Uludağ Üniversitesi Tıp Fakültesi Dergisi
Journal of Uludağ University Medical Faculty
52, 1842802, 2026
DOI: https://doi.org/10.32708/uutfd.1842802

ORIGINAL RESEARCH

Evaluation of Androgen Receptor Expression in Different Histological Subtypes of Basal Cell Carcinoma

Arzu Yıldırım ÖZLÜK, Gülay TURAN

Balıkesir University, Faculty of Medicine, Department of Pathology, Balıkesir, Türkiye.

ABSTRACT

The most common skin cancer, basal cell carcinoma (BCC), has the most common subtypes: adenoid, nodular, and superficial. The androgen receptor (AR) gene, thought to have a potential oncogenic role, is a member of the steroid hormone receptor family and is localized on the X chromosome. Our study aimed to evaluate androgen expression in nodular, superficial, and adenoid BCC subtypes. This study included 60 cases diagnosed with adenoid, nodular, and superficial BCC subtypes at the Department of Pathology at Balıkesir University. AR immunohistochemical expression was evaluated by light microscopy using staining ratios. Positive cells were assigned to one of four groups based on their staining ratios: Group 1: (0-4%), Group 2: (5-29%), Group 3: (30-59%), and Group 4: (60-100%). A significant difference was found between the BCC subtypes in terms of AR expression (%) distribution, and this difference was highly statistically significant ($p<0.001$). In conclusion, when the findings in the literature and our study are evaluated together, these findings suggest that androgen expression may be a significant determinant in distinguishing BCC subtypes. The significantly higher androgen expression, particularly in superficial BCC, suggests that it may contribute to subtype classification.

Key words: Basal Cell Carcinoma. Subtype. Androgen.

Bazal Hücreli Karsinomun Farklı Histolojik Alt Tiplerinde Androjen Reseptörü Ekspresyonunun Değerlendirilmesi

ÖZET

En sık görülen deri kanseri olan Bazal Hücreli Karsinom (BHK)'un sık rastlanan alt tipleri adenoid, nodüler ve yüzeyel tipleridir. Potansiyel bir onkogen rolü olduğu düşünülen Androjen reseptör (AR) geni, steroid hormon reseptör ailesinin bir üyesidir ve X kromozomunda lokalizedir. Çalışmamızda, androjen ekspresyonunun nodüler, yüzeyel ve adenoid BHK alt tiplerinde değerlendirilmesi amaçlanmıştır. Bu çalışmaya Balıkesir Üniversitesi Patoloji Bölümünde, BHK'un; adenoid, nodüler ve süperfisyal alt tip tanısı alan 60 olgu dahil edildi. Androjen'in immunohistokimyasal ekspresyonu, ışık mikroskobunda boyanma oranı açısından değerlendirildi. Pozitif boyanan hücrelerin boyanma oranı semikantitatif olarak derecelendirilerek aşağıdaki kategorilerden birine dahil edildi; Grup 1: (0-4%), Grup 2:(5-29 %), Grup 3: (30-59 %), Grup 4: (60-100 %). Androjen yüzdesinin dağılımı açısından BHK alt tipleri arasında anlamlı fark bulundu ve bu fark istatistiksel olarak ileri düzeyde anlamlıydı ($p<0,001$). Sonuç olarak, literatürdeki bulgular ile çalışmamızın verileri birlikte değerlendirildiğinde, androjen ekspresyonunun BHK alt tiplerinin ayrımında anlamlı bir belirleyici olabileceği görülmüştür. Özellikle yüzeyel tip BHK'da androjen ekspresyonunun belirgin düzeyde yüksek olması, alt tip sınıflandırmasına katkı sağlayabileceğini düşündürmektedir.

Anahtar Kelimeler: Bazal Hücreli Karsinom. Alt tip. Androjen.

Basal cell carcinoma (BCC) is the most common type of skin cancer, accounting for approximately 75% of all cutaneous malignancies[1]. Ultraviolet (UV) radiation is the most significant etiological factor, and the incidence is higher in fair-skinned individuals[2]. BCC is thought to originate from undifferentiated cells in the basal layer of the epidermis and from skin adnexa. Its incidence continues to rise each year. Although its metastatic potential is low, untreated BCC may enlarge over time, leading to local invasion and destruction, which can result in functional impairment and cosmetic deformity. Therefore, early diagnosis is critical[3].

BCC most frequently arises in sun-exposed areas of the body, with 80% occurring in the head and neck region. Additionally, other locations such as the trunk (15%), axilla, breast, nail bed, perianal, genital, and acral sites have also been reported[2]. BCC exhibits a wide range of histological subtypes with heterogeneous clinical characteristics that vary

Date Received: 15.December.2025
Date Accepted: 1.June.2026

Dr. Arzu Yıldırım ÖZLÜK
Balıkesir University Faculty of Medicine,
Department of Pathology, Balıkesir, Türkiye
E-mail: arzuozluk@hotmail.com

AUTHORS' ORCID INFORMATION
Arzu YILDIRIM ÖZLÜK: 0000-0002-3238-5422
Gülay TURAN: 0000-0002-3702-8811

according to the histopathological pattern. The most common subtypes—nodular and superficial BCC—are considered low-risk[4].

Different histopathological subtypes tend to show predilection for certain anatomical locations. Superficial BCC predominantly occurs on the trunk, whereas the majority of BCCs on the head and neck are of the nodular subtype[5]. Adenoid BCC may arise in diverse areas, including the axilla, back, leg, chin, forehead, and medial canthus of the eye. Histomorphologically, the adenoid subtype may mimic adenoid cystic carcinoma in some cases, necessitating careful differential diagnosis[6-7].

The histopathological subtype of BCC is an important prognostic factor that directly influences the likelihood of complete surgical excision. Nodular and adenoid types typically exhibit well-defined clinical and histological margins, making complete excision with clear borders more feasible. In contrast, superficial, infiltrative, and micronodular subtypes often display diffuse growth patterns and poorly defined margins, leading to higher rates of positive surgical margins[8].

The androgen receptor (AR) gene, a member of the steroid hormone receptor family, is located on the X chromosome[9]. AR is expressed in normal skin, including keratinocytes, sebaceous glands, and hair follicles, and plays a role in skin homeostasis and cellular proliferation[9-10]. Androgens influence the function of multiple organ systems, including the hypothalamic–pituitary axis, mammary gland, uterus, bone, and cardiovascular system[10,11]. Various histochemical and immunohistochemical markers are used to establish the diagnosis of BCC, determine its subtype, estimate prognosis, and develop targeted therapeutic approaches. It has been suggested that AR may have a potential oncogenic role in various tissues[10,11]. Several studies have demonstrated AR expression in different skin tumors, suggesting a possible role in tumor development and progression[9, 10]. However, the role of AR expression in basal cell carcinoma subtypes remains unclear, and limited studies have evaluated its distribution among different histological subtypes[9].

Accordingly, the present study aimed to evaluate androgen receptor expression in the nodular, superficial, and adenoid histological subtypes of basal cell carcinoma.

Materials and Methods

A total of 60 cases diagnosed with the adenoid, nodular, or superficial subtypes of basal cell carcinoma (BCC) in the Pathology Department of Balıkesir University between 01/01/2023 and 30/06/2024 were included in this study. Each subtype consisted of 20 cases. The cases were retrospectively identified through a review of a pathological database. Cases were selected consecutively based on availability in the database to ensure representation of each subtype. Pathological data were obtained from hospital medical archives and pathology reports. The study was approved by the Balıkesir University Health Sciences Non-Interventional Research Ethics Committee (Approval No: 08.02.2025 / E-52859568-050.04-483421).

Inclusion criteria included cases with a definitive histopathological diagnosis of BCC and sufficient tissue for immunohistochemical evaluation. Exclusion criteria were cases with inadequate tissue samples, recurrent lesions, re-biopsies, or cases with a history of prior treatment.

All tissue samples included in the study were fixed, processed routinely, embedded in paraffin blocks, and sectioned at a thickness of 5 µm. Hematoxylin–eosin staining was applied using standard protocols, and the slides were evaluated under a light microscope. Histopathological subtypes were classified according to established diagnostic criteria (WHO classification)[2] and confirmed by an experienced pathologist.

Immunohistochemical Analysis

For immunohistochemical evaluation, paraffin blocks from cases diagnosed with BCC were processed according to the following steps. Slides were placed in the Ventana Medical System Benchmark XT/ISH Staining Module, and procedures were performed using the Ultraview Universal DAB Detection Kit.

Sections cut from paraffin blocks were mounted on positively charged slides at a thickness of 4 µm and incubated in a 70°C oven for 1 hour. The slides were then transferred to the Ventana Benchmark XT immunohistochemistry device, where antigen retrieval was performed with ethylenediaminetetraacetic acid (EDTA), pH 8 (CC1). Primary antibody incubation was carried out for 30 minutes using a ready-to-use anti-androgen receptor antibody (clone SP107; rabbit monoclonal, Cell Marque, USA). Prostate tissue was used as a positive control, while omission of the primary antibody served as a negative control.

For counterstaining, Harris hematoxylin (Ventana Medical Systems) was applied for 16 minutes, followed by Bluing Reagent (Ventana Medical Systems) for 4 minutes. The slides were washed with detergent-containing water, rinsed twice in absolute alcohol, dried, and then coverslipped using a xylene-based mounting medium.

Evaluation of Immunoreactivity

Immunohistochemical expression of androgen receptor (AR) was evaluated under a light microscope

based on the percentage of positively stained tumor cells**.** Nuclear staining was considered positive for AR expression. The staining ratio was semiquantitatively graded and classified into the following categories:

- **Group 1:** 0–4%
- **Group 2:** 5–29%
- **Group 3:** 30–59%
- **Group 4:** 60–100%

Staining intensity (weak, moderate, strong) was not separately evaluated, as the study focused on the percentage of positively stained cells to ensure reproducibility.

Statistical Analysis

After coding the data obtained from the study, the data were transferred to a computer and analyzed using the SPSS software package (Version 22 for Windows, SPSS Inc., Chicago, IL, USA). The normality of distribution for all continuous variables was assessed using the *Shapiro–Wilk test*. Continuous variables were expressed as mean ± standard deviation (SD) and median (minimum–maximum). Categorical variables were presented as frequency and percentage (%).

For comparisons of categorical variables, the *Pearson chi-square test* was used. Since continuous variables did not show normal distribution, non-parametric tests were employed. Comparisons among three groups were performed using the *Kruskal–Wallis test*, and, when necessary for post-hoc evaluation, the *Bonferroni-corrected Mann–Whitney U test* was applied.

Correlation analysis between continuous variables was performed using the Spearman correlation test.

A p-value of <0.05 was considered statistically significant.

Results

A total of 60 patients were included in the study: 20 with the adenoid subtype, 20 with the superficial subtype, and 20 with the nodular subtype of basal cell carcinoma (BCC). The mean age of the patients was 67.4±11.1 years, and 48.3% were female while 51.7% were male. The mean tumor diameter was 1.2±0.9 cm, ranging from 0.2 to 4.5 cm. The mean tumor invasion depth was 0.2±0.2 cm, with a median value of 0.2 cm (0.1–1.0 cm). Based on androgen receptor (AR) staining classification, 23.3% of the patients were in Group 1, 50.0% in Group 2, 20.0% in Group 3, and 6.7% in Group 4 (Table I).

When the three BCC subtypes (adenoid, superficial, nodular) were compared, no statistically significant difference was detected in median age values (p=0.499). Male patients constituted 60.0% of adenoid, 55.0% of superficial, and 40.0% of nodular BCC cases. However, the difference in sex distribution among subtypes was not statistically significant (p=0.420).

Table I. Descriptive characteristics of patients diagnosed with Basal Cell Carcinoma

Variables		Total
Age	Mean±SD Median (min-max)	67.4±11.1 68 (34-97)
Sex	Female	29 (48.3)
	Male	31 (51.7)
Carcinoma subtype	Adenoid	20 (33.3)
	Superficial	20 (33.3)
	Nodular	20 (33.3)
Tumor diameter(cm)	Mean±SD Median (min-max)	1.2±0.9 1.0 (0.2-4.5)
Invasion depth(cm)	Mean±SD Median (min-max)	0.2±0.2 0.2 (0.1-1.0)
AR expression	Group 1	14 (23.3)
	Group 2	30 (50.0)
	Group 3	12 (20.0)
	Group 4	4 (6.7)

The median tumor diameter was 1.5 cm (0.3–4.5) in adenoid BCC, 0.6 cm (0.2–3.0) in superficial BCC, and 0.8 cm (0.2–2.0) in nodular BCC. Adenoid subtype demonstrated a significantly larger tumor diameter compared to the other two subtypes (p=0.041).

Median invasion depth values were 0.35 cm (0.1–1.0) in adenoid, 0.10 cm (0.1–0.2) in superficial, and 0.20 cm (0.1–0.4) in nodular BCC, showing statistically significant differences among all three groups (p<0.001).

Ten of the adenoid BCC cases (50.0%) were in Group 1 AR percentage. Nine superficial BCC cases (45.0%) were in Group 3, while 14 nodular BCC cases (70.0%) were in Group 2. Group 4 AR percentage was observed only in superficial BCC (4 patients, 20.0%).

A statistically significant difference was found between BCC subtypes in terms of androgen percentage distribution, and this difference was highly significant (p<0.001) (Table II).

Table II. Comparison of patients according to Basal Cell Carcinoma subtypes

Variables		ADENOID type (n:20) Median (min–max)	SUPERFICIAL type(n:20) Median (min–max)	NODULAR type (n:20) Median (min–max)	p
Age		68 (43–97)	70 (34–82)	65 (47–89)	0.499
Sex	Female	8 (40.0)	9 (45.0)	12 (60.0)	0.420
	Male	12 (60.0)	11(55.0)	8 (40.0)	
Tumor diameter (cm)		1.5 (0.3–4.5)	0.6 (0.2–3.0)	0.8 (0.2–2.0)	0.041
Invasion depth (cm)		0.35 (0.1–1.0)	0.10 (0.1–0.2)	0.20 (0.1–0.4)	<0.001
AR expression	1	10 (50.0)	0 (0.0)	4 (20.0)	<0.001
	2	9 (45.0)	7 (35.0)	14 (70.0)	
	3	1 (5.0)	9 (45.0)	2 (10.0)	
	4	0 (0.0)	4 (20.0)	0 (0.0)	

Superficial BCC demonstrated higher androgen expression compared with adenoid and nodular types (Figure 1a-1b, Figure 2a-2b, Figure 3a-3b).

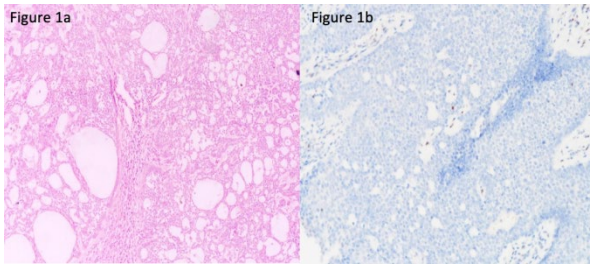

Figure 1.
(a) Adenoid-type BCC, H&E, ×100; (b) AR expression in adenoid-type BCC (Group 1), DAB×100.

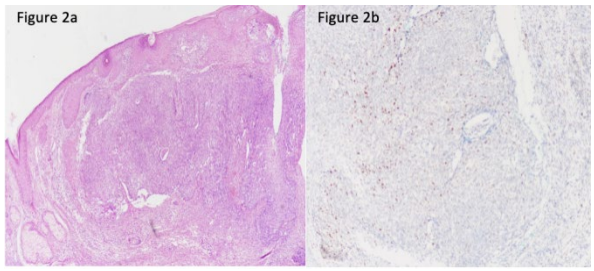

Figure 2.
(a) Nodular-type BCC, H&E, ×40; (b) AR expression in nodular-type BCC (Group 2), DAB×100.

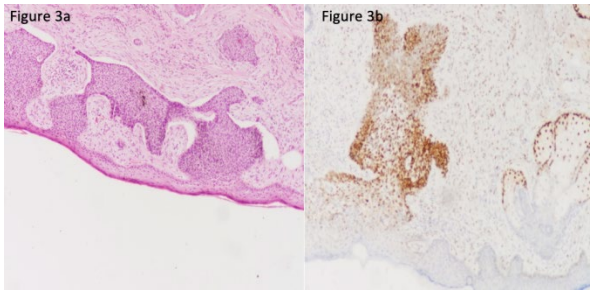

Figure 3.
(a) Superficial-type BCC, H&E, ×100; (b) AR expression in superficial-type BCC (Group 4), DAB×100.

Correlation analysis showed no statistically significant association between age and tumor diameter, invasion depth, or androgen percentage ($p>0.05$ for all comparisons). Similarly, no significant correlation was found between tumor diameter and AR expression (%) ($p=0.626$). However, a moderate and significant positive correlation was identified between tumor diameter and invasion depth ($r=0.39$; $p=0.002$), indicating that larger tumors tended to have greater invasion depth. A significant moderate negative correlation was observed between invasion depth and androgen percentage ($r=–0.41$; $p=0.001$), demonstrating that increased invasion depth was associated with lower androgen expression (Table III).

Table III. Correlation analysis among continuous variables (n=60)

Variables	Age		Tumor diameter		Invasion depth		AR expression(%)	
	r	p	r	p	r	p	r	p
Age	1		-0.04	0.748	-0.09	0.495	0.08	0.566
Tumor diameter	-0.04	0.748	1		0.39	0.002	-0.06	0.626
Invasion depth(cm)	-0.09	0.495	0.39	0.002	1		-0.41	0.001
AR expression(%)	0.08	0.566	-0.06	0.626	-0.41	0.001	1	

Discussion and Conclusion

Basal cell carcinoma (BCC) is the most common tumor among all cutaneous malignancies and is typically characterized by slow growth and a tendency for local invasion. BCC develops as a result of the proliferation of basaloid cells originating from the basal layer of the epidermis or from epithelial cells of the hair follicle[12]. Its macroscopic appearance varies widely, ranging from erythematous plaques to ulcerated exophytic lesions[13]. Immunohistochemistry (IHC) is frequently used in the differential diagnosis of BCC from other adnexal tumors and plays an important role in the diagnosis and prognosis of many benign neoplasms and skin cancers[14]. Various markers have been investigated for this purpose, including T cell death–associated gene 51 (TDAG51), nestin, CD34, bcl-2, androgen receptor (AR), Ki-67, p53, p21, Ber-EP4, and neurofilament. Among these, CD10, AR, and cytokeratin 20 (CK20) have been reported as the most useful markers[15].

However, the proportion of AR-positive BCC cases has varied considerably across studies conducted by different authors[16]. These discrepancies may arise from several factors, including the number of lesions analyzed, differences in laboratory techniques and methodologies, threshold values used to define AR positivity, and sample selection influenced by the relative frequency of certain histological subtypes.

In the present study, AR expression was evaluated immunohistochemically in 60 BCC cases, including 20 superficial, 20 adenoid, and 20 nodular subtypes. AR expression was detected in 76.6% of cases, which is consistent with some previous reports[16,17]. BCC comprises numerous histological subtypes. The most common are the nodular and superficial types, classified as low-risk groups. In contrast, the adenoid subtype is considered a high-risk variant due to its histomorphological resemblance to adenoid cystic

carcinoma in certain cases, necessitating careful differential diagnosis[5]. The clinical features of BCC are heterogeneous and may vary depending on the histopathological subtype. Importantly, the subtype directly influences the likelihood of complete surgical excision with clear margins[4].

The histomorphology of BCC may be directly associated with AR expression in neoplastic cells. In the study by Arits et al., 22 of 23 BCC cases (superficial or nodular) demonstrated AR positivity (95.6%)[18]. Consistent with these findings, our study identified a positive relationship between AR expression and the low-risk subtypes of BCC—namely, superficial and nodular types. These findings are in line with previous studies suggesting a potential association between AR expression and less aggressive tumor characteristics[18]. This supports the hypothesis that reduced AR expression in BCC cells may be associated with a more aggressive tumor phenotype; however, this interpretation should be considered with caution due to the retrospective design of the study and the lack of clinical follow-up data.

In our study, AR expression was highest in the superficial subtype, moderate in the nodular subtype, and lowest in the adenoid subtype. Various histochemical and immunohistochemical markers are used to identify histopathological subtypes of BCC, estimate prognosis, and guide targeted therapies. With the hypothesis that androgens may have a potential oncogenic role in the common BCC subtypes (superficial, nodular, adenoid), we found a high rate of AR expression overall, with significant differences in expression levels among subtypes.

All 20 superficial BCC cases demonstrated AR expression, and in 13 of these, AR positivity exceeded 60%. Additionally, we observed a significant decrease in AR expression as tumor invasion depth increased.

Overall, when the literature and our findings are evaluated together, androgen expression may be considered a meaningful marker for distinguishing BCC subtypes. The prominently high AR expression in superficial BCC suggests that this marker may contribute to subtype classification.

This study has several limitations. First, the relatively small sample size and single-center design may limit the generalizability of the findings. Second, the retrospective nature of the study and the absence of clinical follow-up and recurrence data restrict the ability to evaluate the prognostic significance of AR expression. Therefore, further studies with larger case series and prospective designs are needed to better clarify the role of AR expression in BCC subtypes.

Researcher Contribution Statement:
Idea and design: A.Y.Ö., G.T.; Data collection and processing: A.Y.Ö., G.T.; Analysis and interpretation of data: A.Y.Ö.,G.T.; Writing of the manuscript: A.Y.Ö.,G.T.
Support and Acknowledgement Statement:
There was no financial support for this study.
Conflict of Interest Statement:
--The authors of the article have no conflict of interest declarations.
Ethics Committee Approval Information:
Approving Committee: Balıkesir University Health Sciences Non-Interventional Research Ethics Committee
Approval Date: 08.02.2025
Desicion 59568-050.04-483421

References

1. Goto M, Kai Y, Arakawa S, Oishi M, Ishikawa K, Anzai S, et al. Analysis of 256 cases of basal cell carcinoma after either one-step or two-step surgery in a Japanese institution. J Dermatol. 2012;39:68–71.
2. Patterson JW. Tumors of the epidermis. In: Patterson JW, ed. Weedon's Skin Pathology. 5th ed. Elsevier; 2021:848858.
3. Hauschild AH, Breuninger H, Kaufmann R, et al. S2k guidelines—Basal cell carcinoma of the skin. J Dtsch Dermatol Ges. 2013;3:10 15.
4. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med. 2005;353(21):2262 2269.
5. Messina J, Epstein EJ, Kossard S, et al. Basal cell carcinoma. In: Elder DE, Massi D, Scolyer RA, Willemze R, eds. WHO Classification of Skin Tumors. 4th ed. Lyon: IARC; 2018:26 34.
6. Tambe SA, Ghate SS, Jerajani HR. Adenoid type of basal cell carcinoma: Rare histopathological variant at an unusual location. Indian J Dermatol. 2013;58:159.
7. Kim SH, Ko WT, Suh MK, Lee JI. A case of axillary adenoid basal cell carcinoma. Ann Dermatol. 2008;20:22 25.
8. Koplin L, Zarem HA. Recurrent basal cell carcinoma: A review concerning the incidence, behavior, and management of recurrent basal cell carcinoma, with emphasis on the incompletely excised lesion. Plast Reconstr Surg. 1980;65(5):656–664.
9. Aristomenis A, Van Marion AM, Lohman BG, et al. Differentiation between basal cell carcinoma and trichoepithelioma by immunohistochemical staining of the androgen receptor: An overview. Eur J Dermatol. 2011;21(6):870 873.
10. Lamont KR, Tindall DJ. Alternative activation pathways for the androgen receptor in prostate cancer. Endocr Relat Cancer. 2011;18:R183 R196.
11. Liao DJ, Dickson RB. Roles of androgens in the development, growth, and carcinogenesis of the mammary gland. J Steroid Biochem Mol Biol. 2002;80(2):175 189.
12. Nadeen AM, Raja H, Mohammad AS, et al. Trichoblastoma mimicking basal cell carcinoma and approach to its treatment: A case report. Int J Surg Case Rep. 2021;86:106318.
13. Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. Br J Dermatol. 2008;159:35 48.
14. Kanitakis J, Bourchany D, Claudy A. Expression of CD10 antigen (neutral endopeptidase) by mesenchymal tumors of the skin. Anticancer Res. 2000;20:3539 3544.
15. Evangelista MT, North JP. Comparative analysis of cytokeratin 15, TDAG51, cytokeratin 20 and androgen receptor in sclerosing adnexal neoplasms and basal cell carcinoma variants. J Cutan Pathol. 2015;42:824 831.

16. Astarcı HM, Gürbüz GA, Şengül D, et al. Significance of androgen receptor and CD10 expression in cutaneous basal cell carcinoma and trichoepithelioma. Oncol Lett. 2015;10(6):3466–3470. doi:10.3892/ol.2015.3743.
17. Lee YF, Chang YT, Liu HN. Differentiating basal cell carcinoma from trichoepithelioma by using androgen receptor expression. Dermatologica Sinica. 2009;27(3):154–160. doi:10.1016/S1027-8117(09)70037-3.
18. Arits AH, Van Marion AM, Lohman BG, et al. Differentiation between basal cell carcinoma and trichoepithelioma by immunohistochemical staining of the androgen receptor: An overview. Eur J Dermatol. 2011;21(6):870–873. doi:10.1684/ejd.2011.1506.