

Statistical Association between Clinical and Histopathological Parameters for Keratinocyte Carcinomas

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ABSTRACT: The most common tumor of the western world is comprised of forms of non-melanoma skin cancers, previously known as keratinocyte carcinomas (KCs). The purpose of this study was to determine the incidence of non-melanoma skin tumors and the relationship between histopathological risk factors in patients with skin cancers. The study was composed from 332 cases of skin malignancies for which clinical and histopathological aggressivity factors were statistically analyzed through comparison tests and also stored digitally. For basal cell carcinoma (BCC) statistical analysis indicated significant relationships between pT category and gender, tumor size, ulceration, depth of invasion and positive resection limits. For squamous cell carcinoma (SCC) statistical analysis indicated significant relationships between pT category and tumor size, depth of invasion and positive resection limits. Clinical and histological analysis of certain characteristics of the above-mentioned skin cancers is an essential step in documenting and improving both prognosis and therapy standards.

KEYWORDS: Keratinocyte carcinomas, clinical parameters, histopathological parameters.

Introduction

Basal cell carcinoma (BCC) a form of keratinocyte carcinomas (KCs) comprise 80% of these types of malignancies, meanwhile cutaneous squamous cell carcinoma (cSCC) represents the latter 20% of such cancers [1,2,3].

Worldwide, an increasing rate of appearance for BCC has led to a lifetime risk of occurrence of 20-30% [4].

In comparison SCC has seen a rise of the worldwide lifetime risk to 9-14% for males and 4-9% for females [5].

BCC known before as basal cell epithelioma, is one of the most common cancers in the human species [5].

It occurs mostly on skin that has been exposed long enough to be damaged by the sun's radiation. It has been noted to also occur although rarely on mucous membranes or the palms or soles of the limbs. It's usually a slow growing tumor which will almost never metastasize [5,6].

Though as mentioned before it is highly unlikely to metastasize it does lead to many disfigurements caused by its highly destructive nature towards the surrounding tissues.

It's most common areas of interest are the regions of the face or neck area though some cases have been reported on the thorax or extremities [5,6].

Forming in the middle and exterior layer of squamous cells of the skin SCC is a common type of cancer [3,7].

In comparison to BCC it poses a greater threat due to its aggressive nature and ability to metastasize. Prolonged exposure to UV sunlight without added protection is the leading cause of SCC and the most common topographical regions affected by SCC are the head and neck [3,7].

Material and Methods

This retrospective study included 332 cases of BCC and cutaneous SCC, diagnosed over a period of 3 years (2019-2021), from the Plastic Surgery Clinic of the Emergency County Hospital of Craiova and were processed in the Laboratory of Pathological Anatomy of the same hospital.

The surgical excision specimens were fixed in buffered formalin 10%, processed using the paraffin embedding technique and Hematoxylin-Eosin (HE) staining.

The classification of the lesions was done according to WHO (World Health Organization) and AJCC (American Joint Committee on Cancer) [8,9].

Based on the selected tumors for analysis, clinical parameters were assessed such as age, gender and topography as well as histopathological parameters (tumor size, presence of ulceration, perineural and perivascular invasion, depth of invasion, but also resection limits invasion and inclusion in an pT category.

Imaging was accomplished using the Panthera L research microscope accompanied by a 5 Megapixel digital camera (MOTIC) as well as the software integrated within the microscope.

Statistical support was realized by the chi square comparison test (χ^2 test) in the SPSS10

(statistical package for social Sciences), a significant corroboration being at $p < 0.05$.

Ethical aspects were respected, patients having given informed consent, while the study itself being approved by the Local Ethics Commission (no. 65/20.04.2022).

Results

From a total of 332 cases, 197 were BCC (59.3%), 135 were SCC (40.7%).

The mean age of diagnostic was 70.74 for SCC (predominantly in sixth decade-27.4%) and 69.26 for BCC (predominantly in seventh decade-32.5%).

The majority of cases were males (>55%) for all analyzed cases (Table 1).

Table 1. Cases distribution and associations of the investigated clinico-pathological parameters.

Parameters	No. cases		Percentages %		p value χ^2 test		
	SCC	BCC	SCC	BCC	pT SCC	pT BCC	
Age	<60	26	34	19.3	17.3	p>0.05	p>0.05
	≥60	109	163	80.7	82.7		
Gender	female	56	86	41.5	43.7	p>0.05	p<0.05
	male	79	111	58.5	56.3		
Localization	upper limb	11	6	8.1	3.0	p>0.05	p>0.05
	head and neck	106	164	78.5	83.3		
	thorax	6	23	4.4	11.7		
	lower limb	12	4	8.9	2.0		
Tumor size (cm)	≤2	65	133	48.1	67.5	p=0,000	p=0,000
	>2-<4	45	40	33.3	20.3		
	≥4	25	24	18.5	12.2		
Ulceration	present	84	152	62.2	77.2	p>0.05	p<0.05
	absent	51	45	37.8	22.8		
Depth of invasion	dermis	69	146	51.1	74.1	p=0,000	p=0,000
	hypoderm	34	18	25.2	9.1		
	striated muscle	26	24	19.3	12.2		
	cartilage	3	7	2.2	3.6		
	bone	3	2	2.2	1.0		
Perineural invasion	present	8	0	5.9	0	p>0.05	-
	absent	127	197	94.1	100		
Vascular invasion	-	0	0	0	0	-	-
Resection limits	positive	31	55	23	27.9	p=0,000	p=0,001
	negative	104	142	77	72.1		
pT category	pT1	61	134	45.2	68.0	-	-
	pT2	48	37	35.6	18.8		
	pT3	22	24	16.3	12.2		
	pT4	4	2	3.0	1.0		

For SCC, the majority of studied cases were located in the head and neck area (78,5%), followed by lower limb (8.9%), upper limb (8.1%) and thorax region (4.4%).

The analysis of tumor size showed that the majority of patients had tumors under 2cm (48.1%), followed by >2-<4cm tumors (33.3%), and tumors over 4cm (18.5%).

Presence of ulceration was discovered in most of cases (62.2%), with invasion in dermis (51.1%), followed by hypoderm (25.2%), striated muscle (19.3%), cartilage (2.2%) and bone (2.2%).

In all studied cases there was no vascular invasion, but in some cases, we had perineural

invasion (5.9%) and positive resection limits (23%).

Most cases were diagnosed in pT1 category (45.2%), followed by pT2 (35.6%), pT3 (16.3%) and pT4 (3%) (Table 1).

Statistical analysis indicated significant relationships between pT category and tumor size ($p=0.000$, χ^2 test), tumors under 2cm being diagnosed in pT1 category and tumors larger than 4 cm being diagnosed in pT4 category.

Depth of invasion indicated also significant relationships with pT category ($p=0.000$, χ^2 test), in this case tumors who invaded striated muscle, cartilage and bone, being diagnosed in advanced categories.

Last but not the least, positive resection limits indicated significant relationships with pT category ($p=0.000$, χ^2 test), in this case tumors from all categories showed positive resection limits (Figure 1).

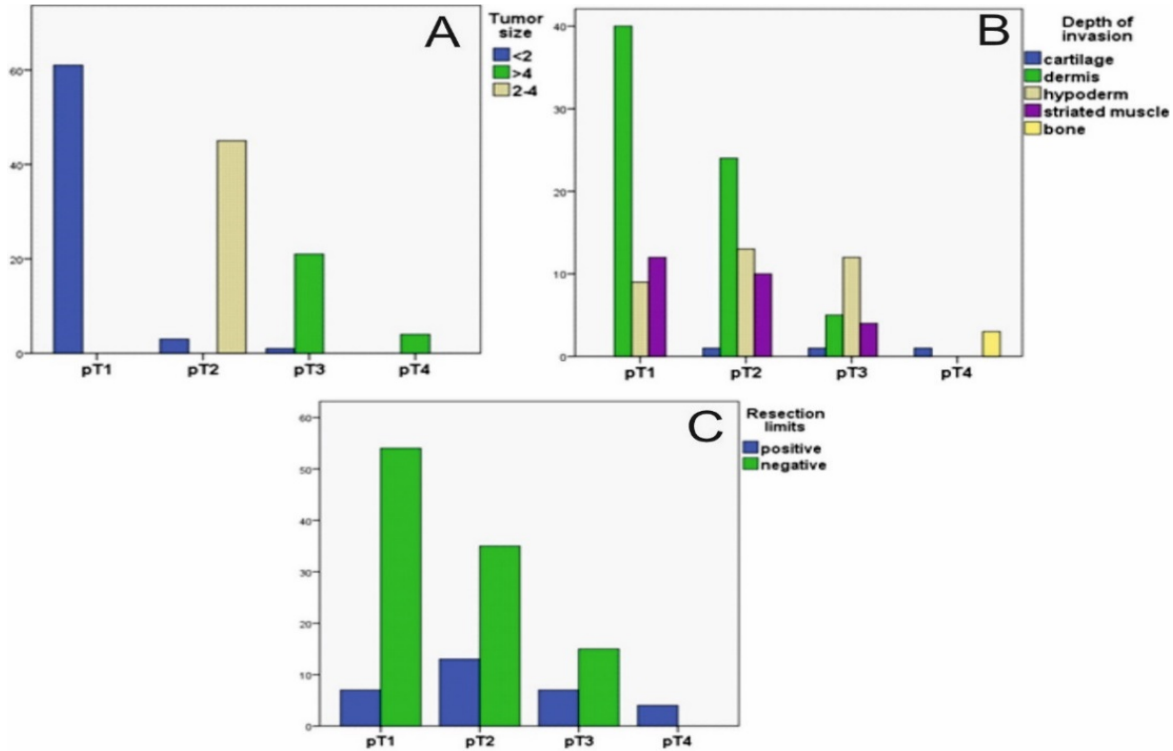


Figure 1. Cases distribution depending on pT category and tumor size (A), depth of invasion (B) and invasion of resection limits (C).

For BCC, most of the cases topography was limited to the head and neck area (83.3%), followed by chest (11.7%), hand (3.0%) and leg (2%).

The analysis of tumor size showed that the majority of patients had tumors under 2cm (67.5%), followed by >2-<4cm tumors (20.3%), and tumors over 4cm (12.2%).

Ulceration was present in most cases (77.2%) and also invasion in dermis (74.1%), followed by striated muscle (12.2%), hypoderm (9.1%), cartilage (3.6%) and bone (1.0%).

In all studied cases there was no vascular and perineural invasion, but we found cases with positive resection limits (27.9%).

Most cases were diagnosed in pT1 category (68.0%), followed by pT2 (18.8%), pT3 (12.2%) and pT4 (1%) (Table 1).

Statistical analysis indicated significant relationships between pT category and gender

($p<0.05$, χ^2 test), males being diagnosed with advanced tumors.

Tumor size and pT category indicated also significant relationships ($p=0.000$, χ^2 test), in this case tumor larger than 4cm were diagnosed in pT3 and pT4.

Another analysed parameter was ulceration which indicated significant relationships with pT category ($p<0.05$, χ^2 test), in comparison with SCC who not showed relationships with pT category ($p>0.05$, χ^2 test).

Depth of invasion ($p=0.000$, χ^2 test), and positive resection limits ($p=0.001$, χ^2 test) indicated significant relationships with pT category, because tumors who invaded striated muscle, cartilage and bone, were advanced tumors who had also positive resection limits (Figure 2).

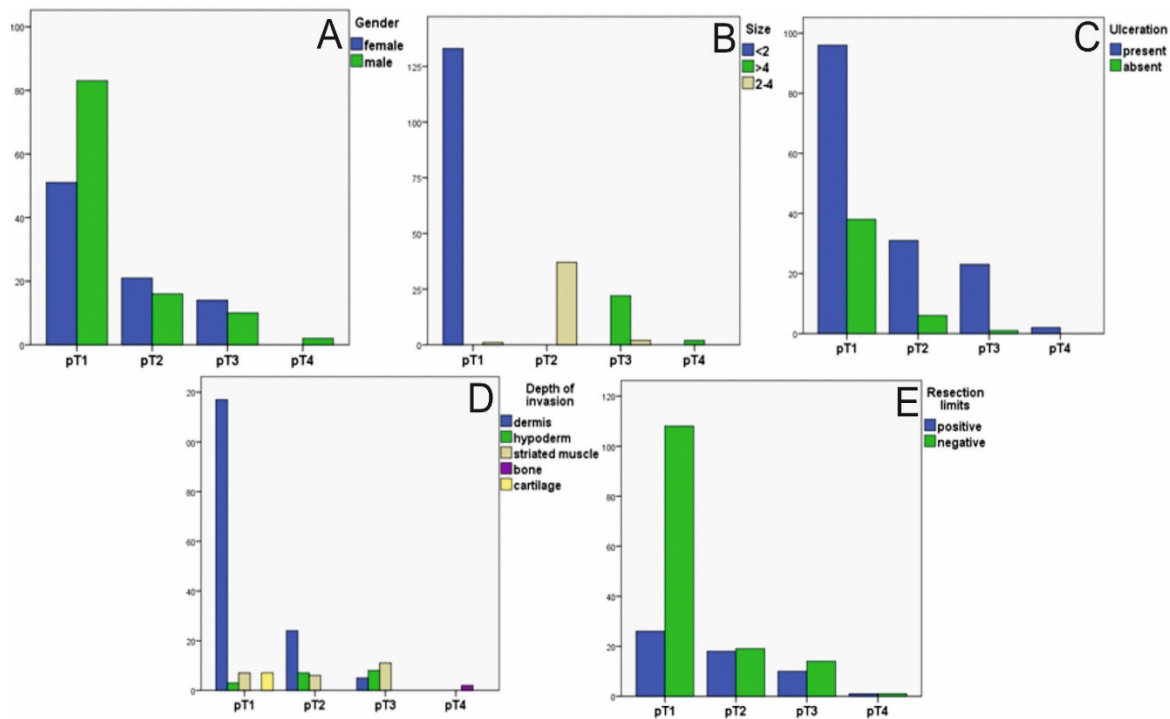


Figure 2. Cases distribution depending on pT category and gender (A), tumor size (B), ulceration (C), depth of invasion (D) and resection limits (E).

Discussions

From a total of 332 cases, 197 were BCC (62.7%) and 135 were SCC (37.3%), most of them being diagnosed in seventh decade of life.

Rahul Rajbhar et al, in a study published in 2020 discovered that from the total number of total studied tumors the most common were SCC (56.76%) and BCC (24.32%), data which can be compared to our study [2].

Keratinocyte carcinomas are one of the most common occurring tumors in the Western World [2,3].

This is summarized in an increase of occurrence of both cSCC and BCC worldwide [1].

In our study SCC and BCC was shown to occur more frequently in males over the age of 60, and most of the cases were located on the head and neck area.

In this study we found significant relationships between pT category and gender. Similar studies also showed the patients age distribution to be primarily in the seventh decade with an increased distribution in males [2,3,5].

In a recent study by Adinarayan and Krishnamurthy [4], most cases of BCC were discovered in the seventh and eighth decade of life.

Regarding the patient gender, many studies showed that the majority of cases were diagnosed in males [4,5,6].

However, other studies showed that there was a female preponderance [3,10,11].

In one study from 2020 which covered topographical distribution, similar to our study the most common topographical region was the head and neck area [2].

By comparison, other studies, revealed that SCC was most commonly found in the lower extremity [2,12].

The vast majority of cancers pertaining to the head and neck regions are represented by head and neck squamous cell carcinomas, totaling more than 90% [13].

Some histopathological features seen in KCs are very important in predicting its malignant potential.

These include tumor size, ulceration, depth of invasion, perineural and perivascular invasion [12,14].

Data from literature showed that of the most important high-risk factors which lead to recurrence are prior tumors, aggressive histologic patterns, perineural invasion and positive status of resection limits [15].

For SCC and BCC statistical analysis indicated significant relationships between pT category and tumor size.

SCC lesions smaller than 2cm had no added risk of recurrence and metastasis [16].

One study showed that the most common primary tumor size was between 1,5cm and 8cm [17].

In both SCC and BCC ulceration was present in most cases and also invasion in dermis.

Data from literature showed that ulcerative tumor features had worse survival outcomes [18].

For SCC statistical analysis indicated significant relationships between pT category and depth of invasion.

Recurrence and metastasis are mostly influenced by a single important determining factor which is the depth of tumor invasion.

Studies have shown that a penetration in the lower levels of the dermis or the subcutaneous layer is correlated with a more aggressive evolution and a higher risk of metastasis [19].

In concordance with the above-mentioned risk factors, invasion through the subcutaneous layers of the skin is correlated with an increased risk for metastatic disease [20,21].

A study which analysed 358 SCCs demonstrated that the invasion depth was less than 2cm with 85% of them having premalignant lesions.

A tumor thicker than 4cm, in comparison showed that 55% of cases had premalignant tumors [22].

For BCC statistical analysis indicated significant relationships between pT category and ulceration and also depth of invasion.

Regarding a study from 2015 the ulceration rate was significantly associated with aggressive histopathological subtypes [19].

Also, in this study it is showed that BCC infiltrates in the papillary dermis and in the deeper reticular dermis [19], same as our study.

In all studied cases of BCC there was no vascular and perineural invasion.

In comparison in all studied cases of SCC there was no vascular invasion, but in some cases, we had perineural invasion.

Although surgical excision is still regarded as the gold standard therapy of both SCC and BCC, some parameters need to be taken into account before performing the intervention, parameters such as stage, location, patient associated pathology or histopathological subtype [1].

Both tumors had most cases with positive resection limits.

Statistical analysis indicated significant relationships between pT category and positive resection limits in both non-melanoma skin cancers

A study highlighting the recurrence rates in 720 BCC lesions, due to invasion of the resection limits demonstrates the prognostic factors for recurrence were found to be aggressive histopathological subtype [23].

Reports from other studies showed that BCC size correlates with the probability of subclinical extension, thus a 4mm excision margin is sufficient for a BCC smaller than 2cm.

Meanwhile a tumor greater than 2 cm with added risk patterns may require a marginal resection limit greater than 13mm.

The recommendation for deep margin resection differs for varying topographical locations, thus in skin the excision should go as deep as the fat layer while in face tumors up to the level of the fascia, perichondrium or periosteum [24].

As suggested by published literature, perineural involvement is present in 14% of all SCC that arise from the head and neck [14] and run a greater risk of recurrence [14].

Universal literature also seems to suggest that perineural invasion is associated with a higher mortality rate [25] being used as a marker of unfavorable prognosis and an independent risk factor [26].

A study of SCC done by Rahadiani et al. revealed that their patient samples showed extensive tumors 62,9% in T4, while 44,2% had lymph node involvement, 54,7% presented with lympho-vascular involvement [27].

Trials which included SCC of the face and mouth, invasion was seen as an independent risk factor being associated with local recurrence metastasis and a lower median patient survival.

The thickness of the tumor coupled with neural and bone invasion had been associated with higher chance of lymphogenic spreading.

Thus, perineural invasion may prove to be a valuable tool in clinical practice [28].

BCC was found that in one primary and 3 metastatic tumors perineural invasion had been documented [29].

Morphological characteristics of KCs tumors that directly translate to an increased aggressiveness are size, depth, location and tumor differentiation grade, while tumors larger than 2cm have a higher risk of recurrence and metastasis, tumors that cover a depth larger than 4 mm are also more likely to metastasize [30].

Although excision of the tumor represents the go-to method of treatment, alternative may need to be used when the tumor has become invasive either by local invasion of adjacent structures or by metastasis [1].

A recent study has shown that invaded resection margins remain one of the biggest risk factors in local tumor recurrence.

Thus, an emphasis on avoiding invaded resection margins is placed whenever such a procedure is done [31].

An increased risk of metastatic disease is associated with a number of histopathological characteristics such as deep invasion of the skin, tumors with a diameter of 2cm or more and perineural invasion [32].

As such a high quality and precise diagnosis of these parameters is crucial for the management of these malignancies.

Conclusions

This study showed statistically relevant corroborations of both clinical and histopathological parameter that were analyzed.

Identification of such high risk prognosis factors for each patient with malignant skin tumors, may prove useful in developing better and more targeted oncological treatment.

Conflict of interests

None to declare.

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