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ORIGINAL ARTICLE

Sinonasal cancer in Denmark 2008–2015: a population-based phase-4 cohort study from DAHANCA

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ABSTRACT

Background: Sinonasal cancer is considered a rare disease with poor survival. Its treatment has changed profoundly in recent years, primarily following the introduction of intensity-modulated radiation therapy (IMRT) and minimally invasive endoscopic surgery. Danish national guidelines on treatment of patients diagnosed with sinonasal carcinoma were introduced in 2007. The aim of this phase-4 study was to assess the effect of the implementation of guidelines by describing treatment outcomes in a consecutive nationwide cohort.

Methods: All patients diagnosed with sinonasal carcinoma in Denmark from 2008 to 2015 were identified in the nationwide clinical database, DAHANCA, and were followed until May 2020. Overall survival (OS) was analysed using Kaplan–Meier estimator. Cumulative incidence of locoregional failure (LRF) and disease-specific mortality (DSM) were analysed using the Aalen–Johansen estimator. 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. Start of follow-up was time of diagnosis. The results are presented as estimates with 95% confidence intervals (95% CIs).

Results: A total of 331 patients were identified. Curatively intended treatment was performed in 264 patients (80%). Non-compliance with treatment guidelines was registered in 24 patients (9%). Non-compliance was associated with LRF (hazard ratio [HR], 2.0 [95% CI: 1.1–3.5]). Among patients qualified for curative treatment, failure occurred in 109 patients (41%), primarily at the primary tumour site (81%). Anatomical tumour site and disease stage were independent prognostic factors. The 5-year OS was 56% in patients treated with curative intent, and a combined treatment strategy showed reduced LRF (HR, 0.53 [95% CI: 0.30–0.92]) in a multivariate analysis.

Conclusions: Guideline compliance and a combined treatment approach reduced the incidence of LRF and thereby increased OS. Our results confirm those of international studies. Treatment of sinonasal carcinoma remains a challenge that requires multidisciplinary team coordination.

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Sinonasal carcinoma; guidelines; national population study; phase-4; treatment outcome

Introduction

Sinonasal cancer is a rare disease encompassing a variety of pathologies presenting at different sites in the nasal cavity or the paranasal sinuses. Patients with these cancers present unspecific symptoms and are easily misjudged as suffering from various, more common non-malignant diseases, e.g., chronic rhinosinusitis [1–3]. Studies in this field are dissimilar in terms of the histopathology and tumour localisation of their study populations. Previous reports have described a pronounced tendency to local recurrence and relatively low survival rates [4,5].

The most recent Danish overview of sinonasal cancer, which covered all subsites and all histopathological diagnoses, was an epidemiological study performed by *Sjöstedt et al.* [6]. This study reported a stable incidence and improved survival in the period 1980–2014 [6]. A smaller Danish study followed 242 patients diagnosed from 1995 to 2004; it reported data on histopathology and treatment and showed a 5-year overall survival (OS) rate of 55% [7]. This study inspired the national Danish guidelines on treatment of sinonasal carcinoma proposed by the Danish Head and Neck Cancer Group (DAHANCA) and introduced in 2007. The national guidelines recommend that patients presenting with

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Supplemental data for this article can be accessed here.

Union for International Cancer Control (UICC) 7th edition stages I and II sinonasal carcinomas should be treated with surgery or radiotherapy (RT) as monotherapy. Postoperative RT is recommended in case of non-radical surgery, in all stages of adenoid-cystic carcinoma and in case of stages III or IV tumour [8].

Neuroendocrine carcinomas were included because they commonly occur in the sinonasal area.

Recommendations regarding treatment of carcinoma of the nasal vestibule and non-carcinomatous lesions, e.g., malignant melanoma, sarcoma and lymphoma in the nasal cavity, and paranasal sinuses are not included in the present Danish guidelines. The treatment strategy for these tumours is primarily determined by histopathology rather than tumour localisation [9].

The aim of this phase-4 study was to assess the effect of the implementation of the national guidelines in a consecutive nationwide cohort with a focus on compliance, treatment and patterns of failure, and using locoregional failure (LRF), disease-specific mortality (DSM), and OS as endpoints.

Material and methods

DAHANCA has existed since 1976 and aims to coordinate, align, and continuously update the head and neck cancer treatment regimens throughout Denmark. In this setting, a nationwide database was developed. The DAHANCA database consists of prospectively, manually collected data on all patients diagnosed with head and neck malignancies in Denmark [10]. The DAHANCA database contains information on tumour site and size, TNM classification, and histopathology. Information on recurrence, primary and salvage treatment, follow-up status, and cause of death is also available.

The present analysis was performed on data from the DAHANCA database. All patients with sinonasal carcinoma diagnosed and treated in Denmark from 1 January 2008 to 31 December 2015 were included and followed until May 2020. 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 [11] (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 sinonasal cancer, 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). Start of follow-up was time of diagnosis for all endpoints. 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, tumour site, histopathology, 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, 65 years) and T and N classification were pre-selected to be included in univariate analysis. All variables were defined at time of diagnosis (or time of treatment for treatment modality). The results are presented as estimates with 95% confidence intervals (95% CIs). Statistical analysis was performed using Stata version 14.2 (StataCorp, TX, USA).

Results

The cohort

From 2008 to 2015, 455 patients were identified in the DAHANCA database. Patients with malignant melanoma or carcinoma of the nasal vestibule were subsequently excluded from the study as they were not included in the cohort. The DAHANCA database was cross-checked with the Danish Cancer Registry (DCR) and an overview of the clinical course is shown in Figure 1. Among patients in the DCR, 81 patients (16%) did not appear in the DAHANCA database, and only 41 (8%) of the patients identified in the DCR were, therefore, included in the analysis. A total of 40 patients (8%) from the DCR did not have sinonasal carcinoma but other malignancies, e.g., lymphoma, sarcoma, or other sites, e.g., cavum oris, oro-, or rhinopharyngeal carcinoma. Among the patients in the DAHANCA database, 38 (8%) did not occur in the DCR [12].

A total of 331 patients fulfilled the criteria for treatment according to the current guidelines. Of these, 264 patients received treatment with curative intent. Their characteristics and demographics are listed in Table 1. The median age at the time of diagnosis was 65 years; 63% were male. The tumour was located in the nasal cavity in 61% of the patients. The tumour originated from the maxillary (31%), the ethmoid (5%), the sphenoid (2%), or the frontal sinuses (1%) in the remaining patients (Table 1). The most common histopathology was squamous cell carcinoma, which was found in 59% of the patients. Adenocarcinoma was found in 17% of the patients. Cases of undifferentiated carcinoma, adenoid-cystic carcinoma, and neuroendocrine carcinoma were rare. More than two-thirds of the patients had stages III or IV disease at the time of diagnosis.

Treatment failure and survival

The median follow-up time was 5.1 years (interquartile range 3.3–6.5), and the 5-year OS was 46% (95% CI: 40–52%) (Figure 2(A)). Figure 1 presents an overview of all treatments performed. A total of 67 patients (20%) were referred to either palliative ($n = 50$) or supportive care ($n = 17$), which was not covered by the treatment guidelines. This group of patients had a median age of 75 years and 82% presented with stage IV disease. Distant metastasis was present in 19% of these patients.

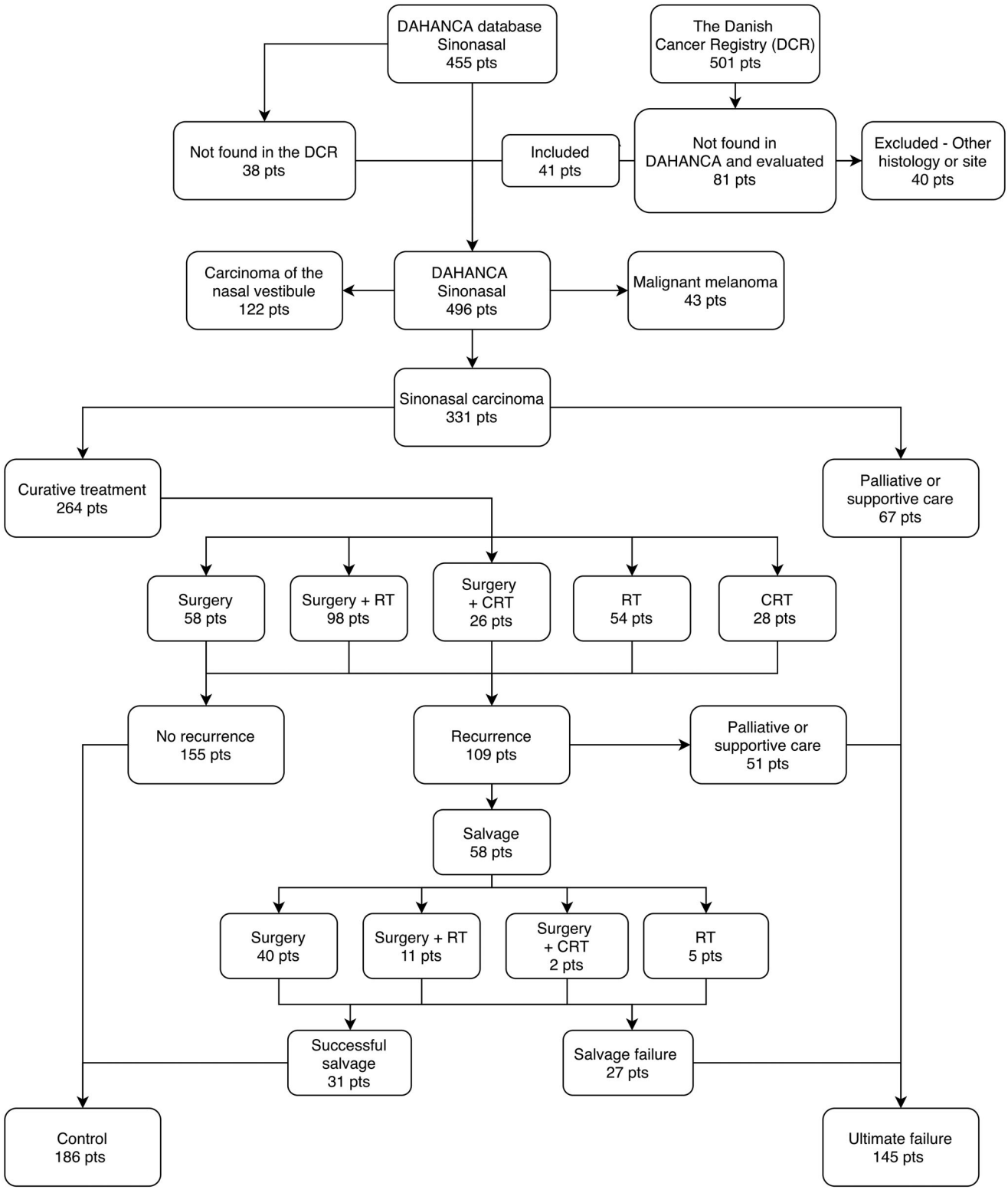

Figure 1. Clinical course diagram. RT: Radiotherapy; CRT: chemoradiotherapy.

A total of 264 patients were treated with curative intent, 24 (9%) of whom were not treated in accordance with the guidelines. These 24 patients were characterised by adenoid-cystic carcinoma and/or stages III and IV disease and received curative intended surgery as monotherapy, which was not in accordance with the DAHANCA guidelines, which recommends postoperative RT for these patients. Among these 24 patients, 15 patients remained disease-free either as a result of primary treatment ($n = 11$) or because of salvage treatment after recurrent disease ($n = 4$).

Non-compliance with treatment guidelines was associated with LRF (HR, 2.0 [95% CI: 1.1–3.5]) and with inferior OS (HR, 1.9 [95% CI: 1.1–3.3]); the 5-year OS was 57% (95% CI: 50–64%) for patients treated according to the guidelines and

Table 1. Patient characteristics.

	All patients		Patients treated with curative intent		Palliative treatment	
	(*n* =331)		(*n* = 264)		(*n* = 67)	
	n	%	*n*	%	*n*	%
Age						
0–65	162	49	150	57	12	18
65+	169	51	114	43	55	82
Median age (years)	65 years		63 years		75 years	
Gender						
Male	209	63	170	64	39	58
Female	122	37	94	36	28	42
Head and neck cancer centre						
Rigshospitalet, Copenhagen, Denmark	98	30	77	29	21	31
Herlev, Denmark	61	18	52	20	9	13
Odense, Denmark	73	22	66	25	7	11
Aarhus, Denmark	80	24	56	21	24	36
Aalborg, Denmark	19	6	13	5	6	9
Tumour site						
Nasal cavity	203	61	177	67	26	39
Maxillary sinus	103	31	66	25	37	55
Frontal sinus	2	1	2	1	0	0
Sphenoid sinus	7	2	6	2	1	1
Ethmoid sinus	16	5	13	5	3	5
Histopathology						
Squamous cell carcinoma	194	59	154	58	40	60
Adenocarcinoma	56	17	47	17	9	13
Undifferentiated carcinoma	18	5	10	4	8	12
Adenoid-cystic carcinoma	14	4	12	5	2	3
Carcinoma ex pleomorphic carcinoma	14	4	12	5	2	3
Neuroendocrine carcinoma	6	2	5	2	1	1
Small cell carcinoma	6	2	4	1	2	3
Esthesioneuroblastoma	15	5	15	6	0	0
Other histology	8	2	5	2	3	5
T classification						
T1	63	19	56	21	7	10
T2	49	15	44	17	5	8
T3	40	12	36	13	4	6
T4	176	53	126	48	50	75
TX / N.E.	3	1	2	1	1	1
N classification						
N0	276	83	236	89	40	60
N+	54	16	28	11	26	39
NX / N.E.	1	0	0	0	1	1
M classification						
M0	318	96	264	100	54	81
M1	13	4	0	0	13	19
Stage						
I	59	18	54	20	5	8
II	47	14	43	16	4	6
III	37	11	35	13	2	3
IV	185	56	130	49	55	82
N.E.	3	1	2	1	1	1

TNM classification: UICC 7th edition.
N.E.: not evaluable

38% (95% CI: 17–59%) for patients who were not treated in accordance with the guidelines (Supplementary Figure 1(A)). Non-compliance with guidelines remained associated with LRF (HR, 1.8 [95% CI: 1.0–3.4]) when tested in a multivariate analysis (Figure 2(B)).

Failure in the 264 patients treated with curative intent appeared most frequently at the primary tumour site (81% of failures) (Supplementary Figure 2). Failure at the primary tumour site was isolated in 69% of 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 38% (95% CI: 32–44%) (Figure 2(C)). Failure occurred in 109 patients (41%), 31 of whom were treated with successful salvage, which left 78 with ultimate failure (Figure 1).

Salvage consisting of surgery, either as monotherapy or in combination with RT/chemoradiotherapy (CRT), was applied to 58 patients (53% of failures). Of these, only five received RT as monotherapy. Among all patients receiving salvage, 27 developed re-recurrence, whereas the other 31 patients with primary failure remained disease-free. The latter consisted of 20 failures at the primary tumour site, two combined failure at the primary tumour site and regional lymph node failure, and nine isolated regional lymph node failures. Patients with isolated regional lymph node failure, were characterised by being node negative at time of primary treatment. Squamous cell carcinoma was found in four patients, adenocarcinoma in three patients, small neuroendocrine carcinoma in one patient and other histology in two patients. Four patients had stage I disease, one patient had stage III disease

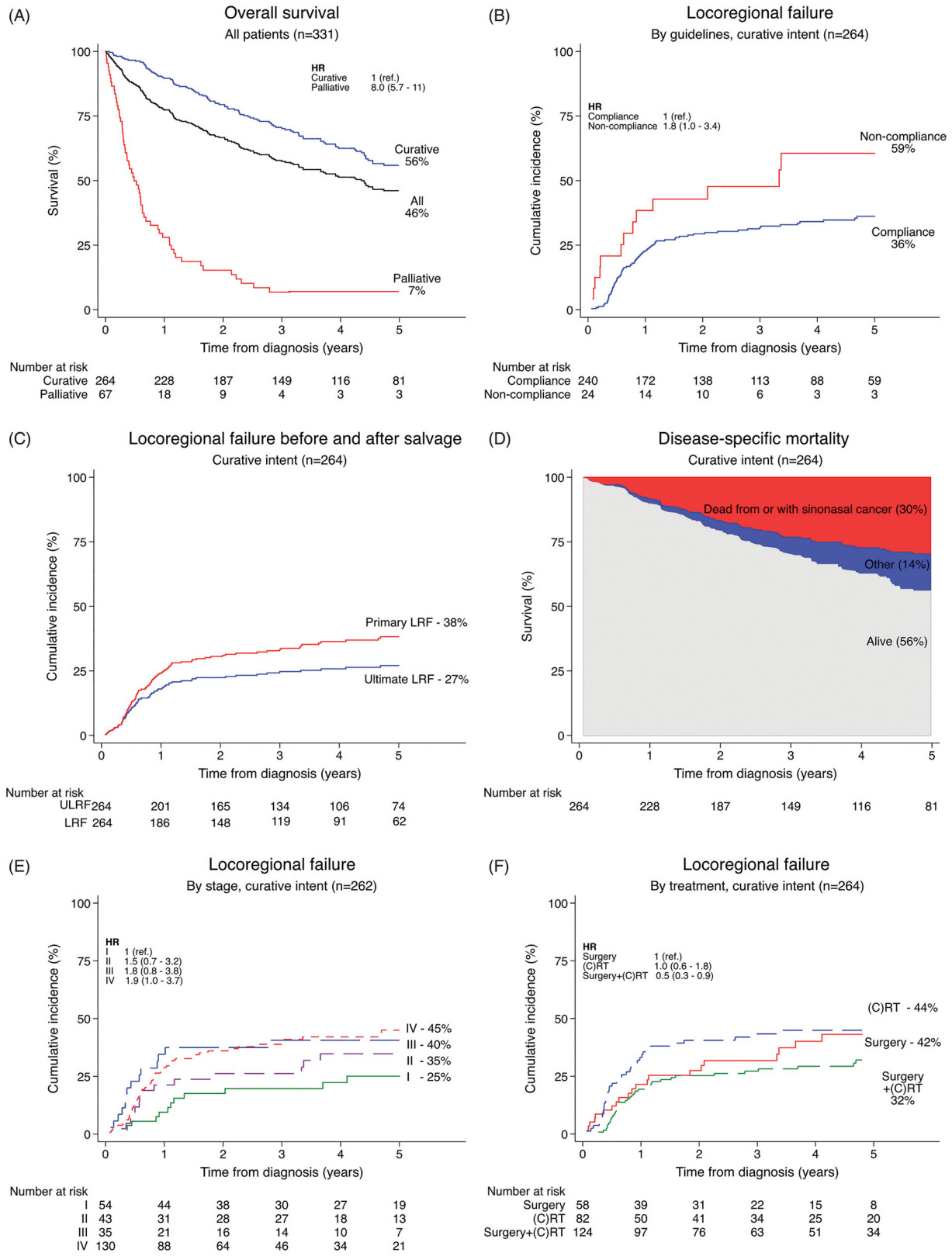

Figure 2. Estimates of overall survival in patients treated with either curative intent or palliative treatment/supportive care and all patients (A), competing risk-corrected cumulative incidence estimates of locoregional failure by guidelines (B), competing risk-corrected cumulative incidence estimates of locoregional failure (Primary LRF), and ultimate locoregional failure (Ultimate LRF) in patients treated with curative intent (C), cause-specific survival in patients treated with curative intent (D) and competing risk-corrected cumulative incidence estimates of locoregional failure by stage (E), and treatment (F).

Table 2. Overall survival in all patients.

			Overall survival			
			Univariate		Multivariate	
	n	Events	HR	(95% CI)	HR	(95% CI)
All patients	331	187				
Age[a]					1.03	(1.02–1.04)
0–65	162	62	1 (Ref.)			
65+	169	125	2.3	(1.7–3.1)		
Gender						
Male	209	117	1 (Ref.)		1 (Ref.)	
Female	122	70	0.92	(0.68–1.2) 0.83		(0.61–1.1)
T classification						
T1	63	21	1 (Ref.)			
T2	49	19	1.5	(0.78–2.8)		
T3	40	25	2.6	(1.5–4.8)		
T4	176	120	3.4	(2.1–5.5)		
TX / N.E.	3	2				
N classification						
N0	276	140	1 (Ref.)			
N+	54	46	2.7	(1.9–3.7)		
NX / N.E.	1	1				
Stage						
I	59	18	1 (Ref.)		1 (Ref.)	
II	47	18	1.6	(0.84–3.2)	1.8	(0.89–3.5)
III	37	23	3.0	(1.6–5.6)	3.4	(1.8–6.5)
IV	185	126	3.9	(2.3–6.4)	3.1	(1.8–5.4)
N.E.	3	2				
Tumour site						
Nasal cavity	203	92	1 (Ref.)		1 (Ref.)	
Sinus	128	95	2.5	(1.8–3.3)	1.7	(1.2–2.4)
Histopathology						
Squamous cell carcinoma	194	111	1 (Ref.)		1 (Ref.)	
Adenocarcinoma	56	30	0.80	(0.53–1.2)	0.74	(0.46–1.2)
Other	81	46	0.82	(0.58–1.2)	1.2	(0.82–1.8)
Treatment						
Surgery	58	23	1 (Ref.)		1 (Ref.)	
(Chemo)radiotherapy	82	45	1.2	(0.73–2.0)	0.78	(0.45–1.4)
Surgery+(chemo)radiotherapy	124	56	0.91	(0.56–1.5)	0.64	(0.38–1.1)
Palliative or supportive care	67	63	8.1	(5.0–13)	3.9	(2.2–6.8)

Hazard ratios (HRs) from uni and multivariate Cox regression.
N.E.: not evaluable; ref.: reference
[a]Age was included as a continuous variable in multivariate models of DSM and OS (HR per 1 year increase).

and five patients had stage IV disease. The primary tumour was located in the nasal cavity in nine patients. The 5-year ULRF was 27% (95% CI: 21–33%) (Figure 2(C)). The results of the univariate and multivariate Cox proportional hazard analysis for this endpoint are listed in Supplementary Table 1.

In the group of patients treated with a curative intent ($n = 264$), the 5-year DSM was 30% (95% CI: 24–36%) (Figure 2(D)) and the 5-year OS was 56% (95% CI: 49–62%) (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 and histopathology were not associated with any difference in LRF, DSM, or OS.

Stage and tumour site were independent prognostic factors for all outcomes. Advanced stage at the time of diagnosis caused the incidence of LRF to increase (Stage IV [HR, 1.9 (95% CI: 1.0–3.7])) (Figure 2(E)). The DSM was increased in patients with stage II disease (HR, 4.8 [95% CI: 1.3–18]), stage III disease (HR, 6.5 [95% CI: 1.8–24]), and stage IV disease (HR, 6.6 [95% CI: 2.0–22]). For patients with advanced stage the OS was inferior; stage III (HR, 3.2 [95% CI: 1.6–6.6]) and stage IV (HR, 3.1 [95% CI: 1.7–5.8]). Tumours originating in the paranasal sinuses were associated with LRF (HR, 1.8 [95% CI: 1.1–2.7]) (Supplementary Figure 1(B)), an increase in DSM (HR, 1.9 [95% CI: 1.2–3.2]), and inferior OS (HR, 1.6 [95% CI: 1.1–2.4]) compared with tumours confined to the nasal cavity. Univariate analysis showed no difference in LRF or OS between monotherapies in cases treated with a curative intent (Table 3). In contrast, a combined treatment approach with surgery and either RT or C-RT were associated with LRF (HR, 0.53 [95% CI: 0.30–0.92]) compared with surgery or RT as monotherapy when adjusted for age, stage, tumour site, histopathology, and treatment (Figure 2(F)).

Discussion

This large phase-4 prospective cohort study reporting the outcome for 264 patients treated with a curative intent showed that 24 patients (9%) were not treated in accordance with the DAHANCA guidelines with regards to postoperative RT. Non-compliance with the guidelines was associated with LRF, and failure patterns showed that recurrence most commonly appeared at the primary tumour site.

A recent study of 1720 patients from the DCR performed by *Sjöstedt et al.* showed a stable incidence of sinonasal

Table 3. Prognostic factors in patients treated with curative intent. Hazard ratios (HRs) from uni and multivariate Cox regression.

	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	264	124					264	75					264	99				
Age[a]					1.04	(1.02–1.05)					1.02	(1.00–1.04)						
0–65	150	51	1 (Ref.)				150	38	1 (Ref.)				150	53	1 (Ref.)			
65+	114	73	1.8	(1.3–2.6)			114	37	1.3	(0.82–2.0)			114	46	1.2	(0.79–1.7)		
Gender																		
Male	170	80	1 (Ref.)		1 (Ref.)		170	53	1 (Ref.)		1 (Ref.)		170	67	1 (Ref.)			
Female	94	44	0.83	(0.57–1.2)		(0.60–1.3)	94	22	0.68	(0.41–1.1)		(0.40–1.1)	94	32	0.76	(0.50–1.2)		(0.49–1.2)
				0.89						0.68						0.76		
T classification																		
T1	56	16	1 (Ref.)				56	4	1 (Ref.)				56	15	1 (Ref.)			
T2	44	14	1.5	(0.72–3.2)			44	10	3.6	(1.1–11)			44	15	1.4	(0.70–2.9)		
T3	36	21	3.2	(1.7–6.3)			36	12	6.4	(2.1–20)			36	14	1.9	(0.92–4.0)		
T4	126	72	3.0	(1.7–5.3)			126	49	7.0	(2.5–19)			126	55	2.1	(1.2–3.6)		
TX / N.E.	2	1					2	0					2	0				
N classification																		
N0	236	103	1 (Ref.)				236	60	1 (Ref.)				236	85	1 (Ref.)			
N+	28	21	2.1	(1.3–3.3)			28	15	2.5	(1.4–4.3)			28	14	1.5	(0.86–2.7)		
NX / N.E.																		
Stage																		
I	54	15	1 (Ref.)		1 (Ref.)		54	3	1 (Ref.)		1 (Ref.)		54	14	1 (Ref.)		1 (Ref.)	
II	43	14	1.6	(0.77–3.5)	2.0	(0.95–4.4)	43	10	4.8	(1.3–17)	4.8	(1.3–18)	43	15	1.5	(0.73–3.2)	1.5	(0.73–3.2)
III	35	21	3.4	(1.7–6.7)	3.2	(1.6–6.6)	35	12	8.4	(2.4–30)	6.5	(1.8–24)	35	14	2.0	(0.95–4.2)	1.8	(0.84–3.8)
IV	130	73	3.1	(1.8–5.7)	3.1	(1.7–5.8)	130	50	8.9	(2.8–29)	6.6	(2.0–22)	130	56	2.1	(1.2–3.8)	1.9	(1.0–3.7)
N.E.	2	1					2	0					2	0				
Tumour site																		
Nasal cavity	177	69	1 (Ref.)		1 (Ref.)		177	36	1 (Ref.)		1 (Ref.)		177	58	1 (Ref.)		1 (Ref.)	
Sinus	87	55	2.1	(1.5–3.1)	1.6	(1.1–2.4)	87	39	2.7	(1.7–4.3)	1.9	(1.2–3.2)	87	41	1.8	(1.2–2.6)	1.8	(1.1–2.7)
Histopathology																		
Squamous cell carcinoma	154	72	1 (Ref.)		1 (Ref.)		154	42	1 (Ref.)		1 (Ref.)		154	52	1 (Ref.)		1 (Ref.)	
Adenocarcinoma	47	22	0.89	(0.55–1.4)	0.79	(0.45–1.4)	47	12	0.87	(0.46–1.6)	1.1	(0.52–2.3)	47	19	1.1	(0.67–1.9)	1.5	(0.81–2.6)
Other	63	30	0.75	(0.49–1.2)	0.99	(0.61–1.6)	63	21	1.0	(0.61–1.7)	1.4	(0.80–2.5)	63	28	1.2	(0.75–1.9)	1.4	(0.88–2.3)
Treatment																		
Surgery	58	23	1 (Ref.)		1 (Ref.)		58	9	1 (Ref.)		1 (Ref.)		58	22	1 (Ref.)		1 (Ref.)	
(Chemo)radiotherapy	82	45	1.2	(0.73–2.0)	0.81	(0.45–1.5)	82	31	2.2	(1.1–4.6)	1.5	(0.66–3.4)	82	38	1.2	(0.72–2.1)	1.0	(0.55–1.8)
Surgery+(chemo)radiotherapy	124	56	0.90	(0.55–1.5)	0.68	(0.40–1.2)	124	35	1.5	(0.74–3.2)	1.0	(0.48–2.2)	124	39	0.69	(0.41–1.2)	0.53	(0.30–0.92)
Guidelines																		
Compliance	240	109	1 (Ref.)		1 (Ref.)		240	66	1 (Ref.)		1 (Ref.)		240	86	1 (Ref.)		1 (Ref.)	
Non-compliance	24	15	1.9	(1.1–3.3)	1.6	(0.86–2.9)	24	9	1.8	(0.87–3.5)	1.4	(0.66–3.0)	24	13	2.0	(1.1–3.5)	1.8	(1.0–3.4)

N.E.: not evaluable; ref.: reference

[a]Age was included as a continuous variable in multivariate models of DSM and OS (HR per 1 year increase).

carcinoma in Denmark from 1980 to 2014 and a significantly improved relative survival rate from 1980–1984 to 2010–2014; however, like us, they found no improvement in survival in the recent decades [6]. The study by *Sjöstedt et al.* was entirely descriptive and information on treatment and TNM stage was missing [6]. These data, however, are reported in this study, which is an important strength. Especially TNM stage is a strong predictor of survival outcome and therefore important when comparing cohorts. Figure 1 illustrates that the cohorts are not comparable. Hence, our validation showed that some patients in the DCR did not represent sinonasal carcinoma but other malignancies, and some patients in the DAHANCA database were not registered in the DCR. Furthermore, *Thorup et al.* [7] reported an improved 5-year OS in a consecutive cohort of patients with sinonasal carcinoma diagnosed from 1995 to 2004 compared with patients participating in an earlier DAHANCA study by *Grau et al.* 1991 [4] covering the period of 1982–1991,. Regrettably, the study populations were not comparable with regards to treatment intention and included pathologies. Interestingly, neither our patients considered as a whole nor patients treated with a curative intent achieved a better OS than the patients reported in the study by *Thorup et al.* [7]. This is remarkable, first, as the very motivation for introducing treatment guidelines was to improve OS; second, as failure to abide by the current treatment guidelines was associated with LRF.

The role of endoscopic endonasal surgery has expanded over the past two decades [13–16]. This minimally invasive approach has been shown to result in lower post-operative morbidity and mortality than open transcranial surgery in cases of anterior skull base-related tumours [2,17–21]. High-precision RT has also evolved over the past decades; however, the critical normal tissue adjacent to the sinonasal tumours poses a major challenge in target dose coverage [22]. Intensity-modulated RT (IMRT) outperforms older techniques by allowing shaping of the dose to the tumour target, hence reducing normal tissue radiation and its associated morbidity [23,24]. Proton therapy is also under consideration as an alternative to IMRT because its physical properties potentially enable further dose sparing to adjacent organs at risk [25]. The positive effects of proton therapy on OS and LRF have previously been reported in several studies [26–28].

The expected survival difference between single-modality (surgery or RT) and combined modality treatment approaches has been addressed in earlier studies [1,29]. The differences reported could be due to selection bias, since patients treated with RT alone might present with advanced-stage disease where surgery was not an option. Another recent cohort study described a significantly improved OS in cases where multimodality treatment strategies had been used [3].

Multimodality treatment regimens, including neoadjuvant chemotherapy, are widely used in patients presenting with advanced stage or recurrent disease [30,31]. The results of the cohort study have been confirmed in a recent systematic review by *Morand et al.*, in which patients undergoing multimodality treatment regimens showed an improved disease-specific survival compared with patients undergoing single-modality treatment [32].

In our study of 331 patients, relapse primarily appeared at the primary tumour site. The use of combined treatment approaches was associated with LRF. This suggests, first, that perhaps treatment at the primary tumour site should be intensified and, second, that multimodality treatment strategies may outperform single-modality treatment strategies in advanced disease [7,33].

Recent retrospective cohort studies report 5-year OS rates comparable to the rates reported in this study although these included only squamous cell carcinoma [3,30]. However, they suggested a drift towards improved survival in comparison with earlier results [1,34]. Another international study evaluating treatment outcomes over a period of five decades showed no improvement in OS, but a reduced rate of morbidity following treatment [35].

Most studies in this field of research are descriptive, and systematic reviews are few. A recent systematic review on sinonasal carcinoma by *Rawal et al.* [1] showed improved survival measures compared with an earlier review by *Dulguerov et al.* [36] conducted in 2001. However, the study by *Rawal et al.* has some limitations, and the cohort is not comparable to ours with respect to distribution of histopathology and stage [35].

Patients with sinonasal carcinomas often present with advanced-stage disease, which could be due to the rather non-specific symptoms of this disease, often delaying diagnosis [33,34,37]. A total of 20% of the patients included in our study were referred to palliative or supportive care. This group differs in particular by their high median age (75 years) and high rate of stage IV disease (82%), which may explain why curatively intended treatment was not performed. Guideline compliance and a combined treatment strategy were associated with LRF and a trend towards improved survival measures. These results may be due to patient factors such as age, comorbidity and performance status. However, no particular difference in performance status was found in our cohort, and age did not change the results when added as a continuous covariate in the multivariate analysis of LRF. The overall level of compliance with guidelines in each centre was 88% or higher. Aalborg University Hospital worked as an oncological subcentre, hence all patients were discussed at a multi-disciplinary team meeting at Aarhus University Hospital.

In 2017, the Danish sinonasal carcinoma guidelines were renewed, and the guidelines now recommend that patients presenting with stage II sinonasal carcinomas should be considered for a combined treatment strategy [38]. Since the symptoms of sinonasal cancer are scarce and non-specific, the diagnostic awareness among ear, nose, and throat specialists and general practitioners should be heightened. Early diagnosis probably remains the most important parameter in terms of survival, and the establishment of broad multidisciplinary teams is thus crucial for proper treatment planning.

Conclusion

In conclusion, this phase-4 prospective cohort study showed that compliance with guidelines reduced the incidence of LRF and as a consequence increased OS. We found that failures primarily appeared at the primary tumour site. Tumour site and stage proved to be independent prognostic factors, and a combined treatment approach reduced LRF in multivariate analysis. Our results are comparable to those of international studies. Treatment of sinonasal carcinoma remains a challenge which requires multidisciplinary team coordination.

Disclosure statement

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