Accurate diagnosis of basal and squamous cell carcinomas in general practice

By Dr Gabriel Scripcaru and Dr Predrag Nikolic

Recognising the defining clinical features of various types of skin cancer, and an appropriate approach to the biopsy, are essential for their diagnosis and management. The importance of a timely diagnosis cannot be overemphasised, in view of achieving the best possible outcome and minimising the complications.
This article aims to discuss squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), two of the most common cancers in Australia.

**Patient skin history**

It is important to record the relevant patient skin history prior to completing a full body skin check or examining a particularly concerning new or changing lesion, including:

- Family history of skin cancers
- Previous skin cancers
- Previous excisions
- Occupation
- Past UV exposure/sunburn including use of solariums
- Frequency of sun protection

**Squamous cell carcinoma (SCC)**

SCC is a malignant epithelial tumour of keratinocytes arising most commonly in sun-damaged skin. The vast majority of cases are associated with pre-existing actinic (solar) keratosis, squamous cell carcinoma in situ, or both. SCCs account for nearly 30% of non-melanoma skin cancers.

Some SCCs may be associated with human papillomavirus, chronic inflammation or radiation therapy.

From a histological point of view, these lesions may be well differentiated, moderately differentiated or poorly differentiated. The degree of differentiation is an essential marker of progression, risk of metastasis and prognosis. Many lesions display areas of varying degrees of differentiation, however, the worst area is to be considered when finally grading the lesion. It is the least differentiated area that ultimately determines the management and prognosis.

SCC with focal basaoid differentiation or basosquamous carcinoma, is regarded as a moderately differentiated lesion. Poorly differentiated SCCs are characterised by the absence of keratinisation. SCC may be slow or fast growing. In some cases, significant clinical changes may be evident within months, or even weeks.

**Clinical Features**

- May be pigmented, raising the clinical suspicion of a pigmented lesion
- May be tender to touch
- Thickened red, scaly spot
- Slowly or rapidly growing papule or nodule
- Non-healing ulcers or recurrently bleeding
- May be recurrent and bleeding
- Recurrent bleeding or ulceration
- Pearly, translucent papule, plaque or nodule
- Fixation to underlying structures
- Symptoms indicating perineural invasion (e.g. tingling, pain, paraesthesia, formication, dysesthesia impaired motor function)
- Aggressive histologic subtypes (e.g. micronodular, infiltrative, morphoeic or basosquamous/metatypical)
- Symptoms indicating perineural invasion (e.g. tingling, pain, paraesthesia, formication, dysesthesia impaired motor function)
- Fixation to underlying structures
- Genetic disposition of the patient (e.g. Gorlin syndrome or Xeroderma pigmentosum) and use of immunosuppressants

**Histology**

- The plane of section examined histologically is relevant to the distance from the tumour to the nearest margin, hence, it does not necessarily represent the greatest tumour dimension.

**Steps prior to removing SCC/BCC**

Prior to the excision of the tumour, the diameter should be measured and recorded. Tumour measurement after excision is not accurate due to tissue shrinkage, which occurs after excision and during specimen fixing and processing. The plane of section examined histologically is relevant to the distance from the tumour to the nearest margin, hence, it does not necessarily represent the greatest tumour dimension.

**Basal cell carcinoma (BCC)**

Basal cell carcinoma (BCC) is a slow-growing locally invasive tumour, arising most commonly in sun-damaged skin from the basal layer of the epidermis. Progression of disease usually takes the form of local tissue destruction, but rarely progresses to metastases.

Histologically, tumours display several architectural patterns: nodular, superficial (which may represent an early phase of a nodular pattern), superficial multifocal, infiltrative, micronodular, morphoeic and metatypical (i.e. squamous or sebaceous differentiation). Often, a mixed pattern is observed in the same lesion.

Patient-related factors and the presence of high-risk features determine the course of treatment. BCC is the most common cancer in humans and accounts for nearly 70% of non-melanoma skin cancers.

**Clinical Features**

- Pearly, translucent papule, plaque or nodule
- Scaly, dry area, shiny and pale or bright pink in colour
- Recurrent bleeding or ulceration
- May be pigmented, raising the clinical suspicion of a pigmented lesion
- Head and neck BCCs >10 mm are considered to be high-risk tumours
- Trunk and extremities BCCs >20 mm are considered to be high-risk tumours
- Aggressive histologic subtypes (e.g. micronodular, infiltrative, morphoeic or basosquamous/metatypical)
- Symptoms indicating perineural invasion (e.g. tingling, pain, paraesthesia, formication, dysesthesia impaired motor function)
- Fixation to underlying structures
- Genetic disposition of the patient (e.g. Gorlin syndrome or Xeroderma pigmentosum) and use of immunosuppressants

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**Confirming the diagnosis and notes on the histology report**

In the first instance, the surgical options include a shave or punch biopsy for diagnostic purposes, or complete curative excision without prior tissue diagnosis. Primary curative excision is usually undertaken in cases of high clinical suspicion or at the patient’s request.

A punch biopsy has the advantage of including the deeper aspect of the lesion and is easily processed with a lower risk of tissue artefacts.
Depending on its size, a shave biopsy may better reveal the architectural pattern and it may include a larger portion of the lesion, however, it may not include the deeper aspect of the tumour and it may be prone to artefacts, if it is too thin. A thicker shave is preferred to avoid folding or fragmentation which could significantly impair the histological assessment. A thicker shave biopsy also provides better insight into the tumour depth and architecture. It is important to note that margins cannot be accurately assessed in a punch or shave biopsy, although small lesions may be often completely excised employing one of these biopsy types. The presence of clear edges may be mentioned in such cases in the histological report, however clinical correlation is essential when determining the need for further excision.

Surgical excision is the treatment of choice for both SCC and BCC.

There is no clear evidence-based recommendation regarding the minimum excision margin. Factors such as risk status of the tumour, surgical accessibility, patient age, co-morbidities and wound-healing capacity should be considered when deciding on the excision margin.

Clinical guidelines are regularly communicated and updated in publications and at conferences. Regardless of the guidelines followed by the clinician, it is important to note that due to tissue shrinkage, the reported histological margins may be as little as half of the clinical margin measured at the time of surgery.

The histological report indicates the clearance of margins in the planes of section examined rather than representing an absolute guarantee of complete excision of the tumour. Re-excision, with the same recommended clinical margins as in the initial excision, should be attempted when involved margins are reported.

In approximately 50% of cases where a tumour was present at the edges of the biopsy, or at the margins of the excision in the initial specimen, there will be no further residual tumour in the re-excised specimen. This is explained by the fact that a minimal amount of residual tumour at the edge of the initial biopsy has been eradicated by the immune response and the regenerative process leading to repair and scarring following the initial surgical intervention.

Additional aspects of management

In cases of SCC with perineural invasion (PNI) or lymphovascular invasion (LVI), the patient should be referred to a specialist (radiation oncologist or hospital skin cancer unit). In cases of LVI, further investigations in view of staging may be indicated, while in cases of PNI, adjuvant therapy, such as radiation therapy may be employed.

Non-surgical options for BCC

Unlike in cases of SCCs, non-surgical options exist for a subset of BCCs. Cryotherapy, curettage and cautery can be used in combination in patients who cannot tolerate surgery. BCC rarely presents with LVI. Those cases should be treated like a moderately differentiated SCC with radiation therapy. Radiation therapy may be indicated in these cases and the patient should therefore be referred to a specialist (radiation oncologist or hospital skin cancer unit) for further staging and management. Superficial BCC can be managed using a non-surgical approach.

Other treatment options, reserved for superficial BCC, include topical therapy such as Imiquimod (Alldara) cream and topical photodynamic therapy. These methods are generally not suitable for cases of BCC with high-risk features.

OCP use. A number of authorities suggest that additional laboratory markers may be helpful in the assessment of patients for iron deficiency. Iron studies can certainly offer more information regarding iron deficiency with a low transferrin saturation (<20%) supporting the diagnosis of iron deficiency in patients with concomitant inflammation or systemic illnesses (even in the presence of a normal serum ferritin). You may avoid the need for the patient to have another test done, if you order iron studies instead of just serum ferritin.

A/Prof Chris Barnes (Pathologist)

One of my female patients in her late 30s presents with being tired. What tests should I order to see if she is iron deficient?

A/Prof Chris Barnes (Pathologist)

Iron deficiency is a common cause for fatigue and up to 1 in 6 females in the reproductive age range has iron deficiency and this may be even higher in certain ethnic groups. A complete assessment of iron studies is recommended, by a number of groups, as an important first step in the investigation of patients with lethargy.

Dr Jon Barrell (General Practitioner)

Should I order iron studies or just ferritin?

A/Prof Chris Barnes (Pathologist)

Trying to keep it simple, I first look at the serum ferritin and the transferrin saturation. If both are low, the patient is iron deficient. If the serum ferritin is normal (or low normal) and the transferrin saturation is also low, then I would be suspicious that the patient is also low in iron and act accordingly (e.g. consider excluding sources of blood loss, review dietary history, consider a trial of iron supplementation with close review).
Patients’ vitamin D levels drop significantly during winter

By Dr David Deam

Vitamin D levels fluctuate significantly depending on the season, especially in the Southern states of Australia. At the end of winter, approximately 36% of Australians are vitamin D deficient, in comparison to 14% at the end of summer. Therefore, making the end of winter the best time to test patients for vitamin D deficiency.

The below diagrams indicate the percentage of Australians with a vitamin D deficiency in summer (diagram 1) versus winter (diagram 2).

Health implications of vitamin D deficiency

Vitamin D deficiency is of concern as it can lead to a variety of health conditions including the loss of bone density, which can contribute to osteoporosis and fractures in adults and children. Low levels of vitamin D have also been found in association with other health conditions, such as cardiovascular disease, diabetes, immune system diseases, microbial and respiratory diseases, cognitive impairment in older adults, mental health and cancer.

Target vitamin D levels

The international recommendations for adequate vitamin D levels vary, but based on a review of current literature and recent publications, Australian Clinical Labs suggests that adequate vitamin D status is a serum level equal to, or greater than, 50 nmol/L at the end of winter. This level should be 10-20 nmol/L higher at the end of summer to allow for seasonal decrease.

This figure is based on the level below which parathyroid hormone concentrations begin to rise and the risk of fractures increases.

As for all tests, Australian Clinical Labs’ pathologists and scientists will continue to evaluate current literature and our target range may change as new evidence emerges.
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Thank you

Who to test

Vitamin D testing should be ordered for patients at risk of vitamin D deficiency, including:

- Housebound people - including the sick and disabled
- Elderly in high care
- People with darker skin
- People who cover their skin due to religious or cultural reasons
- People who regularly avoid the sun
- People who work indoors

Also patients with:

- Signs, symptoms and/or planned treatment of osteoporosis or osteomalacia
- Increased alkaline phosphatase with otherwise normal LFTs
- Hyperparathyroidism, hypo- or hypercalcaemia or hypophosphataemia
- Malabsorption (i.e. CF, IBD, coeliac, etc)
- Medications known to decrease vitamin D levels (i.e. anticonvulsants)
- CRF and transplant recipients

Vitamin D testing

Vitamin D testing at Clinical Labs measures the concentration of total 25-hydroxyvitamin D (25-OHD) in a patient’s serum. The report will also include previous test results, for comparison (if applicable), and suggested cut points to define sufficient, deficient and severely deficient vitamin D levels.

Further testing

When ordering a vitamin D test for a patient, also ordering a serum calcium assessment and parathyroid hormone (PTH) test, will assist in placing the vitamin D level within the context of overall calcium homeostasis. If Osteoporosis is present, fasting blood crosslaps (CTX) will provide a way of monitoring bone turnover in response to therapy.

Treatment

To ensure adequate levels of vitamin D are maintained throughout the year, the following sun exposure times (mins per day) are recommended for 1/3MED for moderate fair skin, at either 10am or 2pm daily.

<table>
<thead>
<tr>
<th>Location</th>
<th>December-January</th>
<th>June-August</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perth</td>
<td>5-6 mins</td>
<td>20-28 mins</td>
</tr>
<tr>
<td>Adelaide</td>
<td>5-7 mins</td>
<td>25-38 mins</td>
</tr>
<tr>
<td>Melbourne</td>
<td>6-8 mins</td>
<td>32-52 mins</td>
</tr>
<tr>
<td>Hobart</td>
<td>7-9 mins</td>
<td>40-47 mins</td>
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<tr>
<td>Sydney</td>
<td>6-8 mins</td>
<td>26-28 mins</td>
</tr>
<tr>
<td>Brisbane</td>
<td>6-7 mins</td>
<td>5-19 mins</td>
</tr>
<tr>
<td>Cairns</td>
<td>6-7 mins</td>
<td>9-12 mins</td>
</tr>
</tbody>
</table>

If patients are unable, for a variety of reasons, to gain the required amount of sun exposure for vitamin D production, supplementation may be required.

A maintenance dose of up to 1000 IU/day may be adequate, however some individuals will require higher doses. Severe vitamin D deficiency (serum level <20 nmol/L) may require 3000-5000 IU/day for 6-12 weeks.

Supplements should be vitamin D3. Adequate dietary calcium is also required, at least 1g/day and up to 1.3g/day, for older adults. Many patients will require supplementation to achieve this amount.

Note: Calcium supplements are best taken before sleep to ensure maximum absorption and suppression of peak bone turnover which usually occurs between approximately 2am and 3am.

Serum 25-OHD should be retested no earlier than 3 months following commencement of supplementation with vitamin D or a change in dose. Once a desirable target has been achieved, especially at the end of winter, no further testing is required unless risk factors change.

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2. RCPA Position Statement: Use and Interpretation of Vitamin D testing. The Royal College of Pathologists of Australasia, May 2013.

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