



Non-surgical treatments for skin cancer

Stephen P Shumack, Dermatologist, Royal North Shore Hospital, Sydney

Summary

Skin cancers have traditionally been treated with surgical excision. This is the most effective treatment option, but over the last few decades non-surgical treatments have become available. These include cryotherapy, topical fluorouracil and imiquimod creams, and photodynamic therapy with methyl aminolevulinate hydrochloride. While they may sometimes have a superior cosmetic result, non-surgical treatments should not be used when the diagnosis is unclear or if follow-up is not assured.

Key words: fluorouracil cream, imiquimod cream, photodynamic therapy.

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Introduction

In Australia, the number of skin cancers treated each year exceeds the total number of other cancers treated. Non-melanoma skin cancers are the most common type and include basal and squamous cell carcinomas. Precancerous lesions (solar keratoses) are also extremely common. Other rarer forms of skin cancer such as melanoma and atypical fibroxanthoma are usually surgically removed.

Surgical excision is still the most commonly used and most effective treatment for skin cancers. For the treating practitioner, it provides histopathological confirmation of the diagnosis and evidence of margin control. However, because of the relatively benign nature of non-melanoma skin cancers, other non-surgical treatment options have been developed over the last few decades.

Non-melanoma skin cancers – the problem

Basal cell carcinomas

Statistically we know that almost 50% of Caucasian Australians will develop a basal cell carcinoma before the age of 70. Once a basal cell carcinoma has developed, it is likely that the same person will develop another within three years. They rarely metastasise but can be locally invasive.

Solar keratoses and squamous cell carcinomas

Solar keratoses are premalignant skin lesions that are very common in Caucasian Australians after the age of 45 years. They have a very small risk of transformation (approximately 1%) into squamous cell carcinomas.

Squamous cell carcinomas are potentially more serious than basal cell carcinomas as they can occasionally metastasise and even sometimes prove fatal.

Non-surgical treatments

Given the very large numbers of skin cancers seen in Australia and their relatively benign course, non-surgical treatments, which have minimal morbidity associated with the treatment and in many cases a superior cosmetic result, have been investigated. These non-surgical treatment options, however, are often not as effective as surgical excision and have lower cure rates. They are not generally indicated for treatment of recurrent skin cancers.

Cryotherapy

Liquid nitrogen cryotherapy is the primary treatment for solar keratoses in Australia. Most solar keratoses are treated with a short (2–5 seconds) freeze. This effectively removes about 70% of all solar keratoses treated.

Cryotherapy is most suited for low-risk primary tumours of basal cell carcinoma or Bowen's disease (squamous cell carcinoma *in situ*) on the trunk and limbs. It has lower cure rates on the face so is not recommended for treating facial skin cancers. Cryotherapy should only be used for well-defined skin cancers and is contraindicated for morpheaic basal cell carcinomas.

For basal cell carcinomas, the lesion is marked out with a 1 cm margin. The area is frozen and kept solid for 20–30 seconds, then allowed to thaw for approximately 3–5 minutes before being refrozen for 20–30 seconds. This produces a weeping wound which may take 1–2 months to heal. Because of the slow healing, this treatment should not be used below the knee, particularly in people with compromised circulation. An excellent scar is achieved with liquid nitrogen cryotherapy for basal cell carcinomas although it tends to be hypopigmented so it should not be used in those with pigmented skin.

Bowen's disease can be treated with cryotherapy as a single freeze of approximately 5–10 seconds. Again, healing times can be prolonged so care needs to be used on the lower leg or sites with poor healing. Smaller lesions (<1 cm diameter) are often best treated in this way.

Fluorouracil cream (5%)

This has been available for over 30 years. It is used twice a day for three weeks as a treatment for multiple solar keratoses, particularly on the head and scalp areas. The cream usually produces significant inflammation that will take 1–2 weeks to settle. This can be eased with cold compresses and medium potency steroid creams. The greater the inflammatory reaction,

the more efficacious the treatment.

There are also a small number of case reports indicating that 5% fluorouracil cream can be used quite effectively to treat Bowen's disease. This is usually used twice a day for 4–6 weeks with excellent cosmetic results. Significant inflammation tends to occur during the latter period of this treatment course.

As a general rule, fluorouracil cream should not be used as a treatment for basal cell carcinomas as there is little evidence of its efficacy.

Imiquimod cream (5%)

Topical imiquimod has been investigated as a treatment for solar keratoses and basal cell carcinomas over the last 15 years. Initially it was developed and marketed as a treatment for external genital warts. We know that imiquimod activates the local immune system through toll-like receptor 7. This activation causes an inflammatory reaction which clears cancerous and precancerous cells. There is evidence that imiquimod cream is effective as a treatment for solar keratoses.¹ In Australia, it is approved for three applications a week up to 16 weeks, or alternatively one or two cycles of four weeks of treatment. It produces varying degrees of inflammation but treatment frequency can be titrated to ensure low to moderate inflammation. If significant inflammation develops treatment should be stopped until it has almost subsided. Topical steroid creams should not be used to settle the inflammation as they have a theoretical risk of reducing efficacy.

Imiquimod cream is listed on the Pharmaceutical Benefits Scheme as a treatment for biopsy-proven superficial basal cell carcinomas where other treatment options are unsuitable. The treatment schedule is five times a week for six weeks. Efficacy rates of around 80% are less than with surgical excision but are still acceptable, particularly when considering the sometimes large defects and scars seen with surgical excision.

There have been a number of small case series looking at imiquimod as a treatment for Bowen's disease. This is not an approved indication in Australia, but nevertheless imiquimod does work relatively well in this condition when applied 3–5 times a week for up to six weeks.²

Photodynamic therapy

In Australia, photodynamic therapy with red light and methyl aminolevulinate hydrochloride has been approved as a treatment for Bowen's disease, solar keratoses and basal cell carcinoma. Efficacy rates are around 80–85%. The cream is left on for approximately three hours and then a special red light is applied. This can cause some degree of pain during the illumination process. Occasionally the patient needs rest periods or local anaesthetic to reduce the pain. Inflammation occurs after treatment which usually settles within a week or so. Treatment is repeated 1–4 weeks later to ensure high efficacy rates with superficial basal cell carcinoma, thin nodular basal cell carcinoma and Bowen's disease. This is currently not a subsidised treatment in Australia.

For solar keratoses, only a single treatment is usually required and 'field areas' are treated such as the scalp, temples or forehead.

Radiotherapy

This was the traditional non-surgical option for skin cancers and was used commonly until the late 1960s. Since then, the use of surgical excision as a treatment option has increased significantly. Radiotherapy provides an excellent alternative in many cases of non-melanoma skin cancer, particularly when surgery is relatively contraindicated. It is also useful as an adjunctive therapy to surgery in difficult or recurrent cases of skin cancer.

Newer treatments

There are a number of new topical treatments that have been investigated over the last few years. One of these promising products is ingenol mebutate, which was originally developed in Australia. Phase III studies have been undertaken for basal cell carcinoma and solar keratoses.

Conclusion

Given the relatively benign nature of basal cell carcinomas, Bowen's disease and solar keratoses, non-surgical treatment options have been investigated as an alternative to surgery. These have the advantage of often little treatment-associated morbidity for the patient, as well as often a superior cosmetic outcome. The disadvantage is that these treatments are usually not as effective as surgical excision, so regular follow-up (6–12 monthly) over a number of years is required to guard against recurrence at the treatment site.

References

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2. Patel GK, Goodwin R, Chawla M, Laidler P, Price PE, Finlay AY, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2006;54:1025-32.

Further reading

Basal cell carcinoma, squamous cell carcinoma (and related lesions) – a guide to clinical management in Australia. Sydney: Cancer Council Australia and Australian Cancer Network; 2008.

Dr Shumack has been an investigator and speaker for 3M.

Self-test questions

The following statements are either true or false (answers on page 31)

1. Cryotherapy is not recommended for treating skin cancers on the face.
2. Fluorouracil cream is an effective treatment for basal cell carcinomas.