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Comparison of BCL-2 Ecpression in Periocular Basal Cell Carcinoma Aggressive and Non-Aggressive Types in Mohammad Hoesin Hospital Palembang

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Abstract

Background: Basal cell carcinoma (BCC) is a malignant tumor originating from non- keratinizing cells originating from the basal layer of the epidermis. Basal cell carcinoma is the most common malignant tumor, nearly 90% of all non-melanoma skin cancers. Clinically, BCC is difficult to distinguish, final diagnosis determined based on histopathological examination of complete tumor tissue. Based on histological growth patterns, BCC is divided into two, non- aggressive type (nodular and superficial) and aggressive type (infiltration, micronodular, fibroepithelial, basoskuamosa, keratotic, adnexal differentiation). The examination technique by analyzing the proteins or genes involved is related to the aggressiveness of basal cell carcinoma.

Methods: A cross sectional analytic study from 26 periocular basal cell carcinoma patients in RSUP dr. Mohammad Hoesin Palembang, January 2014- June 2018. Histopathologic features were examined with hematoxylin-eosine staining and imunohistochemical were examined with Bcl-2 monoclonal antibody. Data were analyzed by bivariate analysis, using chi-square test and fisher exact test.

Results: Positive Bcl-2 expression was more common in periocular basal cell carcinoma (93.8%) than aggressive (50%), and nodular type (93.8%) compared to other types of histological differentiation. Positive Bcl-2 expression was also higher in female patients (90.9%) than males (66.7%). There is a significant relationship between expression of Bcl-2 and growth patterns, differentiation of cell histology and also sex of patients with basal cell carcinoma.

Conclusion: In this study, there was a significant correlation between expression of Bcl-2 and aggressive and non-aggressive periocular basal cell carcinoma in RSUP dr. Mohammad Hoesin Palembang.

Keywords: Bcl-2 expression, histological growth pattern, basal cell carcinoma

Introduction

Basal cell carcinoma (BCC) is a malignant tumor which comes from nonkeratinized cells originating from the basal layer of the epidermis.[1,2] The clinical course of BCC is slow and can cause extensive tissue damage.[3] BCC is often present in the head, neck and periocular. The most frequent periocular location is inferior palpebra, media canthus, superior palpebra and lateral canthus. Lesions on the media canthus have the highest risk of orbital involvement.[1,4,5]

Basal cell carcinoma is the most common malignant tumor, almost 90% of all non-melanoma skin cancers. The incidence of BCC in the United States is more than 500 per 100,000 and in Australia it reaches 2,400 per 100,000. Most cases occur in Australia, which reaches 2% of the population. The incidence of BCC is 14.35 per 100,000 individuals per year and it is estimated that more than one million new cases each year in the United States.[2,5-7] Data from the Cancer Registry of the Indonesian Pathologist Association and the Ministry of Health of the Republic of Indonesia in 2011, skin cancer ranks 4th out of 10 primary cancers most often in men and ranks 6th out of 10 primary cancers most often in women. The highest incidence of skin cancer is BCC (49%), followed by squamous cell carcinoma (44%), and malignant melanoma (7%).[7] BCC develops on skin that is exposed to ultraviolet light, which is a major risk factor that can cause tumor suppressor gene mutations and oncogen activation that play a role in the pathogenesis of BCC.[2,6]

Basal cell carcinoma has a different clinical and histological description. BCC is clinically difficult to distinguish, the final diagnosis is based on histopathological examination of tumor tissue that has been completely removed.[4,7-10] The histological classification of BCC according to WHO 2006 is divided into eight types, namely nodular, superficial, infiltration, micronodular, fibroepithelial, basosquamosa, keratotic, and with adenexal differentiation.[10,11] Histological classification based on growth patterns provides more meaningful information about biological properties, which are important for assessing risk of disease recurrence and comparing therapeutic outcomes.[3,9,12] Based on the pattern of histological growth, KSB can be divided into two types, namely non-aggressive and aggressive types. KSB which are non- aggressive (low risk) types are nodular and superficial types.[13,14] KSB which is included in the aggressive type (high risk), namely the type of infiltration, micronodular, fibroepithelial, basosquamosa, keratotic, and adnexal differentiation.[10,13,14]

Pathogenesis of tumors is influenced by mutation of tumor suppressor genes and activation of oncogens which can cause excessive cell proliferation and differentiation. Appropriate apoptosis

control is very important to control tumor development. B-cell lymphoma / leukemia- 2 (B-cell lymphoma / leukemia-2), is the first protein found because of its activation in many B cell lymphoma Bcl-2 is the first identified and best known anti-apoptotic oncogenic protein. This gene extends the life of cells without stimulating proliferation.[3,15,16]

Each cell must be in a constant balance to maintain genome integrity. Genomic lesions must be repaired immediately before DNA replication and cell division occur. Apoptosis and the cell cycle are interrelated phenomena. The cell cycle has two check points, at the G1-S and G2- M transitions. Check points that control entry to the S phase prevent cells from replicating damaged DNA mediated by P53, which will induce whether the cell will remain retained in the G1 phase or will undergo apoptosis. Increased Bcl-2 will increase cell survival and keep cells in the G0-G1 phase so they last longer in the phase that does not proliferate. Increased Bcl-2 decreases the rate of proliferation and a better prognosis in some carcinomas and selective- down regulation has been observed in tumor development in some cancers.[17-20]

The velocity of BCC growth has a relationship with mitotic activity in the cell cycle. The BCC cell cycle is 217 hours, which shows that the average cell is produced every nine days. Based on this data, tumor cells can double every few weeks, but this does not match the results of clinical observations of several months to several years. This can be explained by the delayed phase of DNA synthesis (S phase) of the BCC or due to spontaneous necrosis in tumor cells.[21,22] Increased Bcl-2 can keep cells in the G0-G1 phase, so that proliferation is lower. Cells in the S phase have a high proliferation capacity.[22]

Non-melanoma skin cancer associated with exposure to ultraviolet light which can cause P53 gene mutations and activation of BCL-2 oncogens. The difference in expression of Bcl-2 protein in nonmelanoma skin cancer according to some experts is still contradictory. The research of Wikonkal et al (1997) states that there is a significant negative relationship between Bcl-2 and p53 expression in BCC but not in squamous cell carcinoma (SCC) and there is a negative relationship between Bcl-2 and apoptosis in BCC, but not in SCC. Nakagawa et al. Found no expression of Bcl-2 in the normal epidermis, but Bcl-2 expression was positive in 67% BCC and 100% SCC. Delehedde et al. Found expression of Bcl-2 in normal epidermal basal keratinocytes, in SCC not found, but increased 5.5-fold in BCC.[23-25]

The study of Lonescu et al, stated that Bcl-2 is a marker that can distinguish between BCC and tricoprocelioma, whose expression is limited to the outermost layer of neoplastic cells. Lonescu

et al also stated that Bcl-2 is a promoter of cell survival, the presence of Bcl-2 expression is an indicator of phenolytic indolent neoplastic cells with good clinical properties.[26] Research on the relationship between clinical manifestations and growth patterns of BCC and basosquamosa cell carcinoma has also been carried out by evaluating the expression of cyclin D1 which is a cell cycle regulator and Bcl-2 which is an anti-apoptotic oncogene. Sivrikoz et al (2012) stated that there were significant differences in the expression of Bcl-2 and Cyclin D1 between nodular and micronodular BCC types, infiltrative, and basosquamous cell carcinoma. Cyclin D1 expression was higher in micronodular and infiltrative BCC types, and basosquamosa cell carcinoma, while Bcl-2 expression was lower in the group.[3,13]

Various examination techniques are associated with non-melanoma skin cancer prognosis factors, among others, by analyzing the proteins or genes involved. Previous research revealed an inverse relationship between the expression of Bcl-2 protein and the expression of p53 protein and Cyclin D1 in nonmelanoma skin cancer. Research on the expression of p53 and Cyclin D1 proteins in nonmelanoma skin cancer has been carried out, and states that the expression of both proteins can be linked to the aggressiveness of nonmelanoma skin cancer.[23-25]

BCC in the facial area is associated with more aggressive clinical manifestations and higher recurrence than in areas that are not exposed to continuous ultraviolet exposure. Periocular BCC shows a tendency for higher periosteal and pericondrial invasion. This is related to thinner periocular tissue and the difficulty of doing adequate initial management. In previous studies of 1,392 BCC excision, 97 of the 99 tumors whose presence was incomplete were most common in the nose and periorbita.27 The proportion of periocular BCC that causes local invasion is quite high and causes significant morbidity, thus requiring more careful management and stricter follow-up.[28,29]

This study aims to determine whether Bcl-2 can be used as a marker to determine the aggressiveness of periocular basal cell carcinoma, so that it can help determine more appropriate management and stricter follow-up. An immunohistochemical study was conducted to determine the comparison of Bcl-2 expression in aggressive and non-aggressive type of periocular basal cell carcinoma in RSUP Dr. Mohammad Hoesin Palembang.

Methods

This study is a cross sectional analytic design study to determine the correlation between the expression of Bcl-2 expression in aggressive and non-aggressive type of periocular basal cell carcinoma in RSUP dr. Mohammad Hoesin Palembang. This research was conducted at the Ophthalmology Clinic of RSUP dr. Mohammad Hoesin Palembang and Department of Anatomical Pathology Dr. Mohammad Hoesin Palembang with the implementation period from March 2018 to July 2018.

The target population is all patients diagnosed with periocular basal cell carcinoma who are attending the Ophthalmology Clinic who performed surgery to remove the tumor. The research sample was determined by a time-based method. The study sample was patients who were diagnosed with periocular basal cell carcinoma who came for treatment at the Ophthalmology Clinic at RSUP Dr. Mohammad Hoesin Palembang and performed tumor removal surgery, had signed an agreement and informed consent for patients who had just undergone 42 tumor removal operations, and his medical record fulfilled the inclusion criteria in the January 2014- June 2018 period.

Samples were taken by consecutive sampling technique. Patients with suspected basal cell carcinoma that met the inclusion criteria were given informed consent, ophthalmological examination in the form of vision, eyeball position, eyeball movement, anterior segment and posterior segment. Histopathological results of basal cell carcinoma that meet the inclusion criteria are taken as samples until they meet the specified sample size and are divided according to the histological type of basal cell carcinoma. Histopathologic features were examined with hematoxylin-eosine staining and imunohistochemical were examined with Bcl-2 monoclonal antibody. Data were analyzed by bivariate analysis, using chi-square test and fisher exact test.

Results

This study had 26 samples which were patients diagnosed with periocular basal cell carcinoma who came for treatment at the Ophthalmology Clinic of RSUP Dr. Mohammad Hoesin Palembang and met the inclusion criteria. This study uses chi square analysis and fisher exact test.

Based on table I, the periocular basal cell carcinoma patients who took part in this study consisted of 15 (57.7%) patients who were male and 11 (42.3%) patients who were female.

The age of the periocular basal cell carcinoma patients in this study ranged from 36 to 77 years with an average age of 60.8 ± 13.1 years. Age characteristics in this study consisted of 30-44 years, 45-60 years and > 60 years. There were 4 (15.4%) patients aged 30-44 years, 10 (38.5%) patients aged 45-60 years and 12 (46.2%) patients aged> 60 years. Characteristics of the level of education of periocular basal cell carcinoma patients in this study based on the National Education System of the Republic of Indonesia are divided into elementary / equivalent, junior high / equivalent, high school / equivalent and Higher Education. In this study, most patients had an education level of SD / equivalent, which was 19 (73.1%) patients. There are, 1 (3.8%) patients who have a junior high school / equivalent, 3 (11.5%) patients have a high school / equivalent education level, and at least a tertiary education, as many as 3 (11.5%) patients.

Table 1. Sociodemographs Characteristic

Sociodemographs Characteristic	n	%
Gender		
Men	15	57.5
Women	11	42.3
Total	26	100.0
Age		
30-44 years	4	15.4
45-60 years	10	38.5
>60 years	12	46.2
Total	26	100.0
Education		
Primary High School	19	73.1
Junior High School	1	3.8
Senior High School	3	11.5
University	3	11.5
Total	26	100
Education		
Laborers	3	11.5
Farmers	14	53.8

Housewife	5	19.2
Retired	1	3.8
Teacher	3	11.5
Total	26	100.0

Comparative analysis of Bcl-2 expression with tumor cell histology growth patterns using bivariate fisher's exact test analysis obtained a p-value of 0.018. This shows that there is a significant relationship between Bcl-2 expression and tumor cell histology growth patterns. In this study, positive Bcl-2 expression was higher in non-aggressive histological growth patterns of 93.8% (15 patients) than in aggressive histological growth patterns of 50% (5 patients). The results of this analysis can be seen in Table 2.

Tabel 2. Comparison of Bcl-2 expression with tumor cell histology growth patterns

Tumor Cell Histology Growth Pattern	Bcl-2 expression				Total	p*
	Positive		Negative			
	n	%	n	%		
Agresive	5	50.0	5	50.0	10	0.018
Non-agresive	15	93.8	1	63.3	16	
Total	20	76.9	6	23.1	26	

**Fisher's exact test*, significant if p <0.05

Comparison analysis of Bcl-2 expression with tumor cell histology differentiation using bivariate analysis Chi-square test obtained p-value of 0.005. This shows that there is a significant relationship between Bcl-2 expression and tumor cell histology differentiation. In this study, positive Bcl-2 expression was higher in nodular cell types by 93.8% (15 patients). The positive expression of Bcl-2 in the infiltrative type was 28.6% (2 patients), in the fibroepithelial type 100% (1 patient) and the micronodular type was 100% (2 patients). The results of this analysis can be seen in Table 3

Tabel 3. Comparison of Bcl-2 expression with tumor cell histology differentiation

Diferensiasi Histologi Sel Tumor	Bcl-2 Expression				Total	p*
	Positive		Negative			
	n	%	N	%		
Nodular	15	93.8	1	6.3	16	0.005
Infiltrative	2	28.6	5	71.4	7	
Fibroepithelial	1	100.0	0	0.0	1	
Micronodular	2	100.0	0	0.0	2	
Total	20	76.9	6	23.1	26	

**Chi-square test*, significant if p <0.05

Comparative analysis of Bcl-2 expression with the sex of the patient using bivariate analysis

Chi-square test obtained p-value of 0.0197. This shows that there is a significant relationship between Bcl-2 expression and the sex of the patient. In this study the positive expression of Bcl-2 was higher in the female by 90.9% (10 patients) than in the male by 66.7% (10 patients). The negative expression of Bcl-2 was higher in male by 33.3% (5 patients) than in female by 9.1% (1 patient). The results of this analysis can be seen in Table 4.

Tabel 4. Comparison of Bcl-2 Expression with Patient Gender

Gender	Bcl-2 Expression				Total	p*
	Positive		Negative			
	n	%	n	%		
Male	10	66.7	5	33.3	15	0.0197
Female	10	90.9	1	9.1	11	
Total	20	76.9	6	23.1	26	

**Chi-square test*, significant if p <0.05

Discussion

A total of 26 patients were diagnosed with periocular basal cell carcinoma who came for treatment at the Eye Polyclinic at RSUP Dr. Mohammad Hoesin Palembang and fulfilling the inclusion criteria were included as research subjects.

Periocular basal cell carcinoma patients who participated in the study were more male (57.7%) than female patients (42.3%). This study is in line with data from the Cancer Registration Board of the Indonesian Pathologist Association and the Ministry of Health of the Republic of Indonesia in 2011, Skin cancer ranks 4th out of the 10 most common primary cancers in men and ranks 6th out of 10 most common primary cancers in women . The most common skin cancer is BCC (49%), with a higher frequency of males than females (3: 2 ratio).[7,30] The Sizrikoz and Kandiloglu study showed that of the 92 KSB patients studied, the frequency of men was higher (68%) compared to women (42%). Croowson et al (1995) also found that the frequency of BCC was higher in males (15 patients) compared to females (6 patients) in the mean age group of 64.5 years.[13] This is related to work and higher ultraviolet exposure in men.[14,30]

Periocular basal cell carcinoma patients in this study were aged 36 to 77 years with an average age of 60.8 ± 13.1 years. Periocular basal cell carcinoma is most prevalent in patients aged >60 years (45%), followed by patients aged 45-60 years (40%), and at least in patients aged 30 44 (15%). In accordance with data from the Cancer Registration Agency of the Indonesian Pathologist Association (1991), BCC often occurs in the elderly, ranging between 40-80 years, on average, occurring at the age of 60 years.[7,30] This study is also in line with the data obtained in the medical records of periocular basal cell carcinoma patients who are hospitalized and outpatient at Dr. Wahidin Sudirohusodo General Hospital for the 2014-2016 period, each with the highest age group (41-65 years) and senior citizens. (> 65 years) with percentages of 4.3% and 7.1%.

Croowson et al. (1995) also found that the frequency of BCC was higher in the average age group of 65.4 years (± 12.3 years) in 21 patients out of a total of 30 patients taking part in the study.[13,48] The study was dominated by patients who worked as farmers (53.8%), followed by housewives (19.2%), laborers (11.5%), teachers (11.5%), and retirees (3.8%). Basal cell carcinoma originates from the stratum basale or stratum germinativum from the epidermis and the outer sheath of the hair follicle roots (infundibular cells of hair follicles). Exposure to ultraviolet B is a major risk factor, which causes mutations in tumor suppressor genes and oncogenic deregulation that play a role in the pathogenesis of BCC. 1,2,4 Based on previous meta-analysis and sensitivity

analysis studies, it is known that people who work outdoors have risks which is significantly higher for suffering from BCC.14 Patients who work outdoors, for example farmers and laborers get longer exposure to ultraviolet light than patients who work indoors such as teachers and housewives, so patients who work outdoors have a higher risk of mutation of tumor suppressor genes or oncogenic deregulation that can trigger basal cell carcinoma. This is what causes the high frequency of basal cell carcinoma in patients who work outside the room, especially farmers.

The most patient education in this study was elementary education/ equivalent (73.1%), followed by high school/equivalent education and tertiary education respectively 11.5%, and at least junior high school education/ equivalent (3.8%). In this study it was found that in patients who have an elementary education level/ equivalent have jobs that require patients outside the room such as farmers and laborers. As explained earlier, one of the risk factors for basal cell carcinoma is prolonged exposure to ultraviolet B and can cause mutations in tumor suppressor genes and deregulation of oncogens that can trigger basal cell carcinoma. 1,2,4 This can cause high frequency of basal cell carcinoma in patients with an elementary school/ equivalent level in this study.

The most tumor locations in this study were in the inferior palpebra (61.5%), followed by medial canthus (26.9%), and superior palpebra (11.5%). This is consistent with previous research, that BCC is a common skin cancer of the eyelids (80-90%), which is mostly located in the inferior palpebra (50-60%), followed by medial canthus (25-30%), superior palpebra (15%) and most rarely in the lateral canthus (5%). [2-7,30]

The most common form of tumor in this study was a nodular mass of 17 patients (65.4%) followed by an unspecified mass of 9 patients (34.6%). The nodular type is the most frequent, 30 to 75% of all BCC. Clinical features are small, slowly enlarged dome-shaped papules that are irregular in shape. The surface of the tumor epithelium is usually smooth, often described as pearl, with clear telangiectasis underneath. When growing, central ulceration and necrosis can occur, often referred to as rodent ulcers. Ulceration can develop and be filled with crusted exudates. [1, 4, 8, 3, 33-35]In this study, there was no involvement of lymph nodes and distant metastases in all patients. This is consistent with the literature, basal cell carcinoma has limitations for metastasis.[1,2,4] BCC is very rarely metastasized, it is estimated that metastases occur in 0.0028 to 0.01% of patients.[4,8,14]

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Micronodular type consists of small circular nodules that are well-defined, scattered irregularly with minimal palisade, which show extension so that they require more careful management than usual nodular tumors. [11,14,27,34-38] The most frequent pattern of tumor cell histology growth in this study was non-aggressive type (61.5%) compared to aggressive type (38.5%). The study of Croowson et al (1995) also found that more BCC types were non-aggressive types than aggressive types.[13] Non-aggressive type basal cell carcinoma is non-diffuse, low frequency of recurrence and complete excision, which belongs to this type, namely nodular and superficial.[13,14] The aggressive type has further subclinical spread, local aggressiveness, higher frequency of recurrence and incomplete excision, which includes this type, namely infiltrative, micronodular, fibroepithelial, basosquamosa, keratotic and adnexal differentiation. [13.14]

Immunohistochemical examination of Bcl-2 in this study showed that the most expression of Bcl-2 was strong positive (46.2%), followed by moderate positive (30.8%), and the least number of patients with negative Bcl-2 expression (23.1%). This study is in line with Sayeed Imran et al (2015) who found that the most expression of Bcl-2 was strong positive (50%) followed by moderate positive (30%), and negative (20%) .[15] Bcl-2 expression in BCC was investigated. because there are similarities between the biological characteristics of non- aggressive KSB growth and low-grade lymphoproliferative disease that express Bcl-2.

Similarities include a low rate of proliferation and a high level of proportion of neoplastic cells in the GO phase of DNA synthesis. Bcl-2 expression in basal cells of hair follicles and in embryonic tissue of hair cells, structures that have histological similarities with tumors whose growth is non-aggressive. These results show greater expression of Bcl-2 in the superficial BCC and nodular, which is biologically calm and most closely resembles morphologically embryonal hair tissue.[23,46,47] This is consistent with the results of the study found that the most cell types many are nodular (61.5%) which will show positive Bcl-2 expression.

In this study there is a significant relationship between the expression of Bcl-2 with the pattern of tumor cell histology growth with a p-value of 0.018. In this study the positive Bcl-2 expression was higher in non-aggressive basal cell carcinoma by 93.8% compared with aggressive type basal cell carcinoma by 50%. This is in line with the research of Croowson et al (1995) which states that Bcl-2 expression is higher in non-aggressive basal cell carcinoma types than aggressive ones. Croowson et al, ttated that the Bcl-2 protein increased cell age and reduced apoptosis.13 The

Sivrikoz and Kandiloglu (2012) study, also stated the same thing, higher Bcl-2 expression was found in non-aggressive (nodular and superficial) types compared to aggressive types.

This study also states that there is a significant relationship between Bcl-2 expression and tumor cell histology growth patterns with a p-value of 0.01.3 The study of Wikonkal et al (1997) states that there is a significant negative relationship between Bcl-2 and p53 expression in BCC and there is a negative relationship between Bcl2 and apoptosis in BCC.[24] This is consistent with the literature that the role of Bcl-2 in BCC is related to cell survival and keeps cells in the G0-G1 phase. Increased Bcl-2 will keep cells in the G0-G1 phase, so they last longer in the phase that does not proliferate, but also does not inhibit cell development following the cell cycle. Increased Bcl2 decreases the rate of proliferation and a better prognosis in some carcinomas and selective-down regulation has been observed during tumor development in some cancers.[17-20,47] A significant relationship also exists between Bcl-2 expression and histological differentiation of tumor cells with a p-value of 0.005. In this study, positive Bcl-2 expression was higher in nodular cell types by 93.8% compared to other cell types (infiltrative, fibroepithelial, micronodular). This study is in line with the study of Croowson et al. (1995) which states that Bcl-2 expression is higher in indolent BCC variants, that is, superficial types and which are strictly limited (nodular) than other types. This study also states that there is a significant relationship between the expression of Bcl-2 with the type of tumor cell histology differentiation with a p value of 0.028.[13]

Research by Sivrikoz and Kandiloglu (2012) also states that there are significant differences in the expression of Bcl-2 and Cyclin D1 in nodular and micronodular basal cell carcinoma, infiltrative, and basosquamosa. Cyclin D1 expression was higher in micronodular, infiltrative, and basosquamosa, while Bcl-2 expression was lower in the group. Higher expression of Bcl- 2 is found in the non-aggressive type (nodular and superficial) compared to the aggressive type. This study also states that there is a significant relationship between the expression of Bcl-2 and the type of tumor cell histology differentiation.[3,13]

The most positive expression of Bcl-2 is in basal cell carcinoma located in the inferior palpebra (87.5%). Whereas the negative expression of Bcl-2 was mostly in basal cell carcinoma located in the medial canthus (42.9%). Basal cell carcinoma of the medial canthus is more invasive and more frequent with orbitals. [1,4,7,14] Research suggests lower expression of Bcl-2 in aggressive ones.[3] This is consistent with the results of this study that negative Bcl-2 expression is most many basal cell carcinomas located in the medial canthus, because basal cell carcinomas in the medial canthus are more aggressive and invasive. In this study, a p-value of 0.256 showed no significant

relationship between tumor location and Bcl-2 expression. The results of this study are in line with research by Sivrikoz and Kandiloglu (2012) which found no relationship between Bcl-2 expression and tumor location.

Nodular basal cell carcinoma has more positive Bcl-2 expression (88.2%) compared to non-specific form (55.6%), with a p-value of 0.084 which shows no significant relationship between Bcl-2 expression and tumor shape. The results of this study are in line with research by Sivrikoz and Kandiloglu (2012) which found no relationship between Bcl-2 expression and tumor shape.[3]

In this study there was no involvement of lymph nodes and distant metastases in all patients. Lymph node and distant metastase data are monotonous data so that bivariate analysis cannot be performed. According to Azwar's 2015 study, there was no significant relationship between lymph nodes and Bcl-2 expression.[48,49]

In this study also found a significant relationship of Bcl-2 expression with the sex of the patient with a p-value of 0.0197. In this study, positive Bcl-2 expression was higher in female sex (90.9%) than male gender (66.7%) and negative Bcl-2 expression was higher in male sex.

Conclusion

There was a significant correlation between expression of Bcl-2 and aggressive and non-aggressive periocular basal cell carcinoma in RSUP dr. Mohammad Hoesin Palembang.

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