A systematic review of observational management of cutaneous basal cell carcinoma

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Abstract

Background

Cutaneous basal cell carcinoma (BCC) is the commonest cancer in the United Kingdom and United States. Surgical excision is the most common treatment. This review summarises all published outcomes of observational/non-interventional management of cutaneous BCC.

Methods

This PRISMA-compliant systematic review searched MEDLINE, EMBASE and CENTRAL databases from inception-June 2021. All studies reporting outcomes of observational management for BCC were included.

Results

We identified 2529 titles, from which 4 full-text articles were eligible, reporting on 2298 individuals. Two studies were randomised controlled trials (RCTs) comparing histological clearance rates and adverse events following treatment with an inactive strategy (placebo cream) versus topical 5%-imiquimod (at different frequencies) for 6-12 weeks. Clearance rates ranged from 52-100% for imiquimod and 2-19% for placebo, with more adverse events associated with imiquimod.

The other two studies used prospective cohort designs. One study assessed the natural history of BCCs managed expectantly in 39 individuals aged ≥80years. During the 15.8-month follow-up, 46.2% of lesions did not increase in size and 10.3% resolved. The remaining study compared treatment patterns of 1360 patients with non-melanoma skin cancer (NMSC) in individuals with or without limited life-expectancy (LLE). The LLE subgroup had a 5-year mortality rate of 43.3%, with no deaths attributed to NMSC. Only 3.3% of individuals with LLE underwent observational treatment. No study examined quality-of-life or cost-effectiveness.

Conclusion

There has been limited investigation of observational management of BCC, despite possible advantages of this strategy. Future RCTs should compare quality-of-life outcomes and utility-adjusted survival following interventional or observational management of BCC.

Keywords:
Basal cell carcinoma; observational management; active surveillance; systematic review

Introduction

Cutaneous basal cell carcinoma (BCC) is the most common cancer in both the United Kingdom (UK)[1] and United States (US)[2,3]. BCCs are typically slow growing[4-7], have low morbidity[8] and metastatic rates[9,10], and are not associated with increased mortality[8,11-14]. The incidence of BCC increases with age[15,16], with a median age of 67 years at diagnosis[17]. Ageing in western populations has been reflected by an increase in overall BCC incidence and treatment costs[18-20]. In Europe and the US, the incidence of BCC has increased by between 2.5-5% per year over recent decades[3], which has resulted in over 2.5 million US citizens per year receiving treatment for BCC[3,21,22].

As patients age, they undergo BCC treatment more frequently[11]. The most common treatment for BCC is surgical excision[17,23], and this treatment choice appears largely unaffected by patient age or demographic[11,24]. Non-surgical treatments, including topical, photodynamic and radio therapies are also widely used[25-28].

All excisional and ablative treatments for BCC generate risks and costs[25,29]. The annual direct costs of BCC treatment surpass $600 million in the US[30] and £100 million in the UK[31,32], but robust cost-utility and cost-effectiveness analyses to support the value of these treatments to patients are lacking.

International clinical practice guidelines, including those informing practice in the US[33] and UK[34], recommend observational management, also described as active surveillance, as an alternative option for select individuals with clinically suspicious (or histologically proven) BCC. Observational management - chosen as a shared-decision by clinician and patient - may be particularly suitable for individuals with limited life expectancy, where risks of iatrogenic morbidity might outweigh treatment benefits. Despite this, each year over 100 000 US citizens will undergo surgical treatment for BCC in their final year of life[11,24].

Outcome data are needed to guide the selection of patients for observational BCC management, to rationalise costs and avoid unnecessary treatment risks. The aim of this systematic review was to identify and summarise all available outcome data surrounding the observational management of cutaneous BCC.

Methods

This systematic review is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[35]. The protocol was registered prospectively on the PROSPERO online database (CRD42021254684).

Search strategy

Bespoke search strategies comprising index and free text terms were designed with a search strategist, and applied to MEDLINE, EMBASE, Cochrane CENTRAL and NHS EED databases from inception until June 4th, 2021 (**Supplementary Figure 1**). We searched clinicaltrials.gov (http://clinicaltrials.gov) to seek registered ongoing clinical trials relevant to the study question. Additional references were identified through grey literature searches of Grey Literature Report and OpenGrey databases, and through screening of relevant review article reference lists.

Eligibility criteria

All study types reporting original data on the outcomes of observational management for cutaneous BCC were included, except for case reports and review articles, which were excluded. All titles and abstracts were independently screened by two study authors against pre-agreed criteria. Full-text screening (including reference list screening) was subsequently performed by two study authors. Disagreements were resolved through discussion with a third review author and reasons for exclusion were recorded. Where necessary, translations were obtained, and no article was excluded for reasons related to language.

Participants

Adult patients (aged over 18 years) with primary BCC (biopsy proven or clinically suspicious) of any histological subtype (e.g. superficial or nodular) who had undergone a period of intentional observational management were eligible for inclusion. We excluded patients with recurrent BCC, or incompletely excised BCC, for whom a subsequent active surveillance strategy was used.

Comparators

Studies did not require comparator treatment arms for inclusion in narrative synthesis, however where data presenting outcomes from observational management were compared with data from interventional treatment for BCC, the outcome data for interventional treatments were also recorded, and only comparative studies were considered for quantitative synthesis. Interventional treatments included any that did not have a purely observational approach: examples include (but are not limited to) surgical treatments (excisional and destructive), topical treatments (e.g. 5-fluorouracil), photodynamic therapy and radiotherapy.

Outcomes

The primary outcome of interest was any assessment of skin cancer associated quality of life, which would typically be measured with a patient- or proxy-reported outcome measure. Any additional outcome reported following observational management of BCC was also included, which could include disease progression, mortality, metastasis, cost-effectiveness, estimated indirect and/or societal costs, failure of observational management (i.e. progression to ablative intervention), and generic health-related quality of life (typically measured with patient-reported outcome measures).

Data extraction

Two review authors independently extracted data. Disagreements were resolved by discussion if possible, and if not, by involving a third review author. A final check of data entry was performed by a further author. The following data (where available) were extracted onto a pre-defined data collection form: author, year of publication and journal (including language), country, study setting, population demographic, comparator intervention, clinical outcomes and adverse events. Heterogeneity of

study designs, comparator arms and outcomes assessed across eligible studies precluded quantitative synthesis of results via meta-analysis.

Risk of bias assessment

Assessment of the reporting bias in the included studies was performed by two study authors independently. The Cochrane Risk of Bias tool[36] was used to assess the methodological quality of randomised controlled trials (RCTs), and the National Institute for Health (NIH) quality assessment tool[37] was used to assess cohort studies.

Results

The search strategy identified a total of 2529 titles, from which 4 full-length articles met the inclusion criteria, reporting on a total of 2298 individuals[11,38-40]. 473 of the total 2298 individuals were treated with observational management for BCC, and the remaining individuals were treated with interventional approaches. (**Figure 1)**

Study characteristics and participant demographics

Of the four eligible studies, two were RCTs and two were prospective cohort studies.

The two RCTs[38,39] were multi-centre double-blinded studies from the US, in which a total of 852 individuals with superficial BCCs were randomised to either topical 5% imiquimod (at different frequencies/week) or vehicle cream (placebo treatment considered as equivalent to an observational treatment strategy) for 6-12 weeks. At 6 weeks post treatment completion, all lesions were excised to enable comparison of clearance rates.

One prospective cohort study[40] assessed 39 community-residing individuals aged 80 years and older from Greece who had lesions which were clinically "very suspicious" for BCC which were managed with an observational approach. Patients were counselled and educated on the likely diagnosis of BCC, and given treatment options including general practitioner-led biopsy or referral to a dermatologist at no financial cost. The natural history of the lesions was observed with four study visits between June 2014 and July 2016.

The other eligible prospective cohort study[11] recruited 1360 patients with non-melanoma skin cancer (NMSC) at two dermatology clinics in California between January 1999 and December 2000, and followed patients for a total of 10 years after initial treatment. The authors compared treatment patterns of individuals with NMSC who had limited life expectancy (LLE) with those who did not have LLE. LLE was defined as patients 85 years or older at the time of diagnosis, or patients with multiple comorbidities (Charlson Comorbidity Index of ≥3). NMSC lesions were not subcategorised by subtype (e.g. BCC or SCC). 332 individuals were deemed to have LLE and 1028 were not. Overall, only 3.1% of all patients underwent observational treatment and amongst individuals with LLE, 3.3% underwent observational treatment.

Quality of included studies

Using the Cochrane risk of bias tool for RCTs, the two RCTs - Geisse 2002 and Geisse 2004 - were deemed low risk of selection, detection and reporting bias. In addition, Geisse 2002 was deemed to be at unclear risk of attrition bias, whereas Geisse 2004 was at low risk of attrition bias. Using the NIH quality assessment tool for cohort studies, Linos 2013 was deemed fair-poor quality and Wehner 2018 deemed poor quality. Detailed description of the quality of included studies and their associated risk of bias can be found in **Supplementary Table 1.**

Outcomes

A summary of the outcomes from eligible studies is shown in **Table 1**. In the two eligible RCTs[38,39] comparing topical 5% imiquimod with placebo for clinically diagnosed superficial BCCs, outcomes assessed included histological clearance rates at 6 weeks following the end of treatment and adverse events during treatment. Depending on the frequency of cream administration, histological clearance rates ranged from 51.7-100% for those treated with 5% imiquimod and from 2.0-18.8% for individuals in the placebo (i.e. observational) group. Adverse events related to treatment were higher in the topical 5% imiquimod group versus placebo (39% vs 7%), which included local skin reactions varying in severity from erythema to ulceration and erosion, occurring at a higher intensity in individuals treated with more frequent dosing regimens of topical 5% imiquimod (up to 7 times/week). Rates of headache, application site reaction, and upper respiratory tract infection were higher in individuals treated with 5% imiquimod compared with placebo. No quality of life data were reported in either RCT.

The prospective cohort study[40] examining the natural history of 39 lesions deemed clinically "very suspicious" for BCC in community dwelling individuals in Greece (aged 80 or over), examined: whether BCCs were symptomatic; size change of individual BCCs (increase/decrease in mm^2); and lesion resolution. Over the mean follow-up duration of 15.8 months, only 39% of lesions were symptomatic at any one of the four study visits. 49% of lesions increased in size, with a mean overall increase of $2.5mm^2$ (3.3%) per month. 46% of lesions did not increase in size (including 10% which resolved). No quality of life or survival data were reported in this prospective cohort study.

The remaining prospective cohort study[11] compared treatment patterns of 1360 patients with 1739 NMSCs. The included participants had a median age of 69 (interquartile range 55-78 years). Subgroup data for those with a diagnosis of BCC were unavailable. 3.1% of 1360 individuals underwent observational treatment of their NMSC. 24.4% of patients had LLE, of whom 3.3% underwent observational treatment. All participants were asked "during the past week, how often were you bothered by your skin cancer?", to which only 22% of all individuals answered being "frequently bothered" by the skin cancer at the time of study enrolment. No outcome data specific to individuals treated with an observational approach were reported. The most common treatment for both LLE and non-LLE subgroups was surgical (68.7% and 70.1% respectively) regardless of patient life expectancy, and the choice of surgery was not influenced by patient prognosis following multi-variable analysis. The 5-year mortality rate in individuals with LLE treated for NMSC was 43.3% (versus 11.0% for non-LLE (p<0.001)), with no deaths resulting from NMSC. 20% of individuals with LLE

reported treatment-induced complications, compared with 15% of individuals without LLE. Commonly reported complications included poor wound healing, itch, and pain.

None of the eligible studies explored patient or provider experience of care or factors influencing treatment choice, with no data on quality of life or utility-adjusted survival. In addition, no cost-utility analyses comparing observation with intervention for BCC were performed.

Discussion

There is a lack of published data on the outcomes of observational management of cutaneous BCC, with only four articles identified by this review. No prospective RCTs have compared outcomes of interventional treatments with a truly active surveillance approach to cutaneous BCC management. This is despite active surveillance being a recognised treatment option recommended for this common and expensive condition.

Data identified in this systematic review suggest that clinically suspicious cutaneous BCCs have variable growth patterns, which can include very slow growth, regression, or in some cases complete resolution. Many individuals, particularly elderly patients, or patients with LLE, reported that they were not frequently "bothered" by their BCC, and a proportion of these individuals chose an observational approach as a shared and informed decision. Despite this, in one cohort of individuals with LLE treated in the US for NMSC, only 3.1% received an observational treatment strategy, with surgical intervention representing the most common treatment approach for those both with or without LLE. In the LLE cohort, the 5-year mortality was almost 50%, with no deaths resulting directly from skin cancer. Across all included studies, the complication rates in those receiving interventional treatment for BCC (both surgical and non-surgical) were high.

Specific outcome data reporting on BCC growth/regression, metastasis and survival following an observational approach were lacking. Furthermore, changes in the outcomes that matter most to patients were not explored through patient-reported outcome measures (either generic or skin cancer-specific), or through qualitative research techniques. Historically, accurately exploring patient preferences and experiences in skin cancer and its management has been challenging due to a lack of skin cancer-specific patient-reported outcome measures. The recent development of instruments such as the Skin Cancer Quality of Life Impact Tool[41] and the FACE-Q[42] addresses this challenge and provides validated disease-specific quality of life questionnaires to better capture the outcomes which are most important to patients with skin cancer. These patient-reported outcome measures could be used (alongside preference-based utility measures) in future studies to compare quality of life outcomes and utility-adjusted survival following interventional or observational management strategies for cutaneous BCC.

A prospective trial of observational versus interventional BCC management is timely, as the COVID-19 pandemic has heightened the need for healthcare services resource rationalisation. This, combined with growing waiting lists, reduced outpatient capacity, and the additional safety implications of hospital attendance may build enthusiasm for observational management amongst patients, clinicians, and policymakers.

The practicalities of an active surveillance approach would need consideration. The development of teledermatology infrastructure has accelerated during the pandemic[43]. This is acceptable to (and in some cases preferred by) patients and may have a role in the expectant management of BCC[44,45]. Accurate diagnoses are also important for the initial shared decision, and these will either be made clinically or histologically. A recent systematic review of the diagnostic accuracy of dermoscopy for BCC identified a pooled estimate of 91% sensitivity and 95% specificity[46]. This may be an appropriate alternative to biopsy in some cases.

Future work should examine which specific patient groups benefit more from an observational approach compared with interventional treatment for BCC, and experts in dermatology, plastic surgery, oncology and geriatric medicine should reach consensus with patients to establish protocols for patient selection, frequency of follow-up and thresholds for ending active surveillance (e.g. based on symptomatology or growth rate). Such consensus would help in avoiding unnecessary treatment for many BCCs and may limit the associated distress, complications, and costs, but these discussions must be informed by high quality RCT evidence.

Limitations

Several limitations of this study should be recognised. Firstly, two of the four eligible studies were deemed to be of fair-poor/poor quality. Secondly, multiple combinations of authors screened the title and abstracts which may have affected the consistency of the process. Thirdly, a limited search for grey literature was performed, with only two grey literature databases searched. Finally, we recognise that only a small number of heterogenous studies were identified, with variable patient demographics and outcomes assessed.

Conclusion

This systemic review identifies a lack of published data reporting outcomes following observational management of BCC, despite possible advantages of this treatment strategy. Future RCTs should compare quality of life outcomes and utility-adjusted survival following interventional or observational management of BCC.

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Contributions

RG, MC, CH and JR discussed the idea for the review and co-wrote the protocol. RG, MC, NW, KB and CH all contributed to title and abstract screening and full text review. Data extraction was performed by RG, MC and NW. The review was written by RG, MC, NW, KB and JR.

Conflicts: None to disclose.

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Figure Legends

Figure 1: PRISMA flow diagram

Geisse 2002

Study title   Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: A double-blind, randomized, vehicle-controlled study

Methods   Multi-centre double-blind RCT randomising patients to either topical 5% imiquimod (patients randomised to either 1x/day, 2x/day, 3x/week or 5x/week dosing) or a placebo cream for 12 weeks.

Participants   128 individuals with histologically diagnosed superficial BCC at 13 centres in the US.

Mean age 59.

Follow-up duration 18 weeks.

Outcomes   Six weeks following treatment completion, lesions were excised to assess histological clearance rates.

Clearance rates (intention to treat analysis):

Topical 5% imiquimod

   o   1x/day dosing: 87.1% (27/31)

- 2x/day dosing: 100% (10/10)

- 3x/week dosing: 51.7% (15/29)

- 5x/week dosing: 80.8% (21/26)

Placebo cream

- 18.8% (6/32)

92.2% of participants reported at least one adverse event related to treatment.

No outcomes pertaining to quality of life data were reported.

Geisse 2004

Study title	Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: Results from two phase III, randomized, vehicle-controlled studies
Methods	Multi-centre double-blind RCT randomising patients to either topical 5% imiquimod (patients randomised to either 5x/week or 7x/week dosing) or a placebo cream for 6 weeks.
Participants	724 individuals with histologically diagnosed superficial BCC at 55 centres in the US. Mean age 57.6-59.9.

Follow-up duration 12 weeks.

Outcomes   Six weeks following treatment completion, lesions were excised to assess histological clearance rates.

Clearance rates (intention to treat analysis):

Topical 5% imiquimod

- 5x/week dosing: 75% (139/185)

- 7x/week dosing: 73% (132/181)

Placebo cream

- 2% (7/360)

58% of subjects in the 5x/week topical 5% imiquimod group reported at least one adverse event.

64% of subjects in the 7x/week topical 5% imiquimod group reported at least one adverse event.

36% of subjects in the topical placebo cream group reported at least one adverse event.

No outcomes pertaining to quality of life data were reported.

Linos 2013

Study title	Treatment of Nonfatal Conditions at the End of Life: Nonmelanoma Skin Cancer
Methods	Prospective cohort study assessing treatment patterns and outcomes of individuals with non-melanoma skin cancer (NMSC).
Participants	1536 individuals with histologically diagnosed NMSC (type not specified) at two centres in the US.
	Median age: 69 years (interquartile range 55-78).
	Median follow-up: 9 years (interquartile range 8.5-9.7).
	Participants were subgrouped into those with limited life expectancy (LLE) (age > 85 years or older, or Charlson Comorbidity Index 3.0 or higher) (n=332), and those without LLE (n=1204).
Outcomes	69% of NMSCs were treated surgically, regardless of patient life expectancy.
	3.1% of total patients received observational treatment.
	3.3% of patients with LLE received observational treatment.

20% of patients with LLE reported post-operative complications. 15% of patients without LLE reported post-operative complications.

5-year mortality in individuals with LLE was 43%, with no mortality attributed to NMSC.

Outcomes specific to individuals treated with observational management were not reported.

No outcomes pertaining to quality of life data were reported.

Wehner 2018

Study title	Natural history of lesions suspicious for basal cell carcinoma in older adults in Ikaria, Greece
Methods	Prospective cohort study assessing outcomes of observational management of clinically suspicious cutaneous BCC.
Participants	39 community dwelling individuals with clinically suspicious (but not histologically diagnosed) cutaneous BCC in Greece.
	Mean age (+/- standard deviation): 89 (+/- 5.4) years.

Mean follow-up (+/- standard deviation): 15.8 (+/- 6.8) months.

Outcomes

48.7% (19/39) of lesions suspicious for BCC increased in size over the course of follow-up.

46.2% (18/39) of lesions did not increase in size, including 4 (10.3%) that resolved.

The surface area changed at a rate of 2.5mm^2 per month, or 3.3% per month.

No outcomes pertaining to quality of life data were reported.