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Long-term results of postoperative and definitive (chemo)radiotherapy in sinonasal carcinoma. Adult Comorbidity Evaluation 27 score as a predictor of survival

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Long-term results of postoperative and definitive (chemo)radiotherapy in sinonasal carcinoma. Adult Comorbidity Evaluation 27 score as a predictor of survival

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Abstract

Background: The objective was to evaluate the efficacy and toxicity of curative radiotherapy in patients with sinonasal carcinoma and to identify prognostic factors influencing treatment outcomes.

Materials and methods: The authors conducted a retrospective study of 61 consecutive patients treated with postoperative or definitive radiotherapy from 2002 to 2018 (median age 59 years, current/former smokers 71%, maxillary sinus 67%, nasal cavity 26%). The majority of patients were diagnosed with locally advanced disease (85% clinical stage ≥ III). Regional cervical metastases were initially diagnosed in 23% of patients. The most common histology was squamous cell carcinoma (61%). Radiation therapy was preceded by radical surgery in 64% of patients. 29 patients received chemotherapy (48%).

Results: The median follow-up was 53 months. The median total dose of radiotherapy achieved was 70 Gy. The 5- and 10-year locoregional control, distant control, overall survival, and disease-free survival were 74% and 64%, 90% and 90%, 51% and 35%, and 38% and 25%, respectively. Severe acute toxicity occurred in 36%, severe late toxicity in 23% of

patients. Severe unilateral visual impairment occurred in 6 patients, temporal lobe necrosis in 1 patient, and osteoradionecrosis requiring surgery in 2 patients.

Conclusion: The results of the study demonstrated the high effectiveness of curative treatment in patients with sinonasal carcinoma with long-term locoregional and distant control. The multivariate analysis indicated that N-staging, age, comorbidity score [as assessed by Adult Comorbidity Evaluation 27 (ACE-27)] and initial response to treatment were the strongest prognostic factors.

Key words: sinonasal carcinoma; curative radiotherapy; chemoradiotherapy; prognostic factors

Introduction

Sinonasal carcinomas are relatively rare, representing < 5% of all head and neck cancers. Treatment options are limited due to the presence of tumors near the risk organs (eyes, optic nerve, chiasma opticum, brain, brain stem, pituitary gland). Achieving maximum local control through radical treatment while minimizing its consequences is a considerable challenge facing this group of tumors. Patients with an early form of the disease are treated surgically, either endoscopically or through an open procedure. Locally advanced tumors require a multidisciplinary approach – surgery followed by radiotherapy in resectable tumors, or definitive radiotherapy ± chemotherapy in unresectable tumors [1].

In retrospective evaluations, N-staging was found to be the strongest prognostic factor with negative impact of regional spread on tumor control and survival [2–8]. Other prognostic factors reported in retrospective studies are: age [2, 3, 8, 11]; sex [2, 8]; race [12]; performance status [13]; smoking [13]; comorbidities [14]; T-staging [2, 3, 5, 6, 8, 11, 15, 16]; clinical stage [6, 10]; intracranial extension [4,5,17]; intraorbital extension [3,17,18]; invasion to lamina cribriformis [12, 15, 17]; infratemporal fossae extension [16]; invasion of the dura mater [16]; sublocality [16]; histological type [5, 12, 16]; tumor cell differentiation [8, 19]; neuroinvasion [18]; surgical resection [2–4, 6, 10, 16]; radicality of resection [2]; total dose of radiotherapy [2, 3, 20]; total time of radiotherapy [2]; and; chemotherapy [11].

In this study we aim to analyze long-term treatment outcomes and toxicity in a consecutive group of patients treated with curative radiotherapy at Institute of Radiation Oncology and identify prognostic factors that affect treatment results.

Materials and methods

Over the period of January 2002 to December 2018, 83 patients were treated for nasal cavity and paranasal sinus tumors. 22 patients were excluded (palliative treatment for bad general conditions 11, metastatic disease 4, synchronous tumor in the head neck region 1, sarcoma 4, ameloblastoma 2). In the study, all 61 consecutive patients with sinonasal carcinoma who started postoperative or definitive radiotherapy with a curative intent were included. The median follow-up was 53 months. The median age at the time of treatment initiation was 59 years (32–85). The female to male ratio was 1: 2.8. Most patients were smokers or former smokers (71%); about a third of patients admitted to daily alcohol consumption. A significant proportion of patients had severe comorbidities; the Adult Comorbidity Evaluation score 27 (ACE-27) was ≥ 1 in 48% of patients. All tumors were retrospectively reclassified according to the 7th version of the tumour–nodes–metastases (TNM) classification. The majority of patients were treated for locally advanced disease (85% clinical stage ≥ III). In 23 patients (38%), the tumor propagated into the orbit. Regional cervical metastases were initially diagnosed in 23% of patients. Squamous cell carcinoma was the most frequent histology (Tab. 1).

Treatment

Surgery

In 39 (64%) patients, radiotherapy was preceded by resection of the primary tumor; 12 of these patients underwent bilateral or unilateral neck dissection. A total of 8 patients underwent endoscopic resection for the primary tumor (ethmoidal sinus 1, maxillary sinus 2, nasal cavity 5). Other patients underwent open surgical approaches. An orbital exenteration was performed in 6 patients with tumor spread to the orbit. Full radicality (resection margins ≥ 5mm) was declared only in 26% of patients who underwent resection. In the rest of the patients, surgery was limited to biopsy verification.

Radiotherapy

Before 2007, patients were treated with 2D and 3D conformal radiotherapy (19 cases). Patients were treated with the intensity-modulated radiation therapy (IMRT) technique from 2007 onwards (42 cases). In the first phase clinical target volume (CTV) included the tumor/bed and the entire paranasal cavity and other risky parts of the sinonasal system & regional lymph nodes in T3/4 and N+ tumors (areas Ib–III ± retropharyngeal). The decision

on unilateral or bilateral irradiation of the neck was made on the basis of initial clinical indicators (tumor localization, spread of the tumor across the midline, etc.). In the second phase, the tumor/bed and entire paranasal cavity & areas with initial lymphadenopathy were irradiated. Prescribed dose was 56 Gy/28 fractions for definitive radiotherapy or 50 Gy/25 fractions for postoperative radiotherapy (first phase) and 14 Gy/7 fractions (second phase). Organs at risk and dose constrains are shown in Table 3.The median total dose was 70 Gy. Irradiation of regional lymph nodes was given to 37 patients (61%). Of the 47 patients with initial N0 staging, 23 had regional areas irradiated (18 bilaterally, 5 unilaterally). Of the 14 patients with initial N+ staging, 12 had the regional areas irradiated bilaterally and 2 unilaterally).

Chemotherapy

A total of 29 patients (48%) received chemotherapy, 27 of them with cisplatin 40 mg/m^2 weekly concomitantly. 4 patients received neoadjuvant chemotherapy based on platinum derivatives (all received concomitant chemotherapy as well). The median cumulative cisplatin dose in concomitant chemotherapy was 200 mg/m^2. 2 patients (small cell carcinoma 1, neuroendocrine carcinoma 1) were treated with chemotherapy in combination cisplatin + etoposide. The basic characteristics of the treatment are summarized in Table 2.

Analysis

For statistical analysis, all data were recorded and analyzed on XLSTAT software (Addinsoft) version 18.07. Kaplan-Meier methods were used to estimate locoregional control (LRC), distant metastasis-free interval (DMFI), overall survival (OS), and disease-free survival (DFS). The survival or disease-free periods counted from the start of radiation to the time of relapse (LRC, DMFI) or death (OS) or relapse and death (DFS). The log-rank test was used to compare survival and recurrence rates between various parameters. We used the Cox regression hazard model to analyze multivariate data. All analyses were performed with a two-sided significance level of ≤ 0.05. Acute and late toxicity were evaluated according to Radiation Therapy Oncology Group (RTOG) criteria [21].Comorbidities present at the time of diagnosis were collected retrospectively using the ACE-27 index [22].

Results

Acute toxicity

All patients were assessed for acute radiation toxicity (Tab. 4). Severe radiation mucositis (grade 3/4) was observed in 21% of treated patients. Severe radiation dermatitis was not observed in this cohort. Severe grade 3 ocular toxicity occurred in 2 patients. Serious swallowing difficulties (grade 3) were reported in 15% of patients. The average weight loss was 5.2 kg (7% of the input weight). All patients were assessed for hematological toxicity as well. 3% of patients had severe neutropenia (grade 3), 3% had severe anemia (grade 3). In summary, all severe acute toxicities occurred during treatment or within three months of treatment in 22 patients (36%). Two patients died during treatment (extensive myocardial infarction 1, septic complications 1).

Late toxicity

The late toxicity of the treatment could be assessed in 48 patients (92% of survivors > 3 months post-treatment). Severe late toxicity was expressed in 11 patients (23% of the evaluated number of patients). Severe late ocular toxicity was more prevalent (grade 3/4 in 12% of surviving patients), which led to amaurosis in 3 patients. In the first patient treated for neuroendocrine carcinoma of the nasal cavity, 2D postoperative radiotherapy was administered up to a dose of 70 Gy; ocular toxicity developed 4 months after the end of treatment, resulting in bulb evisceration 26 months following the completion of radiotherapy. The second patient was treated for olfactory neuroblastoma of the nasal cavity and paranasal sinuses with postoperative IMRT radiotherapy up to 70 Gy; 10 months following end of radiotherapy, the patient developed a trophic corneal ulcer which was resolved by eviscerating the bulb 42 months following the end of radiotherapy. The third patient was treated for adenoid-cystic carcinoma of the maxillary sinus with definitive IMRT radiotherapy up to 70 Gy; 6 months after radiotherapy, the patient developed a corneal ulcer and secondary glaucoma, resulted in total amaurosis 13 months after radiotherapy ended. Three cases of severe grade 3 ocular toxicity have been reported in patients treated for maxillary sinus carcinoma 2D (1) and IMRT (2) at intervals of 6, 34, and 55 months after treatment ended. 2 patients developed osteoradionecrosis 134 months (2D postoperative chemoradiotherapy up to 70 Gy) and 12 months after treatment (IMRT postoperative chemoradiotherapy up to 70 Gy). In both cases, osteoradionecrosis required surgical treatment. None of the 26 patients who had prophylactically introduced percutaneous endoscopic gastrostomy remained permanently fully PEG-dependent. One patient developed brain necrosis; the treatment was conservative. No patients suffered severe spinal toxicity (Table 4).

Locoregional control

A total of 20 local failures were detected in 18 patients (30%). There was local persistence in 7 patients after the end of treatment (initially 1 T2, 5 T4a, 1 T4b); 11 patients failed locally during follow-up (initially 1 T1, 1 T2, 2 T3, 3 T4a, 4 T4b). Only one patient (squamous cell carcinoma of the maxillary sinus initially T4aN2b) failed regionally at the site of initial presentation 4 months after the end of radiotherapy. The majority of locoregional failures (79%) were detected in the first 36 months after the end of radiotherapy (range 2–84 months). Five-year and ten-year locoregional control was 74% and 67%, respectively (Fig. 1). A total of 7 patients (37%) underwent salvage surgery out of the 18 patients with local failure. After the detection of local failure, 2 patients died 51 and 105 months later, while 5 patients survived after salvage surgery 20, 55, 62, 140, and 203 months later. One patient who had regional failure died after undergoing reirradiation 8 months after detection of the recurrence. 2 patients were treated with palliative chemotherapy and died 3 and 29 months after recurrence. The remaining 9 patients received only symptomatic treatment.

Distant control

Distant failure was reported in 6 patients (10%), including 5 patients within 36 months following completion of radiotherapy (range 5.8–39.4 months). 90% of patients did not develop distant metastases after 5 and 10 years, respectively (Fig. 2). One of the six distant failure patients had brain metastasis, which was treated by neurosurgery; the patient died three months after the failure. 2 patients underwent palliative chemotherapy, the first died 14 months after the failure, and the other patient with metastases to the lungs and liver was in complete remission for a long time after palliative chemotherapy and died 59 months after the first metastases were detected. 1 patient with local recurrence and liver metastases was treated with radiofrequency ablation and lived 3 months. 2 patients were treated only symptomatically.

Survival

A total of 38 patients died. Tumor progression was the primary cause of death in 16 patients. In 20 patients, the cause of death was unrelated to cancer. During the follow-up, 4 metachronous duplicate tumors outside the head and neck area were diagnosed in 4 patients 28–85 months after treatment. Duplicate tumor progression was the cause of death in 2 of them. The 5- and 10-year overall survival was 58% and 41%, respectively (Fig. 3). The 5- and 10-year DFS was 38% and 25%, respectively.

Univariate and multivariate analysis

Parameters that reached statistical significance in the univariate analysis were: age; N-status; clinical stage; comorbidities; initial surgery; weight loss; grade 3/4 hematological toxicity and; initial response to treatment (Tab. 5). The multivariate analysis of variables showed the following independent prognostic parameters: Age for overall survival [hazard ratio (HR): 4.132; 95% confidence interval (CI): 1.529–11.166; p = 0.005], N-staging for overall survival (HR: 2.535; 95% CI: 1.096–5.859; p = 0.030) and disease-free survival (HR: 2.494; 95% CI: 1.084–5.737; p = 0.032), comorbidities for disease-free survival (HR: 4.479; 95% CI: 1.649–12,163; p = 0.003) and initial response for overall survival (HR: 4.043; 95% CI: 1.330–12.290; p = 0.014) and DFS (HR: 66.968; 95% CI: 15.119–296.239; p < 0.0001). The multivariate analysis showed a trend towards overall survival deterioration in patients of the advanced clinical stage (p = 0.065), patients with a higher ACE score (p = 0.073), and in patients who achieved severe acute hematological toxicity during treatment (p = 0.045) (Tab. 6).

Discussion

The optimal treatment of sinonasal carcinoma still remains unknown. The rareness of the disease means that there are no prospective clinical studies readily available, so we have to rely on retrospective studies, which are burdened by the heterogeneity of patients and inconsistencies in treatment procedures. Retrospective studies [2–6, 10, 12, 13, 16–18, 20, 23–26] report 5-year local control in the range of 43–80%, regional control 79–93% and distant control 66–90% (Tab. 7).

The majority of studies reported better treatment outcomes for patients treated with surgical resection and postoperative radiotherapy compared to radiotherapy alone. The authors from Washington University found that initial surgery had a statistically significant impact on 5-year DFS in 106 patients with paranasal sinus carcinomas treated with postoperative or definitive radiotherapy[4]. Furthermore, other retrospective studies showed that combined treatment resulted in better local control and survival [2, 3, 6, 10, 17]. Radical surgery followed by postoperative radiotherapy is therefore a generally accepted method of choice. Our cohort included mainly patients with locally advanced (39% stage IVA, 23% stage IVB, 23% N+) sinonasal carcinoma. Long-term tumor control rate has been high for most patients treated. The positive impact of the initial resection on locoregional control was recorded only in the univariate analysis (Fig. 4). In the multivariate analysis, this difference did not reach statistical significance. In the case of N0 staging, there is an ambiguous view concerning the need for elective irradiation of cervical nodes. The risk of regional

involvement increases especially in patients with squamous cell and non-differentiated carcinomas and, therefore, some authors recommend irradiating regional areas of these tumors even if there are no signs of their involvement [7, 12]. In our cohort, regional nodes were irradiated in half of the treated patients. We did not detect regional failure in patients with initial N0 staging.

The benefit of chemotherapy in the curative treatment of sinonasal carcinomas has not been ascertained. In a retrospective analysis of 36 patients with squamous cell carcinoma of the maxillary sinus, adjuvant chemotherapy was statistically significant in prolonging overall survival [11]. Some studies have suggested a potential benefit of chemotherapy for patients with undifferentiated carcinoma [27]. However, due to the small number and heterogeneity of the evaluated groups, it is difficult to draw any definite conclusions. Nearly half of the patients in our study received chemotherapy, the vast majority of which was concomitant chemotherapy with a weekly regimen of cisplatin. Univariate analysis failed to demonstrate the impact of added chemotherapy on cancer control or survival.

In retrospective evaluations, N-staging was found to be the strongest prognostic factor. Regional metastases affect a minority of patients and are initially diagnosed in < 15% of patients with sinonasal carcinoma [2, 3, 12]. The Surveillance, Epidemiology, and End Results database reported only 5% of patients with regional metastases in the analysis of 783 patients with nasal carcinomas [8]. Retrospective studies have shown a negative impact of regional spread on locoregional control, distant control and overall survival [2–7]. In our study, the pre-treatment presence of regional metastases proved to be an essential prognostic factor for overall survival (HR: 2.535; 95% CI: 1.096–5.859; p = 0.030) and DFS (HR: 2.494; 95% CI: 1.084–5.737; p = 0.032) in multivariate analysis.

The prognostic significance of age has been repeatedly reported [2, 3, 8, 11]. In line with these data, we also noted a significant negative prognostic impact of age >65 years on overall survival in multivariate analysis (HR: 4.132; 95% CI: 1.529–11.166; p = 0.005).

A 5-year overall survival rate ranging from 27 to 67% was reported in retrospective trials [2–6, 10, 12, 13, 16–18, 20, 23–26] (Tab. 7). The 5-year overall survival of our group was 51%. Non-tumor mortality contributed to it to a greater extent. A large proportion of patients were affected by severe comorbidities and elements of self-destructive lifestyle. Deaths due to progression or recurrence of primary disease were recorded in less than half of the deaths. 5% of the patients died as a result of progression of their duplicate tumors. Various

methodologies, including ACE-27, have repeatedly demonstrated the significant prognostic significance of comorbidities in patients with head and neck tumors. The study by Rietbergen et al. showed that there is a 62% increased risk of death in patients with moderate to severe comorbidities assessed by ACE-27, compared to patients with mild or without comorbidities [28]. Yung et al. reported the prognostic significance of the comorbidities in 183 patients with head and neck tumours at the time of diagnosis and at the last post-treatment follow-up and demonstrated that the comorbidity score assessed with ACE-27 was in both cases associated with overall survival [29]. The prognostic impact of comorbidity severity (Charlson comorbidity index ≥ 6) in sinonasal carcinoma was reported in a clinical study by Suzuki et al. [14]. According to our knowledge, ACE-27 assessment of comorbidities in sinonasal carcinoma has yet to be published. A multivariate analysis of our group revealed a statistically significant impact of ACE-27 score on disease-free survival (HR: 4.479; 95% CI: 1.649–12.163; p = 0.003) and a trend toward worsening overall survival (p = 0.073) in patients with ACE score >1 (Fig. 5).

Due to the localization of the tumor near the organs at risk, the risk of severe toxicity in patients treated with curative doses of radiotherapy increases. An older retrospective study from the M.D. Anderson Cancer Center reported unilateral vision loss in 16 of the 44 patients treated with postoperative radiotherapy in whom enucleation was not part of the initial surgery [23]. Katz et al. reported unilateral amaurosis due to radiation damage in 27% of the 78 patients treated for sinonasal carcinoma, and 4 patients even developed bilateral amaurosis [10]. Le et al. in 73 patients with sinonasal carcinoma (with extension into the orbit in 52%), reported severe ocular toxicity in 26% of patients [2]. Mendenhall et al. reported in 109 patients treated with postoperative or definitive radiotherapy unilateral vision loss in 14 patients and bilateral vision loss in 1 patient; 1 patient required surgery for osteoradionecrosis of the upper jaw, 1 patient required surgery for temporal lobe necrosis. Serious complications affected 25% of patients treated with a combination approach and 19% of patients treated with radiotherapy alone [6]. In our study, we found severe late toxicity in 23% of patients. Severe grade 3/4 ocular toxicity was observed in 12% of patients, of which 3 patients experienced permanent unilateral vision loss. In total, 12 patients (15%) experienced unilateral vision loss as a result of surgical or radiation treatment.

With modern radiotherapy techniques, it is possible to obtain better dose distribution and thus minimize the risk of damage to the optic nerve, chiasma opticum, brain stem, and other healthy tissues that surround the tumour. Recent clinical studies reporting treatment results of

IMRT or proton radiotherapy point to lower levels of radiation toxicity. Because of the small number of patients evaluated and the short follow-up period, outcomes of these studies has limited value. Due to the delayed onset of late toxicity, no definitive conclusions can be drawn from these evaluations [5, 15, 20, 30–32].

Conclusion

The results of the retrospective study demonstrated the high effectiveness of curative postoperative and definitive (chemo)radiotherapy in patients treated for sinonasal carcinoma with long-term locoregional and distant control. Severe acute toxicity was found in 36% of treated patients and involved not only radiation toxicity but also systemic toxicity in a large proportion of patients who received systemic treatment. Severe late toxicity was observed in 23% of patients, including unilateral vision loss in 3 patients, temporal lobe necrosis in 1 patient, and osteoradionecrosis requiring surgery in 2 patients. A multivariate analysis identified N-staging, age, comorbidity score (as evaluated by ACE-27), and initial response to treatment as the strongest prognostic factors in predicting survival.

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Figure 1. Locoregional control

Locoregional control
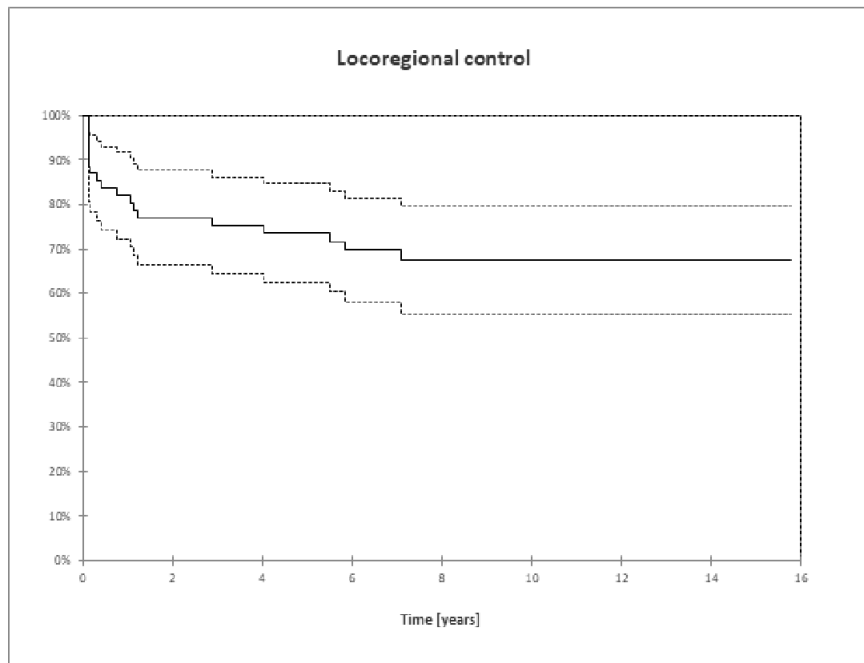
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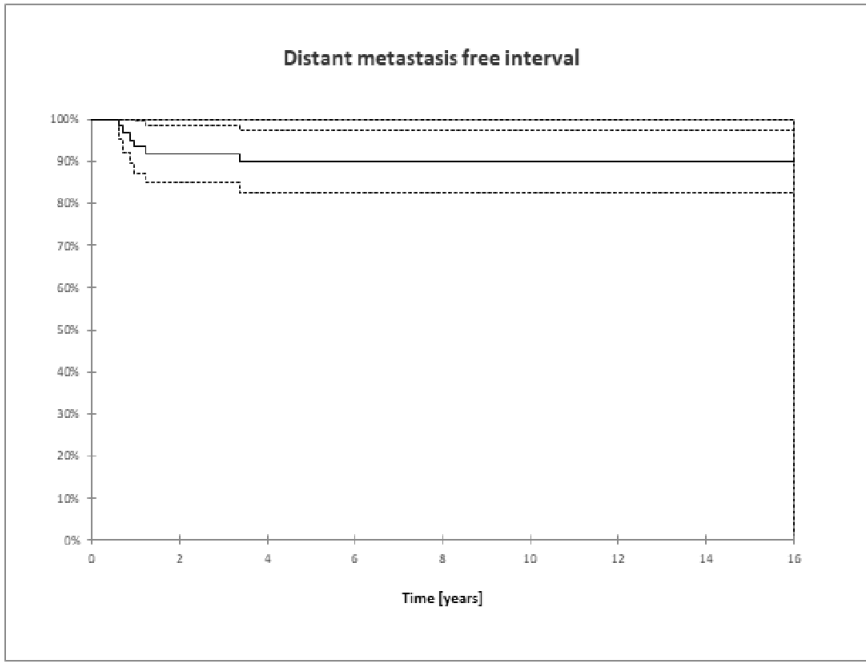
Figure 3. Overall survival
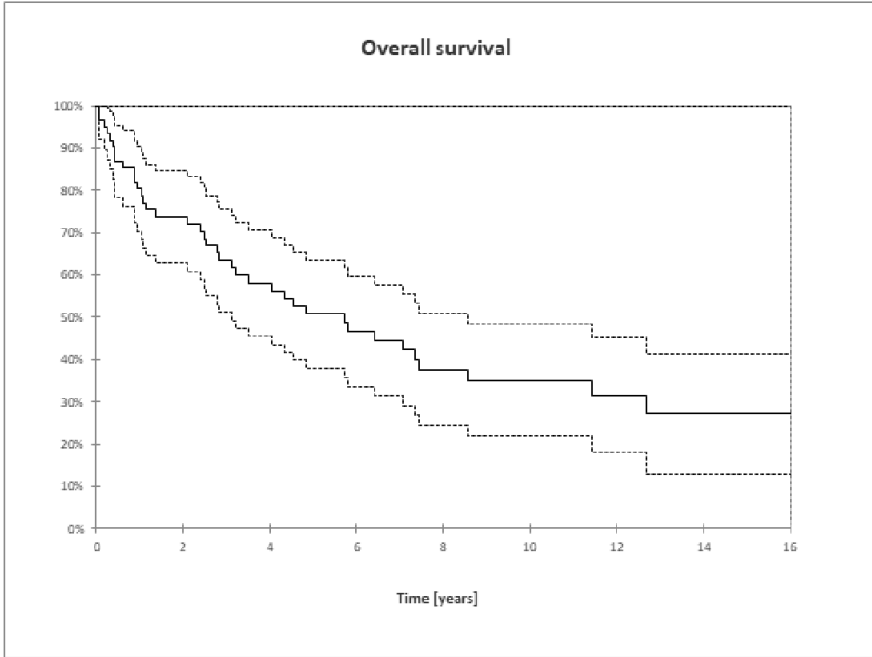
Figure 4. Locoregional control — postoperative/definitive raditherapy
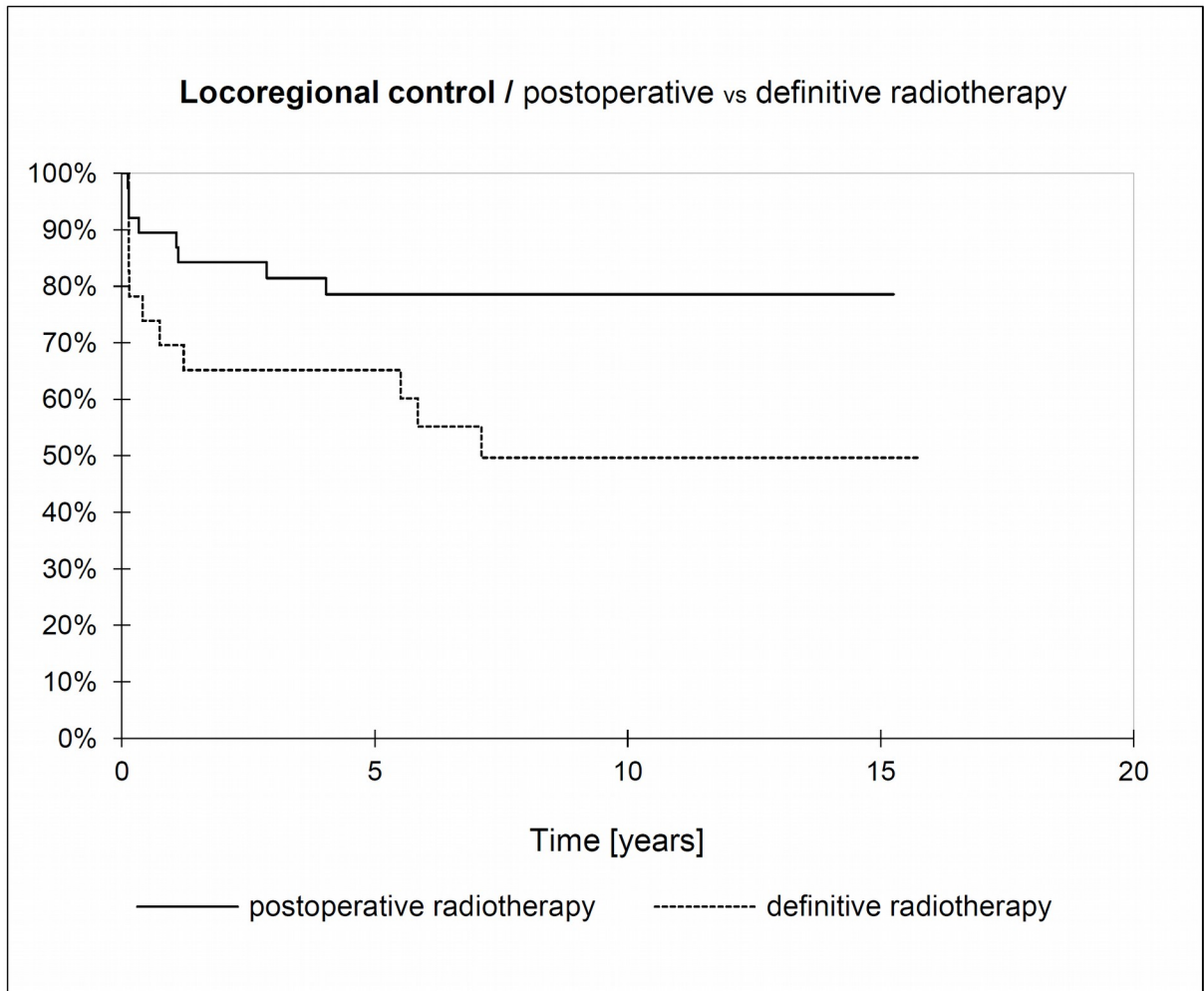
Figure 5. Prognostic impact of comorbidities on disease free survival. ACE-27 — Adult Comorbidity Evaluation 27
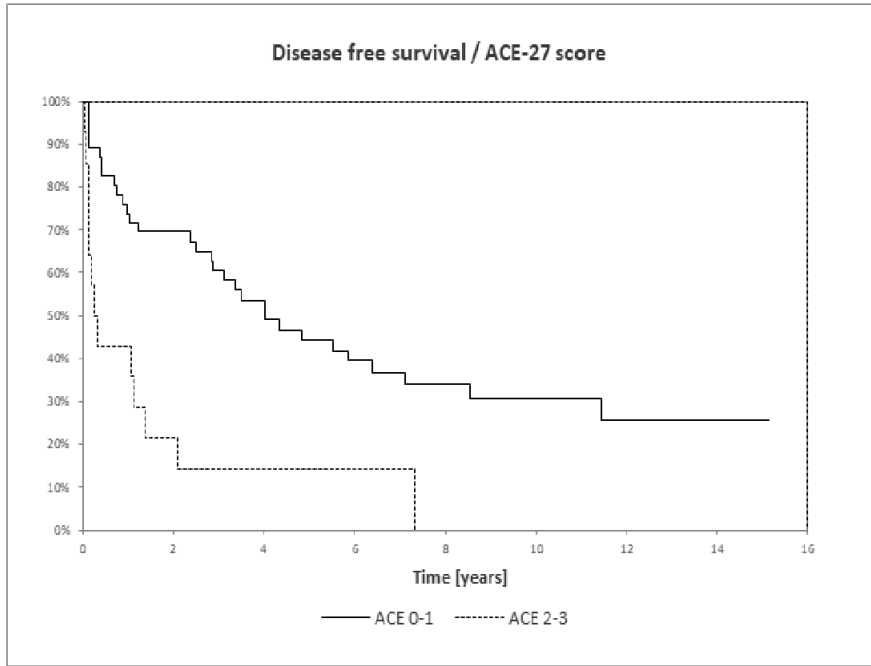
Table 1: Demographic and tumor characteristics

Parameter	n	%
Age (y)	(32–85)	
Median	59.19	
Sex		
Males	45	74
Females	16	26
Smoking		
Chronic nicotinism	29	48
Former (> 5 years)	14	23
Non-smoker	16	26
Unknown	2	3
Alcohol		
Daily	20	33
Occasionally	33	54
None	7	11
Unknown	1	2
Comorbidities		
ACE 0	31	51
ACE 1	15	25
ACE 2	11	18
ACE 3	3	5
Unknown	1	2
Locality		
Nasal cavity	16	26
Sinus maxillaris	41	67
Sinus ethmoidalis	3	5
Sinus frontalis	1	2
T-staging		
T1	3	5
T2	9	15
T3	15	25
T4a	21	34

T4b	13	21
N-staging		
N0	47	77
N1	3	5
N2a	0	0
N2b	6	10
N2c	4	6
N3	1	2
Clinical stage		
I	3	5
II	6	10
III	15	24
IVA	23	39
IVB	14	23
Histological type		
Epidermoid carcinoma	37	61
Undifferentiated carcinoma	8	13
Adenoid-cystic carcinoma	7	11
Schneiderian membrane carcinoma	2	3
Adenocarcinoma	2	3
Neuroendocrine carcinoma	1	2
Adenosquamous carcinoma	1	2
Sarcomatoid carcinoma	1	2
Small cell carcinoma	1	2
Olfactory neuroblastoma	1	2
Primary tumor	53	87
Local recurrence	8	13
Grading		
G1	4	7
G2	18	30
G3/4	27	44
Unknown	12	20

ACE — Adult Comorbidity Evaluation

Table 2. Treatment

Treatment	n	%
Surgery		
Radical surgery	39	64
No surgery	22	36
Type of surgery	39	100
Endoscopically	8	21
Open resection	31	79
Radicality of resection	39	100
R0 (^{3} 5 mm)	10	26
R0 (> 1 < 5mm)	2	5
R1 (0 ≤ 1 mm)	17	44
R2	3	8
RX	7	18
Neck dissection		
Unilateral	11	18
Bilateral	1	2
Radiotherapy		
Postoperative	39	64
Definitive	22	36
Radiotherapy technique		
2D/3D-CRT	19	31
IMRT	42	69
Regional radiotherapy	37	61
N+	14	23
N0	23	38
Total irradiation dose [Gy]	(18–72)	
Median	70	
Mean	64.13	
Chemotherapy		
Concomitant	23	38
Adjuvant	2	3
Neoadjuvant + concomitant	4	7
No chemotherapy	32	52
Concomitant chemotherapy	27	
Number of cycles — median (n)	5	
≥ 5 cycles	14	67
	13	33

< 5 cycles		

2D — two dimensional; 3D — three dimensional; CRT — conformal radiation therapy; IMRT — intensity-modulated radiation therapy

Table 3. Organs at risk (OAR) and dose constraints

OAR	Dose constraints	Auxiliary crieria
Spinal cord	Dmax ≤ 5000 cGy	
Brainstem	Dmax ≤ 5400 cGy	V55 Gy 1–5%
Optic nerve	Dmax ≤ 5400 cGy	
Optic chiasm	Dmax ≤ 5400 cGy	V55 Gy 1–5%
Cochlea	Dmax < 6000 cGy	Dmax < 3500 cGy contralateral
Brain	Dmed < 3500 cGy	
Temporal lobe	Dmax < 2200 cGy	
Parotid glands	Dmean ≤ 2800 cGy	

Table 4. Side effects of radiotherapy

Acute radiation toxicity								
N = 61	Mucous membrane	Skin	Salivary gland	Eye	Ear	Larynx	Pharynx/ Esophagus	Upper GI
Grade 0	5%	7%	25%	37%	90%	86%	39%	19%
Grade 1	23%	44%	42%	37%	7%	14%	27%	26%
Grade 2	51%	49%	33%	23%	3%	0%	19%	42%
Grade 3	16%	0%	-	3%	0%	0%	15%	12%
Grade 4	5%	0%	0%	0%	0%	0%	0%	0%
Late radiation toxicity								
N = 48	Mucous membrane	Skin	Subcutaneous tissue	Salivary gland	Eye	Larynx	Pharynx	Brain	Spinal cord
Grad	32%	35	56%	23%	67	100%	75%	96%	100

		%			%				%
Grade 0									
Grade 1	56%	60%	33%	42%	17%	0%	17%	2%	0%
Grade 2	10%	5%	8%	29%	4%	0%	8%	0%	0%
Grade 3	2%	0%	2%	6%	6%	0%	0%	0%	0%
Grade 4	0%	0%	0%	0%	6%	0%	0%	2%	0%

Table 5. Univariate analysis — results

Parametr	Groups	LRC	OS	DFS
Age	≤ 65 vs. > 65 years	0.7219	**0.0392**	0.1732
Gender	Female vs. male	0.2363	0.1303	0.0726
Education	Higher vs. basic	0.6983	0.4721	0.7228
Marrital status	Married vs. others	0.4973	0.8674	0.4558
Locality	Nasal cavity vs. others	0.6279	0.1884	0.1585
Primarity	Primary vs. recurrent	0.5105	0.5567	0.8953
T-staging	T1–3 vs. T4	0.0926	0.0662	0.1291
N-staging	N0 vs. N+	0.6253	**0.0185**	**0.0087**
Stage	I–III vs. IV	0.0517	**0.0227**	**0.0169**
Histology	Squamous cell vs. others	0.5377	0.0746	0.1952
Grading	G1/2 vs. G3	0.6383	0.5535	0.5527
Comorbidities	ACE 0–1 vs. 2–3	0.1945	**< 0.0001**	**0.0003**
Smoking	Non-smoker vs. smoker	0.8246	0.3803	0.3390
Alcohol	No/occasionally vs. daily	0.6907	0.2070	0.0915
Duration of symptoms	≤ 3 m vs. > 3m	0.9134	0.7563	0.9142
Radiotherapy	Postoperative vs. definitive	**0.0363**	0.2463	0.0704
Prolongation of radiotherapy	≤ 3 vs. > 3 days	0.7239	0.6865	0.6283
Total dose [Gy]	≤ 69 vs. > 69	0.7521	0.0515	0.2078
Concomitant CHT	Yes vs. no	0.7637	0.5742	0.7472
Weight loss	≤ 10% vs. > 10%	0.9403	**0.0500**	0.3039
Anemia	Hb ≥ 100 vs. Hb < 100	0.3024	0.2502	0.6776
Hematotoxicity G3/4	Yes vs. no	0.7594	**0.0447**	0.2411
Feeding tube	Yes vs. no	0.1843	0.7713	0.8949
Response	CR vs. nonCR	**< 0.0001**	**0.0109**	**< 0.0001**
Epoch	2002–2011 vs. 2012–2018	0.7625	0.4777	0.5683

ACE — Adult Comorbidity Evaluation, CHT — chmotherapy; Hb — haemoglobin; CR — complete response

Table 6. Multivariate analysis — results

Parametr	Groups	HR	95% CI	p-value
Locoregional control				
Radiotherapy	Postoper vs. definitive	1.138	0.381–3.041	0.819
Initial response	CR vs. nonCR	14.120	4.348–45.855	**< 0.0001**
0verall survival				
Age	≤65 vs. >65	4.132	1.529–11.166	**0.005**
N-staging	N0 vs. N+	2.535	1.096–5.859	**0.030**
Stage	I–III vs. IV	2.348	0.947–5.823	0.065
Comorbidities	ACE 0–1 vs. 2-3	2.753	0.908–8.347	0.073
Weight loss	≤ 10% vs. > 10%	0.380	0.125–1.161	0.090
Hematological toxicity G3/4	Yes vs. no	2.632	0.943 – 7.342	0.065
Initial response	CR vs. nonCR	4.043	1.330–12.290	**0.014**
Disease free survival				
N-staging	N0 vs. N+	2.494	1.084–5.737	**0.032**
Stage	I–III vs. IV	1.513	0.703–3.258	0.290
Comorbidities	ACE 0-1 vs. 2-3	2.753	0.908–8.347	**0.073**
Initial response	CR vs. nonCR	66.968	15.119-296.639	**< 0.0001**

ACE — Adult Comorbidity Evaluation, CHT — chmotherapy; Hb — haemoglobin; CR — complete response

Table 7. Retrospective clinical trials reporting results of 5-year locoregional control, distant control and overall survival in groups > 50 patients

Study	n	Treatment	LC	RC	DMC	OS
Jiang 1991 [23]	73 SM 36 SCC, 20 ACC, 6 AC, 2 MEC, 9 UDC	S + RT 100%	78%	84%	77%	–

Le 1999 [2]	97 SM 58 SCC, 4 AC, 19 ACC, 16 UDC	S + RT 63% RT 37%	43%	90%	66%	34%
Jansen 2000 [3]	73 PNS 40 SCC, 14 AC, 8 ACC, 11 UDC	S 4% RT 25% S + RT 68%	63%	79%	86%	46%
Waldron 2000 [24]	110 SM SCC 95, UDC 15	RT 75% S + RT 25%	43%	–	90%	–
Dulguerov 2001 [16]	220 NC & PNS 66 NC, 103 SM, 38 SE 126 SCC, 35 ACC, 25 AC 30 UDC	S 20% S + RT 46% RT 21%	59%	–	–	40%
Katz 2002 [10]	78 NC & PNS 48 NC, 24 SE 25 SCC, 31 AC + ACC + MEC 14 UDC, 8 ENB	RT 65% S + RT 35%	60%	88%	73%	50%
Blanco 2003 [4]	106 PNS 81 SM, 19 SE 87 SCC, 14 ACC, 5 AC	S + RT 65% RT 35%	58% 39%	–	71%	27%
Porceddu 2004 [18]	60 NC & PNS 32 SCC, 25 AC, 3 UDC	S 8% S + RT 67% RT 25%	49%	88%	90%	40%
Chen 2007 [25]	127 NC & PNS 83 SCC, 28 ACC, 28 AC	S+RT 84% RT 16%	62%	–	–	52%
Dirix 2007 [5]	127 NC & PNS 8 NC, 45 SM, 70 SE 48 SCC, 66 AC, 3	S+RT 88% RT 12%	53%	93%	75%	54%

	ACC, 10 UDC					
Hoppe 2007 [12]	85 NC & PNS 24 NC, 45 SM, 14 SE 42 SCC, 11 ACC, 6 AC 3 UDC, 9 Sa, 7 ENB	S+RT 100%	62%	87%	82%	67%
Madani 2008 [20]	84 NC & PNS 16 NC, 19 SM, 47 SE 17 SCC, 4 ACC, 54 AC, 9 ENB	S + RT 89% RT 11% IMRT	71%	–	82%	59%
Mendenhall 2009 [6]	109 NC & PNS 69 NC, 33 SE, 6 SS 32 SCC, 9 AC 16 ACC, 2 MEC, 14 UDC, 22 ENB	S + RT 49% RT 51%	63%	91% (N0) 51% (N+)	81%	55%
Khademi 2010 [26]	71 NC & PNS 20 NC, 29 SM, 19 SE 19 SCC, 18 ACC, 3 AC, 5 UDC, 6 ENB	S 21% S + RT 51% RT 28%	60%	–	–	55%
Duprez 2011 [17]	130 NC & PNS 31 NC, 24 SM, 74 SE 23 SCC, 82 AC	S + RT 78% IMRT	59%	98%	84%	52%
Russo 2016 [13]	54 NC & PNS 7 NC, 24 SM, 9 SE, 14 SS, 54 SCC	S + RT 69% RTp	80%	83%	78%	47%

NC — nasal cavity, PNS — paranasal sinuses, SM — sinus maxillaris, SE — sinus

ethmoidalis, SS — sinus sphenoidalis, SCC — squamous cell carcinoma, ACC — adenoid-

cystic carcinoma, MEC — mucoepidermoid carcinoma, ENB — esthesioneuroblastoma, UDC — undifferentiated carcinoma, NEC — neuroendocrine carcinoma, Sa — sarcoma, S — surgical resection, RT — radiotherapy, LC — local control, RC — regional control, DMC — distant metastasis control, OS — overall survival