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Systematic Review of Management of Superficial Basal Cell Carcinoma

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Abstract **Original Research Article**

Prevalence of Superficial Basal Cell Carcinoma (BCC) is ever increasing along with its referral to the dermatology and plastic surgery clinics. The multidisciplinary team is essential for decision making, especially where surgery can cause significant cosmetic deformities. This systematic review conglomerates various treatment options in superficial BCC management, particularly in anatomically sensitive areas. A database search using PubMed and Scopus from 2010 to 2022 was conducted. English language randomised controlled trials (RCT), non-randomised clinical trials and prospective studies were included. ROB 2 and ROBINS-I tools were used for risk of bias assessment of randomised controlled trials and prospective studies respectively. Topical treatments, photodynamic therapy (PDT), surgical excision, cryosurgery, curettage, laser therapy and combination therapies were analysed in 20 studies, 9 of which were RCTs with a total cohort of 2807 patients. Imiquimod emerged as gold standard treatment but current combination therapies, such as CO2 laser and PDT, and novel treatment modalities, such as topical ascorbic acid, can offer good results in terms of tumour free interval and cosmetic outcomes. Newer and combination treatments should be considered in the management armamentarium of superficial BCCs.

Keywords: Prevalence of Superficial Basal Cell Carcinoma (BCC), plastic surgery clinics, robust database, randomised controlled trials (RCT).

INTRODUCTION

Superficial basal cell carcinoma (BCC) is commonly referred to dermatology and plastic surgery clinics. The disease burden is significant in the elderly population [1]. Deciding the type of treatment is sometimes challenging, especially in anatomically sensitive areas [2]. Cosmetic outcome is relevant to the choice of appropriate therapeutic strategy. Coping with compliance and adverse reactions of topical treatment options can be problematic [3]. This systematic review explores the varied surgical and non-surgical therapeutic approaches in the management of superficial BCC.

METHODS

Information sources

PubMed and Scopus databases were examined through a detailed search strategy from 01/01/2010 until 01/05/2022 [4, 5]. The complete PubMed search strategy is provided as an example in Figure 1. Articles were also included by hand-searching through reference lists. Search results have been summarised in Table 1.

1) PubMed document search:
   - ("Superficial BCC" OR "superficial basal cell carcinoma") AND
   - ("imiquimod" OR "5- fluorouracil" OR "PDT" OR "Photodynamic therapy" OR "cryosurgery" OR "laser therapy" OR "surgical excision")
2) Limits:
   - Year of publications: 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022
   - Language: English
   - Publication stage: Final
   - Document type: clinical trial, RCT

Figure 1: PubMed search strategy

Table 1: Table summarising the search results

Topic	Database	Initial results	Final results with filters	Number after duplicates removed	Number of articles after screened for title	Results after screening abstracts	Results after reading the full text articles	Total number of papers
Treatment of Superficial Basal cell carcinoma	Scopus	531	162	163	42	24	19 10 RCTs 9 prospective studies	19+1 (hand searched) = 20
	PubMed	294	26					

Design and eligibility criteria

Only full-text reviews concerning superficial BCCs written in the English language were included (due to limitations in translation services). Articles involving patients with genetic predispositions to BCC, recurrent and other types of BCC (apart from superficial) were excluded.

Table 2: Summary of the inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Year of study	2010-2022	All articles prior to 2010
Species	Humans	Any other species
Article type	Clinical trials, RCT, article, controlled clinical trial	Letters, editorial short-surveys, systematic reviews, meta-analyses
Publication stage	Final	Articles in press
Language	English	Any other language

Study selection and data extraction

The online platform Rayyan was used for de-duplication and screening of titles and abstracts [6]. Screening was performed by two reviewers independently (SG and MB). All potential full-text articles were then assessed for inclusion by two reviewers (SG and MB). Inclusion and exclusion criteria have been provided in Table 1.

Assessment of risk of bias

Risk of bias was assessed using the *Risk of Bias 2* (RoB 2) tool for RCTs [7]. Overall risk was then graded as low, high or some concern as per guidelines. The *Risk of Bias In Non-Randomized Studies- of Interventions (ROBINS-I) tool was utilised for non-randomized studies* with overall risk scored as moderate, serious, critical or low [8].

RESULTS

20 studies including 9 RCTs and 11 prospective studies were evaluated. 2807 patients were included with an estimated equal male to female ratio. Treatments including Imiquimod, 5- Fluorouracil, Photodynamic therapy, surgical excision, cryosurgery, curettage, laser therapy and combination therapies were analysed. The search, screening and selection results are summarised in the PRISMA flow chart (Figure 2). Table 3 summarises the overall risk of bias for the RCTs (RoB 2) and prospective studies (ROBINS I).

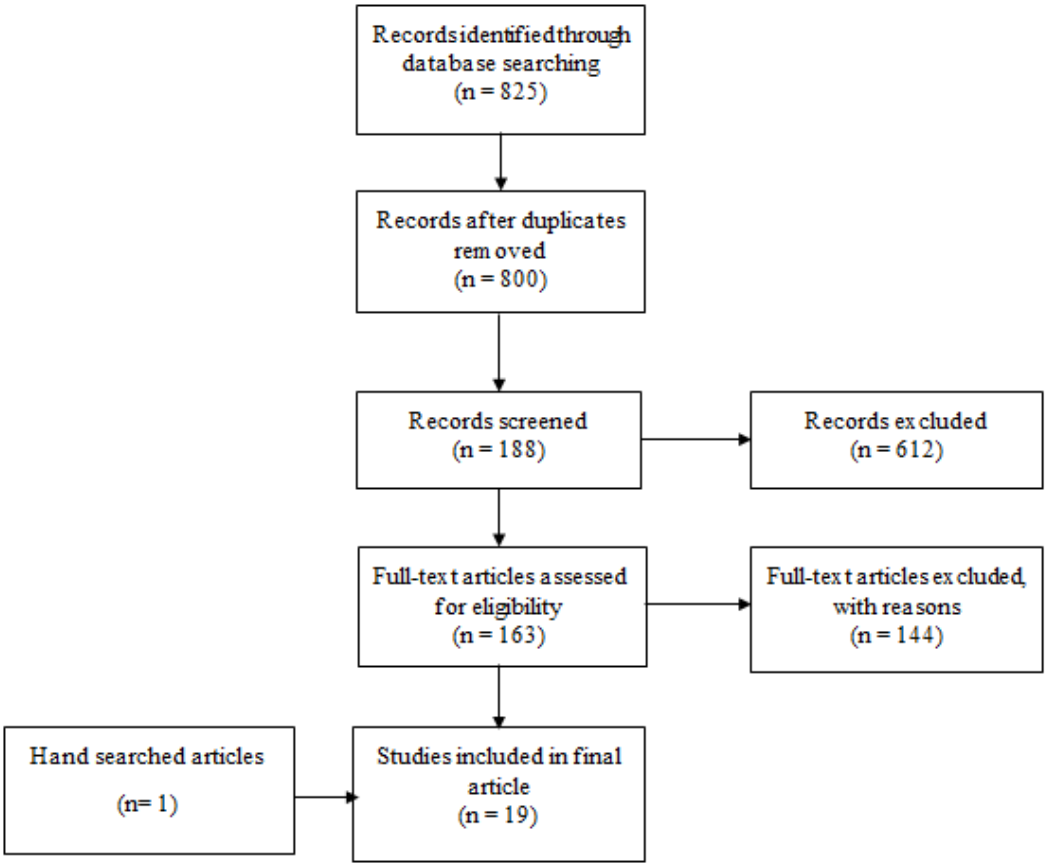

Figure 2: Prisma flow chart summarising the search on SCOPUS and PubMed

Table 3: Summary of Risk of bias assessment

ROBS 2- risk of bias for RCTs		
Study name	**Author**	**Risk of bias (Low risk/ high risk/ some concern)**
A randomized, multinational, noninferiority, phase III trial to evaluate the safety and efficacy of BF-200 aminolaevulinic acid gel vs. methyl aminolaevulinate cream in the treatment of nonaggressive basal cell carcinoma with photodynamic therapy.	Morton et al.	Low risk
Effectiveness of a 595-nm Pulsed Dye Laser for the Treatment of Basal Cell Carcinoma Using One Double-Stacked Pulse Session: A Randomized, Double-Blinded Controlled Trial	Chow et al.	Low risk
Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy	De Haas et al.	Low risk
Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial.	Arits et al.	Low risk
Pulsed dye laser in the treatment of basal cell carcinoma: A single session versus two sessions - A randomized controlled trial	El Naby et al.	Low risk
Randomized trial of topical ascorbic acid in DMSO versus imiquimod for the treatment of basal cell carcinoma	Burke et al.	Low risk
The role of the 595-nm pulsed dye laser in treating superficial basal cell carcinoma: Outcome of a double-blind randomized placebo-controlled trial	Karsai et al.	Low risk
The SINS trial: A randomised controlled trial of excisional surgery versus Imiquimod 5% cream for superficial basal cell carcinoma.	Ozolins et al.	Low risk
Treatment of superficial basal cell carcinoma by topical photodynamic therapy with fractionated 5-aminolaevulinic acid 20% vs. two-stage topical methyl aminolaevulinate: results of a randomized controlled trial.	Kessels et al.	Low risk

ROBINS I- risk of bias for prospective studies		
Study name	**Author**	**Risk of bias (Moderate/ serious/ critical/ low)**
Ablative Fractional Laser-Assisted Topical Fluorouracil for the Treatment of Superficial Basal Cell Carcinoma and Squamous Cell Carcinoma in Situ: A Follow-Up Study	Hsu et al.	Low risk
Ambulatory photodynamic therapy using low irradiance inorganic light-emitting diodes for the treatment of non-melanoma skin cancer: an open study	Ibbotson et al.	Low risk
Basal cell carcinoma treated with combined ablative fractional laser and ingenol mebutate – an exploratory study monitored by optical coherence tomography and reflectance confocal microscopy	Banzhaf et al.	Low risk
Combined carbon dioxide laser with photodynamic therapy for nodular and superficial basal cell carcinoma	Shokrollahi et al.	Low risk
Effectiveness and satisfaction with imiquimod for the treatment of superficial basal cell carcinoma in daily dermatological practice	Dauden et al.	Low risk
Efficacy and Safety of Laser-Assisted Combination Chemotherapy: An Explorative Imaging-Guided Treatment With 5-Fluorouracil and Cisplatin for Basal Cell Carcinoma	Wenande et al.	Low risk
Evaluation of recurrence after photodynamic therapy with topical methylaminolaevulinate for 157 basal cell carcinomas in 90 patients	Lindberg Larsen et al.	Low risk
Prospective trial of curettage and cryosurgery in the management of non-facial, superficial, and minimally invasive basal and squamous cell carcinoma.	Peikert J.	Low risk
Sustained clearance of superficial basal cell carcinomas treated with imiquimod cream 5%: Results of a prospective 5-year study	Quirk et al.	Low risk
Topical 5-aminolevulinic acid-mediated photodynamic therapy for basal cell carcinoma	Filonenko et al.	Low risk

DISCUSSION

Imiquimod

A review by Papakostas et al [9] evaluated topical treatment of BCC with immune response modifier TLR 7 agonist Imiquimod. A high clearance rate of up to 80% was achieved when treated 5 times a week for a duration of 6 weeks, in a multicentre randomised open label dose response study. Two double blind phase 3 vehicle-controlled studies with target tumours smaller than 2 cm in diameter, achieved 75% clearance in 12 weeks. There was no difference between 5 times a week and 7 times a week regimen. The studies concluded that Imiquimod is a fair alternative to surgery especially in multiple superficial BCCs. However, adequate patient education and awareness is important for improving patient compliance during treatment despite mild to moderate skin reaction.

Dauden et al [10] conducted a prospective observational multicentre study on the efficacy and safety of Imiquimod (5% cream 5 times per week for 6 weeks) in 370 patients with 471 sBCC (Superficial basal cell carcinoma). Clearance rate was 83.2% which was independent of tumour size with 82.1% of the patients satisfied with the overall outcome. The study reported high compliance; however, the diary cards were collected in only 46% of the patients.

Quirk et al [11] reported initial clearance rate of 94.1% at 12 weeks and 85.1% at 60 months in their prospective multicentre phase 3 open label study of topical 5% Imiquimod cream in 157 patients, with good cosmetic outcome. 80% of the patients had no hyperpigmentation or scarring.

Surgery vs Imiquimod

Multicentre randomised noninferiority controlled phase 3 trial was conducted by Ozolins et al [12] involving a robust cohort of 500 patients. They compared excisional surgery with imiquimod for superficial BCCs with a defined set of primary and secondary outcomes. They concluded that for large sBCCs Imiquimod achieved 90% clearance rate and was hence the treatment of choice because of better cosmetic results despite being slightly inferior to excisional surgery. Imiquimod also achieved a similar response in small sBCCs.

Topical Ascorbic Acid in DMSO versus Imiquimod (IMQ)

Burke et al [13] conducted a randomised clinical trial, of topical 30% ascorbic acid, for 7 days a week versus 5% Imiquimod cream 5 days a week in compliance with institutional guidelines. The methodology was robust recruiting patients from primary care and dermatology clinics with a defined inclusion and exclusion criteria. Primary outcome was the presence or absence of residual tumour as confirmed by punch biopsy. Complete resolution was confirmed in 86.7% of the cases in the ascorbic acid group and 57.1% in the IMQ group after 8 weeks; and 78.6% after 12 weeks, which was statistically significant. The authors identified a small sample size and the lack of

ethnic diversity as weaknesses. High risk areas were excluded and any role of DMSO beyond its permeation was not explored. They concluded that DMSO is well tolerated, inexpensive and an easy-to-use topical preparation that achieved better results and warrants larger clinical trials.

Photodynamic therapy (PDT)

PDT is a well-recognised non-invasive therapy for sBCC.

Kessels et al [14] conducted a single blind multicentre randomised trial of 5 amino levulinic acid (ALA) and its ester, methyl aminolaevulinate (MAL) randomising 162 patients of superficial BCC. ALA-PDT scheme resulted in fewer recurrences but the differences between 2 groups were not statistically significant. Randomisation was robust using computer generated lists. Investigators were blinded but the patients could not be blinded for treatment allocation because of different illumination schemes. They concluded a trend of better efficacy for twofold ALA-PDT but also with higher risk of pain and side effects.

Filonenko et al [15] conducted a prospective study of topical 5-aminolevilinic acid mediated PDT in 82 patients with 119 tumours. The therapy achieved a recurrence free rate of 92.1% at 1 year and 88.3% at 3 years follow up and excellent cosmesis. Hence topical 5-aminolevilinic acid mediated PDT seems to be a safe and effective treatment option.

De-Haas et al [16] explored the role of fractionated illumination in improving response of Sbcc to ALA-PDT in a randomised trial of 154 patients with 505 primary BCCs (with 12 month follow up). The clearance response following 2-fold illumination of ALA-PDT was significantly higher (97%) compared to single illumination (89%) based on Kaplan-Meier analysis.

Arits et al [17] conducted a single blind non - inferiority randomised controlled multicentre trial with 601 cases of biopsy proven sBCC using topical imiquimod, topical fluorouracil and MAL-PDT photodynamic therapy. This study provided results with the longest follow-up period of 1 year. Results were reported for tumour free interval (3 and 12 months follow up). The imiquimod group had a longer tumour free interval (Imiquimod= 83.4%, MAL-PDT= 72.8%, fluorouracil= 80.1%). A high attrition rate hinders the results of the study (1/3rd of the cohort refused to participate). In addition, half of this cohort had a preference for one of the study treatments. This might affect the generalisability of this RCT's findings.

Lindberg-Larsen et al [18] conducted a prospective evaluation of recurrence after MAL-PDT in 157 superficial BCCs. Recurrence rates were 19% at 6 months and 31% at 24 months. The higher recurrence rate was in the population above 60 years which was statistically significant. PDT is still preferable in superficial BCC especially below 60 years.

Ibbotson et al [19] evaluated ambulatory PDT using low irradiance inorganic light-emitting diodes for 30 Sbcc prospectively with an endpoint of pain during treatment (Numerical Rating scale NRS) and outcome at 1 year. Lesion clearance was 84% and median NRS was 2. Ambulatory PDT is comparative to conventional PDT with good clearance rates and less painful with increased compliance.

Morton et al [20] conducted a randomised multinational noninferiority phase 3 trial to evaluate BF-200 aminolaevulinic acid (ALA) gel vs methyl aminolaevulinate cream in the PDT treatment of low-risk superficial BCC. Complete responders were 93.4% in the ALA group vs 91.8% in the MAL group which was statistically significant. They concluded BF-200 ALA is an excellent alternative in the treatment of sBCC.

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Curettage and Cryosurgery

Peikart et al [21] conducted a prospective study of curettage and cryosurgery in 69 patients with 100 non-facial tumours, 81% of which was superficial BCCs with two freeze-thaw cycles. No tumour recurred after 1 year follow up and achieved 99% recurrence -free endpoint within the 5-year interval. They concluded that curettage and cryosurgery is a simple, highly effective and reliable treatment for a selected group of low risk superficial BCCs, also at lower cost with great time savings.

Pulsed Dye Laser

BCC has a special microvasculature system and selective thermolysis can be targeted by PDL laser.

Recent studies have shown effective treatment of low-risk BCC with pulsed dye laser (PDL).

Chow *et al*., [14] conducted a randomised double blinded controlled trial of PDL in 24 patients, 14 patients in the laser treatment group and 10 patients in the control group. 71.4% of the patients in the treatment group was successful with no residual tumour compared to 30% in the control group. However, the limitations were small sample size and lack of ethnic variation. PDL can achieve cure in low risk BCCs with their settings of 7.5 J/cm2 but may not be effective in high risk BCCs.

A randomized controlled trial has been conducted by EL-Naby et al [23] comparing single versus two sessions of PDL in 22 patients showing more effective treatment in two sessions. Small sample size and site of lesion along with lack of adequate study power were the main limitations of the study. This can also be used to debulk large lesions prior to surgery.

Karsai *et al*., [16] conducted a double-blind randomized placebo-controlled trial in 39 patients with a total of 100 BCCs randomised to receive PDL treatment with wavelength 595 nm and fluence 8J/cm2 or sham treatment with a primary endpoint of complete clinical and histological remission at 6 month follow up and secondary endpoints of evaluation of pain and side effects and patient satisfaction. Complete remission was achieved in 78.6% of the patients in the laser group versus 4.5% in the sham treatment group. The satisfaction score was 72% in the 'satisfied' group and 25% in the 'very satisfied' group. They concluded that PDL is an effective treatment for Sbcc but the occurrence of superficial dyspigmentation still limits the potential for excellent cosmetic outcomes.

Banzhaf *et al*., [17] investigated the efficacy of BCC treatment with a combination of ablative fractional laser (ABL) and Ingenol Mebutate (IMB) in 20 patients and the response was evaluated by optical coherence tomography (OCT) and reflectance confocal microscopy (RCM). Clearance rate at day 90 was 70%, showing potential to treat low risk BCCs with acceptable tolerability. The treatment remains off-label and large controlled studies are needed prior to implementation.

Laser assisted topical 5-FU

Wenande et al [26] investigated laser assisted combination cisplatin and 5- Fluorouracil (FU) treatment in 20 patients of biopsy proven superficial BCC, in an open label proof-of-concept trial. This involved fractional CO2 laser followed by 60 minutes of cisplatin and 7-day exposure of 5% 5-FU cream. At 3 months, clinical clearance was achieved in 94% of the patients and 79% of the physicians rated cosmesis as 'good' or 'excellent'. If self-application option is not available, this combination treatment showed potential as an effective and tolerable treatment option for low risk BCCs. The strengths of the study were that it was standardized, frequent outcome evaluations and application of both image -guided and histological assessment of response were recorded. However, the limitations were small sample size, lack of conventional treatment control, short follow up time and use of punch biopsy rather than excision biopsy for histological clearance evaluation.

Hsu et al [27] reported short-term efficacy of ablative fractional laser assisted delivery of topical fluorouracil in the treatment of sBCC in 30 patients. Overall success was 92% with no significant impact related to tumour location or size. The combination treatment achieved good patient satisfaction and all patients recommended the treatment to others..

Combined CO2 Laser and PDT

Shokrollahi et al [28] conducted a prospective dual-modality treatment of UltraPulse CO2 laser and MAL-PDT in 110 patients with 177 lesions with a repeat PDT 1 week later. Total recurrence-free rate was 97.1% in medium- and long-term follow (8 years). They concluded that this combination can achieve excellent outcomes with scarless cosmesis in the anatomically sensitive areas. The CO2 Laser facilitates depth of penetration of PDT which help in greater clearance.

CONCLUSION

While deciding a specific therapeutic approach for superficial BCC from the wide armamentarium, treatment duration, cosmetic outcome, patient compliance, adverse reactions, cost and risk factors for recurrence should be considered.

While Imiquimod still emerge as the gold standard (response rate 90-97%) treatment, combination treatments, such as CO2 Laser and Photodynamic Therapy and new treatment, such as, topical ascorbic acid can offer similar outcome.

Newer treatment options can be reviewed with photographic documentation and long-term outcome.

Further prospective studies of newer and combination treatments will increase the safety and efficacy of the treatment of superficial BCCs.

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