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ORIGINAL ARTICLE

Nasal vestibule squamous cell carcinoma: a population-based cohort study from DAHANCA

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ABSTRACT

Background: Cancer of the nasal vestibule is a rare type of malignancy dominated by squamous cell carcinoma (SCC), and with poor survival. The treatment is either radiotherapy, surgery or a combination of both. Previous studies have shown a 5-year disease-specific survival of 74% and overall survival (OS) of 50%.

Background: Our objective was to describe the consecutive cohort of patients diagnosed with SCC of the nasal vestibule in Denmark from 2008 until 2018 and evaluate prognostic factors and treatment outcome using locoregional failure (LRF), disease-specific mortality (DSM), and OS as endpoints.

Methods: All patients diagnosed with SCC of the nasal vestibule from 2008 until 2018 were identified in the nationwide clinical database, DAHANCA and were followed for LRF and death (DSM and OS) until March 2021. OS was analysed using Kaplan–Meier estimator, and cumulative incidence of LRF and DSM were analysed using the Aalen–Johansen estimator. Analysis of prognostic factors was performed using Cox proportional hazard models.

Results: A total of 162 patients were identified. The median age was 71 years and 54% were male. Disease stage at the time of diagnosis were stage I (70%), II (17%), III (2%) and IV (11%). Curatively intended treatment was performed in 146 patients (90%), of which treatment failure occurred in 42 patients (29%). Most failures occurred at the primary tumour site (64%). Cancer Patient Pathways recommended time to treatment was fulfilled in 71% of patients.

The 5-year OS and DSM in patients treated with curative intent were 65% and 11%, respectively. Stage was a significant independent prognostic factor. No difference in LRF, DSM or OS were shown between the applied treatments.

Conclusions: Stage is the main independent prognostic factor, and failure most commonly appear at the primary tumour site.

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KEYWORDS
Nasal vestibule cancer; squamous cell carcinoma; national population study; survival; treatment outcome

Introduction

Cancer of the nasal vestibule is a rare type of malignancy dominated by squamous cell carcinoma (SCC), and it account for less than one percent of all head and neck tumours [1,2]. The nasal vestibule is anatomical defined by the nostril anteriorly and posteriorly by the limen nasi. Treatment strategies consist of either radiotherapy (RT), surgery or a combination of both. Brachytherapy is an effective alternative to external beam radiotherapy (EBRT) in the treatment of nasal vestibule carcinoma [3–5]. Different staging systems are available, and the Union International Cancer Control (UICC) or the classification of Wang are the most widely used [6–9]. Several studies suggest that T1 tumours can be successfully handled by single treatment modality, whereas more advanced tumours should be considered for a combined treatment strategy [2,10–15]. A large Danish study performed by *Agger et al.* showed a 5-year disease-specific survival of 74% and overall survival (OS) of 50% [8].

In 2007, the Ministry of Health in Denmark introduced Cancer Patient Pathways (CPPs) to improve and accelerate diagnostic work-up and treatment [16]. The aim of CPPs in head and neck cancers was to insure surgical treatment or RT within 22 or 26 days, respectively. Our objective was to describe the consecutive cohort of patients diagnosed with SCC of the nasal vestibule in Denmark from 2008 until 2018.

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Supplemental data for this article can be accessed here.

Using locoregional failure (LRF), disease-specific mortality (DSM) and OS as endpoints to evaluate prognostic factors and assess the effect of the implementation of CPPs with the focus on treatment and patterns of failure.

Material and methods

The Danish Head and Neck Cancer Group DAHANCA and its nationwide database was established in 1976, and aims to standardise and coordinate treatment regimens of head and neck cancer in Denmark [17]. The DAHANCA database contains prospectively collected data on all patients diagnosed with head and neck malignancies in Denmark.

The DAHANCA database includes information on tumour characteristics such as site and size, the TNM classification and histopathology. Information on primary and salvage treatment, recurrence, follow-up status, and cause of death.

The Danish treatment guidelines [3] recommend single treatment modality, either surgery or EBRT, to T1 tumours with respect of cosmetic outcome and nasal function, whereas T2-4 tumours should be treated with EBRT as single treatment modality or in combination with initial surgery. Surgery consist of endoscopic endonasal resection and lateral rhinotomy, whereas nasal amputation are preserved as salvage procedure. The EBRT recommended dose is 66 Gy in 33 fractions, or in small T1 tumours hypofractionated treatment with 54 Gy in 18 fractions. Chemotherapy and elective neck irradiation is not recommended in the Danish treatment guidelines for either nasal vestibule cancer or SCC of the skin.

The analysis was performed on data retrieved from the DAHANCA database. All patients with nasal vestibule carcinoma diagnosed and treated in Denmark from 1 January 2008 until 31 December 2018 were included and followed until March 2021. Patients were censored at the latest clinical follow-up or at the time of death. In case of missing or conflicting data, medical records and pathology reports were thoroughly reviewed. The study was reported according to the STROBE guidelines for observational studies [18] (Checklist in Supplementary Material).

Statistical analysis

OS was analysed using the Kaplan–Meier estimator, and DSM and LRF were analysed using the Aalen-Johansen estimator. With regard to DSM, an event was defined as death from or with nasal vestibule SCC, and LRF was defined as recurrence at the primary tumour site and/or regional lymph nodes. Ultimate locoregional failure (ULRF) was defined as LRF including the effect of salvage treatment. Competing risks were death from other causes (DSM) and distant failure and death (LRF). Analysis of prognostic factors was performed using Cox proportional hazard analysis, and proportional hazards assumption was evaluated visually using the log-minus-log plots. Gender, disease stage and treatment modality, either as RT, surgery or combined RT and surgery, were pre-selected to be included in multivariate models with age as a continuous variable included in models of OS and DSM. Additionally, age (binary variable at mean age) and T and N classification were pre-selected to be included in univariate analysis. All variables were defined at the time of diagnosis (or time of treatment for treatment modality). The results are presented as estimates with 95% confidence intervals (95% CI). Statistical analysis was performed using Stata 14.2 (StataCorp, TX, USA).

Results

The cohort

In the time period 2008–2018, a total of 162 patients were identified in the DAHANCA database. The data were cross-checked with the Danish Cancer Registry (DCR) [19]. The characteristics of all patients and the demographic data are listed in Table 1. The median age at the time of diagnosis was 71 years; 54% were male. More than two-thirds of the patients had stage-I disease at the time of diagnosis.

Treatment failure and survival

The median follow-up time was 5.0 years (interquartile range 4.6–5.0) and the 5-year OS of all patients was 60% (CI: 52–68%) (Figure 2(A)). Figure 1 presents an overview of the patients and all treatments performed. An overview of the treatments and tumour stage are shown in Supplementary Table 2. Two patients were treated with concomitant cisplatin, administered weekly due to an individually assessment. A total of 16 patients (10%) were referred to either palliative or supportive care. This group of patients was characterised by a median age of 78 years, distant metastasis was present in three patients (19%) and six patients (38%) presented with stage-4 disease at the time of diagnosis.

A total of 146 patients (90%) were treated with curative intent, 103 (71%) of whom were treated with curative RT either as single treatment modality or as adjuvant therapy after surgery. Of these a total of 22 patients (21%) were treated with hypofractionated EBRT 54 Gy in 18 fractions, all with T1 tumours. Curative treatment within the CPPs recommendations was performed in 103 patients (71%), of which 40 patients were treated with surgery and 63 patients were treated with RT as the initial treatment.

The pattern of failure is shown in Figure 2(F). Treatment failure appeared most frequent in the primary tumour site (64% of failures). Isolated failure at the primary tumour site appeared in 57% of these cases and was thus more common than failure combined with either regional lymph node or/and distant failure or isolated regional lymph node or/and distant failure. The 5-year LRF was 28% (CI: 20–35%) (Figure 2(C)). Overall treatment failure occurred in 42 patients (29%).

Salvage surgery and RT, either as single treatment modality or in combination was applied to 33 patients (79% of failures). Of these, only four patients received RT as single treatment modality. Among all patients receiving salvage, 12 developed re-recurrence, whereas the other 21 patients with primary failure remained disease free (Figure 1). This group consisted of 16 failures at the primary tumour site and five

Table 1. Patient characteristics.

	All patients ($n = 162$)		Patients treated with curative intent ($n = 146$)		No or palliative treatment ($n = 16$)	
	n	%	*n*	%	*n*	%
Age						
0–71	82	51	77	53	5	31
71+	80	49	69	47	11	69
Median age (years)	71		70		78	
Gender						
Male	87	54	77	53	10	62
Female	75	46	69	47	6	38
T classification						
T1	117	72	110	75	7	44
T2	29	18	24	17	5	31
T3	3	2	3	2	0	0
T4	13	8	9	6	4	25
N classification						
N0	156	96	140	96	16	100
N+	6	4	6	4	0	0
M classification						
M0	159	98	146	100	13	81
M1	3	2	0	0	3	19
Stage						
I	114	70	108	74	6	38
II	28	17	24	16	4	24
III	3	2	3	2	0	0
IV	17	11	11	8	6	38
Treatment						
Surgery	43	10	43	29	0	0
(Chemo)radiotherapy	89	26	89	61	0	0
Surgery + (chemo)radiotherapy	14	55	14	10	0	0
No or palliative treatment	16	9	0	0	16	100

TNM classification: UICC 7th edition.

isolated regional lymph node failures. The 5-year ultimate locoregional failure (ULRF) was 13% (CI: 8–19%) (Figure 2(C)) and the univariate and multivariate Cox proportional hazard analysis for this endpoint are listed in Supplementary Table 1.

In the group of patients treated with curative intent ($n = 146$) the 5-year DSM was 11% (CI: 6–17%) (Figure 2(B)) and the 5-year OS was 65% (CI: 56–73%) (Figure 2(A)). The results of the univariate and multivariate Cox proportional hazard analysis for this endpoint are listed in Table 2 (all patients) and Table 3 (patients treated with a curative intent). Age was associated with OS. Gender was not associated with any difference in LRF, DSM or OS.

Stage was an independent prognostic factor for DSM and OS. Advanced stage at the time of diagnosis was associated with an increased incidence of LRF (Stage IV (HR, 2.4 (CI: 0.81–6.9))) (Figure 2(D)). The DSM was increased (HR, 4.6 (CI: 1.2–17)), and the OS was inferior (HR, 4.5 (CI: 2.0–10)) in patients with stage-IV disease, respectively. Univariate analysis showed no difference in LRF, DSM or OS between single modality treatments with curative intent (Table 3).

Discussion

This large prospective cohort study with outcome for 146 patients treated with curative intent, showed that stage was an independent prognostic factor and failure patterns showed that recurrence most commonly appeared at the primary tumour site.

A total of 61% of patients in our study were treated with RT as single treatment modality even though surgery and RT are considered equal for disease control in small localised tumours [11]. However, with respect to cosmetic outcome and nasal function, RT is often preferred [9,10,20–22]. A recent study by *Czerwinski et al.* [5] compared brachytherapy to EBRT in a Dutch setting showing an improvement in 3-year local disease control in patients with T1 and T2 tumours, treated with brachytherapy; however, OS and disease-specific survival was not improved between the two groups. Several studies suggest a drift towards improved survival rates. However, these studies are limited by small cohorts [14,21–23]. The Danish study by *Agger et al.* [8] showed a 5-year disease-specific survival of 74% and OS of 50% in a multicentre study including patients from 1993 to 2002.

When compared to *Agger et al.*, our study shows a decline in the incidence of nasal vestibule SCC. This decline could be caused by underreporting, as some tumours are treated by plastic surgeons and could be classified as skin carcinoma (ICD-10 code DC44.3); however, cross checking the DAHANCA database with the DCR indicates a true decline in incidence.

A total of 71% of patients treated with curative intent were treated within the recommendations of CPPs, and our study suggests that the introduction of CPPs reduced the incidence of LRF and a trend towards improved survival due to shortened time to treatment [16,24]. Comparing tumour stage at the time of diagnosis in our study and the study by *Agger et al.* shows a stage migration towards more patients

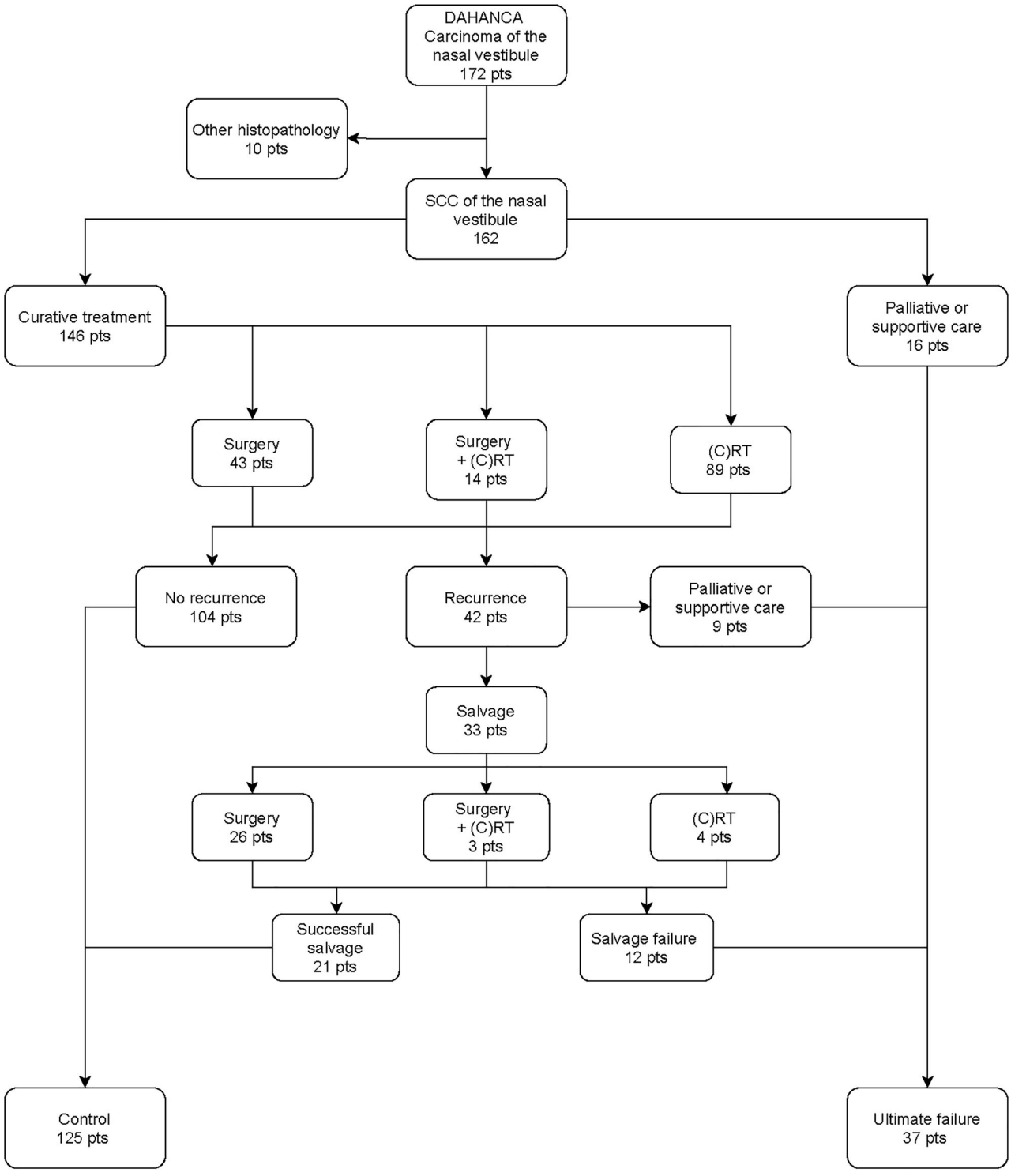

Figure 1. Clinical course diagram. RT: Radiotherapy; CRT: Chemoradiotherapy.

with stage-I tumours and less with stage-IV tumours. However, it is interesting that the incidence of LRF in stage-II disease was relatively high. This could be explained by treatment strategies, as seven of these patients were treated with surgery as single treatment modality and two-thirds of patients with stage-II disease had RT as single treatment modality, whereas previous studies recommend a combined approach [2,22,25]. The staging system by UICC has a disadvantaged, as only few patients were diagnosed with stage-III disease, which could be explained by the more general usage of describing cancer of the nasal cavity and involvement of subsites. The classification of Wang would in fact have been more beneficial to use as it is designed specifically to describe nasal vestibule tumours [9].

In 2017, the Danish sinonasal carcinoma guidelines were reviewed and now also include nasal vestibule SCC. Early

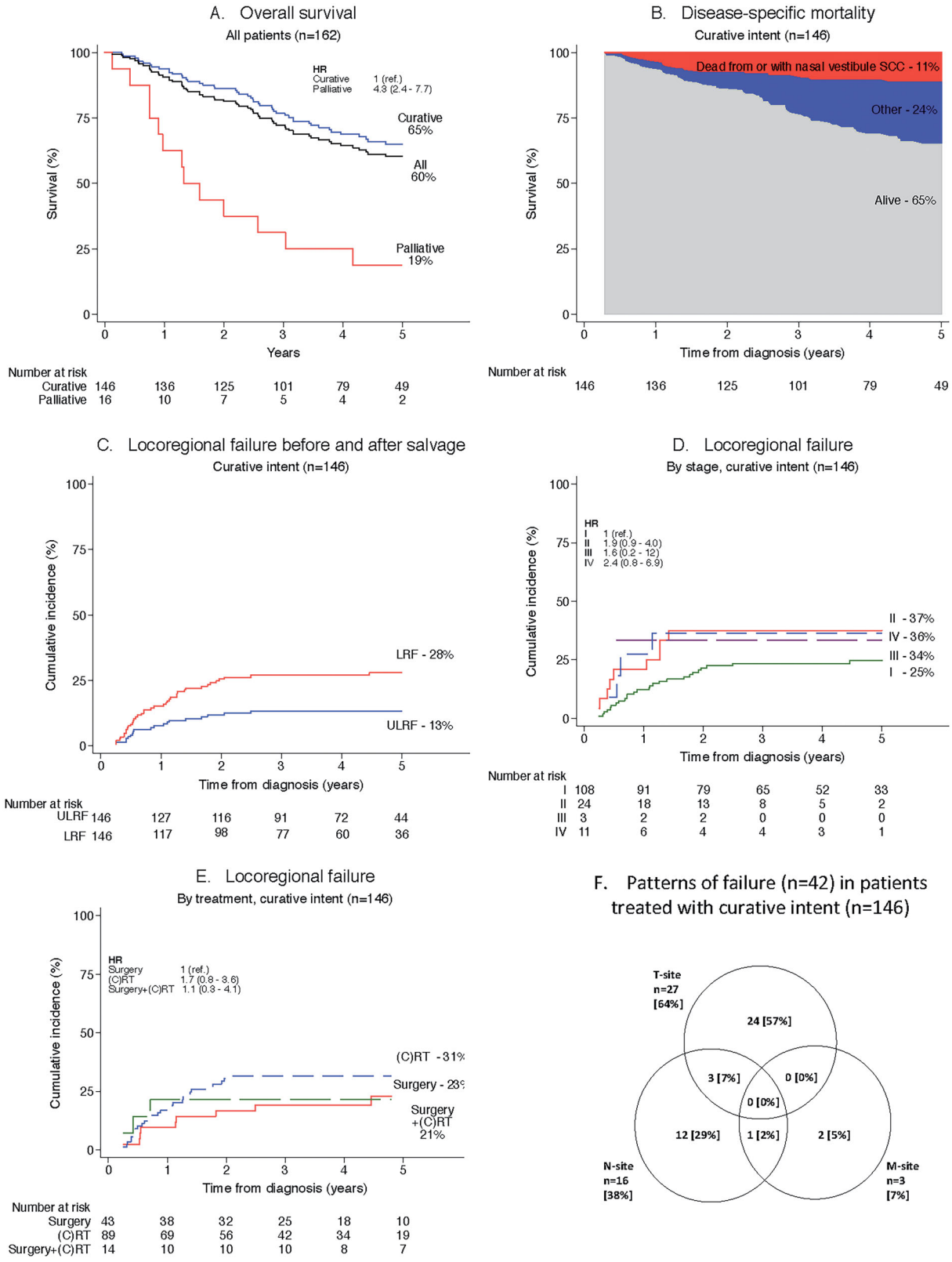

Figure 2. Estimates of overall survival in patients treated with either curative intent or palliative treatment/supportive care and all patients (A), cause-specific survival in patients treated with curative intent (B), competing risk-corrected cumulative incidence estimates of locoregional failure (Primary LRF), and ultimate locoregional failure (Ultimate LRF) in patients treated with curative intent (C), competing risk-corrected cumulative incidence estimates of locoregional failure by stage (D) and treatment (E). Failure pattern for 42 failures in 146 patients treated with curative intent. T-site, N-site and M-site refer to the failure including the primary tumour site, regional lymph nodes and/or distant metastasis, respectively. Percentages presented under the site are the proportion of all failures in a given site (F).

Table 2. Overall survival in all patients.

	Overall survival					
			Univariate		Multivariate	
	n	Events	HR	(95% CI)	HR	(95% CI)
All patients	162	78				
Age*					1.03	(1.01–1.06)
0–71	82	28	1 (ref.)			
71+	80	50	1.8	(1.1–3.0)		
Gender						
Male	87	42	1 (ref.)		1 (ref.)	
Female	75	36	1.0	(0.64–1.6)	1.2	(0.75–2.0)
T classification						
T1	117	47	1 (ref.)			
T2	29	20	2.7	(1.6–4.7)		
T3	3	1	1.5	(0.20–11)		
T4	13	10	4.5	(2.2–9.0)		
N classification						
N0	156	74	1 (ref.)			
N+	6	4	1.8	(0.66–5.0)		
Stage						
I	114	45	1 (ref.)		1 (ref.)	
II	28	19	2.7	(1.6–4.8)	2.1	(1.2–3.8)
III	3	1	1.4	(0.20–11)	1.2	(0.16–8.9)
IV	17	13	4.3	(2.3–8.2)	4.0	(2.0–8.0)
Treatment						
Surgery	43	17	1 (ref.)		1 (ref.)	
(Chemo)radiotherapy	89	42	1.1	(0.63–2.0)	1.3	(0.70–2.3)
Surgery + (chemo)radiotherapy	14	5	0.70	(0.25–1.9)	0.79	(0.27–2.3)
No or palliative treatment	16	14	4.4	(2.2–9.1)	3.0	(1.3–6.5)

HR: hazard ratios from uni- and multivariate Cox regression; ref.: reference.
*Age was included as a continuous variable in multivariate models of DSM and OS (HR per 1- year increase).

Table 3. Prognostic factors in patients treated with curative intent.

	Overall survival						Disease-specific mortality						Locoregional failure					
			Univariate		Multivariate				Univariate		Multivariate				Univariate		Multivariate	
	n	Events	HR	(95% CI)	HR	(95% CI)	*n*	Events	HR	(95% CI)	HR	(95% CI)	*n*	Events	HR	(95% CI)	HR	(95% CI)
All patients	146	64					146	17					146	40				
Age*					1.03	(1.0–1.1)					1.00	(0.96–1.1)						
0–71	77	24	1 (ref.)				77	8	1 (ref.)				77	24	1 (ref.)			
71+	69	40	1.7	(1.0–2.9)			69	9	1.3	(0.51–3.5)			69	16	0.76	(0.40–1.4)		
Gender																		
Male	77	34	1 (ref.)		1 (ref.)		77	9	1 (ref.)		1 (ref.)		77	21	1 (ref.)		1 (ref.)	
Female	69	30	0.98	(0.60–1.6)	0.95	(0.57–1.6)	69	8	0.93	(0.36–2.4)	0.98	(0.37–2.6)	69	19	1.1	(0.57–2.0)	1.1	(0.61–2.2)
T classification																		
T1	110	41	1 (ref.)				110	10	1 (ref.)				110	27	1 (ref.)			
T2	24	15	2.7	(1.4–4.9)			24	4	2.2	(0.70–7.2)			24	10	2.1	(1.0–4.4)		
T3	3	1	1.7	(0.24–13)			3	0	–	–			3	0	–	–		
T4	9	7	5.0	(2.2–11)			9	3	6.2	(1.7–23)			9	3	1.9	(0.58–6.4)		
N classification																		
N0	140	60	1 (ref.)				140	15	1 (ref.)				140	37	1 (ref.)			
N+	6	4	2.2	(0.79–6.1)			6	2	3.8	(0.85–17)			6	3	3.1	(0.96–10)		
Stage																		
I	108	40	1 (ref.)		1 (ref.)		108	10	1 (ref.)		1 (ref.)		108	26	1 (ref.)		1 (ref.)	
II	24	15	2.7	(1.5–5.0)	2.6	(1.4–4.8)	24	4	2.2	(0.69–7.0)	2.0	(0.63–6.6)	24	9	1.9	(0.88–4.0)	1.9	(0.86–4.0)
III	3	1	1.7	(0.23–13)	1.2	(0.16–9.2)	3	0	–	–	–	–	3	1	1.6	(0.22–12)	1.5	(0.20–12)
IV	11	8	3.9	(1.8–8.4)	4.5	(2.0–10)	11	3	4.3	(1.2–16)	4.6	(1.2–17)	11	4	2.1	(0.73–6.0)	2.4	(0.81–6.9)
Treatment																		
Surgery	43	17	1 (ref.)		1 (ref.)		43	2	1 (ref.)		1 (ref.)		43	9	1 (ref.)		1 (ref.)	
(Chemo)radiotherapy	89	42	1.1	(0.63–1.9)	1.2	(0.67–2.2)	89	13	3.1	(0.70–14)	3.2	(0.72–14)	89	28	1.7	(0.79–3.5)	1.7	(0.80–3.6)
Surgery + (chemo)radiotherapy	14	5	0.69	(0.25–1.9)	0.68	(0.23–2.0)	14	2	3.1	(0.43–22)	2.8	(0.38–20)	14	3	1.1	(0.30–4.1)	1.08	(0.29–4.1)

HR: Hazard ratios from uni- and multivariate Cox regressions; ref.: Reference.
*Age was included as a continuous variable in multivariate models of DSM and OS.

diagnosis is probably still the most important parameter in terms of survival and the establishment of broad multidisciplinary teams are thus crucial for proper treatment planning.

Conclusion

Our study corroborates previous data on the favourable prognosis of cancer of the nasal vestibule with a 5-year OS and DSM of 65% and 11%, respectively. Furthermore, stage

seems to be the main independent prognostic factor and failure most commonly appear at the primary tumour site.

CPPs recommended time to treatment were fulfilled in 71% of patients.

Multidisciplinary team coordination remains a cornerstone of the treatment of nasal vestibule SCC.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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