ORIGINAL ARTICLE

A New Classification for Malignant Tumors Involving the Anterior Skull Base

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Objectives: To propose our clinical classification of malignant ethmoid tumors and to compare it with the last American Joint Committee on Cancer (AJCC)–Union Internationale Contre le Cancer (UICC) classification, published in 1997.

Design: Retrospective review.

Setting: Tertiary cancer facility.

Patients: We evaluated 123 consecutive patients undergoing craniofacial resection for malignant ethmoid tumors involving the anterior skull base. The mean follow-up was 60 months. Fifty-nine patients (48%) presented with recurrent disease after prior therapy. We classified them with a new classification system (Istituto Nazionale per lo Studio e la Cura dei Tumori) based on the most commonly accepted unfavorable prognostic factors (involvement of dura mater; intradural extension; involvement of the orbit and, in particular, of its apex; invasion of maxillary, frontal, and/or sphenoid sinuses; and invasion of the infratemporal fossa and skin. We also classified patients with the AJCC classification published in 1997.

Main Outcome Measures: Disease-free status and overall survival rate. To study a possible association with tumor stage, the Cox regression model was adopted.

Results: According to our classification, patient distribution by tumor type was T2, n = 46; T3, n = 29; and T4, n = 48 (no T1 tumors were present in the series). For previously untreated patients, 5-year disease-free survival estimates were T2, 57%; T3, 50%; and T4, 13%. For relapses, corresponding figures were T2, 31%; T3, 23%; and T4, 1%. The prognostic difference among stages was statistically significant ($P<.001$). Similar results were obtained for overall survival. In contrast, patient distribution among different AJCC stages was less balanced, and we failed to detect a significant association with the clinical outcome using this classification.

Conclusion: We propose the use of our staging system by all those specialists in the field willing to validate the classification and possibly apply it for clinical and investigational purposes.

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WHILE A classification of maxillary sinus carcinomas has been available since the publication of the first edition of the *AJCC Manual for Staging of Cancer* of the American Joint Committee on Cancer (AJCC), carcinomas of the paranasal sinuses were not considered in the first 3 editions of the *TNM Classification of Malignant Tumours* of the Union Internationale Contre le Cancer (UICC). Only in the fourth edition of the *TNM Classification of Malignant Tumours*, published in 1987,[1] did a classification of maxillary sinus carcinomas appear—the same as that reported in the fourth edition of the *AJCC Manual for Staging of Cancer*.[2] Ethmoid carcinomas were finally staged in the fifth editions of both the *AJCC Cancer Staging Manual*[3] and the UICC's *TNM Classification of Malignant Tumours*.[4]

Some of the authors who have published articles on nasal and paranasal tumors admitted that without a classification of ethmoid tumors, the cases presented had not been staged. Sisson et al[5] wrote that "The ethmoid cancers were not staged because there is no generally accepted staging system for this site." Spiro et al,[6] after having staged tumors of the maxillary sinuses, wrote that "As there is no widely accepted staging system for the remaining sinuses or the nasal cavity, no attempt was made to stage tumors arising in these sites." This was the case even though the fourth edition of the *AJCC Manual for Staging Cancer* states that a proper classification and staging of cancer will allow the physician to determine treatment for

PATIENTS AND METHODS

PATIENTS

From 1987 through 1996, 130 patients underwent an anterior craniofacial resection for ethmoid malignant tumor at the INT of Milan. Seven of the subjects were excluded from the analyses because they died postoperatively. Our surgical technique has already been published.[14] Patient charts, operative notes, follow-up clinic notes, radiographic study results, and pathologic reports were analyzed for each patient. In particular, radiographic study results and pathologic reports were used to assess the clinical and pathologic T stage.

Patient ages varied from 22 to 79 years (mean age, 54 years), and the male-female ratio was 2.2 (84/39). The main disease characteristics are described in **Table 2**.

Sixty-four patients were previously untreated (52%), whereas 59 (48%) presented with a recurrence after prior treatments performed elsewhere. Eight untreated patients underwent 3 to 5 cycles of primary chemotherapy with cisplatin, fluorouracil, and leucovorin according to a treatment protocol that began in 1996. The prior treatments were surgery (n = 17), surgery followed by radiotherapy (n = 16), radiotherapy followed by surgery (n = 8), radiotherapy (n = 6), chemotherapy followed by radiotherapy (n = 9), and chemotherapy (n = 3). The ethmoid was involved in all cases and was the most probable site of origin of the tumor in all the patients.

Histological diagnosis was always based on a transnasal biopsy specimen or on a specimen from previous surgery performed elsewhere. The extent of the tumor was always assessed with a computed tomographic (CT) scan in axial and coronal projections, whereas magnetic resonance imaging (MRI) scans were obtained for patients who were unable to achieve a proper position for CT scan coronal sections. Magnetic resonance imaging was also used for patients with intracranial and intraorbital extension (documented by CT scan) to assess the infiltration of dura mater and periorbita.

Fifty-six patients underwent planned postoperative radiotherapy with a dose of 50 to 66 Gy. Therefore, 95 patients (77%) received radiotherapy either preoperatively or postoperatively.

According to the INT staging system, the tumors of 46 patients were classified as T2, 29 as T3, and 48 as T4. Of course, no T1 tumors were present in the series, since these rare small tumors are not treated with craniofacial resection. According to the AJCC-UICC staging system, the tumors of 15 patients were classified as T1, 8 as T2, 38 as T3, and 62 as T4. Only 1 patient initially presented with cervical node metastasis; 5 patients had cervical node metastasis after a few months.

STATISTICAL METHODS

The disease-free and overall survival rates were measured from the date of surgery to the date of disease recurrence or death; in the absence of any event, these rates were measured from the date of surgery to the last follow-up assessment available. Disease-free and overall survival curves were estimated with the Kaplan-Meier method.[15] After carefully checking the underlying proportional hazard assumption, the Cox regression model[16] was adopted to study a possible association between tumor stage and clinical outcome in terms of disease-free or overall survival rates. The analyses were adjusted for prior treatment, a factor shown to be an important predictor in our previous article.[14] The tumor stage and prior treatment were entered into the Cox models by means of 0 vs 1 indicator variables. Histological findings turned out to be of negligible importance in the present study and were therefore disregarded. In all of the analyses, the conventional 5% significance level was adopted.

the patient more appropriately, to evaluate results of management more reliably, and to compare statistics reported from various institutions on a local, regional, and national basis more confidently.[2]

Nevertheless, some attempts to stage nasoethmoid tumors have been made. Kadish et al[7] and later Biller et al[8] proposed a classification for esthesioblastomas. Dulguerov and Calcaterra[9] of the University of California, Los Angeles, Medical Center proposed another classification in 1992; this was once again for esthesioblastomas, and the authors of the M. D. Anderson Cancer Center study[10] referred to it to stage their cases.

Ellingwood and Million[11] published a classification for cancers of the nasal cavity and ethmoid/sphenoidal sinuses in 1979. Finally, Roux et al[12] adopted a staging system they called *modified TNM*.

It is evident that there is a lot of confusion in the classification of malignant ethmoid tumors. If we look into the various classifications presented, it is easy to see, as stated by Dulguerov and Calcaterra,[9] that some of them, despite their historical significance as first attempts at staging, are clearly inadequate.

In the absence of a universally accepted staging system and on the basis of our experience with anterior craniofacial resections, we developed in 1993 and presented in 1995 an original classification for malignant ethmoid tumors[13] based on the most commonly accepted unfavorable prognostic factors (involvement of dura mater; intradural extension; involvement of the orbit and, in particular, of its apex; invasion of maxillary, frontal, and/or sphenoidal sinus; and invasion of the infratemporal fossa and skin) (**Table 1**). We applied this classification to all consecutive malignant nasoethmoid tumors that were treated at our institution.[14]

The aims of this article are to verify the prognostic effectiveness of our staging system (Istituto Nazionale per lo Studio e la Cura dei Tumori [INT]) in patients with nasoethmoid tumors who underwent an anterior craniofacial resection and to compare it with the recently published AJCC-UICC classification.

RESULTS

In 121 (98%) of the 123 patients considered, a correspondence was found between clinical and pathologic

Table 1. Istituto Nazionale per lo Studio e la Cura dei Tumori Classification of Malignant Ethmoid Tumors

T1	Tumor involving the ethmoid and nasal cavity, sparing the most superior ethmoid cells
T2	Tumor with an extension to or erosion of the cribriform plate, with or without erosion of the lamina papiracea and without extension into the orbit
T3	Tumor extending into the anterior cranial fossa extradurally and/or into the anterior two thirds of the orbit, with or without erosion of the anteroinferior wall of the sphenoid sinus, and/or involvement of the maxillary and/or frontal sinus
T4	Tumor with intradural extension, and/or involving the orbital apex, the sphenoid sinus, the pterygoid plate, the infratemporal fossa, or the skin

Table 2. Disease Characteristics*

	No. (%) of Patients (N = 123)
Prior treatment	
No	64 (52)
Yes	59 (48)
Histological characteristics	
Adenocarcinoma	62 (50)
Squamous odontogenic tumor	21 (17)
Esthesioneuroblastoma	15 (12)
Adenoid cystic tumor	10 (8)
Melanoma	6 (5)
Other	9 (7)
INT stage	
T2	46 (37)
T3	29 (24)
T4	48 (39)
AJCC-UICC stage	
T1	15 (12)
T2	8 (7)
T3	38 (31)
T4	62 (50)

**INT indicates Istituto Nazionale per lo Studio e la Cura dei Tumori; AJCC-UICC, American Joint Committee on Cancer–Union Internationale Contre le Cancer.*

staging using both the INT and AJCC-UICC classification systems. Only 1 clinically diagnosed T4 tumor turned out to be a pT3 tumor, and 1 diagnosed T2 tumor was really a pT3 tumor.

The median follow-up time was 60 months. Seventy-five patients had disease recurrence. These recurrences were mainly local, either isolated (n = 65) or in combination with other types (n = 5); recurrences only rarely occurred at distant sites (n = 3) or only in the lymphatic nodes (n = 2). Sixty-five deaths were recorded, caused by ethmoid tumor recurrence (n = 59), other primary tumors (n = 2), nonneoplastic causes (n = 3), or unknown causes (n = 1).

Figure 1 shows the disease-free survival curves in the whole series according to the INT and AJCC-UICC tumor classification stages. The same curves are plotted in **Figure 2**, considering only patients with adenocarcinoma, the most frequent type of malignant neoplasm identified with histological testing. It is apparent that a clear separation among the curves was evident only for the INT system of tumor staging. For the AJCC-UICC staging, patients with T2 tumors had a good prognosis, whereas for patients with T1, T3, and T4 tumors, the clinical outcome was almost the same.

Table 3. Disease-Free and Overall Survival Rates*

Variable	Hazard Ratio (95% CI)	P
Disease-free survival		
Tumor stage†		
T3	1.23 (0.66-2.30)	<.001‡
T4	3.59 (2.11-6.11)	
Prior treatment§	2.09 (1.34-3.25)	<.001
Overall survival		
Tumor stage†		
T3	1.45 (0.70-2.99)	<.001‡
T4	3.16 (1.71-5.82)	
Prior treatment§	2.09 (1.25-3.48)	.005

**Results were obtained with Cox proportional hazards regression models. CI indicates confidence interval.*
†The reference category was T2.
‡Test for the overall association, df = *2.*
§The reference category was no prior treatment.

Overall survival curves are shown in **Figure 3** for the whole series and for patients with adenocarcinoma in **Figure 4**. The findings were in accordance with those previously described for disease-free survival.

Significant results were achieved by the INT classification system among different T stages for disease-free and overall survival rates (**Table 3**). Significant results were also obtained for prior treatment, which confirmed that this is a prognostic factor not only for disease-free survival, as already shown,[14] but also for overall survival. By including suitable interaction terms in the Cox models, the prognostic role of the INT tumor stage classification was shown not to be affected by prior treatment. When applying the AJCC-UICC staging system to the Cox models, statistical results among different T stages were not significant for either disease-free ($P = .14$) or overall ($P = .40$) survival rates.

Table 4 reports 3- and 5-year estimates (and corresponding 95% confidence intervals) that were obtained with the Cox models for disease-free and overall survival rates according to prior treatment and the INT tumor stage classification.

COMMENT

The precise identification of the site of origin of some nasoethmoid tumors may be difficult. Shah et al[17] have distinguished ethmoid tumors from nasal tumors. Ellingwood and Million[11] wrote that "An effort was made to specify a single site of origin, but it was sometimes a moot point whether the tumor originated in the nasal cavity or the ethmoid sinus." Moreover, many authors have suggested that "the olfactory neuroblastoma is a malignant neoplasm originating in the upper nasal vault in the region of the cribriform plate."[7-10,17-19] Dulguerov and Calcaterra[9] stated that "Esthesioneuroblastomas either arise

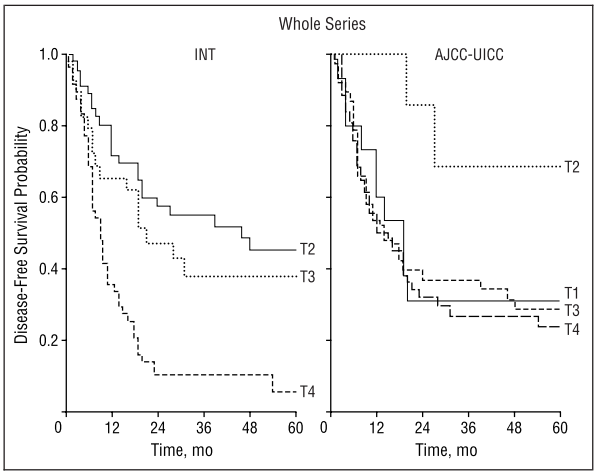

Figure 1. *Disease-free survival curves according to the Istituto Nazionale per lo Studio e la Cura dei Tumori (INT) and American Joint Committee on Cancer–Union Internationale Contre le Cancer (AJCC-UICC) tumor classification stages.*

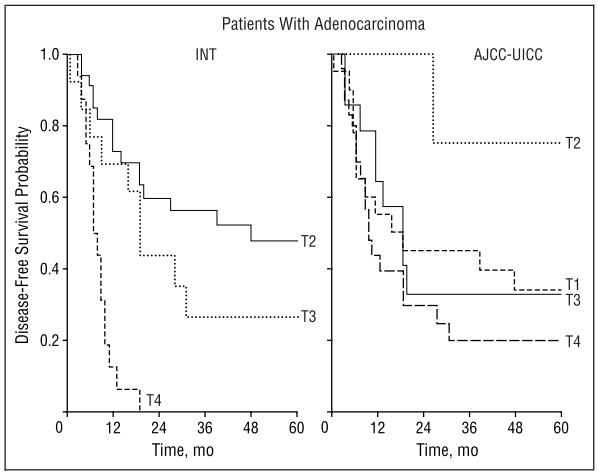

Figure 2. *Disease-free survival curves for patients with adenocarcinoma only according to the Istituto Nazionale per lo Studio e la Cura dei Tumori (INT) and American Joint Committee on Cancer–Union Internationale Contre le Cancer (AJCC-UICC) tumor classification stages.*

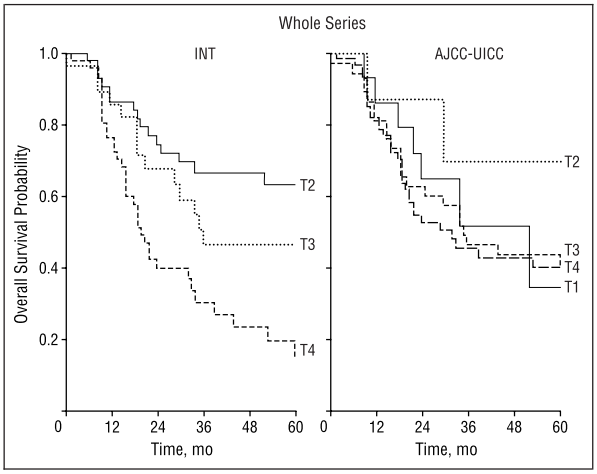

Figure 3. *Overall survival curves according to the Istituto Nazionale per lo Studio e la Cura dei Tumori (INT) and American Joint Committee on Cancer–Union Internationale Contre le Cancer (AJCC-UICC) tumor classification stages.*

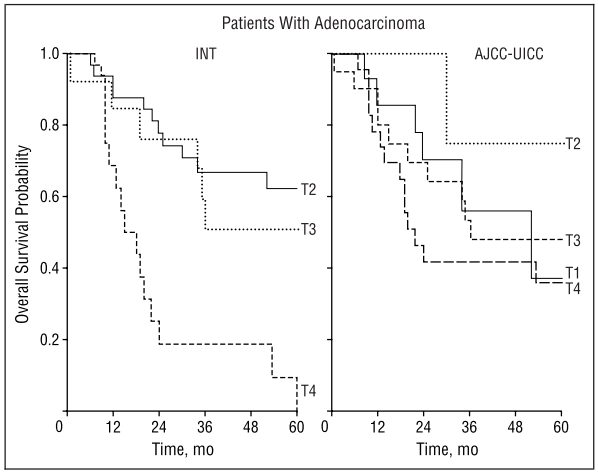

Figure 4. *Overall survival curves for patients with adenocarcinoma only according to the Istituto Nazionale per lo Studio e la Cura dei Tumori (INT) and American Joint Committee on Cancer–Union Internationale Contre le Cancer (AJCC-UICC) tumor classification stages.*

in, or spread very rapidly to, the ethmoid sinuses." In the introduction of their historical article, Kadish et al[7] wrote that "The sense of smell is located in a specialized sensory neuroepithelium that covers the superior nasal turbinates and the upper portion of the nasal septum." Since the superior turbinates, the cribriform plate, and the upper portion of the nasal septum belong to the ethmoid, it seems appropriate to include esthesioneuroblastomas in the classification of ethmoid tumors.

Nodal and distant metastases of malignant ethmoid tumors are uncommon. Therefore, if we perform a radical resection of the tumor, we have a chance to cure the patient. Anterior craniofacial resection is now recognized as the treatment of choice for ethmoid tumors involving the cribriform plate with or without invasion of the anterior cranial fossa. However, it is sometimes difficult to achieve radical resection with this procedure. A clinical classification of a tumor should be able to identify, through a simple and reproducible characterization, the extensions where radical resection is difficult, allowing patients to be divided into prognostic groups accordingly.

Looking into the various staging systems presented, we think that only the classification of Dulguerov and Calcaterra[9] is appropriate, mainly because it introduces a distinction between tumors that do not involve the most superior ethmoid cells (T1) and those that extend to or erode the cribriform plate (T2). The T1 tumors might be excised through a facial approach, whereas the others require craniofacial resection to achieve radical resection. However, it is our opinion that the classification of Dulguerov and Calcaterra is limited by the generic inclusion in the T3 category of tumors invading the orbit. We believe a distinction should be made between tumors with invasion in the anterior two thirds of the orbit and those with orbit apex involvement. In fact, it is possible to achieve radical resection with orbital exenteration for

Table 4. Estimates of Disease-Free and Overall Survival by Prior Treatment and Istituto Nazionale per lo Studio e la Cura dei Tumori (INT) Tumor Stage Classification*

Estimate	Prior Treatment	INT Tumor Stage Classification	Disease-Free Survival (95% CI), %	Overall Survival (95% CI), %
3 y	No prior treatment	T2	62 (47-75)	76 (61-86)
		T3	56 (36-72)	67 (47-81)
		T4	18 (7-33)	42 (24-59)
	Prior treatment	T2	37 (21-54)	56 (36-72)
		T3	30 (13-49)	43 (23-62)
		T4	3 (0-10)	16 (7-30)
5 y	No prior treatment	T2	57 (40-70)	71 (54-83)
		T3	50 (30-67)	61 (39-77)
		T4	13 (4-27)	34 (17-52)
	Prior treatment	T2	31 (15-48)	49 (29-66)
		T3	23 (9-42)	35 (16-55)
		T4	1 (0-7)	10 (3-23)

*CI indicates confidence interval.

tumor invasion in the anterior two thirds of the orbit, but this is not the case for tumors with orbit apex involvement. Furthermore, their classification for the involvement of the sphenoidal sinus is far too general. A tumor that has eroded the anterior-inferior wall of the sphenoidal sinus is very different from a tumor that has largely destroyed the superior-posterior-lateral walls and spread to the cavernous sinuses, the sella turcica, and the clivus. It is easy to achieve radical resection in the first instance, but not in the second. Finally, the classification of Dulguerov and Calcaterra was proposed only for esthesioneuroblastomas.

The UICC-AJCC classification system[3,4] introduces the concept, already used by us,[13] that different prognostic values should be applied for tumor involvement of the anterior orbit and the apex. However, we believe that the UICC-AJCC classification system has some important discrepancies. A T1 tumor may be small, low, and resectable via rhinotomy or endoscopy, but it may also be rather large, eroding the lamina papyracea, even without orbital involvement, and/or eroding the cribriform plate without intracranial extension. In the latter instance, a craniofacial resection is required. Tumor extension into the nasal cavity is the peculiarity of a T2 lesion. We see no reason why neoplastic vegetations in the empty space of the cavity may worsen the prognosis. Also, the possible involvement of turbinates and/or septum may be easily cured with medial maxillectomy. In addition, the UICC-AJCC T4 tumor classification stage is too broad. It includes tumors with little intracranial extension without dural involvement, tumors attached to the outer face of the dura, and tumors with brain infiltration. In the INT classification system, the first 2 situations would be classified as T3 and the third as T4. We believe it is easy to achieve radical resection with a dural resection in the first 2 cases but not when the tumor involves the brain. Moreover, sphenoid involvement is not clearly defined in the AJCC-UICC classification system because a detailed description of its extent is lacking. Finally, a tumor involving the frontal sinus may be resected more easily and radically than a tumor that extends to the pterygoid plate or infratemporal fossa; this is not mentioned in the AJCC-UICC classification system.

Our analyses clearly identified all these problems. According to the AJCC-UICC classification system, no trend was observed in terms of disease-free or overall survival rates among the different tumor stages. Oddly, only the patients with T2 tumors showed a relatively good outcome. Considering the small number of patients with tumors in this category, we believe that a plausible explanation may be the fortuitous selection of less aggressive tumors. Perhaps a tumor fungating in the nasal cavity is less malignant than a tumor confined in the ethmoid cells but eroding the bone.

In contrast, our classification system turned out to have prognostic value. A progressive worsening of the prognosis was shown to occur from T2 to T4. Because our series included many histological types and this might bring into question the validity of the results, we also verified the prognostic value of our classification system for adenocarcinoma, the most frequent type of malignant neoplasm identified with histological testing. Similar results were obtained. However, no conclusions can be drawn for melanomas and undifferentiated carcinomas because of the small number of these histological types.

All features of tumor extension that were used in our classification system to distinguish one stage from another can be easily assessed with clinical examination, CT scan, and MRI. In particular, MRI is able to reveal the involvement of the dura and the periorbita. The clinical classification of T stage changed after surgical resection in only 2 cases.

The only limitation of our series is that we did not include patients with T1 tumors because they did not undergo craniofacial resection. From 1987 through 1996, we saw only 3 patients with T1 tumors—too small a subgroup to warrant statistical analysis. The T1 tumors were resected with a paranasal approach, the patients were treated with postoperative radiotherapy, and all were alive and well at the time of this report.

CONCLUSIONS

Based on our findings, we believe our new system for the classification of malignant tumors involving the anterior skull is valid for a number of reasons. First, it is based on anatomical and not just histological criteria. In fact, we apply our system of classification to all malignant tumors of the ethmoid. Second, it takes into account the possibilities and limitations of the most modern surgical treatment for ethmoid tumors (ie, craniofacial resection) to achieve radical resection. Third, it satisfies one of the main goals of tumor staging, namely the progressive worsening of prognosis for different classes. Finally, our system of tumor classification proved to be valid not only for the overall study but also when applied separately to untreated and recurring

cases. Staging can be done clinically by means of CT scans and MRI examinations, which accurately reveal tumor extension and involvement of those anatomical structures that determine a change of stage. This permits confrontation between homogeneous series treated with surgery, radiotherapy, chemotherapy, and therapeutic combinations.

Therefore, we recommend the INT staging system for malignant tumors of the ethmoid to all specialists in the field who are willing to validate tumor classification and possibly apply it for clinical and investigational purposes.

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Correction

Error in Table Row Heading. In the Original Article titled "A New Classification for Malignant Tumors Involving the Anterior Skull Base," published in the November issue of the ARCHIVES (1999;125:1252-1257), a row heading under "Histological characteristics" in Table 2 (page 1254) was incorrect. "Squamous odontogenic tumor" should have appeared as "Squamous cell tumor."