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Facial basal cell carcinoma

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Basal cell carcinoma (BCC) is a locally invasive cancer of epidermal basaloid cells. It is the most common cancer in humans,[1] and its incidence will soon surpass that of all other cancers.[2] Skin cancers are categorised into two groups—melanomas and non-melanoma skin cancers. Of the non-melanoma skin cancers, 75-80% are BCCs[3-5] and up to 85% of these are on the head and neck.[4-16] The remainder are predominately squamous cell carcinomas. Delay in presentation is associated with increased tumour growth.[17] Timely recognition is important because early identification can limit the extent of facial tissue involvement and subsequent resection, thereby resulting in a better cosmetic and functional reconstruction. Evidence suggests that denial is the main reason for delay in presentation with non-melanoma skin cancer.[17]

This review focuses on the diagnosis, investigation, and management of BCC of the head and neck.

Who gets BCC?

The incidence of BCC varies geographically (table) and is increasing worldwide.[10-15 18-22] In the United States procedures performed for non-melanoma skin cancer at all sites almost doubled from 1994 to 2006.[23] The lifetime risk has been estimated at more than 30% in a white German population,[24] 28-33% in the US,[25] and 15-28% for women and 17-39% for men in Canada.[6] In Australia the lifetime incidence of BCC is now greater than 50% (C Del Mar, personal communication, 2012). About 75 000 new cases of BCC occur each year in the United Kingdom, and the incidence is predicted to rise up to the year 2040. Because of the lack of non-melanoma skin cancer registries, the incidence is probably underestimated.[26 27]

Incidence of basal cell carcinoma (BCC) worldwide

Area	Incidence (male/female)*	Year of study	First author (year published)
Australia	1041/745	2002	Staples (2006)[16]
Australia	955/629	1995	Staples (1998)[22]†
United States (Minnesota)	175/124	1976-84	Chuang (1990)[28]‡
Wales	128/105	1998	Holme (2000)[15]
Netherlands	101/101	2008	Flohil (2011)[11]
Canada	87/68	1992-2001	Hayes (2007)[w84]
United Kingdom	69/53	1996-2003	Bath-Hextall (2007)[w85]
Netherlands	63/58	1998-2000	De Vries (2004)[10]
Scotland	61/47	2001-03	Brewster (2007)[14]
Germany	53.6/44	1998-2001	Katalinic (2003)[5]
Finland	49/45	1991-95	Hannuksela-Svahn (1999)[13]

*Number of patients with BCC per 100 000 per year (world standardised rate).
†Did not state which population used for age standardisation.
‡US standardised population.

Risk factors

The greatest risk factor for the development of BCC is exposure to ultraviolet radiation.[24] This explains geographical variance and why disease is more common in areas of the body exposed to the sun. Sun exposure in childhood is especially important.[24] BCC is usually diagnosed after 40 years of age and is slightly more common in men,[3 6 22 28-32] with some studies showing that the disease is more aggressive in men than in women.[33 34] With increasing age, the proportion of BCCs that occur on the head and neck increase.[7] People with skin types that burn easily and tan poorly have 10-20-fold higher rates of BCC than those with dark skin, even when living in the same area.[31] BCC is far less common in children,[w1] and less than 2% of BCCs occur in pigmented skin because of the photoprotection provided by melanin.[w2] Other risk factors include radiotherapy, arsenic, and immunosuppression,[4] especially in organ transplant recipients, who have a 10-fold higher incidence of this cancer.[w3 w4] BCCs may develop on the face at sites of trauma[w5-w7] and in sebaceous naevi.[w8] A long term follow-up study suggests that exposure to even high doses of PUVA (psoralen and ultraviolet A radiation) does not greatly increase the risk of BCC.[w9]

Genetic conditions that predispose to the development of multiple BCCs—such as naevoid basal cell carcinoma (Gorlin) syndrome, xeroderma pigmentosum, albinism, and Bazex syndrome—are not discussed in this review.

How do BCCs present?

BCC was first described as a rodent ulcer in 1824,[w10] and a spontaneous ulcer or an ulcer on the face that fails to heal should arouse suspicion. BCC has a variety of clinical presentations, but most patients describe a non-healing lump or "sore spot," which grows slowly and is otherwise asymptomatic. The lesion may cycle through bleeding and crust formation, a scab may separate during sleep leaving blood on the pillow, or it may catch on clothing. On the basis of their clinical morphology, BCCs are classified into four main subtypes; nodular or nodulo-ulcerative, superficial, morphoeic, or infiltrative and pigmented. Different types of BCC occur at different anatomical locations and this influences treatment and prognosis.[w11]

SUMMARY POINTS

- Basal cell carcinoma (BCC) is a the most common human cancer and its incidence is increasing
- Most BCCs occur on the head and neck and are easily recognised and treated
- With timely recognition and treatment the outlook is usually excellent
- Many different treatment options are available
- Difficult to treat areas require specialist intervention
- The cost to the NHS of treating BCC and other non-melanoma skin cancers is high

SOURCES AND SELECTION CRITERIA

We searched PubMed using keywords "basal cell carcinoma", "facial basal cell carcinoma", "facial non-melanoma skin cancer", "head and neck basal cell carcinoma", and "head and neck non-melanoma skin cancer". We targeted more recent studies and review articles. We also consulted National Institute for Health and Clinical Excellence guidelines and other national guidance.

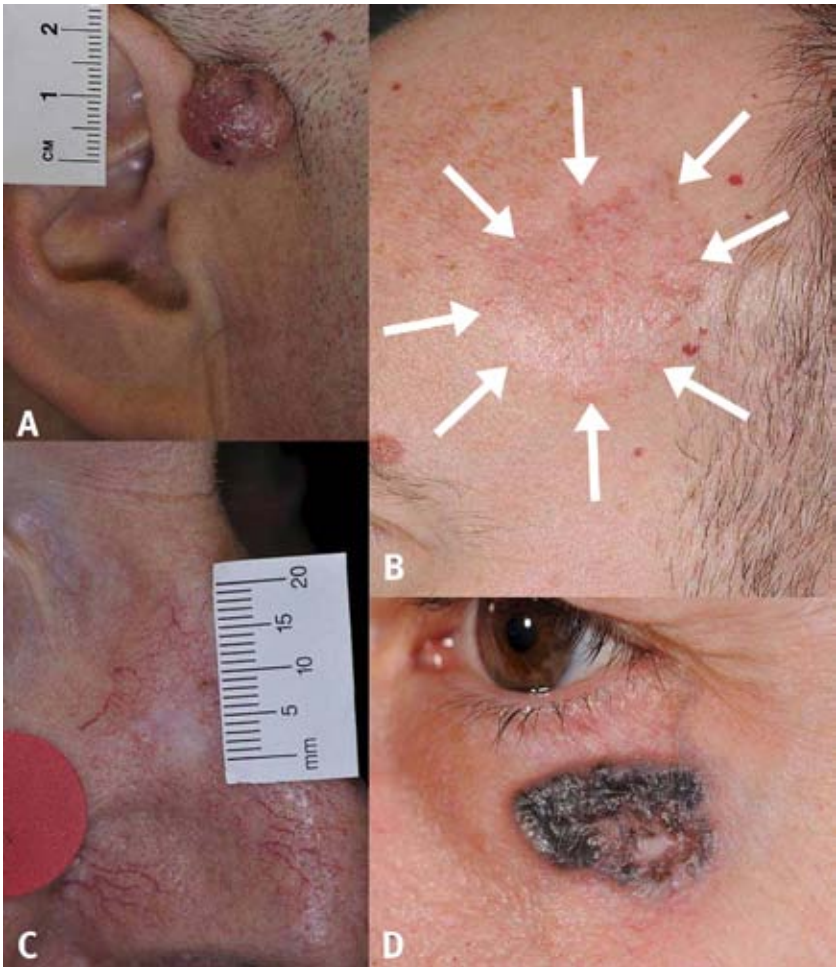

Fig 1 | Types of basal cell carcinoma (BCC). (A) Nodular BCC in preauricular area. (B) Superficial scalp BCC, which can be mistaken for a patch of eczema, psoriasis, or ringworm (fungus, tinea faciei). (C) Scar-like morphoeic BCC, which can have extensive subclinical spread. (D) Pigmented BCC mimicking malignant melanoma

Box 1 | Classic features of nodular basal cell carcinoma

Pearly papule or nodule with central depression or umbilication
Overlying telangiectasia
Central crusting
Raised rolled edge
May enlarge to a dome shaped tumour or ulcerate

- Nodular BCC, which affects mainly the head and neck, is the most common type in the UK.[3 7 9 24 32 w12] It presents as a pearly or translucent papule, plaque, nodule, or cyst-like lump, which has a rolled edge, telangiectasia, and central depression, with or without ulceration (box 1; fig 1A)
- Superficial BCC may present as a slowly growing scaly pink patch or plaque, which resembles eczema, psoriasis, or Bowen's disease (intraepidermal carcinoma) (fig 1B)
- Morphoeic BCC resembles a slowly enlarging whitish scar that can have extensive subclinical spread (fig 1C)
- Some BCCs are pigmented and can look like melanoma (fig 1D).

How are BCCs diagnosed?

Most BCCs can easily be diagnosed on the basis of the history and clinical examination. In case of uncertainty, pathognomonic arborising telangiectasia detected using a hand held dermatoscope will confirm the diagnosis.[2 32 w13] Other features on dermatoscopy include multiple blue-grey globules, maple leaf-like areas, blue-grey ovoid nests, and spoke wheel areas.[w14] Several differential diagnoses exist (box 2), so obtain histological verification if there is any doubt. After diagnosis, the risk of a further BCC is about 10 times greater than in the general population.[w15]

What does a BCC look like histologically?

Lesions usually grow slowly, sometimes by as little as 0.5 mm per 70 days.[w16] Nodular BCC is characterised by large solid lobules of atypical basaloid cells that exhibit a peripheral palisade (fig 2). BCCs infiltrate tissues in a three dimensional manner,[w17] with asymmetrical subclinical finger-like ramifications; they tend to invade along tissue planes, the periosteum, and nerves.[3] The pattern is sometimes described to patients as a tree trunk with spreading roots.

What is high risk BCC?

Most BCCs on the body are "low risk" tumours. However, those on the face exhibit a wider subclinical spread than at other sites.[30] After adjusting for surface area, BCC is at least four times more common on embryonic fusion planes than on other regions of the midface.[w18]

Anatomical areas at high risk for invisible tumour spread and therefore incomplete treatment are the nose, ear, eyelid, eyebrow, and temple (known as the H-zone[w19]; fig 3). Box 3 lists the features of "high risk" BCCs, which should be considered for specialist assessment and treatment by those who are experienced in the management of challenging facial skin cancers.[4] The periocular area merits special attention because 90-95% of all malignant eyelid tumours are BCCs,[w20] and 5-10% of all skin cancer occurs on the eyelid.[w21] Periocular BCCs most commonly occur on the lower eyelid (43%), followed by medial canthus (26%), upper eyelid (12%), and lateral canthus (8%).[w21] Careful examination is needed because 20-40% of periocular BCCs are clinically misdiagnosed.[w22 w23] If left untreated, disease can spread to the globe, which will require exenteration. A screening tool for periocular BCCs in primary care (the LUI key) uses the three clinical features that most consistently predict a malignant process: loss of lashes, ulceration, and infiltration.[w22] Orbital extension (usually along the periosteum) and intracranial spread of the tumour can be fatal.

What are the treatment options for BCC?

The British Association of Dermatologists and the American Academy of Dermatology have issued guidelines for the management of BCC.[19 w24] Treatment options include wide local excision, Mohs micrographic surgery, radiotherapy, photodynamic treatment, imiquimod, curettage and cautery, cryotherapy, and lasers. The choice of treatment is determined by tumour (site, size, subtype, primary, or recurrent lesion) and patient factors (age, comorbidities, preference). Different sites on the face are better suited to different treatment regimens.[w25] Elderly patients or those with serious comorbidities and low risk tumours may be more suited to non-surgical treatments. In addition, local availability of services, experience, and geographical issues may play a role in the choice of treatment. For a small subset of infirm or elderly patients or those with serious comorbidities, it may be best not to start on treatment. Patients are often managed by a multidisciplinary team of dermatologists, plastic surgeons, general practitioners, ophthalmologists, pathologists, oncologists, radiologists, ear nose and throat specialists, maxillofacial surgeons, and

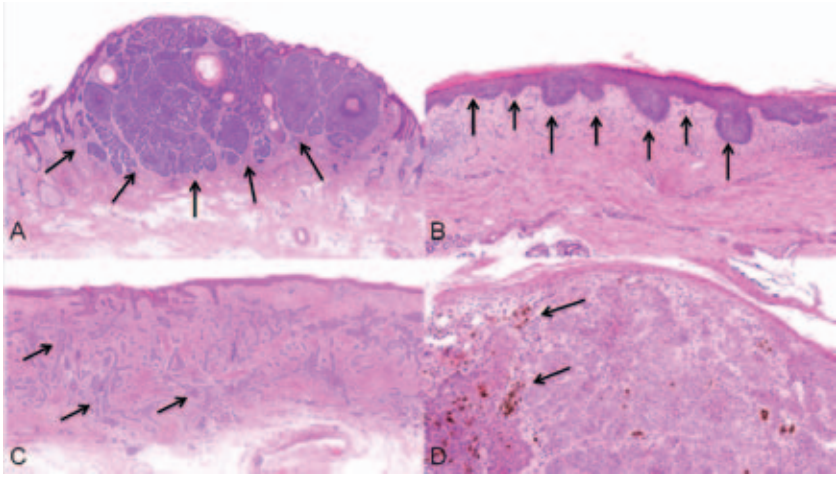

Fig 2 | (A) Histology of nodular basal cell carcinoma (BCC) showing circumscribed "golf ball" shaped area of cancer cells (arrows). (B) Superficial BCC showing a spreading and budding pattern of cancer cells limited to superficial skin (arrows). (C) Infiltrative BCC, with extensive lateral and deeper involvement, a "tree trunk with roots" pattern of infiltrating islands and cords of cancer cells. (D) Pigmented BCC showing clumps of pigment (arrows)

Box 2 | Differential diagnosis

- Bowen's disease (intraepidermal carcinoma)
- Solar or actinic keratosis
- Squamous cell carcinoma
- Psoriasis
- Eczema
- Sebaceous gland hyperplasia (enlarged facial sebaceous glands)
- Intradermal naevus (flesh coloured mole)
- Malignant melanoma, including amelanotic melanoma
- Seborrhoeic keratosis

specialist nurses. Recent guidance from the National Institute for Health and Clinical Excellence (NICE) has advocated several models of care based on lesion complexity and operator experience, with an emphasis on treating certain BCCs closer to patients' communities.[w26] Detailed and clear guidance is available on the provision of skin cancer services in terms of local multidisciplinary teams, specialist multidisciplinary teams, cancer networks, and the role of general practitioners with specialist interests.[w26-w28]

Wide local excision

Most facial BCCs can be treated successfully by standard surgical excision (also called wide local excision or excision with predetermined margins)[w29 w30] under local anaesthesia in the outpatient department. Margins are determined by careful clinical examination or by biopsy. A 4 mm surgical margin for primary well defined BCC measuring less than 20 mm ensures a complete clearance of over 95%.[w31] However, a margin of 3 mm, even for lesions that measure just 6×5 mm on average, will clear only about 85% of tumours.[w32 w33] Aggressive subtypes, such as morphoeic BCC, can have extensive subclinical spread and require wider surgical margins to ensure complete clearance (fig 4).[w32 w34] Despite apparent histological clearance, recurrences can occur.[w35] The cosmetic outcome from standard excisions depends on the experience of the surgeon and the site, size, and histology of the tumour.[w36] In one study, results were better for untreated tumours than for incompletely excised tumours or tumours that recurred after surgery.[w37] Recently, dermoscopy has helped guide surgery for facial BCC.[w38]

Mohs micrographic surgery

Frederic Mohs first described his micrographic surgical technique for treating skin cancer in 1941.[w39] Later, in a consecutive series of 9716 BCCs, he reported a five year cure rate of 99.3%.[w40] Currently, Mohs micrographic surgery is considered the gold standard for morphoeic, micronodular, and infiltrative facial BCCs and recurrent or incompletely excised BCCs at high risk sites (box 3).[w25 w41-w43] The technique involves excising the cancer, drawing a map of the excised tissue, colour coding the margins, sectioning the fresh frozen tissue horizontally, and examining all of the surgical margin while the patient waits.[w44 w45] Further excision is carried out only when tumour is detected microscopically at the surgical margin. This is why Mohs surgery has the highest cure rates for skin cancer and spares normal tissue, thereby allowing more reconstructive options, an important functional and aesthetic consideration for the face. Sites such as the periocular, perioral, and perinasal areas have high functional and cosmetic importance. Several papers show that for periocular tumours Mohs surgery allows important anatomical structures to be preserved.[w46 w47] Cure rates are 98-99% for primary facial BCC and 96% for recurrent BCC.[w41 w48] Because standard excisional surgery has a higher incomplete excision rate for facial BCC, especially those located on the central face, Mohs surgery is the treatment of choice for these, for all high risk BCCs, and for recurrent lesions.[w46 w47 w49] A risk scale can help decisions on treatment.[w50] Attempts to calculate the cost effectiveness of Mohs surgery when compared with standard excisional surgery have resulted in different opinions.[w43 w51-w53]

Radiotherapy

Radiotherapy includes superficial radiography, brachytherapy, and electron beam radiotherapy.[w54] Radiotherapy is mainly effective for primary BCC and sometimes for recurrent or incompletely excised BCC. Tumours of the lower eyelid, inner canthus, lip, nose, and ear may be amenable to radiotherapy,[w37] and it is often used in patients in whom surgery is difficult, inappropriate, or not desired. A recent retrospective analysis of 121 facial BCCs found 90.4% local recurrence-free survival at five years and good cosmetic results.[w55]

A randomised study of radiotherapy compared with standard excision in the treatment of facial BCC found that radiotherapy had a higher recurrence rate (7.5% *v* 0.7%)

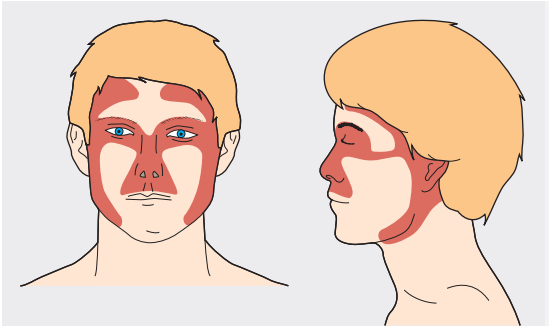

Fig 3 | The H zone (dark red area). Adapted, with permission from Elsevier, from Smeets and colleagues[w25]

Box 3 | High risk basal cell carcinomas

- Size >2 cm diameter
- Location in high risk anatomical areas (centrofacial, periocular, "H zone," and embryological fusion zones of face)
- Poorly defined edges
- Morphoeic, infiltrative, or aggressive histological subtypes
- Perineural or perivascular invasion
- Recurrent or previously incompletely excised basal cell carcinoma
- Host factors (immunosuppression, especially if organ transplant recipient)

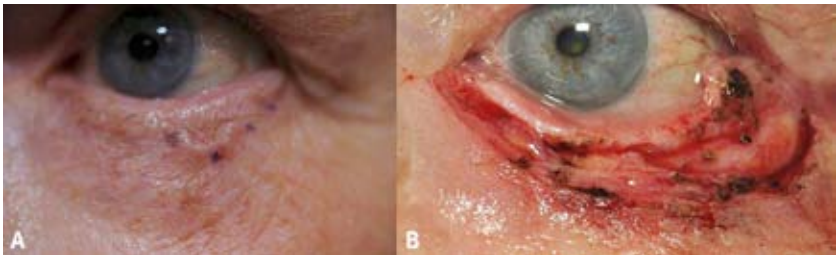

Fig 4 | (A) Margins of lower lid basal cell carcinoma on clinical examination. (B) Extensive area of invisible subclinical spread treated by Mohs surgery

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Previous articles in this series

- Diagnosis and management of peripheral arterial disease (*BMJ* 2012;345:e5208)
- Diagnosis and management of cellulitis (*BMJ* 2012;345:e4955)
- Management of osteoarthritis of the knee (*BMJ* 2012;345:e4934)
- Management of difficult and severe eczema in childhood (*BMJ* 2012;345:e4770)
- Management of chronic epilepsy (*BMJ* 2012;345:e4576)
- The diagnosis and management of tinea (*BMJ* 2012;345:e4380)

at four years and less acceptable cosmetic outcomes than surgery.[w56 w57] Radiotherapy is contraindicated for BCCs that have recurred after previous radiotherapy and in genetic syndromes that predispose to skin cancer. Skin cancers can occur in previous radiotherapy fields. Potential side effects are radionecrosis (especially of the nasal bridge), atrophy, telangiectasia, and damage to the nasolacrimal duct.[w58]

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

National Institute for Health and Clinical Excellence. NICE guidance on cancer services. improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal cell carcinomas in the community. 2010. www.nice.org.uk/nicemedia/live/10901/48878/48878.pdf

American Academy of Dermatology (www.aad.org/)—Provides information including clinical guidelines, access to published material, and continuing medical education tools (membership required)

British Association of Dermatologists (www.bad.org.uk//site/622/default.aspx)—Free access to many published guidelines and educational material including lectures

DermNetNZ (http://dermnetnz.org/)—Further resources for medical professionals and a wealth of clinical information

Resources for patients

National Institute for Health and Clinical Excellence. Understanding NICE guidance. Managing low-risk basal cell carcinomas in the community. 2010. www.nice.org.uk/nicemedia/live/10901/48768/48768.pdf. Explains the guidance provided to healthcare professions on deciding which basal cell carcinomas are low risk and whether they can be managed in the community

Cancer Research UK (http://cancerhelp.cancerresearchuk.org//type/skin-cancer/?script=true)—Lots of easy to digest information for the public on the diagnosis and treatment of non-melanoma skin cancer and access to support networks; also has a helpline for patients

British Association of Dermatologists (www.bad.org.uk/site/800/Default.aspx)—Provides downloadable patient leaflets and patient newsletters

Skin Cancer Foundation (www.skincancer.org/skin-cancer-information/basal-cell-carcinoma)—Provides patient information on different types of skin cancer with photographs and warning signs

Macmillan Cancer Support (www.macmillan.org.uk/Cancerinformation/Cancertypes/Skin/Skincancer.aspx)—Lots of information about skin cancer and the various treatments; also has a helpline for patients

A PATIENT'S PERSPECTIVE

I noticed a small red blotch on my forehead but ignored it because I thought it was just a spot. After a few months it was still there so my husband suggested that I get it looked at by my GP.

My GP referred me to a dermatologist who told me he thought it could be a basal cell carcinoma. He arranged for me to have a biopsy to confirm this.

This was something I had never heard of, and I was very worried to know that it was a form of skin cancer. Even though my consultant reassured me that it was not life threatening and would not harm my health I found this news devastating and emotionally distressing. I just wanted to have it removed as soon as possible—it was continually on my mind.

After a wait of a few months I underwent Mohs surgery, which completely removed the lesion. Two months have passed and it has healed with hardly any scarring. I now feel reassured and am ready to put this behind me and get my life back to normal.

Photodynamic therapy

Photodynamic therapy has become an established treatment for BCC over the past 10 years.[w59 w60] Methylaminolaevulinate is the only licensed form of topical photodynamic therapy. This prodrug is preferentially taken up by cancer cells and converted into protoporphyrin IX, a potent photosensitiser. When exposed to visible red light at 630 nm, a photodynamic reaction creates highly active free radicals and singlet oxygen species, which are cytotoxic to cancer cells. This results in selective treatment of the BCC with little reaction on normal surrounding skin. Pain during treatment can be ameliorated with local anaesthetic. Healing can be quick and the cosmetic outcome is often good. In a multicentre randomised study of superficial BCC on the scalp, face, trunk, and extremities, no difference was seen in five year recurrence rates with cryotherapy versus methylaminolaevulinate (20% *v* 22%). More patients in the photodynamic treatment group than the cryotherapy group reported excellent cosmetic outcome.[w61] A prospective randomised multicentre study of nodular BCC found recurrence rates of 14% and 4% at five years for photodynamic treatment and surgery, respectively, but with better cosmesis for photodynamic treatment.[w62] Photodynamic treatment has been used for difficult to treat BCCs of the face. One study found a complete response rate of 78% after two years,[w63] and a prospective multicentre study found a five year recurrence rate of 38%.[w64]

Topical treatment

Imiquimod is a topical immune response modifier that works by mediating cell death. It is licensed for the treatment of superficial BCCs and should be applied five days a week for six weeks.[w65 w66] One study reported no recurrence in 89.5% of 19 low risk facial BCCs treated with imiquimod cream at 39 months of follow-up.[w67] Another study looking at imiquimod in 15 patients with periocular BCCs showed 100% clearance at 24 months with favourable cosmetic outcome.[w68]

Pretreatment patient education, including preprinted leaflets or website recommendations, is needed because of the severe inflammatory reaction.[w69] Local skin reactions such as redness, soreness, crusting, and blistering, in addition to flu-like symptoms, have been reported.

TIPS FOR NON-SPECIALISTS

Examine the lesion carefully with bright light

Stretch the skin so that the precise extent of tissue involvement can be seen

Use an isopropyl alcohol swab to remove crust or scaling and reveal the underlying lesion. Bleeding often makes diagnosis more straightforward

Palpate the area

Document the size and appearance of the lesion

Effective treatment depends on tissue penetration. For facial BCC, we use imiquimod for small tumours in low risk areas or patients who will not or cannot be treated with better established treatments with known long term clearance rates.[w70]

Topical fluorouracil 5% cream works by destabilising DNA. It is sometimes used to treat small superficial BCCs and should be used only at low risk sites. It is therefore not recommended for the treatment of facial BCC.

Curettage and cautery

Curettage involves scraping of the skin; curettage and cautery are sometimes used in low risk BCC but is operator dependent. For benign skin lesions one cycle of curettage is performed, for cancer two to three cycles are needed, but up to a maximum of five cycles may be used.[w71] High cure rates can be achieved by experienced staff when tumours are carefully selected.[w71] Three cycles of curettage alone in 169 non-aggressive head and neck BCCs achieved a cure rate of 93.5%.[w72] Recurrence rates in some studies range from 6% to 19%, and are significantly higher in the central facial areas.[w73] Curettage is therefore not generally used for treating facial BCC unless other options are inappropriate.

Cryotherapy

Cryotherapy is a destructive method of treatment using liquid nitrogen. Operator technique, length of treatment, and number of freeze-thaw cycles vary. Recurrence rates vary from 39% at two years to as low as 1% at five years.[w74 w75] Cryotherapy is not recommended as a first line treatment for facial lesions because of high recurrence rates and poor cosmetic outcome.[w76]

Carbon dioxide and Erb:YAG laser ablation is an uncommon form of treatment, with limited data on its effectiveness. One series showed some benefit in treating small BCCs in low risk sites,[w77] but a recent report highlights the dangers of laser treatment on the face. These include a longer disease interval to diagnosis, a more aggressive histological pattern, and the need for more stages of Mohs excision in post-laser BCCs than in primary BCCs.[w78]

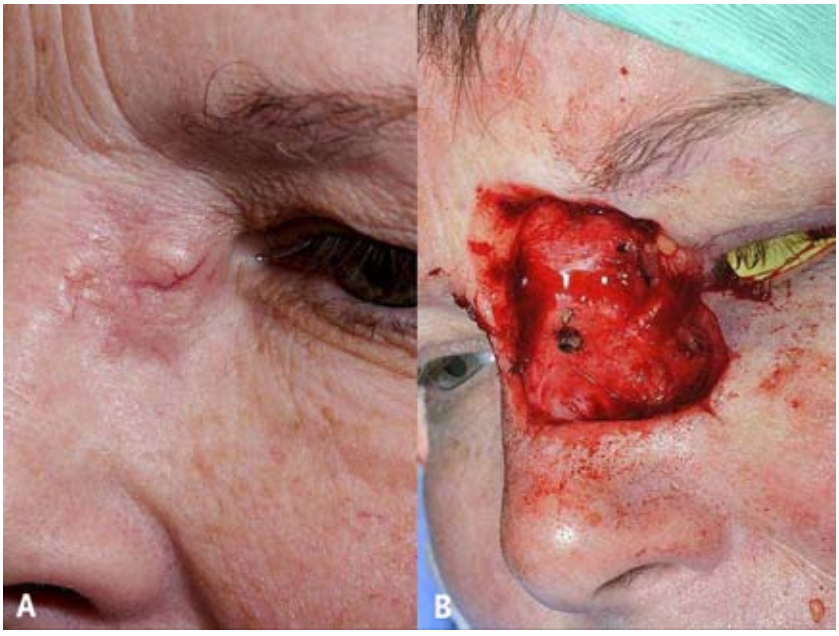

Fig 5 | (A) Neglected basal cell carcinoma (present for 25 years) at the medial canthus, and (B) subsequent large defect from Mohs surgery that required complex reconstruction

QUESTIONS FOR FUTURE RESEARCH

Can subclinical spread of basal cell carcinoma be detected so that surgery plays a more limited role?

Why are increasingly younger people developing basal cell carcinoma?

What is the role of drugs that inhibit the Hedgehog signalling pathway for advanced facial basal cell carcinoma?

What is the prognosis for facial BCCs?

Most BCCs grow slowly, have a non-aggressive course, and can be fairly easily managed. However, longstanding or neglected BCCs (fig 5) can present a therapeutic challenge, especially in terms of functional and cosmetic reconstruction. Some may become large or behave like "rodent ulcers," destroying skin and deeper tissues. Periocular BCC may become inoperable or require exenteration.[w79] BCC can occasionally metastasise (0.0028-0.55%).[4 w80 w81] For all BCCs, the three year risk of developing a second primary lesion can be as high as 44%.[w82] For facial BCC (in one study), up to 39% of patients referred for surgery had multiple primary non-melanoma skin cancer or developed another non-melanoma skin cancer within two years.[w83]

The overall workload of diagnosis and management is predicted to increase by 50% by 2030,[27] and after 2020 the proportion of cases of non-melanoma skin cancer in the over 80 year age group that need treatment will probably rise rapidly worldwide.[27] In individual patients, the time to the development of a new lesion decreases with each successive BCC, and this has implications for follow-up.[29] The case for follow-up—probably for at least three years—is strongest for patients who have been treated for recurrent disease (increased risk of further recurrence after all types of treatment) and those with a history of multiple BCCs (significantly increased risk of further BCC).[19]

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JMB, AP, and SV wrote the manuscript. SV conceived the idea and design, edited the manuscript, and is guarantor.

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Patient consent obtained.

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ANSWERS TO ENDGAMES, p 48

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PICTURE QUIZ A 64 year old woman with headache and breathlessness

1 The primary abnormality of the chest radiograph is severe kyphoscoliosis with profoundly reduced lung volumes.
2 Kyphoscoliosis leads to deformity of the ribcage, which dramatically restricts chest wall movement and the effectiveness of the respiratory muscles. The ensuing alveolar hypoventilation leads to hypercapnic respiratory failure and the associated symptoms of morning headaches, daytime sleepiness, and dyspnoea.
3 Overnight pulse oximetry and transcutaneous monitoring of carbon dioxide followed by analysis of early morning arterial blood gases will confirm the presence of alveolar hypoventilation and evaluate its severity.
4 The most important aspect of her treatment is correction of hypoventilation through the use of non-invasive positive pressure ventilation (NIV). Hypoxia is most safely corrected by entraining oxygen through the NIV circuit. Extreme care should be taken with other forms of oxygen therapy because of the risk of a substantial rise in arterial carbon dioxide tension.

STATISTICAL QUESTION

Why randomise in clinical trials?

Answers *a*, *b*, *d*, and *e* are true, whereas *c* is false.

CASE REPORT Acute skin failure

Severe adverse cutaneous drug reaction seen in this patient

1 This is a severe adverse cutaneous drug reaction (figure), which according to the extent of epidermal detachment, can be classified as Stevens-Johnson syndrome (SJS)-toxic epidermal necrolysis (TEN) overlap.
2 A skin biopsy, typically showing widespread epidermal necrolysis in all layers as a result of extensive keratinocyte apoptosis, can provide histological confirmation.
3 Most cases of SJS and TEN are caused by hypersensitivity to a drug. Infections by agents such as herpes simplex virus and *Mycoplasma pneumoniae* may also lead to SJS, but only exceptionally to TEN.
4 The offending drug must be promptly identified and withdrawn. The cornerstone of treatment is supportive care similar to that for patients with severe burns in an intensive care unit. Special attention must be paid to fluid resuscitation, skin care, and eye care.
5 Immediate complications include hypovolaemic or septic shock and major metabolic abnormalities, which can progress to multiorgan failure and death; late complications are principally ocular.