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Original research

International multicentric validation of a novel T classification system for cancer of the nasal vestibule☆

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ABSTRACT

Study aim: Cancer of the nasal vestibule (CNV) is an underrecognized head and neck malignancy, lacking a distinct ICD-O-3 topography code, and a specific T classification. The goal of this study was to assess which of the currently used T classifications provides the most accurate predictive and discriminatory accuracy.
Methods: The four currently used classifications (UICC Sinonasal, UICC NMSC, Wang and Rome) were assessed in a retrospective multicenter cohort established within the Head & Neck and Skin Groupe Européen de Curiethérapie / European SocieTy for Radiotherapy & Oncology Working Group. Through multivariable disease-specific and recurrence-free survival analyses, it was evaluated which staging system was most valuable.
Results: 609 CNV cases were retrieved from 21 tertiary care centers. Only the Wang and New Rome systems provided accurate prognostic stratification as they showed diminishing survival rates and increasing hazards of disease-specific death and disease recurrence with each successive T category. Compared to Wang, the New Rome system employs more objective criteria and, since it includes four T categories, it can easily be integrated with cN stage to obtain a specific clinical staging for the CNV, which has also resulted superior compared to the current UICC/AJCC systems in this study.
Conclusion: The New Rome classification exhibits a superior predictive and descriptive precision compared to the Wang and both UICC/AJCC systems. The New Rome's T category structure would allow an integration into the wider UICC/AJCC system once the nasal vestibule is acknowledged as a different subsite.

1. Introduction

The nasal vestibule (NV) is the most anterior part of the nasal cavity [1], corresponding to the internal lining of the nasal tip [2,3]. In the World Health Organization's third edition of the International Classification of Diseases for Oncology (ICD-O-3), it is assigned the same topography code (C30.0) as the nasal cavity proper (NCP) [4–6], despite significant clinical and prognostic differences [1,5,7,8]. Unlike NCP

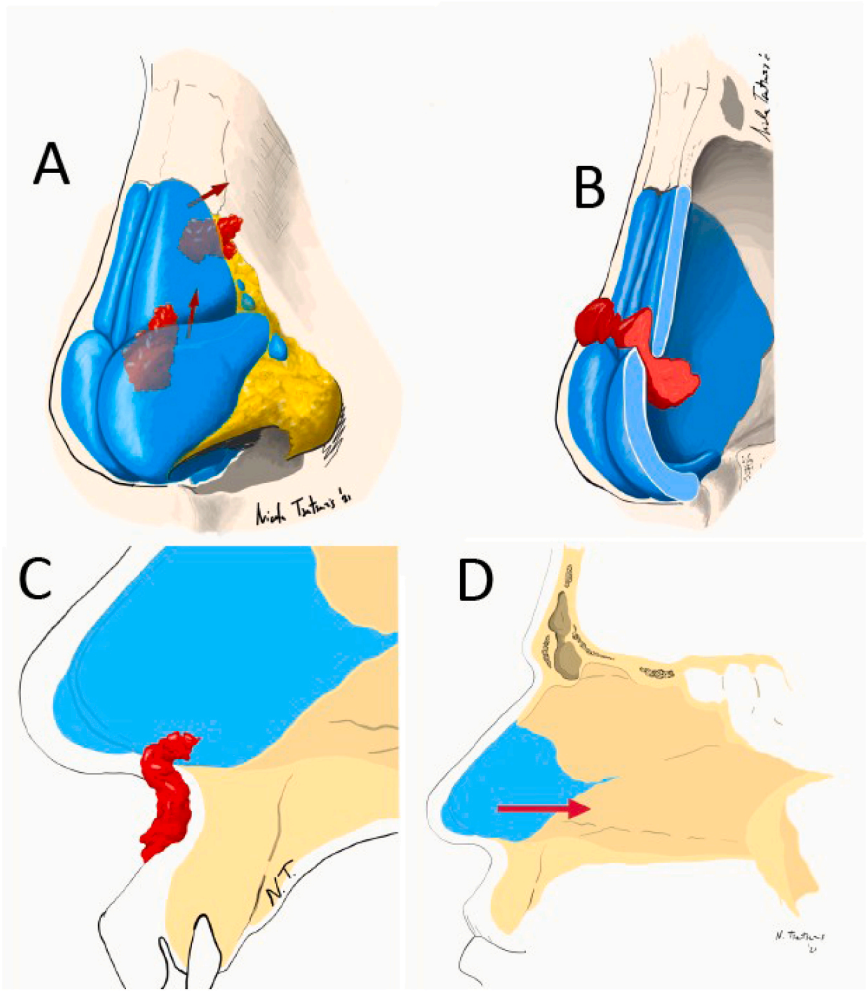


Fig. 1. Preferential cartilaginous tracks driving CNV spread from the lateral (A, B), medial (B, C, D) and inferior (C, D) walls of the nasal vestibule. Most (A, B, C) of these routes bring tumor invasion to the overlying nasal skin. The most typical route of spread is from the mucosa of the nasal valve, along the junction between the alar and the upper lateral cartilage, to the skin surface, just few millimeters away (A). This explains why skin invasion is very common in CNV, which would make most of them cT4a according to AJCC/UICC staging system, without a correspondent prognostic impact.

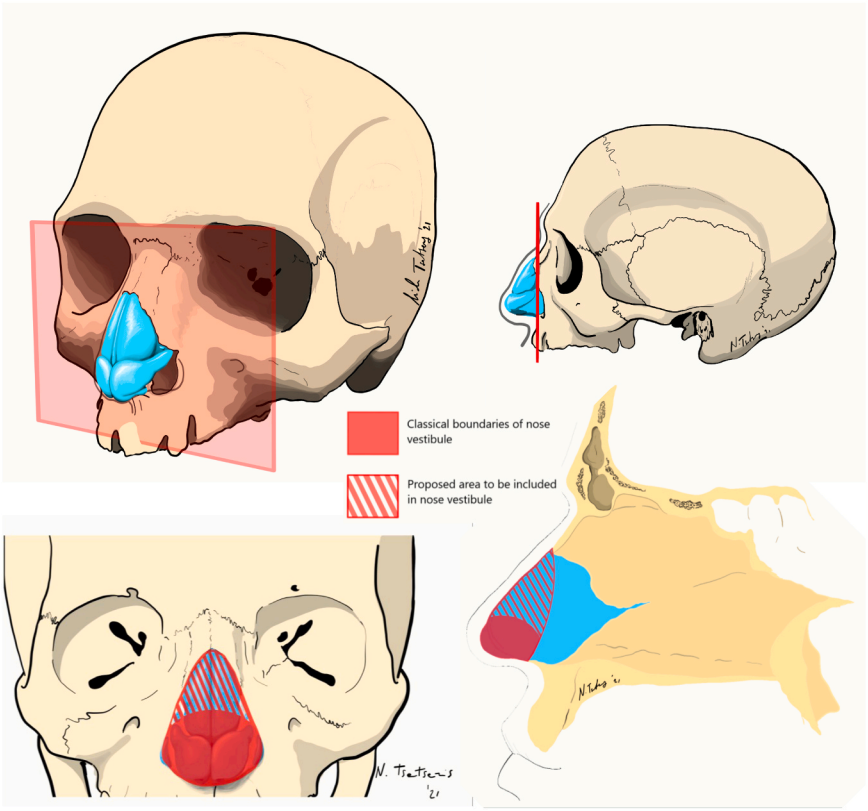


Fig. 2. Topographical definition of the nasal vestibule as a subsite within the nose. The plane tangential to the piriform opening is proposed as the posterior border separating NV from NCP.

(and other paranasal) cancers, squamous cell carcinomas of the NV (CNVs) preferentially spread directly to the overlying skin (Fig. 1) [2,7]. As a result, the most effective surgical approach generally involves a resection through all layers of the nasal wall [9], causing major reconstructive challenges [10,11]. Fortunately, CNVs are radiosensitive, and Interventional RadioTherapy (IRT, Brachytherapy, BT) achieves excellent tumor control and cosmetic results, with superior dose conformity and lower toxicity than External Beam RadioTherapy (EBRT) [12–19]. Combined with CNV's apparent location, facilitating early detection, this therapeutic option contributes to significantly improved survival compared to other sinonasal malignancies [6,20].

To facilitate the distinction between the NV and the NCP, a clearer anatomical and radiological boundary, corresponding to the plane tangential to the piriform aperture, has recently been proposed (Fig. 2) [2,3,5–7,21], allowing borderline lesions to be classified according to their epicenter. A consensus on a separate staging system, however, remains elusive. Within the UICC/AJCC staging system, which lacks specific criteria for the NV, these lesions have been staged either as nasal cavity/ethmoid or cutaneous squamous cell carcinomas (SCC) [22]. The Wang classification [23], on the other hand, is specific to the NV and is widely adopted due to its simplicity and demonstrated superior prognostic utility [6,13,24]. However, its reductionist nature and vague terminology limit its reproducibility and prevent its integration into the UICC/AJCC (Table 1) [7,25].

Recognizing these limitations, a new T classification specific to CNV, referred to as the Rome classification, was proposed by Bussu et al. in 2021 [5,7] and was preliminary validated in 2023 [26,27]. It refines Wang's criteria with objective parameters and the addition of the piriform opening as anatomical landmark and is designed for incorporation into in the wider UICC/AJCC TNM for sinonasal cancers, by the definition of the NV as a separate subsite.

The aim of this study is to compare the Rome classification against the other three currently used classifications within a multicenter cohort, with the ultimate goal to propose a single, dedicated CNV staging system as part of the UICC/AJCC TNM classification.

2. Materials and methods

2.1. Study design

This retrospective, multicenter study was approved by the Medical Ethics Committee of the University Medical Center Utrecht (22–859, 20 September 2022) and was subsequently circulated within the HNS (Head & Neck and Skin) GEC-ESTRO Working Group [28]. Data sharing was authorized by the local ethical review boards of all participating centers. Individual patient consent was not required given the retrospective nature of the study. All procedures complied with the principles of the Declaration of Helsinki (1964) for research involving human subjects.

2.2. Participants

Eligible patients were those diagnosed with primary SCC of the NV between January 2010 and December 2022. Data were collected from 21 tertiary care centers specialized in head and neck oncology, in 11 countries:

- Italy: Azienda Ospedale-Università Padova, ASST Spedali Civili Hospital Brescia, ASST Sette Laghi Hospital Varese, ASST Lariana Como, IRCCS Ospedale Policlinico San Martino Genoa, Istituto Europeo di Oncologia, Azienda Ospedaliera Universitaria di Sassari, Mater Olbia Hospital, and Fondazione Policlinico Universitario Agostino Gemelli IRCCS di Roma
- France: Lariboisière Hospital Paris
- Spain: Institut Català d'Oncologia, and Hospital Clínica Benidorm
- England: University Hospitals Bristol & Weston NHS Trust

Table 1
Staging systems used in CNV classification.

	cT stage (UICC sinonasal)	cT stage (UICC NMSC)	cT stage (Wang)	cT stage (New Rome)
T1	Tumor restricted to one subsite, with or without bony invasion	Tumor 2 cm or less in greatest dimension	The lesion is limited to the nasal vestibule, relatively superficial, involving one or more sites within	Tumor limited to the internal lining of the nasal vestibule (skin and/ or mucosa)
T2	Tumor involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion	Tumor > 2 cm and ≤ 4 cm in greatest dimension	The lesion has extended from the nasal vestibule to its 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	Tumor invading superficial structures (cutis, subcutis) beyond the nasal cavity, in particular the external surface of the nose, the nasolabial fold, philtrum, or upper lip or tumor invading cartilage (quadrangular, triangular, alar) without invasion of bony structures or structures beyond the plane of the piriform aperture[b]
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate	Tumor > 4 cm in greatest dimension or minor bone erosion or perineural invasion or deep invasion[a]	The lesion has become massive with extension to the hard palate, buccogingival sulcus, large portion of the upper lip, upper nasal septum, turbinate and/ or adjacent paranasal sinuses, fixed with deep muscle and bone involvement	Tumor extends posteriorly beyond the plane of the piriform aperture, with or without cartilage invasion, but without bone invasion
T4a	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	Tumor with gross cortical bone/marrow invasion		Tumor invades bony structures (e.g., hard palate, nasal bones, frontal process of the maxilla, ethmoid, or orbit)
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus	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

[a] 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.

[b] Because initial analyses in this study exhibited no clear differences between Rome cT2a and cT2b tumors (appendix pp. 11–13), a modified version (New Rome) was created and used, in which cT2a and cT2b tumors were grouped together.

- Hungary: National Institute of Oncology Hungary (Országos Onkológiai Intézet)
- Poland: Greater Poland Cancer Center
- India: Gujarat Cancer & Research Institute
- Germany: Universitätklinikum Schleswig-Holstein Lübeck
- Australia: Chris O'Brien Lifehouse
- Switzerland: Universitätspital Zürich
- The Netherlands: Radboud University Medical Center and University Medical Center Utrecht

The exact numbers of participants per center are enclosed in the supplementary appendix (p. 2). Part of the study population has already been included in previous works [7,15,16,18,25–27,29].

2.3. Procedures

Data collection was conducted independently at each center using a standardized registration protocol and extracting relevant clinical data from individual patient records. Each primary lesion was restaged according to the following systems:

- The 8th edition of the UICC/AJCC TNM classification for nasal cavity and paranasal sinuses (UICC Sinonasal)
- The 8th edition of the UICC/AJCC TNM classification for non-melanoma skin cancer of the head and neck (UICC NMSC)
- The Wang classification
- The Rome classification

To aid in Rome classification restaging, a manual was distributed to all centers before data collection (appendix pp. 3–10). Following collection, data were reviewed by two authors (WFJS, LJvdV). Any discrepancies and/or staging controversies were resolved in consultation with the original data collectors and the study coordinators (FB, MdR, LT, JAR) before final compilation of the study cohort.

Preliminary analyses using Kaplan-Meier, log-rank, and Cox proportional hazards models revealed no significant difference between Rome cT2a and cT2b tumors (appendix pp. 11–13). Additionally, differentiating between cT2a and cT2b tumors—based on the absence or presence of cartilage invasion—proved difficult to determine in a retrospective cohort, particularly in cases lacking high-quality MRI and/ or thorough clinical assessment. To establish a classification system that could be more broadly implemented and less dependent on local expertise, the New Rome system was developed, consolidating cT2a and cT2b into a single category. The four classification systems utilized for further analysis are summarized in Table 1.

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 30.0.0 and R version 4.4.0.

Baseline characteristics were presented for both the curative and palliative cohorts. Normality of data was assessed through Q–Q plots and Shapiro-Wilk tests and were reported as mean ± standard deviation (SD) when normally distributed, or as median with interquartile range (IQR) otherwise.

Five-year overall survival (OS), disease-specific survival (DSS), and

Table 2
Baseline characteristics for the curative cohort (n = 583).

					Curative (n = 583)			
Age at diagnosis					**Median**		**IQR**	
Years					67		17	
Sex					**N**		**%**	
Male					363		62·3	
Female					220		37·7	
Smoking status					**N**		**%**	
Non-smoker					117		20·1	
Former smoker					130		22·3	
Current smoker					202		34·6	
Unknown					134		23·0	
Smoking amount among smokers					**Median**		**IQR**	
Pack years					36		25	
Tumor diameter (categorized)					**N**		**%**	
< 20 mm					250		42·9	
≥ 20 mm					239		41·0	
Unknown					94		16·1	
cT stage	*UICC Sinonasal*		*UICC NMSC*		*Wang*		*New Rome*	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
T1	272	46·7	281	48·2	261	44·8	203	34·8
T2	93	16·0	124	21·3	228	39·1	244	41·9
T3	30	5·1	97	16·6	68	11·7	60	10·3
T4a	179	30·7	32	5·5	-	-	45	7·7
T4b	5	0·9	4	0·7	-	-	5	0·9
Unknown	4	0·7	45	7·7	26	4·5	26	4·5
cN stage (UICC)					**N**		**%**	
N0					537		92·1	
N1					11		1·9	
N2a					3		0·5	
N2b					12		2·1	
N2c					11		1·9	
N3a					-		-	
N3b					2		0·3	
Unknown					7		1·2	
cM stage (UICC)					**N**		**%**	
M0					574		98·5	
M1					2		0·3	
Unknown					7		1·2	
Clinical stage	*UICC Sinonasal*		*UICC NMSC*		*Wang*		*New Rome*	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
I	266	45·6	269	46·1	*NA*		198	34·0
II	84	14·4	112	19·2			222	38·1
III	29	5·0	95	16·3			63	10·8
IVa	185	31·7	54	9·3			59	10·1
IVb	7	1·2	2	0·3			7	1·2
IVc	2	0·3	-	-			2	0·3
Unknown	10	1·7	51	8·7			32	5·5
Primary tumor treatment					**N**		**%**	
EBRT					30		5·1	
IRT					233		40·0	
S					140		24·0	
S + EBRT					68		11·7	
S + IRT					56		9·6	
S + Syst *(C)* + EBRT					16		2·7	
Syst *(mostly C)* + EBRT					18		3·1	
Other[c]					22		3·8	
None/BSC					-		-	
Neck treatment					**N**		**%**	
Yes					102		17·5	
S					*64*		*11·0*	
EBRT					*29*		*5·0*	
S + EBRT					*4*		*0·7*	
Unknown					*5*		*0·9*	
No					481		82·5	
Follow-up					**Median**		**IQR**	
Median duration (months)					35		44	
Recurrences during follow-up					N		%	
Yes					135		23·2	
Local					*77*		*57·0*	
Regional					*38*		*28·1*	
Distant					*7*		*5·2*	
Multiple locations					*13*		*9·6*	
No					448		76.8	
Outcome					**N**		**%**	
No evidence of disease					423		72·6	

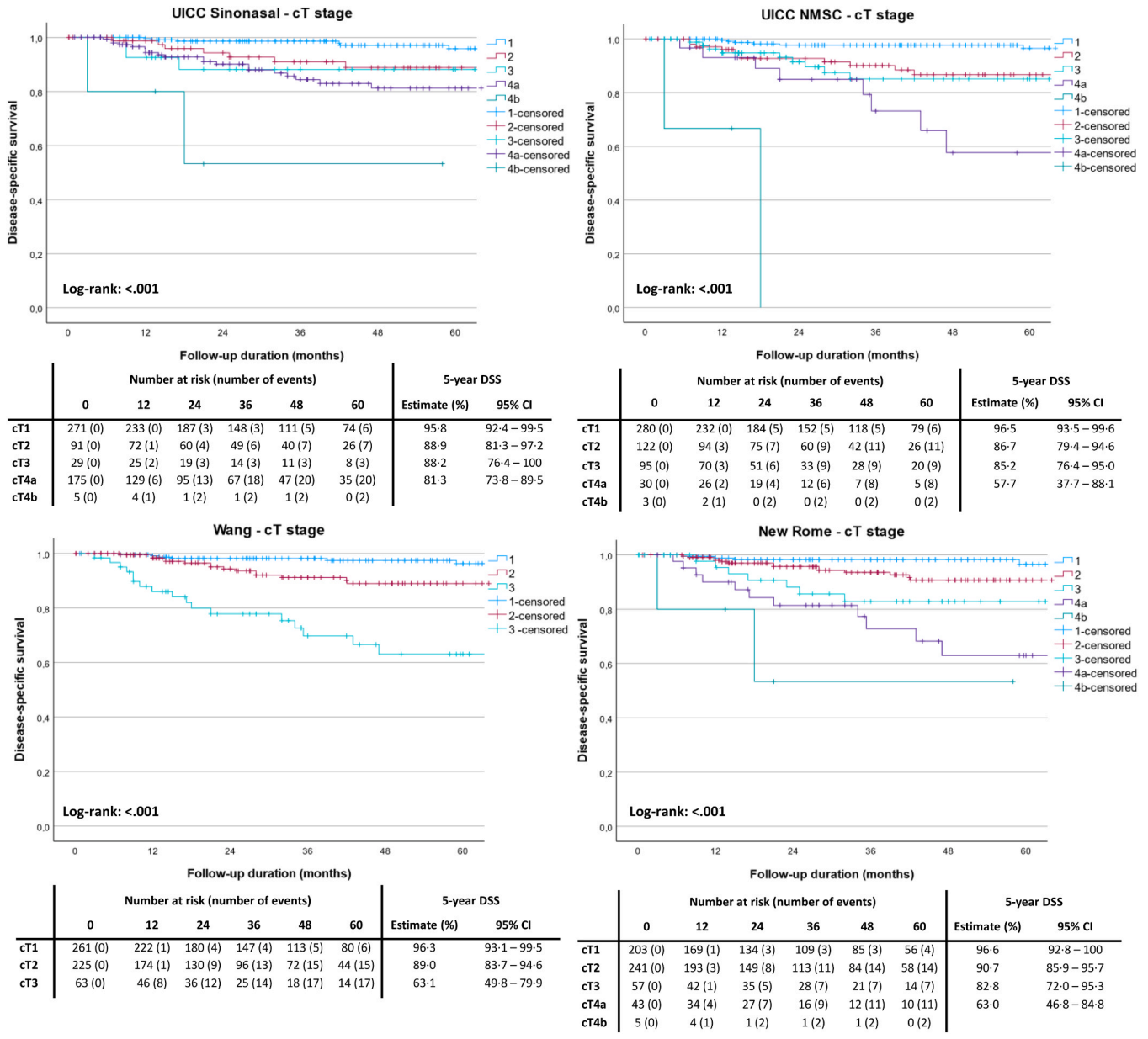
(*continued on next page*)

Table 2 (*continued*)

	Curative (n = 583)	
Age at diagnosis	**Median**	**IQR**
Alive with disease	19	3·3
Death of disease	43	7·4
Death of intercurrent disease	67	11·5
Lost to follow-up	31	5·3

EBRT = External Beam RadioTherapy; IRT = Interventional RadioTherapy (brachytherapy); S = Surgery; Syst = Systemic Therapy; C = Chemotherapy; BSC = Best Supportive Care.

[c] The group 'Other' consisted of different combinations of EBRT/IRT, S and/or Syst based treatment, of which each subgroup contained ≤ 3 patients.



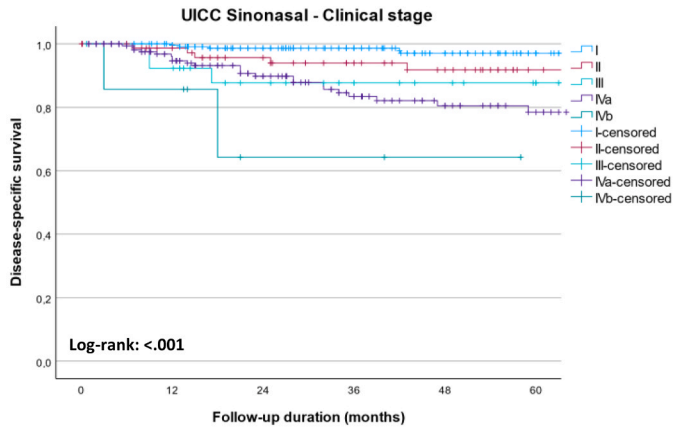
	Number at risk (number of events)						5-year DSS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cT1	271 (0)	233 (0)	187 (3)	148 (3)	111 (5)	74 (6)	95·8	92·4 – 99·5
cT2	91 (0)	72 (1)	60 (4)	49 (6)	40 (7)	26 (7)	88·9	81·3 – 97·2
cT3	29 (0)	25 (2)	19 (3)	14 (3)	11 (3)	8 (3)	88·2	76·4 – 100
cT4a	175 (0)	129 (6)	95 (13)	67 (18)	47 (20)	35 (20)	81·3	73·8 – 89·5
cT4b	5 (0)	4 (1)	1 (2)	1 (2)	1 (2)	0 (2)		

	Number at risk (number of events)						5-year DSS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cT1	280 (0)	232 (0)	184 (5)	152 (5)	118 (5)	79 (6)	96·5	93·5 – 99·6
cT2	122 (0)	94 (3)	75 (7)	60 (9)	42 (11)	26 (11)	86·7	79·4 – 94·6
cT3	95 (0)	70 (3)	51 (6)	33 (9)	28 (9)	20 (9)	85·2	76·4 – 95·0
cT4a	30 (0)	26 (2)	19 (4)	12 (6)	7 (8)	5 (8)	57·7	37·7 – 88·1
cT4b	3 (0)	2 (1)	0 (2)	0 (2)	0 (2)	0 (2)		

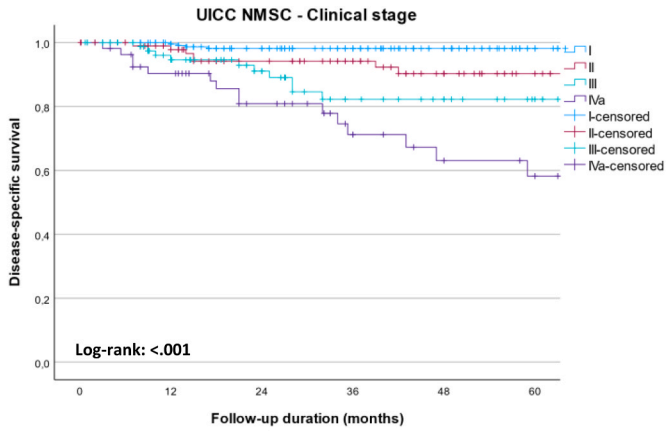
	Number at risk (number of events)						5-year DSS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cT1	261 (0)	222 (1)	180 (4)	147 (4)	113 (5)	80 (6)	96·3	93·1 – 99·5
cT2	225 (0)	174 (1)	130 (9)	96 (13)	72 (15)	44 (15)	89·0	83·7 – 94·6
cT3	63 (0)	46 (8)	36 (12)	25 (14)	18 (17)	14 (17)	63·1	49·8 – 79·9

	Number at risk (number of events)						5-year DSS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cT1	203 (0)	169 (1)	134 (3)	109 (3)	85 (3)	56 (4)	96·6	92·8 – 100
cT2	241 (0)	193 (3)	149 (8)	113 (11)	84 (14)	58 (14)	90·7	85·9 – 95·7
cT3	57 (0)	42 (1)	35 (5)	28 (7)	21 (7)	14 (7)	82·8	72·0 – 95·3
cT4a	43 (0)	34 (4)	27 (7)	16 (9)	12 (11)	10 (11)	63·0	46·8 – 84·8
cT4b	5 (0)	4 (1)	1 (2)	1 (2)	1 (2)	0 (2)		

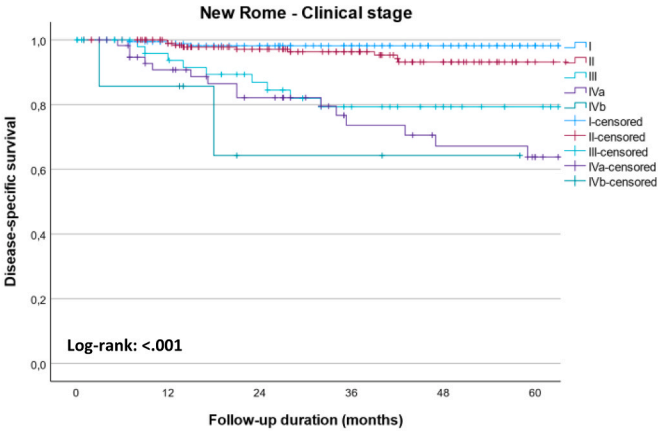
Fig. 3. (part A). DSS Kaplan-Meier survival estimates for each classification, stratified per cT category. Due to limited case numbers and generally poor outcomes, survival estimates could not be calculated for cT4b tumors. Fig. 3 **(part B).** DSS Kaplan-Meier survival estimates for each classification, stratified per clinical stage. Due to limited case numbers and generally poor outcomes, survival estimates could not be calculated for stage IVb. Fig. 3 **(part C).** DSS and RFS Kaplan-Meier survival estimates for each classification, stratified per cN category. Fig. 3 **(part D).** RFS Kaplan-Meier survival estimates for each classification, stratified per cT category. Due to limited case numbers and generally poor outcomes, survival estimates could not be calculated for cT4b tumors. Fig. 3 **(part E).** RFS Kaplan-Meier survival estimates for each classification, stratified per clinical stage. Due to limited case numbers and generally poor outcomes, survival estimates could not be calculated for stage IVb.



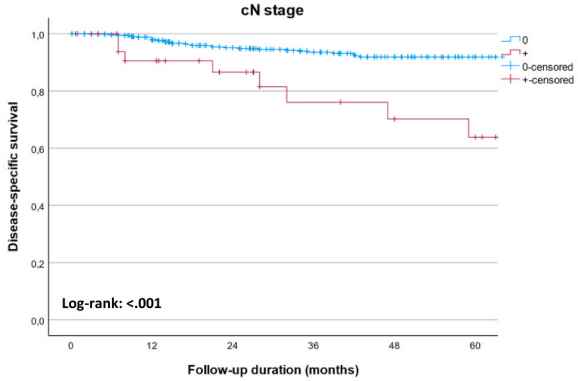
	Number at risk (number of events)						5-year DSS	
	0	12	24	36	48	60	Estimate (%)	95% CI
I	266 (0)	230 (0)	184 (3)	145 (3)	108 (5)	72 (5)	97·0	94·4 – 99·7
II	84 (0)	67 (1)	57 (3)	48 (4)	40 (5)	26 (5)	91·8	85·0 – 99·1
III	29 (0)	24 (2)	17 (3)	13 (3)	10 (3)	7 (3)	87·7	75·5 – 100
IVa	185 (0)	136 (6)	101 (14)	71 (20)	51 (22)	38 (23)	78·5	70·4 – 87·4
IVb	7 (0)	6 (1)	2 (2)	2 (2)	1 (2)	0 (2)		



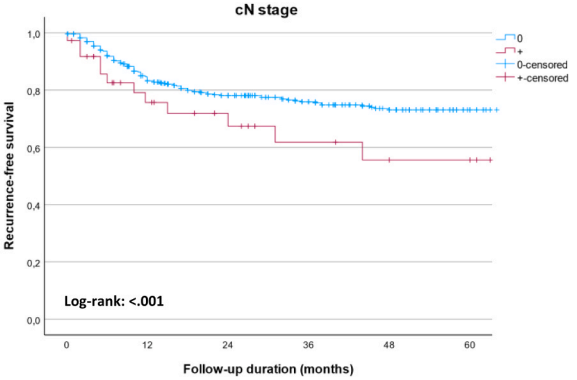
	Number at risk (number of events)						5-year DSS	
	0	12	24	36	48	60	Estimate (%)	95% CI
I	269 (0)	226 (0)	181 (4)	149 (4)	116 (4)	78 (4)	98·2	96·4 – 100
II	112 (0)	87 (1)	69 (5)	56 (5)	38 (7)	22 (7)	90·3	83·5 – 97·7
III	95 (0)	67 (3)	48 (6)	31 (10)	26 (10)	18 (10)	82·3	72·5 – 93·3
IVa	54 (0)	44 (5)	31 (9)	21 (12)	15 (14)	12 (15)	58·2	42·9 – 79·1



	Number at risk (number of events)						5-year DSS	
	0	12	24	36	48	60	Estimate (%)	95% CI
I	198 (0)	164 (1)	130 (3)	105 (3)	82 (3)	54 (3)	98·2	96·2 – 100
II	222 (0)	181 (1)	141 (5)	108 (6)	79 (9)	53 (9)	93·2	88·8 – 97·8
III	63 (0)	45 (2)	36 (6)	28 (9)	21 (9)	14 (9)	79·3	68·0 – 92·4
IVa	59 (0)	46 (5)	37 (9)	24 (12)	20 (14)	17 (15)	63·8	50·1 – 81·3
IVb	7 (0)	6 (1)	2 (2)	2 (2)	1 (2)	0 (2)		

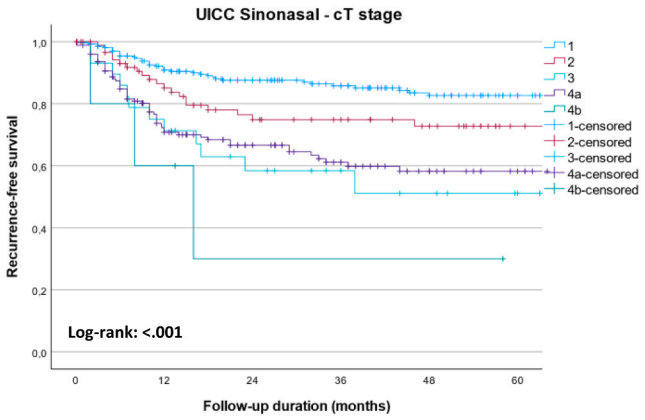


	Number at risk (number of events)						5-year DSS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cN0	537 (0)	439 (7)	344 (21)	266 (26)	198 (30)	133 (30)	91·9	89·1 – 94·8
cN+	37 (0)	27 (3)	20 (4)	14 (6)	12 (7)	10 (8)	63·8	45·7 – 89·2

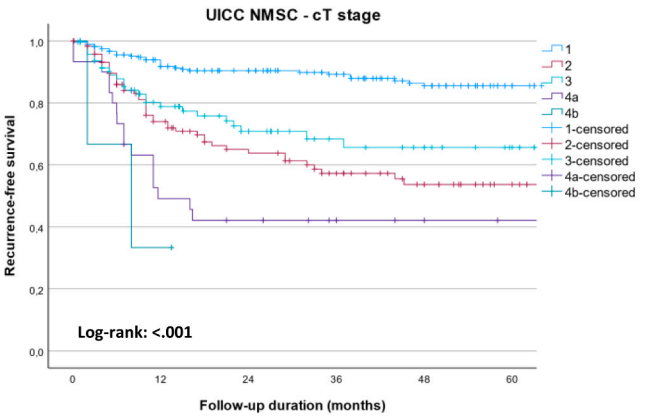


	Number at risk (number of events)						5-year RFS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cN0	537 (0)	381 (76)	288 (103)	226 (110)	164 (116)	117 (102)	73·1	68·9 – 77·6
cN+	37 (0)	22 (8)	16 (9)	11 (11)	9 (12)	8 (12)	55·6	38·4 – 80·4

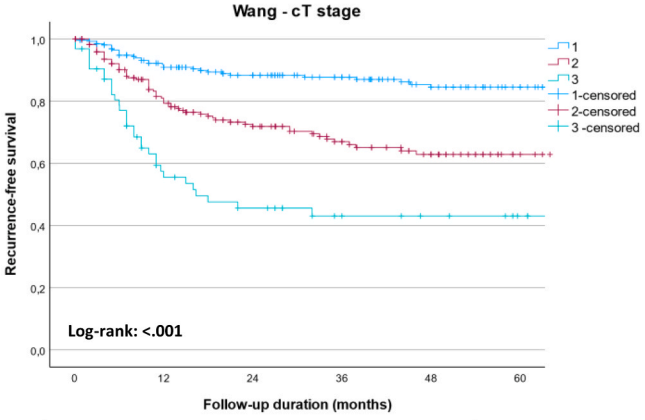
Fig. 3. (*continued*).



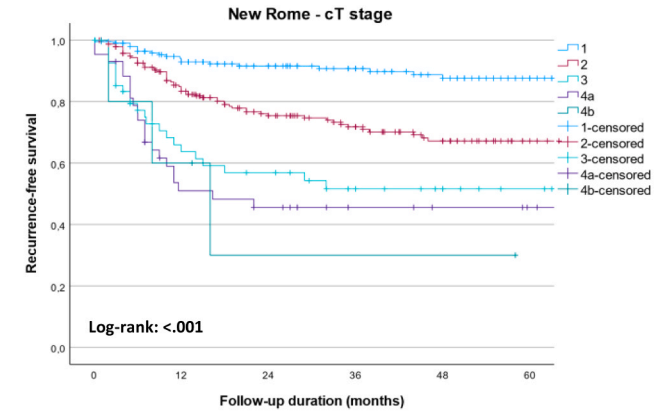
	Number at risk (number of events)						5-year RFS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cT1	271 (0)	215 (21)	169 (30)	136 (33)	100 (36)	65 (37)	82·7	77·5 – 88·2
cT2	91 (0)	64 (11)	49 (18)	41 (19)	33 (20)	20 (20)	72·7	63·0 – 84·0
cT3	29 (0)	20 (7)	13 (11)	11 (11)	6 (12)	3 (12)	51·1	33·6 – 77·7
cT4a	175 (0)	98 (43)	70 (50)	49 (55)	33 (57)	22 (57)	58·2	49·9 – 67·9
cT4b	5 (0)	3 (2)	1 (3)	1 (3)	1 (3)	0 (3)		



	Number at risk (number of events)						5-year RFS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cT1	280 (0)	221 (16)	174 (24)	144 (26)	106 (30)	68 (31)	85·5	80·7 – 90·6
cT2	122 (0)	72 (28)	53 (36)	40 (42)	28 (44)	14 (44)	53·6	44·0 – 65·4
cT3	95 (0)	58 (17)	38 (23)	25 (24)	21 (25)	14 (25)	65·6	54·8 – 78·6
cT4a	30 (0)	14 (15)	11 (17)	8 (17)	5 (17)	3 (17)	42·1	27·5 – 64·5
cT4b	3 (0)	1 (2)	0 (2)	0 (2)	0 (2)	0 (2)		



	Number at risk (number of events)						5-year RFS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cT1	261 (0)	205 (20)	163 (27)	134 (28)	100 (31)	69 (32)	84·5	79·5 – 89·8
cT2	225 (0)	145 (38)	103 (52)	75 (59)	54 (63)	28 (63)	62·8	55·5 – 71·1
cT3	63 (0)	30 (25)	22 (31)	15 (32)	12 (32)	8 (32)	43·1	31·6 – 58·7



	Number at risk (number of events)						5-year RFS	
	0	12	24	36	48	60	Estimate (%)	95% CI
cT1	203 (0)	160 (11)	126 (15)	103 (16)	77 (18)	49 (19)	87·6	82·3 – 93·3
cT2	241 (0)	169 (33)	121 (49)	93 (55)	67 (60)	42 (60)	67·2	60·3 – 74·8
cT3	57 (0)	29 (17)	24 (21)	17 (23)	13 (23)	8 (23)	51·6	38·8 – 68·5
cT4a	43 (0)	20 (19)	16 (22)	10 (22)	8 (22)	6 (22)	45·6	32·4 – 64·1
cT4b	5 (0)	3 (2)	1 (3)	1 (3)	1 (3)	0 (3)		

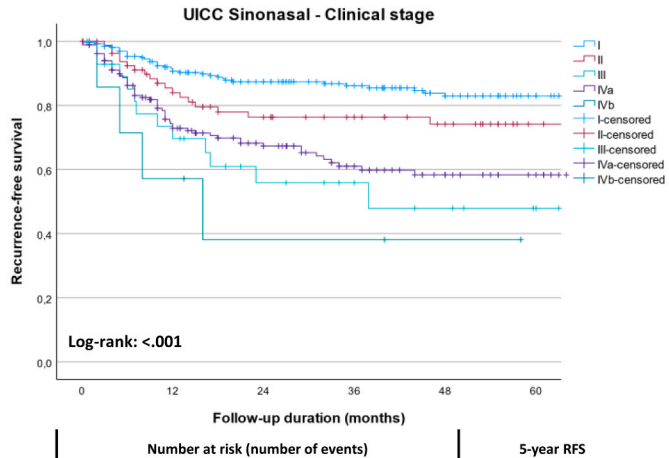
Fig. 3. (*continued*).

recurrence-free survival (RFS) were calculated using the Kaplan-Meier estimator. Follow-up time was measured from treatment initiation to the event or last follow-up. In OS analysis, events included both disease-specific and unrelated deaths, while in DSS only deaths caused by the disease were counted. All other deaths were censored at the time of occurrence. In RFS analysis, the event was the first documented recurrence. Patients lost to follow-up were censored at their last known disease-free status.

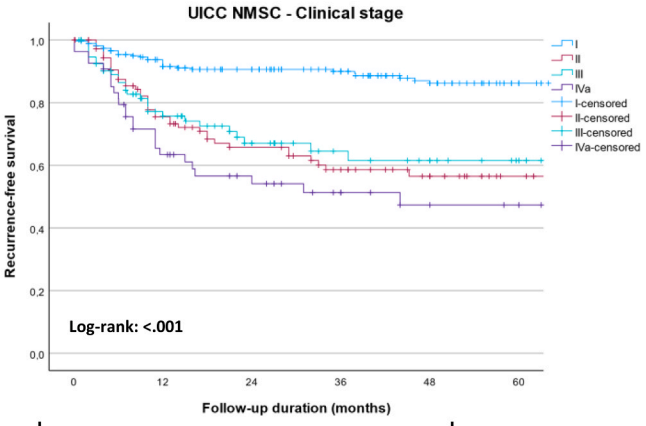
OS and DSS were calculated for both the curative and palliative cohort, while RFS was evaluated in curative patients only. Cases with cM+ disease or unknown cM stage were excluded from the survival analyses to prevent bias in eventual evaluation of the classification systems. Kaplan-Meier analyses (including log-rank tests) for DSS and RFS were performed to assess prognostic stratification by cT category in each classification system. OS was not included in these subgroup analyses to avoid confounding from unrelated comorbidities. After the Kaplan-Meier analyses, uni- and multivariable Cox proportional hazard models were constructed for DSS and RFS to evaluate how well each classification system reflected survival outcomes, while correcting for potential confounders. Variables were included in the multivariable models based on both statistical significance in univariable analysis (*P* value <.05) and assumed clinical relevance, at a maximum of one included variable per every ten events. To adequately compare all classifications, four multivariable models were developed—one for each classification system—with adjustment for the same set of confounders in each model. The variable treatment modality was excluded from multivariable analyses, as it is considered an intermediate variable. Adjusting for it could underestimate the true effect of T stage on DSS and RFS.

After assessing the individual T classifications, the overall performance of the currently used staging systems was assessed. Overall clinical staging for the New Rome classification was obtained by combining the T and N stages following the current UICC Sinonasal guideline. As such, its performance and potential for integration within the TNM could be directly assessed. A similar simulation could not be tested for the Wang classification, as it foresees only three classes, whereas UICC/AJCC classifications are based on four T categories.

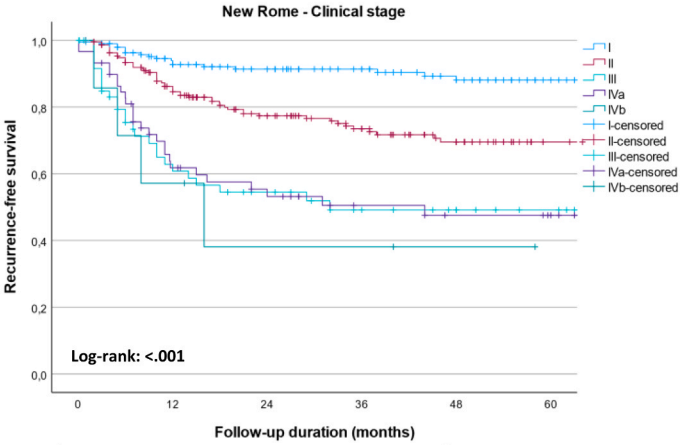
The concordance index (C-index) was calculated for each staging



	Number at risk (number of events)						5-year RFS	
	0	12	24	36	48	60	Estimate (%)	95% CI
I	266 (0)	212 (21)	166 (30)	134 (32)	98 (35)	63 (36)	83·0	77·8 – 88·5
II	84 (0)	59 (11)	47 (17)	40 (17)	33 (18)	20 (18)	74·2	64·3 – 85·5
III	29 (0)	19 (7)	11 (11)	8 (11)	5 (12)	2 (2)	47·9	30·0 – 76·4
IVa	185 (0)	106 (42)	76 (50)	52 (57)	36 (59)	25 (59)	58·3	50·2 – 67·8
IVb	7 (0)	4 (3)	2 (4)	2 (4)	1 (4)	0 (4)		



	Number at risk (number of events)						5-year RFS	
	0	12	24	36	48	60	Estimate (%)	95% CI
I	269 (0)	215 (16)	171 (23)	142 (24)	105 (28)	67 (29)	86·2	81·4 – 91·3
II	112 (0)	67 (24)	49 (32)	37 (37)	26 (38)	12 (38)	56·5	46·5 – 68·6
III	95 (0)	53 (19)	33 (25)	22 (26)	18 (27)	11 (27)	61·5	50·3 – 75·4
IVa	54 (0)	31 (19)	23 (22)	16 (24)	11 (25)	9 (25)	47·3	34·3 – 65·3



	Number at risk (number of events)						5-year RFS	
	0	12	24	36	48	60	Estimate (%)	95% CI
I	198 (0)	155 (11)	122 (15)	100 (15)	75 (17)	47 (18)	88·1	82·8 – 93·7
II	222 (0)	160 (28)	116 (43)	89 (48)	64 (52)	39 (52)	69·5	62·6 – 77·2
III	63 (0)	30 (20)	23 (24)	16 (26)	12 (26)	7 (26)	49·1	36·8 – 65·6
IVa	59 (0)	31 (21)	25 (24)	17 (26)	14 (27)	12 (27)	47·5	35·2 – 64·2
IVb	7 (0)	4 (3)	2 (4)	2 (4)	1 (4)	0 (4)		

Fig. 3. (*continued*).

system to assess its discriminatory power for DSS and RFS, while adjusting for the confounders controlled for in the multivariable Cox models. The C-index ranges from 0.5 (no discriminatory ability) to 1.0 (perfect discrimination).

3. Results

A total of 609 patients were included in the study. At the time of diagnosis, the majority of patients presented with localized disease, with nodal involvement and distant metastases being rare (7.2 % and 0.3 %, respectively). Clinical characteristics for the curative cohort (n = 583, 95.7 %) are presented in Table 2. Characteristics for the palliative and total cohort, are detailed in the appendix (pp. 14–17).

Cases with cM+ disease (n = 2) or unknown cM stage (n = 7) were excluded from the survival analyses to prevent bias in eventual evaluation of the classification systems. For the curative cM0 cohort (n = 574), the estimated 5-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) rates were 77.0 % (95 % CI: 72.7–81.6 %), 89.9 % (95 % CI: 86.6–93.2 %), and 72.1 % (95 % CI: 67.9–76.5 %), respectively. Recurrence patterns within the curative cohort are enclosed in the supplementary appendix (p. 18). Among the palliative cohort, the 1-year OS and DSS were 38.0 % (95 % CI: 21.6–67.0 %) and 44.2 % (95 % CI: 26.3–74.4 %), respectively; no patients in this subgroup were alive or traceable beyond three years.

The Kaplan–Meier analyses and corresponding log-rank tests for each of the staging systems are presented in Fig. 3. Only the Wang and New Rome classification exhibited consistently decreasing survival rates across successive T categories and (for New Rome) overall clinical stages in all DSS and RFS analyses.

Results from the Cox proportional hazards models for DSS are presented in Table 3. Univariable analysis revealed statistically significant associations between DSS and tumor diameter, cT classification across all systems, cN stage, clinical stage, and treatment modality (all $P < .001$). Most cT systems demonstrated increasing risks of disease-specific mortality with advancing cT category, except for the UICC NMSC system. Additionally, minimal differences were noted between cT2 and cT3 categories in the UICC Sinonasal classification. In multivariable analysis (performed separately for each staging system), the HR

Table 3
Univariable and multivariable Cox proportional hazard analysis for disease-specific survival.

	Univariable		
	HR	**95 % CI**	***P***
Age (per 10 years)	1·16	0·89–1·51	·26
Sex			·94
Male	ref		
Female	0·94	0·50–1·77	
Smoking status			·84
Non-smoker	ref		
Former smoker	1·10	0·42–2·86	
Current smoker	1·28	0·55–3·00	
Tumor diameter (categorized)			**< ·001**
< 20 mm	ref		
≥ 20 mm	6·04	2·51–14·5	
cT stage (UICC sinonasal)			**< ·001**
T1	ref		
T2	3·09	1·09–8·82	
T3	4·35	1·26–16·8	
T4a	6·44	2·76–15·0	
T4b	27·9	5·73–135	
cT stage (UICC NMSC)			**< ·001**
T1	ref		
T2	5·57	2·12–14·7	
T3	5·49	1·95–15·4	
T4a	15·1	5·35–42·4	
T4b	104·4	20·2–540	
cT stage (Wang)			**< ·001**
T1	ref		
T2	3·17	1·30–7·71	
T3	12·7	5·30–30·4	
cT stage (New Rome)			**< ·001**
T1	ref		
T2	3·63	1·21–10·9	
T3	6·86	2·01–23·4	
T4a	15·3	4·94–47·6	
T4b	34·0	6·17–187	
cN stage			**< ·001**
N0	ref		
N+	4·58	2·19–9·58	
Clinical stage (UICC Sinonasal)			**< ·001**
I	ref		
II	2·64	0·81–8·65	
III	5·47	1·37–21·9	
IVa	7·86	3·23–19·1	
IVb	21·3	4·26–106	
Clinical stage (UICC NMSC)			**< ·001**
I	ref		
II	5·46	1·64–18·1	
III	9·38	2·94–30·0	
IVa	24·2	8·13–71·9	
Clinical stage (Wang)			
NA			
Clinical stage (New Rome)			**< ·001**
I	ref		
II	3·11	0·86–11·3	
III	11·0	2·98–40·6	
IVa	20·0	5·86–68·2	
IVb	28·9	4·80–174	
Treatment modality			**< ·001**
S	ref		
EBRT	3·52	1·03–12·0	
IRT	0·90	0·33–2·50	
S + EBRT	2·81	1·01–7·76	
S + IRT	0·00	NA[a]	
S + Syst *(C)* + EBRT	9·54	3·19–28·5	
Syst *(mostly C)* + EBRT	5·96	1·74–20·4	
Other[b]	7·27	2·30–22·9	

	Multivariable[c] (including cT and cN separately)											
	UICC Sinonasal			***UICC NMSC***			***Wang***			***New Rome***		
	HR	**95 % CI**	***P***	**HR**	**95 % CI**	***P***	**HR**	**95 % CI**	***P***	**HR**	**95 % CI**	***P***
Age	1·16	0·86–1·57	·34	1·27	0·93–1·74	·13	1·22	0·89–1·68	·22	1·22	0·89–1·69	·22
Tumor diameter			.09			.61			.08			.16
< 20 mm	ref			ref			ref			ref		
≥ 20 mm	2·34	0·88–6·26		1·37	0·41–4·58		2·49	0·89–6·95		2·08	0·75–5·75	
cT stage			**·005**			**< ·001**			**< ·001**			**< ·001**
T1	ref			ref			ref			ref		

(*continued on next page*)

Table 3 (*continued*)

					Univariable							
					HR			**95 % CI**			***P***	
T2	3·17	0·83–12·1		4·01	1·04–15·5		1·90	0·67–5·37		2·88	0·76–10·9	
T3	5·86	1·22–28·1		4·21	1·06–16·7		6·67	2·20–20·2		5·36	1·22–23·5	
T4a	4·74	1·44–15·5		14·2	3·28–61·1		-	-		10·6	2·51–44·9	
T4b	32·0	5·21–197		122	17·2–867		-	-		37·5	5·39–260	
cN stage			**·001**			**< ·001**			**·005**			**< ·001**
N0	ref			ref			ref			ref		
N+	3·66	1·66–8·04		4·00	1·84–8·71		3·07	1·41–6·70		3·96	1·80–8·72	
C-index			0·80			0·81			0·81			0·82
	Multivariable[c] (including clinical stage)											
	UICC Sinonasal			***UICC NMSC***			***Wang***			***New Rome***		
	HR	**95 % CI**	***P***	**HR**	**95 % CI**	***P***	**HR**	**95 % CI**	***P***	**HR**	**95 % CI**	***P***
Age	1.13	0.85–1.50	.40	1·24	0·92–1·67	·16	-			1·18	0·86–1·61	·31
Tumor diameter			.06			.60						.21
< 20 mm	ref			ref			-			ref		
≥ 20 mm	2·49	0·95–6·52		1·33	0·45–3·92					1·89	0·70–5·14	
Clinical stage			**·003**			**< ·001**	-					**< ·001**
I	ref			ref						ref		
II	2·81	0·58–13·6		4·76	0·96–23·6					2·44	0·47–12·6	
III	7·28	1·38–38·5		9·67	2·18–42·8					9·91	1·86–52·9	
IVa	7·60	2·05–28·3		27·4	6·17–121					18·2	3·52–94·1	
IVb	25·8	4·00–166		-						32·0	4·12–251	
C-index			0·77			0·81			-			0·82

Age was included as a continuous variable per 10 years. HR = Hazard Ratio; 95 % CI = 95 % Confidence Interval; EBRT = External Beam RadioTherapy; IRT = Interventional RadioTherapy (brachytherapy); S = Surgery; Syst = Systemic Therapy; C = Chemotherapy. NS = Not Significant. NA = Not Applicable. Significant P values are depicted in bold.

[a] No one experienced disease-specific death in this group during the follow-up period.

[b] The group 'Other' consisted of different combinations of EBRT/IRT, S and/or Syst based treatment, of which each subgroup contained ≤ 3 patients.

[c] The different cT/clinical staging systems were never introduced into the same multivariable model.

for cT3 tumors was higher than for cT4a tumors compared to the reference category within the UICC Sinonasal system. Furthermore, within the UICC NMSC system, only a modest difference was found between cT2 and cT3 compared to the reference category. None of the systems, except the UICC NMSC system, showed a significant difference in HR between cT2 and cT1 tumors. Accordingly, analysis of the overall clinical stage systems evenly showed no significant differences in hazards between stage I and II tumors. Furthermore, all overall staging systems showed increasing hazards with advancing stages, however with very minimal differences in hazards between stages III and IVa tumors for the UICC Sinonasal system.

Table 4 presents the results of Cox proportional hazards models for RFS. Significant associations were found between RFS and tumor diameter, all cT staging systems, clinical staging systems, and treatment modality (all $P = <.001$) in univariable analysis. Only the Wang and New Rome systems maintained consistent stepwise increases in recurrence risk across cT categories in univariable and multivariable analyses, although the HR difference between cT4a and cT4b tumors for the New Rome system was marginal in multivariable analysis. When assessing the overall clinical staging systems, none of the systems pertained stepwise significant increases in hazards across the stages. Within the UICC NMSC system, HRs for stages II and III were similar, whereas the New Rome classification showed comparable HRs for stages III and IVa. Notably, the UICC Sinonasal overall staging system was not independently associated with RFS at all.

In terms of discriminatory performance, all staging systems demonstrated good predictive value for DSS, with concordance indices ranging between 0.77 (UICC Sinonasal) and 0.82 (New Rome, Table 3). For RFS, the corresponding C-indices ranged between 0.70 (UICC Sinonasal) and 0.73 (New Rome, Table 4).

4. Discussion

This international multicenter study, including 609 cases, represents one of the largest and most rigorously curated cohorts of CNVs to date.

CNV has long been considered rare among head and neck and in particular among (sino)nasal malignancies [30]. However, the frequent conflation with skin SCC and the absence of a specific ICD-O code [4] has led to hypothesize that the incidence has been largely underestimated [1,5,7]. In the Dutch population, CNV has in fact been demonstrated to account for 76 % of the cases diagnosed as nasal cavity malignancies, making it one of the most frequent in the sinonasal tract [6]. It is therefore a neglected malignancy, for which the parallel use of multiple staging systems has impaired progress by further increasing fragmentation in disease registration and reporting.

Among the four T classification systems examined in this study, both the Wang and New Rome provided a robust predictive stratification, as they showed diminishing survival rates and increasing hazards of DSS and RFS with each successive T category. This was not found for both UICC/AJCC TNM classifications, where absolute survival rates and HRs highly fluctuated across increasing stages, thereby confirming recent findings in a smaller series [27]. One important remark, however, must be made, as in the majority of DSS analyses across the systems, statistical significance between cT1 and cT2 tumors lacked. This was likely attributable to the low mortality rate in both groups. Nevertheless, the New Rome system consistently showed the highest discriminatory rate, as reflected by the relatively high C-indices.

Assessing the performance of the overall clinical stages, similar results were found. Herein, the New Rome system outperformed the Wang system, as the latter only contains only three T categories, limiting its integration into the existing UICC/AJCC TNM architecture. Furthermore, the Wang classification largely relies on ambiguous descriptors and tends to group patients with distinctly different characteristics, whereas the New Rome system is based on objective criteria and well-defined anatomical landmarks, such as the plane tangential to the piriform aperture.

Beyond its superior statistical performance, the New Rome system also exhibits a rational advantage over both UICC classifications, as the use of these alternatives remain fundamentally flawed. First, the use of the UICC NMSC is conceptually wrong as the NV is anatomically part of the nasal cavity, and it may increase the rate of misdiagnosis and lead to suboptimal treatment decisions [5,7,31]. Second, the UICC Sinonasal

Table 4
Univariable and multivariable Cox proportional hazard analysis for recurrence-free survival.

	Univariable		
	HR	**95 % CI**	***P***
Age (per 10 years)	1·14	0·98–1·31	·09
Sex			·39
Male	ref		
Female	0·86	0·60–1·22	
Smoking status			·90
Non-smoker	ref		
Former smoker	0·97	0·58–1·61	
Current smoker	0·90	0·56–1·44	
Tumor diameter (categorized)			**< ·001**
< 20 mm	ref		
≥ 20 mm	3·42	2·28–5·14	
cT stage (UICC sinonasal)			**< ·001**
T1	ref		
T2	1·57	0·92–2·67	
T3	3·20	1·69–6·09	
T4a	2·82	1·89–4·20	
T4b	5·93	1·83–19·2	
cT stage (UICC NMSC)			**< ·001**
T1	ref		
T2	3·70	2·36–5·78	
T3	2·72	1·62–4·55	
T4a	6·09	3·40–10·9	
T4b	12·8	3·05–53·7	
cT stage (Wang)			**< ·001**
T1	ref		
T2	2·45	1·63–3·70	
T3	5·22	3·23–8·41	
cT stage (New Rome)			**< ·001**
T1	ref		
T2	2·60	1·60–4·24	
T3	5·18	2·88–9·29	
T4a	6·63	3·66–12·0	
T4b	8·23	2·46–27·5	
cN stage			·09
N0	ref		
N+	1·67	0·92–3·02	
Clinical stage (UICC Sinonasal)			**< ·001**
I	ref		
II	2·64	0·81–8·65	
III	5·47	1·37–21·9	
IVa	7·86	3·23–19·1	
IVb	21·3	4·26–106	
Clinical stage (UICC NMSC)			**< ·001**
I	ref		
II	5·46	1·64–18·1	
III	9·38	2·94–30·0	
IVa	24·2	8·13–71·9	
Clinical stage (Wang)			
NA			
Clinical stage (New Rome)			**< ·001**
I	ref		
II	3·11	0·86–11·3	
III	11·0	2·98–40·6	
IVa	20·0	5·86–68·2	
IVb	28·9	4·80–174	
Treatment modality			**< ·001**
S	ref		
EBRT	1·86	0·95–3·63	
IRT	0·55	0·35–0·88	
S + EBRT	1·26	0·74–2·14	
S + IRT	0·55	0·27–1·14	
S + Syst *(C)* + EBRT	2·21	0·99–4·95	
Syst *(mostly C)* + EBRT	1·56	0·66–3·69	
Other[f]	2·44	1·18–5·04	

	Multivariable[g] (including cT and cN separately)											
	UICC Sinonasal			***UICC NMSC***			***Wang***			***New Rome***		
	HR	**95 % CI**	***P***	**HR**	**95 % CI**	***P***	**HR**	**95 % CI**	***P***	**HR**	**95 % CI**	***P***
Age	1·15	0·98–1·34	·09	1·19	1·02–1·40	**·03**	1·19	1·02–1·40	·03	1·20	1·02–1·41	**·03**
Tumor diameter			**< .001**			.18			.001			**.01**
< 20 mm	ref			ref			ref			ref		
≥ 20 mm	2·54	1·57–4·11		1·53	0·83–2·82		2·20	1·36–3·56		1·92	1·20–3·09	
cT stage			·**005**			**< ·001**			**< ·001**			**< ·001**
T1	ref			ref			ref			ref		

(*continued on next page*)

Table 4 (*continued*)

					Univariable							
					HR			**95 % CI**			***P***	
T2	1·23	0·67–2·26		2·62	1·36–5·04		1·74	1·06–2·84		2·17	1·22–3·87	
T3	2·47	1·17–5·22		2·07	1·07–4·04		3·51	1·91–6·45		3·92	1·96–7·84	
T4a	1·72	1·03–2·86		5·03	2·28–11·1		-	-		5·09	2·45–10·5	
T4b	2·87	0·66–12·4		11·5	2·45–53·7		-	-		5·13	1·13–23·3	
cN stage			·56			.33			·80			·53
N0	ref			ref			ref			ref		
N+	1·21	0·64–2·28		1·37	0·72–2·59		1·09	0·58–2·05		1·22	0·65–2·31	
C-index			0·70			0·71			0·72			0·73
	Multivariable[g] (including clinical stage)											
	UICC Sinonasal			***UICC NMSC***			***Wang***			***New Rome***		
	HR	**95 % CI**	***P***	**HR**	**95 % CI**	***P***	**HR**	**95 % CI**	***P***	**HR**	**95 % CI**	***P***
Age	1·14	0·98–1·33	·10	1·17	1·00–1·37	·051	-			1·17	0·995–1·37	·058
Tumor diameter			**< .001**			.09						**.01**
< 20 mm	ref			ref			-			ref		
≥ 20 mm	2·61	1·61–4·23		1·68	0·93–3·03					1·94	1·21–3·12	
Clinical stage			.06			**·004**	-					**< ·001**
I	ref			ref						ref		
II	1·17	0·62–2·21		2·36	1·21–4·61					2·02	1·11–3·68	
III	2·40	1·14–5·08		2·35	1·22–4·53					4·19	2·09–8·39	
IVa	1·67	1·00–2·79		3·74	1·83–7·60					4·05	1·98–8·30	
IVb	3·22	0·96–10.9		-						5·50	1·55–19.5	
C-index			0·70			0·71			-			0·73

Age was included as a continuous variable per 10 years. HR = Hazard Ratio; 95 % CI = 95 % Confidence Interval; EBRT = External Beam RadioTherapy; IRT = Interventional RadioTherapy; S = Surgery; Syst = Systemic Therapy; C = Chemotherapy. NS = Not Significant. Significant P values are depicted in bold.

[f] The group 'Other' consisted of different combinations of EBRT/IRT, S and/or Syst based treatment, of which each subgroup contained ≤ 3 patients.

[g] The different cT/clinical staging systems were never introduced into the same multivariable model.

classification has been clearly designed for cancers posterior to the piriform opening for which skin involvement is late and ominous, logically leading to a cT4a, while in NV the above described patterns of spread along cartilages (Fig. 1) lead to an early skin invasion with a markedly inferior impact on prognosis [2,7]. This creates in the current UICC sinonasal staging a marked prognostic gap between cT4a cases of NCP/ethmoid and those of NV, similarly to what happened for the oropharyngeal HPV related cancers before their separation from HPV-unrelated ones in the UICC/AJCC [22]. Likewise, the adoption of the New Rome classification would ultimately lead to a treatment de-escalation in CNV passing from cT4a for skin involvement to cT2.

This study, which is the product of a collaborative effort of 21 tertiary care centers with endorsement of GEC-ESTRO, supports the integration of the New Rome system into the broader UICC/AJCC system. Main limitations of the present study, however, are its retrospective nature and the considerable heterogeneity in treatment approaches, whose impact on prognosis was unsurprisingly confirmed [6], resulting from the lack of standardized treatment guidelines for CNV. The effects of differences in treatment strategies (surgical, non-surgical, and combined), and the ability of the New Rome system to serve as a framework for treatment selection should be addressed in future studies. Additionally, the effectiveness of various treatment strategies for different types of recurrences (local, regional, and distant), should be further investigated in these studies. Both topics, however, will remain (statistically) challenging, given the considerable heterogeneity in treatment and the relative favorable survival rates compared with other malignancies (which result in a relatively low number of events per subgroup).

The epidemiological underestimation, combined with the ominous impact of misdiagnosis, the absence of a consensus on T classification and the huge impact of surgery (rhinectomy) on the quality of life are clear unmet needs in CNV management. Assigning a distinct anatomical code in the ICD-O-3 and defining a dedicated T classification within the UICC/AJCC system would effectively address at least three of them. The findings of this study support the integration of the New Rome system into the broader UICC/AJCC system.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116245.

Data Availability

Deidentified participant data are available upon reasonable request to the corresponding author. Access will be granted subject to approval and in accordance with the ethical guidelines of the collaborating institutions.

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