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Original Article

Radiotherapy as nose preservation treatment strategy for cancer of the nasal vestibule: The Dutch experience

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ABSTRACT

Background and purpose: Primary radiotherapy is often preferred for early-stage cancer of the nasal vestibule (CNV), combining high disease control with preservation of nasal anatomy. However, due to practice variation and an absence of comparative trials, no consensus exists on preference for brachytherapy (BT) or external beam radiotherapy (EBRT). We compared these modalities in terms of disease control, nose preservation rates and toxicity.

Materials and methods: Medical records of 225 patients with T1-T2 squamous cell carcinoma of the nasal vestibule treated with 3D image-guided primary radiotherapy between Jan 2010 and Dec 2016 in 6 Dutch institutions were reviewed retrospectively.

Results: 153 of 225 patients were treated with BT, 65 with EBRT and 7 with other modalities. Median follow-up was 46 months. Overall 3-year local control (LC) and regional control (RC) were 87% and 89%. Five-year disease-specific survival (DSS) and overall survival (OS) were 94% and 82%. Three-year survival with preserved nose (SPN) was 76%.

BT provided higher 3-year LC (95% *vs* 71%, $p < 0.01$) and SPN compared with EBRT (82% *vs* 61%, $p < 0.01$). Multivariable and propensity-score-matched cohort analyses confirmed better outcomes after BT. No difference was seen in DSS or OS. Five-year incidence of CTCAE 5.0 grade $\geq$2 toxicity was higher after BT (20% *vs* 3%, $p = 0.03$) and consisted mostly of radiation ulcers. 50% of all late toxicity recovered.

Conclusion: In this largest-to-date multicenter analysis of T1-T2 CNV, BT achieved superior LC and SPN compared with EBRT. Grade 1–2 radiation ulcers occurred more frequently after brachytherapy, but were transient in half the cases. Considering these results, BT can be recommended as first-line treatment for T1-T2 CNV.

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Cancer of the nasal vestibule (CNV) is a rare form of squamous cell carcinoma with a yearly incidence of 0.32 per 100,000 [1]. Due to its readily visible location, CNV is often diagnosed early, and has a good prognosis when treated adequately [2]. Optimal treatment will result in cure with preservation of the nose, and cosmetically and functionally satisfactory outcomes. On the contrary, improper management can imply serious mutilation, since salvage treatment constitutes of nasal amputation.

Surgery and brachytherapy (BT) provide comparable, excellent oncologic results for early stage T1-T2 disease [3–6]. As surgical treatment usually results in disfiguring facial defects with need for reconstruction or prosthesis [3], radiotherapy is often preferred for preservation of cosmesis and nasal function [5,7–10].

Both BT and external beam radiotherapy (EBRT) are used routinely in clinical practice. However, no randomized trials comparing BT and EBRT have been performed, and only few retrospective comparisons are available [9,11–13]. Hence, no clear consensus on radiotherapy treatment strategy for T1-T2 CNV has been established. Treatment choice appears to depend on patient and disease characteristics, as well as institutional preference and expertise.

BT allows for a higher tumor dose, potentially resulting in better local control (LC), thereby limiting the need for mutilating salvage nose amputations. EBRT provides a more homogeneous dose distribution, possibly reducing the incidence of late radiation toxicity. Still, it is unclear whether and how one modality outweighs the

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other in terms of tumor control and long-term sequelae. For CNV, this is particularly relevant with regard to organ preservation and functional outcomes.

Our previous single-center research provided a detailed analysis of BT results, showing excellent tumor control and patient satisfaction [5,10]. Furthermore, a subgroup of patients at increased risk of nodal recurrence was identified. To further increase knowledge of this rare tumor, a multi-center cohort study was performed. Primary aims were to compare oncological outcomes, nose preservation rates and late toxicity between BT and EBRT. The secondary objectives was to identify risk factors for local–regional disease relapse.

Materials and methods

Study population

A pilot questionnaire was distributed to radiation oncologists in all head and neck oncology centers in the Netherlands. Six centers treating CNV with primary radiotherapy agreed to participate. Patient referral during the investigated period was based mainly on location, with smaller hospitals referring patients to the nearest center of expertise.

Medical files of patients treated for early-stage (Wang T1-T2 [14]) CNV with primary radiotherapy between Jan 2010 and December 2016 across 6 Dutch head and neck centers were included. Tumors were restaged according to the Wang staging system by reviewing clinical data and imaging. Ethical board approval was obtained in the initiating center, along with additional local ethical board reviews. Pre-selection of participants was performed automatically using electronic health record software, according to the abovementioned criteria.

Staging

Clinical evaluation and histopathologic confirmation was performed for all patients and reviewed by local multidisciplinary head and neck oncology teams. Further staging usually consisted of ultrasound examination of the neck, fine-needle aspiration of suspected lymph nodes and chest X-ray. Larger tumors were often assessed by MRI. Two centers incidentally performed additional FDG-PET-scans.

Radiation therapy

Three centers used high-dose rate (HDR) BT only, two EBRT only, and one both. EBRT with brachy boost and orthovoltage X-ray treatment were employed rarely, each in one center for 2 and 5 patients, respectively. A detailed overview of radiotherapy techniques and dosages is provided in supplementary material 1.

3D-image guided treatment planning was used for all patients, except in orthovoltage X-ray treatment. Prescribed radiation doses varied between 44 Gy and 70 Gy. Because of institutional variation in BT implantation techniques, treatment planning practices and dose reporting, no isoeffect calculations were performed.

Follow-up

Patient follow up was scheduled according to local protocols. During treatment, patients were evaluated regularly by the treating radiation oncologist. After treatment, alternating follow-up visits with the radiation oncologist and head-and-neck surgeon were scheduled at regular intervals for three to five years.

When local or regional recurrence was suspected, imaging was performed (ultrasound, CT, MRI and/or FDG-PET), and histopathological or cytological confirmation was obtained. Thereafter, patients were re-evaluated by the multidisciplinary tumor board for salvage therapy. After salvage treatment, follow up was extended to 5 years from the time of relapse. For distant metastases, radiological confirmation was deemed sufficient if clinically convincing.

Endpoints

Survival-related outcomes were measured from the date of treatment initiation until date of event. A disease-related event was defined by pathologically confirmed local–regional recurrence. In case of distant metastasis, radiological confirmation sufficed. Overall survival (OS) and disease specific survival (DSS) were defined as death by any cause, or due to CNV, respectively. For survival with preserved nose (SPN), nose amputation and death were considered competing events. Late toxicity data (radiation ulcers, septal defects and chondritis/chondronecrosis) were extracted from follow-up records of the treating physicians and retrospectively scored according to CTCAE 5.0 criteria [15].

Statistical analysis

Comparisons of baseline characteristics were performed using Mann-Whitney U and Fisher's Exact tests for continuous and categorical variables respectively. Patients treated with combined EBRT + BT and orthovoltage X-rays were excluded from analyses where BT *vs* EBRT were compared due to small sample sizes. Actuarial outcomes were calculated using the Kaplan-Meier estimator. Log-rank tests were performed for univariable subgroup analyses. *P* values $\leq$0.05 were considered statistically significant. Clinically relevant variables and variables with *p*-value <0.20 in univariable analysis were included in backward elimination Cox regression analysis for multivariable examination of survival endpoints. For LC and SPN, additional associative Cox regression tests were performed, with stepwise adjustment for age, smoking status, T-stage and tumor diameter as possible confounders.

For propensity-score matching, multivariable logistic regression analysis was performed, predicting treatment by radiotherapy modality (BT *vs.* EBRT) adjusted for baseline prognostic factors (T-stage, age, sex and smoking status). Patients that received EBRT were matched without replacement to BT patients on a 1:1 basis, using a narrow propensity-score-match tolerance of 0.01 [16]. Analyses were performed using SPSS version 25 (IBM, Armonk, NY).

Results

225 patients with T1-T2 CNV treated with primary radiation therapy between January 2010 and December 2016 were identified, with a median follow-up time of 46 months (range 1–113 months). An overview of baseline characteristics can be found in Table 1. Additional information on patients treated and techniques used per center is provided in supplementary material 2.

Four patients had nodal spread at presentation (two N2b and two N2c disease). Three of these patients underwent combined neck dissection and BT catheter implantation, followed by BT for the primary tumor and post-operative regional EBRT afterwards. One patient received EBRT only, for both the primary tumor and neck.

Two cN0 patients underwent EBRT + BT boost for the primary tumor and received elective nodal irradiation. Comparing patient and tumor characteristics, there were more T2 tumors and non-smokers in the EBRT group (Table 1).

Overall 3-year LC was 87%. One local recurrence was observed after 3 years. BT provided significantly higher 3-year LC compared to EBRT (95% *vs* 71%, $p < 0.01$) (Fig. 1A). This effect persisted after

Table 1
Overall baseline characteristics and BT *vs* EBRT comparison.

	Overall population	BT	EBRT	p-value	Excluded[#]
No. of patients	225	153	65		7
Mean age (range)	67.3 years (40–88)	67.5 years	66.9 years	0.92[*]	
Sex				0.46[§]	
Male	119 (52.9%)	78 (51%)	28 (43.1%)		
Female	106 (47.1%)	75 (49%)	37 (56.9%)		
Smoking status				**<0.01**[§]	
Ever smoked	182 (80.9%)	133 (86.9%)	47 (72.3%)		
Never smoked	37 (16.4%)	16 (10.5%)	17 (26.2%)		
Unknown	6 (2.7%)	4 (2.6%)	1 (1.5%)		
T stage				**0.03**[§]	
T1	166 (73.8%)	120 (78.4%)	41 (63.1%)		
T2	59 (26.2%)	33 (21.6%)	24 (36.9%)		
N status				1[§]	
N0	221 (98.2%)	150 (98.5%)	64 (98.5%)		
N+	4 (1.8%)	3 (2%)	1 (1.5%)		
Mean tumor diameter (range)	1.39 cm (0.1–5.1 cm)	1.34 cm	1.52 cm	0.25[*]	
Tumor diameter category				0.6[§]	
<1,5cm	99 (44%)	63 (41.2%)	22 (33.8%)		
≥1.5cm	87 (38.7%)	76 (49.7%)	21 (32.2%)		
Unknown	39 (17.3%)	14 (9.2%)	22 (33.8%)		

Statistical significance in bold.
#Treatment with EBRT + BT boost and orthovoltage X-rays was excluded from BT *vs* EBRT comparison.
[*]Mann-Whitney *U* test.
§Two-tailed Fisher's exact test.

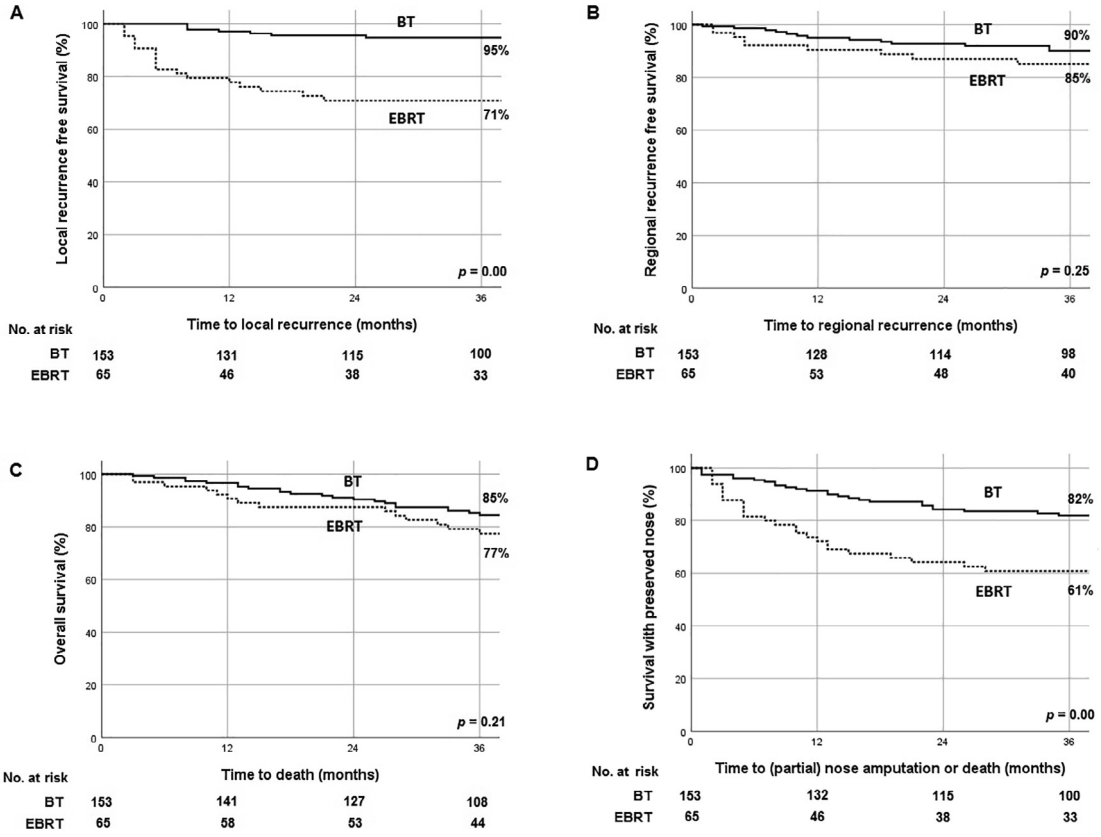

Fig. 1. Survival end point comparison, BT *vs* EBRT.

multivariable adjustment for possible confounders. An overview of univariable analyses can be found in supplementary material 3. In multivariable risk factor analysis, treatment with EBRT was the sole significant risk factor for local recurrence (Table 2).

In case of local failure (n = 27), curative salvage treatment was performed in 24 cases (89%) and consisted of total nose amputation (n = 18), total nose amputation with adjuvant EBRT (n = 3) or partial nose amputation (n = 3). Primary re-irradiation with EBRT (27 × 2 Gy) was employed once. Two patients received best supportive care. Local salvage was successful in 18 out of 24 cases (75%), resulting in 3-year ultimate local control of 96%.

Three-year regional control (RC) for all patients was 89%. Thirteen of 22 regional recurrences occurred in the first year of follow-up. No recurrences were observed after 34 months. No sig-

Table 2
Multivariable Cox regression analysis of survival endpoints.

	Local failure	Regional failure	Nose amputation or death	Death	Disease-specific death
	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI
Age (per year)	1.01 (0.95–1.06)	1.03 (0.98–1.08)	**1.05 (1.02–1.09)**	**1.08 (1.04–1.13)**	1.04 (0.97–1.12)
Treatment modality (EBRT vs BT)	**7.09 (2.6–19.2)**	1.08 (0.34–3.45)	**2.8 (1.47–5.36)**	1.81 (0.77–4.26)	2.32 (0.61–8.82)
Tumor diameter (≥vs <1.5 cm)[#]	1.59 (0.61–4.13)	**8.24 (1.87–36.3)**	1.13 (0.61–2.11)	1.37 (0.65–2.89)	**10.50 (1.32–83)**
Age (per year)	1.00 (0.95–1.04)	1.02 (0.97–1.07)	**1.04 (1.01–1.08)**	**1.08 (1.04–1.13)**	1.04 (0.98–1.11)
Treatment modality (EBRT vs BT)	**6.60 (2.73–16)**	1.48 (0.62–3.50)	**2.66 (1.53–4.65)**	1.80 (0.90–3.6)	1.92 (0.62–5.9)
T-stage (T2 vs T1)[#]	1.26 (0.55–2.88)	2.3 (0.98–5.38)	1.20 (0·66–2.17)	1.01 (0.48–2.11)	1.09 (0.33–3.57)

Abbreviations: HR, hazard ratio; CI, confidence interval. Statistical significance in bold.
#Due to a correlation between tumor diameter and T-stage these variables were analyzed separately.

nificant difference in 3-year RC was observed between BT and EBRT (Fig. 1B).

In univariable analysis, both tumor diameter ≥1.5 cm and T2 stage were found to be significant risk factors for regional recurrence (table 2), with 3-year RC rates of 83% and 81% respectively. In multivariable analysis, tumor diameter ≥1.5 cm (table 2) and T-stage both remained significant. T-stage and diameter were not simultaneously entered in multivariable analysis due to mutual association. Substitution of diameter by T-stage provided a significant hazard ratio of 2.45 (1.05–5.7) for T2 stage.

If regional failure occurred (n = 22), salvage treatment was attempted in 18 cases (82%). Neck dissection of involved and adjacent levels (n = 9), with adjuvant EBRT in case of extra-nodal extension or multiple pathological nodes (n = 9) were common strategies. Two patients received palliative EBRT of the neck (8 × 4 Gy and 10 × 3 Gy). Two patients received best supportive care. Six attempted salvage treatments were unsuccessful. Three-year ultimate regional control including successfully salvaged cases was 95%.

Three-year OS and DSS for all patients were 82% and 94%, respectively. Both OS and DSS did not differ between patients treated with BT and EBRT (Fig. 1C). In multivariable risk factor analysis, tumor diameter ≥1.5 cm was a significant risk factor for DSS (Table 2).

Local and regional recurrence both had significant impact on OS and DSS in univariable analysis. Three-year OS and DSS were 57% *vs* 86% (p < 0.01) and 68% *vs* 98% (p < 0.01) for local recurrence *vs* no recurrence, respectively. For regional recurrence *vs* no recurrence, 3-year OS and DSS were 46% *vs* 86% (p < 0.01) and 60% *vs* 98% (p < 0.01) respectively.

Distant metastases (DM) were rare (n = 7) and occurred in the lungs, bones and skin. All patients with DM had synchronous (n = 2) or previous (n = 5) regional recurrences. Overall 3-year metastasis-free survival (MFS) was 97%. No difference in MFS was found between BT and EBRT.

For all patients, 3-year SPN was 76%. SPN was significantly higher for BT when compared with EBRT (82% *vs* 61%, p < 0.01) (Fig. 1D). EBRT remained a significant risk factor for lower SPN in multivariable risk analysis (Table 2) and after adjustment for all possible confounders.

Propensity-score matching provided 57 well matched case pairs (Table 3A). An overview of matching statistics and the improvements in Cohen's d of baseline statistics can be found in supplementary material 4.

Multivariable risk factor analysis in the propensity-score-matched cohort showed that treatment by EBRT was a significant risk factor for local recurrence and decreased survival with preserved nose (Table 3B).

Radiation toxicity-free survival at 5 years was 71%. Radiation ulcers, septal defects and chondronecrosis had overall 5-year incidence rates of 24%, 10% and 4%, respectively. According to CTCAE 5.0 scores [15], late toxicity was grade 1 for 23 patients, grade 2 for 18 patients and grade 3 for three patients. Recovery of toxicity, with or without treatment, occurred for 52%, 44% and 67% of grade 1, 2 and 3 sequelae, respectively (Fig. 2A).

Table 3
Propensity-score-matched cohort analysis.

A: Group characteristics

	All	BT	EBRT	p-value
No. of patients	114	57	57	
Mean age (range)	67.7 years (40–88)	67.5 years	67.4 years	0.79[#]
Sex				
Male	71 (62.3%)	21 (37%)	22 (39%)	1.0*
Female	43 (37.7%)	36 (63%)	35 (61%)	
Smoking status				
Ever smoked	93 (81.6%)	47 (82.5%)	46 (80.7%)	1·0*
Never smoked	21 (18.4%)	10 (17.5%)	11 (19.3%)	
T stage				
T1	79 (69.3%)	39 (68.4%)	40 (70.2%)	1.0*
T2	35 (30.7%)	18 (31.6%)	17 (29.8%)	

B: Multivariable Cox regression analysis of local control and survival with preserved nose

	Local failure	Nose amputation or death
	HR 95% CI	HR 95% CI
Age (per year)	1.04 (0.98–1.10)	**1.07 (1.02–1.12)**
Treatment modality (EBRT vs BT)	**5.06 (1.69–15.1)**	**3.11 (1.43–6.79)**
T-stage (T2 vs T1)	2.07 (0.88–4.95)	1.70 (0.82–3.50)

#Mann-Whitney U test.
*Two-tailed Fisher's exact test.
B: Multivariable Cox regression analysis of local control and survival with preserved

Common treatments for ulcers were antimicrobial or corticosteroid ointments (n = 15), hyperbaric oxygen (n = 10), pentoxiphyllin (n = 3) and surgery (n = 2). Chondronecrosis was treated with hyperbaric oxygen (n = 3) or surgery (n = 1). Septal defects were mostly left untreated, rarely receiving hyperbaric oxygen therapy (n = 2) or septal buttons (n = 2). Smoking patients were urged to quit at consultation.

Five-year any toxicity free survival, and grade ≥2 toxicity free survival were both lower after BT compared to EBRT (60% *vs* 93%, p < 0.01 and 80% *vs* 97%, p = 0.03 respectively, Fig. 2B). Ulcers occurred significantly more often after BT compared with EBRT (34% *vs* 4%, p < 0.01), but incidence of septal defects and chondronecrosis did not differ.

Discussion

Local control

Three-year LC rates were 95% and 71% for BT and EBRT, respectively. Significantly higher LC after BT remained present in multi-

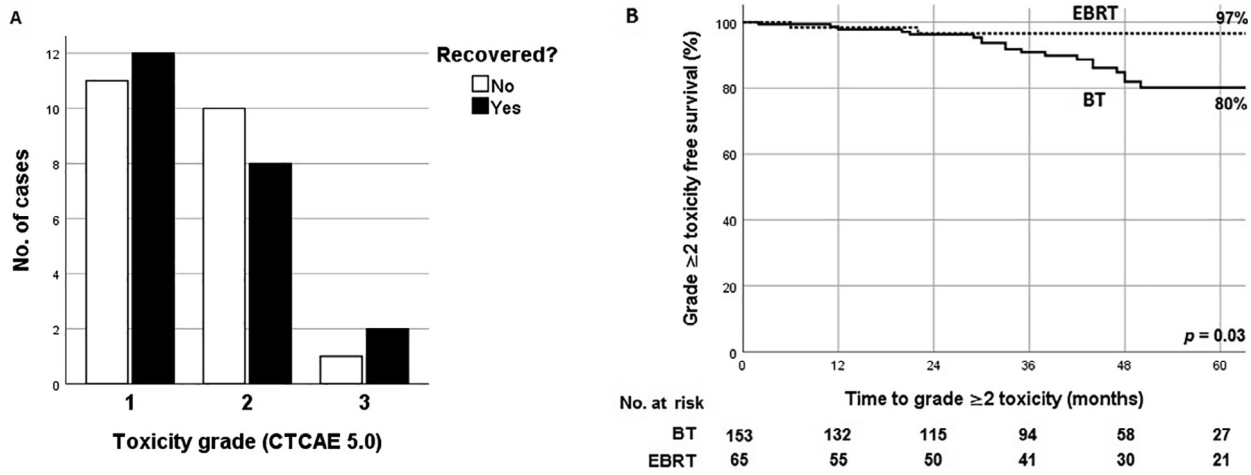

Fig. 2. Toxicity recoverability and BT *vs* EBRT comparison.

variable analysis. Improved LC achieved with BT is not surprising, as BT allows for higher localized doses to small volumes, and a shorter overall treatment time. Excellent BT results confirm findings from previous retrospective analyses [5,7–11]. Prior single-center analyses of T1-T2 CNV treated with HDR BT by Lipman et al. [5], and the update by Czerwinski et al. [10], report 3-year LC of 91% and 5-year LC of 95%, in cohorts of 60 and 102 cases, respectively. In a similar cohort, Levendag et al. reported a 5-year LC of 92% among 64 patients [7].

For EBRT, Horsmans et al. report 5-year recurrence free survival of 66% among 41 patients with mostly T1-T2 disease, with 76% of recurrences being local [17]. Langendijk et al. report 2-year LC rates of 79% in 56T1-T2 tumors treated with EBRT, or EBRT with BT boost [8]. In a mixed BT-EBRT series of Vanneste et al. local recurrences occurred only after EBRT, resulting in 5-year LC of 55%, but with selection bias of T2 tumors being treated more often with EBRT [9]. Wray et al. present another mixed series of 99 patients, with 5-year LC of 100% and 84% for BT and EBRT, respectively [11]. Kummer et al. reported equivalent LC between BT and EBRT, achieving local remission in 40 out of 44 T1-T2 CNV patients [13].

In conclusion, literature shows trends of increased LC using BT, albeit that EBRT is employed more often for T2 tumors. Higher T-stage was associated with decreased LC in the study by Vanneste et al. [9]. However, in series investigating only BT, generally no such correlation is found [5,7,10,18]. In the current study, LC was not worse for T2-stage. Furthermore, multivariable adjustment for T-stage and diameter did not reject superiority of BT in LC, despite T2 tumors being more prevalent in the EBRT cohort. Finally, the propensity-score-matched cohort analysis further substantiated this hypothesis, as the higher risk of local failure following EBRT compared to BT persisted even after the ratio of T2 tumors was equalized.

Survival with preserved nose

Twenty-four of 27 patients with local failure underwent salvage treatment, with a success rate of 75% and ultimate control rate of 95%. Similar results with ultimate LC rates ranging between 93–98% at two to five years have been reported previously [5,8,10,11,19].

However, all curative salvage attempts implied either total nose amputations (n = 21), or partial nose amputations (n = 3). Despite high ultimate LC, nose amputations are mutilating, with significant impact on functioning and quality of life [20,21]. Therefore, avoiding salvage surgery should be an important consideration in management of early-stage CNV management.

To account for nose amputations in relation to survival, we calculated the SPN. Three-year SPN was higher after BT when compared to EBRT (82% vs 61%, p < 0.01), and this effect remained significant after multivariable adjustment for confounders and also in the propensity-score-matched cohort analysis.

Toxicity

Overall 5-year radiotherapy-induced long-term toxicity was 29% for all grades and 15% for grade ≥2. Radiation ulcers, septal defects and chondronecrosis occurred in 24%, 10% and 4% of cases, respectively. Nasal crusts and dryness, both often observed in patients [7,13], were not recorded in the current study, as reporting in the patients' charts was incomplete. In literature, variation in toxicity reporting complicate putting our results into context. Lipman et al. reported a 19% incidence of chondritis after interstitial BT, albeit that about 40% of the patients were treated with a higher dose than currently employed in interstitial BT [5]. Vanneste et al. reported an overall late sequelae incidence of 28% in a mixed BT-EBRT series, with 11% of patients complaining of epistaxis [9]. Wallace et al. reported complications in 21% of 71 patients after definitive BT or EBRT, the majority of which was self-limiting soft tissue necrosis [19]. Bacorro et al. scored toxicity according to RTOG criteria in patients with squamous cell carcinoma of the nasal vestibule or nasal cavity treated with low-dose-rate and pulse-dose-rate BT. They reported any grade sequelae in 56% of 34 patients and, most severely, grade 3 chondronecrosis in two patients and grade 3 fibrosis in one [18].

In the current study, radiation ulcers in particular were observed more frequently after BT. Due to physical properties of BT, locally delivered doses can exceed the prescription dose up to 200% in close proximity to the source position, resulting in higher strain to surrounding normal tissues, albeit to small volumes. It is also worth noting that the BT cohort had significantly more smoking patients, as smoking is associated with worse outcomes and increased late toxicity rates in HNC treated with radiation therapy [22].

However, most of reported toxicity was grade 1, and up to 50% of all complications was self-limiting or recovered with treatment. Furthermore, in previous research, we reported patient satisfaction using the NAFEQ questionnaire [23], resulting in scores of 3.7 and 4.0 of 5 for cosmetic and functional satisfaction, respectively [10]. Levendag et al. reported good to excellent cosmetic and functional results in a dedicated follow-up study [7]. Research by Bussu et al. and Tagliaferri et al. demonstrated high cosmetic satisfaction [24] and better nasal function after BT compared to EBRT [25]. Better nasal function may be attributed to a decreased low-to intermedi-

ate dose bath to the entire nose achieved by BT for small tumors. Overall, current experience suggests that BT-related late sequelae usually do not impact patient satisfaction in a major way.

Regional control

RC at 3 years was 89% for all patients and did not differ significantly between BT and EBRT. Most relapses occurred in the first year after treatment. Talmi et al. reviewed lymph node metastases in all stages of CNV, and reported RC rates varying between 60–96% [26]. A pooled meta-analysis on various stages of both nasal cavity and vestibule squamous cell carcinoma by Scurry et al. showed a pooled 82% RC rate [27]. In studies on T1-T2 CNV, RC rates usually are around 90% [7,8,10,13,18].

Management of the neck in T1-T2N0 CNV is an ongoing matter of debate. Elective treatment is generally not recommended after adequate staging [26,27]. However, previous studies revealed a subgroup with tumor diameter $\geq$1.5 cm or tumor volume $\geq$2.3 cm^3 at increased risk of regional recurrence, despite routine ultrasound examination of the neck [5,10].

In the current study, tumor diameter $\geq$1.5 cm and T2 stage were identified as risk factors for regional failure, with 3-year regional recurrence rates of 17% and 19% respectively, confirming previous findings. Although neck dissection cured more than half of the regional recurrences, in 10 out of 22 cases it was either not feasible, or failed.

Therefore, elective neck treatment could be considered for CNV patients with tumor diameter $\geq$1.5 cm, or T2 stage. Alternatively, an attempt could be made to improve neck staging, by imaging such as PET-CT [28], or by introducing sentinel node biopsy, as is the standard of care in oral squamous cell carcinoma [29].

Overall- and disease-specific survival

3-year OS and DSS were 82% and 94% for all patients, respectively, with no differences between treatment modalities. In a review by Mukai et al. encompassing all stages of CNV, OS was ranging between 50 and 92% at 3–5 years [12]. In literature on T1-T2 disease specifically, 5-year OS rates vary between 59 and 82%, and 5-year DSS is high, ranging between 87 and 97% [7,8,10,18].

For DSS, tumor diameter $\geq$1.5 cm came forward as a risk factor in multivariable analysis. Since tumor diameter $\geq$1.5 cm was also found to predict for regional recurrence, and regional failure significantly influenced DSS, the impact of tumor diameter on RC appears to be reflected in DSS rates.

Limitations

Selection bias and missing data are inherent to the retrospective nature of this, and all other studies in the literature. This is a particular problem with toxicity reporting, as recognition, severity estimation and grading are all subject to the treating physician's opinion. Another limitation is the lack of patient-reported outcomes such as nasal function and cosmetic satisfaction. A dedicated study on nasal function, appearance and quality of life comparing BT and EBRT could further substantiate clinical decision making.

Conclusion

In this largest-to-date multicenter analysis of T1-T2 CNV, BT yields considerably better local tumor control and survival with preserved nose over EBRT. Radiation ulcers occurred more often after BT, but were nearly all grade $\leq$2 and transient in half of the cases. Therefore, BT can be recommended as first line treatment for T1-T2 CNV.

Influence of funding sources

None.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.08.018.

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