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ORIGINAL ARTICLE

Squamous cell carcinoma of the nasal vestibule in the Netherlands: A clinical and epidemiological review of 763 cases (2008–2021)

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Abstract

Background: Squamous cell carcinoma of the nasal vestibule (SCCNV) is a rare disease, distinctly different in presentation, treatment, and outcome from squamous cell carcinoma (SCC) of the nasal cavity and paranasal sinuses. However, these are often not analyzed separately.

Methods: The Netherlands Cancer Registry (NCR) and pathology reports from the Dutch Nationwide Pathology Databank (PALGA) were used to identify all newly diagnosed SCCNV cases in the Netherlands between 2008 and 2021.

Results: A total of 763 patients were included. The yearly incidence rate displayed a significant downward trend with an annual percentage change (APC) of −3.9%. The 5-year overall survival (OS) and disease-free survival were 69.0% and 77.2%, respectively. The 5-year relative survival was 77.9% and improved slightly over the inclusion period. OS for patients who were staged cT3 appeared to be worse than those staged cT4a, calling the applicability of the TNM-classification into question.

Conclusion: SCC of the nasal vestibule is rare, with declining incidence rates. Introducing a specific topography code for SCCNV is recommended to enhance registration accuracy. The TNM classification seems poorly applicable to SCCNV, suggesting the need to explore alternative staging methods.

KEYWORDS

cancer of the nasal vestibule, head and neck cancer, nasal vestibule, nose cancer, sinonasal cancer, squamous cell carcinoma

1 | INTRODUCTION

The nasal vestibule, located at the junction of internal and external body surfaces, is an epithelial transition area. Malignant tumors in this area, predominantly squamous cell carcinoma (SCC), are rare. The scarcity of accurate incidence estimates for SCC of the nasal vestibule (SCCNV) can be attributed to its classification under the same topography code as nasal cavity tumors, and misclassification as skin cancers, which likely results in under-registration. As such, SCCNV is staged according to the Union for International Cancer Control (UICC) TNM-classification for tumors of the nasal cavity and paranasal sinuses, although alternate staging systems are also used.[1–3] These tumors are typically easily detectable, allowing for prompt diagnosis at an early stage. For early-stage disease (cT1/2), both primary surgery and radiotherapy yield excellent outcomes.[4–14] Yet, surgery may lead to disfigurement, necessitating additional reconstruction or epithesis.[4,6,15,16] Radiotherapy has the benefit of "organ preservation," but delivery of accurate doses at curvy, thin, superficial targets which are surrounded by air, is not straightforward. Brachytherapy overcomes most of these problems and has emerged as the preferred treatment for early-stage SCCNV due to its superior oncological, functional, and aesthetic outcomes compared with surgery and external radiotherapy.[17–23] Conversely, surgery followed by external radiotherapy remains the treatment of choice for more advanced SCCNV. The aforementioned evidence is primarily based on limited retrospective research. Large databases are crucial for advancing our understanding of rare cancers. However, with only two registry studies conducted on SCCNV to date, it remains insufficiently recognized as a distinct entity.[24,25] This gap in recognition contributes to the absence of consensus on treatment strategies.

This study investigates the incidence trends of SCCNV in the Netherlands from 2008 to 2021, alongside an analysis of patient characteristics and treatment practices in relation to patient outcomes. It provides a clinical and epidemiological baseline for SCCNV management, and it supports the push for acknowledging SCCNV as a distinct entity deserving of a dedicated topography code.

2 | METHODS

2.1 | The Netherlands Cancer Registry and Dutch Nationwide Pathology Databank

The Netherlands Cancer Registry (NCR) is a comprehensive registry containing information on newly diagnosed cancer cases nationwide. Established in 1989, the NCR covers over 95% of all new patients.[26] Dedicated registrars extract data from individual patient health records, adhering to a progressively evolving dataset. Researchers can request data for studies through a structured query. PALGA, the Dutch Nationwide Pathology Databank, systematically gathers pathology data and tissue samples for all patients in the Netherlands. By linking these databases, additional valuable information can be obtained, enhancing the overall depth and breadth of the available data.

2.2 | Study population

Adult patients with a histopathologically confirmed primary SCCNV, diagnosed between January 1, 2008 and December 31, 2022 were eligible for inclusion. Cases were excluded if an SCCNV was identified during autopsy but was not considered the primary cause of death. Patients were identified through morphology and topography codes according to the International Classification of Diseases for Oncology (ICD-O-3). These codes covered the nasal cavity (C30.0) and all relevant subtypes of SCC (8051, 8052, 8070–8076, 8078, 8082–8086).[27] In order to identify patients with a primary tumor originating in the nasal vestibule, cases were matched with excerpts of histopathological examination from PALGA. Patients with a tumor of the nasal cavity proper or a tumor of unknown origin were excluded (Figure 1).

2.3 | Operationalization

Tumors were staged per the 6th edition (for patients diagnosed between 2008 and 2009), the 7th edition (for

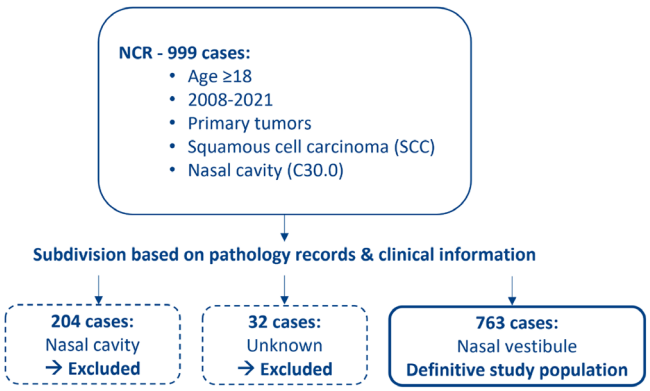

FIGURE 1 Study population selection process. NCR, the Netherlands Cancer Registry. [Color figure can be viewed at wileyonlinelibrary.com]

patients diagnosed between 2008 and 2016), or the 8th edition (2017 onwards) of the Union for International Cancer Control (UICC) TNM-classification for tumors of the nasal cavity and paranasal sinuses.[3,28,29] Tumors could not be restaged per other staging systems, such as the Wang or Rome classifications, due to a lack of available clinical information.[1,30] Certain variables from the query were not available from the start of the inclusion period because of the continued development of the NCR. The variables treatment intent, recurrence/disease progression, tumor diameter, and depth of invasion were registered from 2015 onward, with registration of surgical margins starting in 2016. All other variables were available for the entire study population. Missing values for treatment intent were filled in based on other clinical characteristics, as outlined in Appendix A (Table A1). Sensitivity analyses were conducted to assess the accuracy of this process.

2.4 | Statistical analysis

Incidence rates were adjusted for the composition and size of the Dutch population using the revised European Standard Population and reported as Revised European Standardized Rates (RESR) per 100 000 persons per year.[31] Trends over RESR were calculated using Joinpoint Trend Analysis Software (version 4.2.0.2) and expressed as an annual percentage change (APC) with 95% confidence intervals (CI). All other analyses were conducted using Stata/SE version 17.0. Normality was assessed through Q–Q plots. Patient characteristics at baseline were presented as means with standard deviations (SD) for normally distributed variables and medians with the 25th and 75th percentile (p25–p75) for non-normally distributed variables. Survival rates were estimated using the Kaplan–Meier method. Follow-up time was measured from the date of diagnosis until the date of death or date of linkage to the municipal registry to obtain vital status. Relative survival (RS) was defined as the observed survival rate compared with the expected survival rate in the general Dutch population (obtained from Statistics Netherlands).[32,33] Disease-free survival (DFS) was measured from the date of diagnosis until the date of disease recurrence or progression as registered during the most recent moment of clinical follow-up. Patients diagnosed before 2019 were eligible for DFS analyses if they were staged cM0, were treated with curative intent, and received treatment other than best supportive care (BSC). Univariable and multivariable analyses were conducted using the Cox proportional hazards model. The proportional hazards assumption was visually tested for categorical variables, and for continuous variables, interaction with time was assessed. The assumption was met for all variables except for age at diagnosis. Age at diagnosis and age at diagnosis*time were therefore both included in the analysis, with age at diagnosis as the determinant. The relative excess risk of dying (RER) was estimated in a univariable and multivariable model. Age at diagnosis, age at diagnosis*time, and sex were included in multivariable analyses (Cox and RER) regardless of statistical significance. Other variables with a probability (p) value <0.10 in univariable analysis were introduced in multivariable analysis and eliminated in a stepwise-backward manner. Probability values <0.05 were considered statistically significant. The variables tumor size, invasion depth, and resection margins were excluded from the analyses because of insufficient data. In order to ensure an adequate sample size per variable category, surgery and radiotherapy were grouped with surgery + chemoradiotherapy. Similarly, cT2 and cT3 were grouped for the DFS Cox proportional hazard analysis. This distinction was made based on the clinical characteristics of these stages.

3 | RESULTS

3.1 | Trends in incidence

The incidence rates standardized to the revised European population and the number of SCCNV in the Netherlands between 2008 and 2021 are depicted in Figure 2. The number of diagnosed cases ranged between 66 in 2008 and 42 in 2020. Over the study period, the annual RESR for the overall population fluctuated between 0.47 and 0.24 per 100 000. There was a clear downward trend in incidence rates with an APC of −3.9% (95% CI, −5.2% to −2.6%). Incidence was generally higher in males than females, but the decrease over time was more pronounced in females. Over the same period, the APC was −3.7% (95% CI, −6.1% to −1.2%) and −5.1% (95% CI, −8.1% to −2.0%) in male and female patients, respectively.

3.2 | Study population

A comprehensive cohort of 763 adult patients with a primary SCCNV was registered in the NCR from 2008 to 2021. The clinical characteristics of these patients are presented in Table 1. A more detailed breakdown, categorized by treatment intent, is given in Appendix B (Table B1).

The majority of patients had early-stage disease. Out of the 763 patients, nearly two thirds (63.4%) presented

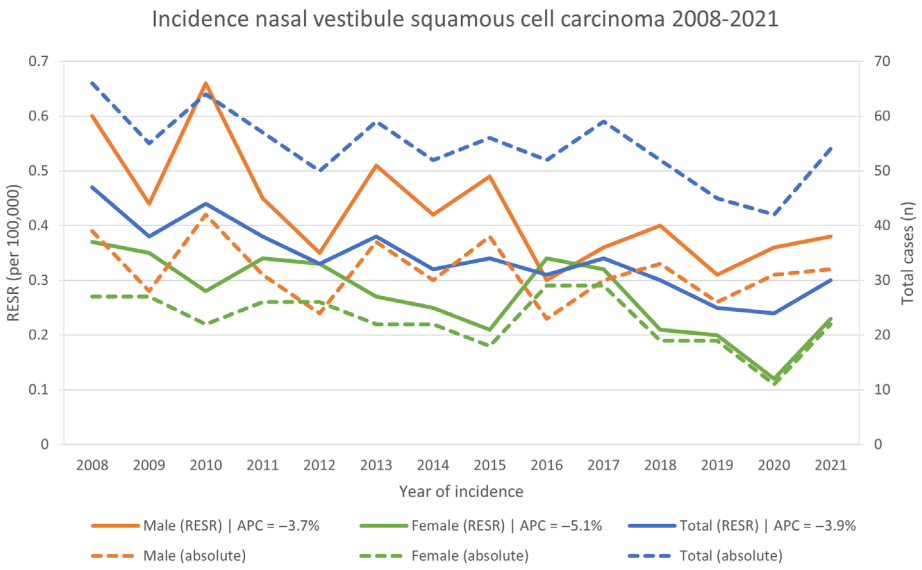

FIGURE 2 Incidence rates of squamous cell carcinoma of the nasal vestibule in the Netherlands between 2008 and 2021. RESR, revised European standardized incidence rate. The solid lines represent the annual incidence expressed as RESR. The dashed lines indicate the absolute incidence. APC, annual percentage change. [Color figure can be viewed at wileyonlinelibrary.com]

with T1 tumors. These included three patients with in situ tumors and one patient with a cT0 tumor, all of whom were later upstaged to pT1. One hundred sixty-eight (22.0%) had cT2 disease, while 27 (3.6%) and 49 (6.4%) presented with cT3 and cT4a tumors, respectively. Lymph node metastases were observed clinically in 31 patients (4.1%), while two (0.3%) presented with distant metastases. Out of the 31 patients with lymph node metastases, 16 (51.6%) were staged cN1, 5 (16.1%) had cN2b disease, and seven (25.8%) had cN2c disease. Two patients (6.5%) displayed signs of extranodal extension and were therefore staged cN3b.

The majority of patients (94.1%) were treated with curative intent. The most frequently used treatment modality was radiotherapy, either in combination with surgery (15.8%) or standalone by means of brachytherapy (34.6%) or external radiotherapy (32.5%). Sixteen (2.1%) received BSC. Out of the 31 patients with cN+ disease, seven (25.8%) patients underwent neck dissection, resulting in seven (22.6%) pN+ patients. Out of the 711 patients with cN0 disease, six (0.8%) patients underwent elective neck dissection, resulting in three (0.4%) pN+ patients. Information on radiotherapy of the neck was unavailable.

3.3 | Outcome

As of the latest moment of follow-up, out of 763 patients, 441 (47.8%) remained alive, and 322 (42.2%) had died. The median duration of follow-up was 60.7 months (p25–p75: 28.1–105.8). The 5-year overall survival (OS) estimate was 69.0% (95% CI, 65.4%–72.3%) for the entire cohort. Kaplan–Meier survival estimates for OS stratified by cT-stage and treatment modalities are depicted in Figure 3.

3.4 | Survival

The results of the Cox proportional hazard analysis for OS are given in Table 2. In the univariable analysis, a statistically significant correlation was observed between OS and all investigated variables, except for differentiation grade. This statistically significant association persisted for all variables included in the multivariable analysis. In this cohort, female patients (hazard ratio [HR] = 0.67, 95% CI, 0.53–0.86) had a decreased mortality hazard compared with male patients. Notably, there was no statistically significant increased risk for patients who were staged cT4a (HR = 1.41, 95% CI, 0.90–2.23) compared with cT1 (ref). Additionally, patients who received external radiotherapy (HR = 1.69, 95% CI, 1.11–2.55) had a significantly higher hazard of dying than patients who underwent surgery alone (ref).

A total of 208 patients were eligible for the DFS analysis. The estimated 5-year DFS was 77.2% (95% CI, 70.1%–82.9%). The findings of the Cox proportional hazard analysis for DFS are given hown in Table 3. A statistically significant association was observed between DFS and age at time of diagnosis*time, sex, and cT-classification. This association remained statistically significant in the multivariable analysis, including sex and cT-classification. Female patients (HR = 0.39, 95% CI, 0.19–0.80) had a statistically significant lower hazard of disease recurrence/progression compared with male patients.

The 5-year RS for the entire cohort was 77.9% (95% CI, 73.4%–81.8%; Figure 4). The RS increased from 75.3%

TABLE 1 Patient characteristics for patients ($n = 763$) with a squamous cell carcinoma of the nasal vestibule diagnosed between 2008 and 2021 in the Netherlands.

Age	Median	p25–p75
At diagnosis (years)	68	61–74
Sex	*N*	%
Male	444	58.2
Female	319	41.8
Differentiation grade	*N*	%
Well (G1)	182	23.9
Moderate (G2)	243	31.8
Poor (G3)	71	9.3
Unknown	267	35.0
cT classification	*N*	%
T1[a]	484	63.4
T2	168	22.0
T3	27	3.6
T4a	49	6.4
Unknown	35	4.6
cN classification	*N*	%
N0	711	93.2
N+	31	4.1
Unknown	21	2.7
cM classification	*N*	%
M0	752	98.5
M1	2	0.3
Unknown	9	1.2
Treatment intent	*N*	%
Curative	718	94.1
Palliative	19	2.5
Unknown	26	3.4
Primary tumor treatment modalities	*N*	%
S	104	13.6
S + RT	121	15.8
S + CRT	5	0.7
RT, brachytherapy	264	34.6
RT, external	248	32.5
Other[b]	5	0.7
None/BSC	16	2.1
Follow-up	Median	p25–p75
Duration (months)	60.7	28.1–105.8
At end of follow-up	N	%
Alive	441	57.8
Deceased	322	42.2

Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy; p25–p75, 25th and 75th percentile; RT, radiotherapy; S, surgery.

[a]Includes three Tcis patients and one cT0 patient.

[b]Includes patients treated with a combination of surgery/radiotherapy and topical 5-FU and/or systemic therapy.

(95% CI, 68.1%–81.1%) in 2008–2012 to 84.5% (95% CI, 67.6%–93.0%) in 2018–2021. Additionally, RS was higher in female patients compared with male patients and decreased with increasing age at the time of diagnosis. There was a statistically significant association between RS and the variables age, sex, cT, cN, and treatment modalities in univariable analysis (Table 4). The association between RS and these variables persisted in the multivariable model. Notable, female patients had a significantly lower RER of dying (RER = 0.58, 95% CI, 0.39–0.87) compared with male patients. The RER of dying compared with cT1 (ref) was highest for cT2/T3 patients (RER = 3.09, 95% CI, 1.59–6.02).

4 | DISCUSSION

The incidence rate standardized to the revised European population of SCCNV ranged between 0.24 and 0.47 per 100 000 over the inclusion period, highlighting the rarity of this tumor.

The APC over standardized incidence rates showed a clear downward trend. Tobacco smoking has previously been identified as one of the critical risk factors for developing SCCNV[24]. As tobacco smoking has been declining in the Netherlands for several years now, the downward trend in SCCNV may, at least in part, be attributable to this.[34] It is important to note that these incidence rates may be underestimated. Given that tumors of the nasal vestibule are registered under the same topography code as tumors of the nasal cavity proper (C30.0), cohort selection depends on the arduous process of manually identifying the correct cases by assessing pathology reports. Therefore, a dedicated topography code is necessary for accurate registration and research on SCCNV.

It can also be challenging to distinguish between cutaneous SCC (CSCC) of the head and neck and SCCNV, particularly if a tumor extensively involves both sites. Incidence rates for CSCC have steadily risen in the Netherlands due to an increase in ultraviolet (UV) light exposure.[35] UV exposure has been hypothesized to play an important role in the development of SCCNV. However, the differing incidence trends for SCCNV and CSCC suggest that this relation may not be as significant or may not exist at all.

Most patients (85.5%) in this study presented with either cT1 or cT2 tumors. This finding aligns with previous literature, which reported shares of 80%–90% in non treatment-specific cohorts.[2,24,25,36,37] Only 31 patients in this cohort presented with lymph node metastases, which seems to be a relatively small proportion. Previous studies, including a review by Talmi et al.,[38] reported percentages of cN+ patients at presentation ranging from 4% to

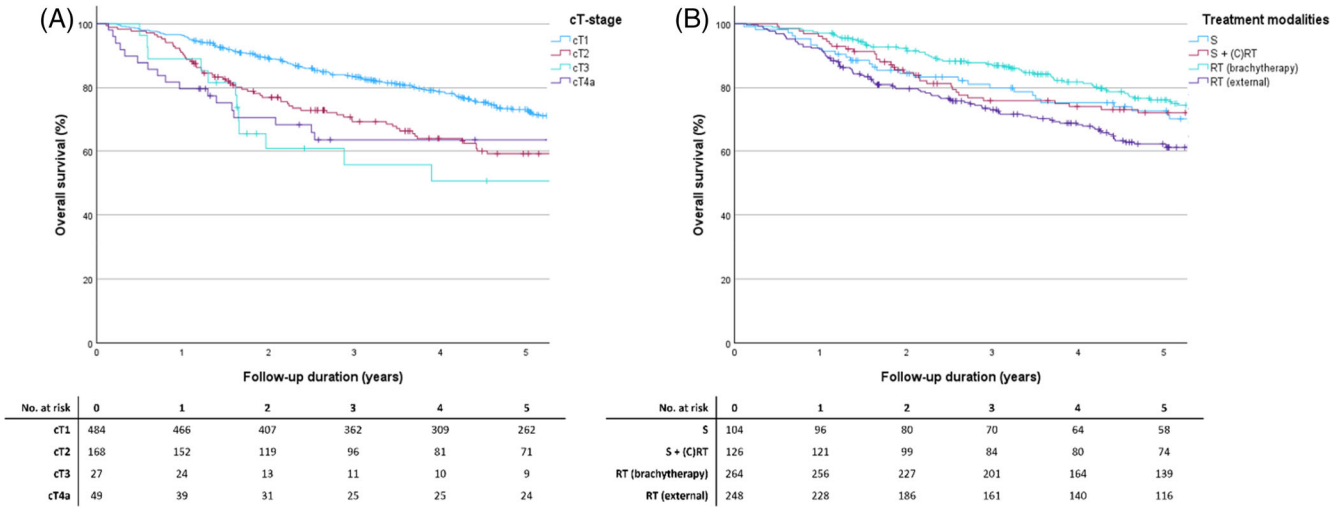

FIGURE 3 Kaplan–Meier survival estimates for overall survival for squamous cell carcinoma of the nasal vestibule in the Netherlands between 2008 and 2021. (A) cT-stage; (B) treatment modalities. (C)RT, (chemo)radiotherapy; RT, radiotherapy; S, surgery. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Univariable and multivariable Cox proportional hazard analysis for overall survival.

	Univariable			Multivariable[a]		
	HR	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-value**
Age (per 10 years)	2.01	1.78–2.27	**<0.001**	1.44	1.18–1.76	**<0.001**
Age (per 10 years)*time	1.07	1.03–1.11	**0.001**	1.09	1.04–1.13	**<0.001**
Sex			**0.001**			**0.001**
Male	Ref			Ref		
Female	0.67	0.54–0.84		0.67	0.53–0.86	
Differentiation grade			0.319			
Well (G1)	Ref					
Moderate (G2)	1.27	0.93–1.72				
Poor (G3)	1.12	0.71–1.75				
cT classification			**<0.001**			**0.003**
T1	Ref			Ref		
T2	1.51	1.16–1.96		1.43	1.09–1.88	
T3	2.17	1.30–3.62		2.22	1.31–3.76	
T4a	1.52	0.99–2.33		1.41	0.90–2.23	
cN classification			**<0.001**			**<0.001**
N0	Ref			Ref		
N+	2.50	1.62–3.86		2.61	1.66–4.11	
Treatment modality			**<0.001**			**<0.001**
S	Ref			Ref		
S + (C)RT	1.01	0.66–1.54		1.21	0.75–1.94	
RT, brachytherapy	0.97	0.66–1.41		1.13	0.74–1.72	
RT, external	1.40	0.97–2.01		1.69	1.11–2.55	
Other[b]	1.96	0.60–6.35		2.55	0.60–10.84	
None/BSC	4.50	2.43–8.33		9.22	4.60–18.48	

Note: Age was included as a continuous variable per 10 years. Significant *p*-values are depicted in bold.
Abbreviations: (C)RT, (chemo)radiotherapy; 95% CI, 95% confidence interval; BSC, best supportive care; HR, hazard ratio; S, surgery.

[a]All variables with $p < 0.10$ in univariate analysis were introduced in multivariable analysis.

[b]Includes patients treated with a combination of surgery/radiotherapy and topical 5-FU and/or systemic therapy.

TABLE 3 Univariable and multivariable Cox proportional hazard analysis for disease-free survival.

	Univariable			Multivariable[a]		
	HR	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**
Age (per 10 years)	1.26	0.87–1.82	0.224	2.08	1.11–3.89	**0.022**
Age (per 10 years)*time	0.60	0.36–0.98	**0.043**	0.64	0.40–1.04	0.072
Sex			**0.005**			**0.010**
Male	Ref			Ref		
Female	0.36	0.18–0.73		0.39	0.19–0.80	
Differentiation grade			0.619			
Well (G1)	Ref					
Moderate (G2)	1.13	0.50–2.54				
Poor (G3)	1.70	0.58–4.98				
cT classification			**0.003**			**0.005**
T1	Ref			Ref		
T2/T3	3.03	1.58–5.80		2.71	1.41–5.22	
T4a	2.63	0.90–7.67		3.06	1.04–8.96	
cN classification			0.096			
N0	Ref					
N+	3.36	0.81–13.99				
Treatment modality			0.128			
S	Ref					
S + (C)RT	1.50	0.42–5.32				
RT, brachytherapy	1.07	0.35–3.24				
RT, external	2.35	0.79–7.00				

Note: Age was included as a continuous variable per 10 years. Significant *p*-values are depicted in bold.
Abbreviations: (C)RT, (chemo)radiotherapy; 95% CI, 95% confidence interval; HR, hazard ratio; S, surgery.
[a]All variables with $p < 0.10$ in univariate analysis were introduced in multivariable analysis. cN classification was subsequently excluded in a stepwise backward fashion.

40%.[25] However, the reported lymph node metastases in this cohort only constitute the clinically detected metastases. Elective neck irradiation in the Netherlands is performed in accordance with the European Society for Radiotherapy and Oncology (ESTRO) guidelines.[39] For SCCNV, it is typically not performed because the risk of occult lymph node metastases is deemed too low. Nevertheless, the true incidence of lymph node metastases may be higher when occult lymph node metastases are taken into consideration.

Notably, the HR and RER for patients with cT4a tumors were not statistically different from those with cT1 tumors, suggesting that the TNM-classification may not be adequately tailored to the characteristics of SCCNV. There is increasing doubt regarding the applicability of the UICC TNM-classification for tumors of the nasal cavity and paranasal sinuses to SCCNV.[2,30,40] Alternative classifications, such as the Wang classification or the TNM-classification for CSCC of the head and neck, have been used to varying degrees.[1,41] Several studies have reported that the Wang classification provides superior prognostic value compared with other classifications.[5,17,18,24] Restaging the cohort according to other staging systems was impossible because the necessary clinical information was unavailable. A novel classification has recently been introduced to improve staging, but it still requires validation.[2,30]

The estimated 5-year OS was 69.0%, which is comparable to previous reports.[25,36] Direct comparison with other studies is challenging as these often focus on specific treatment modalities.[5,6] The estimated 5-year DFS was 77.2%. Here, sex and the cT-classification were the only variables significantly associated with DFS. The lack of association between DFS and most investigated variables may have resulted from a small sample size since only a subset of patients could be analyzed. The 5-year RS for the entire cohort was 77.9% and improved slightly over the course of the inclusion period.

Comparing surgery alone to surgery combined with additional treatment modalities, such as (chemo)

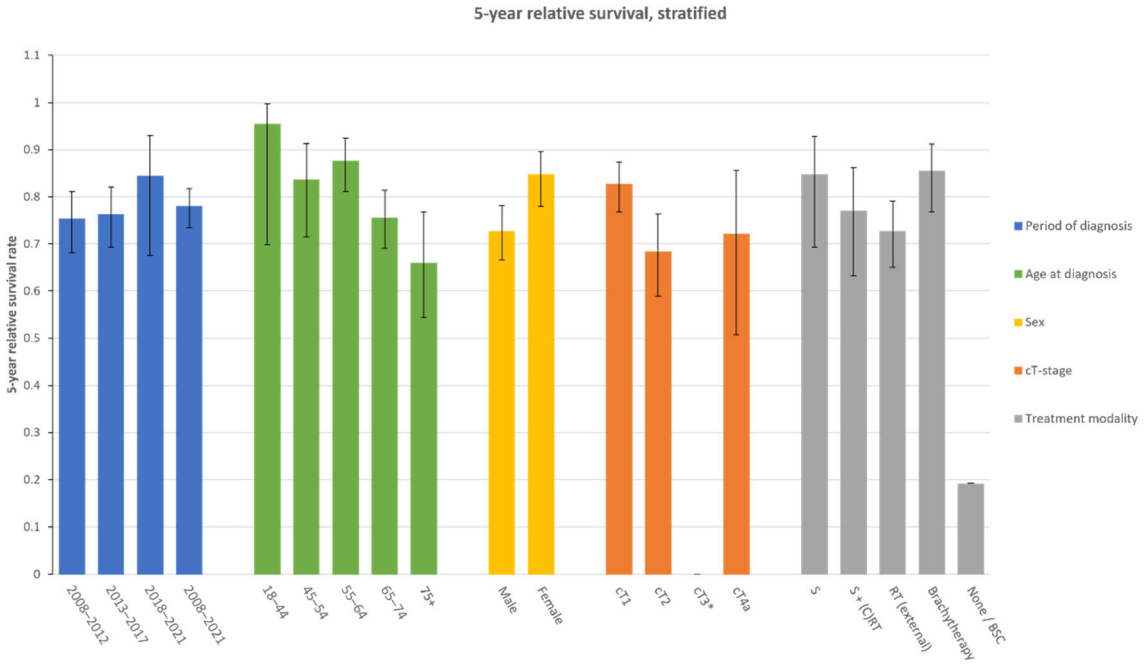

FIGURE 4 Five-year relative survival rates for squamous cell carcinoma of the nasal vestibule in the Netherlands between 2008 and 2021, stratfied by period of diagnosis, age at diagnosis, cT-stage, and treatment modalities. BSC, best supportive care; (C)RT, (chemo) radiotherapy; S, surgery. *The RS rate for cT3 patients could not be calculated due to low numbers. [Color figure can be viewed at wileyonlinelibrary.com]

radiotherapy, we found no statistically significant difference in patient outcomes, suggesting no direct benefit from these additional treatment modalities. Patients who received external radiotherapy had a significantly higher HR (OS) and RER than those who received surgery. This disparity may be attributed to confounding by indication, as patients selected for external radiotherapy were likely considered unsuitable candidates for surgery or brachytherapy due to their clinical condition. Brachytherapy and surgery as a single modality did not show a significant difference. However, it is important to consider the benefits of brachytherapy, such as functional and aesthetic outcomes, which were not evaluated in this study.[15,18,20,22]

This study population is the product of prospective registration through the NCR, ensuring data accuracy. One of the limitations that ought to be taken into consideration is the frequent occurrence of missing values. Furthermore, for any information to be extracted by registrars, it needed to have been recorded in a patient's electronic health record to begin with. Consequently, the quality of data relies on the consistent and detailed documentation practices of individual hospitals. Missing values for the variable treatment intent required manual complementing because of its importance to patient selection for subsequent analyses. Sensitivity analyses were conducted wherever possible to assess the potential impacts of this process. Additionally, the inability to distinguish between cancer-specific death and death from other causes limits the calculation of disease-specific survival.

Classification of tumors as in this study as either nasal vestibule or nasal cavity proper relied on manual identification through examining pathology reports, which is susceptible to errors. Subsequent research stands to benefit from uniform and agreed upon registration of important clinical variables for sinonasal tumors by all hospitals involved in diagnosing and treating these patients. Similarly, pathology reports throughout the Netherlands have recently been standardized. This is anticipated to further mitigate variations in registration. However, to improve the registration and classification of SCCNV effectively, it is essential first to recognize SCCNV as a distinct entity and then to introduce a dedicated topography code along with a universal tailored staging system.

5 | CONCLUSION

In conclusion, SCCNV is a rare tumor with a declining incidence trend in the Netherlands, but this may be an

TABLE 4 Univariable and multivariable relative excess risk of dying (RER).

	Univariable			Multivariable[a]		
	RER	**95% CI**	***p*-Value**	**RER**	**95% CI**	***p*-Value**
Age (per 10 years)	1.57	1.31–1.88	**<0.001**	1.52	1.27–1.83	**<0.001**
Sex			**0.008**			**0.008**
Male	Ref			Ref		
Female	0.60	0.41–0.87		0.58	0.39–0.87	
Differentiation grade			0.414			
Well (G1)	Ref					
Moderate (G2)	1.43	0.84–2.43				
Poor (G3)	1.32	0.64–2.73				
cT classification			**<0.001**			**<0.001**
T1	Ref			Ref		
T2	2.11	1.40–3.18		1.76	1.16–2.67	
T3	3.48	1.80–6.73		3.09	1.59–6.02	
T4a	2.32	1.28–4.18		2.16	1.20–3.88	
cN classification			**<0.001**			**<0.001**
N0	Ref			Ref		
N+	3.67	2.17–6.23		3.40	1.92–6.00	
Treatment modality			**<0.001**			**<0.001**
S	Ref			Ref		
S + (C)RT	1.16	0.56–2.43		1.41	0.61–3.29	
RT, brachytherapy	0.86	0.42–1.76		1.11	0.48–2.59	
RT, external	1.79	0.94–3.42		2.40	1.10–5.22	
Other[b]	3.00	0.74-12.23		3.71	0.67–20.42	
None/BSC	8.83	3.86–20.18		16.36	6.31–42.43	

Note: Age was included as a continuous variable per 10 years. Significant *p*-values are depicted in bold.
Abbreviations: (C)RT, (chemo)radiotherapy; 95% CI, 95% confidence interval; RER, relative excess risk of dying; S, surgery.
[a]All variables with $p < 0.10$ in univariate analysis were introduced in multivariable analysis.
[b]Includes patients treated with a combination of surgery/radiotherapy and topical 5-FU and/or systemic etherapy.

underestimation. The introduction of a dedicated topography code would allow for improved registration. The applicability of current staging systems for SCCNV is increasingly being called into question. Future studies should consider incorporating alternative classifications and further investigate factors influencing survival.

AUTHOR CONTRIBUTIONS

Lise J. van de Velde: Data curation; formal analysis; investigation; roles/writing—original draft. **W. F. Julius Scheurleer:** Conceptualization; data curation; formal analysis; investigation; project administration; visualization; roles/writing—original draft. **W. Weibel Braunius:** Writing—review and editing. **Mischa de Ridder:** Writing—review and editing. **Lot A. Devriese:** Writing—review and editing. **Remco de Bree:** Conceptualization; supervision; writing—review and editing. **Gerben E. Breimer:** Supervision; writing—review and editing. **Boukje A. van Dijk:** Formal analysis; investigation; methodology; supervision; writing—review and editing. **Johannes A. Rijken:** Conceptualization; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data will not be made available.

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APPENDIX A

A.1 | TREATMENT INTENT REGISTRATION PROCESS.

Treatment intent was registered from 2015 and onward. Treatment intent of cases between 2008 and 2015 was filled in based on clinical characteristics by using rules set up by discussion with a head neck specialist. These rules were as follows:

- Curative intent if:
  - Patient had a cT1/cT2 tumor of the nasal vestibule and was treated with radiotherapy
  - Surgery was one of the primary treatment modalities
- Palliative intent if:
  - Patient had metastasis at diagnosis (cM+)
  - Patient did not receive any treatment

Above mentioned rules were tested on accuracy by performing a sensitivity analysis. This sensitivity analysis was performed by comparing the treatment intent assigned to patients diagnosed from 2015 and onward based on the defined rules to the information on treatment intent that was already known within this subset of patients. In this sensitivity analysis, >95% was correctly filled in by using the established rules. The rules were therefore considered accurate and were used in further analyses.

Additionally, one case could be filled in based on clinical information that was available about malignancy diagnosis <2 years before until 2 months after sinonasal primary tumor diagnosis.

TABLE A1 Sensitivity analysis of the treatment intent registration process based on the ≥2015 cohort.

		Treatment intent based on established rules		
		Curative	**Palliative**	**Total**
Priorly defined treatment	Curative	281	3	284
	Palliative	1	2	3
	Unknown	5	0	5
	Total	287	5	292

APPENDIX B

TABLE B1 Baseline characteristics subdivided by treatment intent.

	Curative ($n = 718$)		Palliative ($n = 19$)		Unknown ($n = 26$)	
Age	Median	p25–p75	Median	p25–p75	Median	p25–p75
At diagnosis (years)	68	61–74	75	63–81	66	60–74
Sex	*N*	%	*N*	%	*N*	%
Male	418	58.2	14	73.7	12	46.2
Female	300	41.8	5	26.3	14	53.8
Differentiation grade	*N*	%	*N*	%	*N*	%
Well (G1)	177	24.7	5	26.3	0	0
Moderate (G2)	229	31.9	5	26.3	9	34.7
Poor (G3)	68	9.5	0	0	3	11.5
Unknown	244	33.9	9	47.4	14	53.8
cT classification	*N*	%	*N*	%	*N*	%
T1[a]	478	66.6	6	31.6	0	0
T2	165	23.0	3	15.8	0	0
T3	19	2.6	1	5.2	7	26.9
T4a	27	3.8	6	31.6	16	61.6
Unknown	29	4.0	3	15.8	3	11.5
cN classification	*N*	%	*N*	%	*N*	%
N0	674	93.9	15	79.0	22	84.6
N+	27	3.7	3	15.8	1	3.9
Unknown	17	2.4	1	5.2	3	11.5
cM classification	*N*	%	*N*	%	*N*	%
M0	710	98.9	16	84.2	26	100
M1	0	0	2	10.6	0	0
Unknown	8	1.1	1	5.2	0	0
Primary tumor treatment modalities	*N*	%	*N*	%	*N*	%
S	104	14.5	0	0	0	0
S + RT	121	16.8	0	0	0	0
S + CRT	5	0.7	0	0	0	0
RT, brachytherapy	257	35.8	0	0	7	26.9
RT, external	226	31.5	5	26.3	17	65.4
Other	2	0.3	1	5.2	2	7.7
None/BSC	3	0.4	13	68.5	0	0
Follow-up duration	Median	p25–p75	Median	p25–p75	Median	p25–p75
Months	61.2	30.0–105.2	8.5	3.4–47.1	92.0	18.9–117.5
At end of follow-up	*N*	%	*N*	%	*N*	%
Alive	430	59.9	3	15.8	8	30.8
Deceased	288	40.1	16	84.2	18	69.2

Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy; p25–p75, 25th and 75th percentile; RT, radiotherapy; S, surgery.
[a]Includes three TCis patients and one cT0 patient.