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Functional results of exclusive interventional radiotherapy (brachytherapy) in the treatment of nasal vestibule carcinomas

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ABSTRACT

PURPOSE: Surgery, external beam radiotherapy (EBRT), and interventional radiotherapy (IRT, BrachyTherapy BT) are the current therapeutic options for nose vestibule (NV) squamous cell carcinoma (SCC). In this article, we evaluate the nose functional parameters of patients affected by SCCs of the NV, primarily treated by interstitial IRT comparing them with healthy controls and with patients treated with intensity-modulated EBRT.

METHODS: Ten patients treated by using IRT (group 1), 10 healthy controls and eight patients treated by EBRT (group 2) on the region of the nose were submitted to clinical evaluation (with the NOSE scale score), rhinomanometry, olfactory testing, nasal citology, and evaluation of mucociliary clearance through saccharine test.

RESULTS: No long-term skin or cartilaginous toxicity are recorded. The olfactometry threshold discrimination identification TDI is lower in EB group. The mean NOSE scale score was significantly higher in group 2 than in group 1 and healthy controls ($p < 0.05$). The distribution of cytologic patterns resulted significantly different as well. Patients treated by EB have a significantly impaired mucociliary clearance, with a mean time for the transport of the stained marker, which is more than double in the patients treated by EB than in those treated with IRT ($p < 0.001$).

CONCLUSIONS: Nasal function and cytological findings are significantly better, substantially preserved, in patients treated by IRT than in those treated by EBRT, bringing new relevant evidence for the establishment of interstitial IRT as the new standard for the treatment of the primary lesion in cT1 and cT2 -Wang staging NV SCCs.

Keywords: Nasal vestibule carcinoma; Brachytherapy; External beam radiotherapy; Mucociliary transport; Olfaction; Nasal cytology

Introduction

The NV is defined as that part of the anterior nasal cavity that is lined by squamous epithelium up to the limen nasi, which is the mucocutaneous junction [1]. Squamous cell carcinoma (SCC) of the nasal vestibule (NV) is a relatively rare condition believed to account for about 1% of all head and neck malignancies. A Danish group recently estimated, as a rounded down approximation, an annual incidence of

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SCC of the NV of 0.41 per 100.000 inhabitants [2]. The anatomical location and the rarity of the disease itself contributes probably to further underestimate their incidence, as these malignancies are often classified as skin cancers or as nose cancers, but seldom as a specific different entity. A consensus about the optimal staging system is lacking [1–4], as an old classification of primary lesions (T), specific for the nose vestibule (NV), proposed by C. C. Wang [5], has been reported to predict prognosis better than recent AJCC/UICC T classification for nose cavity malignancies [1, 6, 7].

Surgery, external beam radiotherapy (EBRT), and interventional radiotherapy (IRT, brachytherapy, BT) are the current therapeutic options in clinical practice [7–9]. When choosing one of these treatment modalities for vestibule SCCs, as for the other head and neck malignancies, functional issues are being currently taken into increasing consideration.

Among such functional issues there is for sure the esthetic appearance, which can be deeply impacted by any therapeutic procedure involving the nose and the nose vestibule in particular [4].

Also, the nose is primarily part of the respiratory system, being the first section to be passed through by inhaled air. All the other main physiologic functions derive mostly from this specific condition. In fact, on one hand the nose allows an adequate sampling of molecules to be analyzed and recognized in the areas occupied by specialized cells, which are responsible for smelling (olfactory cells part of the olfactory system), directly influencing also the perception of taste. For the proper functioning of the olfactory system, both an adequate airflow and functionally preserved olfactory cells are required in the nose. On the other hand, the frontline position toward inhaled air regularly exposes nose to altered environmental conditions as well as to environmental pollutants, respiratory pathogens, and aerosolized toxins. Thus, the nose has evolved multiple physiologic strategies to regulate flow speed, temperature, and humidification (somehow conditioning the inhaled air headed to bronchi and alveoli) of the inspired air, as well as to tightly modulate its ability to protect and defend itself and the respiratory system as a whole. Among such physiologic strategies, there are the maintenance of adequate intranasal resistances within the physiologic variations due to the nasal cycle [10], the sneeze reflex [11], and the complex immunological and mechanical defensive system constituted by the nose mucosa, with all its cellular components (both in the ciliated epithelium and in the stroma) and by the mucous itself. One of the most characteristic and well-known expression of such defensive system is the mucociliary clearance.

Disruption of any of the above-cited physiologic functions can be secondary to gross anatomic variations, as after oncological surgery, or to other pathological processes involving and impairing one or more of the above-cited mechanisms, mainly at the level of nose mucosa, as in case of irradiation.

In the present study, we evaluate for the firstime nose functional parameters of patients affected by SCCs of the NV, primarily treated by exclusive interstitial IRT, comparing them with matched healthy controls and with patients treated with external beam intensity-modulated radiotherapy (IMRT).

Methods

Study population and study design

We evaluated 19 consecutive previously untreated patients affected by NV SCC treated at Fondazione Policlinico Universitario Agostino Gemelli IRCCS institution through interstitial IRT between 2012 and 2017 [12]. We adopted the Wang staging system for T, while still using the AJCC system for N classification. We classified vestibular SCCs in three groups, according to the subsite of origin, and namely ‘‘ala/limen nasi,’’ ‘‘columella/septum,’’ ‘‘inferior border/superior lip.’’ Patient and tumor characteristics are summarized in Table 1.

We always studied the neck at least with a contrast-enhanced computed tomography (CT). We recommended a comprehensive neck dissection (level I to Va) on clinically involved side of the neck, performing in non-involved sides of cN + cases a prophylactic neck dissection (level IA/B, II, and III). We also performed bilateral prophylactic neck dissection (level IA/B, II, and III) in the cT3 case.

We proposed an evaluation of nose function to the 12 patients without evidence of disease 24 months after the completion of IRT and 10 patients (Group 1– IRT cases)

Table 1
Characteristics of the 19 patients treated by brachytherapy for nose vestibule malignancy

Characteristic	
Age	
Median	66
Range	48–82
Sex, *n* (%)	
Male	11 (58)
Female	8 (42)
Karnofsky p.s., *n* (%)	
100	11 (58)
90	4 (21)
80	2 (10.5)
90	2 (10.5)
Subsite of primary, *n* (%)	
Ala/limen nasi	9 (47.4)
Inferior border/superior lip	4 (21)
Septum/columella	6 (31.6)
Wang T classification, *n* (%)	
T1	6 (31.6)
T2	12 (63.1)
T3	1 (5.3)
AJCC/UICC N classification, *n* (%)	
cN0	18 (94.7)
cN2b	1 (5.3)

accepted to be submitted to the tests, which included rhinomanometry, olphactometry, nasal citology, and evaluation of mucociliary clearance through saccharin test [13]. Median follow-up in IRT group has been 34 months (range 24–70). We compared the functional results of group 1 with eight patients irradiated by intensity-modulated external photon beams between 2007 and 2012, with a dose of at least 40 Gy in the area of nose vestibulum for nasal/ethmoid/vestibular malignancies (Group 2—*EB cases*), and with 10 sex and age matched healthy subjects, with no history of rhinosinusitis or nasal symptoms (healthy controls) (see Table 2).

IRT at our institution

Flexible Implant Tubes 6F were inserted, spaced 0.8–1.2 cm apart, using guide channels previously placed with a needle, and fixed by buttons sutured to the skin. The exact configuration and number of catheters had been tailored to the extent, depth, and shape of the lesion [4, 14, 15]. The implants were applied under general anesthesia by the head and neck surgeon under the supervision of radiation oncologist, taking care, while making the tubes run parallel, also of avoiding piercing both layers of perichondrium and the enclosed cartilage (''anatomic implantation'') and exposing the tubes in the nasal cavities (Fig. 1), to avoid perichondritis and septal/alar perforations. Knowledge of the surgical anatomy and in particular of the dissection planes during functional and cosmetic surgery of the nose, is fundamental to this aim.

The dose was prescribed encompassing the full clinical target volume (CTV) and sparing as much as possible the surrounding healthy structures. The tumor is irradiated by a standardized fractionation: 44 Gy total dose, 3 Gy per fraction, except first and last fraction 4 Gy, two fractions per day (b.i.d.), 6 h interval between the fractions, maximum overall treatment time 10 days. After the procedure, all patients underwent a CT. CTV and organs at risk

Table 2
Clinical and functional parameters in the 28 subjects who accepted to undergo functional rhinologic evaluation

	Group 1 (10)	Group 2 (8)	Healthy (10)	Whole series (28)
Age (years)				
Median	56	66	58	60
Range	53–79	58–79	50–76	50–79
Sex, *n* (%)				
Male	6 (60)	6 (75)	7 (70)	19 (68)
Female	4 (40)	2 (25)	3 (30)	9 (32)
Karnofsky p.s., *n* (%)				
100	6 (60)	4 (50)	7 (70)	17 (60)
90	3 (30)	3 (37.5)	3 (30)	9 (32)
80	0	1 (12.5)	0	1 (4)
70	1 (10)	0	0	1 (4)
Time from treatment (in months)				
Median	34	64	-	45
Range	24–70	40–83	-	24–83
T stage, *n* (%)	Acc. to Wang	Acc. to AJCC		
T1	3 (30)	2 (25)	-	5 (28)
T2	7 (70)	3 (37.5)	-	10 (55)
T3	0	2 (25)	-	2 (11)
T4a	0	1 (12.5)	-	1 (6)
N stage, *n* (%)				
N0	9 (90)	2 (25)	-	11 (65)
N1	0	1 (12.5)	-	1 (6)
N2a	0	1 (12.5)		1 (6)
N2b	1 (10)	2 (25)	-	3 (17)
N2c	0	1 (12.5)	-	1 (6)
NOSE scale score, mean value + SD	9,5 + 1,2	16 + 1.9	8,1 + 1.1	33,6 + 1.7
Rhinomanometry parameters				
Total inspiratory flows (mL/s) (mean ± SD)	739 ± 259	959 ± 222	642 ± 312	726 ± 293
Total inspiratory resistances (Pa/ml/s) (mean ± SD)	0.26 ± 0.12	0.16 ± 0.03	0.29 ± 0.14	0.25 ± 0.12
Total expiratory resistances (Pa/ml/s) (mean ± SD)	0.25 ± 0.12	0.14 ± 0.02	0.29 ± 0.12	0.25 ± 0.12
Other functional parameters				
Olfactometry (TDI) (mean ± SD)	22 ± 6	16 ± 8.6	26 ± 5	23 ± 6.6
Mucociliary tMCT (minutes) (mean ± SD)	13 + 5.8	32 ± 2	17 ± 3	18.5 ± 8
Nasal cytology report, *n* (%)				
Normal	7 (70)	2 (25)	6 (60)	15 (54)
Neutrophilic flogosis with muciparous metaplasia	0	4 (40)	0	4 (14)
Neutrophilic flogosis	2 (20)	2 (25)	3 (30)	7 (25)
Eosinophilic flogosis	1 (10)	0	1 (10)	2 (7)

tMCT, transport time.

Fig. 1. A nose vestibule cT1 (according to Wang staging) squamous cell carcinoma (SCC) of the columella (a and b) treated by IRT (implants shown in c and d), with complete response and good cosmetic results 2 years after treatment (e and f).

(OARs) were then contoured and catheters were reconstructed. The treatment planning was implemented through Oncentra Brachy (Elekta) following the general rules of the Paris system, with manual optimization. The irradiation started in the second to third postoperative day. Dose homogeneity within CTV and dose to OARs were documented using dose−volume histogram. All patients were treated with an Elekta Micro-Selectron HDR machine containing an Ir-192 point-source (370 MBq).

Nasal function evaluation

All patient and controls underwent a nasal function tests including clinical evaluation, Mucociliary transport time (tMCT), nasal citology, rhinomanometry and olfactometry.

a .Clinical evaluation including NOSE scale questionnaire and nasal endoscopy. Patients were asked to complete a NOSE Scale questionnaire [16]. We obtained for every patient a total NOSE scale score from 0 to 20; rigid nasal endoscopy was performed in all subjects under local anesthesia with topical application of 2% xylocaine and using 0 degrees and 30 degrees, 4 mm diameter rigid nasal endoscope (Karl Storz, Germany). Nasal endoscopy was done by using the standard three-pass technique as described by Kennedy.

b tMCT. we used the method devised by Passali [13], we put a mixture of an insoluble substance (vegetable carbon powder) and a soluble one (saccharin, which is, however, subjectively detected by the sweet taste) on the nasal mucosa at the level of the head of the inferior turbinate; we considered as tMCT the time from the moment of deposition of the tracer to that of its appearance in the pharynx.

c .Nasal citology was performed on scraped nasal tissue, obtained from the inferior turbinate bilaterally. Scraping was performed using Rhinoprobe (Farmark s.n.c, Milan, Italy). The sample was gently spread on glass slides and immediately fixed in 95% ethyl alcohol and stained with May−Grunwald−Giemsa. The slides were examined under oil immersion by light microscopy at a magnification of ×1000. Cells were counted and categorized as neutrophils, eosinophils, mast cells, basophils, lymphocytes, epithelial cells and goblet cells. Cells counts were expressed as percentage of the total cells, at high power field, as the mean of at least 10 fields observed. The mean percentage of the cell type per 100 cells is reported. Neutrophilic flogosis was defined if neutrophils were >50% of total cells. Eosinophilic flogosis was

defined if eosinophils were > than 20% of total cells. Nasal mucosa metaplasia was defined when we observed a rearrangement of the epithelium in favor of mucous-secreting cells (mucous-secreting metaplasia). In this case, an increase of mucous-secreting cells and a decrease of ciliated cells were observed [17, 18].

d .Active anterior rhinomanometry (AAR) and nasal decongestion test (NDT). We performed AAR following the modalities codified by the Standardization Committee on Objective Assessment of the Nasal Airway (SCOANA) [19] AAR with a mask is our method of choice. The nasal mask was well adherent to the face without modifying the nasal structures. Baseline test and NDT were performed. The baseline test allows the objective exploration of the nasal respiratory function, through the measurement of airflow and resistance to the passage of air through the nasal cavities. For the execution of the examination, the patients were asked to suspend at least 1 week before any nasal topical therapy. The NDT was performed by nebulizing two puffs per nostril of a nasal decongestant with a short latency of action. We waited 5 min and repeated the administration of the drug. The test closes with a new rhinomanometric evaluation after another 5 min of waiting.

e .Olfactometry: All patients were studied through the Sniffin' Sticks olfactory test (Burghart instruments, Wedel, Germany), performing the threshold, detection and identification tests, as previously published [20]. All these tests were preceded by AAR, to measure the airflow and resistance of sinonasal cavities, and sensitized with nasal decongestion (realized by spraying two puffs per nostril of a nasal decongestant with short latency of action, naphazoline), to allow a correct odorants' diffusion to olfactory epithelium. Odorants were presented in felt tip pens. For odor presentation, the cap was removed for 3 s, and the pen's tip was placed at a distance of approximately 2 cm from both nostrils. Odor thresholds for n-butanol were assessed using a single staircase, three alternative forced choice (3-AFC) procedure. Sixteen dilutions were prepared in series starting from a 4% n-butanol solution (dilution ratio 1:2 in deionized water as solvent). Three pens were presented in randomized order, two containing the solvent and the third the odorant. Patients had to identify the odor-containing pen. Triplets were presented at intervals of approximately 20 s. Reversal of the staircase was triggered when the odor was correctly identified in two successive trials. Threshold was defined as the mean of the last four of eight staircase reversals. The subjects' scores ranged between 0 and 16. In the odor discrimination task, again using a 3-AFC, triplets of pens were presented in randomized order, with two containing the same, and one a different odorant. Subjects had to determine which of the three pens smelled different. Triplets were subsequently presented with a 20−30 s interval between them; the interval between the presentation of individual pens was approximately 3 s. Because 16 triplets were tested the subjects' scores ranged from 0 to 16. When measuring odor thresholds and odor discrimination, subjects were blindfolded to prevent visual identification. Odor identification was assessed for 16 common odors. Using a multiple choice task, identification of individual odors was performed through lists of four descriptors each. The interval between odor presentations was 20/30 s. Again, the subjects' scores ranged from 0 to 16. Finally, we calculated the threshold discrimination identification (TDI) score, with a range from 0 to 48. TDI values < 15 identify an anosmic subject, whereas values < 5 must not be considered as reliable.

Statistical analysis

Statistical analysis was implemented using the JMP in software, release 7.0.1, by the SAS institute. The α level was fixed at 0.05 for all statistical tests. Numeric parameters were first evaluated using ANOVA and then for the comparison between groups we used the Student's t test. Nominal variables among groups were compared using contingency analysis evaluating statistical significance through likelihood ratio and Pearson tests.

Results

Five-year disease-specific survival of the 19 patients with NV SCC primarily treated with interstitial IRT was 92.3%, the only disease related death occurring in the cT3 case who refused to undergo demolitive surgery and died 8 months after treatment. No long-term skin or cartilaginous toxicity are recorded in EB and IRT groups. In particular, no chondritis, chondronecrosis nor septal/alar perforations can be evidenced in the IRT group, probably thanks to the anatomic implantation technique.

Descriptive statistics of the functional parameters in the three groups is given in Table 2.

Symptom evaluation by NOSE scale score revealed that the mean NOSE scale score was significantly higher in patients of group II than those in group I and healthy controls ($p < 0.05$).

The results of rhinomanometry showed that patients in group 2 (treated with external beams) presented higher nasal flow and lower resistance than patients of group 1 and healthy controls ($p < 0.05$). In group I, nasal flow and resistance were quite similar to those in healthy control ($p > 0.05$).

The mucociliary clearance was significantly reduced in group 2 compared with group 1 and healthy control. The mean time for the transport of the stained marker was more than double in the patients treated by EB than in those treated with IRT ($p < 0.001$ at ANOVA and Student's t test).

The olphactometry TDI is lower in group 2 than group 1 and healthy control, and at Student's t test, a significant difference ($p < 0.05$) was detected.

The distribution of cytologic patterns resulted significantly different at contingency analysis ($p = 0.035$ at Likelihood Ratio test), with the mucous cell metaplasia being typical of the noses previously irradiated by EB, which display most often (75%) an abnormal cytology (Table 2).

Discussion

Interstitial IRT has been demonstrated to be an oncologically effective local treatment of primary SCCs of the NV, with control rates comparable with surgery [2, 4, 7, 15, 21, 22]. Nevertheless, when planning surgical treatment of these lesions, while obtaining a resection with clear margins is usually quite easy, the achievement of a satisfying esthetical restoration seems often almost impossible [1, 23] even if several options have been tried and suggested [24]. Differently from most of the other subsites in the head and neck region, free-flap surgery has had little or no impact on the management of cancers of the nasal vestibulum [23]. Therefore, according to several authors [2, 23, 25], bone-anchored prostheses remain the best option under an esthetical point of view in case of total rhinectomy defects. Also for these reasons, a clearly better satisfaction in terms of esthetical appearance in patients treated for NV SCC by interstitial IRT than those treated by surgery has been demonstrated [4], which leads us to prefer the first modality to treat the primary lesion in cT1 and cT2 cases according to Wang. In fact, considering the complex anatomy of nose tip, made up of thin skin covering cartilages, with small hollows and relieves, and its condition as the most exposed and the first noted area in the human face the best reconstructive option remains without doubts the preservation of the cartilaginous framework itself, which on the whole is pretty resistant to radiotherapy especially when perichondrium is preserved. We do believe that an anatomic implantation technique which avoids piercing perichondrium and cartilage, can optimize such esthetical results and avoid septal and alar perforation as in the present IRT series, differently from previous ones [21].

For the same reasons also external beam radiotherapy, with similar survival figures than IRT [2, 21, 22] is considered a valid alternative option also under an esthetical point of view [6, 8, 23, 26, 27] and is probably the most frequently recommended primary treatment in Western countries at present [8, 26]. Another extremely promising option for NV malignancy is the described combination of external beams and brachytherapy through a surface mold [28].

External beam radiotherapy harbors well-known acute and, most of all, late, toxicities, but a systematic evaluation of its impact on nasal functions in comparison with an oncologically comparable, if not better, option, as interstitial IRT, had never, to our knowledge, been performed. The nasal functions are notoriously affected by irradiation [29–31], and many complaints, as crusting [31], dry nose [32], dysosmia [30, 33], dysgeusia [30], in patients with a previous irradiation of nasal region are clearly linked to the disruption of physiological mechanisms by mucosal toxicity of radiotherapy [32, 34, 35]. In the present study, most of these previous data are confirmed with specific test as the nose after EB irradiation seems to have lower resistances, slower mucociliary clearance, impaired olfaction, and typical cytological alterations as mucous cell metaplasia, compared with controls. These data are suggestive of an atrophic condition of nasal mucosa that is associated to a paradoxical subjective sensation of nasal obstruction as demonstrated by the NOSE scale score data.

On the contrary, in patients treated with IRT, nasal function and cytological findings are substantially preserved when compared to healthy non-irradiated subjects. The rapid dose fall off of the IRT, exploited also in the adjuvant/perioperative setting [36, 37], with a drastic reduction of the irradiated mucosal surface inside the nasal/paranasal cavities, may be decisive factors for the functional preservation.

Conclusion

Such original evidence, together with the confirmation of oncological effectiveness, which remains of course the most relevant argument, and the very favourable eshtetic results, supports the establishment of interstitial IRT as the new standard for the treatment of the primary lesion in cT1 and cT2 (according to the Wang staging) NV SCCs.

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