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Squamous Cell Carcinoma of the Nasal Vestibule: A Multi-Centric Observational Cohort Study

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Objectives: Squamous cell carcinoma of the nasal vestibule (NV-SCC) is a rare but challenging entity, due to the complex anatomy of the region. Consensus on the best treatment strategy is still lacking, as well as a dedicated staging system. Our aim was to analyze oncological outcomes of surgically treated patients and to investigate possible prognostic factors.

Methods: We performed a retrospective multi-centric observational study including six Academic Hospitals over a 10-year period, including only patients who underwent upfront surgery for primary NV-SCC. Patients were staged according to all currently available staging systems. The Kaplan–Meier method was used to compute overall, disease-free, and disease-specific survival. Logistic regression models were used to correlate between survival outcomes and clinical and pathological variables.

Results: Seventy-one patients with a median follow-up of 38 months were included in the study. Partial and total rhinectomy were the most commonly performed procedures, respectively, in 49.3% and 25.4% of cases. Neck dissection was performed on 31% of patients, and 45.1% of them underwent adjuvant radiotherapy. Three years overall, disease-specific and disease-free survival were, respectively, 86.5%, 90.3%, and 74.2%. None of the currently available staging systems were able to effectively stratify survival outcomes. Factors predicting lower overall survival on multivariate analysis were age ($p = 0.021$) and perineural invasion ($p = 0.059$), whereas disease-free survival was negatively affected by age ($p = 0.033$) and lymphovascular invasion ($p = 0.019$).

Conclusion: Currently available staging systems cannot stratify prognosis for patients who underwent surgery for NV-SCC.

Key Words: Nasal cartilages, Nasal surgical procedures, Nose, Nose diseases, Nose neoplasms.

Level of Evidence: 4

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INTRODUCTION

Malignancies of the nasal vestibule (NV) are rare tumors originating at the entrance of the nasal cavity, in the area between the nostril and the limen nasi, bounded by the columella, the nasal septum, the medial crus and the lateral crus of the alar cartilage. The NV is lined by hair bearing squamous epithelium till its most posterior border (i.e., the limen nasi), where the mucocutaneous junction sets the limit between the NV and the nasal cavity.[1]

They account for less than 1% of all head and neck cancers and are mostly squamous cell carcinomas (SCC). Due to their rarity, available data are insufficient to precisely define risk and prognostic factors; however, we do know that SCC of the nasal vestibule (NV-SCC) may show various patterns of diffusion, and advanced cases have a poor prognosis. Tumor can spread superficially to the skin or to the mucosal lining of the nasal fossa, invade the bone of the pre-maxilla, or spread downwards to the upper lip and reach the oral mucosa. Lymphatic drainage is to the first facial and submandibular lymph nodes (level IA and IB), but regional involvement is quite sporadic.[1–3]

There is no consensus on the best treatment modality for early-stage tumors, indeed both surgery[4–8] and radiotherapy (RT),[9–12] either interstitial or external, are applied upfront with comparable oncological outcomes; mostly, the strategy is chosen depending on the aesthetic

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result that can be achieved. For locally advanced tumors, however, surgery is usually the mainstay followed by adjuvant RT.

Nowadays, there are three available staging systems for NV-SCC: the Wang Classification,[13] the 8th edition of the American Joint Committee on Cancer for non-melanomatous skin cancer (AJCC8-NMSC),[14] and for cancer of the nasal cavity and ethmoid sinus (AJCC8-nasal).[14] None of them is consensually depicted as the standard staging system to be used; however, the Wang Classification is more commonly applied. Treatment recommendations are generally based on low-quality evidence, limited data, non-randomized studies, and relatively small case-series.

The aim of our retrospective multi-centric study was to analyze oncological outcomes and survival of NV-SCC, in order to better identify its prognostic factors, and to assess the accuracy of the three staging systems currently available.

MATERIALS AND METHODS

This is a retrospective multi-centric observational study involving patients undergoing treatment for NV-SCC in 6 Academic Hospitals, from June 2011 to December 2021. The study was approved by the Ethical Committee of IRCCS Humanitas Research Center (protocol number: ICH/743/22) and was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. Patients' informed consent for data collection and use was obtained.

Inclusion criteria were: (1) diagnosis of NV-SCC, (2) upfront surgical treatment with curative intent performed in one of the six centers involved in the study, (3) availability of clinical and radiological information for cT reassessment, (4) availability of histological findings for pT reassessment, and (5) follow-up of at least 6 months after surgery. Exclusion criteria were: (1) patients who initially referred for disease recurrence, (2) any previous treatment for NV-SCC at another hospital.

Patients' charts were reviewed retrospectively to identify demographic and clinical features, the classification adopted by each Institution at the initial staging, type of surgery and pathological reports, adjuvant treatment and follow-up. Each patient's clinical (cT) and pathological (pT) stages were reassessed according to the three classifications available (i.e., Wang, 8th AJCC-NMSC, 8th AJCC-nasal). Types of surgery were distinguished in: limited resection (LR), if only the internal lining of the vestibule was removed; total rhinectomy (TR, that is, full-thickness excision of the nasal pyramid at the level of the piriform aperture, including the anterior septum and triangular lateral cartilages, as well as nasal bones if necessary); partial rhinectomy (PR, that is, surgeries with preservation of one or more of the abovementioned structures); and extended total rhinectomy (ETR), if structures adjacent to the nose were also removed. Indications to a specific type of resection were the same among the groups included in the study. Neck dissection (ND) was always performed in case of cN+ neck at diagnosis. Adjuvant RT alone was proposed in advanced stages. Adjuvant RT-chemotherapy (CHT) was always proposed in cases of positive margins (that were not re-resectable) and/or extranodal extension (ENE+).

Pathological reports were analyzed in detail for involvement of specific subsites of the NV (i.e., columella, septum, nasal ala), of nasal cartilages (medial/lateral crus of the alar cartilage, triangular cartilages, quadrangular cartilage of the nasal septum), bone and other adjacent structures (e.g., skin of the cheek, mimic muscles, buccal mucosa); infiltration of the upper lip was distinguished between < or ≥5 mm from the nostril opening. Also, tumor grade and dimensions, depth of infiltration, perineural and lymphovascular invasion, and margin status were collected.

Main endpoints were Overall Survival (OS), Disease-Free Survival (DFS), Disease-Specific Survival (DSS); secondary endpoints were the identification of predictive factors of recurrence, based on clinical and pathological features.

STATISTICAL ANALYSIS

The data were collected and stored in a Microsoft Excel® spreadsheet. Categorical variables were summarized by counts and percentage, while continuous variables were reported as means ± standard deviations (SD) after confirming normality using the Shapiro–Wilk test. The Kaplan–Meier method was used to compute OS, disease free survival (DFS) and regional recurrence; entry time was the date of surgery, then patients were censored at latest clinical follow-up or at time of death. Differences between Kaplan–Meier curves were analyzed using the log-rank test, with an alpha-error set at 0.05. Correlation between survival outcomes and clinical and pathological variables was calculated using univariable binary logistic regression models. Parameters with a p-value <0.10 in the univariable analysis were included in the multivariable analysis (Cox proportional-hazard model) to define

TABLE I.
Demographics, Clinical, and Pathological Data.

Age, mean (range, SD)	59.23 (35–90, ±11.81)
Females (%)	49 (69)
Males (%)	22 (31)
Site (%)	
Limited to the nasal vestibule	50 (70.4)
Beyond the nasal vestibule	21 (29.6)
Grading (%)	
Well differentiated (G1)	13 (18.3)
Moderately differentiated (G2)	42 (59.2)
Poorly differentiated (G3)	16 (22.5)
Pathologic features (%)	
PNI	18 (25.4)
LVI	6 (8.5)
Surgical margins (%)	
Negative	55 (77.5)
Positive	15 (22.5)
Neck dissection (%)	
No	51 (71.8)
Yes	20 (28.2)
Ipsilateral	6 (30.0)
Bilateral	14 (70.0)
Neck dissection, intent (%)	
Elective	11 (55.0)
Therapeutic	9 (45.0)

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion.

A

	TNM skin (NMSC)	TNM nasal cavity	Wang
SUBSITES (ICD-O)	• Lip (excluding vermilion surface) (C44.0) • External ear (C44.2) • Other and unspecified parts of face (C44.3) • Scalp and neck (C44.4)	Nasal cavity (C30.0) • Septum • Floor • Lateral wall • Vestibule	n.a.
T1	Tumor 2 cm or less in greatest dimension	Tumor restricted to one subsite of nasal cavity or ethmoid sinus, with or without bony invasion	Limited to the nasal vestibule, relative superficial, involving one or more sites within
T2	Tumor >2 cm and ≤4 cm in greatest dimension	Tumor involves two subsites in a single site or extends to involve an adjacent site within the naso-ethmoidal complex, with or without bony invasion	Extended from the nasal vestibule to adjacent structures, such as the upper nasal septum, upper lip, philtrum, skin of the nose, and/or nasolabial fold, but not fixed to the underlying bone
T3	Tumor >4 cm in greatest dimension or minor bone erosion or peri- neural invasion or deep invasion*	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate	Massive with extension to the hard palate, buccogingival sulcus, large portion of the upper lip, upper nasal septum, turbinate, and/or paranasal sinuses, fixed with deep muscle or bone involvement undefined
T4a	Tumor with gross cortical bone/marrow invasion	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid, or frontal sinuses	
T4b	Tumor with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus	

B

C

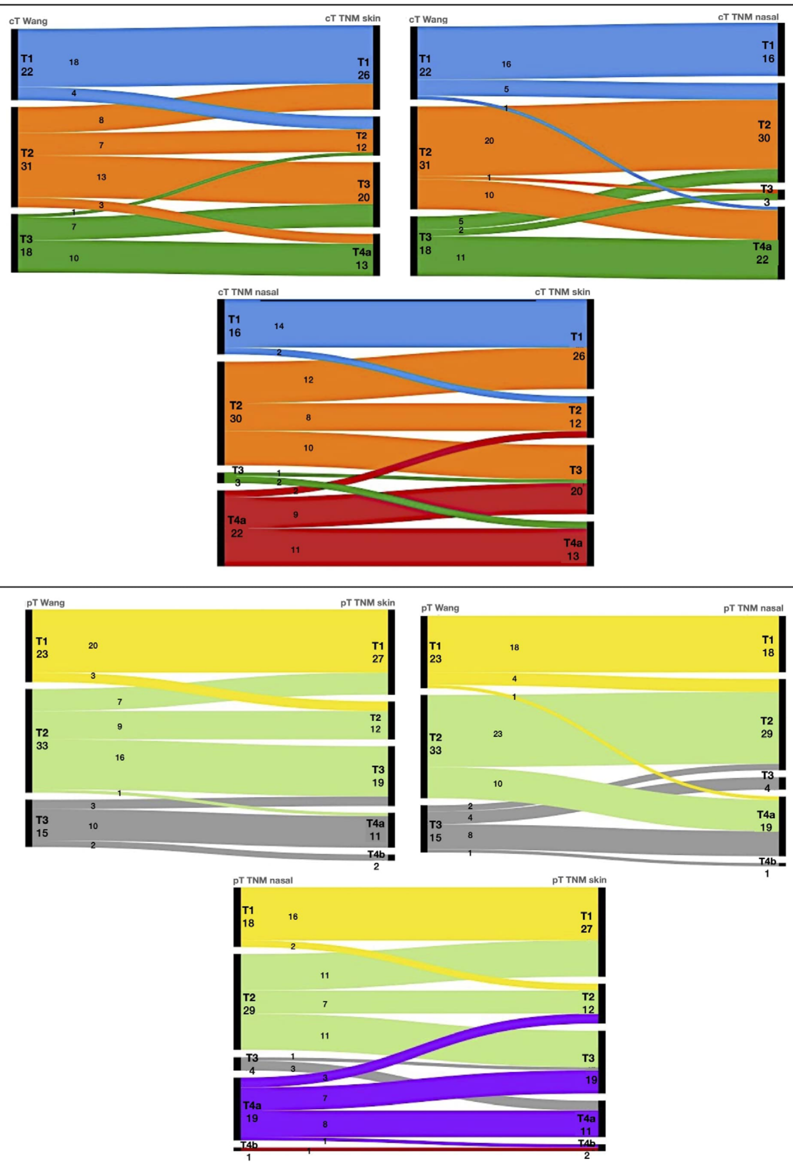

Fig. 1. Legend on next page.

independent predictors of recurrence. Results were summarized with odds ratios (OR) and 95% confidence intervals (CIs).

Distribution and migration of stages among the three classifications were represented through alluvial plots, and their frequencies calculated.

Statistical analysis was performed using IBM® SPSS® Statistics 26. All statistical tests were two-sided, and alpha and beta errors were set at 0.05 and 0.20.

RESULTS

Ninety patients with SCC of the NV were enrolled. Among them, 19 presented with local recurrences and were, therefore, excluded; the final analysis included 71 patients, of whom 49 (69%) males, with a mean age of 59 ± 12 years (range, 35–90). Characteristics of the patients are shown in Table I. All of them were treated with upfront surgery; median time of follow-up was 38 months (range 6–132), and no patients were lost to follow-up. At the end of the observation time, 9 (12.6%) deaths were recorded, of which 5 (55.6%) were cancer-related. Recurrences occurred in 17 (23.9%) patients, 4 (23.5%) local, 10 (58.8%) regional, and 6 (35.3%) distant. At 1 and 3 years of follow-up, OS was 93.5% and 86.5%, DSS was 95.2% and 90.3%, DFS was 87.5% and 74.2%, respectively.

LR was performed in 6 (8.5%) patients, PR in 35 (49.3%), TR in 18 (25.4%), and ETR in 12 (16.9%). Twenty-two (31%) patients received ND, ipsilateral in 7 (31.8%) and bilateral in 15 (68.2%) cases; only 11 (50%)

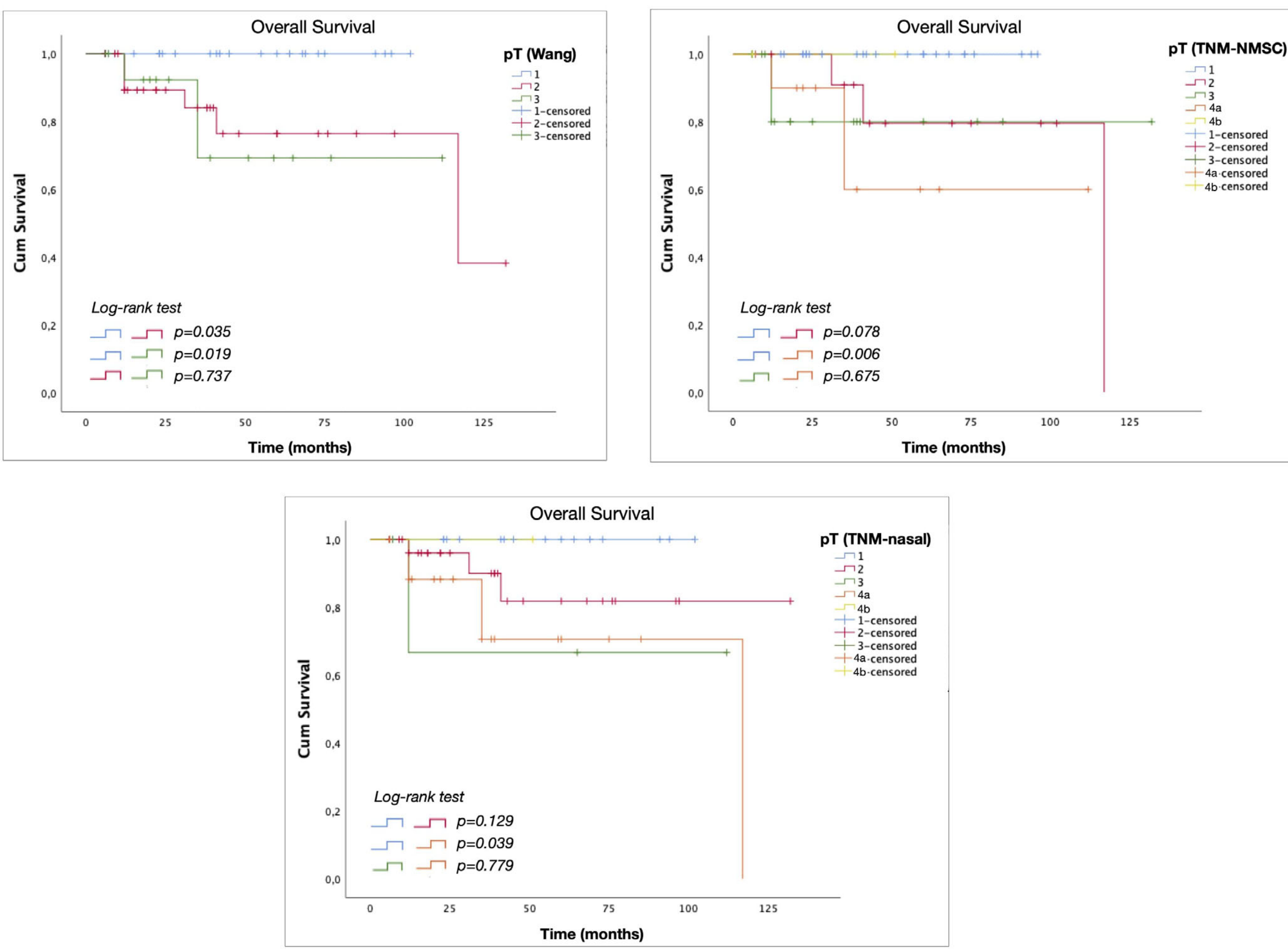

Fig. 2. Kaplan–Meier curve for overall survival (OS). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Fig. 1. (A) T-stage definition according to TNM of the skin for Non-melanomatous Skin Cancer (NMSC), TNM of the nasal cavity, and Wang's Classification. n.a. = not applicable; * = "Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor), perineural invasion for T3 classification is defined as clinical or radiographic involvement of named nerves without foramen or skull base invasion or transgression." (sec. TNM 8th ed.). (B) Alluvial plots showing distribution and migration for cT stages according to the system used. (C) Alluvial plots showing distribution and migration for pT stages according to the system used. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

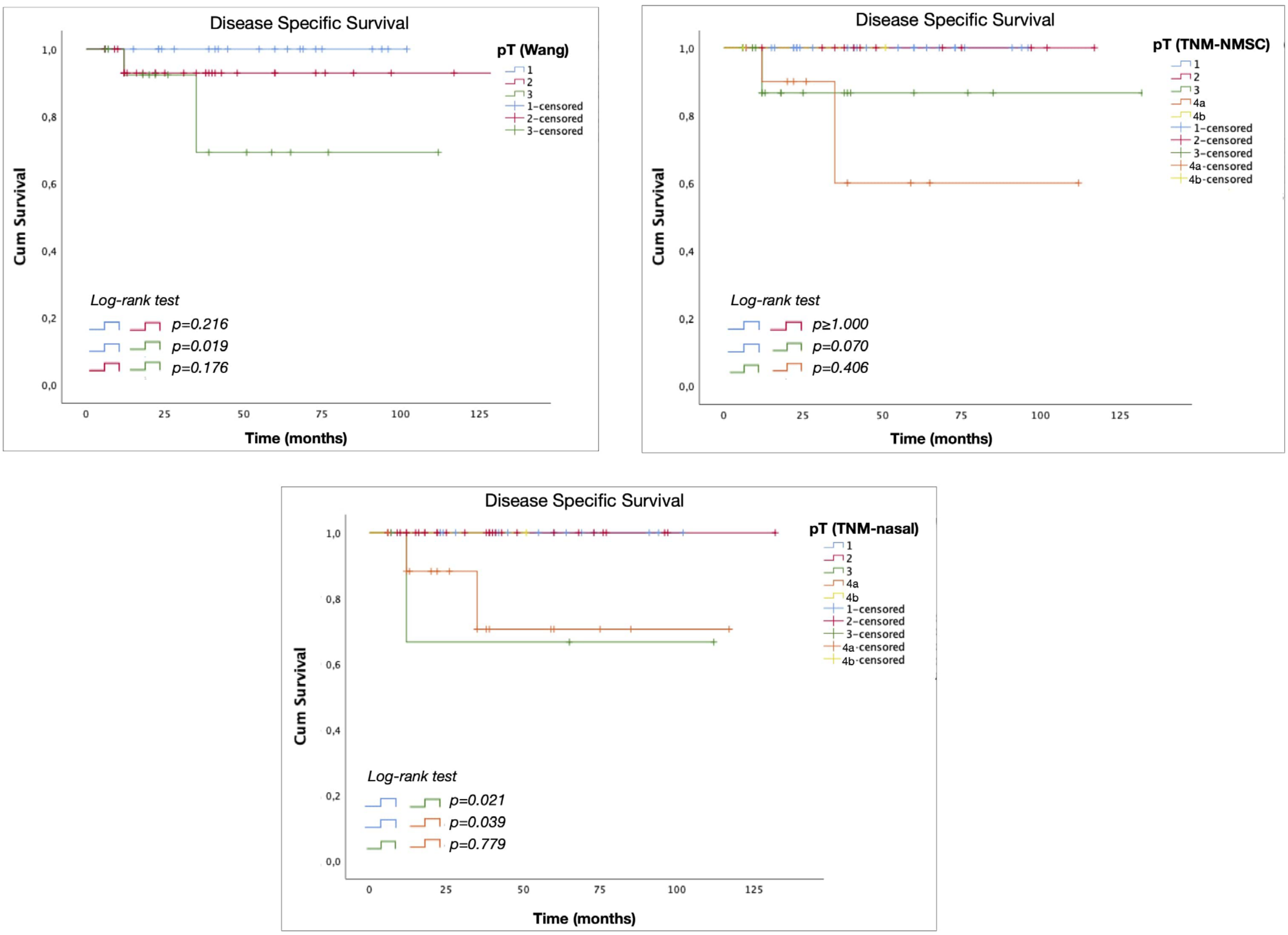

Fig. 3. Kaplan–Meier curve for disease specific survival (DSS). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

underwent elective ND, and no occult metastases were found. The rate of pN+ patients was 25% (5 out of 20 ND had positive nodes). Adjuvant RT was indicated in 32 (45.1%) cases. Adjuvant RT-CHT was indicated in 7 patients (one of them, with ENE+, refused CHT); these cases were all advanced tumors with R1 disease that were not amenable to re-resection, except for one with R0 margins but invasion of the hard palate, maxillary sinus and contralateral nasal fossa.

The cT and pT distribution and migration among the three classifications are shown in the alluvial plots (Fig. 1). Among the six centers, 32 (45.1%) cases were initially staged using the Wang classification, 31 (43.7%) using the TNM-nasal, and 8 (11.3%) with the TNM-NMSC. With stage re-assignment for each patient according to all three classifications, primary tumor upstaging and downstaging occurred in several cases (Fig. 1).

When analyzing the OS within the Wang pT stages (Fig. 2), we did not find significant difference between pT2 and pT3 ($p = 0.737$), while significance was found in comparing pT1-pT2 and pT1-pT3. Similarly, in the TNM-NMSC system, difference in OS was seen between pT1 and pT2, pT1 and pT3, pT1 and pT4a; however, adjacent categories did not show significant differences (pT2-pT3, p = 0.925; pT3-pT4a, $p = 0.675$). Also, pT2 and pT4a were not significantly different in OS, $p = 0.267$. The validity of comparison was limited as pT4b category included only 1 patient. In the TNM-nasal system, OS was significantly different between categories pT1-pT3 ($p = 0.021$) and pT1-pT4a ($p = 0.039$), yet there was no difference in survival between adjacent pT1-pT2 ($p = 0.129$), pT2-pT3 ($p = 0.418$), nor pT3-pT4a ($p = 0.779$).

Results of pairwise comparisons for DSS (Fig. 3), within the Wang stages, showed significance only for pT1 vs pT3 ($p = 0.019$), whereas pT1 vs pT2, and pT2 vs pT3, were not significant. For the TNM-NMSC, the only difference in DSS was between categories pT1 vs pT4a, and pT2 vs pT4a; all remaining adjacent categories were non-significantly different.

Moving to the DFS analysis (Fig. 4), the pairwise comparison between pT2 and pT3 in the Wang classification still showed no significance; similarly occurred between adjacent classes in the TNM-NMSC, in which the only statistically significant difference was found between nonadjacent pT1 and pT4a ($p = 0.015$). For

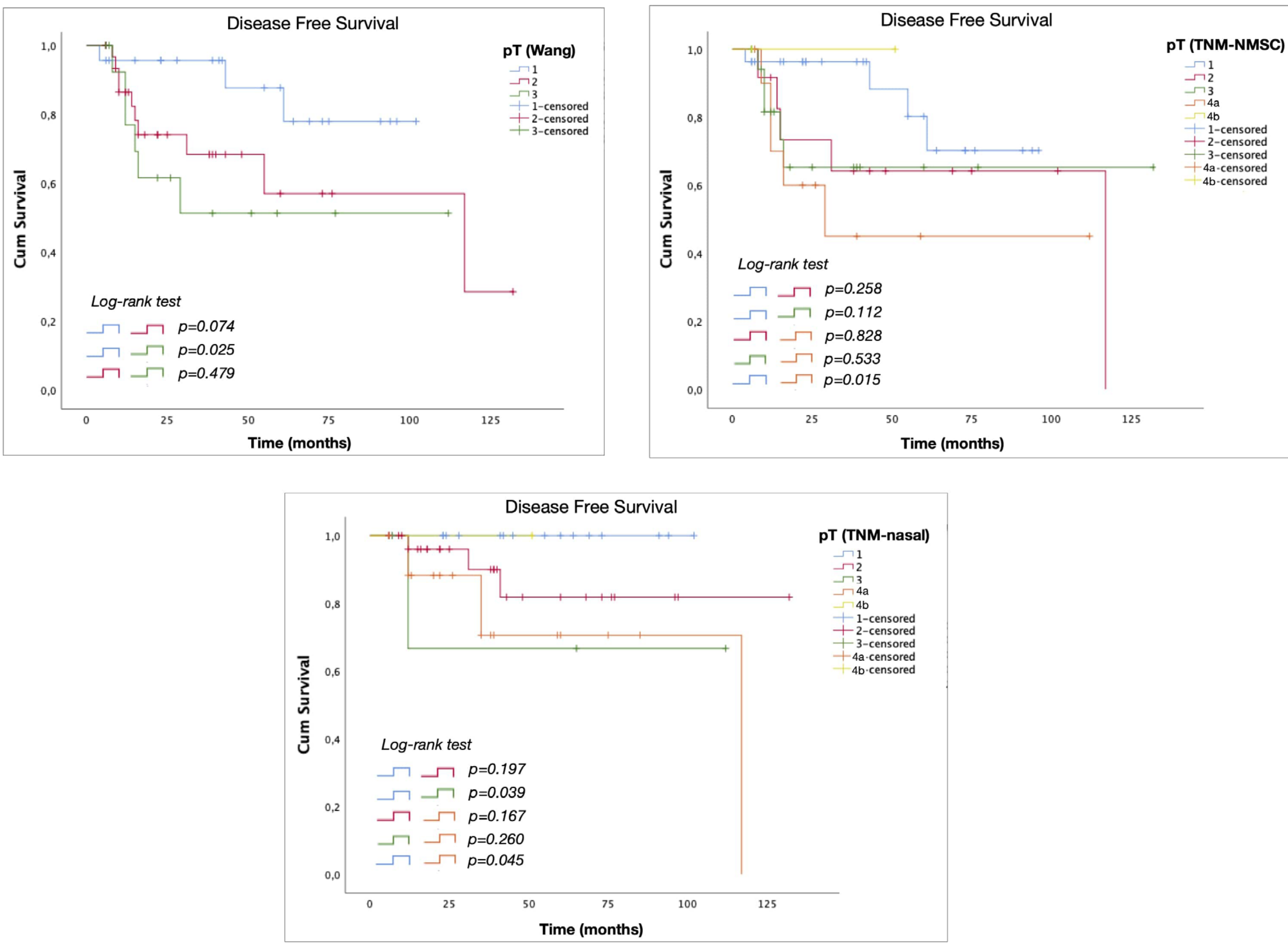

Fig. 4. Kaplan–Meier curve for disease free survival (DFS). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

the TNM-nasal, DFS was different only amid pT1 and pT3 ($p = 0.039$), as well as for pT1 and pT4a ($p = 0.045$).

In univariable analysis (Tables II–IV), the presence of PNI ($p = 0.020$), medial crus infiltration ($p = 0.095$), and age ($p = 0.010$) were associated with poorer OS. Worse DSS was associated with R1 margins ($p = 0.018$), the presence of bone infiltration ($p = 0.056$), the extension beyond the NV boundaries ($p = 0.044$), and with medial crus infiltration ($p = 0.096$). Factors that were associated with poorer DFS at univariable analysis were age ($p = 0.033$), pT category according to Wang (pT2 vs pT1, $p = 0.099$; pT3 vs pT1, $p = 0.039$), maximum diameter of the tumor ($p = 0.025$), the presence of PNI and LVI ($p = 0.022$ and $p = 0.004$, respectively), and the invasion of the skin of the columella ($p = 0.074$).

In multivariable analysis (Tables II–IV), factors that reached statistical significance to predict poorer OS were age ($p = 0.021$) and PNI-positivity ($p = 0.059$), whereas those associated with poorer DFS were age ($p = 0.033$) and LVI-positivity ($p = 0.019$). No features were significantly associated with worse DSS.

DISCUSSION

In this large multi-centric international study, we collected data and analyzed prognostic factors associated with survival in a homogeneous subset of patients affected by primary NV-SCC treated with upfront surgery. We excluded tumors of the skin of the pyramid to ensure the homogeneity of the sample, since they are more easily detectable and usually receive earlier treatment.

Recurrence-free survival of NV-SCCs ranges between 20% and 92% at 5 years,[1,15] varying according to series characteristics and treatments. In a large cohort of 174 Danish patients,[16] the incidence of NV-SCC was 0.32/100.000 inhabitants; however, this series was not homogeneous since 120 patients received upfront RT while the remaining had surgery with/without adjuvant RT. Locoregional control at 5 years was $67 \pm 4\%$, DSS was 74% and OS 50%. Similar results were found by Filtenborg[17] from 162 patients included in the clinical database DAHANCA, that showed an OS of 60% at 5 years of follow-up. In their subset of 146 (90%) patients treated with curative intent, disease-specific mortality at

TABLE II.
Uni-Variable and Multi-Variable Analysis Results for Overall Survival (OS).

	Univariable analysis (OS)			Multivariable analysis (OS)		
VARIABLE	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.07	1.02–1.13	**0.010**	1.08	1.01–1.14	**0.021**
Gender						
Male	—	—				
Female	0.03	0.00–14.91	0.263			
pT category Wang						
T1	—	—				
T2	123315.07	0.00–4.94E+147	0.944			
T3	156564.72	0.00–6.28E+147	0.943			
pT category TNM-NMSC						
T1	—	—				
T2	136942.97	0.00–9.25E+155	0.947			
T3	152727.70	0.00–1.03E+156	0.946			
T4a	251440.45	0.00–1.68E+156	0.944			
T4b	0.99	NA	1.000			
pT category TNM-nasal						
T1	—	—				
T2	29172.76	0.00–3.59E+108	0.933			
T3	81141.75	0.00–1.00E+109	0.926.			
T4a	72261.85	0.00–8.89E+109	0.927			
T4b	0.99	NA	1.000			
pN category						
N0	—	—				
N+	2.14	0.35–12.98	0.410			
N2b	1.26	0.13–12.20	0.841			
N3b	9.02	0.750–108.04	**0.082**			
Margins						
R0	—	—				
R+	2.43	0.57–10.31	0.230			
Grade						
G1	—	—				
G2	20866.27	0.00–4.98E+131	0.947			
G3	137537.47	0.00–3.28E+132	0.937.			
Max diameter	1.04	0.97–1.09	0.079			
PNI						
No	—	—				
Yes	5.60	1.31–24.03	**0.020**	4.35	0.95–19.97	**0.059**
LVI						
No	—	—				
Yes	1.40	0.17–11.43	0.753			
Subsite						
Limited to the NV	2.84	0.75–10.71	0.124			
Outer skin	1.72	0.35–8.53	0.508			
Nasal ala	0.98	0.25–3.95	0.981			
Columella	1.69	0.41–7.10	0.470			
Septum	0.99	0.24–4.15	0.990			
Other structures**	5.02	1.25–20.24	0.023			
Cartilage infiltration						
No	—	—				
Yes	3.54	0.44–28.82	0.237			

(Continues)

TABLE II. Continued						
	Univariable analysis (OS)			Multivariable analysis (OS)		
VARIABLE	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Medial crus	3.27	0.81–13.14	**0.095**	2.72	0.61–12.19	0.192
Lateral crus	0.88	0.18–4.40	0.881			
Quadrangular	2.41	0.49–11.96	0.282			
Triangular	1.09	0.22–5.45	0.916			
Bone infiltration						
No	—	—				
Yes	1.62	0.39–6.70	0.506			
Nasal bone	0.58	0.07–5.04	0.617			
Maxillary bone	1.94	0.39–9.63	0.416			

Note: Significance level set at $p \leq 0.10$; significant values are in bold. * = upper lip, skin of the cheek, mimic muscles, endo-oral mucosa.
Abbreviations: LVI, lymphovascular invasion; NV, nasal vestibule; PNI, perineural invasion.

5 years was 11% and OS was 65%. According to another recent series of 30 cases by Vital,[2] treated with either surgery or RT alone, or surgery and adjuvant RT, DSS was 96% and OS was 91.8% at 1 year of follow-up, while recurrence-free survival (RFS) was 81%, 77%, and 70% at 1, 2 and 5 years respectively. In our cohort rates were similar; at 1- and 3-years, OS was 93.5% and 86.5%, DFS was 87.5% and 74.2%, and DSS was 95.2% and 90.3%, respectively.

Treatment for NV-SCC may vary not only due to the stage of the primary tumor, but also for cosmetic outcomes and/or the possibility of a valid reconstruction, rather than the use of prostheses. The Danish treatment guidelines[16] recommend single treatment modality, either surgery or external beam RT (EBRT) for cT1 cases, always depending on cosmetic results and residual nasal function, while cT2-cT4 tumors should receive either upfront EBRT or surgery followed by adjuvant EBRT. Total rhinectomy is recommended only as salvage procedure.

The problem in defining which treatment strategy is the most appropriate reflects not only the rarity of the tumor, but also the lack of consensus on which staging system fits best.[18] Three classifications are available and are concomitantly used in the clinical practice: the American Joint Committee on Cancer (AJCC) for non-melanomatous skin cancers (NMSC), the AJCC for cancers of nasal cavity and ethmoid sinus, and the Wang Classification. However, each one has weak points, leading to uncertainties on clinical evaluation, treatment, pathological examination, and, therefore, prognosis.[18]

The Wang system was proposed in 1976, and even though it was based on a group of only 36 patients, it is still considered the most proper since it was specifically designed for NV tumors.[16,17] However, in 1999, Horsman[19] applied the Wang classification to 66 patients with NV-SCC ($cT1 = 55\%$; $cT2 = 35\%$; $cT3 = 11\%$) and found there was no significant prognostic value. Interestingly, in their series, gender, age, T-status, tumor volume, surgical margins, and primary treatment did not correlate with survival, whereas septal origin was significantly associated with worse RFS. Conversely, Kummer[20] defined the Wang staging system as more tailored to the growth characteristics of NV carcinomas, and Agger,[16] in a series of 174 NV-SCCs, found a significant association between DSS and Wang system. In 2013, Vital[2] brought again to attention the controversy whether the AJCC-NMSC or the Wang system had higher prognostic value, eventually evaluating the latter as insufficient for staging purposes. In our cohort, we re-staged each patient according to all three classification systems based on results of the pathological examination. At univariable analysis, only the Wang showed significant correlation with DFS, but it was not confirmed at multivariable analysis.

In this scenario, to answer the need for a more detailed and appropriate classification system for NV-SCC, it is fundamental to precisely identify which factors have a prognostic significance.

Chabrillac[21] demonstrated that positive margins after TR were predictive of tumor recurrence; age was found to significantly correlate with OS at both uni- and multivariable analysis by Filtenborg.[17] Similar results were presented in our series, as positive margins were associated with worse DSS ($p = 0.018$), as well as age was associated with worse OS and DFS at both uni- and multivariable analysis.

Dowley[3] reported that deep tissues involvement at the level of the septum and columella, particularly around the anterior nasal spine (i.e., T2 or T3 by Wang's system) had worse prognosis. This is similar to what we found, as at univariable analysis, the invasion of the columella was significantly associated with worse DFS ($p = 0.074$), as well as the extension of the tumor beyond the limits of the NV (i.e., beyond the limen nasi, to involve structures of the nasal cavity) was correlated with lower DSS ($p = 0.044$). Likewise, we found that tumor infiltration to the medial crus of the alar cartilage was associated with worse OS ($p = 0.095$) and DSS ($p = 0.096$). Since there seems to be consistency among some works demonstrating worse outcomes in case of

TABLE III.
Uni-Variable and Multi-Variable Analysis Results for Disease Specific Survival (DSS).

	Univariable analysis (DSS)			Multivariable analysis (DSS)		
VARIABLE	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.02	0.95–1.10	0.515			
Gender						
Male	—	—				
Female	0.03	0.00–82.0	0.379			
pT category Wang						
T1	—	—				
T2	45486.24	0.00–1.45E+146	0.949			
T3	142682.26	0.00–4.53E+146	0.943			
pT category TNM-NMSC						
T1	—	—				
T2	0.99	0.00–4.72E+204	1.000			
T3	75034.38	0.00–7.04E+127	0.938			
T4a	152921.33	0.00–1.43E+128	0.934			
T4b	0.98	NA	1.000			
pT category TNM-nasal						
T1	—	—				
T2	1.00	0.00–1.36E+162	1.000			
T3	116999.82	0.00–2.09E+130	0.937			
T4a	86926.19	0.00–1.54E+130	0.938			
T4b	0.99	NA	1.000			
pN category						
N0	—	—				
N+	2.89	0.40–20.72	0.290			
N2b	1.74	0.16–19.22	0.652			
N3b	9.98	0.79–126.81	**0.076**			
Margins						
R0	—	—				
R+	8.60	1.44–51.46	**0.018**	5.70	0.48–68.06	0.169
Grade						
G1	—	—				
G2	15771.03	0.00–4.13E+138	0.951			
G3	86372.42	0.00–2.26E+139	0.943			
Max diameter	1.05	0.99–1.11	0.114			
PNI						
No	—	—				
Yes	4.43	0.74–26.60	0.104	2.09	0.33–13.39	0.439
LVI						
No	—	—				
Yes	2.38	0.27–21.38	0.439			
Subsite						
Limited to the NV	9.50	1.06–85.03	**0.044**	3.31	0.21–51.71	0.394
Outer skin	3.31	0.55–19.82	0.190			
Nasal ala	1.42	0.24–8.58	0.700			
Columella	1.83	0.31–10.96	0.508			
Septum	0.90	0.15–5.41	0.911			
Other structures**	7.98	1.33–47.75	0.023			
Cartilage infiltration						
No	—	—				
Yes	1.94	0.22–17.38	0.553			

(Continues)

TABLE III.
Continued

VARIABLE	Univariable analysis (DSS)			Multivariable analysis (DSS)		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Medial crus	4.58	0.76–27.43	**0.096**	2.43	0.34–17.46	0.377
Lateral crus	0.62	0.07–5.58	0.671			
Quadrangular	3.21	0.36–28.82	0.297			
Triangular	0.76	0.09–6.86	0.809			
Bone infiltration						
No	—	—				
Yes	5.72	0.95–34.34	**0.056**	0.76	0.05–11.78	0.842
Nasal bone	1.69	0.19–15.18	0.641			
Maxillary bone	3.82	0.64–22.87	0.142			

Note: Significance level set at $p \leq 0.10$; significant values are in bold. * = upper lip, skin of the cheek, mimic muscles, endo-oral mucosa.
LVI, lymphovascular invasion; NV, nasal vestibule; PNI, perineural invasion.

infiltration of the septum, the columella, and the medial crus, it could be speculated that the involvement of medial structures of the NV (i.e., on the midline) is associated with worse prognosis due to contiguity and higher risk of infiltration of the bone (i.e., the anterior nasal spine) and of the upper lip (with possible extension to the oral cavity mucosa), irrespective of the size of the tumor. Also, in our series, bone involvement was significantly associated with worse DSS ($p = 0.056$).

Another valuable consideration was drawn by Fornelli[15] from a series of 32 patients: the author emphasized the fact that multiple-subsites disease shows worse prognosis compared to single-subsite disease, even if each subsite presents with small diameters. Thus, to their judgement, this would justify a more aggressive management in multiple-subsites cases. Interestingly, they did not find tumor size, histologic grade, gender, smoking and alcohol habits, initial treatment, and type of salvage therapy as significant in predicting survival.

Horsman[19] reported worse RFS in subjects with pN + disease, as well as the septal origin significantly correlated with worse RFS at both uni- and multivariable analysis. In 2007, Jeannon[1] demonstrated that older age, nodal status, and Wang stage were associated with worse OS, whereas tumor grade, depth of invasion and nodal status correlated with DFS. Furthermore, in a work by Wallace,[12] T4 tumors with bone involvement and greater than 4 cm were associated with worse local control. In our cohort, other features of aggressiveness that correlated with an unfavorable survival were PNI and LVI, at both uni- and multivariable analysis; however, we did not find agreement on this in literature.

Recommendations on neck management are heterogeneous and often conflicting, as some authors propose ND only in cN+ patients, maintaining surveillance on cN0 cases,[16,22] while others[12,23] suggest an elective neck treatment (ND or radiotherapy) in patients with locally-advanced (cT3–cT4) tumors, especially if poorly differentiated, and in recurrent cases.[8] Surely, the application of different staging systems complicates the definition of a consensus strategy on the management of the neck in NV-SCCs. In a systematic review by Talmi,[22] the overall incidence of nodal metastases varied from 4% to 40%. Scurry[24] published a meta-analysis addressing the need of prophylactic neck treatment in nasal cavity SCCs, reporting a 18.1% rate of regional recurrence, that is close to the 20% cut-off often used to suggest END. In our series, a limited number of patients (31%, Table I) underwent END, but not all of them were advanced stages (according to Wang's, T2: 5/11, T3: 6/11; according to TNM-NMSC, T1: 1/11, T2: 2/11, T3: 5/11, T4a: 3/11; according to TNM-nasal, T2: 4/11, T3: 1/11, T4a: 6/11). Among them, no occult neck metastases cases were found.

This study is burdened by some limitations, primarily its retrospective nature. Additionally, the sample size of this multicentric cohort was relatively small, yet it remained notably homogeneous. The limited number of N + and/or M+ patients within the cohort precluded us from drawing comprehensive conclusions due to insufficient data in these subgroups. Inconsistency in the staging systems and in the treatment modalities should be considered not only as a limitation, but also as an important reason of debate, need for data collection and further analysis.

CONCLUSION

From the comparative analysis, Wang's and the 8th AJCC-NMSC seem to correlate better with prognosis than the 8th AJCC-nasal. However, the TNM classifications lack prognostic accuracy when applied to NV-SCC, especially for specific subsites. The introduction of new criteria that better specify soft tissue and bone involvement in the median NV compartment (composed by medial crus, nasal septum, upper lip and anterior nasal spine) could help stratify high-risk from low-risk tumors; therefore, set the base for randomized trials that would guide clinicians in the future management of this rare type of tumor.

TABLE IV.
Uni-Variable and Multi-Variable Analysis Results for Disease Free Survival (DFS).

VARIABLE	Univariable analysis (DFS) OR	Univariable analysis (DFS) 95% CI	Univariable analysis (DFS) *p*-value	Multivariable analysis (DFS) OR	Multivariable analysis (DFS) 95% CI	Multivariable analysis (DFS) *p*-value
Age	1.04	1.00–1.08	**0.033**	1.05	1.00–1.10	**0.033**
Gender						
Male	—	—				
Female	0.43	0.12–1.49	0.182			
pT category Wang						
T1	—	—		—	—	
T2	3.03	0.81–11.32	**0.099**	2.34	0.24–22.96	0.465
T3	4.35	1.08–17.55	**0.039**	1.59	0.12–21.80	0.782
pT category TNM-NMSC						
T1	—	—				
T2	2.47	0.65–9.36	0.184			
T3	2.41	0.63–9.20	0.198			
T4a	4.12	1.10–15.49	**0.036**			
T4b	NA	NA	NA			
pT category TNM-nasal						
T1	—	—				
T2	2.44	0.50–11.80	0.269			
T3	8.51	1.19–60.86	**0.033**			
T4a	4.80	1.00–22.99	**0.050**			
T4b	NA	NA	NA			
pN category						
N0	—	—				
N+	1.10	0.22–5.45	0.909			
N2b	1.00	0.19–5.25	1.000			
N3b	1.00	0.00–6536.32	1.000			
Margins						
R0	—	—				
R+	1.11	0.31–3.96	0.875			
Grade						
G1	—	—				
G2	3.59	0.46–27.85	0.221			
G3	8.70	1.04–72.77	**0.046**			
Max diameter	1.04	1.00–1.07	**0.025**	1.04	0.98–1.10	0.188
PNI						
No	—	—		—	—	
Yes	3.14	1.18–8.35	**0.022**	5.04	1.30–19.54	0.716
LVI						
No	—	—		—	—	
Yes	5.79	1.76–19.06	**0.004**	5.04	1.30–19.54	**0.019**
Subsite						
Limited to the NV	1.49	0.58–3.81	0.408			
Outer skin	1.59	0.52–4.84	0.419			
Nasal ala	1.01	0.40–2.56	0.991			
Columella	2.34	0.92–5.94	**0.074**	1.62	0.61–4.35	0.336
Septum	1.08	0.40–2.88	0.877			
Other structures**	2.58	0.90–7.35	0.077			
Cartilage infiltration						
No	—	—				
Yes	2.79	0.81–9.69	0.106			

(Continues)

TABLE IV.
Continued

VARIABLE	Univariable analysis (DFS)			Multivariable analysis (DFS)		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Medial crus	2.10	0.81–5.46	0.126			
Lateral crus	1.53	0.57–4.14	0.398			
Quadrangular	2.22	0.79–6.23	0.131			
Triangular	1.67	0.62–4.51	0.308			
Bone infiltration						
No	—	—				
Yes	1.37	0.49–3.87	0.550			
Nasal bone	1.15	0.32–4.12	0.826			
Maxillary bone	1.98	0.65–6.05	0.228			

Note: Significance level set at $p \leq 0.10$; significant values are in bold. * = upper lip, skin of the cheek, mimic muscles, endo-oral mucosa.
Abbreviations: LVI, lymphovascular invasion; NV, nasal vestibule; PNI, perineural invasion.

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