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A systematic review on the use of cryotherapy versus other treatments for basal cell carcinoma

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Abstract

Background: Cryotherapy is a commonly discussed method for treatment of basal cell carcinoma skin cancer. Some uncertainty remains about its efficacy relative to other modalities.

Objective: To determine the efficacy and adverse events profile of cryotherapy for the treatment of basal cell carcinoma compared to other therapeutic options or non-intervention.

Methods: We systematically searched PubMed, OVID, Cochrane Library, EMBASE, CINHAL, and CANCERLIT databases for the following terms: "cryotherapy", AND "basal cell carcinoma", OR "cryosurgery" OR "cryoablation" up to April 2018. Two independent reviewers screened the results and extracted the data. Study endpoints included basal cell carcinoma recurrence, cosmetic outcome, and healing time. Study quality was assessed using the Jadad scale.

Results: Six clinical studies met our inclusion criteria. The efficacy and safety of cryotherapy alone or with curettage in the treatment of primary superficial and nodular basal cell carcinoma was comparable to photodynamic therapy and surgery, respectively. Cryotherapy was inferior to radiation in terms of recurrence rate. Most patients had better cosmetic outcomes with photodynamic therapy and surgery compared to cryotherapy alone, and cryotherapy with curettage.

Conclusion: Current available data suggests equivalent efficacy of cryotherapy alone compared to photodynamic therapy or surgery, but inferior to radiotherapy. More studies are necessary to draw definitive conclusions.

Keywords: basal cell carcinoma, cryotherapy, cryosurgery

Introduction

Basal cell carcinoma a, a non-melanoma skin cancer (NMSC) with the highest prevalence is diagnosed 4-5 times more often than squamous cell carcinoma [1]. The most common etiologic factor for basal cell carcinoma is sun exposure, especially those with light complexion [1, 2]. The growing use of tanning beds and recreational sun exposure has increased the incidence of basal cell carcinoma in younger people [1, 2]. Therapeutic modalities for basal cell carcinoma include definitive surgical excision and/or Mohs micrographic surgery [1, 2], destructive options, and non-invasive techniques. Commonly used modalities include: electrodessication with curettage [3], cryotherapy with or without curettage [4, 5], radiation therapy [6], photodynamic therapy [7], ablative laser [8], topical 5-fluorouracil [9], topical imiquimod [9], intralesional interferon [10], combination of therapies such as cryotherapy followed by imiquimod [11, 12], or more recently, inhibitors of the hedgehog pathway [13].

Cryotherapy is a long-standing method used for basal cell carcinoma treatment. The objective of this systematic review is to determine the efficacy, in terms of recurrence rate and adverse events profile of cryotherapy treatment compared to other therapeutic options or non-intervention.

The research protocol with detailed methods is available at PROSPERO (registration CRD42016049157).

Search strategy

A systematic review of the literature was conducted to identify randomized controlled trials (RCTs) on cryotherapy for the treatment of basal cell carcinoma. We searched PubMed, OVID, the Cochrane Library, EMBASE, CINHAL, and CANCERLIT (up to April 2018). The following search terms were used: "cryotherapy", AND "basal cell carcinoma", OR "cryosurgery" OR "cryoablation". There were no restrictions placed on language, publication date, or funding sources.

Study selection

Two independent reviewers (CTF and DE) screened the search results using the eligibility criteria.

Inclusion and exclusion criteria

Relevant publications included Randomized controlled trials) RCTs that investigated the use of cryotherapy for the treatment of any basal cell carcinoma type (**Figure 1**). We excluded systematic reviews, studies reporting use of cryotherapy for non-basal cell carcinoma, and use of cryotherapy in combination with another therapy (curettage was allowed), such as photodynamic therapy, imiquimod or 5-fluorouracil. We also excluded retrospective studies, case reports, case series, in-vitro studies, and animal studies. The study endpoints were provided by each study including recurrence of basal cell carcinoma at one year, two-year, 5-year follow-up. Parameters assessed also included cosmetic outcome, complete response at three months, and healing time. No restrictions were placed on the treated population.

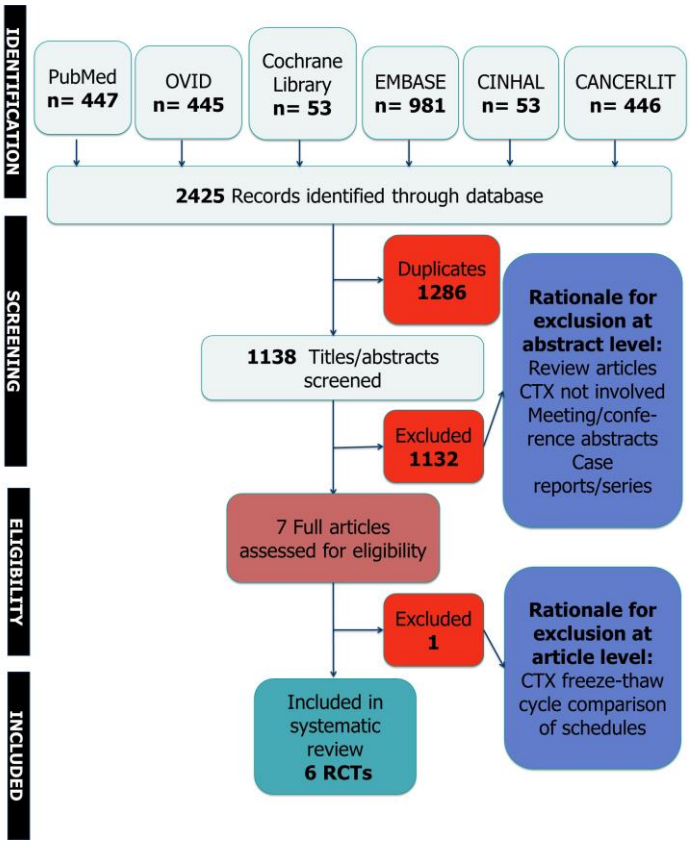

Figure 1. *Flow diagram of study selection for systematic review.*

Data extraction

Two reviewers (CTF and DBE) independently extracted data from eligible studies, and discrepancies were resolved through discussion. Conflicts would be resolved by consulting a third investigator. The data extraction form was entered into the Systematic Review Data Repository database (https://srdr.ahrq.gov/projects/1113).

Data synthesis

We performed an electronic screening of titles and abstracts followed by the selection of full-text publications that met the inclusion criteria. Information on study concept, number of patients, number of lesions, tumor location, interventions, study outcomes, adverse events, and follow-up intervals was retrieved. The study quality (range 1-5) was independently assessed by two reviewers using the Jadad scale for RCTs [14]. The Jadad is a 5-point scoring system based on three criteria: two questions evaluating for randomization and masking, and one question for reporting withdrawals and dropouts. A study is awarded one point if it is a randomized trial and gets additional points if it is double-blinded and if withdrawal and drop-outs are included. Points may be lost if the randomization method is inappropriate or if the method of blinding is inappropriate. Each study was assigned a quality rating scheme [14-16]. In addition, allocation concealment was assessed using the Cochrane Collaboration criteria [17]. Meta-analysis was planned if studies with consistent treatment methods and outcome measures could be identified. Study consistency was to be assessed by I^2 analysis if appropriate. Subgroup analysis was not planned. If quantitative assessment was

inappropriate, outcomes were to be reported descriptively from available evidence.

Results

From the initial search, 2425 manuscripts were obtained. Duplicate records were removed and resulted in 1139 unique articles. After screening titles, abstracts, and full-text, 6 RCT articles were suitable for our systematic review (**Tables 2-7**), [18-24]. These 6 RCTs examined the effectiveness and safety of cryotherapy for the treatment of primary superficial or nodular basal cell carcinoma, including two studies using curettage for tumor debulking prior to cryotherapy.

One RCT [18], (Hall, 1986) compared radiotherapy to cryotherapy (**Table 2**), [16]. The study enrolled 49 patients in the radiotherapy arm with basal cell carcinomas on the neck and face (40), eyelids (3), and trunk (6). The cryotherapy arm had 44 patients with basal cell carcinomas on the neck and face (30), eyelids (6) and trunk (8). The tumor diameter was categorized as less than 1cm, 1-to-2cm, and more than 2cm. Patients in the radiotherapy arm were treated with 130KV and 5mA with different fractionation regimens depending on tumor size. Tumors less than 10mm received 5 fractions of 700cGy in 5 days or 3×650cGy at weekly intervals, whereas tumors over 10mm were illuminated with 375cGY in 10 treatments administered over 12 days. Cryotherapy was performed with a spray gun, two freeze cycles of 60 seconds with a thawing interval of 90 seconds over the face and trunk; it was similarly performed around the eyes with addition of a local anesthetic. A thermocouple needle was used to monitor freezing temperatures (recorded between -25°C and -30°C). During the follow-up intervals at four weeks, 6, 12, and 24 months post-treatment, patients were assessed for tumor recurrence (proven histologically) and cosmetic appearance. Outcome assessment (such as tumor recurrence) was based on the intention-to-treat principle. At one-year follow-up, the radiotherapy group showed 4% tumor recurrence compared to 39% in the cryotherapy group (no P value reported). In light of this finding, enrollment was halted. At the two-year mark, no further recurrence was noted in either group. Cosmetic outcome was recorded at one-year based on mean score for atrophy, scarring, pigmentary change, and overall photographic score. No differences were detected, although no P value was reported. Adverse events such as pain, discharge, and bleeding were reported as similar in both groups. Finally, the authors concluded that cryotherapy was not an acceptable treatment for basal cell carcinoma given the recurrence rate and lack of cosmetic advantage [18].

A non-blinded prospective phase III clinical trial (**Table 3**) [19] compared photodynamic therapy with topically applied delta-aminolevulinic acid to cryotherapy for nodular and superficial basal cell carcinoma located on the trunk, head and neck, and extremities [19]. A 20% weight-based delta-aminolevulinic acid was applied under occlusion over the lesion. Six hours later, the lesion and marginal zone were irradiated with Nd:YAG laser at 635nm at 5kHz (pulse width of 100ns; light dose of 60J/cm^2). Cryotherapy was performed using a spray technique with a double freeze cycle of 25-30 seconds and thawing time between 2-4 minutes depending on tumor size and thickness. It was not specified whether the assessment of the outcomes (such as tumor recurrence) was based on the intention-to-treat principle or per protocol. At three months, any residual or recurrent tumor that was proven clinically and histopathology was re-treated and similarly, a final evaluation was done at 12 months. The study reported significantly higher percentage of lesions needing to be re-treated in the delta-aminolevulinic acid-photodynamic therapy group (30%, in particular the superficial type of basal cell carcinoma) compared to the cryotherapy group (3%), although no P value was reported. The study showed no difference in lesions that persisted on histopathology at the 12-month evaluation ($P>0.05$). Healing time characterized by diminution of leakage and edema was significantly shorter with delta-aminolevulinic acid-photodynamic therapy ($P<0.01$). The cosmetic outcome was based on the scoring of pigmentation, scarring, and tissue defect. The results were in favor of the delta-aminolevulinic acid-photodynamic therapy group ($P<0.001$). The adverse events included pain and discomfort in the delta-

aminolevulinic acid-photodynamic therapy patient and one bacterial infection in a cryotherapy patient. There was one death in each group that was unrelated to either treatment at the three months follow-up. The study concluded that both treatments were equivalent in terms of efficacy, but delta-aminolevulinic acid -photodynamic therapy was more favorable for patients in terms of healing time and cosmetic results. They also concluded that a second irradiation cycle would benefit patients with bigger lesions and the superficial type of basal cell carcinoma [19].

A phase III clinical trial (**Table 4**), [20] compared photodynamic therapy with topically applied delta-aminolevulinic acid to cryotherapy for nodular (48 tumors) and superficial (35 tumors) basal cell carcinoma located on the trunk, head and neck, and extremities [20]. Photodynamic therapy was performed on 24 nodular basal cell carcinomas and 20 superficial basal cell carcinomas with 20% delta-aminolevulinic acid. After a 6h-interval, the lesions were irradiated using a frequency doubled Nd: YAG laser (635nm light emission; 60J/cm^2 light dose; 10-20min exposure depending on the size of the tumor), [20, 21]. Cryotherapy was performed with liquid nitrogen sprayed on 24 nodular basal cell carcinoma and 15 superficial basal cell carcinoma for 25-30 seconds and 2-4 minutes thawing interval, depending on the tumor size. The study endpoint was the evaluation of the lesion for healing and recurrence using a Laser-Doppler perfusion imaging with a probing laser beam. Punch biopsies were performed at three-month and 13-month visits on sites clinically suspicious for the presence of basal cell carcinoma. Tumor recurrence was defined as any residual or recurrent tumor in the histopathological evaluation. The study did not state if the outcomes were assessed based on the intention-to-treat principle or per protocol. Whereas delta-aminolevulinic acid-photodynamic therapy was applied following any recurrent lesion, cryotherapy was only performed on both clinically-evident and histopathologically-confirmed residual tumor. The final evaluation was done at 24 months. At the three-month visit, 12 tumors recurred in the delta-aminolevulinic acid-photodynamic therapy group (8 nodular/4 superficial) and four in the cryotherapy group (4 nodular, P value not reported). At 13 months, two tumors remained in each group (superficial in delta-aminolevulinic acid-photodynamic therapy and nodular in cryotherapy). New recurrences were observed in both groups at the 13-month visit, including three nodular/four superficial in delta-aminolevulinic acid-photodynamic therapy and three nodular/one superficial in the cryotherapy group (no P value reported). No adverse events were documented.

A multi-centered European RCT (**Table 5**), [22], evaluated the efficacy of one cycle of methyl aminolevulinate-photodynamic therapy compared to cryotherapy for basal cell carcinoma [20]. The study involved 115 patients with 201 primary superficial basal cell carcinomas. The lesions were located on the face (6-15 mm), neck, extremities (<20mm), and the trunk (<30mm). The patients in the methyl aminolevulinate-photodynamic therapy arm underwent a light surface debridement of the tumor with a curette or scalpel blade prior to the application of methyl aminolevulinate (160mg/g) under occlusion for three hours. Illumination was performed at wavelength 570-670nm and light dose of 75 J/cm^2. Patients in the cryotherapy arm received treatment via a spray technique of double freeze (20 seconds)-thaw (60 seconds) cycle with a 3mm margin of healthy skin. Outcomes of the study included a clinical evaluation of the response to both treatments at three months and each subsequent year up to 5 years. The trial outcomes were assessed based on the protocol. Complete response rate at three months was similar in both groups (P=0.49) and almost overlapping at 5 years (P=0.90). There was no difference in recurrence rate at each year up to 5 years post-treatment (P=0.86). The number of patients and number of lesions retreated were equivalent in both groups (no P value reported). Significant differences were observed in the cosmetic outcome evaluated at both three months and 5 years (P=0.00078). Adverse events (local pain, crusting, erythema, itching, and suppuration) did not lead to any patient discontinuation. The authors concluded that methyl aminolevulinate-photodynamic therapy had the same efficacy as

cryotherapy but offered a superior cosmetic outcome [22].

Another prospective RCT (**Table 6**), [23] investigated surgery versus curettage and cryotherapy for the treatment of basal cell carcinoma [23]. The study enrolled 103 patients with 103 biopsy-proven nodular and superficial basal cell carcinoma, measuring less than 20mm in diameter and located on the head and neck. Surgical excision was performed with primary closure in the majority of patients in the surgery group. Transposition flaps (23% cases) or full thickness skin grafts (2% cases) were employed in a minority of cases. Cryotherapy was performed using a cone spray and a double freeze (20 seconds) and thaw (60 seconds) cycle. The outcomes included tumor recurrence at 12 months follow-up, reported as failure rate, (unknown if clinically or histologically verified) and cosmetic results. The authors did not state if these outcomes were assessed based on the intention-to-treat principle or per protocol. During the follow-up interval, three patients were absent at the control visit and one passed away from causes unrelated to the study. In addition, three patients from the cryotherapy group had a recurrent basal cell carcinoma within the first year post-treatment. Consequently, a total of 96 treated basal cell carcinomas were evaluated. The surgery group did not show any recurrence out of 48 tumors treated, whereas three recurrences occurred in the cryotherapy arm (no P value recorded). Recurrences were surgically excised with histopathologic evaluation of the margins. The cosmetic assessment was done via a three-point scale photographic evaluation by patients and a panel of clinicians blinded to treatment. According to clinicians, cosmetic appearance after surgery was significantly better compared to cryotherapy ($P<0.01$). There was no difference in cosmetic outcome from the beautician's ($P=0.35$) nor patients' perspective ($P=0.15$), [23]. Adverse events included secondary wound infections in the first two weeks following surgery, which required a ten-day course of systemic antibiotics. In the cryotherapy group, moderate to severe swelling with exudate leakage from the defect were reported in 90% of the cases. The authors concluded that surgical excision remained the preferred treatment for primary basal cell carcinoma over cryotherapy [23].

The last RCT (**Table 7**), [24] compared the efficacy of surgical excision versus curettage and cryotherapy for the treatment of basal cell carcinoma [24]. A total of 88 patients with 100 previously untreated and biopsy-proven nodular or superficial basal cell carcinomas were evaluated. Patients underwent a similar surgical excision as described above by Thissen et al. [23]. Patients in the second group had curettage after local anesthesia followed by cryotherapy with freezing in two cycles of 20 seconds each and a thawing time of 60 seconds. Tumor localization mirrored the prior RCT by Thissen et al. [23], with lesions involving the forehead/temple (27), cheek/chin (16), nose/paranasal (22), lips/mouth (5), periocular area (13), ears/periauricular areas (7), neck (8), and chest/back (2). Mean tumor size ranged from one to 20mm. Follow-ups at 7 and 30 days post-treatment were done; additional evaluations were performed at 3, 6, 9, and 12 months intervals.

Study outcomes were defined as recurrence rates (determined via histopathology) at each consecutive year up to year 5. Cosmetic outcome was not assessed. The outcomes analysis was based on the intention-to-treat principle [22]. The overall 5-year recurrence was determined as 8.4% in the surgical group versus 19.6% in the curettage/cryotherapy group ($P=0.1$). Three tumors were re-excised with one referral for MMS in the surgery arm, whereas no residual tumor was identified in the curettage/cryotherapy arm. There were 2 tumors lost to follow-up in the surgery arm owing to death. In the curettage/cryotherapy arm, 15 tumors from 13 patients were lost to follow-up, including 9 deaths due to unrelated cause, one due to illness, and three for unknown reason.

Adverse events were reported as secondary wound infection treated with systemic antibiotics. Although there was no statistical significance between the two arms, the authors suggested that surgical excision was preferable to curettage/cryotherapy in the treatment of primary basal cell carcinoma in the head and neck area [24].

The clinical studies in this review did not allow for a meta-analysis. They were heterogeneous in many aspects, including study design, interventions, outcomes, and follow-up intervals. The sample size was small across all the studies; even a multicenter European trial had only 115 patients.

The patient demographics and characteristics were not consistently reported but typically included patients between 18 to 90 years old. The method of randomization was clearly demonstrated in three RCTs (block stratification by Wang [19], computer generated by Basset Seguin [22], and Kuijpers [24]) with unclear or inadequate allocation concealment [25] except for one RCT [19], which used a regional cancer registry.

Owing to the nature of the interventions (cryotherapy with/without curettage, radiotherapy, photodynamic therapy or surgery), it was not possible to blind the patients. As a result, the first [18], third [20], and fifth [23] studies scored two out of a possible 5 on the Jadad scale, whereas the other [19, 22, 24] studies scored three for quality. Although the procedures were well described, it was not clearly mentioned they were performed by whom. There was no blinded outcome assessment for the response to treatment or recurrence rate.

An independent assessment of the aesthetic outcome was performed with photographic evidence in four studies [18, 19, 22, 23], but it was unclear in the multicenter European trial [22]. Data analysis was conducted in accordance with the intention-to treat principle [26] in two of the studies [18, 24].

Discussion

Our review of cryotherapy for the treatment of primary superficial and nodular basal cell carcinoma provides evidence that treatment with radiotherapy results in less tumor recurrence at one year, but there were similar cosmetic outcomes and adverse events between radiotherapy and cryotherapy [18]. This review also shows both delta-aminolevulinic acid-photodynamic therapy [19, 20] and methyl aminolevulinate-photodynamic therapy [22] had similar efficacy compared to cryotherapy with no difference in tumor recurrence at one-year and 5-years, respectively. However, delta-aminolevulinic acid-photodynamic therapy [19] and methyl aminolevulinate-photodynamic therapy [22] demonstrated more favorable cosmetic results compared to cryotherapy and an equivalent adverse events profile.

It is unclear whether surgery is more effective than curettage and cryotherapy in the treatment of basal cell carcinoma from the two RCTs [23, 24]. According to Thissen et al., surgical excision led to a better cosmetic outcome [23]. There were 4 RCTs comparing cryotherapy alone (without curettage) to either radiotherapy or photodynamic therapy. We found 2 RCTs comparing cryotherapy and curettage versus surgery [23, 24]. There was no RCT comparing cryotherapy alone to the commonly performed methods of topical 5-fluorouracil or imiquimod, electrodessication with curettage, or excision.

The recurrence rate was reported after 12 months in 5 studies [18-20, 22, 23], whereas 2 studies assessed the recurrence rate at 5 years [22, 24]. In addition, those rates were not reported using conventional methods such as the Kaplan-Meier survival curve [27] except in one RCT [24]. Considering that 60% of basal cell carcinomas tend to recur within the first year post-treatment, 50% recur within 2 years [28-31], and 18% recur between 5-10 years after therapy [28-31], this makes the case for longer follow-up of at least three-to-5 years. Therefore, the length of follow-up seems adequate in only two of the RCTs [22, 24].

Some of the RCTs' limitations reside in the one cycle regimen of photodynamic therapy [19, 20, 22], which some advocate as insufficient; in general, two sessions have been advocated 7 days apart [32]. The authors of the multicenter European trial acknowledged that their study was conducted prior to the regulatory approval of the double cycle at one week apart [22] and more sessions could have led to better recurrence rates since they observed that lesions re-treated with photodynamic therapy had fewer recurrences. Two of the RCT reports also pointed out that tumor recurrence was noted more in the superficial [19, 20] and larger basal cell carcinomas [19], prompting the need for re-treatment [19, 20] or for referral [19].

The only study using radiotherapy [18] had the most distinct results; the recurrence rate was much higher with cryotherapy at one year, warranting the halt of patient enrollment [18]. In addition, that same study reported equivalent cosmetic outcome between radiotherapy and cryotherapy. However, the authors failed to include a statistical analysis with their data [18].

Non-invasive modalities in the treatment of NMSC seem appealing because of their less-destructive nature [2, 33]. However, the disadvantages can be a deterrent. Such drawbacks include the length of treatment [1, 18-20, 22, 34], the discomfort and pain during treatment [18, 19, 22, 34-36], persistent wound drainage post treatment [34, 37], and secondary wound infections that may require antibiotics [19, 37].

The benefit of cryotherapy is that it is fairly inexpensive [1] and quickly performed [1, 34]. Its best use is reported with well-demarcated, well-differentiated small, low risk subtypes of basal cell carcinoma [1] or those basal cell carcinomas covering cartilaginous areas [38] as discussed in the last 2 RCT reports [23, 24]. Cryotherapy is a favorable option for elderly individuals and for those with co-morbidities which preclude the use of surgery [1]. The efficacy of cryotherapy is independent of patients' compliance and there are also minimal contraindications to its use.

However, cryotherapy is operator-dependent and the freeze-thaw cycle has been inconsistent among different trials [1, 18-20, 22-24, 39]. Adverse events during and after treatment have been reported and include local pain from the cryogenic temperature [1, 34], extended healing time [1] associated with increased risk for local infection [19, 24], and poor cosmetic results (scarring, pigmentary changes, tissue defects), [1].

Also, with cryotherapy there is no histologic confirmation that the tumor has been eradicated [1]. Furthermore, only two of the reviewed studies clearly indicated the location of the basal cell carcinoma in regard to locations at higher risk of recurrence [19, 24]. In fact, two of the studies excluded patients with lesions on the nose [18, 22], the pinna, or near the eye.

In retrospective studies of the double freeze-thaw cycle of cryotherapy, the recurrence rates at 5-year post-basal cell carcinoma treatment have been reported as low as 7.1% for primary basal cell carcinoma and 13% for recurrent basal cell carcinoma [1]. However, in this review, the RCTs with the longest follow-up showed a 5-year recurrence rate of 20% (cryotherapy alone), [22] and 19.6% (curettage and cryotherapy), [24]. These RCTs were not large enough to show limitations such as tumor size (more than 10mm) or location in the H-zone (central face, periorbital, eyelids, nose, lips, chin, mandible, preauricular cheek, ears, postauricular scalp). Thus, it is unclear whether curettage has an additive benefit to cryotherapy alone.

Currently, 5 clinical studies involving cryotherapy for the treatment of basal cell carcinoma are listed on ClinicalTrials.gov, among which three are completed, one study is suspended, and one has an unknown status. More information may be available in the future to further delineate the effectiveness of cryotherapy for the treatment of basal cell carcinoma.

Conclusion

Our review of the treatment of basal cell carcinoma suggests that cryotherapy alone is equivalent to photodynamic therapy and cryotherapy with curettage is comparable to surgery. However, photodynamic therapy and surgery appear more cosmetically appealing than cryotherapy. In addition, radiotherapy seems to have a superior efficacy compared to cryotherapy, but both treatments yield similar cosmetic outcomes. Given the small number of studies, more RCTs are warranted to draw substantive conclusions.

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References

1. Kauvar AN, Cronin Jr T, Roenigk R, Hruza G, Bennett R. Consensus for nonmelanoma skin cancer treatment: basal cell carcinoma, including a cost analysis of treatment methods. *Dermatol Surg*. 2015;41(5):550-71. [PMID: 25868035].
2. Bath-Hextall FJ, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. *Cochrane Database of Systematic Reviews*. 2007(1). [PMID: 17253489].
3. Barlow JO, Zalla MJ, Kyle A, DiCaudo DJ, Lim KK, Yiannias JA. Treatment of basal cell carcinoma with curettage alone. *J Am Acad Dermatol*. 2006;54(6):1039-45. [PMID: 16713459].
4. Kuijpers DI, Thissen MR, Neumann MH. Basal cell carcinoma: treatment options and prognosis, a scientific approach to a common malignancy. *Am J Clin Dermatol*. 2002;3(4):247-59. [PMID: 12010070].
5. Peikert JM. Prospective trial of curettage and cryosurgery in the management of non-facial, superficial, and minimally invasive basal and squamous cell carcinoma. *Int J Dermatol*. 2011;50(9):1135-8. [PMID: 22126880].
6. Hulyalkar R, Rakkhit T, and Garcia-Zuazaga J. The role of radiation therapy in the management of skin cancers. *Dermatol Clin*. 2011;29(2):287-96, x. [PMID: 21421152].
7. Kim RH, Armstrong AW. Nonmelanoma skin cancer. *Dermatol Clin*. 2012;30(1):125-39, ix. [PMID: 22117874].
8. Brightman L, Warycha M, Anolik R, Geronemus R. Do lasers or topicals really work for nonmelanoma skin cancers? *Semin Cutan Med Surg*. 2011;30(1):14-25. [PMID: 21540017].
9. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. *Arch Dermato*l. 2009;145(12):1431-8. [PMID: 20026854].
10. Chitwood K, Etzkorn J, Cohen G. Topical and intralesional treatment of nonmelanoma skin cancer: efficacy and cost comparisons. *Dermatol Surg*. 2013;39(9):1306-16. [PMID: 20026854].
11. Moutran R, Maatouk I, Stephan F, Tomb R. Treatment of nodular basal cell carcinoma with cryotherapy and reduced protocol of imiquimod. *Cutis*. 2012;90(5):256-7. [PMID: 23270198].
12. MacFarlane DF, El Tal AK. Cryoimmunotherapy: superficial basal cell cancer and squamous cell carcinoma in situ treated with liquid nitrogen followed by imiquimod. *Arch Dermatol*. 2011;147(11):1326-7. [PMID: 22106125].
13. Nix NM, Burdine O, Walker M. Vismodegib: First-in-Class Hedgehog Pathway Inhibitor for Metastatic or Locally Advanced Basal Cell Carcinoma. *J Adv Pract Oncol*. 2014;5(4):294-6. [PMID: 26110074].
14. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1): 1-12. [PMID: 8721797].
15. Moher D, Jones A, Lepage L, Consort Group. Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. *JAMA*. 2001;285(15):1992-5. [PMID: 11308436].
16. Bhogal SK, Teasell RW, Foley NC, Speechley MR. The PEDro scale provides a more comprehensive measure of methodological quality than the Jadad scale in stroke rehabilitation literature. *J Clin Epidemiol*. 2005;58(7):668-73. [PMID: 15939217].
17. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. [PMID: 22008217].
18. Hall VL, Leppard BJ, McGill J, Kesseler ME, White JE, Goodwin P. Treatment of basal-cell carcinoma: comparison of radiotherapy and cryotherapy. *Clin Radiol*. 1986;37(1):33-4. [PMID: 3514075].
19. Wang I, Bendsoe N, Klinteberg CA, Enejder AM, Andersson‐Engels S, Svanberg S, Svanberg K. Photodynamic therapy versus. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol*. 2001;144(4):832-40. [PMID: 11298545].
20. Enejder AM, af Klinteberg C, Wang I, Andersson-Engels S, Bendsoe N, Svanberg S, Svanberg K. Blood perfusion studies on basal cell carcinomas in conjunction with photodynamic therapy and cryotherapy employing laser-Doppler perfusion imaging. *Acta Derm Venereol*. 2000;80(1):19-23. [PMID: 10721826].
21. Svanberg K, Andersson T, Killander D, Wang I, Stenram U, ANDERSSON‐ENGELS S, Berg R, Johansson J, Svanberg S. Photodynamic therapy of non-melanoma malignant tumours of the skin using topical delta-amino levulinic acid sensitization and laser irradiation. *Br J Dermatol*. 1994;130(6):743-51. [PMID: 8011500].
22. Basset-Seguin N, Ibbotson SH, Emtestam L, Tarstedt M, Morton C, Maroti M, Calzavara-Pinton P, Varma S, Roelandts R, Wolf P.. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. *Eur J Dermatol*. 2008;18(5):547-53. [PMID: 18693158].
23. Thissen MR, Nieman FH, Ideler AH, Berretty PJ, Neumann HA. Cosmetic results of cryosurgery versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck. *Dermatol Surg*. 2000;26(8):759-64. [PMID: 10940063].
24. Kuijpers DI, Thissen MR, Berretty PJ, Ideler FH, Nelemans PJ, Neumann MH. Surgical excision versus curettage plus cryosurgery in the treatment of basal cell carcinoma. *Dermatol Surg*. 2007;33(5):579-87. [PMID: 17451581].
25. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet*. 2002;359(9306):614-8. [PMID: 11867132].
26. Altman DG. Randomisation. *BMJ*. 1991;302(6791):1481-2. [PMID: 1855013].
27. Bewick V, Cheek L, Ball J. Statistics review 12: survival analysis. *Crit Care*. 2004;8(5):389-94. [PMID: 15469602].
28. Thissen MR, Neumann HA, Berretty PJ, Ideler AH.. The treatment of basal cell carcinoma patients by dermatologists in Netherland. *Ned Tijdschr Geneeskd*. 1998;142(27):1563-7. [PMID: 9763832].
29. Rowe DE, Carroll RJ, Day Jr CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol*. 1989;15(4):424-31. [PMID: 2925988].
30. Bath-Hextall F, Bong J, Perkins W, Williams H. Interventions for basal cell carcinoma of the skin: systematic review. *BMJ*. 2004;329(7468):705. [PMID: 15364703].
31. Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. British Association of Dermatologists. *Br J Dermatol*. 1999;141(3):415-23. [PMID: 10583044].
32. De Vijlder HC, Sterenborg HJ, Neumann HA, Robinson DJ, De Haas ER. Light fractionation significantly improves the response of superficial basal cell carcinoma to aminolaevulinic acid photodynamic therapy: five-year follow-up of a randomized, prospective trial. *Acta Derm Venereol*. 2012;92(6):641-7. [PMID: 22964973].
33. Roozeboom MH, Arits AH, Nelemans PJ, Kellener-Smeets NW. Overall treatment success after treatment of primary superficial basal cell carcinoma: a systematic review and meta-analysis of

randomized and nonrandomized trials. *Br J Dermatol*. 2012;167(4):733-56. [PMID: 22612571].

34. Ceilley RI, Del Rosso JQ. Current modalities and new advances in the treatment of basal cell carcinoma. *Int J Dermatol*. 2006;45(5):489-98. [PMID: 16700779].
35. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. *Lancet*. 2010;375(9715):673-85. [PMID: 20171403].
36. Morton CA, McKenna KE, Rhodes LE, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: Update. *Br J Dermato*l. 2008;159(6):1245-1266. [PMID: 18945319].
37. Clark CM, Furniss M, Mackay-Wiggan JM. Basal cell carcinoma: an evidence-based treatment update. *Am J Clin Dermatol*. 2014;15(3):197-216. [PMID: 24733429].
38. Nordin P, Stenquist B. Five-year results of curettage-cryosurgery for 100 consecutive auricular non-melanoma skin cancers. *J Laryngol Otol*. 2002;116(11):893-8. [PMID: 12487665].
39. Baxter JM, Patel AN, Varma S. Facial basal cell carcinoma. *BMJ*. 2012;345:e5342. [PMID: 22915688].

Table 2. *Randomized controlled trial comparing radiotherapy to cryotherapy [18].*

Author	Study Type	Sample size	BCC type	Intervention	Outcomes	Adverse Events	f/u	Comments	Jadad Score
Hall, 1986 [18]	Prospective randomized	Randomized: 105 Evaluated: 93 XRT: 49 CTX: 44	Primary type-not indicated XRT: 40 neck & face, 3 eyelids, 6 trunk CTX: 30 neck & face, 6 eyelids, 8 trunk Lesion size: <10mm XRT: 19 CTX: 19	XRT: 130KV @5mA, filter of 1mmA Tumor < 10mm: 5 fractions 700cGy in 5 days or 3x650cGy at weekly intervals Tumor > 10mm: 375cGy in 10 treatments over 12 days CTX: Face/trunk: spray gun 2 F (60s) - T (90s) cycles	Recurrence at 1 year with histologic identification: XRT: 2 (4%) CTX: 17 (39%) **CTX > XRT No P value reported** No further recurrence at 2 years in both groups Cosmetic results at 1 year: Hypopigmentation XRT: 81% CTX: 88%	Necrosis XRT: 1 pt (tumor size 40mm, trunk) CTX: 1 pt (tumor size 25mm, trunk) Radiation telangiectasia XRT: 7 pts Milia (disappeared after 1 year): CTX: 5 pts Pain/discharge/bleeding: XRT = CTX (number not specified)	1, 6, 12 & 24 months	Withdrawals: 12 5 deaths unrelated to treatment within 6 months 5 lost to f/u 2 refused f/u XRT: 1 pt took 3 weeks off work due to pain & discharge CTX: 1 pt stayed in house for 2 weeks due to swollen face and pain	2 Allocation concealment not specified

BCC: Basal cell carcinoma; sBCC: Superficial type basal cell carcinoma; nBCC: Nodular type basal cell carcinoma; T1: Treatment arm 1; T2: Treatment arm 2; XRT: Radiotherapy; CTX: Cryotherapy or cryosurgery; cCTX: Curettage + cryotherapy or cryosurgery; F-T: Freeze-thaw; PDT : Phototodynamic therapy; ALA: Delta-aminolevulinic acid; MAL: Methyl aminolevulinate; f/u: Follow-up; MMS: Mohs micrographic surgery; pt(s): patient(s).

Table 3. *Randomized controlled trial comparing photodynamic therapy with topically applied delta-aminolevulinic acid to cryotherapy [19].*

Author	Study Type	Sample size	BCC type	Intervention	Outcomes	Adverse Events	f/u	Comments	Jadad Score
Wang, 2001 [19]	Non blinded, prospective phase III clinical trial	Randomized: 83 Evaluated: 33 ALA-PDT: 44 CTX: 39	nBCC & sBCC 47 trunk, 25 head & neck, 10 legs, 6 arms ALA-PDT: 22sBCC 25nBCC CTX: 17sBCC 24 nBCC	ALA-PDT 20% weight-based ALA under tegaderm occlusion, then laser 6 hours later (635nm, quasicontinuous, 5 kHz, pulse width 100ns, light dose 60 J/cm2) CTX: Spray technique with 2 F (25-30s) - T (2-4min) cycles depending on lesion size and thickness	Recurrence at 1 year: ALA-PDT: 5% CTX: 13% ALA-PDT = CTX (p>0.05) Lesions retreated: ALA-PDT: 30% CTX: 3% No p value reported Lesions with persistent growth on histopathology @12 months: ALA-PDT: 25% CTX: 15% ALA-PDT = CTX (p>0.05) Healing time: ALA-PDT shorter than CTX (p<0.01) Cosmetic outcome: ALA-PDT >> CTX (p<0.001)	Referral for surgical removal: ALA-PDT: 1 pt with nBCC One diagnosis not verified: ALA-PDT: 1 pt Wrong diagnosis (SCC): CTX: 1 pt Pain & discomfort during first week after treatment: ALA-PDT: 1 pt Bacterial infection: CTX: 1 pt	1, 4, 8 weeks, 3 & 12 months	Withdrawal: Death unrelated to treatment after 3 month-f/u : ALA-PDT: 1 pt with nBCC CTX: 1 pt with sBCC 3 lost to f/u	3 Cancer registry indicated for allocation concealment

BCC: Basal cell carcinoma; sBCC: Superficial type basal cell carcinoma; nBCC: Nodular type basal cell carcinoma; T1: Treatment arm 1; T2: Treatment arm 2; XRT: Radiotherapy; CTX: Cryotherapy or cryosurgery; cCTX: Curettage + cryotherapy or cryosurgery; F-T: Freeze-thaw; PDT : Phototodynamic therapy; ALA: Delta-aminolevulinic acid; MAL: Methyl aminolevulinate; f/u: Follow-up; MMS: Mohs micrographic surgery; pt(s): patient(s).

Table 4. *Randomized controlled trial comparing photodynamic therapy with topically applied delta-aminolevulinic acid to cryotherapy using Laser Doppler Perfusion Imaging [20].*

Author	Study Type	Sample size	BCC type	Intervention	Outcomes	Adverse Events	f/u	Comments	Jadad Score
Enejder, 2000 [20]	Non blinded, prospective phase III clini-cal trial	Randomized: 83 Evaluated: 83 ALA-PDT: 44 CTX: 39	nBCC & sBCC 44 trunk, 25 head & neck, 14 extremities ALA-PDT: 20sBCC 24nBCC CTX: 15sBCC 24 nBCC	ALA-PDT: 20% water-in-oil cream-based ALA, then laser 6 hours later (635nm, light dose 60 J/cm2, fluence below 100mW/cm2) CTX: Spray technique with 2 F (25-30s) - T (2-4min) cycles depending on lesion size	No p value reported Recurrence at 3 months: ALA-PDT: 12 CTX: 4 Lesions with persistent growth on histopathology @13 months: ALA-PDT: 2 CTX: 2 New recurrence @13 months: ALA-PDT: 7 CTX: 4 Laser Doppler Perfursion Imaging: reaching normal values at ~ 1 month s/p ALA-PDT, & after 3 months s/p CTX Higher perfusion post treatment of superficial lesions	None reported	1, 4, 8 weeks, 3, 13 & 24 months	None reported	2 Allocation concealment & blinding not specified

BCC: Basal cell carcinoma; sBCC: Superficial type basal cell carcinoma; nBCC: Nodular type basal cell carcinoma; T1: Treatment arm 1; T2: Treatment arm 2; XRT: Radiotherapy; CTX: Cryotherapy or cryosurgery; cCTX: Curettage + cryotherapy or cryosurgery; F-T: Freeze-thaw; PDT : Phototodynamic therapy; ALA: Delta-aminolevulinic acid; MAL: Methyl aminolevulinate; f/u: Follow-up; MMS: Mohs micrographic surgery; pt(s): patient(s).

Table 5. *Randomized controlled trial comparing photodynamic therapy with topically applied methyl-aminolevulinic acid to cryotherapy [22].*

Author	Study Type	Sample size	BCC type	Intervention	Outcomes	Adverse Events	f/u	Comments	Jadad Score
Basset-Seguin 2008 [22]	Multicenter RCT (13 centers in 7 European countries	Randomized: 120 pts Evaluated: 115 pts MAL-PDT: 58 CTX: 57	201 Primary sBCC MAL-PDT: 103 CTX: 98 Lesion size: Face: 6-15mm Neck & extremities: <20mm Trunk: <30mm	MAL-PDT: 1 cycle Surface debridement with curette/scalpel, 1mm layer of MAL 160mg/g cream applied under occlusion x 3 hours PDT: 570-670nm, light dose 75J/cm2 CTX: Spray technique with 2 F (20s) - T (60) cycles with 3mm rim of healthy tissue	Complete response - at 3 months: MAL-PDT = CTX (p=0.49) - at 5 years: MAL-PDT: 75% CTX: 74% MAL-PDT = CTX (p=0.90) Recurrence at 5 years: MAL-PDT: 22% CTX: 20% MAL-PDT = CTX (p=0.86) Cosmetic outcome at 5 years: MAL-PDT: 60% CTX: 16% MAL-PDT >> CTX (p=0.00078) Lesions retreated at 3 months: MAL-PDT: 20 pts (34%) with 31 lesions (30%) CTX: 16 pts (28%) with 31 lesions (32%)	Local adverse events (resolved with mean of 5 days except crusting, erythema, itching in both treatments) and suppuration in CTX Pain: MAL-PDT: 37% pts CTX: 33% pts Crusting: MAL-PDT: 35% pts CTX: 47% pts Erythema: MAL-PDT: 30% pts CTX: 21% pts	3 months, 1, 2, 3, 4 & 5 years	Withdrawal: 42 before 5-year due to: - treatment failure: MAL-PDT : 17 CTX: 14 - other reasons: MAL-PDT: 9 CTX: 5 Tumors lost to f/u: MAL-PDT: 14 CTX: 12	3 Block stratification for allocation concealment

BCC: Basal cell carcinoma; sBCC: Superficial type basal cell carcinoma; nBCC: Nodular type basal cell carcinoma; T1: Treatment arm 1; T2: Treatment arm 2; XRT: Radiotherapy; CTX: Cryotherapy or cryosurgery; cCTX: Curettage + cryotherapy or cryosurgery; F-T: Freeze-thaw; PDT : Phototodynamic therapy; ALA: Delta-aminolevulinic acid; MAL: Methyl aminolevulinate; f/u: Follow-up; MMS: Mohs micrographic surgery; pt(s): patient(s).

Table 6. *Randomized controlled trial comparing cosmetic results of surgery versus curettage and cryotherapy [23].*

Author	Study Type	Sample size	BCC type	Intervention	Outcomes	Adverse Events	f/u	Comments	Jadad Score
Thissen, 2000 [23]	Prospective randomized	Randomized: 103 tumors Evaluated: 96 tumors Surgery: 48 CTX: 48	96 nBCC & sBCC BCC < 20 mm in diameter on head & neck Surgery: 6sBCC 42nBCC CTX: 8sBCC 40 nBCC	Surgery: Surgical excision Primary closure/ transposition/transplantation technique 3mm margins of normal skin CTX: Curettage + CTX (c-CTX) Tumor debulking with 3mm curette and 1mm curette for borders Cone spray 2 F (20s) - T (60s) cycles	Recurrence at 1 year-assessed clinically: Surgery: 0/48 c-CTX: 3/48 No p value reported Cosmetic results at 1 year assessed by: - Clinicians: Surgery > c-CTX ($p<0.01$) - Patients: Surgery = CTX ($p<0.15$) - Beautician: Surgery = CTX ($p=0.35$)	Secondary wound infections treated with systemic antibiotics: Surgery: 4% in 1st & 2nd weeks after surgery c-CTX: 6% No p value reported c-CTX: 90% (42/48) with moderate to severe swelling & long-lasting discharge	3, 6, 9, 12 months	Withdrawals: 3 1 Death unrelated to treatment 3 lost to f/u	2 Allocation concealment not specified

BCC: Basal cell carcinoma; sBCC: Superficial type basal cell carcinoma; nBCC: Nodular type basal cell carcinoma; T1: Treatment arm 1; T2: Treatment arm 2; XRT: Radiotherapy; CTX: Cryotherapy or cryosurgery; cCTX: Curettage + cryotherapy or cryosurgery; F-T: Freeze-thaw; PDT : Phototodynamic therapy; ALA: Delta-aminolevulinic acid; MAL: Methyl aminolevulinate; f/u: Follow-up; MMS: Mohs micrographic surgery; pt(s): patient(s).

Table 7. *Randomized controlled trial comparing cosmetic results of surgery versus curettage and cryotherapy [24].*

Author	Study Type	Sample size	BCC type	Intervention	Outcomes	Adverse Events	f/u	Comments	Jadad Score
Kuijpers, 2007 [24]	RCT	Randomized: 88 Evaluated: 88 Surgery: not specified CTX: not specified	100 nBCC & sBCC Surgery: 4sBCC 45nBCC CTX: 0sBCC 51nBCC BCC < 20mm in diameter on head & neck	Surgery: Surgical excision Primary closure/ transposition/transplantation technique 3mm margins of normal skin Tumor mean size: 5.3mm Curettage + CTX (c-CTX) Curettage Cone spray: 2 F (20s)-T (60s) Tumor mean size: 5.4mm	Recurrence at 5 years: Surgery: 8.4% c-CTX: 19.6% Surgery = c-CTX (p=0.1) Lesions retreated: Surgery: 3 lesions c-CTX: 0	Secondary wound infections treated with systemic antibiotics: Surgery: 4 pts in 1st & 2nd weeks after surgery (8.1%) c-CTX: 3/51 cases (5.9%) No p value reported Referral for MMS: Surgery: 1 pt after 2 excisions	Day 7, & 30 after Surgery 3, 6, 9, 12, 18 months 2, 3, 4 & 5 years	Withdrawal: 13 pts (15 tumors) Tumors lost to f/u because of: - death unrelated to treatment : Surgery: 2 (4%) c-CTX: 9 (25%) -Illness c-CTX: 1 -Unknown reason: c-CTX: 1	3 Computer generated for allocation concealment

BCC: Basal cell carcinoma; sBCC: Superficial type basal cell carcinoma; nBCC: Nodular type basal cell carcinoma; T1: Treatment arm 1; T2: Treatment arm 2; XRT: Radiotherapy; CTX: Cryotherapy or cryosurgery; cCTX: Curettage + cryotherapy or cryosurgery; F-T: Freeze-thaw; PDT : Phototodynamic therapy; ALA: Delta-aminolevulinic acid; MAL: Methyl aminolevulinate; f/u: Follow-up; MMS: Mohs micrographic surgery; pt(s): patient(s).