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The Role of Embryologic Fusion Planes in the Invasiveness and Recurrence of Basal Cell Carcinoma: A Classic Mix-Up of Causation and Correlation

Linus T. D. Armstrong, BMedSc (Hons)*
Mark R. Magnusson, MBBS, FRACS (Plast)†
Michelle P. B. Guppy, MBBS, MPH, FRACGP*

Background: The facial embryologic fusion planes as regions of mesenchymal and ectodermal fusion of the primordial facial processes during embryological development have been suggested to influence the spread, invasiveness, pathogenesis, and recurrence of cutaneous carcinoma. This study sought to establish whether basal cell carcinoma (BCC) originating in embryologic fusion planes has a greater propensity for earlier depth of invasion, leading to an increased rate of lesion recurrence.
Methods: Facial BCCs excised in a single surgeon practice over 2 years were allocated into 2 anatomic domains according to their correlation with embryologic fusion planes. Lesion depth of invasion, surface area, and margins of excision were analyzed in conjunction with recurrence data over the following 70–80 months.
Results: Of the 331 lesions examined, 70 were located in embryologic fusion planes. No difference was found in the mean surface area and depth of invasion for lesions located in the 2 domains ($P > 0.05$). Ten lesion recurrences were identified, none of which were located in embryologic fusion planes. Recurrent lesions were excised with a significantly greater percentage of close and incomplete excision margins ($P < 0.05$).
Conclusions: BCC arising in embryologic fusion planes are not more invasive or at greater risk of recurrence. Excision margins seem to have the greatest influence on lesion recurrence. Because of the paucity of superfluous tissue and the cosmetic and functionally sensitive nature of these areas of embryologic fusion, specialist treatment of these lesions is recommended to ensure that adequacy of excision is not neglected at the cost of ease of closure and cosmesis. *(Plast Reconstr Surg Glob Open 2015;3:e582; doi: 10.1097/GOX.0000000000000571; Published online 18 December 2015.)*

*From the *University of New England, School of Rural Medicine, Armidale, New South Wales, Australia; and †Toowoomba Plastic Surgery, Allure Cosmetic Clinic, Toowoomba, Queensland, Australia.*
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Embryologic fusion planes (EFPs)—the regions of mesenchymal migration and fusion of the primordial facial processes during embryological development, have been implicated in the pathogenesis and spread of basal cell carcinoma (BCC) for some time.[1,2] It is postulated that EFPs differ in connective tissue structure from that of the surrounding area and offer a path of least resistance for lesions to spread deeply and aggressively throughout, often

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evading clinical detection.[2–7] Carcinoma arising in EFPs is believed to invade to unexpected depths and with greater pace, which is attributed to the changes in connective tissue stroma lying perpendicular to these zones. This mechanism is believed to account for the increased prevalence and higher recurrence rate of BCC reported in these areas.[3,4,6,8]

There are conflicting opinions as to the exact relationship between EFPs and BCC, however, with research also opposing this proposed pathogenesis. In a cadaveric study, EFPs did not exist as histologically identifiable structures upon microscopic examination of midfacial specimens, leading the authors to conclude that EFPs cannot influence the spread and invasiveness of BCC.[9]

Despite significant research examining the role of EFPs, no studies compared the excision margins of recurrent lesions in these planes. As excision margins greatly influence the rate of lesion recurrence, it seems that previous studies have not taken this factor into account when analyzing BCC recurrence in EFPs. Additionally, no studies have directly analyzed the depth of invasion for lesions in these locations despite postulations that tumors in these areas may become more deeply invasive at an earlier stage.

Adequately excising midfacial lesions (where EFPs are primarily located) are widely accepted to be especially challenging because of the complex topographical anatomy present in this region.[10] The area has a paucity of superfluous tissue and has complex functional and cosmetic features. This is highlighted in a study that analyzed the excision margins for 1539 consecutive cases of excised BCC and found that significantly smaller peripheral and deep excision margins were present for lesions located in cosmetically sensitive midfacial areas (periorbital, nose, cheek, lip, neck, and chin).[11] As a direct relationship exists between width of excision margin and rate of recurrence, it is possible that an increased rate of recurrence seen in the midfacial region is a result of the functional and cosmetically sensitive nature of this area, and its influence on the surgeon achieving adequate excision margins.

This study aimed to further investigate the influence EFPs and excision margins have on the invasiveness and recurrence of facial BCC. Surface area and depth of invasion for all lesions were analyzed, as well as the rate of recurrence and excision margins of lesions located in these planes.

PATIENTS AND METHODS

Study Design and Formation of Participant Cohort

This study was a retrospective cohort study. Patients from a single surgeon clinic in Toowoomba, Australia, were analyzed from January 1, 2006 to December 31, 2007. All patients who had a facial lesion excised during this period were extracted from the database (n = 869). Patients were included if the lesion treated was a BCC located anterior to the ear, superior to the mandibular border, and contained above by the temporal and forehead hairlines (or equivalent locations in the presence of baldness; Fig. 1). In total, 538 lesions were excluded (Table 1), leaving a remaining 331 lesions in the participant cohort.

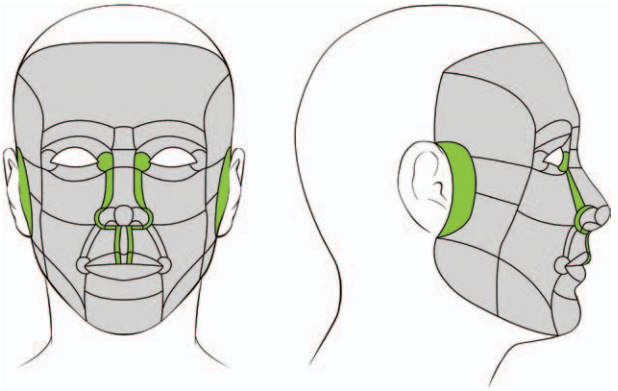

Fig. 1. Anatomic diagram of the face: facial units and embryologic fusion planes. Each zone has a code used in allocating lesions to the position of its approximate centre. Embryologic fusion planes are highlighted in green (medial canthus, paranasal, ala crease, inferior naris, philtral ridge, vertical lip, and preauricular).[8]

Data Extraction

Participant cohort pathology data, operative notes, and consultation notes were obtained. Data variables extracted included date of birth, gender, lesion location (including EFP and non-EFP location status), future recurrence on file, re-excision required because of insufficient margins, postoperative adjuvant treatments required (imiquimod or radiotherapy), and primary or recurrent lesion status. Data variables extracted from the lesion pathology report included tissue sample depth and dimensions, lesion dimensions, depth of lesion invasion, subtype, deep and peripheral excision margin clearance, and perineural involvement.

Excision Margins

Standardized margins of excision were used for all lesions in the participant cohort (Table 2).

Table 1. Participant Cohort Formation

Total Facial Lesions Excised	869
No diagram or lesion pathology available	15
Lesion other than BCC or located on ears and scalp	522
Patient death	1
Total lesions for inclusion	331

Table 2. Peripheral Excision Margins

Lesion Diameter (cm)	Border Acuity	Margin* (mm)
<1.0	Well defined	3
<1.0	Less well defined	4
1.0–2.0	Well defined	4
>2.0	Well to poorly defined	≥5
Recurrent lesions (all sizes)	Well to poorly defined	≥5

*Standard margins of excision were employed irrespective of location.

Excision with immediate definitive closure and delayed pathology was used for the majority of lesions. Frozen section was considered for aggressive infiltrative BCC subtypes with unknown extent of invasion, where tissue sparing could greatly influence the overall reconstruction and patient outcome.

Protocol for Retreatment

On the basis of histology, lesions received early retreatment if the margins on primary excision were inadequate either laterally or at the deep margin. Superficial BCC may be treated with topical imiquimod, and this was considered an option for close or microscopically involved lateral margins. Close margins were defined as a microscopic tumor free zone of 1 mm or less on the deep and or lateral margin of the pathology sample. Imiquimod was preferred for the treatment of incompletely excised superficial BCC in locations that were appropriate and in patients with normal immune function. Close or involved margins for invasive BCC were retreated with surgery or possibly radiotherapy if there were additional indications (ie, extensive perineural infiltration or patient request).

By virtue of the anatomical locations that these lesions occupied, there is frequently only a relatively thin layer of superfluous tissue for excision without functional or cosmetic consequences. Although tumor extirpation is paramount, it was the senior author's belief that an unbreached fascial plane is an effective barrier and important in the determining the adequacy of deep surgical margins.

For example, a lesion that seems superficial at the inner canthus is routinely removed including denuding the orbicularis of its fascia without complete muscle excision. A deep margin of 0.6–0.8 mm would be accepted and subject to follow up rather than re-excision as long as the lesion does not breach the underlying fascial plane histologically, there are no adverse histological features present (ie, perineural infiltration/infiltrative subtype), and the patient agrees to commit to this process.

Anatomical Allocation of Lesions

Diagrams drawn in consultation and operative notes were used to allocate lesions to their precise location on the studies anatomical diagram (Fig. 1). The anatomical diagram was a modified version of the diagram used in a study assessing the correlation of EFPs and anatomical distribution of BCC.[8] Two embryologic fusion domains added were the inferior naris plane (extending horizontally from the inferior portion of the ala crease to meet the superior philtral ridge) and the vertical lip plane (extending inferiorly from the philtral ridge plane to the oral aperture). The EFPs of the face (highlighted in Fig. 1) include the medial canthus, paranasal area, ala crease, philtral ridge, inferior naris, vertical lip, and preauricular area. Non-EFPs were defined as the remaining areas of the face indicated on the anatomical diagram. After lesion allocation was completed, lesions were separated into a control (non-EFP lesion) and test group (EFP lesion).

Search of Lesion Recurrence

A search for lesion recurrence was conducted within the clinic database, and through all main statewide pathology laboratories from time of excision over the following 70–80 month period.

Recognizing Recurrent Lesions

Pathology criteria were established to recognize recurrent lesions. Lesion location and lesion description, macroscopic and microscopic examination (hypertrophic changes and dermal scarring), and lesion subtype were criteria used to establish lesion recurrence. Lesions with the potential to be recurrent were analyzed in conjunction with a senior pathologist.

Surface Area and Depth of Invasion Calculation

Lesion surface area was calculated using axial dimensions provided in the pathology report and consultation notes. Irregularly shaped lesions (for which 2 axial dimensions were provided) were calculated using the formula of an ellipse. Depth of invasion was recorded as the deepest structure to which the lesion invaded (using the Clark classification).

Statistical Analysis

Variables were coded for and statistically analyzed using SPSS Version 21 (SPSS IBM, New York, N.Y.). A P value less than 0.05 was considered significant for all tests. The mean surface area of lesions in EFPs and non-EFPs, and the surface area of recurrent and non-recurrent lesions, was analyzed using an independent samples t test. Depth of invasion and sample tissue thickness between the 2 groups was analyzed using

crosstabulation analysis and a χ^2 test. A comparison of the recurrence rate within the 2 domains was performed using crosstabulation analysis and a Fisher exact test. Deep and peripheral excision margins for recurrent and nonrecurrent lesions, as well for lesions located in EFPs and non-EFPs were analyzed using a Fisher–Freeman–Halton exact test. Incidence of invasive subtypes between recurrent and nonrecurrent lesions, as well as EFP and non-EFPs, were compared using crosstabulation and a Fisher exact test.

RESULTS

The participant cohort consisted of 273 patients, with a total of 331 lesions excised from 2006 to 2007. The mean patient age was 66 years (range, 28–99 years). Females accounted for 146 lesions (53.5%) and males for 127 lesions (46.5%). The majority of lesions were primary (92.1%). Twenty-three (6.9%) lesions required early re-excision (as distinct from late re-excision for lesion recurrence) because of incomplete or insufficient margins, with residual BCC being identified in 9 (39.1%) of the re-excision samples. No difference was found in the re-excision rate for lesions in the 2 groups ($P = 0.185$).

Postoperative treatment with topical imiquimod was used for 13 (3.9%) lesions. Four were located in EFPs, and 10 of the 13 lesions were located in the nasal region. Radiotherapy was used postoperatively in 4 (1.2%) cases because of infiltrative differentiation with significant perineural infiltration. None of these lesions were located in EFPs. Only 1 had positive margins after initial excision. None were found to recur.

Lesion excision with immediate frozen section was used in 3 cases (0.9%). Two of these BCCs were located on the ala nasi covering almost the entire subunit, and the remaining lesion was located on the medial aspect of the lower eyelid. All 3 BCCs were deeply infiltrative fibrosing subtypes invading to Clark level 5. All lesions were located in non-EFP zones. Adequate margins were achieved, and none were found to recur.

Seventy lesions were located in EFPs (21%), and 261 lesions were located in non-EFPs (79%). The nasal region had the highest BCC incidence of all regions (142/331; 42.9%; Table 3).

Nodular differentiation was identified in 198 lesions (59.8%), followed by 127 containing superficial/multifocal differentiation (38.4%). Infiltrative, micronodular, and fibrosing/sclerosing subtypes were evenly distributed, with 84 (25.4%), 71 (21.5%), and 67 (20.2%) lesions containing components of these subtypes, respectively. Comparison of subtypes between the control and test groups showed uniform distribution of subtypes between EFPs and non-EFPs (Fig. 2).

Table 3. Incidence of BCC in Nasal Region

Location	EFP Status	No. of Lesions	% of Total
Nasal tip	Non-EFP	37	11.2
Ala nasi	Non-EFP	34	10.3
Nasal dorsum	Non-EFP	34	10.3
Para nasal	EFP	22	6.6
Ala crease	EFP	15	4.5

Lesion surface dimensions were present for 307 of 331 lesions (92.8%), 68 of which were located in an EFP and 239 that were not. The mean surface area of lesions located in EFPs and non-EFPs was 54.77 and 74.5 mm^2, respectively; however, this was not a statistically significant difference ($P = 0.123$; Table 4).

The depth of lesion invasion was reported in 299 of 331 (90.3%) lesion pathology reports. There was no difference in depth of invasion between the control and test groups ($P = 0.347$; Table 5 and Fig. 3).

Ten lesion recurrences were found within the observation period (3%; Table 6). All 10 recurrences were found to be located in non-EFPs; however, there was no statistically significant difference between the 2 groups ($P = 0.128$). Recurrent lesions had a greater number of close and incomplete peripheral and deep excision margins than nonrecurrent lesions ($P = 0.013$ and $P = 0.048$, respectively). Peripheral and deep excision margins were not significantly different for lesions located in EFPs and non-EFPs ($P = 0.465$ and $P = 0.591$, respectively). Recurrent lesions were more likely to contain infiltrative and micronodular differentiation than nonrecurrent lesions, with 24.3% of nonrecurrent lesions containing infiltrative subtype compared with 60% of recurrent lesions ($P = 0.02$), and 20.6% of nonrecurrent lesions containing micronodular subtype compared with 50% of recurrent lesions ($P = 0.041$). There was no difference in the mean surface area of recurrent lesions compared with nonrecurrent lesions (103.85–69.17 mm; $P = 0.273$). Fourteen cases

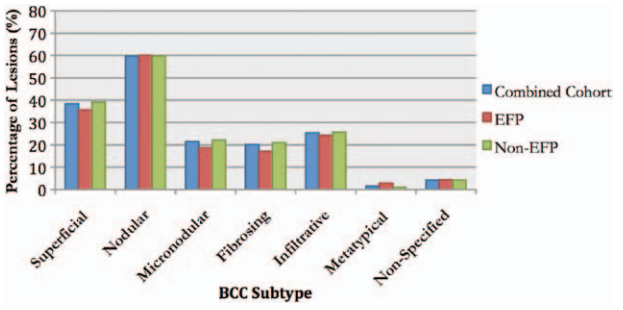

Fig. 2. Incidence of lesion subtypes in EFPs and non-EFPs.

Table 4. Mean Surface Area of Lesions in EFPs and Non-EFPs ($P = 0.123$)

Location	No. of Lesions	Mean Surface Area (mm^2)	Standard Deviation
EFP	239	74.58	101.63
Non-EFP	68	54.77	53.20

of perineural invasion were found in nonrecurrent lesions, with only 1 case of perineural invasion found in a recurrent lesion ($P = 0.375$).

Sample tissue thickness was provided for 291 of 331 lesions (88.5%). Lesions located in non-EFPs were excised with a thicker sample of tissue (4.3 mm) on average than EFP lesions (3.6 mm; $P = 0.023$).

DISCUSSION

Previous research implicated EFPs in higher rates of BCC recurrence and poorer treatment outcomes, postulating the facilitation of rapid and deep invasion of tissue in these planes. We hypothesized that BCC in EFPs are not predisposed to greater invasiveness and do not become deeply infiltrative at an earlier stage of development because of an embryologic phenomenon. We believe that BCC originating in EFPs are prone to excision with narrow margins because treating physicians may be concerned with their ability to close the wound, to obtain a superior aesthetic result, and to minimize the functional impact of excision or because there is a thin subcutaneous tissue plane in these areas. This hypothesis was supported by the study results, as EFPs were not areas where lesions were significantly more invasive, larger, or recurrent, and excision margins were the greatest predictor of recurrence irrespective of lesion EFP status.

Lesions located in EFPs do not seem to be at greater risk of recurrence because of an embryologic phenomenon, with no difference in recurrence rate found between the 2 study groups ($P = 0.128$). Additionally, none of the 10 lesion recurrences were located in EFPs. This result differs from previous research, which has reported a higher rate of recurrence for BCC arising in these planes, with 1 study reporting a recurrence rate of 16.4%.[3,4] Previous research that has examined BCC recurrence rate in EFPs has not concurrently assessed excision margins. The low rate of recurrence observed in EFPs for this study is believed to be because of the adequacy of excision margins achieved in these zones. The surgical goal was to achieve a standard margin of excision irrespective of location, which is demonstrated by there being no difference in deep and peripheral excision margins between EFPs and non-EFPs ($P = 0.591$ and $P = 0.465$). Additionally, only 23 lesions (6.9%) were found to have incomplete or insufficient margins after primary excision, subsequently requiring early re-excision for involved or narrow margins. This result represents a low rate of re-excision within the literature, with 1 study finding a re-excision rate as high as 18%.[12]

Table 5. Depth of Invasion in EFPs and Non-EFPs

		Non-EFP	EFP	Total
Clark's level				
Level 1	No. of lesions	13	3	16
	% of lesions in each group	5.5	4.9	5.4
Level 2	No. of lesions	8	2	10
	% of lesions in each group	3.4	3.3	3.3
Level 3	No. of lesions	39	10	49
	% of lesions in each group	16.4	16.4	16.4
Level 4	No. of lesions	128	40	168
	% of lesions in each group	53.8	65.6	56.2
Level 5	No. of lesions	50	6	56
	% of lesions in each group	21.0	9.8	18.7
Total	Total number of lesions	238	61	299
	% of all lesions analyzed	79.6	20.4	100.0

Excision margins had the greatest influence on future lesion recurrence, with recurrent lesions having significantly more close or incomplete peripheral and deep excision margins ($P = 0.013$ and $P = 0.048$, respectively) after excision. In conjunction with no recurrent EFP lesions found, this supports the authors' belief that increased recurrence in EFPs is attributed to the anatomical and surgical complexity in these areas, rather than a pathogenic role of EFPs. Adequate excision margins had the greatest impact in decreasing BCC recurrence, and it is believed that the low rate of recurrence found in this study is because of a noncompromising approach to the adequacy of excision margins. As EFPs are cosmetically sensitive areas, appropriate excision margins could be achieved without excising conservatively, as specialized closure techniques (ie, flaps and grafts) could be used to maintain form and function.

BCC arising in EFPs do not seem to invade to greater depths or have greater propensity for horizontal spread. No significant difference in mean surface area or depth of invasion of lesions within the 2 groups was found ($P = 0.123$ and $P = 0.347$). This differs from previous research that suggested cutaneous carcinoma arising in EFPs to be more invasive, infiltrating deeper into tissue at an earlier stage of development.[2–7] Previous studies have not directly analyzed the depth of invasion and surface area of lesions in these 2 domains, with only a single observational account found to suggest increased invasiveness of lesions in EFPs.

The depth of tissue in EFPs was significantly thinner (3.6 mm) than in non-EFPs (4.3 mm; $P = 0.023$);

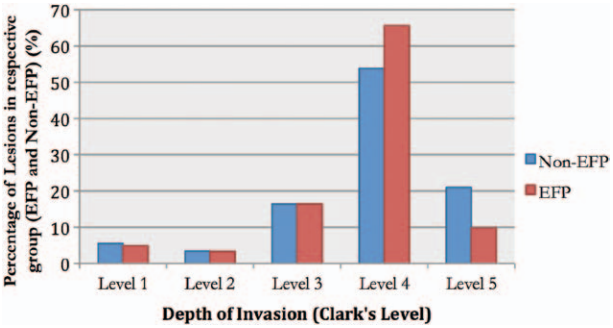

Fig. 3. Depth of invasion in EFPs and non-EFPs ($P = 0.347$).

however adequate surgical margins were always sought. In EFPs where subcutaneous tissue is relatively sparse, the removal of a histologically intact/unbreached fascial plane was accepted as an adequate deep margin even when the measured margin may be as low as 0.6 mm (in the absence of additional aggressive histological features).

Study Limitations

As lesions still have potential to recur after a 6 or 7 year follow-up (risk < 18%), a small number of lesions may not yet have recurred and therefore have not been included in the study.[13] If the patient had the recurrence excised by a different physician outside of the region/state and sent to an alternate pathology laboratory not included in the study, the recurrence would not have been identified by the search conducted. To mitigate this risk, a large-scale search for recurrence was conducted within all major pathology laboratories in the region and state (Pathology Queensland, Sullivan and Nicolaides and QML Pathology). During the research period, these were the only laboratories servicing our rural region and service a far greater catchment than just our region. This search identified 4 additional recurrences. The senior author was also the sole plastic surgeon operating in the town and surrounding region at the time.

CONCLUSIONS AND IMPLICATIONS

This study is the first to take into account excision margins when comparing BCC recurrence in EFPs and non-EFPs. Additionally, it is the first to directly compare the depth of invasion for lesions in these locations. In conclusion, it appears that EFPs do not predispose BCC to increased depth of invasion or increased recurrence because of an embryologic phenomenon. Inadequacy of excision margins seems to have the greatest influence on BCC recurrence irrespective of location. Increased recurrence of BCC in EFPs previously reported may be because of the inadequacy of excision margins, owed to the difficulty of achieving adequate tumor clearance in these functionally and cosmetically sensitive areas.

It is important to ensure that adequate excision margins are achieved when removing facial BCC. Achieving an adequate excision requires familiarity with the anatomy of this zone. This may also put pressure on less specialized physicians to refer lesions in these highly sensitive zones for specialized excision and closure, to ensure a decreased chance of recurrence and achieve the maximum functional and cosmetic outcome.

Table 6. Recurrence of Lesions by Anatomic Zone

Location	EFP Status	Recurrences
Temple	Non-EFP	1
Forehead	Non-EFP	1
Lower eyelid	Non-EFP	2
Ala nasi	Non-EFP	2
Nasal tip	Non-EFP	2
Zygoma	Non-EFP	1
Medial mandible	Non-EFP	1

Mark R. Magnusson, MBBS, FRACS (Plast)
Toowoomba Plastic Surgery
Allure Cosmetic Clinic
8 Margaret St, East Toowoomba
Queensland 4350, Australia
E-mail: mark@toowoombaplasticsurgery.com.au

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