Photodynamic therapy for skin and mucosal cancer

May 1999

MSAC application 1008

Final assessment report

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care on the strength of evidence available on new medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which new medical services should attract funding under Medicare.

This report was prepared by the Medicare Services Advisory Committee (MSAC). The report was endorsed by the Commonwealth Minister for Health and Aged Care on 11 May 1999.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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The procedure

Photodynamic therapy (PDT) is an evolving, two-stage procedure for treating non-melanoma skin cancers and related skin lesions. These include basal cell carcinomas (BCC), squamous cell carcinomas (SCC), squamous cell carcinomas-in-situ ('Bowen's disease'), and actinic (solar) keratoses. Solar keratoses are pre-cancerous lesions, many of which will not develop into skin cancer.

Medicare Services Advisory Committee - role and approach

MSAC is a key element of a measure taken by the Commonwealth to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Aged Care on the evidence relating to the safety, effectiveness and cost effectiveness of new medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. For PDT, a search of the medical literature available on the procedure was undertaken, and the evidence was assessed and classified according to the NHMRC hierarchy of evidence. Articles which examined the role of PDT for indications other than skin and mucosal cancer were excluded. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

Assessment of PDT

The clinical studies undertaken to date on PDT are generally single arm, quasi-experimental ones. Their quality is variable, some being largely anecdotal, and they have generally involved small numbers or lacked sufficient control to draw conclusions about the effectiveness of PDT in comparison to alternative treatments. Sufficient follow-up of patients is also lacking.

Clinical need

Non-melanoma skin cancer is the most common of all malignancies. Of all cancers in Australia, non-melanoma skin cancer is the highest contributor to direct health system costs, with estimated costs of \$232 million. While only a small number of deaths are due to non-melanoma skin cancer (379 in 1993), it dominates new cases, with over 243 000 in 1995 (78% of all new cancers).

Safety

Photodynamic therapy (PDT) appears, from the available evidence, to be a safe procedure.

Effectiveness

There is insufficient evidence regarding PDT's effectiveness in comparison with effective treatment modalities already available. There are also unanswered scientific questions regarding the physics and dosimetry of PDT.

Cost effectiveness

Since it was considered that the safety and effectiveness of PDT have not been sufficiently established, no cost effectiveness analysis has been undertaken.

Recommendation

Since there is currently insufficient evidence pertaining to photodynamic therapy, MSAC recommended that public funding should not be supported at this time for this procedure.

Introduction

The Medicare Services Advisory Committee (MSAC) has assessed photodynamic therapy, an evolving procedure for the treatment of skin and mucosal cancer. MSAC evaluates new health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost effectiveness, taking into account other issues such as access and equity. MSAC uses an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from disciplines such as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health administration and health economics.

This report summarises the assessment of current evidence for photodynamic therapy in the treatment of skin and mucosal cancer.

Photodynamic therapy

How it works

Photodynamic therapy (PDT) is an evolving, two-stage procedure for treating non-melanoma skin cancers and related skin lesions. These include basal cell carcinomas (BCC), squamous cell carcinomas (SCC), squamous cell carcinomas-in-situ ('Bowen's disease'), and actinic (solar) keratoses. Solar keratoses are pre-cancerous lesions, many of which will not develop into skin cancer.

PDT is based on the photochemical destruction of tumour tissue by means of a systemic or topical photosensitising drug, while preserving surrounding normal tissue. Aminolaevulinic acid (ALA) is the most commonly used topical sensitiser for non-melanoma skin cancer, and is the focus of most of the studies undertaken to date in the context of dermatological conditions. The application of the photosensitiser is followed by irradiation with red light at a wavelength of approximately 630 nanometres, usually produced by a laser.

Intended purpose

PDT is intended for the lesions detailed above. When used for SCC, it is generally for the insitu form, Bowen's Disease. The procedure is not advocated for use in tumours where other treatments have failed, nor is it a viable treatment for primary melanomas.

PDT offers the advantages of being non-invasive and of being able to be delivered on an outpatient basis. It is useful for patients who refuse surgery, have pacemakers, or have a bleeding tendency.

In addition to skin tumours, the literature also discusses the use of PDT for many other indications. For example, PDT with Photofrin is used in the treatment of bladder cancer, oesophageal and lung cancers. However this report is confined to topical PDT using the photosensitising agent ALA, as proposed by the applicant, and the evidence regarding the role of ALA-PDT in skin and mucosal cancer.

PDT for cutaneous tumours is undertaken by a limited number of dermatologists. The procedure is undertaken at limited sites in Australia at present, eg at the Skin and Cancer Foundation in Victoria, at the Royal Perth Hospital, and at some private dermatology centres. The procedure is not included in the Medicare Benefits Schedule.

Clinical need/burden of disease

Non-melanoma skin cancer is the most common of all malignancies. Of all cancers in Australia, non-melanoma skin cancer is the highest contributor to direct health system costs, with estimated costs of \$232 million. While only a small number of deaths are due to non-melanoma skin cancer (379 in 1993), it dominates new cases, with over 243 000 in 1995 (78% of all new cancers). These cost estimates include health interventions for benign skin tumours and in-situ skin cancers, frequently aimed at excluding or preventing invasive cancer, as well as for invasive cancers.¹ It is not known precisely at this stage which particular types of non-melanoma skin cancers would be suitable for PDT.

There are no incidence data for solar keratoses or Bowen's Disease, for which PDT has been proposed as a treatment modality. However, prevalence data collected in a variety of Australian studies indicate that at least 40 per cent of people over the age of 50 are likely to have one or more solar keratoses, the average number being six per person.

There are no accurate data available on the frequency of Bowen's Disease in Australia.

Existing procedures

Currently, both surgical and non-surgical treatments are used for these cutaneous lesions. Surgical excision is the standard, first-line therapy. Other treatment modalities are curettage and electrodesiccation, cryotherapy, and Mohs' micrographic surgery. Cryotherapy is the most common treatment for Bowen's Disease.

Topical chemotherapy is also used for the treatment of extensive solar keratoses, and on occasion, for Bowen's Disease. Laser ablation or skin resurfacing has a place in diffuse actinic damage. Interferon has been used in selective cases for the treatment of BCC.

Radiotherapy now provides only a small proportion of the treatments used for these lesions.

Marketing status of the technology

A number of different light sources used for PDT and other procedures, including both laser and incoherent light sources, have been listed by the Therapeutic Goods Administration.

Current reimbursement arrangement

Currently there is no specific Medicare Benefits Schedule item number for PDT.

Approach to assessment

MSAC reviewed the literature available on photodynamic therapy and convened a supporting committee to evaluate the evidence of the procedure and provide expert advice.

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period between 1993 to 1998. Searches were conducted via Medline, HealthStar and EMBASE.

The search terms used included 'photodynamic therapy', 'aminolaevulinic acid', 'ALA', 'skin cancer', 'squamous cell carcinoma' 'Bowen's Disease' 'basal cell carcinoma', 'keratosis', and 'actinic (solar) keratoses'. Articles which examined the role of photodynamic therapy for indications other than skin and mucosal cancer were excluded.

Among 221 articles identified, those which addressed the role of PDT in the treatment of skin and mucosal cancer were examined (see References). From these articles, the evidence presented in twelve studies which investigated PDT using ALA as the photosensitiser was assessed and classified according to the MSAC preferred hierarchy of evidence set out below:

Table 1 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
П	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.
Source:	NHMRC ²

The remaining articles in the References consist of overviews of studies undertaken of PDT, and descriptions of PDT and its stage of development at the time the particular article was printed.

Expert advice

A supporting committee with expertise in dermatology, plastic surgery and general practice was established to evaluate the literature and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

The clinical studies undertaken to date on photodynamic therapy for skin and mucosal cancer are generally single arm, quasi-experimental ones. Their quality is variable. Some are largely anecdotal, and they have generally involved small numbers or lacked sufficient control to draw conclusions about the effectiveness of PDT in comparison to alternative treatments. Sufficient follow-up of patients is also lacking.

With the exception of one randomised controlled trial which compared PDT with cryotherapy for the treatment of Bowen's Disease, the studies located all provide level IV evidence concerning PDT. Further detail is provided below.

Is it safe?

Until recently, patients were treated systemically rather than topically with PDT, using firstgeneration photosensitisers. However, prolonged photosensitivity lasting about 6 weeks was the major disadvantage of this form of therapy, due to retention of the photosensitising drug in the skin. Patients affected need to avoid sunlight and bright, artificial lights for this period of time. Topical PDT bypasses this unwanted effect, clearing from the skin in about 24 hours, and enabling repetitive treatment of lesions, as indicated above.^{3,4,5}

The only known side effects of topical PDT with ALA is some burning or stinging pain during irradiation, which can be quite severe if larger areas are treated.^{3,5,6}

Is it effective?

A randomised controlled trial by Morton et al found that PDT, using a non-laser light source and topical ALA, appears to be at least as effective as cryotherapy in the treatment of Bowen's Disease, with fewer adverse effects and a lower recurrence rate.⁷ However, the follow-up period was short. Further, these pre-cancerous lesions are a common condition in later life, and neither their presence, nor their recurrence, should represent a major health risk.

Several level IV studies of PDT using topical ALA have been undertaken. Unfortunately, among the various studies reported, the treatment parameters such as patient selection, drug dose, light dose, anatomical location and patient follow-up time have varied, making cross-study comparison difficult.

Level	Author	Objective	Results/Conclusions
II	Morton et al 1996 ⁷	Compare efficacy and suitability of PDT with cryotherapy for treatment of Bowen's Disease. (19 patients; 12 months follow-up)	PDT, using a non-laser light source and topical ALA, appears to be at least as effective as cryotherapy in the treatment of Bowen's Disease, with fewer adverse
		Non-laser light source; 20% ALA	effects and a lower recurrence rate.
IV	Wolf et al, 1993 ³	Assess effectiveness of PDT on patients with precancerous conditions and various skin cancers (13 patients, median 7 months follow-up).	Topical PDT with endogenous porphyrins is effective for superficial epithelial skin tumours.
		Non-laser light source; 20% ALA	

Table 2 Evidence summary

Level	Author	Objective	Results/Conclusions
IV	Cairnduff et al 1994 ⁸	Investigate safety and efficacy of PDT for skin cancer treatment (patient nos. and follow-up varied according to lesion investigated, but sample and follow-up time were small). Laser light source; 20% ALA	Complete response rate of 89% in 36 areas of Bowen's Disease reported. Treatment of BCC was less successful, with 50% complete responses at median follow-up of 17 months. Metastatic nodules responded poorly.
IV	Svanberg et al 1994 ⁹	Investigate effects of topical PDT on non-melanoma skin cancers (21 patients; median follow-up 6-14 months). Laser light source; 20% ALA	100% response reported on superficial BCC; 64% of 25 nodular BCC; and 90% of 10 Bowen's disease lesions.
IV	Hurlimann A, Panizzon R, Burg A 1994 ⁶	Investigate responses of skin tumours to topical PDT. Non-laser light source; 20% ALA	Complete responses shown in 68 of 72 superficial BCC, 5 of 15 nodular BCC, all of 6 Bowen's disease, and all of 4 treated SCC. However cutaneous metastases of malignant melanoma were therapeutic failures.
IV	Calzavara- Pinton 1995 ¹⁰	Investigate safety and efficacy of PDT for superficial, non-melanoma skin tumours (85 patients; median follow-up 29 months). Laser light source; 20% ALA	ALA-PDT is an effective and safe alternative in the routine treatment of superficial skin tumours. However its use in the treatment of nodular and heavy pigmented tumours is disappointing.
IV	Wennberg et al 1996 ⁴	Evaluate the treatment of superficial BCC using PDT with ALA and a short arc xenon lamp as a light source (48 patients; 5 years follow-up intended). <i>Non-laser light source; 20% ALA</i>	For superficial BCC, clearance rate of 92% after 6 months. Thicker lesions such as nodular BCC responded poorly to the treatment. Authors considered this was due to combined effect of insufficient light and ALA penetration.
IV	Szeimies et al 1996 ⁵	Demonstrate the efficacy and tolerability of topical PDT using 5- aminolevulinic acid in the treatment of actinic keratoses (10 patients; 84 days follow-up). Laser light source; 10% ALA	Study demonstrated the potential of good efficacy and tolerability, however queried whether PDT can concur with established treatment modalities.
IV	Jeffes et al 1997 ¹¹	Examine safety and efficacy of PDT using topical 5-aminolevulinic acid and red light to treat actinic keratoses (40 patients; 4 months follow-up). <i>Laser light source; 10% /20%/30%</i> <i>ALA</i>	Topical PDT with ALA is an effective treatment of typical actinic keratoses. Hypertrophic actinic keratoses did not respond effectively.
IV	Fink-Puches et al 1997 ¹²	Investigate the immediate and long- term effect of topical (ALA) PDT on solar keratoses (28 patients; median 13 months follow-up). <i>Non-laser light source; 20% ALA</i>	Primary complete response rate was 64% after one treatment, but 85% when the responses to a second treatment were included, indicating that repetitive ALA-PDT might increase the primary clinical response rate. 'Mostly excellent' cosmetic results.
IV	Fink-Puches et al 1998 ¹³	Investigate the immediate and long- term effects of PDT with ALA on superficial BCC and SCC (47 patients; median 19 months follow-up). Non-laser light source; 20% ALA	Poor long-term cure rates for superficial BCC and SCC, which cannot be explained by insufficient penetration of the therapy effect.
IV	Morton et al 1998 ¹⁴	Investigate effect of tumour thickness of basal cell carcinoma and duration of photosensitiser application on response to PDT (53 patients; follow-up continuing). <i>Non-laser light source; 20% ALA</i>	PDT may be useful therapy for BCC less than 1mm thick, but with topical application of δ -ALA , appears to have a limited role in treatment of thicker lesions.

As indicated in Table 2, most studies used an emulsion containing 20% ALA. However Szeimies et al and Jeffes, used different ALA dosages in their studies.^{5,11} The latter assigned dosages of 10%, 20% and 30% on a nonblinded basis, yet reported that no significant differences in clinical responses for the varying dosages were observed. Peng et al contend that the optimal dose is still not known, and that 20% concentration is likely to be an overdose in some clinical treatments.¹⁵

Of the studies cited, most used a non-laser light source (column 3 in Table 2). According to Morton et al, coherence of light is not required for effective PDT, although with some incoherent light sources there is difficulty in achieving an intensity comparable with laser.^{7,14} Wennberg et al note that a non-laser source was sufficient in their study because they were treating easily accessible sites.⁴ Morton et al state that the lamp used was developed to provide many of the benefits of a laser, but at a much lower capital cost, and with low maintenance requirements.⁷

These caveats regarding different treatment protocols notwithstanding, the studies cited above indicate the following:

- PDT may be an effective treatment for solar keratoses,^{3,5,10,11,12} small, superficial BCC,^{4,6,9,10} and Bowen's Disease.^{3,6,7,8,9,10} For these kinds of superficial tumours, varying degrees of success ranging from 50% to 100% have been reported, with the highest success rates being for Bowen's Disease.
- Reported success rates generally decline as length of follow-up time after treatment increases: Cairnduff et al found that only 50% of patients with superficial BCC remained disease-free at a median follow-up of 17 months.⁸ Calzavara-Pinton reported a slight decrease in complete response rates in longer term follow-up of up to 36 months.¹⁰ Fink-Puches et al reported "poor" long-term cure rates for superficial BCC and SCC.¹³
- Thickened, nodular or pigmented tumours are less responsive to PDT.^{3,4,8,10,11} For these tumours, varying degrees of success ranging from about 10% to 65% were reported. The exception was the study by Svanberg et al, which reported superior results with these tumours.⁹ However, this study included a second treatment cycle in the reported rates of complete response.
- Tumour thickness appears to closely predict therapeutic response to topical ALA-PDT,¹⁰ although Svanberg et al's view was that histological type, not thickness, was the most important factor influencing the outcome of therapy.⁹ Other reasons for poor response may include insufficient penetration by either drug or light, or both,^{8,10} although one study refuted this explanation.¹³
- Clinical response to ALA-PDT may be site-dependent: Jeffes et al reported a better response to the treatment of solar keratoses on the face and scalp than on the trunk and extremities.¹¹ Fink-Puches reported a complete clinical response rate of 94% for solar keratoses located on the face, scalp and neck, compared with 49% for these lesions on the hands and forearms.¹² Szeimies et al reported similar results.⁵ For BCC and SCC, however, Fink-Puches reported no site-dependence.¹³

- PDT is a tissue-saving method with cosmetic advantages. Investigators agree that there is minimal dermal damage and little or no scarring, with skin surrounding the tumour remaining intact and functional.^{4,5,7,8,9}
- Repetitive treatment of lesions is possible with topical PDT, and is suggested in some studies as a means of improving the response.^{4,9,10,12}

What are the economic considerations?

While there is no information in the literature to date regarding comparative cost data for the procedure, given the incidence of non-melanoma skin cancer (previously mentioned on Page 2 in 'Clinical need/burden of disease'), it is possible that large numbers of lesions may prove suitable for PDT.

The Supporting committee for this application noted the need to be precise about indications for PDT in order to avoid its inappropriate use, eg as an 'add-on ' to alternative treatments.

The light source used is an expensive element of the treatment. Advice from the Supporting committee is that the future trend will be towards non-coherent or broad band light sources, because of the prohibitive costs of lasers. This could result in PDT being a very cost-effective treatment.

Other considerations

The literature notes that careful patient selection for PDT treatment is necessary, especially for skin cancers such as SCC, which have the potential to become invasive and to metastasize. Knowledge of the extent and thickness of the tumour is also required.^{5,16,17}

Peng et al note that because there is no clear line of demarcation between "thin" and "thick" BCC and SCC, errors resulting from clinical evaluation can strongly affect the results of ALA-PDT.¹⁵ Investigators also pointed to the need for thorough marking of tumours prior to treatment.^{12,13}

Tissue penetration achieved by PDT is about 5-10 mm from the point of application of the light.¹⁶ Insufficient penetration of PDT could result in the lesion healing on the surface with tumour cells still intact underneath, necessitating the taking of punch biopsies at regular intervals to detect this outcome.⁴

Fink-Puches cites studies which indicate that the cure rates for BCC and SCC using standard treatment modalities are very high, micrographic surgery was reported to result in a 98% to 99% cure rate for BCC and a 94% cure rate for SCC after 5 years of follow-up.¹³ However, the quality of these studies is not indicated.

Conclusions

Safety

PDT appears to be a safe procedure with no major complications.

Effectiveness

Clinical information on PDT's effectiveness in treating non-melanoma skin cancers, in comparison with effective treatment modalities already available, is largely anecdotal. Most of the trials which have been undertaken to date have been either too small or have lacked sufficient controls for researchers to determine how well PDT works in comparison with existing treatments. They also demonstrate that long-term follow-up is necessary to evaluate the effects of ALA-PDT. Unanswered questions include :

- PDT's precise role in the management of non-melanoma skin cancers and related skin lesions;
- the appropriate indications for PDT;
- PDT's effectiveness *vis a vis* other treatment modalities;
- how to select patients for this particular treatment; and
- the most appropriate treatment venue.

Controlled trials which compare PDT with other therapies will determine whether PDT compares favourably with other established, standard treatment modalities, especially for thicker lesions. Studies of PDT are underway in Brisbane, and at the Skin and Cancer Foundation in Melbourne.

Cost effectiveness

While large numbers of skin lesions may prove suitable for this therapy, no cost comparisons with other treatment therapies are available at this stage.

Other considerations

Further attention also needs to be paid to the physics and dosimetry of PDT. Research is continuing on the most appropriate light delivery system and photosensitiser, including drug dosage, for the procedure. New photosensitisers for topical PDT are emerging.^{13,18} Alternative light sources with better tissue-penetrating properties are also under development. Less expensive solid-state lasers which require minimal maintenance and facilities are also becoming available.^{18,19}

Properly designed comparative trials, together with the progression of the scientific issues pertaining to the photosensitiser and the light source, will provide stronger evidence on which more definitive conclusions regarding PDT's role can be drawn in the future.

Recommendation

Since there is currently insufficient evidence pertaining to photodynamic therapy, MSAC recommended that public funding should not be supported at this time for this procedure.

? The Minister for Health and Aged Care accepted this recommendation on 11 May 1999 ?

Appendix A MSAC terms of reference and Membership

The terms of reference of the Medicare Services Advisory Committee are to advise the Commonwealth Minister for Health and Aged Care on:

- the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness; and
- references related either to new and/or existing medical technologies and procedures.

The membership of the Medicare Services Advisory Committee comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Dr Richard King	gastroenterology
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	paediatrics
Dr David Robinson	plastic surgery
Ms Penny Rogers	Assistant Secretary of the Diagnostics and Technology Branch of the Commonwealth Department of Health and Aged Care
Associate Professor John Simes	clinical epidemiology and clinical trials
Dr Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council (from 1/1/99)
Dr Doris Zonta	population health, representing the Australian Health Ministers' Advisory Council (until 31/12/98)

Appendix B Supporting committee

Supporting committee for MSAC application No 1008 Photodynamic therapy for skin and mucosal cancer

Dr Paul Hemming (Chair) MB, ChB, MRCGP, FAMA General Practitioner; Chair, General Practice Divisions, Victoria

Mr Allan MacLeod

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Professor Robin Marks

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Ms Penny Rogers

Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care

Dr Carl Vinciullo MBBS, FACD Visiting Dermatologist, Royal Perth Hospital; Clinical Lecturer, Department of Medicine, University of Western Australia nominated by the Royal Australasian College of Surgeons

co-opted member

member of MSAC

nominated by the Australasian College of Dermatologists

member of MSAC

Abbreviations

ALA	Aminolaevulinic acid
BBC	Basal cell carcinomas
MSAC	Medicare Services Advisory Committee
NHMRC	National Health and Medical Research Council
PDT	Photodynamic Therapy
SCC	Squamous cell carcinomas-in-situ

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