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SMARCB1 (INI-1) Deficient Carcinomas of the Sinonasal Tract

Justin A. Bishop, M.D.^{1,2,*}, Cristina R. Antonescu, M.D.³, and William H. Westra, M.D.^{1,2,4}

¹Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland

²Department of Otolaryngology/Head and Neck Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland ³Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York ⁴Department of Oncology, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Abstract

SMARCB1 (*INI-1*) is a tumor suppressor gene located on chromosome 22q11.2. Its gene product is ubiquitously expressed in nuclei of all normal tissues. *SMARCB1* gene inactivation has been implicated in the pathogenesis of a diverse group of malignant neoplasms that tend to share “rhabdoid” cytomorphology. This group of *SMARCB1*-deficient tumors is now further expanded by a subset of carcinomas arising in the sinonasal tract. *SMARCB1* immunostaining was performed on 142 sinonasal carcinomas. Tumors that showed loss of expression were further characterized for *SMARCB1* deletions by fluorescence in situ hybridization (FISH). Nine of 142 (6%) primary sinonasal carcinomas showed loss of *SMARCB1* expression by immunohistochemistry. Five patients were women, and patients ranged in age from 33–78 years (mean 59). The *SMARCB1* deficient tumors were characterized by nests, sheets, and cords of cells without any histologic evidence of specific (e.g. squamous or glandular) differentiation. The tumors were comprised of varying proportions of basaloid and rhabdoid cells. The *SMARCB1* deficient carcinomas had been diagnosed as non-keratinizing squamous cell carcinomas (n=3), sinonasal undifferentiated carcinomas (n=2), myoepithelial carcinoma (n=2), non-intestinal adenocarcinoma (n=1) and carcinoma, not otherwise specified (n=1). FISH analysis revealed *SMARCB1* deletions in 6 of 8 (75%) carcinomas. The *SMARCB1* deficient carcinomas did not harbor human papillomavirus or NUT-1 alterations. Six patients presented with T4 disease, 5 patients developed local recurrences and/or distant metastases, and four died of their disease. Inactivation of the *SMARCB1* tumor suppressor gene appears to be involved in the pathogenesis of a subset of sinonasal carcinomas, further expanding the family of *SMARCB1* deficient neoplasms and further delineating a bewildering group of poorly/undifferentiated, aggressive carcinomas arising at this site. The ability to detect *SMARCB1* loss by immunohistochemistry, particularly when dealing with poorly differentiated carcinomas with basaloid or rhabdoid features, should facilitate a more comprehensive understanding of these sinonasal carcinomas including clinical behavior and response to targeted therapies.

*Address correspondence to: Justin A. Bishop, M.D., The Johns Hopkins University School of Medicine, 401 N. Broadway, Weinberg 2249, Baltimore, MD 21231, Telephone (410) 955-8116, Facsimile (410) 955-0115, jbishop@jhmi.edu.

Keywords

sinonasal tract; sinonasal undifferentiated carcinoma; SMARCB1; INI-1; SNF5; rhabdoid

Introduction

Carcinomas of the sinonasal tract account for 3% of those malignant neoplasms occurring in the head and neck,(1) and they afflict 0.5 to 1.0 patients per 100,000 per year.(2, 3) Although some of these are squamous cell carcinomas, the sinonasal tract is a site where highly aggressive and poorly differentiated carcinomas that defy straightforward histologic subclassification are often encountered. The mechanisms underlying the development of sinonasal cancer are also elusive. Exposure to occupational carcinogens (e.g. wood dust, formaldehyde) has been implicated in a only a small subset of sinonasal carcinomas, and the link between cigarette smoking and cancer development is much weaker in than in other head and neck sites suggesting alternative genetic mechanisms and distinct genetic targets.(4–6) As these non-tobacco-related mechanisms of head and neck tumorigenesis become better defined, the group of poorly/undifferentiated carcinomas may turn out to represent a heterogeneous mix of tumors defined by distinct pathogenic mechanisms. Recent studies, for example, have shown that 20–25% of non-keratinizing sinonasal cancers are caused by oncogenic human papillomavirus;(7–10) and a subset of tumors previously regarded as poorly differentiated squamous cell carcinoma or sinonasal undifferentiated carcinoma has been found to harbor activating translocations involving the *NUT* gene (i.e., *NUT* midline carcinomas).(11–13) Despite these recent developments, the underlying mechanisms for most sinonasal carcinomas remain unknown.

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (*SMARCB1*, also known as *INI-1* or *SNF5*) is a tumor suppressor gene located on chromosome 22q11.2.(14) Its gene product is member of the SWI/SNF chromatin-remodeling complex that regulates transcription, and it is ubiquitously expressed in the nuclei of all normal tissues at levels that can be readily detected by routine immunohistochemistry.(14–18) Deficiency of *SMARCB1* was first recognized as a distinguishing feature of atypical teratoid/rhabdoid tumor of the central nervous system and malignant rhabdoid tumors of the kidney and soft tissue.(19–25) Since then, the list of *SMARCB1* deficient tumors has grown to include epithelioid sarcoma,(26–28) renal medullary carcinoma,(29) myoepithelial carcinoma of soft tissue,(26, 30) epithelioid malignant peripheral nerve sheath tumor,(26) and extraskelatal myxoid chondrosarcoma.(31) While these diverse tumor types differ in many respects, they all tend to include the presence of “rhabdoid” cells, defined as large cells with abundant eosinophilic cytoplasm and eccentrically placed nuclei with open chromatin and prominent nucleoli. Ultrastructurally, the cytoplasmic eosinophilia reflects the accumulation of compact whorls of intermediate filaments. Although the list of anatomic sites is growing, the sinonasal tract has not yet been identified as a site of *SMARCB1* deficient tumors.

Methods

Cases/Tissue microarray

A tissue microarray was constructed from the paraffin embedded tissue blocks of 140 consecutive primary sinonasal carcinomas of all histologic types, as previously described.⁽⁷⁾ The tumors included on the tissue microarray consisted of 81 squamous cell carcinomas and variants (including 40 non-keratinizing forms), 34 salivary-type adenocarcinomas, 14 sinonasal undifferentiated carcinomas, 6 non-salivary type adenocarcinomas, 3 NUT midline carcinomas, and 2 small cell carcinomas. Three cores, each 1 mm in diameter, were taken from each donor block to address tumor heterogeneity. Two additional cases from the authors' (WHW and JAB) consultation practice were selected for SMARCB1 testing based on morphologic similarity to SMARCB1 deficient tumors identified from the tissue microarray. Pertinent clinical information was obtained from The Johns Hopkins Hospital's electronic medical records.

Immunohistochemistry

All 142 sinonasal cancers were evaluated by immunohistochemistry for SMARCB1 (BAF47, BD Biosciences, San Diego, CA) on 5-micron sections on a Leica Bond-III autostainer (Leica Biosystems, Buffalo Grove, IL). Normal tonsil served as positive control tissue, while an epithelioid sarcoma served as an SMARCB1-deficient tumor control. For cases that demonstrated loss of SMARCB1 immunoexpression on TMA, additional immunohistochemical stains were performed on full sections using the Ventana Benchmark XT autostainer (Ventana Medical Systems, Inc. Tucson, AZ). Antigen retrieval was completed using high pH buffer, followed by primary antibody incubation for 32 minutes. The samples were then stained using a Ventana BenchMark ULTRA automated stainer and an ultraView detection system according to manufacturer's instructions (Ventana). The primary antibodies and final dilutions of the extended immunohistochemical panel were: p63 (clone 4A4; Cell Marque Corp., Rocklin, CA; prediluted by manufacturer); p40 (Ab-1; Oncogene Research Products, Cambridge, MA; 1:2000 dilution); muscle specific actin (clone HHF35; Ventana); calponin (clone CALP; Dako, Carpinteria, CA); S100 protein (clone 4C4.9; Ventana; prediluted); synaptophysin (clone 27G12; Leica; prediluted), chromogranin (clone LK2H10; Ventana; prediluted), and AE1/AE3 (clone PCK26; Ventana; prediluted). Finally, mucicarmine histochemical staining was done on all SMARCB1 deficient cases, adhering to the methods described in the *AFIP Laboratory Methods in Histotechnology*.⁽³²⁾ NUT-1 (C52B1, Cell Signaling Technologies, Inc., Danvers, MA) and p16 (clone INK4a; MTM Laboratories, Heidelberg, Germany; prediluted) immunohistochemistry, as well as DNA in situ hybridization for human papillomavirus, were carried out and reported as previously detailed.^(7, 11) The in situ hybridization testing utilized both type-specific assays for type 16, 18, and 31/33 (Dako) and a cocktail for high risk types, 18, 33, 35, 45, 51, 52, 56, and 66 (Ventana Inform HPV III Family 16 Probe (B) kit).

SMARCB1 and EWSR1 fluorescence in situ hybridization (FISH)

All SMARCB1 deficient tumors were then tested by FISH for the presence of *SMARCB1* gene abnormalities. Subsequently, cases that were SMARCB1 negative by

immunohistochemistry but lacked *SMARCB1* gene alterations were further tested by FISH for potential rearrangements in *EWSR1*; the latter previously reported in a subset of *SMARCB1* deficient myoepithelial carcinomas of soft tissue.(28) FISH was performed using custom BAC probes as previously described.(28) Copy number abnormalities were assessed on 100 nuclei. Normal copy number pattern was defined when two copies of the *SMARCB1* gene or other members of the SWI/SNF complex were identified, with a 1:1 ratio to the control probe (i.e. telomeric-*EWSR1* or 22q11). Heterozygous deletion was defined as only one copy of the gene of interest being present compared to the reference control probe on 22q (ratio 2:1). Homozygous deletion of *SMARCB1* was interpreted when both copies of the gene were lost, compared to the control probes, either telomeric-*EWSR1* or 22q11.

Results

SMARCB1 immunohistochemical staining

Seven (5%) of the 140 consecutive primary sinonasal carcinomas studied on the tissue microarray demonstrated complete loss of *SMARCB1* immunohistochemical expression. Based on the morphologic appearance of these *SMARCB1* deficient carcinomas (see below), two additional consultation cases were also tested for *SMARCB1* immunohistochemistry, and both were negative for *SMARCB1* expression. Thus a total of 9 *SMARCB1* deficient sinonasal carcinomas were included in the study. In all these 9 cases, strong nuclear *SMARCB1* staining was present in the surrounding non-neoplastic tissues (Figure 1).

Morphologic findings

Histologic examination of the *SMARCB1* deficient sinonasal carcinomas revealed tumors that typically grew as rounded and anastomosing nests of tumor cells separated by bands of fibrous stroma. In areas, some of the tumors became more sheet-like or cord-like in architecture. A single case demonstrated a spindled (i.e. sarcomatoid) component. The carcinomas tended to be highly infiltrative with frequent bone invasion. The tumor nests were comprised of cells that had enlarged round nuclei with prominent nucleoli, but their cytoplasmic qualities varied. Where the tumor cells had scant cytoplasm, they were basaloid in morphology; but all of the tumors harbored at least a subset cells with abundant, eccentric, eosinophilic cytoplasm imparting a rhabdoid appearance. The rhabdoid cells were often scattered singly among the more basaloid cells (Figure 2A), but in some cases they were the predominant cell type (Figure 2B). Tumor necrosis was a frequent finding, and the mitotic rate was high (ranging from 3 to 30 mitoses per 10 high power fields, mean 12). Despite these aggressive histologic features, the carcinomas lacked significant pleomorphism at the cellular level. None of the carcinomas showed overt evidence of squamous or glandular differentiation by routine histology. There was no evidence of dysplasia or carcinoma in situ in the overlying surface epithelium. Five of the carcinomas demonstrated duct-like spaces that were sometimes associated with necrotic tumor cells and appeared to represent pseudoglandular spaces. Intracellular mucin was detected in 2 cases (22%), but its presence was a very focal finding..

Immunohistochemistry

The immunohistochemical findings are summarized in Table 1. All 9 SMARCB1 deficient carcinomas were positive for AE1/AE3, 4 of 9 (44%) showed nuclear labeling for p63 and p40 which was either diffuse (n=3) or focal (n=1); 5 of 8 (63%) were focally positive for synaptophysin (staining not done on one case due to insufficient tissue), and one (11%) showed focal S100 protein staining. All tumors were negative for actin, chromogranin and NUT-1. Two (33%) cases were diffusely positive for p16, but high risk HPV was not detected in any of the carcinomas by DNA in situ hybridization.

Original tumor classification

The original diagnostic classification of these SMARCB1 deficient carcinomas, as based on the morphologic and immunohistochemical features, is shown in Table 1. Three of the carcinomas were originally diagnosed as non-keratinizing squamous cell carcinomas, largely based on the presence of diffuse p63 staining. In the absence of any squamous, glandular or other specific differentiation, two of the carcinomas were classified as sinonasal undifferentiated carcinomas. One case was originally regarded as a high grade non-intestinal adenocarcinoma based on pseudoglandular spaces and focal mucicarmine staining. Despite negative immunostaining for p63, S100, and actin, two of the tumors were originally regarded as myoepithelial carcinoma. These 2 tumors were lower grade than the others, and had an appearance that was originally interpreted as plasmacytoid rather than rhabdoid (Figure 3). Overall, the SMARCB1 deficient carcinomas represented 3 of 40 (8%) tumors that had been regarded as non-keratinizing squamous cell carcinomas, 2 of 14 (14%) sinonasal undifferentiated carcinomas, 2 of the 34 (9%) of tumors that were regarded as salivary in origin (including 2 of the 3 originally classified as myoepithelial carcinoma), and 1 of 6 (17%) non-salivary adenocarcinomas.

SMARCB1 fluorescence in situ hybridization

FISH for the presence of *SMARCB1* gene abnormalities was successfully performed in 8 of 9 cases on full-sections. One case failed due to decalcification of the only available tumor block. Six of 8 (75%) of the SMARCB1 deficient carcinomas showed *SMARCB1* copy number alterations. Five cases showed homozygous deletion of *SMARCB1* (Figure 4A), while an additional case showed a heterozygous deletion pattern (Figure 4B). Interestingly, the two SMARCB1 deficient carcinomas lacking *SMARCB1* gene abnormalities by FISH were associated with a lower histologic grade, and were originally felt to represent myoepithelial carcinoma. Because rare SMARCB1 deficient myoepithelial tumors of soft tissue harbor *EWSR1* gene rearrangements,(28) these two carcinomas were also tested for *EWSR1* FISH, but no gene abnormalities were noted.

Clinical findings

The clinical characteristics of the patients with SMARCB1 deficient sinonasal carcinomas are summarized in Table 2. Five of patients with SMARCB1 deficient sinonasal carcinomas were female, and four were male. The patients ranged in age from 33–78 years (mean 59). Three patients (33%) had histories of smoking, and one patient (11%) also had a history of alcohol abuse. The presenting symptoms included pain (n=5), eye symptoms (e.g., blurry

vision, tearing) (n=4), and nasal obstruction (n=2). The carcinomas involved the paranasal sinuses (n=9), orbit (n=5), nasal cavity (n=4), brain (n=3), and skull base (n=2) (Figure 5). The affected paranasal sinuses were: ethmoid (n=8), maxillary (n=3), and frontal (n=2). The tumor sizes were known in 8 cases; they ranged from 2.5 to 9 cm (mean, 4.9 cm). At the time of presentation, none of the patients had regional or distant metastases. The tumor stages were T2 N0 M0 (n=1), T3 N0 M0 (n=2), and T4 N0 M0 (n=6).

All patients with *SMARCB1* deficient sinonasal carcinoma underwent surgical resection of their tumors. One patient received surgical management alone, while four patients received surgery and radiotherapy, and three patients received surgery with combined chemoradiation. In addition, one patient received surgery and has radiotherapy planned, but it has not yet started. The available follow-up ranged from 0 to 57 months (median, 16 months). For one patient, no follow up information was available because the patient's treatment is not complete. Four patients experienced local recurrences at 7, 9, 11, and 12 months post-treatment; one of these patients also had regional lymph node metastases. All four patients were then treated with chemotherapy; one patient with local recurrence and regional metastasis also underwent additional surgery (local re-excision and neck dissection). Two patients experienced distant metastases, at 13 and 17 months respectively. These distant metastases were present in the brain (n=2), bone (n=1), lung (n=1), and scalp (n=1). Unfortunately, 4 of the 8 patients with follow-up information died of their disease, at 15, 15, 29, and 30 months post-treatment. These patients included 3 of the 6 tumors found to have *SMARCB1* deletions and 1 of the 2 tumors without *SMARCB1* deletion. The remaining 4 are alive with no evidence of disease at 10, 16, 26, and 57 months post-treatment.

Discussion

Using immunohistochemistry to screen a large and diverse group of sinonasal carcinomas for loss of *SMARCB1* expression, we found that 5% exhibited complete loss of staining. The genetic basis for loss of protein expression was confirmed in most of these cases: 6 of the 8 tumors demonstrating homozygous (n=5) or heterozygous (n=1) deletions of the *SMARCB1* tumor suppressor gene by FISH. The lack of *SMARCB1* deletions in two cases points to alternative inactivating events below the FISH resolution such as intragenic mutations, small deletions or epigenetic silencing. Additionally, one *SMARCB1* deficient myoepithelial carcinoma of soft tissue has been previously reported to harbor an *EWSR1* gene rearrangement without *SMARCB1* gene abnormalities by FISH,(28) although this mechanism was not confirmed in our two *SMARCB1* deficient tumors that had been originally diagnosed as myoepithelial carcinomas.

SMARCB1 loss was not randomly distributed across all types of sinonasal carcinomas, but tracked with tumors demonstrating rhabdoid features – a cytomorphologic trait shared by *SMARCB1* deficient tumors across diverse anatomic sites. The degree of rhabdoid differentiation was highly variable and ranged from rhabdoid cells singly dispersed among basaloid cells to confluent sheets of polygonal cells with a more plasmacytoid appearance. Recognition of these rhabdoid features was useful in identifying two additional *SMARCB1* deficient sinonasal carcinomas that were sent for second opinion consultation. Conversely, failure to appreciate these rhabdoid features can cause confusion with other poorly/

undifferentiated carcinomas of the sinonasal tract. While SMARCB1 deficient carcinomas represent only a small subset of primary sinonasal carcinomas overall, they accounted for 14% of those tumors that had been originally diagnosed as sinonasal undifferentiated carcinoma. Just as with the recent discovery of *NUT-1* gene activation in some undifferentiated sinonasal carcinomas, and the detection of integrated high risk human papillomavirus in some basaloid sinonasal carcinomas, identification of SMARCB1 deficiency could help redefine the classification in a more precise and relevant way.

Secondary SMARCB1 loss in a conventional tumor type resulting in a composite rhabdoid tumor is a well-recognized phenomenon. The rhabdoid phenotype has been encountered as a separate and distinct constituent within conventional parent tumors showing carcinomatous, sarcomatous, melanocytic, glial, meningothelial and other lines of differentiation.(33, 34) This phenomenon has prompted the notion that some extrarenal rhabdoid tumors do not warrant separate classification as a unique tumor type.(35, 36) In the cases we report, there was no evidence of an associated conventional differentiated carcinoma. Some were originally categorized as squamous carcinoma based on diffuse immunostaining for p63, but there was no histologic evidence of squamous differentiation or surface squamous dysplasia in any of the cases. Two were originally classified as myoepithelial carcinoma largely based on the myoepithelial-like plasmacytoid appearance of the tumor cells, but myoepithelial differentiation could not be confirmed by immunohistochemistry. In effect, the SMARCB1 deficient sinonasal carcinomas that we report may represent a distinct tumor type.

In other sites, the rhabdoid morphology heralds an aggressive type associated with a dismal clinical outcome. Based on our limited number of cases, SMARCB1 deficient sinonasal carcinomas also have a tendency to behave aggressively as evidenced by advanced local stage at time of presentation, a potential for regional and distant spread, and a mortality rate of 50% with a mean survival of 22 months. The recognition of *SMARCB1* loss as a driving genetic alteration now provides a rational target for the development of targeted therapies. (37–44)

In summary, a subset of sinonasal carcinomas harbors inactivating alterations of the *SMARCB1* tumor suppressor gene. Although these tumors are likely to be classified as non-keratinizing squamous cell carcinomas, sinonasal undifferentiated carcinomas and myoepithelial carcinomas, they likely represent a unique type of sinonasal carcinoma that further expands the family of SMARCB1 deficient tumors. Although the number of cases we report is limited, use of routine SMARCB1 immunohistochemistry as an easy way to recognize this entity and separate it from other poorly differentiated sinonasal carcinomas should facilitate the accrual of additional cases towards a more complete understanding of its pathological and clinical features.

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Figure 1.

Most of the carcinomas were composed of basaloid nests and lobules with intervening desmoplastic stroma (A, X200, case 3). All tumors exhibited complete loss of SMARCB1 immunostaining, with stromal and inflammatory cells serving as a internal positive control (B, X400, case 3).

Figure 2.

Each SMARCB1 deficient sinonasal carcinoma exhibited a component of rhabdoid cells, but their distribution was variable. In some cases, the rhabdoid cells were individually dispersed among the basaloid tumor cells (A, X400, case 2), while in others the rhabdoid cells predominated (B, X400, case 6).

Figure 3.

Two cases of SMARCB1 deficient sinonasal carcinoma lacked prominent nucleoli and had more evenly dispersed chromatin, imparting a plasmacytoid appearance to the tumors. These neoplasms were originally diagnosed as myoepithelial carcinoma on the basis of the plasmacytoid appearance (X400, case 7).

Figure 4.

FISH showing loss of both red signals (*SMARCB1*), showing only two green signals (*EWSR1*) in the tumor cells. On the right side few normal cells with retained two green/two red signals as an internal control (A, case 1). FISH showing most cells lost one copy of the red signal (*SMARCB1*), while retaining two green copies (*EWSR1*) (B, case 6).

Figure 5. Most of the SMARCB1 deficient sinonasal carcinomas exhibited aggressive clinical behavior. This tumor extended from the right sinonasal tract to involve the orbit and brain (T2-weighted magnetic resonance imaging).

Table 1

SMARCB1 deficient sinonasal carcinomas.

Case	Original diagnosis	Mucicarmine	INI-1	AE1/AE3	p63/p40	S100	SMA	SYN	CHR	NUT-1	p16/HR HPV	ISH	INI-1 FISH
1	Non-intestinal adenocarcinoma	Focal	-	+	Focal	Focal	-	Focal	-	-	-/-	-	Homozygous deletion
2	NKSCC	-	-	+	+	-	-	Focal	-	-	+/-	+/-	Homozygous deletion
3	SNUC	-	-	+	-	-	-	-	-	-	+/-	+/-	Homozygous deletion
4	NKSCC	-	-	+	+	-	-	-	-	-	-/-	-/-	Homozygous deletion
5	SNUC	-	-	+	-	-	-	Focal	-	-	-/-	-/-	Homozygous deletion
6	NKSCC	-	-	+	+	-	-	-	-	-	-/-	-/-	Heterozygous deletion
7	Myoepithelial carcinoma	-	-	+	-	-	-	Focal	-	-	-/-	-/-	Normal
8	Myoepithelial carcinoma	-	-	+	-	-	-	Focal	-	-	-/-	-/-	Normal
9	Carcinoma NOS	Focal	-	+	-	-	-	NA	-	-	-/-	-/-	NA

SMA, smooth muscle actin; SYN, synaptophysin; CHR, chromogranin; HR HPV, high risk human papillomavirus in situ hybridization; NKSCC, non-keratinizing squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma; NOS, not otherwise specified; NA, not available due to inadequate tissue.

Table 2

Clinical characteristics of the patients with SMARCB1 deficient sinonasal carcinomas.

Case	Age	Sex	Presentation	Site	Stage	Primary treatment	Clinical course	current status (months follow-up)
1	71	F	Sinus pain	Maxillary	T3 N0 M0	Surgery + XRT initially	Local recurrence	DWD (15)
2	46	F	Headaches	Frontal, ethmoid	T4 N0 M0	Surgery + XRT	NED	NED (57)
3	33	M	Proptosis, vision defects	nasal, ethmoid, frontal	T4 N0 M0	Surgery + XRT	Local recurrence, distant metastases	DWD (30)
4	60	M	Nasal obstruction	ethmoid	T4 N0 M0	Surgery + XRT	NED	Died of unclear reasons (10)
5	54	F	Headache, nasal discharge	Nasal, ethmoid, maxillary	T4 N0 M0	Surgery+ CT + XRT	Local recurrence	DWD (15)
6	44	M	Eye swelling, tearing	Ethmoid	T4 N0 M0	Surgery + planned XRT	N/A	N/A (0)
7	78	F	Nasal obstruction	nasal, ethmoid	T3 N0 M0	Surgery	NED	NED (26)
8	77	M	Headache, eye pain	Ethmoid	T4 N0 M0	Surgery + CT + XRT	Distant metastases	DWD (17)
9	67	F	Headache, ear ache	Ethmoid	T4 N0 M0	Surgery + CT + XRT	Locoregional recurrence	NED (16)

F, female; M, male; RT, radiation therapy; CT, chemotherapy; LR, local recurrence; DWD, died with disease; NED, no evidence of disease; DM, distant metastases; RM, regional metastases; NA, not applicable.