

## A study on the expression of EZH2, Bcl-2 and Ber-EP in BCC

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### Summary

Basal cell carcinoma is the most common malignant tumour in humans. In cases with indistinct morphology on H&E-stained slides, immunohistochemistry may help distinguish basal cell carcinoma from other similar-appearing lesions. Our study aimed to investigate the expression of a marker panel comprising EZH2, Bcl-2, and Ber-EP4 in morphologically diagnosed, CK20-verified cutaneous basal cell carcinomas.

**Materials and methods:** A cross-sectional study of 50 histologically confirmed cases of basal cell carcinoma was conducted. Immunohistochemical staining was performed using the following markers: EZH2, Bcl-2, Ber-EP4, and CK20. Due to the lack of a standardised method for evaluating markers, we adopted and modified the staining index (SI), which semi-quantitatively combines staining intensity and the percentage of positive cells. The results were systematised and interpreted using IBM SPSS.

**Results:** All 50 examined tumours tested negative for CK20 (100%), thereby excluding mimics. All 50 tumours stained positive for EZH2 and Bcl-2 (100%), and only one stained negative for Ber-EP4 (98% positive). We found no association between histological type and EZH2 ( $p = 0.376$ ), Bcl-2 ( $p = 0.376$ ), and Ber-EP4 ( $p = 0.318$ ), respectively, or their co-expression ( $p = 0.258$ ). High co-expression of two of the three markers was observed in 33 of the 50 examined cases (66%), and a low co-expression in 4 cases (8%).

**Conclusion:** The marker panel demonstrates co-expression of the three markers in the context of negative CK20 in over 90% of the cases. In challenging cases, it is important to consider clinical, morphological, and immunohistochemical features together.

**Key words:** Basal cell carcinoma, Bcl-2, Ber-EP4, CK20, co-expression patterns, EZH2



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### Introduction

Basal cell carcinoma (BCC) is the most common malignant tumour in humans worldwide (Chinem and Miot 2011). It is one of the so-called keratinocytic tumours (together with squamous cell carcinoma), whose incidence surpasses that of all other neoplasms (Albert and Weinstock 2003). The rising frequency and decreasing age of onset in recent years have made it a socially significant disease, associated with high morbidity and costs (Hu et al. 2022; Sendín-Martín et al. 2025). Clinically and histologically, basal cell carcinoma is a heterogeneous tumour that presents in different variants - nodular, cystic,

morpheaform, infiltrative, micronodular, superficial, pigmented, and others. These different subtypes of BCC exhibit diverse biological behaviour, clinical and histological profiles, and prognoses (Raasch et al. 2006; Cameron et al. 2021). The basosquamous, infiltrative, morpheaform, and micronodular types are among the most aggressive (Peris et al. 2023).

Currently, the gold standard in the histological diagnosis of BCC is hematoxylin and eosin (H&E) staining. However, this examination does not always reliably distinguish some types of BCC from other carcinomas, such as basosquamous carcinoma, whose treatment differs substantially from that of BCC due to its higher risk of metastasis (Karahan et al. 2006; Sunjaya et al. 2017). In practice, certain immunohistochemical (IHC) markers are used to support morphological diagnosis. The most commonly applied among them are Cytokeratin 20 (CK20), which should be negative in BCC, and positive markers, including Bcl-2, Ber-EP4, EZH2, among others (Crowson et al. 1996; Ramdial et al. 2000; Ramezani et al. 2016; Rao et al. 2016; Ozkanli 2023).

Numerous studies have aimed to identify optimal diagnostic IHC panels for distinguishing BCC from other morphologically similar lesions. For example, (Ramezani et al. 2016) showed that positivity for Bcl-2 and CD10 differentiates BCC (from squamous cell carcinoma) with an accuracy of 88% and specificity of 100%. It is worth noting that the authors reported Bcl-2 positivity in 3.5% of squamous cell carcinomas. In their study, Bcl-2 positivity was observed in all BCCs examined.

Other studies do not support the claim that all BCCs are positive for Bcl-2. Moreover, Crowson AN et al. have noted that Bcl-2 is expressed at varying levels, and this variability may be linked to tumour biological features or tumour progression.

The pattern of positivity, however, is often weak and diffuse (Bcl-2), or incomplete and patchy with variable intensity -Ber-EP4 or EZH2 (Crowson et al. 1996; Ramdial et al. 2000; Rao et al. 2016; Ozkanli 2023).

According to Ozkanli (2023), Ber-EP4 expression can differ between morphological variants and within different tumour areas of BCCs.

There is relatively limited experience with using a panel of markers, including Bcl-2, Ber-EP4, EZH2, and CK20, for BCC, as well as analysing their expression and intensity both among BCCs in general and within their histological variants.

## Objective

To investigate the expression of a marker panel including EZH2, Bcl-2, and Ber-EP4 in morphologically diagnosed and CK20-verified cutaneous basal cell carcinomas.

## Materials and methods

### Sample selection

A cross-sectional study was conducted at the Dr Georgi Stranski University Hospital and Medical University - Pleven. Fifty histologically confirmed cases of basal cell carcinoma were randomly selected during 2023–2024 from the GAMMA Codemaster system of the University Hospital. The tumours were grouped by histological subtype. Clinical data, including sex and age at diagnosis, were collected.

## **Histologic examination**

Corresponding H&E-stained slides were reviewed by a pathologist at the Department of Pathology. Histological types were confirmed.

## **Immunohistochemistry**

At the Competence Centre of Medical University - Pleven, standard histological sections were prepared from paraffin blocks on adhesive slides. Immunohistochemical staining was performed using the studied markers: EZH2, Bcl-2, Ber-EP4, and CK20. Sections from formalin-fixed, paraffin-embedded tissue samples were cut at 3  $\mu$ m thickness. After deparaffinisation and rehydration, staining was performed. Reagents and protocols from Biocare Medical (USA) were mainly used; the EZH2 antibody was from GenomeMe (Canada). Staining was carried out with antibodies CK20 (clone Ks20.8), Ber-EP4 (clone Ber-EP4), Bcl-2 (clone 100/5D), and EZH2 (clone IHC 770). Visualisation was done with the MACH 1 Universal HRP-polymer detector (Biocare Medical, USA). Controls and interpretation followed the manufacturer's documentation.

## **Expression grading**

The evaluation was performed by a histopathologist using a light microscope equipped with standard magnifications and a digital camera. Normal epidermis in each section served as an internal negative control. Only histological areas including the tumour were assessed. Due to the lack of a standardised method for evaluating the markers EZH2, Bcl-2, and Ber-EP4, we applied a modified method of our own. The H-score (0–300), used by some authors, would yield highly heterogeneous results with the small sample size of 50 cases. Therefore, we did not consider it suitable for this study (Petronilho et al. 2021). Instead, we adopted another method reported in the literature: the staining index (SI) – semi-quantitatively summing the staining intensity (0 – negative, 1 – weak, 2 – moderate, 3 – strong) and the percentage of positive cells (1 – <33%, 2 – 34–66%, 3 – >67%). We assessed the tumour areas with the highest percentage of positivity and recorded the staining intensity in these areas. A total score >4 was considered high expression of the marker, while a total score  $\leq$ 4 was considered low expression (Van Rijn 1994; Bachmann et al. 2006; Puizina-Ivić et al. 2008; Rao et al. 2016; Mendez-Flores et al. 2022). The positivity pattern was recorded as predominantly peripheral or predominantly diffuse (modified from Ozkanli 2023). CK20 was recorded as either positive or negative. The obtained results were summarised and analysed.

## **Statistical analysis**

The results were systematised and interpreted using IBM SPSS® Statistics version 26. To assess the presence of an association between categorical data, the chi-square test was used. Values of  $p < 0.05$  were considered statistically significant.

## Ethical approval

This study was approved by the Ethics Committee of Scientific Research (ECSR) at MU Pleven (Ref. No. 782/ECSR/14.06.24, Protocol No. 79) and conducted in accordance with the Declaration of Helsinki.

## Results

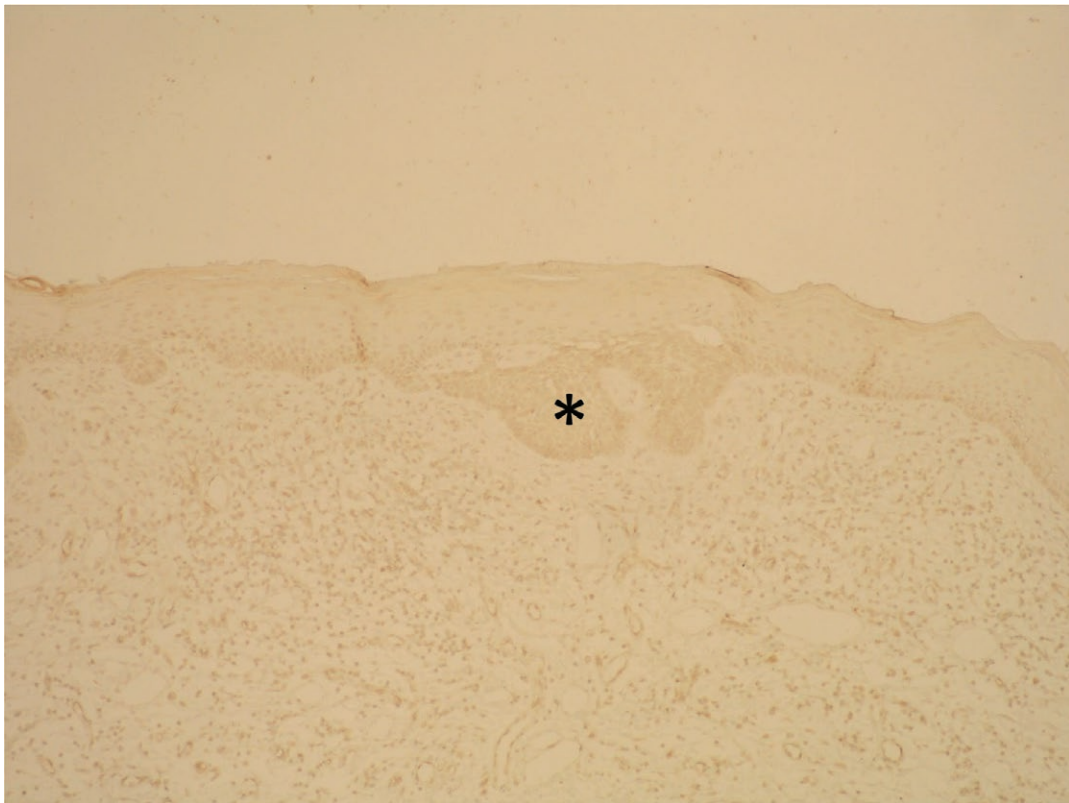
### CK20

All 50 examined tumours tested negative for CK20, thereby confirming that they are basal cell carcinomas, with no trichoblastomas or Merkel cell carcinomas (MCC) present (Fig. 1).

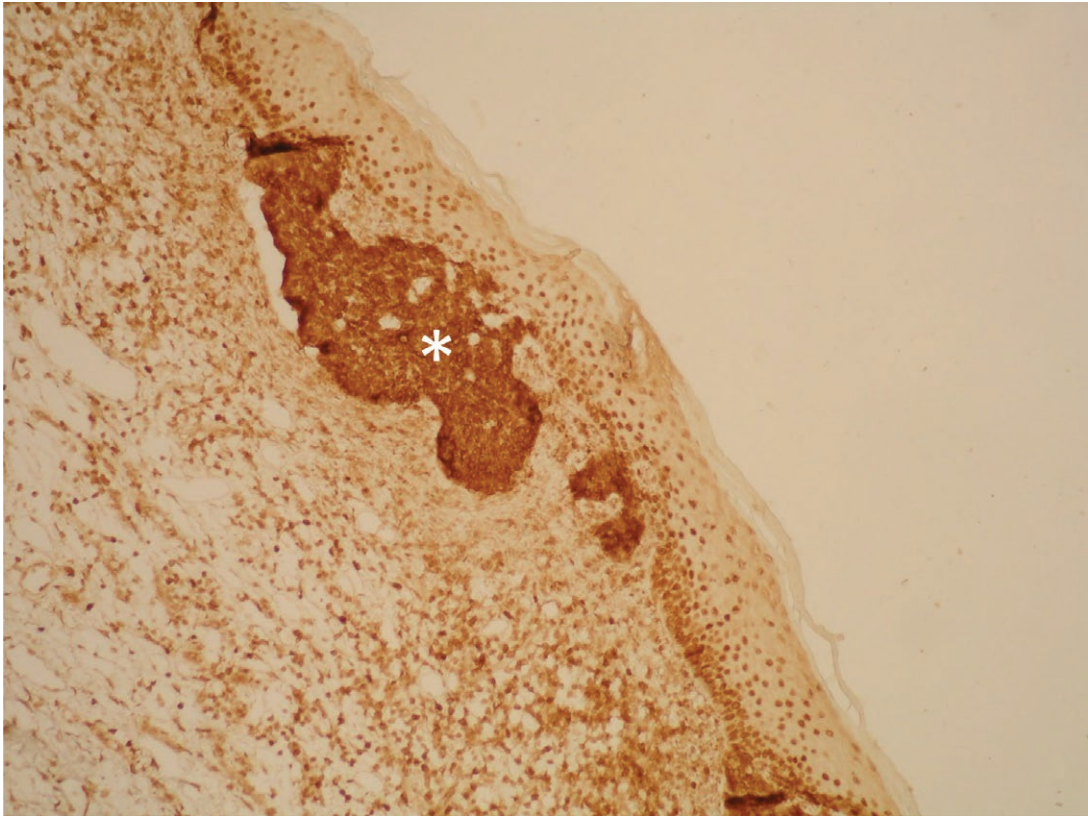
### Individual expression of EZH2, Bcl-2, and Ber-EP4

All 50 tumours were positive for EZH2. Low expression ( $\leq 4$ ) was observed in 15 cases, while high expression ( $>4$ ) was found in 35 cases. No negative samples were recorded (Fig. 2). In larger tumours, a less intensely stained centre of the tumour nests was observed compared to the more intensely stained periphery.

All 50 tumours were positive for Bcl-2, with no negative samples. Tumour expression of Bcl-2 was low ( $\leq 4$ ) in 14 cases, and high ( $>4$ ) in 36 cases (Fig. 3). Again, in larger tumours, a less intensely stained centre of the tumour nests was seen in contrast to the more intensely stained periphery.

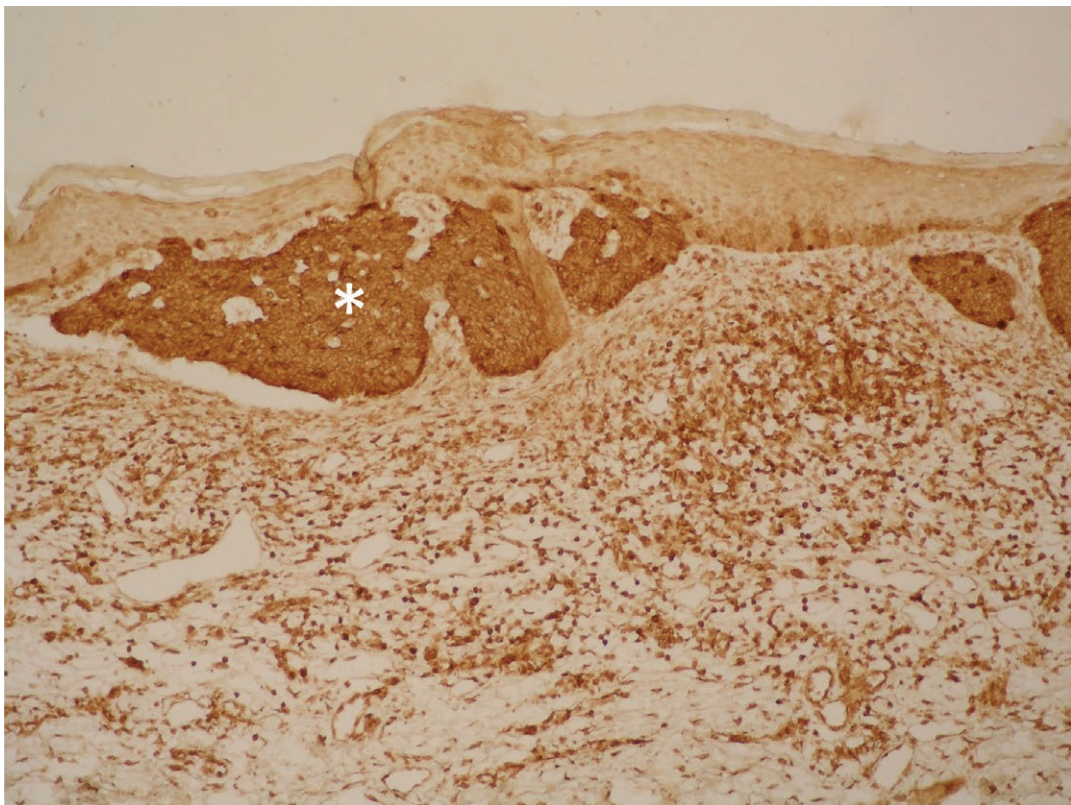


**Figure 1.** Cytokeratin 20 (CK20) expression in BCC – Superficial BCC (\*) with no positive cells for CK20 staining (original magnification  $\times 100$ ). Normal epidermis is also CK20-negative (internal control).



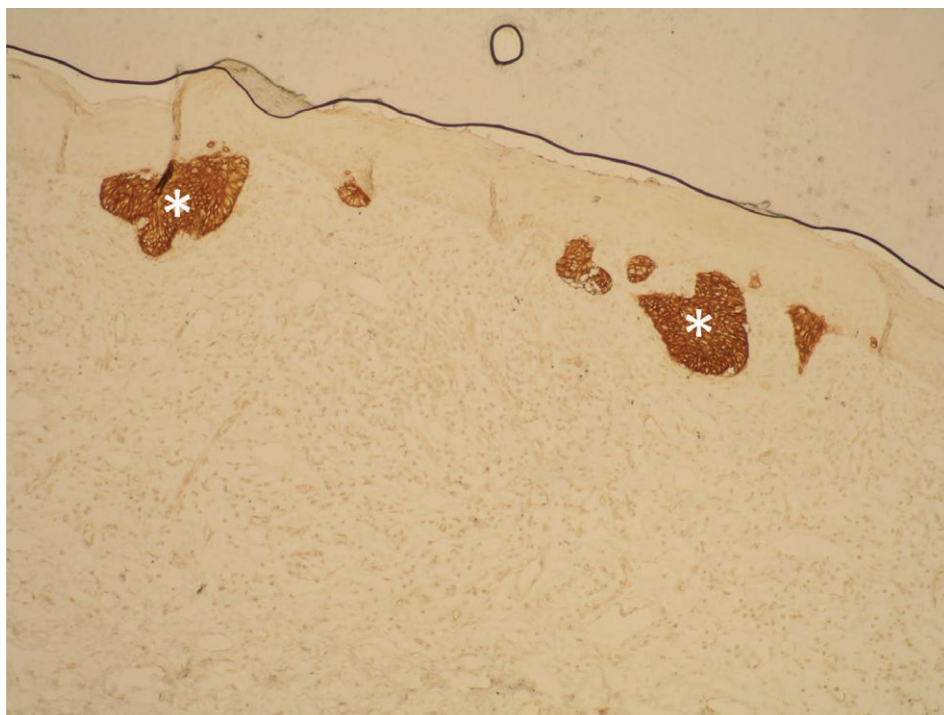
**Figure 2.** EZH2 expression in BCC – The same BCC (\*), with apparent positive staining with strong intensity (6/6) for EZH2 in the majority of the tumour cells (original magnification  $\times 100$ ).

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**Figure 3.** Bcl-2 expression in BCC – The same BCC (\*) with intense homogenous staining for Bcl-2 (6/6) in the majority of the tumour cells (original magnification  $\times 100$ ).

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**Figure 4.** Ber-EP4 expression in BCC – Superficial multifocal BCC (\*) with positive (6/6) staining for Ber-EP4 with strong intensity diffusely in the whole tumour (original magnification  $\times 100$ ). Normal epidermis is Ber-EP4 negative (internal control).

Of all samples ( $n = 50$ ), 49 were positive for Ber-EP4, and one was negative. Low expression ( $\leq 4$ ) was found in 14 carcinomas. In contrast, high expression ( $>4$ ) was observed in 35 cases (Fig. 4). Here, too, in larger tumours, a less intensely stained centre of the tumour nests was seen compared to the more intensely stained periphery.

In smaller tumours, the staining was more homogeneous, without the aforementioned variation in staining for the investigated markers. This trend, however, was not absolute, and it is difficult to precisely evaluate in a small series of cases.

### Coexpression of EZH2, Bcl-2 and Ber-EP4

High co-expression of two of the three studied markers was observed in 33 of the 50 examined cases. At the same time, low co-expression was observed in only 4 cases. Details are presented in Table 1.

The majority of tumours showed high expression of all three or at least two of the markers with high intensity in a large percentage of tumour cells (score  $>4$ ).

**Table 1.** Co-expression of EZH2, Bcl-2, and Ber-EP4.

Combined expression of the three markers	Number of tumours
EZH2 $>4$ , BCL2 $>4$ , BEReP4 $>4$	18
EZH2 $<4$ , BCL2 $>4$ , BEReP4 $>4$	2
EZH2 $<4$ , BCL2 $<4$ , BEReP4 $>4$	2
EZH2 $<4$ , BCL2 $>4$ , BEReP4 $<4$	7
EZH2 $>4$ , BCL2 $>4$ , BEReP4 $<4$	9
EZH2 $<4$ , BCL2 $<4$ , BEReP4 $<4$	4
EZH2 $>4$ , BCL2 $<4$ , BEReP4 $>4$	4
EZH2 $>4$ , BCL2 $<4$ , BEReP4 $<4$	4

### Individual expression of EZH2, Bcl-2 and Ber-EP4 in the different morphological variants of BCC

After comparing EZH2 expression across the different morphological variants of BCC, we found no association between histotype and EZH2 (Chi-Square = 7.529, Df = 7; p = 0.376) (see Table 2). Here, too, the distribution was not statistically reliable enough.

**Table 2.** EZH2 staining in the different histologic subtypes of BCC.

Histotype	EZH2_score	
	</=4 – weak expression	>4 – strong expression
superficial	3	5
nodular/solid (= pigmented, keratotic)	7	19
micronodular	1	1
infiltrative (sclerosing, morpheaform)	2	5
basosquamous	0	1
cystic	0	1
mixed	2	0
NOS (not otherwise specified)	0	3

70% of the examined tumours (35 out of 50) showed strong expression (>4) of EZH2 across the different morphological subtypes.

When comparing Bcl-2 expression across the different histological types of BCC, no association was found between histotype and Bcl-2 (Chi-Square = 7.528, Df = 7; p = 0.376) (see Table 3). Again, the statistical result is not reliable enough due to the small number of cases.

**Table 3.** BCL-2 staining in the different histologic subtypes of BCC.

Histotype	Bcl-2_score	
	</=4 – weak expression	>4 – strong expression
superficial	2	6
nodular / solid (= pigmented, keratotic)	8	18
micronodular	0	2
infiltrative (sclerosing, morpheaform)	1	6
basosquamous	0	1
cystic	1	1
mixed	0	2
NOS (not otherwise specified)	2	1

Of the 50 tumours, 36 (72%) showed intense Bcl-2 staining, and this was observed across the majority of histotypes.

After comparing Ber-EP4 expression across the different morphological variants of BCC, no association was found between histotype and Ber-EP4 (Chi-Square = 8.168, Df = 7; p = 0.318) (see Table 4). The small sample size (n = 50) and its distribution render the statistical results insufficiently reliable. Overall, the tumour type does not determine the intensity of Ber-EP4 expression.

26 of 50 tumours showed strong expression of Ber-EP4 (52%), and only one stained negative.

**Table 4.** Ber-EP4 staining in the different histologic subtypes of BCC.

Histotype	Ber-EP4_score	
	</=4 – weak expression	>4 – strong expression
superficial	4	4
nodular / solid (= pigmented, keratotic)	11	15
micronodular	2	0
infiltrative (sclerosing, morpheaform)	2	5
basosquamous	1	0
cystic	0	1
mixed	2	0
NOS (not otherwise specified)	2	1

### Co-expression of the markers in the different morphological variants of BCC

The combination of EZH2, Bcl-2, and Ber-EP4, along with their levels of expression, did not show a statistically significant association with histological distribution (Pearson Chi-Square = 54.994; Df = 49; p = 0.258). It is notable that, most often, all three markers, or at least two of them, showed intense staining (see Table 5).

There was no clear correlation between the expression of the three markers and histologic subtype. It is noteworthy, however, that, in most cases, either all three markers or at least two of them showed intense staining.

### Discussion

Morphologically, basal cell carcinomas are distinct tumours composed of atypical basaloid cells, with some variants exhibiting a clearly palisaded arrangement of tumour cells along the periphery of the tumour nests. Often, the tumours show a fibro-myxoid stroma, and occasionally contain melanin pigment. The differential diagnosis for these tumours can be quite broad, including Merkel cell carcinoma, sebaceous carcinoma, basaloid follicular neoplasms, and basaloid squamous cell carcinomas. Frequently, markers such as Bcl-2, BerEP-4, CK20, CD10, p40, CK5/6, p63, AR, EMA, CEA, and others are used depending on the case (Liu et al. 2024; Ramezani et al. 2016; WHO Classification of Skin Tumours 2023).

According to Sari Aslani et al. (2013), CD10 expression by tumour cells in basal cell carcinoma was observed in 42 of 55 cases; meanwhile, in trichoepithelioma,

**Table 5.** Co-expression of EZH2, Bcl-2, and Ber-EP4 and histologic subtype of BCC.

BCC histologic subtype	EZH2>4; Bcl2>4; BerEP4>4	EZH2<4; Bcl2>4; BerEP4>4	EZH2<4; Bcl2<4; BerEP4>4	EZH2<4; Bcl2>4; BerEP4<4	EZH2>4; Bcl2>4; BerEP4<4	EZH2<4; Bcl2<4; BerEP4<4	EZH2>4; Bcl2<4; BerEP4>4	EZH2>4; Bcl2<4; BerEP4<4
Superficial	3	1			2	2		
Nodular	10	1	2	3	4	1	2	3
Micronodular				1	1			
Infiltrating	5			1		1		
Basosquamous					1			
Nodulocystic							1	
Mixed				2				
NOS					1		1	1

no expression was observed in the neoplastic epithelial cell population. The mentioned fact suggests that positivity for CD10 may have real clinical value.

The use of negative markers, such as EMA, for identifying squamous carcinomas among basal cell carcinoma epidermal tumours of the skin is generally useful. However, areas of squamous differentiation are positive and may be confusing to the inexperienced in dermatopathology (Hussein et al. 2022). Furthermore, not all squamous cell carcinomas are EMA-positive, which may further complicate interpretation (Beer et al. 2000).

The androgen receptor (AR) can be added to the diagnostic panel of markers to distinguish basal cell carcinoma, as it is generally positive. In contrast, trichoblastoma is usually negative (Izickson et al. 2005). When used in a panel in the proper context, EMA, AR, and CD10 may provide diagnostic benefit.

The negativity or positivity of tumours for Cytokeratin 20 (CK20) is an important aspect in the immunohistochemical diagnostic clarification of basaloid skin tumours. CK20 is part of the cytoskeleton of epithelial cells. It is used to distinguish trichoblastomas from basal cell carcinomas in difficult-to-assess cases. Basal cell carcinoma expresses a cytokeratin profile similar to that of follicular germinative cells, characterised by CK5/6 and CK14 expression and the absence of CK20. In some trichoblastomas, a small number of Merkel cells are positive for CK20, scattered and few in number, unlike in MCC, where diffuse perinuclear positivity is observed. Most MCCs are CK20-positive, while BCCs are CK20-negative (Yang et al. 2004).

EZH2 and Ki67 have been identified as biomarkers associated with aggressive BCC types, suggesting that EZH2 may represent a potential therapeutic target. Further research is needed to determine its predictive and prognostic value regarding treatment response.

The results of the present study highlighted several important aspects of the immunohistochemical expression of EZH2, Bcl-2, and Ber-EP4 in BCC. First, no tumour was found to be simultaneously negative for all three markers, with only one case being entirely negative for Ber-EP4. The pattern of positivity and the staining intensity (although presented here in a more summarised form) support the data reported in the literature (Ozkanli, 2023). Nevertheless, the variability in expression among individual tumours limits their use as standalone markers, thus underscoring the need for a standardised diagnostic panel for BCC.

EZH2 (Enhancer of Zeste Homolog 2) is a key enzyme that regulates gene expression by repressing tumour suppressor genes, thereby facilitating tumour growth. The expression of EZH2 in basal cell carcinomas has been described by other authors and is considered a marker of tumour aggressiveness (Rao et al. 2016, 2018). EZH2 is expressed in a variety of skin tumours, and its positivity as a standalone IHC marker is not sufficient to determine histogenesis (Xie et al. 2014).

Bcl-2 (B-cell lymphoma 2) is a mitochondrial proto-oncogene that blocks apoptosis in the pro-B lymphocyte cell line (Hockenbery et al. 1990). Like CK20, Bcl-2 distinguishes basal cell carcinomas (in which it is positive) from trichoblastomas, in which Bcl-2 is usually negative (Rijn 1994). Several other skin neoplasms can also express Bcl-2. Notably, the pattern of Bcl-2 expression varies among the different variants of basal cell carcinoma (Puizina-Ivić et al. 2008). Bcl-2 is expressed in basal cell carcinomas predominantly with moderate and weak intensity over a large proportion of the tumor volume (diffusely).

Our results are consistent with the data reported in the literature (Memije et al. 2014; Mendez-Flores et al. 2022).

Ber-EP4 is a monoclonal antibody that binds to the membrane glycoprotein EpCAM (CD326), which is present in all non-squamous epithelial cells. EpCAM is overexpressed in certain carcinomas such as BCC, colorectal carcinoma, and breast carcinoma, and its use in targeted therapy is being studied. According to a study by Dasgeb et al. (2013), Ber-EP4 positivity among the more common skin neoplasms is observed in trichoepitheliomas and Merkel cell carcinomas. Less commonly, squamous cell carcinomas and sebaceous adenomas can also be positive, necessitating the use of and interpretation of the marker in a panel rather than individually, with morphology serving as the primary guide.

In rare cases, squamous cell carcinoma (SCC) can be challenging to distinguish from BCC. In these cases, Ber-EP4 is often used, with BCC showing strong expression while SCC is negative. It is important to note that Ber-EP4 may not be expressed in areas of keratinisation within BCC (Yu et al. 2009), and focal staining has been reported in SCC (Dasgeb et al. 2013; Stanoszek et al. 2017).

Our study confirms the need for a marker panel in BCC to enhance the diagnostic capabilities of immunohistochemistry (Liu et al. 2024). In our case, the panel would support the diagnosis of tumours with basaloid features, while keeping in mind that tumour morphology remains the primary guide. Various marker panels have been proposed by other authors (Córdoba et al. 2009). Each panel has its strengths and weaknesses, with some specifically designed to distinguish a particular lesion (Raheem et al. 2014).

A limitation of our study is the small sample size (n = 50). Larger studies are needed to investigate the immunohistochemical patterns and staining intensities of EZH2, Bcl-2, and BerEP4 across different morphological variants of BCC, as well as their differences from other tumours.

## Conclusion

The marker panel demonstrates co-expression of the three markers, with negative CK20 in over 90% of cases. Variability in staining intensity and the percentage of positive cells can create diagnostic challenges when markers are used individually. Nevertheless, using a panel of the three markers can support the diagnostic process and help distinguish basal cell carcinoma from many other tumours that do not co-express all three markers in the context of negative CK20.

While Merkel cell carcinomas are relatively well distinguishable morphologically from basal cell carcinomas, trichoblastomas, and other germinative follicular tumours, these tumours are difficult to differentiate from BCC. The presence of CK20-positive Merkel cells within these lesions confirms that they are not basal cell carcinomas.

Immunohistochemistry helps differentiate BCC from its mimics, but no single marker has 100% specificity and sensitivity. Therefore, in challenging cases, it is important to consider all clinical, morphological, and immunohistochemical features together. The panel needs to be validated in practice, and its diagnostic sensitivity and specificity should be studied.

## Additional information

### Conflict of interest

The authors have declared that no competing interests exist.

### Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: UMHAT "Dr. Georgi Stranski" Pleven.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

### Use of AI

No use of AI was reported.

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### Author contributions

Conceptualization: II, BA. Data curation: II, BA. Methodology: II. Supervision: DG. Visualization: II. Writing - original draft: II, BA. Writing - review and editing: DG.

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### Data availability

All of the data that support the findings of this study are available in the main text.

## References

- Albert MR, Weinstock MA (2003) Keratinocyte carcinoma. *CA: A Cancer Journal for Clinicians* 53: 292–302. <https://doi.org/10.3322/CANJCLIN.53.5.292>
- Bachmann IM, Halvorsen OJ, Collett K, Stefansson IM, Straume O, Haukaas SA, Salvesen HB, Otte AP, Akslen LA (2006) EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. *Journal of clinical oncology* 24: 268–273. <https://doi.org/10.1200/JCO.2005.01.5180>
- Beer TW, Shepherd P, Theaker JM (2000) Ber EP4 and epithelial membrane antigen aid distinction of basal cell, squamous cell and basosquamous carcinomas of the skin. *Histopathology* 37: 218–223. <https://doi.org/10.1046/J.1365-2559.2000.00999.X>

- Cameron MC, Lee E, Hibler BP, Barker CA (2021) Basal cell carcinoma: Epidemiology; pathophysiology; clinical and histological subtypes; and disease associations. *Journal of the American Academy of Dermatology* 85: 535. <https://doi.org/10.1016/j.jaad.2021.02.027>
- Chinem VP, Miot HA (2011) Epidemiology of basal cell carcinoma. *Anais Brasileiros de Dermatologia* 86: 292–305. <https://doi.org/10.1590/S0365-05962011000200013>
- Córdoba A, Guerrero D, Larrinaga B, Iglesias ME, Arrechea MA, Yanguas JI (2009) Bcl-2 and CD10 expression in the differential diagnosis of trichoblastoma, basal cell carcinoma, and basal cell carcinoma with follicular differentiation. *International journal of dermatology* 48: 713–717. <https://doi.org/10.1111/J.1365-4632.2009.04076.X>
- Crowson AN, Magro CM, Kadin ME, Stranc M (1996) Differential expression of the bcl-2 oncogene in human basal cell carcinoma. *Human Pathology* 27: 355–359. [https://doi.org/10.1016/S0046-8177\(96\)90108-2](https://doi.org/10.1016/S0046-8177(96)90108-2)
- Dasgeb B, Mohammadi TM, Mehregan DR (2013) Use of Ber-EP4 and Epithelial Specific Antigen to Differentiate Clinical Simulators of Basal Cell Carcinoma. *Biomarkers in cancer* 5: 7–11. <https://doi.org/10.4137/BIC.S11856>
- Hockenbery D, Nuñez G, Milliman C, Schreiber RD, Korsmeyer SJ (1990) Bcl-2 is an inner mitochondrial membrane protein that blocks programmed cell death. *Nature* 348: 334–336. <https://doi.org/10.1038/348334A0>
- Hu W, Fang L, Ni R, Zhang H, Pan G (2022) Changing trends in the disease burden of non-melanoma skin cancer globally from 1990 to 2019 and its predicted level in 25 years. *BMC Cancer* 22: 836. <https://doi.org/10.1186/S12885-022-09940-3>
- Hussein MR, Ahmed AM (2022) Expression Profile of CD10, BCL-2, p63, and EMA in the Normal Skin and Basal Cell Carcinomas: An Immunohistochemical Reappraisal. *Actas dermo-sifiliográficas* 113: 848–855. <https://doi.org/10.1016/j.ad.2022.05.012>
- Izickson L, Bhan A, Zembowicz A (2005) Androgen receptor expression helps to differentiate basal cell carcinoma from benign trichoblastic tumors. *The American Journal of dermatopathology* 27: 91–95. <https://doi.org/10.1097/01.dad.0000154392.92099.aa>
- Karahan N, Başpınar Ş, Yıldırım M, Barut İ (2006) The use of Ber-EP4 antigen in the differential diagnosis of basosquamous carcinoma from squamous and basal cell carcinoma. *Turkish Journal of Pathology* 22: 87–91. <https://turkjpath.org/text.php?id=151>
- Liu YA, Ciurea AM, Aung PP (2024) A diagnostic approach to basaloid neoplasms of the skin: squamous is red; basals are blue but alas! If only that were true. *Diagnostic Histopathology* 30: 60–76. <https://doi.org/10.1016/j.jmpdhp.2023.10.006>
- Memije MEV, Luna EM, De Almeida OP, Taylor AM, González JCC (2014) Immunohistochemistry panel for differential diagnosis of basal cell carcinoma and trichoblastoma. *International Journal of Trichology* 6: 40–44. <https://doi.org/10.4103/0974-7753.138583>
- Mendez-Flores RG, Martínez-Fernández DE, Vega-De la Torre DE, Zambrano-Román M, Muñoz-Valle JF, Toledo-Lelevier MG, Guevara-Gutiérrez E, Ramírez-Padilla M, Valdés-Alvarado E (2022) Role of Bcl-2, p53, and Ki-67 expression in basal cell carcinoma and their association with aggressive and non-aggressive histological phenotypes. *Postępy dermatologii i alergologii* 39: 517–523. <https://doi.org/10.5114/ada.2022.117598>
- Ozkanli S (2023) Ber-EP4 staining patterns on basal cell carcinomas. *Northern Clinics of Istanbul* 10: 666–674. <https://doi.org/10.14744/NCI.2022.25675>
- Peris K, Fargnoli MC, Kaufmann R, Arenberger P, Bastholt L, Seguin NB, Bataille V, Brochez L, del Marmol V, Dummer R, Forsea AM, Gaudy-Marqueste C, Harwood CA,

- Hauschild A, Höller C, Kandolf L, Kellerners-Smeets NWJ, Lallas A, Leiter U, Leiter U, Malvey J, Marinović B, Mijuskovic Z, Moreno-Ramirez D, Nagore E, Nathan P, Stratigos AJ, Stockfleth E, Tagliaferri L, Trakatelli M, Vieira R, Zalaudek I, Garbe C (2023) European consensus-based interdisciplinary guideline for diagnosis and treatment of basal cell carcinoma—update 2023. *European journal of cancer* 192: 113254. <https://doi.org/10.1016/J.EJCA.2023.113254>
- Petronilho S, Sequeira JP, Paulino S, Lopes P, Lisboa S, Chacim S, Lobo J, Teixeira M, Jerónimo C, Henrique R (2021) Prognostic value of histone modifying enzyme EZH2 in RCHOP-treated diffuse large B-cell lymphoma and high grade B-cell lymphoma. *Journal of personalized medicine* 11: 1384. <https://doi.org/10.3390/jpm11121384>
- Puizina-Ivić N, Sapunar D, Marasović D, Mirić L (2008) An overview of Bcl-2 expression in histopathological variants of basal cell carcinoma, squamous cell carcinoma, actinic keratosis and seborrheic keratosis. *Collegium Antropologicum* 2: 61–65. <https://pubmed.ncbi.nlm.nih.gov/19138009/>
- Raasch BA, Buettner PG, Garbe C (2006) Basal cell carcinoma: histological classification and body-site distribution. *The British journal of dermatology* 155: 401–407. <https://doi.org/10.1111/j.1365-2133.2006.07234.x>
- Raheem SA, Alsahaer R, Tealeb A, Rushdy E (2014) The Role of Bcl-2, CD10 and CD34 Expression in Differentiation between Basal Cell Carcinoma and Trichoepithelioma. *Open Journal of Pathology* 4: 116–124. <https://doi.org/10.4236/ojpathology.2014.43018>
- Ramdial PK, Madaree A, Reddy R, Chetty R (2000) Bcl-2 protein expression in aggressive and non-aggressive basal cell carcinomas. *Journal of cutaneous pathology* 27: 283–291. <https://doi.org/10.1034/j.1600-0560.2000.027006283.x>
- Ramezani M, Mohamadzaheer E, Khazaei S, Najafi F, Vaisi-Raygani A, Rahbar M, Sadeghi M (2016) Comparison of EMA, CEA, CD10 and Bcl-2 biomarkers by immunohistochemistry in squamous cell carcinoma and basal cell carcinoma of the skin. *Asian Pacific journal of cancer prevention* 17: 1379–1383. <https://doi.org/10.7314/APJCP.2016.17.3.1379>
- Rao RC, Chan MP, Andrews CA, Kahana A (2016) EZH2, proliferation rate, and aggressive tumor subtypes in cutaneous basal cell carcinoma. *JAMA oncology* 2: 962–963. <https://doi.org/10.1001/jamaoncol.2016.0021>
- Rao RC, Chan MP, Andrews CA, Kahana A (2018) Epigenetic markers in basal cell carcinoma: universal themes in oncogenesis and tumor stratification? *Cellular oncology* 41: 693–698. <https://doi.org/10.1007/s13402-018-0402-8>
- Sari Aslani F, Akbarzadeh-Jahromi M, Jowkar F (2013) Value of CD10 Expression in Differentiating Cutaneous Basal from Squamous Cell Carcinomas and Basal Cell Carcinoma from Trichoepithelioma. *Iranian Journal of Medical Sciences* 38: 100–106. <https://pmc.ncbi.nlm.nih.gov/articles/PMC3700055/>
- Sendín-Martín M, Bueno-Molina RC, Hernández-Rodríguez JC, Cayuela L, Cayuela A, Pezra-Rodríguez JJ (2025) Incidence and mortality of nonmelanoma skin cancer in Europe: current trends and challenges. *Clinical & translational oncology*. <https://doi.org/10.1007/s12094-025-03985-z>
- Stanoszek LM, Wang GY, Harms PW (2017) Histologic Mimics of Basal Cell Carcinoma. *Archives of pathology & laboratory medicine* 141: 1490–1502. <https://doi.org/10.5858/arpa.2017-0222-RA>
- Sunjaya AP, Sunjaya AF, Tan ST (2017) The Use of BERP4 Immunohistochemistry Staining for Detection of Basal Cell Carcinoma. *Journal of skin cancer* 2017: 2692604. <https://doi.org/10.1155/2017/2692604>

- Van Rijn MD (1994) bcl-2 expression reliably distinguishes trichoepitheliomas from basal cell carcinomas. *British journal of dermatology* 131: 28–31. <https://doi.org/10.1111/j.1365-2133.1994.tb08453.x>
- WHO Classification of Skin Tumours (2023) WHO Classification of Tumours Editorial Board. 5<sup>th</sup> edn. Vol. 12. Geneva: World Health Organization.
- Xie Q, Wang H, Heilman ER, Walsh MG, Haseeb MA, Gupta R (2014) Increased expression of enhancer of Zeste Homolog 2 (EZH2) differentiates squamous cell carcinoma from normal skin and actinic keratosis. *European journal of dermatology* 24: 41–45. <https://doi.org/10.1684/EJD.2013.2219>
- Yang DT, Holden JA, Florell SR (2004) CD117, CK20, TTF-1, and DNA topoisomerase II-alpha antigen expression in small cell tumors. *Journal of cutaneous pathology* 31: 254–261. <https://doi.org/10.1111/j.0303-6987.2003.00175.x>
- Yu L, Galan A, McNiff JM (2009) Caveats in BerEP4 staining to differentiate basal and squamous cell carcinoma. *Journal of cutaneous pathology* 36: 1074–1176. <https://doi.org/10.1111/j.1600-0560.2008.01223.x>