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

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**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.)

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.

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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 clefts5 (Fig. 1).
2. The anatomic diagram by Moore et al6 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 lateralocervical 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.

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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

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**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.
anterior midline,\textsuperscript{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.\textsuperscript{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.\textsuperscript{14,15}

As well dissertated by Pinkus\textsuperscript{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
The Hedgehog signaling pathway plays a relevant role in embryogenesis across multiple species including mammals and humans.\textsuperscript{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.\textsuperscript{19} Such an evidence has been further confirmed by a number of experimental animal studies.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{24} and the most intricate and destructive one.\textsuperscript{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 1. Tumors Distribution in the Cleft Sites

| Site          | Tumors Distribution | P  |
|---------------|---------------------|----|
|               | n (%)               |    |
| 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      | 5 (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 × 10\(^{-6}\) |

P value given by the binomial test.

\(n\), count and frequency (%) of tumors by site; NT, not tested; site, analyzed site.

### Table 2. Age at Surgical Intervention by Site

| Site          | Age at Surgical Intervention (Years) | Specific Cleft | Other Clefts | Noncleft | P\textsuperscript{*} | P\textsuperscript{†} |
|---------------|-------------------------------------|---------------|-------------|---------|---------------------|---------------------|
|               |                                     |               |             |         |                     |                     |
| 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 × 10\(^{-5}\) | < 1 × 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)    | 73 (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.

\(\text{P}\textsuperscript{*}\) value from the comparison of age at surgical intervention in specific cleft sites vs other cleft sites.

\(\text{P}\textsuperscript{†}\) 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 on 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 disembyrogenic potential.

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