OPEN

ORIGINAL ARTICLE
Reconstructive

Sites of Basal Cell Carcinomas and Head and Neck Congenital Clefts: Topographic Correlation

Giovanni Nicoletti, MD, FEBoPRAS*†‡
Federica Brenta, MD*‡
Alberto Malovini, PhD§¶
Omar Jaber, MD*‡
Angela Faga, MD, FICS*†‡

Background: The embryologic fusion planes might be related with the sites of onset of basal cell carcinoma (BCC), thus supporting an embryologic role for its pathogenesis.
Methods: A study involving 495 patients with 627 BCCs of the head and neck was carried out over a period of 5 years by correlating the distribution of all BCCs with the sites of congenital clefts of the head and neck using (1) the original anatomic diagram of the Tessier classification of craniofacial clefts, (2) the anatomic diagram by Moore et al featuring the paths of the "hairline indicators" of craniofacial clefts that represent the cranial extensions of the Tessier classification, and (3) an anatomical diagram featuring the sites of congenital clefts of the neck.
Results: The proportion of BCCs localized within a cleft site was significantly higher than those in the noncleft sites. The age of patients with BCCs localized within the Tessier cleft number 3 was the lowest among all cleft regions.
Conclusions: A topographic correspondence between the sites of BCCs and the sites of congenital clefts was demonstrated in the head and neck. This evidence would support the hypothesis of an embryologic role for the pathogenesis of BCC. The existence of clusters of embryological stem cells in the sites of fusion and/or merging of embryonic processes might therefore be proposed. There may be special biology/physiology along these cleft lines that predispose BCC formation. *(Plast Reconstr Surg Glob Open 2014;2:e164; doi: 10.1097/GOX.0000000000000119; Published online 3 June 2014.)*

It has long been held that embryologic fusion planes might be related with the sites of onset and spread paths of basal cell carcinomas (BCCs) thus supposing an embryologic role for the pathogenesis of such a peculiar malignancy.[1–3]

A recent clinical study demonstrated that BCCs were more than 4 times more likely to occur on the embryonic fusion planes than on other regions of the midface.[4]

In our study, we correlated the distribution of all BCCs of the head and neck admitted at our unit over the last 5 years with the typical sites of craniofacial clefts and of congenital clefts, fistulas, and cysts of the neck.

*From the *Plastic and Reconstructive Surgery, Department of Clinical Surgical Diagnostic and Paediatric Sciences, University of Pavia, Pavia, Italy; †Advanced Technologies for Regenerative Medicine and Inductive Surgery Research Centre, University of Pavia, Pavia, Italy; ‡Plastic and Reconstructive Surgery Unit, Salvatore Maugeri Research and Care Institute, Pavia, Italy; §Department of Computer Engineering and Systems Science, University of Pavia, Pavia, Italy; and ¶Laboratory of Informatics and Systems Engineering for Clinical Research, Salvatore Maugeri Research and Care Institute, Pavia, Italy.*

Received for publication November 14, 2013; accepted April 15, 2014.

DOI: 10.1097/GOX.0000000000000119

MATERIALS AND METHODS

An overall number of 495 patients with 627 BCCs of the head and neck were admitted at the Plastic and Reconstructive Surgery Unit of the University of Pavia, Salvatore Maugeri Research and Care Institute, Pavia (Italy), over a period of 5 years, from June 2008 to May 2013.

All the cases underwent medical preoperative digital photography and the records were stored in the unit's dedicated master file.

The archived digital images were coded according to the specific location of each BCC using

1. The original anatomic diagram of the Tessier classification of craniofacial clefts[5] (Fig. 1).
2. The anatomic diagram by Moore et al[6] featuring the paths of the "hairline indicators" of craniofacial clefts that represent the superior and lateral extensions of the Tessier original craniofacial cleft classification (Fig. 2).
3. A detailed anatomical diagram featuring the typical sites of congenital clefts, fistulas, and cysts of the neck (Fig. 3).

All of the cases were aggregated into 2 groups: one including all of the BCCs sitting on the sites of craniofacial clefts and congenital clefts, fistulas, and cysts of the neck and another including all of the tumors sitting out of the former sites. The first group was then divided in subgroups corresponding to the sites of the Tessier classification of craniofacial clefts and the typical sites of congenital clefts, fistulas, and cysts of the neck. On the face, each site of the Tessier cleft classification accounted for a subgroup except for the clefts number 1 and 2 that were gathered into a single subgroup as their exact projection on the overlying soft tissue is virtually undistinguishable. On the neck, the typical sites of congenital clefts, fistulas, and cysts accounted for 2 subgroups: the laterocervical line and the anterior neck midline, the latter corresponding to the Tessier cleft number 30. The number of tumor records was calculated per each group and subgroup.

The tumors of the external ear were excluded from the study as the Tessier classification and subsequent modifications do not provide a detailed cleft line pattern in this anatomical site.

A formal informed written consent was obtained by all of the patients and the study conformed to the Declaration of Helsinki.

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

Statistical Analysis

The 1-sided exact binomial test was applied to evaluate whether the proportion of BCCs deriving from cleft sites was significantly higher than that expected by chance (assumed to be ≤ 50%). The Shapiro-Wilk test of normality was applied to evaluate whether the quantitative variable reporting the age at surgical intervention deviated from the normal distribution ($P < 0.05$). Global differences in terms of age at the time of surgical excision among groups of BCC samples deriving from different sites were performed by the nonparametric Kruskal-Wallis test. Binary comparisons in terms of median age at the time of surgical excision of BCC samples deriving from different sites were performed by the nonparametric 2-sided Wilcoxon rank-sum test. Differences in terms of sex distribution among groups of BCC samples deriving from different sites were evaluated by the 2-sided Fisher exact test for count data. The threshold for identifying statistically significant associations was set to $P < 0.003$, based on the Bonferroni correction for multiple comparisons [estimated by dividing $\alpha = 0.05$ by the number of sites evaluated ($n = 17$)]. Statistical analyses were performed by the R statistical software v.3.0.0 (www.r-project.org).

RESULTS

A total number of 627 BCC samples deriving from 495 patients were analyzed. Globally, 323 samples (52%) derived from males, the median age at surgical intervention was 74 years, and interquartile range (IQR) was 64–80.

The distribution of BCC samples by specific sites is reported in Figure 4 and Table 1. Of the analyzed BCC samples, 556 (88.68%) were localized within cleft sites, the remaining 71 (11.32%) were localized within noncleft sites. The proportion of BCCs localized within a cleft site was significantly higher than that we would expect to observe by chance in the same sites, assumed to be 50% (frequency = 88.68%; 95% confidence interval = 86–100%, $P < 1 \times 10^{-10}$).

Results showed that the median age at the time of surgical excision was different among tumors deriving from different sites ($P < 1 \times 10^{-3}$). In particular, the age at the time of surgical excision of BCCs localized within the Tessier cleft number 3 was the lowest, and it was significantly lower than that characterizing other cleft regions ($n = 144$, 26%, median age = 68.5 years, IQR = 55–77 vs $n = 412$, 74%, median age = 74.5 years, IQR = 67–80, $P < 1 \times 10^{-5}$) or the remaining sample ($n = 144$, 23%, median age = 68.5, IQR = 55–77, vs $n = 483$, 77%, median age = 74 years, IQR = 67–80, $P < 1 \times 10^{-5}$) (Table 2). No statistically significant difference in terms of

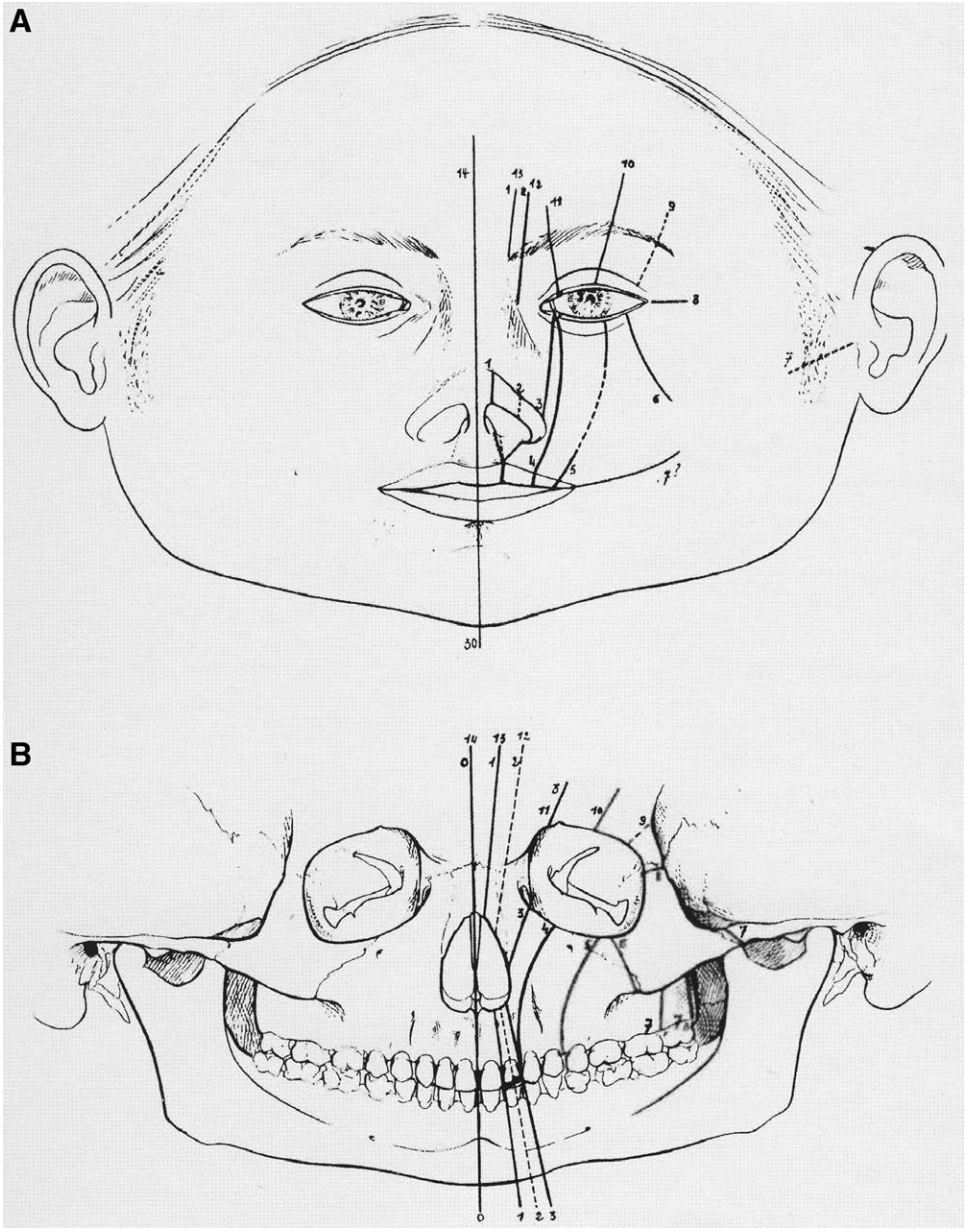

Fig. 1. The original Tessier anatomical diagram of craniofacial clefts: localization on the soft tissues (A) and skeleton (B). Dotted lines are either uncertain localizations or uncertain clefts. Reprinted with permission from Elsevier: Tessier P. Anatomical classification facial, craniofacial and latero-facial clefts. *J Maxillofac Surg*. 1976;4:69–92.

sex distribution was observed among different sites ($P = 0.53$), suggesting that the proportion of cleft sites harboring BCCs was equally distributed between males and females.

DISCUSSION

Our study demonstrated a statistically significant correspondence between the sites of onset of BCCs of the head and neck and the sites of craniofacial clefts and congenital fistulas and cysts of the neck. In detail, a greater number of tumor records were also demonstrated in the sites of most frequent craniofacial clefts and neck clefts, cysts, and fistulas.

The Tessier classification of craniofacial clefts,[5,7,8] subsequently completed by Moore et al[6] and David et al,[9] ordered the paths of various congenital clefts of the face with progressive numbers from 0 to 14 plus number 30 (Figs. 1, 2). The congenital cleft malformations of the neck are known to sit on well-established sites along the anterior border of each sternocleidomastoid muscle and along one line running from the chin to the clavicular notch in the

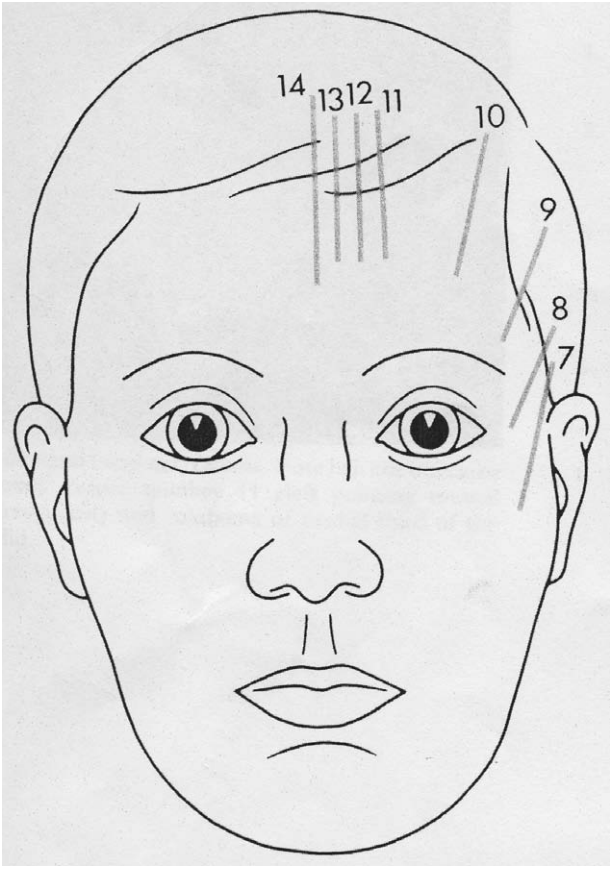

Fig. 2. The hairline indicators are the superior and lateral extensions of the Tessier original craniofacial cleft classification. Reprinted with permission from Wolters Kluwer Health: Moore MH, David DJ, Cooter RD. Hairline indicators of craniofacial clefts. *Plast Reconstr Surg.* 1988;82:589–593.

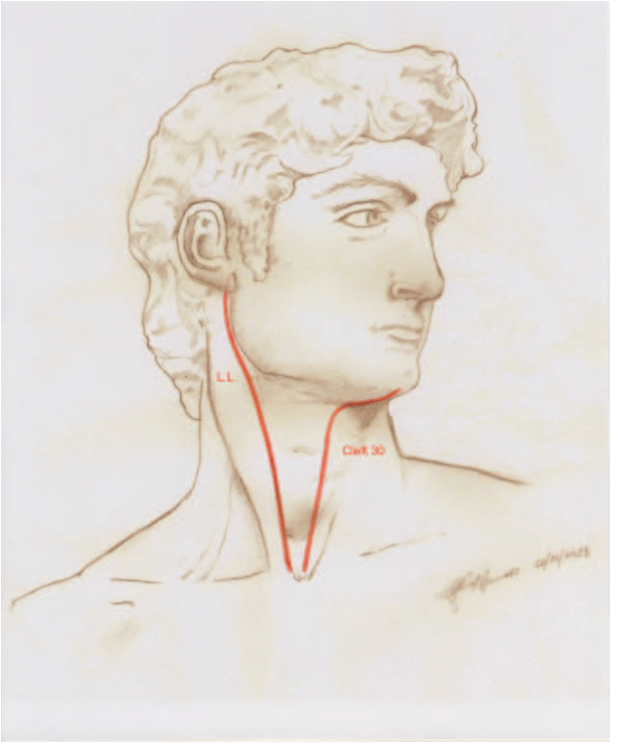

Fig. 3. Anatomical diagram of the typical sites of congenital clefts, fistulas, and cysts of the neck: the laterocervical line (L.L.) and the anterior neck midline (Tessier cleft number 30).

anterior midline,[10–13] the latter corresponding to the Tessier cleft number 30 (Fig. 3). All these clefts may display a variable degree of clinical expression ranging from a proper cleft, to a fistula, a cyst, and/or a fibrotic band.

In postnatal life, the sites of congenital head and neck cleft malformations are likely to match the sites of fusion and/or merging of embryonic processes.

It has long been held that embryologic fusion planes might be related with the sites of onset and spread paths of BCCs thus suggesting an embryologic role for the pathogenesis of such a peculiar malignancy.[1–4]

It is common knowledge in clinical dermatology that several skin proliferative diseases have a predilection for the pathways of epidermal cell migration and proliferation during the fetal development. These pathways, the so-called Blaschko lines, are believed to trace the migration of embryonic cells.[14,15]

As well dissertated by Pinkus[16] since 1966, BCC might be supposed at the "red hot" end of a spectrum featuring a sort of progressive regression of skin organoid structure with constant combined involvement of epithelium and stroma. Such a close interaction between epithelium and stroma differentiates BCCs from other pure epithelial malignancies where there is transformation of individual epithelial cells into strains of cancer cells featuring a typical stroma-dissociated invasiveness. Even in their most

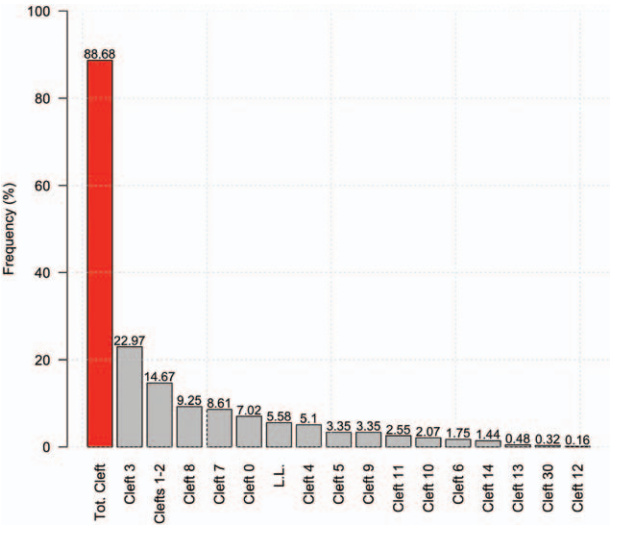

Fig. 4. BCC distribution by cleft sites. Tot. cleft, frequency of BCC samples within cleft sites; L.L., laterocervical line.

Table 1. Tumors Distribution in the Cleft Sites

Site	Tumors Distribution	
	n (%)	*P*
Cleft 0	44 (7.02)	NT
Clefts 1–2	92 (14.67)	NT
Cleft 3	144 (22.97)	NT
Cleft 4	32 (5.1)	NT
Cleft 5	21 (3.35)	NT
Cleft 6	11 (1.75)	NT
Cleft 7	54 (8.61)	NT
Cleft 8	58 (9.25)	NT
Cleft 9	21 (3.35)	NT
Cleft 10	13 (2.07)	NT
Cleft 11	16 (2.55)	NT
Cleft 12	1 (0.16)	NT
Cleft 13	3 (0.48)	NT
Cleft 14	9 (1.44)	NT
Cleft 30	2 (0.32)	NT
Laterocervical line	35 (5.58)	NT
Total cleft sites/total	556/627 (88.68)	$< 1 \times 10^{-6}$

P value given by the binomial test.
n, count and frequency (%) of tumors by site; NT, not tested; site, analyzed site.

primordial form, BCCs preserve the basic feature of adnexal primordial in the skin like some sort of fibroepithelial products of organized interdependent growth. Such evidence has directed the question for pathogenesis to embryogenesis. It seemed therefore not unreasonable to conceive of such an organoid skin tumor as a monstrous attempt at adnexogenesis in postnatal life through interaction of pathological ectodermal and mesodermal components which form fibroepithelial growths of varying degrees of maturity.

The Hedgehog signaling pathway plays a relevant role in embryogenesis across multiple species including mammals and humans.[17–21] Its activity seems to be reduced or absent in adult individuals. Recent clinical translational investigations demonstrated that aberrant reactivation of the pathway is involved in the development of a number of human malignancies including both inherited and sporadic BCCs.[19] Such an evidence has been further confirmed by a number of experimental animal studies.[20] All these reports would strongly support the time honored hypothesis of an embryologic role for the pathogenesis of BCC. Actually ongoing clinical studies are evaluating the response to Hedgehog pathway inhibitors for inoperable and locally advanced BCCs.[19,22] Perturbed Hedgehog signaling is also demonstrated to play a major role in craniofacial development, and mutations in a number of pathway constituents underlie craniofacial disease.[23]

According to our data, the greatest number of tumor records was observed along the Tessier cleft number 3. The latter is both the most common of the Tessier craniofacial clefts[24] and the most intricate and destructive one.[5] Such a correspondence would support our hypothesis that a greater link might exist between both disembryogenic and carcinogenic potential in the same anatomical site.

Interestingly, our data also demonstrated a statistically significant correlation between the site accounting for the greatest number of tumor records, the Tessier cleft number 3, and an earlier age of onset. Such a finding might suggest a reduced resistance to carcinogenic effects of the well-known

Table 2. Age at Surgical Intervention by Site

Site	Age at Surgical Intervention (Years)				
	Specific Cleft	Other Clefts	Noncleft	*P**	*P*†
Cleft 0	73 (63–77.25)	74 (64–80)	74 (65–80)	0.35	0.31
Clefts 1–2	76 (68–80)	73 (63–80)	73 (63–80)	0.08	0.12
Cleft 3	68.5 (55–77)	74.5 (67–80)	74 (67–80)	$< 1 \times 10^{-5}$	$< 1 \times 10^{-5}$
Cleft 4	70 (62–78.25)	74 (64–80)	74 (64–80)	0.38	0.35
Cleft 5	78 (67–85)	74 (64–80)	74 (64–80)	0.19	0.21
Cleft 6	69 (61.5–76.5)	74 (64–80)	74 (64–80)	0.45	0.44
Cleft 7	75.5 (69.75–82.25)	73 (63–79)	74 (63–80)	0.02	0.03
Cleft 8	75 (70–80)	73 (63–80)	74 (63–80)	0.09	0.12
Cleft 9	76 (62–83)	74 (64–80)	74 (64–80)	0.83	0.86
Cleft 10	67 (37–74)	74 (64–80)	74 (64.75–80)	0.02	0.02
Cleft 11	73 (62–79)	74 (64–80)	74 (64–80)	0.92	0.9
Cleft 12	76 (76–76)	74 (64–80)	74 (64–80)	0.74	0.76
Cleft 13	79 (76.5–79)	74 (64–80)	74 (64–80)	0.36	0.39
Cleft 14	80 (74–83)	74 (64–80)	74 (64–80)	0.08	0.1
Cleft 30	69 (68–70)	74 (64–80)	74 (64–80)	0.52	0.51
Laterocervical line	77 (71.5–80)	73 (63–80)	74 (63.25–80)	0.02	0.02
Total cleft sites	74 (64–80)	NT	74 (66.5–81)	NT	0.48

Age at surgical intervention = median (IQR) age at surgical intervention within specific cleft sites (specific cleft), other cleft sites (other clefts), and noncleft sites (noncleft), respectively.
**P* value from the comparison of age at surgical intervention in specific cleft sites vs other cleft sites.
†*P* value from the comparison of age at surgical intervention in specific cleft sites vs noncleft sites.
NT, not tested; site, analyzed site.

external environmental causes in the sites of fusion and/or merging of embryonic processes.

Further studies should be focused in identifying the presence of dormant embryonic stem cells along these fusion lines using embryonic or stem cell and/or Hedgehog pathway proteins markers.

Undoubtedly, the results of these forthcoming studies might significantly contribute to a thorough understanding of both the pathogenesis and the clinical behavior of such a unique skin tumor.

CONCLUSIONS

The results of our study support the hypothesis of an embryologic role for the pathogenesis of BCC, with elective reactivation of the Hedgehog pathway in specific anatomical sites characterized by a high disembryogenic potential.

Giovanni Nicoletti, MD, FEBoPRAS
Plastic, Reconstructive and Aesthetic Surgery Unit,
University of Pavia,
Salvatore Maugeri Research and Care Institute
Via Salvatore Maugeri
10, 27100 Pavia, Italy
E-mail: giovanni.nicoletti@unipv.it

ACKNOWLEDGMENTS

We thank Alan Serge McGhee, MSc, Glasgow City Council Education Department, for his contribution to the submission of this dissertation. We also thank Floriana Cazzola and Gian Mario Pelizzoli for their much appreciated technical support.

REFERENCES

1. Wentzell JM, Robinson JK. Embryologic fusion planes and the spread of cutaneous carcinoma: a review and reassessment. *J Dermatol Surg Oncol.* 1990;16:1000–1006.
2. Granström G, Aldenborg F, Jeppsson PH. Influence of embryonal fusion lines for recurrence of basal cell carcinomas in the head and neck. *Otolaryngol Head Neck Surg.* 1986;95:76–82.
3. Panje WR, Ceilley RI. The influence of embryology of the mid-face on the spread of epithelial malignancies. *Laryngoscope* 1979;89:1914–1920.
4. Newman JC, Leffell DJ. Correlation of embryonic fusion planes with the anatomical distribution of basal cell carcinoma. *Dermatol Surg.* 2007;33:957–964; discussion 965.
5. Tessier P. Anatomical classification facial, cranio-facial and latero-facial clefts. *J Maxillofac Surg.* 1976;4:69–92.
6. Moore MH, David DJ, Cooter RD. Hairline indicators of craniofacial clefts. *Plast Reconstr Surg.* 1988;82:589–593.
7. Tessier P. Colobomas: vertical and oblique complete facial clefts. Simultaneous operation of the eyelid, inner canthus, cheek nose and lip Orbitomaxillary bone graft. *Panminerva Med.* 1969;11:95–101.
8. Tessier P. Fente orbito-faciales verticales et obliques (colobomas) completes et frustes. *Ann Chir Plast.* 1969;14:301–311.
9. David DJ, Moore MH, Cooter RD. Tessier clefts revisited with a third dimension. *Cleft Palate J.* 1989;26:163–184.
10. Jellouli Elloumi A, Souissi R, Trabelsi A, et al. [Congenital cysts and fistulas of the face and neck: often unrecognized dysembryoplasias]. *Tunis Med.* 1999;77:117–126.
11. Stricker M, Flot F, Malka G, et al. [Cysts and fistulas of embryonal origin of the face]. *Rev Stomatol Chir Maxillofac.* 1976;77:109–112.
12. Beauvillain de Montreuil C, Hamon S, Litoux P. Congenital cysts and fistulae of the face and the neck. *Ann Dermatol Venereol.* 1988; 115:855–858.
13. Lachard J, Gola R. Congenital cysts and fistulas of the neck. *Rev Prat.* 1983; 33:1557–1563.
14. Blaschko A. *Die Nervenverteilung in der Haut in ihrer Beziehung zu den Erkrankungen der Haut. Beilage zu den Verhandlungen der Deutschen Dermatologischen Gesellschaft. VII Congress zu Breslau.* Mai. Wien Leipzig: Braumüller; 1901.
15. Jackson R. The lines of Blaschko: a review and reconsideration: observations of the cause of certain unusual linear conditions of the skin. *Br J Dermatol.* 1976;95:349–360.
16. Pinkus H. Adnexal tumors, benign, not-so-benign and malignant. *Adv Biol Skin* 1966;7:255–276.
17. Callahan CA, Oro AE. Monstrous attempts at adnexogenesis: regulating hair follicle progenitors through Sonic hedgehog signaling. *Curr Opin Genet Dev.* 2001;11: 541–546.
18. Hutchin ME, Kariapper MS, Grachtchouk M, et al. Sustained Hedgehog signaling is required for basal cell carcinoma proliferation and survival: conditional skin tumorigenesis recapitulates the hair growth cycle. *Genes Dev.* 2005;19:214–223.
19. Caro I, Low JA. The role of the hedgehog signaling pathway in the development of basal cell carcinoma and opportunities for treatment. *Clin Cancer Res.* 2010;16:3335–3339.
20. Epstein EH. Basal cell carcinomas: attack of the hedgehog. *Nat Rev Cancer* 2008;8:743–754.
21. Grachtchouk M, Pero J, Yang SH, et al. Basal cell carcinomas in mice arise from hair follicle stem cells and multiple epithelial progenitor populations. *J Clin Invest.* 2011;121:1768–1781.
22. Sandhiya S, Melvin G, Kumar SS, et al. The dawn of hedgehog inhibitors: Vismodegib. *J Pharmacol Pharmacother.* 2013;4:4–7.
23. Metzis V, Courtney AD, Kerr MC, et al. Patched1 is required in neural crest cells for the prevention of orofacial clefts. *Hum Mol Genet.* 2013;22:5026–5035.
24. Bradley JP, Hurwitz DJ, Carstens MH. Embriology, classifications, and descriptions of craniofacial clefts. In: Mathes SJ, Hentz VR, eds. *Plastic Surgery.* Vol. 4, 2nd ed. Philadelphia, PA: Saunders Elsevier; 2006:25.