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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 I. *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	100	Head (mid-face excluded);	90.7	Clinically	12	94.1% excellent/good	SE higher CR than MAL-PDT
	SE	96	trunk; extremities	100			59.8% excellent/good	MAL-PDT better CO than SE
12	SE	36	Face (scalpel and neck	98.3[a]	Clinically with	48	87% good[a]	SE higher CR than RT[a]
	RT	41	excluded)	92.5[a]	histological confirmation		69% good[a]	SE better CO than RT[a]
13	MAL-PDT	114	Head; trunk; extremities	78		60	60% excellent/good	CT and MAL-PDT comparable CR
	CT	105		80			16% excellent/good	MAL-PDT better CO than CT
14	ALA-PDT	22	Head (nose excluded);	62	Histological examination	12	93% excellent/good[a]	CT higher CR than MAL-PDT
	CT	17	trunk; extremities	93.3	of biopsy		54% excellent/good[a]	ALA-PDT better CO than CT
16	Laser light	111	Not mentioned	86	Clinically	12	84% excellent/good	LL and BL comparable CR
	Broadband halogen light	134		82			93% excellent/good	LL and BL comparable CO
17	Verteporfirin 60 J/cm^2	120	Head; neck; trunk;	63	Histological examination	6	80% excellent/good[a]	180 J/cm^2 higher CR than both 120 and 60 J/cm^2
	Verteporfirin 120 J/cm^2	77	extremities	80	punch biopsy treated area		65% excellent/good	60 J/cm^2 higher CO than both 120 and 180 J/cm^2
	Verteporfirin 180 J/cm^2	80		97.2			55% excellent/good	
18	Single illumination	243	Not mentioned	97	Clinically	12	Not mentioned	Fractionated illumination higher CR than single illumination
	Fractionated illumination	262		89				
20	Imiquimod 2×/week occlusion	24	Limbs, trunk, head/neck	50	Post-treatment excision	6	Not investigated	Best results after imiquimod 3×/week without occlusion
	Imiquimod 2×/week no occlusion	21	(high risk areas excluded)	43				Occlusion has no effect on efficacy
	Imiquimod 3×/week occlusion	25		78				
	Imiquimod 3×/week no occlusion	23		87				
22	Imiquimod 2×/day	10	Limbs, trunk, head/neck	100	Post-treatment excision	6	Not investigated	Dosage 1×/day or 5×/week highest efficacy with acceptable safety profiles
	Imiquimod 1×/day	31	(high risk areas excluded)	87.1				
	Imiquimod 5×/week	26		80.8				
	Imiquimod 3×/week	29		51.7				
	Vehicle cream	32		18.8				
23	Imiquimod 5×/week	185	Limbs, trunk, head/neck	75	Post-treatment excision	12	Not investigated	Dosing 5×/week equally effective to 7×/week. Because of improved safety profile with 5×/week dosing and similar clearance rates, the 5×/week regimen is recommended
	Imiquimod 7×/week	179	(high risk areas excluded)	73				
	Vehicle cream	360		2				
24	Imiquimod 7×/ week	84	Limbs, trunk, head/neck	80	Post-treatment excision	12	Not investigated	Imiquimod 5% cream 7×/week is a safe and effective treatment for sBCC
	Vehicle cream	82	(high risk areas excluded)	6				
25	Imiquimod 2×/day	3	Limbs, trunk, head/neck	100	Post-treatment excision	12	Not investigated	Highest efficacy, but unacceptable side-effects with 2×/day dosing
	Imiquimod 1×/day	33	(high risk areas excluded)	87.9				
	Imiquimod 2×/day, 3×/week	30		73.3				
	Imiquimod 1×/day, 3×/week	33		69.7				
26	5-FU in PC	10	Limbs, trunk, head/neck	90	Post-treatment biopsy	16	100% excellent	Increase in short-term eradication of BCC using PC-based vehicle, but not statistically significant
	5-FU in petrolatum	7	(facial BCC)	57			100% excellent	
27	1.0 ml 5-FU 1×/week, 6 weeks	20	Limbs, trunk, head/neck	90[a]	Post-treatment excision	12	Not investigated	Treatment with intralesional 5-FU epigel is both safe and effective[a]
	0.5 ml 5-FU 1×/week, 6 weeks	21	(high risk areas excluded)	95[a]				
	1.0 ml 5-FU 2×/week, 3 weeks	18		94[a]				
	0.5 ml 5-FU 1×/week, 6 weeks	19		79[a]				
	0.5 ml 5-FU 2×/week, 4 weeks	21		90[a]				
	0.5 ml 5-FU 3×/week, 4 weeks	17		100[a]				

[a]Results 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, *n*	Localization	Clearance rate (%)	FU period (months)	Cosmetic outcome	Conclusion
Nodular basal cell carcinoma							
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	96[c]	60	54% excellent/good	SE higher CR than MAL-PDT
	MAL-PDT	52	areas excluded)	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			
Aggressively growing basal cell carcinoma							
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			
Recurrent basal cell carcinoma							
28	Excision	100	Face	97.6	60	Not investigated	MMS higher CR than SE
	MMS	102		87.9			

[a]Results for total study group, including other histological subtypes with no separate analysis available for nodular, aggressively growing and recurrent basal cell carcinoma, respectively, [b]average of cosmetic evaluation of 6 persons including professionals and laymen, [c]non-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.

linate (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 primaryBCC 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 miconodular 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 defendable 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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