

REVIEW ARTICLE

Histology-based Treatment of Basal Cell Carcinoma

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Basal cell carcinoma is the most common type of skin cancer and its incidence is still rising. In recent years, new treatment modalities have been developed and existing modalities refined. The aim of this article is to give a histology-based overview of the available evidence-based research. The literature was searched for randomized controlled trials from which the efficacy of investigated treatments was obtained. Where possible, treatment modalities were evaluated specifically. Selection criteria were histological subtype, primary or recurrent basal cell carcinoma and tumour localization. Although surgery remains the preferred treatment for most basal cell carcinomas, patient and tumour characteristics should be taken into account when choosing the most suitable treatment. Key words: treatment; surgery; basal cell carcinoma; photodynamic therapy; radiotherapy; imiquimod.

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Basal cell carcinoma (BCC) is the most common type of skin cancer and its incidence is still rising (1, 2). Between 1973 and 2000, the incidence of BCC in the Netherlands rose from 40 to 92 per 100,000 person-years in males and from 34 to 79 per 100,000 person-years in females and these numbers will continue to rise (2). Higher incidence rates are found in areas with more sun exposure, such as New Hampshire (USA) (310 per 100,000 men and 166 per 100,000 women in 1997) (3). Increasing (intermittent) ultraviolet radiation exposure is considered by some to be the main cause of the rise in incidence (4).

Surgical excision is a relatively simple treatment with high clearance rates, and therefore remains the most-used treatment modality worldwide. In recent years non-invasive therapies for selected low-risk BCC, such as photodynamic therapy (PDT), 5-fluorouracil (5-FU) and imiquimod 5% cream have increased in popularity, often showing excellent cosmetic outcomes (1).

A BCC can usually be diagnosed on the clinical aspect, but histological confirmation is necessary to determine the best treatment option (5). Although 26 histological subtypes have been described, clustering leads to a more practical classification (5–7).

The choice for a treatment modality should depend on the site, the size and whether the BCC shows indolent (superficial or nodular BCC) or aggressive growth (infiltrative BCC or basosquamous carcinoma) (5, 8). BCCs with mixed histology (almost 40%) should be treated according to their most aggressive histopathological subtype (5). Shave/punch biopsy specimens fail to diagnose one of both subtypes in approximately 20% of cases (5).

Only a few randomized controlled trials (RCTs) have investigated treatment modalities for BCCs. Because other studies are non-comparative and differ in inclusion criteria and treatment protocols, it is difficult to compare results (9). We shortly discuss available RCTs, and on the basis of available evidence we offer a histology-based guide for treatment of BCCs.

METHODS

All RCTs involving the treatment of histologically proven primary BCC (pBCC), published in the Cochrane review were included (1). Furthermore, the literature was searched for more recently published RCTs and RCTs concerning recurrent BCC (rBCC). Efficacy of each therapeutic approach was obtained from clearance rates. Cosmetic outcome was considered in cases of equal efficacy. Treatments were evaluated for specific tumour characteristics (primary or recurrent tumour, histological subtype and localization of the tumour). A practical classification of the histological subtype divided BCCs into three groups: superficial, nodular and aggressive BCC (BCCs with infiltrating and micro-nodular differentiation and basosquamous carcinoma) (8). Available RCTs were summarized (Tables I and II) and systematically discussed; first the results for surgical excision, followed by other invasive treatments and, finally, non-invasive treatment modalities.

RESULTS

Superficial basal cell carcinoma

Superficial BCC (sBCC) is often larger than other subtypes and occurs mainly on the trunk (10). Because of usually visible scarring after invasive treatment and a high risk of hypertrophic scar formation on the trunk, non-invasive treatment options might be a good alternative to surgery. Although the major benefit is a better aesthetic outcome, the absence of histological control is an important restriction of non-invasive treatments.

In two studies the effect of a treatment for sBCC was compared with that of excision (Table I). After 12 months, photodynamic therapy with methyl aminolevu-

Table 1. Randomized controlled trials investigating treatment of superficial basal cell carcinoma (BCC)

Ref.	Intervention	BCC n	Localization	Clearance rate (%)	Method evaluation	CR	FU period (months)	Cosmetic outcome	Conclusion
11	MAL-PDT SE	100	Head (mid-face excluded); trunk; extremities	90.7 100	Clinically		12	94.1% excellent/good 59.8% excellent/good	SE higher CR than MAL-PDT MAL-PDT better CO than SE
12	SE RT	36 41	Face (scalpel and neck excluded)	98.3 ^a 92.5 ^a	Clinically with histological confirmation		48	87% good ^a 69% good ^a	SE higher CR than RT ^a SE better CO than RT ^a
13	MAL-PDT CT	114 105	Head; trunk; extremities	78 80			60	60% excellent/good 16% excellent/good	CT and MAL-PDT comparable CR MAL-PDT better CO than CT
14	ALA-PDT CT	22 17	Head (nose excluded); trunk; extremities	62 93.3	Histological examination of biopsy		12	93% excellent/good ^a 54% excellent/good ^a	CT higher CR than MAL-PDT ALA-PDT better CO than CT
16	Laser light Broadband halogen light	111 134	Not mentioned	86 82	Clinically		12	84% excellent/good 93% excellent/good	LL and BL comparable CR LL and BL comparable CO
17	Verteoporphin 60 J/cm ² Verteoporphin 120 J/cm ² Verteoporphin 180 J/cm ²	120 77 80	Head; neck; trunk; extremities	63 80 97.2	Histological examination punch biopsy treated area		6	80% excellent/good ^a 65% excellent/good 55% excellent/good	180 J/cm ² higher CR than both 120 and 60 J/cm ² 60 J/cm ² higher CO than both 120 and 180 J/cm ²
18	Single illumination Fractionated illumination	243 262	Not mentioned	97 89	Clinically		12	Not mentioned	Fractionated illumination higher CR than single illumination
20	Imiquimod 2x/week occlusion Imiquimod 2x/week no occlusion	24 21	Limbs, trunk, head/neck (high risk areas excluded)	50 43	Post-treatment excision		6	Not investigated	Best results after imiquimod 3x/week without occlusion Occlusion has no effect on efficacy
	Imiquimod 3x/week occlusion Imiquimod 3x/week no occlusion	25 23		78 87					
22	Imiquimod 2x/day Imiquimod 1x/day	10 31	Limbs, trunk, head/neck (high risk areas excluded)	100 87.1	Post-treatment excision		6	Not investigated	Dosage 1x/day or 5x/week highest efficacy with acceptable safety profiles
	Imiquimod 5x/week Imiquimod 3x/week Vehicle cream	26 29 32		80.8 51.7 18.8					
23	Imiquimod 5x/week Imiquimod 7x/week Vehicle cream	185 179 360	Limbs, trunk, head/neck (high risk areas excluded)	75 73 2	Post-treatment excision		12	Not investigated	Dosing 5x/week equally effective to 7x/week. Because of improved safety profile with 5x/week dosing and similar clearance rates, the 5x/week regimen is recommended
24	Imiquimod 7x/ week Vehicle cream	84 82	Limbs, trunk, head/neck (high risk areas excluded)	80 6	Post-treatment excision		12	Not investigated	Imiquimod 5% cream 7x/week is a safe and effective treatment for sBCC
25	Imiquimod 2x/day Imiquimod 1x/day Imiquimod 2x/day, 3x/week Imiquimod 1x/day, 3x/week	3 33 30 33	Limbs, trunk, head/neck (high risk areas excluded)	100 87.9 73.3 69.7	Post-treatment excision		12	Not investigated	Highest efficacy, but unacceptable side-effects with 2x/ day dosing
26	5-FU in PC 5-FU in petrolatum	10 7	Limbs, trunk, head/neck (facial BCC)	90 57	Post-treatment biopsy		16	100% excellent 100% excellent	Increase in short-term eradication of BCC using PC-based vehicle, but not statistically significant
27	1.0 ml 5-FU 1x/week, 6 weeks 0.5 ml 5-FU 1x/week, 6 weeks 1.0 ml 5-FU 2x/week, 3 weeks 0.5 ml 5-FU 1x/week, 6 weeks 0.5 ml 5-FU 2x/week, 4 weeks 0.5 ml 5-FU 3x/week, 4 weeks	20 21 18 19 21 17	Limbs, trunk, head/neck (high risk areas excluded)	90 ^a 95 ^a 94 ^a 79 ^a 90 ^a 100 ^a	Post-treatment excision		12	Not investigated	Treatment with intralesional 5-FU epigel is both safe and effective ^a

^aResults for total study group, including other histological subtypes with no separate analysis for superficial BCC available.

MAL-PDT: methyl aminolevulinate photodynamic therapy; SE: surgical excision; CR: clearance rate; FU: follow-up; CO: cosmetic outcome; CT: cryotherapy; RT: radiotherapy; ALA-PDT: aminolevulinic acid photodynamic therapy; 5-FU: 5-fluorouracil cream 5%; PC: phosphatidylcholine; LL: laser light; BL: broad band halogen light.

Table II. Randomized controlled trials investigating treatment of clinically and histologically confirmed nodular, aggressively growing or recurrent basal cell carcinoma (BCC)

Ref.	Intervention	BCC, <i>n</i>	Localization	Clearance rate (%)	FU period (months)	Cosmetic outcome	Conclusion
<i>Nodular basal cell carcinoma</i>							
12	Excision	36	Face (scalpel and neck excluded)	98.3 ^a	48	87% good ^a	SE higher CR than RT ^a
	RT	41		92.5 ^a		69% good ^a	SE better CO than RT ^a
30	CS	51	Head and neck area	80.4	60	38.5% good ^b	SE and CS comparable CR
	Excision	45		91.6		79.8% good ^b	SE better CO than CS
31	Excision	53	Limbs, trunk, head/neck (high risk areas excluded)	96 ^c	60	54% excellent/good	SE higher CR than MAL-PDT
	MAL-PDT	52		86 ^c		87% excellent/good	
32	Excision		All (BCC on concave areas excluded)	97.7	36	Not investigated	SE higher CR than ALA-PDT
	ALA-PDT			69.7			
<i>Aggressively growing basal cell carcinoma</i>							
12	Excision	36	Face (scalpel and neck excluded)	98.3 ^a	48	87% good ^a	SE higher CR than RT ^a
	RT	41		92.5 ^a		69% good ^a	SE better CO than RT ^a
28	Excision	199	Face	95.9	60	Not investigated	SE and MMS comparable CR
	MMS	198		97.5			
<i>Recurrent basal cell carcinoma</i>							
28	Excision	100	Face	97.6	60	Not investigated	MMS higher CR than SE
	MMS	102		87.9			

^aResults for total study group, including other histological subtypes with no separate analysis available for nodular, aggressively growing and recurrent basal cell carcinoma, respectively, ^baverage of cosmetic evaluation of 6 persons including professionals and laymen, ^cnon-responders after 3 months excluded from this analysis.

PDT: photodynamic therapy; SE: surgical excision; CR: clearance rate; FU: follow-up; CO: cosmetic outcome; CS: cryosurgery; RT: radiotherapy; ALA: aminolevulinic acid; MAL: methyl aminolevulinate; MMS: Mohs' micrographic surgery.

liniate (MAL-PDT) had 90.7% clearance of responding lesions and surgical excision (SE) 100% in small sBCC, but the cosmetic result was better for MAL-PDT (11). When radiotherapy (RT) was compared with SE in facial BCC, 4-year clearance rates of 98.3% and better cosmetic results were found after SE compared with 92.5% in the RT group (12). Nodular, ulcerated, superficial, pagetoid and sclerosing BCC were included in this study and no separate clearance rates were given for sBCC.

Two trials compared MAL-PDT with cryotherapy (CT) in sBCC (13–15). The first study found 5-year clearance rates of 78% and 80%, respectively, with significantly better cosmetic results after MAL-PDT (13) and in the second study clearance rates for MAL-PDT (62%) seemed to be lower than those after cryotherapy (93.3%) (14).

Three RCTs evaluated efficacy of PDT in sBCC by comparing it with placebo or using different methods (16–18). Differences in preparation of the treated area, the type of photosensitizer, light source and illumination scheme that were used are probably responsible for the divergent clearance rates of 74–97% that were found. The maximum follow-up period was 2 years. Recurrence rates after long-term follow-up are expected to be higher, as it is known from the literature, that the number of recurrences after 5 years follow-up can be twice as high as those after a follow-up period of 2 years (8, 19).

Six RCTs have been conducted investigating imiquimod cream in treatment of sBCC (20–25). Histological examination of the treated area after 6 or 12 weeks was the end-point of the studies that were designed either

to compare different dosing regimes or to compare imiquimod with a vehicle. The RCTs that specifically investigated sBCC found clearance rates of 73–100% with a high frequency dosing regime of six times weekly or more; however, unacceptable side-effects, such as erythema, crusting and severe erosion, were seen (22–25). Therefore the highest efficacy results with acceptable safety profiles were found in a 5-times-a-week dosage, showing clearance rates up to 80.8% (22, 23, 25).

The efficacy of 5-FU in sBCC was investigated in two RCTs. A pilot study in only 10 patients compared two vehicles and showed cure rates of up to 90% in lesions treated with 5-FU in phosphatidylcholine (26). In the second study 5-FU was administered intra-lesionally and showed complete histological clearance in all 17 patients who were treated 3 times a week for 2 weeks (27).

Nodular basal cell carcinoma

In 5 RCTs SE was compared with a different treatment modality in nodular basal cell carcinoma (nBCC) (Table II). One RCT comparing SE with Mohs' micrographic surgery (MMS) in facial primary BCC showed no statistically significant difference in efficacy after 5 years of follow-up (28).

One RCT comparing cryosurgery to SE found no significant difference in efficacy, although cosmetic result after SE was better (29, 30). In both studies comparing SE to PDT after tumour-debulking, treatment with PDT appeared to be less effective than SE after long-term follow-up (31, 32). In facial BCC a higher efficacy and better cosmetic result was found after SE compared

with RT, but separate analysis per histological subtype was missing (12).

Aggressive basal cell carcinoma

This subgroup included BCCs with infiltrating or micronodular growth patterns and basosquamous carcinoma (5, 7, 8). Two RCTs included aggressively growing BCCs among other subtypes (Table II). The difference in efficacy between MMS and SE was not statistically significant (28). However, due to larger defects following frequent incomplete excisions in aggressive BCC, the authors concluded that MMS is the preferred treatment for facial aggressive BCC (33). When comparing SE to RT, SE was significantly more effective than RT (12).

Recurrent basal cell carcinoma

Recurrent BCC (rBCC) is known to be a high-risk tumour with a worse prognosis than primary BCC (8, 34–36). This may be due to the fact that scar tissue can cover residual tumour fields or because the appearance of basaloid tumour cells in recurrent tumours is frequently squamified, lacy and morpheaform, which may be easily missed in scar tissue (35).

The only RCT investigating treatment modalities in rBCC showed that after 5 years of follow-up MMS is the preferred treatment for facial rBCC because of statistically significant lower recurrence rates (28) (Table II).

DISCUSSION

There are still many problems unsolved concerning the treatment of BCC. Some topics have not been investigated in RCTs, some issues are difficult to quantify, such as aesthetic outcome of treatments. Therefore, in clinical practice treatments may be performed without RCT evidence.

More RCTs would be desirable to clarify efficacy, aesthetic outcome and patient preference. A possible future study in sBCC might compare the efficacy of different non-invasive methods (PDT, imiquimod and 5-FU cream). It would also be interesting to investigate non-invasive treatments in *facial* sBCC.

In nBCCs at low-risk anatomical sites comparison of the efficacy of cryosurgery and curettage to SE would be useful. As only one RCT studied radiotherapy and techniques have been refined, indications for radiotherapy should be investigated. Furthermore, it would be interesting to investigate whether it is defensible to re-treat recurrent or residual tumour with a non-invasive therapy following an earlier non-invasive treatment or if it should be excised.

Besides tumour characteristics, patient characteristics are of importance when choosing a treatment for an individual. In a few cases where surgery is impossible or undesirable, it may be advantageous to treat a patient with a different, possibly less effective, treatment.

CONCLUSION

Based on the available RCTs, we conclude that SE is the gold standard for treatment of BCC. MMS is preferable for facial rBCC or BCC with an aggressive histological subtype according to one RCT. Radiotherapy is a non-invasive and effective alternative treatment for nodular and aggressive BCC. Selected low-risk sBCCs may be treated with non-invasive treatments, such as PDT or imiquimod.

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