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Long-term oncological follow-up after mold-based pulsed dose rate brachytherapy for early stage squamous cell carcinoma of the nasal vestibule: A single center experience of 68 patients over a 17-year period

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ABSTRACT

PURPOSE: Cancer of the nasal vestibule is a rare type of malignancy constituting less than one percent of all head and neck cancers. These tumors are typically diagnosed at an early stage. Both surgery and radiotherapy provide excellent oncological results, but esthetic results are better after radiotherapy. The aim of this study was to evaluate the long-term oncological follow-up after brachytherapy for early stage squamous cell carcinoma of the nasal vestibule.

METHODS AND MATERIALS: Retrospective analysis of patients with carcinoma of the nasal vestibule who were treated with primary brachytherapy in the Utrecht University Medical Center.

RESULTS: In this single center experience over a 17-year period 68 patients with early stage squamous cell carcinoma of the nasal vestibule were treated with brachytherapy. Two patients had lymph node metastases at first clinical presentation. Median follow-up duration was 46.5 months. Five-year locoregional recurrence-free survival, disease-specific survival, and overall survival were 91.1%, 96.1%, and 66.2%, respectively. All recurrences occurred within the first 3 years of follow-up.

CONCLUSIONS: Brachytherapy offers excellent oncological outcomes and is a safe and effective treatment for early stage carcinoma of the nasal vestibule. Recurrences typically occur within 3 years after treatment.

Keywords: Nasal vestibule; Squamous cell carcinoma; Brachytherapy; Nasal malignancies

Introduction

Cancer of the nasal vestibule (CNV) is a rare type of malignancy and accounts for less than one percent of all head and neck cancers (1). A Danish national registry study estimated the incidence of CNV to be between 0.32 and 0.41 per 100.000 people per year (2). Although CNV is staged as a unique subsite of the nasal cavity in the TNM (8th edition) according to the Union for International Cancer Control (UICC), its behavior is more similar to carcinomas arising from the skin (3). The majority of CNV

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consists of squamous cell carcinomas (SCC), but other tumors such as basal cell carcinoma, cutaneous melanoma, and Merkel cell carcinoma can also originate in the nasal vestibule. As is the case for SCC of the skin, smoking and sunlight exposure are risk factors for developing CNV (2).

Due to its prominent location in the midface, CNV is generally noticeable at an early stage. This results in early identification and diagnosis, subsequent early treatment, and thus improving prognosis (4). The treatment objective is to achieve the best possible oncological outcome while preserving nasal function and aesthetics. As a result of the rarity of CNV, treatment strategies are based exclusively on retrospective data. For early stage disease (T1-T2), both primary surgery and radiotherapy currently provide excellent results (5–10). However, surgical treatment can result in facial disfigurement with the necessity for reconstruction or prosthesis (11,12). Therefore, radiotherapy has become the favored treatment modality for early stage CNV (6,7,13–15). Treatment for more advanced CNV (T3+ or N+) typically consists of surgery followed by radiotherapy.

Both primary brachytherapy (BT) and external beam radiotherapy (EBRT) have been used for the treatment of early stage CNV. BT allows for a higher tumor radiation dose, while limiting radiation exposure of the surrounding tissues (16). Results from a multicenter cohort study showed improved tumor control, survival, nose preservation, and aesthetics for BT compared to EBRT (17). In this single-center retrospective cohort study, we discuss the experiences and results at the University Medical Center Utrecht (UMCU), a tertiary referral center for head and neck malignancies, over the past 17 years regarding mold-based pulsed dose rate (PDR) brachytherapy for squamous cell carcinoma of the nasal vestibule.

Methods and materials

Study population

In this retrospective cohort study, we assessed the health records of all patients with a nasal or paranasal sinus malignancy who had been treated in the UMCU, between August 2004 and June 2022. All consecutive patients who underwent primary BT for a CNV were included. Patients who underwent primary surgery or EBRT were excluded.

Relevant patient information was extracted from the electronic health record. The age at the time of diagnosis was defined on the date of CNV histopathological confirmation. Smoking habits and alcohol consumption were determined based on a patient's medical history as recorded during the first consultation. All patients were seen for clinical evaluation and histopathological confirmation, generally followed by computed tomography (CT), magnetic resonance (MR) imaging, chest X-ray, neck ultrasound, and if necessary, fine needle aspiration cytology of suspected lymph nodes. Before treatment, all patients were reviewed by the UMCU multidisciplinary head and neck oncology board. Histopathological nomenclature and classification were scored in accordance with the 8th edition of the TNM-classification as published by the Union for International Cancer Control (UICC) (18). By reviewing imaging studies and clinical data, tumors that had been staged according to previous editions of the TNM-classification were re-staged per the 8th edition. All tumors were also staged according Wang classification (19) (Table 1).

Patient follow-up was scheduled in accordance with UMCU protocols: patients were alternatingly seen by a radiation oncologist and head and neck surgeon during a 5-year period following treatment. To obtain clarity about the long-term (>5 years) follow-up data, either the general practitioner or the patient was called to obtain an

Table 1
T-staging systems and definitions.

Wang staging system (19)		UICC staging system (18)	
T1	Lesions are relatively superficial and are limited to the nasal vestibule.	T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Lesions extend from the nasal vestibule into adjacent structures, such as the nasal septum, upper lip, or skin of the nose, but are not fixed to underlying bone.	T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Lesions include those tumors with extension to the hard palate, buccogingival sulcus, upper nasal septum, turbinates, or paranasal sinuses, or those that are fixed to deep muscle or bone.	T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
		T4a	Moderately advanced local disease. 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.
		T4b	Very advanced local disease. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus.

UICC = Union for International Cancer Control.

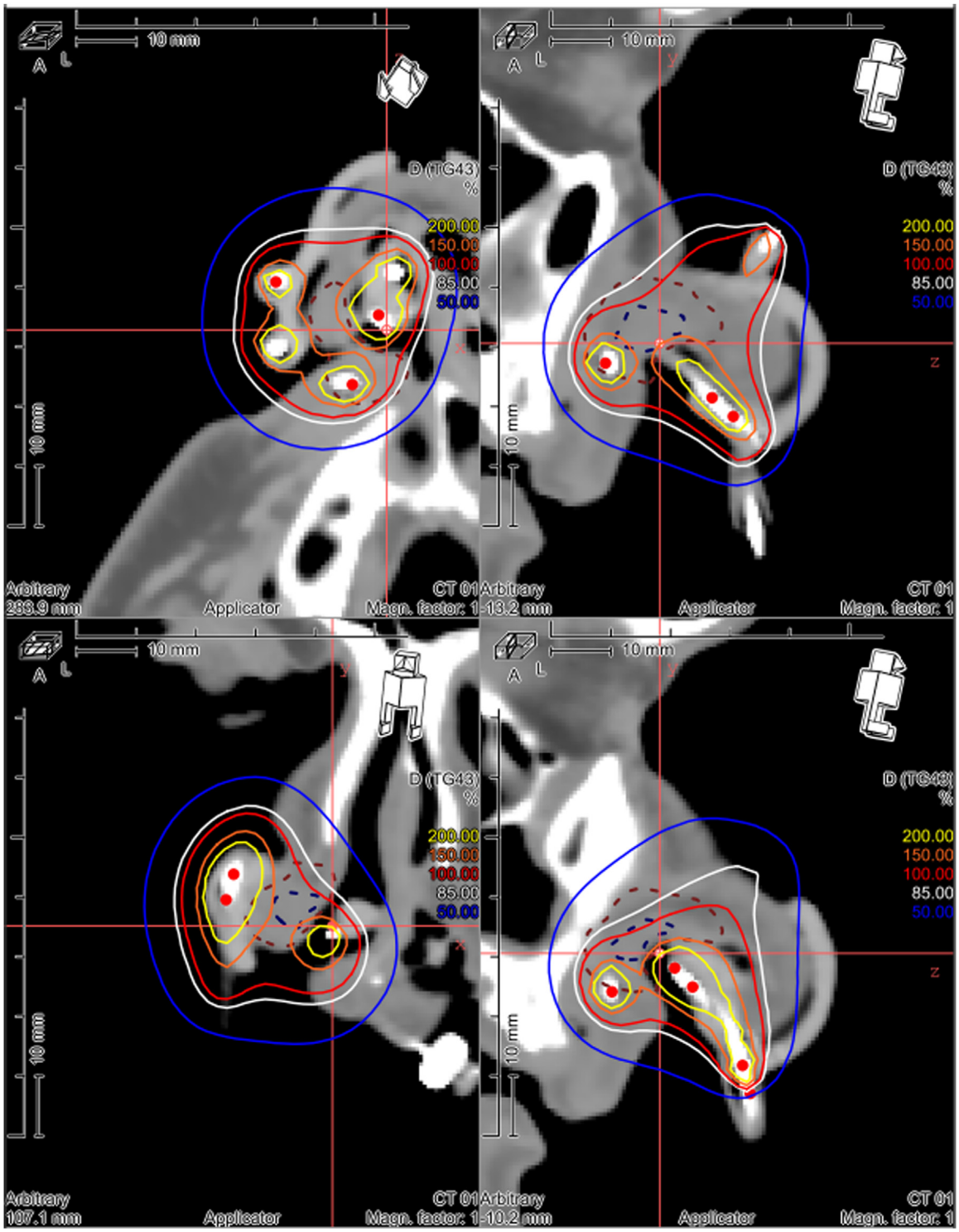

Fig. 1. Dosimetry for a patient with a right-sided cT1N0 nasal vestibule carcinoma of the lateral wall. Gross tumor volume (blue dashed line) and clinical target volume (brown dashed line) have been delineated. Isodose lines are color coded as blue (50%), white (85%), red (100%), orange (150%), and 200% (yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

up-to-date health status. The time to recurrence was calculated from the date of diagnosis to the date of histopathological (or radiological in the case of distant metastases) confirmation of recurrent disease. The duration of follow-up was calculated from the date of diagnosis to the final moment of follow-up or date of death. Outcome was determined at the most recent moment of follow-up or date of death. For disease-specific survival (DSS) and overall

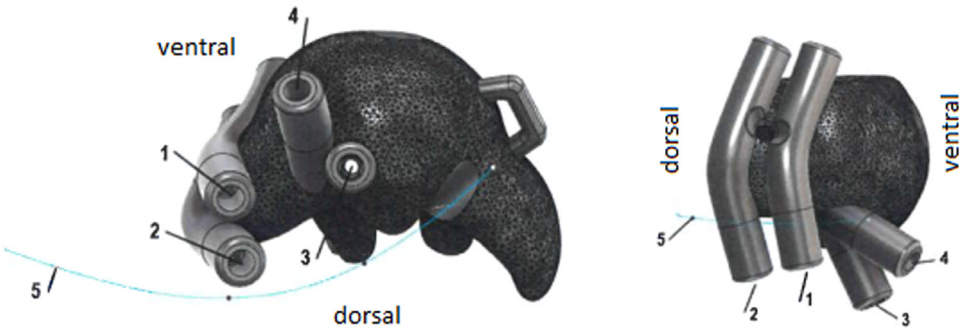

Fig. 2. Schematic of an individual 3D-printed mold with preprinted channels, two on the outside of the nose (1 and 2) and two within the nasal vestibule (3 and 4). A single horizontally placed interstitial catheter (5) was used to achieve coverage on the caudal part of the GTV and CTV.

survival (OS) analyses, events were characterized as death due to CNV and any other cause, respectively.

The study was approved by the medical ethics committee of the UMCU. For this type of study, formal consent was not required. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration. Patients provided formal consent for the use of any images.

Treatment characteristics

Brachytherapy was administered using a PDR afterloader with an Iridium-192 source. The number of catheters varied per patient, based upon an image-guided (CT or MR) preplan (Fig. 1). In this preplan the gross tumor volume (GTV) was defined based upon clinical evaluation and the available imaging. The clinical target volume (CTV) was GTV + 5 mm. An individual (3D-printed from 2019) mold was created to provide optimal catheter placement for target coverage (Fig. 2) without having to insert all catheters interstitially. All catheter canals were constructed out of 2 mm thick material. The resulting minimal distance between two sources, if placed directly next to one another, was 4 mm. However, the aim was to avoid placing two catheters directly next to each other. Additional interstitial hollow needles were placed as necessary if sufficient coverage could not be accomplished using the mold (Fig. 3). If possible, general anesthesia was administered for placement and fixation of the mold and interstitial needles. Treatment planning was performed using Elekta Oncentra, Stockholm Sweden. Treatment planning aims were to cover GTV with the 100% isodose and CTV with at least the 85% isodose. Fusing 200% isodoses was not allowed. Additionally, over 100% isodose in the nasal cartilage was minimized. Treatment delivery ranged from 94 to 96 hourly pulses of 70 cGy up to a total dose of 67.2 Gy.

Statistical analysis

Locoregional recurrence-free survival (LRFS), DSS, and OS were calculated via the Kaplan–Meier estimator (20). Univariate analyses of prognostic factors were performed using log-rank tests. p values $\leq .05$ were considered statistically significant. UICC T-stage and N-stage were omitted from univariate analysis because of the limited subgroup sample size. Variables that proved statistically significant in univariate analysis were subsequently subjected to Cox proportional hazard analysis. Age at time of diagnosis, sex,

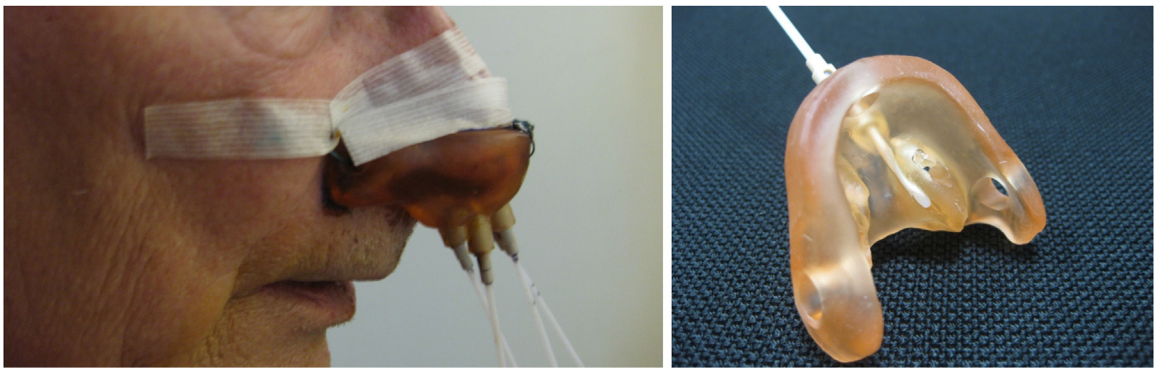

Fig. 3. Left: A brachytherapy implantation for a T1N0 squamous cell carcinoma of the nasal vestibule. A personalized, CT-based 3D printed mold is used with four predefined positions for intracavitary tubes. Right: An example of a personalized, CT-based 3D-printed mold with one of the four tubes already in position. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

smoking status, and alcohol consumption were included in multivariate models. Analyses were performed using IBM SPSS Statistics version 26.0.0.1.

Results

A total of 68 patients with squamous cell carcinoma of the nasal vestibule, who underwent primary BT between August 2004 and June 2022, were identified. The clinical characteristics of these patients are summarized in Table 2.

The majority of patients (73.5%) had smoked at least 10 pack years. Nearly one third of patients (32.4%) drank at least five units of alcohol per week. Patients typically presented with early-stage disease. Out of 68 patients, 60 (88.2%) had T1 disease at presentation, six (8.8%) presented with T2 disease, and two (2.9%) presented with T4a disease (tumor invasion in the skin of the nose). Two (2.9%) patients presented with lymph node metastases (one N2b, and one N2c). None of the patients had distant metastases at first clinical presentation. Mean tumor diameter was 12.8 mm (range = 3–32 mm). Thirty-five (51.5%) presented with a tumor <15 mm, 21 (30.9%) presented with a tumor ≥15 mm, and tumor diameter was not detailed in 12 (17.6%) patients.

Table 2
Patient characteristics of patients with cancer of the nasal vestibule.

Sex	*N*	*%*
Total	68	100
Male	40	58.8
Female	28	41.2
Age	*N*	IQR
Median age in years	71	64–77
Diagnostic imaging	*N*	*%*
Chest X-ray	63	92.6
Neck ultrasound	66	97.1
CT-head/neck	31	45.6
MRI-head/neck	44	64.7
CT + MRI	9	13.2
*T-stage at diagnosis (UICC)**	*N*	*%*
T1	60	88.2
T2	6	8.8
T4a	2	2.9
*T-stage at diagnosis (Wang)***	*N*	*%*
T1	55	80.9
T2	13	19.1
N-stage at diagnosis	*N*	*%*
N0	66	97.1
N+	2	2.9
Tumor diameter	*N*	*%*
<15 mm	35	51.5
≥15 mm	21	30.9
Unknown	12	17.6

* Staged in accordance with the 8th edition of the TNM-classification (Table 1).

** Staged in accordance with the Wang staging system for cancer of the nasal vestibule (Table 1, 19).

Table 3
Treatment and outcome of 68 patients with cancer of the nasal vestibule

Radiotherapy	*N*	*%*
Brachytherapy	65	95.6
Brachytherapy + EBRT neck	3	4.4
Recurrent disease	*N*	*%*
Local recurrence	2	2.9
Regional recurrence	2	2.9
Distant metastases	2	2.9
Follow-up	*N*	IQR
Median duration (months)	39	5–73
Radiation toxicity	*N*	*%*
Extensive nasal crusts	46	67.6
Radiation ulcers	10	14.7
Epistaxis	4	5.9
Chondronecrosis	6	8.8
Septal defect	1	1.5
Outcome	*N*	*%*
NED	42	61.8
AWD	2	2.9
DOD	2	2.9
DID	22	32.4

EBRT = external beam radiotherapy; NED = no evidence of disease; AWD = alive with disease; DOD = died of disease; DID = died of intercurrent disease.

In this cohort of 68 patients, 65 (95.6%) received BT alone, and three (4.4%) received a combination of both BT and EBRT. Of these, 1 patient started with BT but developed a delirium after which treatment was halted. After recovery, treatment was resumed using EBRT. The two other patients (2.9%) received a combination of BT for the primary tumor and EBRT for treatment of lymph node metastases in the neck. One of these patients also underwent subsequent neck dissection because of residual nodal disease. Administered external beam radiation dose ranged from 4300 cGy to 7000 cGy.

The majority of patients experienced radiation toxicity. Out of 68 patients, 46 (67.6%) noticed extensive nasal crusts, ten (14.7%) developed a radiation ulcer, and four (5.9%) experienced recurrent epistaxis (Table 3). Treatment typically consisted of topical corticosteroids, rinsing or antibiotics. Chondroradionecrosis occurred in 6 (8.8%) patients, all of whom were treated with hyperbaric oxygen therapy after a tumor-negative biopsy. One of these 6 patients (1.5%) subsequently developed a septal defect without deformation of the nose.

Patient characteristics and treatment strategies for the patients who developed recurrent disease are shown in Table 4. Two patients (2.9%) developed a local recurrence, one of whom received palliative radiotherapy because of synchronous bone metastases of a primary hepatocellular carcinoma. The other patient was deemed unfit to undergo salvage treatment and thus received best supportive care

Table 4
Patient characteristics and treatment for patients who developed recurrent disease.

Patient no.	Sex	Age at diagnosis	Initial disease stage (UICC)	T-stage (Wang)	Treatment strategy	Recurrent disease location	Time to recurrence (months)*	Recurrent disease treatment	Follow-up duration (months)	Outcome
1	Male	70	cT1N2bM0	T1	BT + EBRT; ND**	Regional (nasolabial); Distant (skin); Distant (larynx);	33	Local surgery (nasolabial); EBRT (skin); EBRT (larynx); Immune therapy	52	AWD
2	Male	77	cT1N0M0	T1	BT	Local (nose)	7	Palliative EBRT***	12	DID
3	Female	57	cT2N2cM0	T2	BT + EBRT	Regional (mediastinum); Distant (pulmonary)	17	Palliative EBRT	22	DOD
4	Male	58	cT2N0M0	T2	BT	Local (nose)	8	BSC	10	DOD

UICC = Union for International Cancer Control; BT = brachytherapy; EBRT = external beam radiotherapy; ND = neck dissection; BSC = best supportive care; AWD = alive with disease; DID = died of intercurrent disease; DOD = died of disease.

* Defined as time since initial treatment.

** Patient no 1. underwent neck dissection following EBRT of the neck because of a residual lymph node metastasis.

*** Patient no 2. received palliative EBRT because of synchronous bone metastases of a synchronous hepatocellular carcinoma.

until his death. Two (2.9%) patients developed regional recurrent disease as well as synchronous distant metastases. The first of these 2 patients received palliative radiotherapy for pulmonary metastases. The other patient had a regional recurrence in the nasolabial fold for which he underwent surgery; distant cutaneous metastases for which he underwent EBRT; and a T2 supraglottic larynx carcinoma for which he was also treated with EBRT. The patient also received adjuvant immune therapy (pembrolizumab) to which he had a complete metabolic response.

The 5-year LRFS for all patients was 91.1% (Fig. 4a). All instances of recurrent disease occurred within the first 3 years of follow-up (range = 7–33 months). There was a statistically significant relation between 5-year LRC, Wang T-stage, and tumor diameter category (Table 5). However, these relations did not persist in multiple Cox regression analysis. There was no statistically significant relation between 5-year LRFS and smoking habits or alcohol consumption (Table 5).

Table 5
Univariate subgroup log-rank analysis for locoregional recurrence-free survival, disease specific survival, and overall survival.

Risk factor	*n*	5-year LRFS (%)*	*p*	5-year DSS (%)*	*p*	5-year OS (%)*	*p*
Total	68	91		96		66	
Age at diagnosis			0.83		0.12		**0.03**
<70 years	29	91		91		87	
≥70 years	39	90		100		51	
Smoking habits			0.49		0.69		0.55
None/unknown	9	100		100		44	
<10 PY	9	100		100		78	
≥10 PY	50	88		95		67	
Alcohol consumption			0.29		0.55		0.84
None/unknown	24	100		100		61	
<5 units/week	22	80		93		69	
≥5 units/week	22	90		95		75	
T-stage (Wang)			**0.05**		**0.00**		0.52
T1	55	94		100		67	
T2	13	77		77		71	
Tumor diameter			**0.02**		0.05		0.19
<15 mm	35	100		100		69	
≥15 mm	21	81		86		44	
Not specified	12						

LRFS = locoregional recurrence-free survival; OS = overall survival; DSS = disease-specific survival; PY = pack years; UICC = Union for International Cancer Control.

Significant *p* values are depicted in bold.

* Kaplan–Meier estimate.

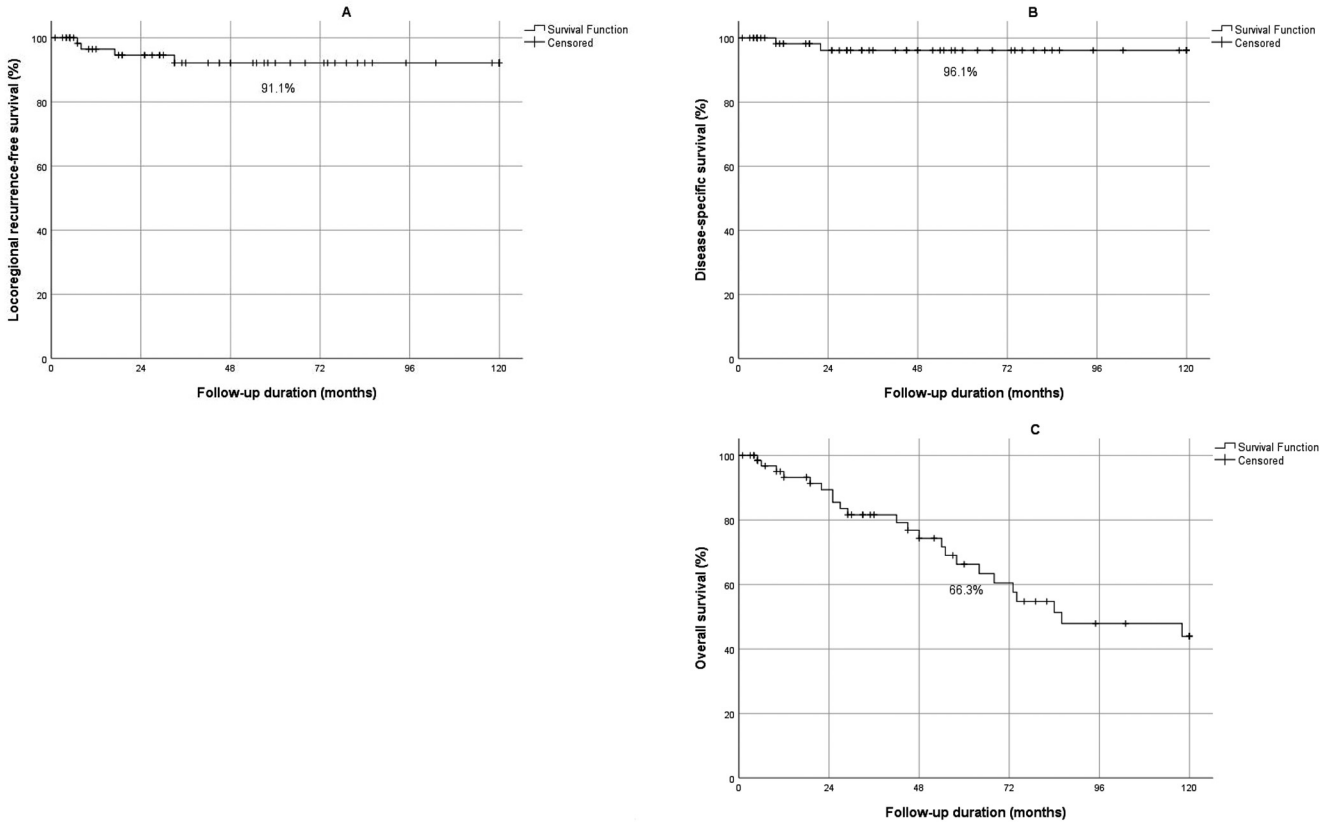

Fig. 4. Kaplan–Meier survival estimates of 68 patients treated with brachytherapy for a squamous cell carcinoma of the nasal vestibule. A = 10-year Locoregional recurrence-free survival; B = 10-year Disease-specific survival; C = 10-year Overall survival.

The median follow-up duration was 39 months (IQR: 5–73). At the most recent moment of follow-up, out of 68 patients, 42 (61.8%) showed no evidence of disease, 2 (2.9%) patients were alive with disease, two (2.9%) died as a result of their disease, and 22 (32.4%) died of intercurrent disease. The 5-year DSS for the entire population was 96.1% (Fig. 4b), while 5-year OS was 66.3% (Fig. 4c). There was a statistically significant association between 5-year DSS and T-stage (Wang) (Table 5). These relations also did not persist in multiple Cox regression analysis.

Discussion

This single-center retrospective cohort study describes 68 patients who underwent mold-based PDR brachytherapy for a primary CNV over a 17-year period.

Locoregional control

Our analyses showed excellent oncological outcome of this treatment. Five-year LRFS was 91.1% for the entire study population and all recurrences occurred within the first 3 years of follow-up. In univariate analysis, Wang T-stage (T2 vs. T1) showed a correlation with decreased LRFS. This correlation, however, did not carry through to a multivariate model. These results are partially in line with previous literature. Prior retrospective cohort studies of T1 and T2 tumors treated with BT describe local control rates varying from 91% at 3 years to 95% at 5 years (7,13,15,17). In a study by Vanneste *et al*., increased T-stage correlated with decreased local control (14). However, in this study, the majority of T2 tumors were treated with EBRT and this association was not replicated in any other studies (7,13,15,17,21). Additionally, Czerwinski *et al*. found EBRT to be the only risk factor for local failure in a propensity-score-matched cohort of patients with T1 and T2 CNV treated with either BT or EBRT. Regional recurrence-free survival (RRFS) for CNV varied heavily. In a review by Talmi *et al*., RRFS varied from 60% to 97% for all disease stages (22). Scurry *et al*. report an RRFS of 81.9% at a mean follow-up of 4.4 years in a pooled analysis of 927 patients with SCC of the nasal cavity and nasal vestibule (23). Neither recommend elective treatment of the neck. In other studies on T1 and T2 CNV specifically, RRFS ranged from 88% to 91% (9,13,15,21,24).Unlike what our findings would suggest, Czerwinski *et al*. recommend considering elective treatment of the neck in patients with a tumor ≥1.5 cm, or T2 stage, as these were identified as risk factors for regional recurrence in their study population (17). In available literature, only 1 patient with early stage CNV who was treated with radiotherapy developed recurrent disease later than 3 years following treat-

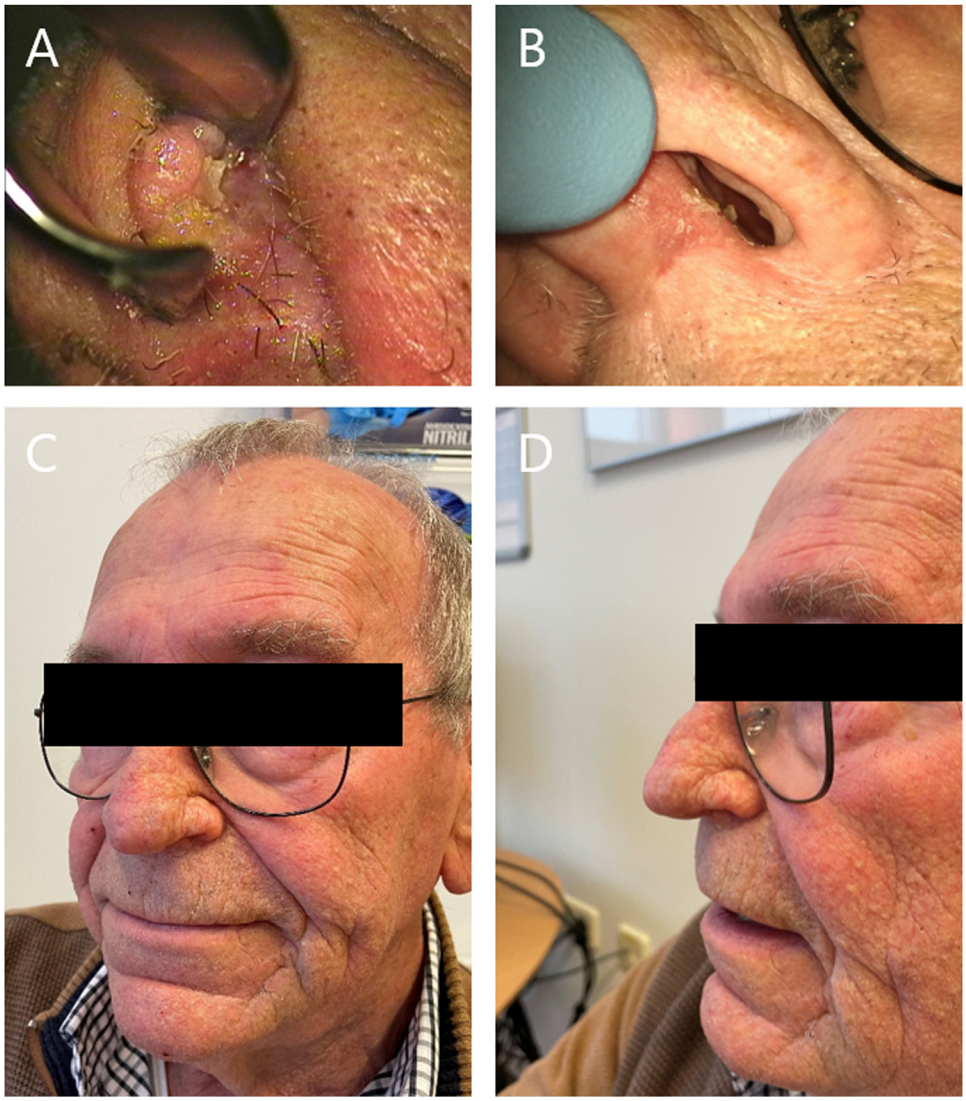

Fig. 5. Images of a patient with a left-sided cT1N0 nasal vestibule squamous cell carcinoma. (a) Anterior rhinoscopy revealing the tumor before treatment. (b) External view 2 years after treatment. (c) Frontal view 2, 5 years after treatment. (d) Lateral view 2, 5 years after treatment.

ment (2,7,8,10,13–15,17,25–27). This suggests follow-up duration could be limited to 3 years.

Survival

Five-year estimated OS and DSS were 66% and 92%, respectively. Similar to LRFS, Wang T-stage (T2 vs. T1) and tumor diameter category (≥15 mm vs. 15 mm) were risk factors for disease specific mortality in univariate analysis. This correlation, however, did also not carry through to a multivariate model. Age at time of diagnosis was the only statistically significant risk factor for OS in univariate analysis, as was to be expected. At 3–5 years of follow-up, DSS varied from 50% to 92% in a literature review by Mukai *et al*. Czerwinski *et al*. report 3-year OS and DSS of 82% and 94%, respectively (17). Furthermore, a tumor diameter ≥1.5 cm was found to be a risk factor for DSS. Other single-center studies report similarly high 5-year DSS (9,13,15,21).

Toxicity

The majority of patients experienced at least some degree of radiation toxicity. In our cohort, this was limited to extensive nasal crusts in the majority of cases (66.1%), followed by radiation ulcers (16.1%), chondroradionecrosis (9.7%), and recurrent epistaxis (6.5%). Such side effects are to be expected as a result of treatment and tend to occur more frequently in patients treated with BT compared to EBRT due to higher surface doses with brachytherapy (17). Czerwinski *et al*. report radiation ulcers, septal defects, and chondroradionecrosis in 24%, 10%, and 4% of patients treated with brachytherapy, respectively (17). Chondritis occurred in up to 19% of patients treated with BT, although

this was likely to be the result of radiation dosages that were higher than currently used in clinical practice (7). Image guided brachytherapy may further diminish cartilage related toxicity. No statistically significant risk factors could be identified for the relatively frequent occurrence of chondroradionecrosis in our cohort. However, five out of six instances of chondroradionecrosis occurred within the first 6 years of the employment of this brachytherapy technique, suggesting that chondroradionecrosis has become less common as the treatment technique evolved over time.

Risk factors

Within the spectrum of nasal cavity and paranasal sinus malignancies, CNV constitute a distinct entity as these tumors display biological behavior similar to cutaneous carcinomas. Risk factors for the development of CNV include smoking, sunlight exposure, especially repetitive sunburn (2,28,29). Accordingly, nearly three quarters of our study population had smoked at least 10 pack years before disease diagnosis. Additionally, a potential relation between (sino)nasal malignancies and alcohol consumption has been described in previous literature, albeit less pronounced than in other types of head and neck cancer (30).

Staging

Currently two separate systems exist for the staging of CNV: the TNM-classification (8th edition, UICC) in which the nasal vestibule is included as a subsite for tumors of the nasal cavity, and the Wang staging system, which was tailored to specifically to the nasal vestibule. Although both systems have their (dis)advantages, several studies promoted the use of the Wang staging system instead of the TNM-system because of its relative simplicity and improved correlation with prognosis (2,13,25,31,32).

Patients with CNV typically present at an early stage. In two separate studies from the nationwide database of the Danish Head and Neck Cancer Group, Agger *et al.* reported that in a study population of 174 patients, 90% presented with T1 or T2 disease (Wang) (2). Similarly, in a more recent study by Filtenborg *et al.*, 92% of 146 patients presented with T1 or T2 disease (UICC) (25). For these early stage tumors, both surgery and radiotherapy have shown similar oncological outcomes (5–10,25). However, surgical resection increases the risk of facial disfigurement and the need for subsequent reconstruction or prosthesis (5,11). Hence, radiotherapy has become the preferred method of treatment for early-stage CNV. Multiple studies have confirmed superior outcomes for BT, compared to EBRT (14,15,17,24,32,33). Both Bussu *et al.* and Tagliaferri *et al.* reported improved nasal function and aesthetics in favor of BT (24,33). Moreover, in the largest multicenter study ($n = 225$) of radiation therapy in CNV, Czerwinski *et al.* noted that BT yielded better local tumor control and nose preservation over EBRT (17). Although, selection bias plays a critical role in this study.

Distant metastases seem to be rare in CNV and have been known to occur in lungs, bones, and skin (14,17). In a nationwide retrospective cohort of 162 CNV patients by Filtenborg *et al.*, 3% of patients presented with distant metastases. Following treatment, 1 patient in our study population developed lung metastases. In a cohort of 225 patients with T1 and T2 CNV who were treated with either BT or EBRT, 3-year distant metastases-free survival was 97% (17). Here, the researchers found no difference in incidence between BT and EBRT. In other studies, distant metastases-free survival ranged from 81% to 100% at varying follow-up duration (10,14,15,21,32,34). Whether these metastases arose more often in patients with more advanced disease, or in patients treated with EBRT, was not consistently disclosed. Yet, multiple studies of CNV patients treated with either BT or EBRT mentioned no distant metastases during follow-up (8,9,13,27).

Brachytherapy technique

As stated previously, a mold-based combined intracavitary and interstitial PDR brachytherapy technique was employed for the treatment of our patients. It is important to note, however, that techniques differ between studies. There is a plethora of different brachytherapy techniques (intracavitary, interstitial, or a combination, with template or with mold, PDR or HDR) used in treatment of CNV (6,7,9,10,13–15,27,32,33). Techniques used are not always described in detail, and specific dosimetric issues are seldom described. The use of 3D printed mold, like the present study, is not common. The benefit of this technique is the personalized and image guided aspect. The downside of intracavitary catheters is the increase of mucosal dose, leading to a possible increase of mucosal toxicity (i.e., ulcers). By combining intracavitary with a few interstitial catheters it is possible to limit this surface dose, without the need for a very invasive approach with many interstitial catheters. The present study shows that this combined approach appears safe with only limited long term toxicity. Which technique yields the best oncological outcomes and most beneficial toxicity profile in the treatment of CNV remains to be investigated. A prospective, European multicenter registration study on this topic is soon to be started.

Limitations

Several limitations have to be taken into consideration. Firstly, selection bias is inherent to a retrospective cohort study design. Second, statistical analyses were impaired due to small subgroups and the infrequent occurrence of endpoints (recurrence, disease-specific death). The difference between our findings and the above-mentioned literature must thus be placed in the context of said sample size.

Thirdly, missing data formed another limitation, especially with regards to incomplete reports on toxicity and lack of quality of life data.

Conclusions

Mold-based PDR brachytherapy offers excellent oncological outcomes based on our findings in a group of 68 patients with early-stage CNV who were treated over a 17-year period. Brachytherapy is a safe and effective treatment for early stage CNV. All recurrences occurred within 3 years after treatment, suggesting follow-up could be limited to 3 years without compromising on a patient's safety.

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