only 5.1% were classified in stage IV). Treatment modality has a significant role in the treatment outcome and can affect the staging systems. It is important to pay attention to this issue in the evaluation of staging systems.[11]

CONCLUSION

This study showed that the simple TANIS system can independently predict the prognosis of laryngeal cancer following non-surgical treatment. Also, the survival curves showed that the separation of prognostic groups by TANIS is better than the AJCC system.

AUTHORS' CONTRIBUTION

Larizadeh: Study concept and design, patient preparation, write-up. Naghibzadeh: Analysis. Eslami: Preparation of the patients and evaluation.

REFERENCES

1. Hassanipour S, Delam H, Nikbakht HA, Abdzadeh E, Salehiniya H, Arab-Zozanih M, *et al*. The incidence of laryngeal cancer in Iran: A systematic review and meta analysis. Clin Epidemiol Glob Health 2019;7(3):457–63.
2. Alizadeh H, Naghibzadeh-Tahami A, Khanjani N, Yazdi-Feyzabadi V, Eslami H, Borhaninejad V, *et al*. Opium use and head and neck cancers: A matched case-control study in Iran. Asian Pac J Cancer Prev 2020;21(3):783–90.
3. Dabirmoghaddam P, Yousefi J, Karimi E, Aghazadeh K, Moteshaker Arani M. Laryngeal cancer in Iranian women. Acta Med Iran 2023;61(1):7–11.
4. Taziki MH, Fazel A, Salamat F, Sedaghat SM, Ashaari M, Poustchi H, *et al*. Epidemiology of head and neck cancers in northern Iran: A 10-year trend study from golestan province. Arch Iran Med 2018;21(9):406–11.
5. Gholizadeh N, Najafi S, Khayam Zadeh M, Afzali S, Sheykhbahaei N. Trend in laryngeal cancer, mortality and survival rate in Iran. J Contemp Med Sci 2018;4(1):7–11.
6. Larizadeh MH, Arabi Mianroodi AA, Eslami H. The patients' characteristics and non-surgical treatment results for hypopharyngeal cancer in southeast of Iran: A 13-year study. J Ayub Med Coll Abbottabad 2023;35(1):118–22.
7. Glastonbury CM. Critical changes in the staging of head and neck cancer. Radiol Imaging Cancer 2020;2(1):e190022.
8. Monden N, Asakage T, Kiyota N, Homma A, Matsuura K, Hanai N, *et al*. A review of head and neck cancer staging system in the TNM classification of malignant tumors (eighth edition). Jpn J Clin Oncol 2019;49(7):589–95.
9. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers 2020;6(1):92.
10. Zanoni DK, Patel SG, Shah JP. Changes in the 8th Edition of the American Joint Committee on Cancer (AJCC) staging of head and neck cancer: rationale and implications. Curr Oncol Rep 2019;21(6):52.
11. Jones GW, Browman G, Goodyear M, Marcellus D, Hodson DI. Comparison of the addition of T and N integer scores with

TNM stage groups in head and neck cancer. Head Neck 1993;15(6):497–503.
12. Sniderman CH, Wagner RL. Superiority of the T and N integer score (TANIS) staging system for squamous cell carcinoma of the oral cavity. Otolaryngol Head Neck Surg 1995;112(6):691–4.
13. Carinci F, Pelucchi S, Farina A, Calearo C. A comparison between TNM and TANIS stage grouping for predicting prognosis of oral and oropharyngeal cancer. J Oral Maxillofac Surg 1998;56(7):832–6.
14. Watts F, Palme CE, Porceddu S, Sundaresan P, Clark JR, Gupta R. Clinician perspectives on the factors influencing prognostic stratification by the American Joint Commission on Cancer Head and Neck Cutaneous Squamous Cell Carcinoma Staging. Surgery 2021;170(5):1467–73.
15. Han C, Khan NI, Mady LJ . Prognosis. Otolaryngol Clin North Am 2023;56(2):389–402.

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Address for Correspondence:

Mohammad Hasan Larizadeh, Associate Professor of radiation oncology, Clinical Research Development Unit, Shafa Hospital, Kerman University of Medical Sciences, Kerman-Iran
Phone: +989131999523
Email: larizad_mh@yahoo.com