Review Article

A local perspective on basal cell carcinoma: frequency of subsequent skin tumours

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Abstract

Background: Basal cell carcinoma (BCC) is the commonest skin malignancy with a significant risk of recurrence and new primaries. The major risk factor is ultraviolet (UV) radiation, which is relevant to Malta, where the UV index is frequently high.

Objective: The aim of this study was to follow up patients diagnosed with BCC, analyse the occurrence of subsequent malignant and pre-malignant skin tumours and assess whether variables like age and gender modify risk. This will aid local screening methods and follow-up protocols.

Method: Patients registered with BCC in the Malta National Cancer Registry in 2007 were included in our study. Histology results belonging to these patients were followed up until the end of 2014. Risk of developing further lesions when accounting for age and gender was calculated using the Chi^2 test for Independence and hazard ratios.

Results: A total of 382 patients were diagnosed with BCC in 2007. Almost one third of these patients (30.1%) had at least another skin tumour biopsied thereafter; 71.7% of these tumours were BCCs. Squamous cell carcinomas and actinic keratoses were also commonly biopsied. Nine patients developed malignant melanoma. The commonest location for BCCs and other non-melanoma skin tumours was the face. Males and the elderly had significantly higher risks to develop further skin tumours, as reflected by our statistical data.

Conclusion: Our results are consistent with international data. BCC fulfils most criteria for screening, thus follow-up in high risk patients is recommended.

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Keywords

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Introduction

Basal cell carcinoma (BCC) is the commonest skin malignancy, and incidence rates are increasing. Individuals with a history of BCC have increased risk of developing new lesions especially in high-risk regions like the face. Although rarely metastatic and overall slow-growing, BCC may cause aesthetic and possibly functional complications from extensive local tissue destruction. The major risk factor for the development of BCC is exposure to ultraviolet radiation.[1] This has important implications for the Maltese Islands, where

the UV indices can go up to very high levels during the spring and summer seasons.[2]

The purpose of this project was to obtain a local perspective on the frequency of new malignant and pre-malignant skin lesions in patients with past BCC and assess whether variables such as age and gender modify risk. This information will provide more knowledge to aid follow-up protocols and screening methods for patients with BCC.

Method

This was a retrospective study, using data from the Malta National Cancer Registry (MNCR) at the Department of Health Information and Research, with the approval of the Data Protection Unit. The MNCR indexes every histopathological confirmation of cutaneous BCC on a yearly basis, gathering reports from all laboratories across the Maltese Islands, most of which come from the Pathology Department of the main general hospital, Mater Dei.

In this study, we included all those patients recorded in the MNCR to have BCC in the year 2007. Data extracted from this list included age at time of diagnosis, gender, date of death for deceased patients, as well as the site and morphology of the BCC. This data did not include information about completeness of margins of excision.

In order to assess whether this cohort of patients developed other skin tumours after 2007, a search for the relevant histopathology reports was performed on iSoft Clinical Manager (iCM), the local electronic database that records patients' investigations. All histopathology results showing skin tumours (pre-malignant and malignant) were included up to the end of 2014. From these reports we gathered the following data: the number of cutaneous malignant and pre-malignant lesions confirmed by histology per individual, the site and morphology of these lesions, and the completeness of the margin of excision.

All data was organised in a spreadsheet and analysed with the software Stata® 11.2 (StataCorp LLC, Texas). For all statistical analyses, confidence levels of 95% were applied and *p*-values of less than 0.05 were taken to be statistically significant.

The Pearson's Chi-Square Test for Independence was used to assess for a relationship between gender and the likelihood to have further skin tumours. The Kaplan-Meier survival estimate was used to measure the time between the initial BCC and development of the first skin malignant or pre-malignant lesion biopsied thereafter, looking for a significant difference between males and females. Hazard ratios (HR) for gender and age in relation to the amount of time passed to the second skin tumour were calculated using a Cox Regression analysis, adjusting for ties with the Breslow Method. A ratio more than one was taken to imply increased risk.

For the deceased patients, the Chi-Square test for Goodness of Fit was used to analyse the difference between the observed and expected number of deaths, correcting for gender. Data was entered into a contingency table, placing male and female variables in rows, and alive and deceased variables in columns. The expected values of deceased patients for each gender were calculated by multiplying the row total with the column total, and dividing that against the total number of patients. In this analysis one patient had to be omitted as the date of death was also the date of incidence.

Results

Demographic analysis

A total of 382 patients were diagnosed with BCC in 2007; no patient was found to

have more than one BCC biopsied in that year. The age ranged from 16-93 years at the time of diagnosis. The mean age of presentation was 66.2 years (see Figure 1). Out of the 382 patients, 115 (30.1%) had further skin tumours biopsied on follow-up, whilst 267 patients (69.9%) had no further biopsies documented. Those patients who developed subsequent skin tumours had a slightly older mean age (69.2 years) when compared to the general study population. In this study, four patients were younger than 30 years at initial presentation. They had no further documented biopsies in the follow-up period; three of these four patients were female.

The majority of patients presenting with a BCC in 2007 were male (*n*=227, 59.4%). When the Chi-Square Test for Independence was used to assess for a relationship between gender and the likelihood to have further tumours, a Chi^2 value of 11.093 and *p*-value of <0.001 were obtained, implying that males were significantly more likely to have further skin tumours.

The Kaplan-Meier estimation (Figure 2) shows marked separation between the female and male groups; thus, the time to develop a second skin tumour after the first BCC is significantly shorter for males. When the Cox regression model was applied to assess the effects of gender and age on the time to develop a second skin tumour, the following values were obtained: HR of 1.84 and *p*-value of 0.004 for male gender, and a HR of 1.02 and *p*-value of 0.016 for age. These hazard ratios suggest that the two variables have a causative effect on the time to second tumour, especially male gender.

Figure 1: *Distribution curve of the age of the patients presenting with BCC in 2007*

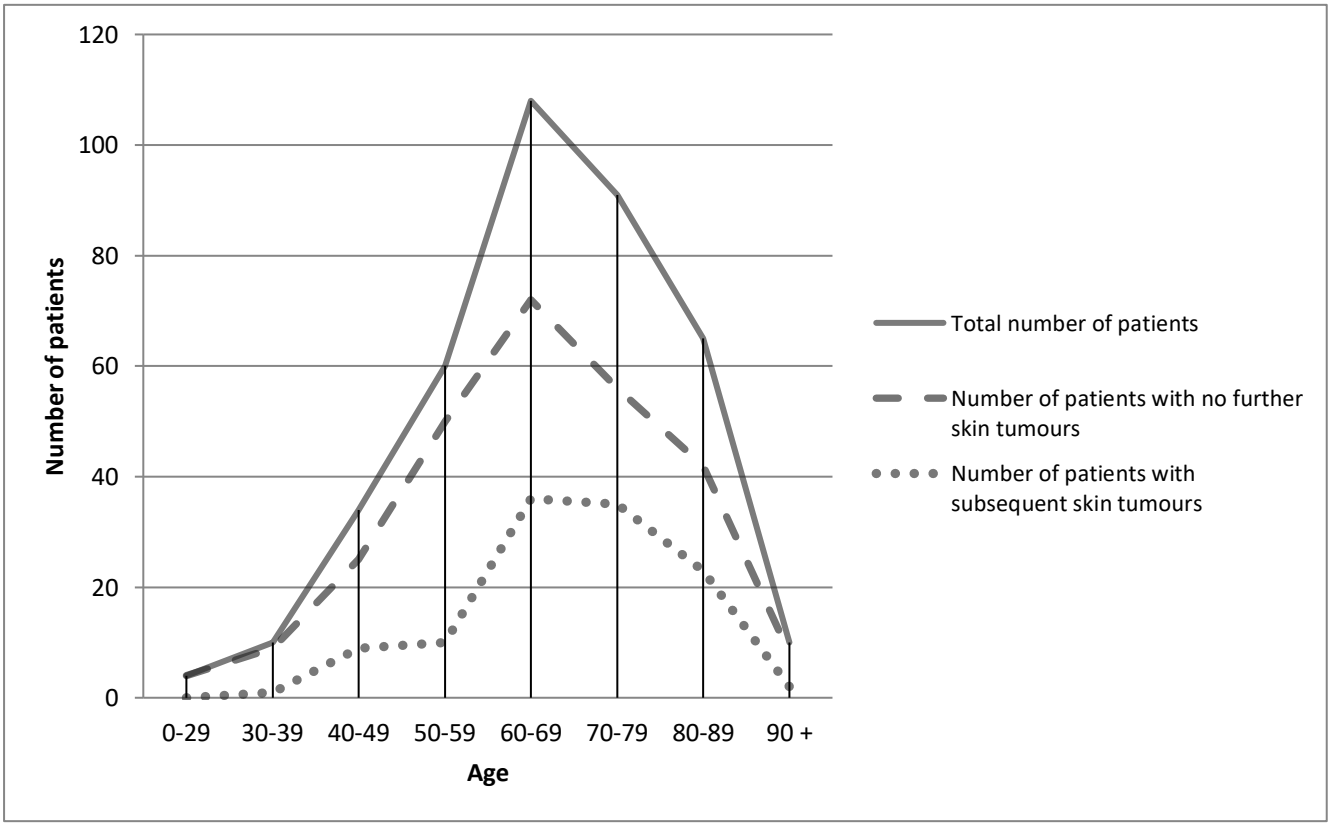
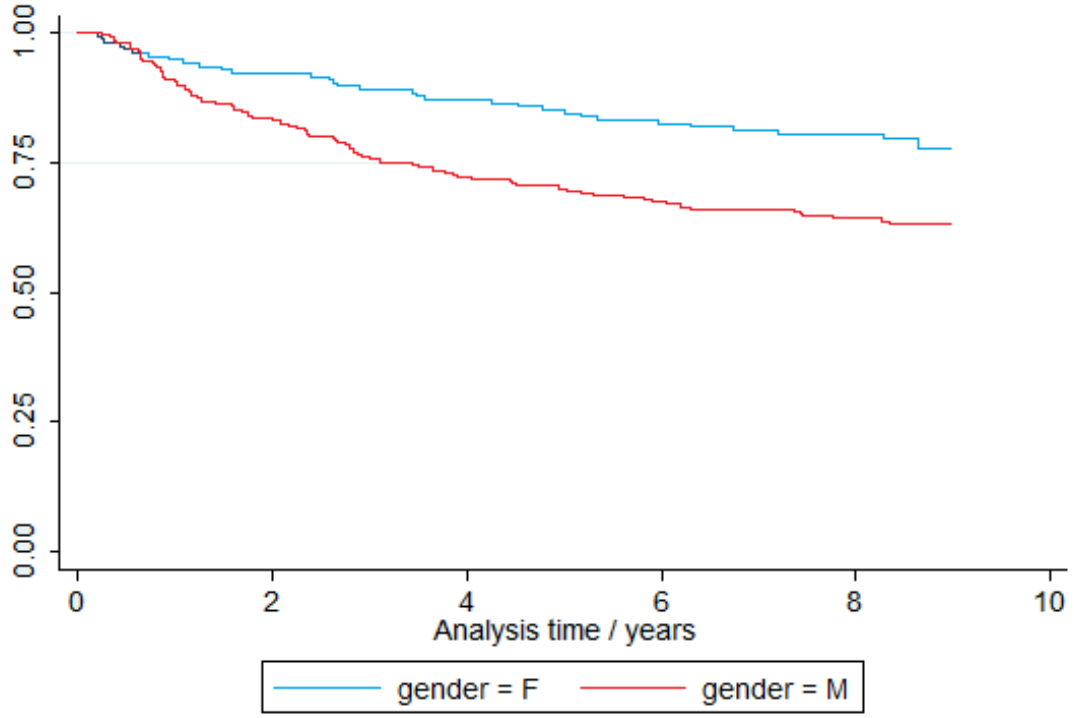


Figure 2: *Kaplan-Meier Estimation for time between first BCC in 2007 until first skin tumour biopsied thereafter according to gender*



At the time of the study, 18.6% of the 382 patients were deceased (*n*=71). When the Chi-Square test for Goodness of Fit was applied, a Chi ^2 value of 2.486 was obtained, with a *p*-value of 0.115. This implies no statistical difference in the number of deaths when correcting for gender.

Analysis of the skin tumours biopsied after 2007

In those 115 patients with further skin tumours, a total of 460 skin tumours were biopsied and sent for histopathology during the follow-up period (refer to Table 1). Whilst the majority of these were BCCs (*n*=330, 71.7%), there was a mixture of other skin lesions, namely squamous cell carcinomas (SCCs), cutaneous malignant melanomas, actinic keratoses (AKs), keratoacanthomas and one Merkel cell carcinoma. Ten melanomas were excised from nine patients in this cohort.

All the tumours included in this study were analysed according to site (refer to Table 2). Of the BCCs excised in 2007, 66.8% were located on the head and neck. The next most common location was the trunk (11.3%). Of the BCCs excised after 2007, 20.3% were located on the trunk, 46.3% (*n*=31) of which were of the superficial type. From the BCCs sent for histology in 2007, 10.2% (*n*=39) were listed under the topographical code C44.9, meaning that the location of the biopsy was undocumented. In view of poor documentation, it was often difficult to recognise which BCCs after 2007 were recurrences at the same site as opposed to new primaries. Regarding the site of the cutaneous malignant melanomas, four of the ten melanomas in our study were located in the head and neck region (one on the face and three on the scalp/neck); the remaining

six melanomas were distributed evenly on the trunk and lower limbs.

The number of malignant and pre-malignant skin tumours biopsied for each individual after 2007 is presented in Figure 3. Ten patients had more than ten skin tumours removed after 2007 (Table 3). One patient had 22 skin tumours removed in this seven-year period. No melanomas were biopsied in this group of patients. The medical records of these patients were reviewed for documentation of any risk factors explaining their high incidence of skin tumours. Documentation occurred in only two cases, both of which were noted to have a history of chronic sun exposure. Notably, there was only one female in this group of patients; she had a documented history of breast cancer and Sjogren's syndrome in addition to a history of sunbathing.

Our final analysis concerns the completeness of the margin of excision for the skin tumours biopsied after 2007 (refer to Table 4). Punch biopsy reports were only taken into consideration if the lesion was not subsequently excised. The percentage of BCCs reported to be incompletely excised and not followed by a subsequent wider excision was 8.8%.

Discussion

In our study we confirmed that the majority of patients presenting with BCC in 2007 were males older than 60. This is similar to trends in international data, although it is well-known that rates in females are on the rise in view of altered sun-seeking behaviour.[3] Some studies show that in younger patients the incidence of BCC is higher in females.[4] Although the number of patients younger than 30 years in our original study cohort was too small to draw accurate conclusions as there were only four, our findings seem to support this as three were female.

***Table 1**: The number of malignant and pre-malignant skin tumours biopsied between 2008 and 2014, according to histology*

Histology	Number of skin tumours
Basal cell carcinomas	330 (71.7%) *(of which 47 were superficial BCCs)*
Squamous cell carcinomas	57 (12.4%)
Actinic keratoses	57 (12.4%)
Malignant melanomas	10 (2.2%)
Keratoacanthomas	5 (1.1%)
Merkel cell carcinoma	1 (0.2%)
TOTAL	**460**

***Table 2**: Sites of basal cell carcinomas biopsied in 2007 and of the skin tumours biopsied thereafter. Codes used are from ICD-O-3*

Topography Code and Anatomical Site		BCC in 2007	BCCs between 2008 and 2014	Other malignant and pre-malignant skin tumours between 2008 and 2014
TOTAL No. of tumours		**382**	**330**	**130**
C44.0	***Lip***	12 (3.1%)	6 (1.8%)	4 (3.1%)
C44.1	***Eyelid***	24 (6.3%)	8 (2.4%)	0
C44.2	***External ear***	20 (5.2%)	10 (3.0%)	9 (6.9%)
C44.3	***Face*** $\rightarrow$ ***(Nose)***	183 (47.9%) -	166 (50.3%) *(47)*	49 (37.7%) *(8)*
C44.4	***Scalp, neck***	16 (4.2%)	18 (5.5%)	24 (18.5%)
C44.5	***Trunk***	43 (11.3%)	67 (20.3%) *(31 of superficial type)*	14 (10.8%)
C44.6	***Upper limb***	24 (6.3%)	20 (6.1%)	14 (10.8%)
C44.7	***Lower limb***	15 (3.9%)	28 (8.5%)	15 (11.5%)
C44.8	***Overlapping***	6 (1.6%)	0	0
C44.9	***Skin, Not specified***	39 (10.2%)	7 (2.1%)	1 (0.8%)

***Figure 3**: Histogram showing the number of malignant and pre-malignant skin lesions biopsied between 2008 and 2014 and the frequency of patients per number*

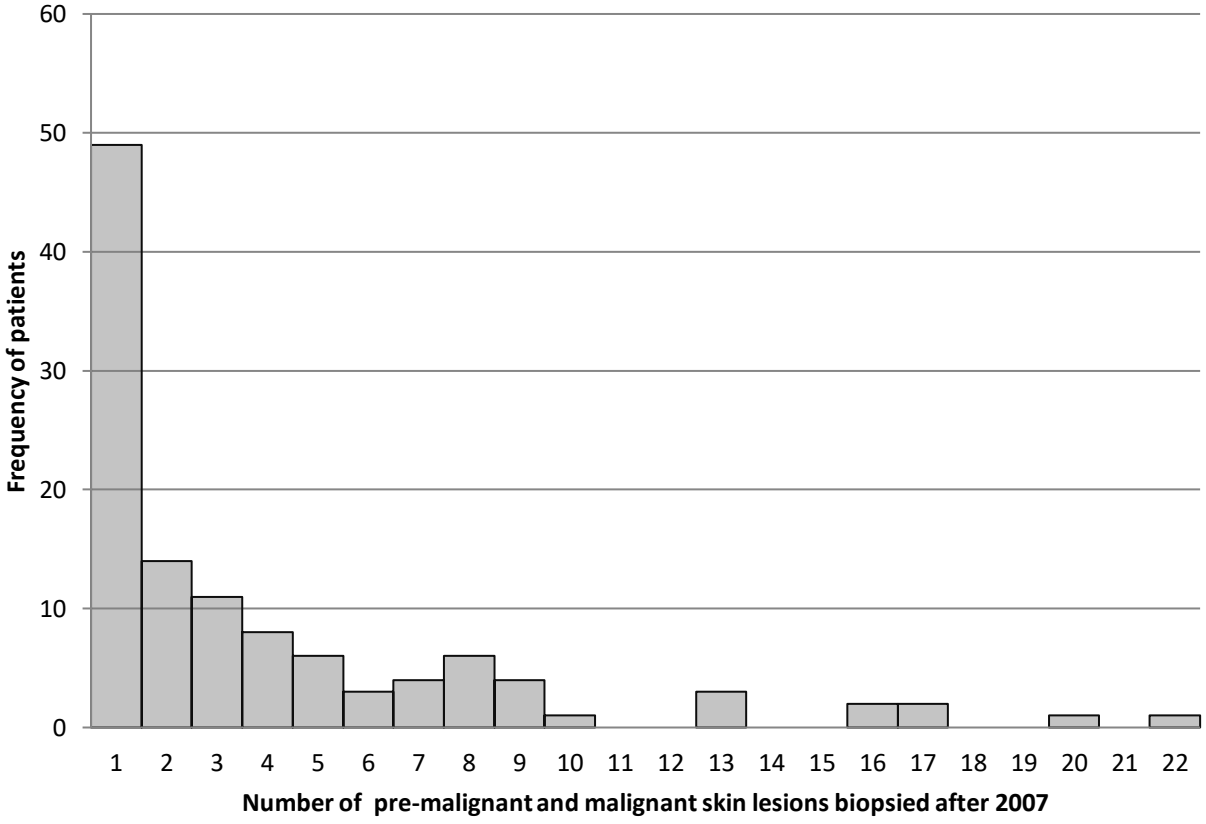


***Table 3**: Patients who had 10 or more tumours biopsied between 2008 and 2014 after the presenting BCC in 2007*

Patient	Gender	Age in 2007	Site of BCC in 2007	No. of subsequent BCCs (2008-2014)	No. of subsequent other skin tumours (2008-2014)	Documented risk factors
1	M	77	Face	4	2 SCC 4 AK	Not documented
2	M	76	Face	9	4 AK	Deceased - records unavailable
3	M	62	Face	4	8 SCC 1 AK	Not documented
4	F	62	Not specified	8	2 AK	**History of sunbathing; Breast Ca; Sjogren's syndrome**
5	M	82	Face	11	2 SCC 3 AK	Not documented
6	M	69	Not specified	5	2 SCC 8 AK 1 KA	Records unavailable
7	M	76	Face	13	4 AK	Records unavailable
8	M	61	Face	10	2 SCC 5 AK	Not documented
9	M	77	Trunk	20	nil	Deceased – records unavailable
10	M	75	Face	18	1 SCC 3 AK	**Outdoor occupation documented**

***Table 4:** Completeness of margin of excision for BCCs and other skin tumours biopsied between 2008 and 2014*

Margin of excision	Basal cell carcinomas	Other skin tumours	TOTAL
Complete	292 (88.5%)	85 (65.4%) (includes all 10 melanomas)	377 (82.0%)
Incomplete	29 (8.8%)	30 (23.1%)	59 (12.8%)
Unspecified or uncertain	9 (2.7%)	11 (8.5%)	20 (4.3%)
Punch biopsies	0	4 (3.1%)	4 (0.9%)
TOTAL	330	130	**460**

We have also found that 30.1% of the 382 patients diagnosed with BCC in 2007 had at least another skin tumour biopsied in the subsequent seven-year period; 71.7% of these were BCCs. This is consistent with other studies, demonstrating that a history of BCC increases the risk for new BCCs.[5-6] It was interesting to note that SCCs and AKs were regularly associated with BCCs, while only nine patients developed cutaneous malignant melanoma. Cutaneous SCCs tend to develop following chronic sun exposure, whilst melanomas are typically associated with sunburns in childhood and adolescence. The risk of BCC seems to depend on the ability of the skin to tan. Good tanners tend to develop BCC after chronic sun exposure, while poor tanners are at increased risk of BCC with chronic sun exposure as well as with intermittent sunburning.[7-8] Immunosuppression increases the risk to develop multiple skin cancers of all types (particularly SCCs) and worsens prognosis.[9] As expected with a tumour that rarely metastasizes, the presence of a BCC did not contribute significantly to mortality when correcting for age and gender.

Not only did males outnumber females in our original study population, but males were also more likely than females to develop subsequent skin cancers. This was especially highlighted in the ten patients who had more than ten subsequent skin tumours – nine were male. The most probable explanation is that males are exposed to heavier sun exposure from occupational and recreational activities. In our study, males also showed a shorter time interval than females to develop the next skin tumour.

The commonest site for BCCs was the head and neck region, as has been observed internationally.[1,3] However, 20.3% of BCCs occurring after 2007, as opposed to 11.3% in 2007, were located on the trunk. With regards to the ten recorded melanomas, six were located on the trunk or lower limbs. This emphasises the importance of not limiting examination to the head and neck when following up patients with BCCs, as skin tumours located on other parts of the body might be missed.

Our last observation is that the local percentage of incompletely excised BCCs was 8.8%. International rates cited vary from 4-16.6%,[10] however these statistics take into account the more accurate technique of Mohs microscopic surgery, which is unavailable in Malta. For SCCs and especially AKs, the rate of incomplete excision was higher, but these are usually clinically less well-delineated than BCCs. Of note is that all melanomas were completely excised. In clinical practice, when a BCC is reported to be incompletely excised, sometimes it is decided to follow up the patient for recurrence rather than perform a wider surgical excision. The decision in these situations would be taken on an individual basis, depending on the histology of the tumour, the location, any associated immunosuppression and patient preference. We have no data on how many of the tumours biopsied that were reported to be incompletely excised subsequently underwent treatment with cryotherapy, topical 5-fluorouracil, imiquimod cream, or radiotherapy.

This study has a number of limitations, such as the fact that it was done retrospectively based on available iCM data and relying on the number of skin tumours biopsied and sent for histology – in this study no patients were examined clinically. The prevalence and frequency of skin tumours between 2008 and 2014 reported here are likely to be an under-representation. Patients having further lesions excised and

sent for histological analysis to private laboratories would not be available through iCM and therefore would not be included in this study. Patients might have developed further skin tumours which were misdiagnosed, or did not seek medical opinion. Finally, further skin tumours (including recurrences) might have been diagnosed by dermatologists, and treated with cryotherapy, 5-fluorouracil or imiquimod cream, without biopsy. This happens occasionally with very superficial non-melanocytic tumours like superficial BCC or Bowen's disease of the skin. Actinic keratoses are also not routinely biopsied before treatment with cryotherapy, 5-fluorouracil or imiquimod cream, but are typically biopsied when hypertrophic or resistant to treatment to rule out invasive disease.

A systematic review published in 2016 dwells on whether screening for early detection of BCC is worthwhile.[11] It concludes that BCC fulfils most of the WHO criteria for screening. Early diagnosis whilst BCCs are relatively small allows for less aggressive treatment options. This would be particularly relevant in the facial region, where the costs and morbidity associated with the removal of large, disfiguring and complex lesions may be significant. Naked-eye inspection and dermoscopy are all that would be needed for early detection, making screening potentially cost-effective.

Mass screening of the entire population is impractical. However, we propose that patients who are diagnosed with BCC and are at high risk of developing further tumours are offered regular follow-up. This would include immunosuppressed patients and those with more than one BCC at first diagnosis.[5] The incidence of subsequent BCC increases rapidly with the number of previous BCCs, so patients with a history of multiple BCCs would also benefit from regular and long-term follow-up.[6] Patient education is also paramount. Patients should be made aware of the significant rate of subsequent skin cancers and what they may look like, so that they may be vigilant and present early with any suspicious lesions that may develop.

Conclusion

In conclusion, our study shows that almost one third of patients diagnosed with a BCC in Malta developed subsequent skin tumours within a seven-year follow-up period. This risk is higher in males, the elderly and those who have had a previous BCC. Regular follow-up is recommended for such patients as well as for immunosuppressed patients.

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