Hovedoppgave ved Medisinske fakultet

A 5 year follow-up study of MAL-PDT treatment of Basal cell carcinoma and Actinic keratosis

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Abstract

Introduction: Non melanoma skin cancer is divided into basal cell carcinoma and squamous cell carcinoma. The incidences of these tumours are increasing in the Caucasian population with increasing sun exposed leisure activities. Traditionally BCCs have been treated with excision surgery, but now several new treatment modalities have emerged. Photodynamic therapy is one of these new therapeutic options, but so far long follow-up time data has been missing.

Materials and Method: From 1997 until 2002 the Norwegian Radium Hospital conducted a compassionate-use study with topical MAL-PDT. The database established during that study has now been updated, which represents the basis of the actual study, with a minimum 5 year follow-up of the material. A total of 424 patients were revised, with 1857 BCC and 601 AK.

Results: The overall complete response rate for BCC was found to be 79%, with decreasing cure rate, in the range of 84% to 52%, for increasing lesion thickness and infiltration grade. For AK we found the overall complete response rate to be 62%, with the results for AK thin and medium, 63% and 56%, respectively. The cosmetic outcome was considered most satisfactory, either “Good or Excellent” for 98% and 99% of BCC and AK, respectively, for complete responding lesions.

Discussion: During the first 3 years, we observed a certain amount of recurrences. Thereafter, the recurrence rate seems to flatten out. The 5 year recurrence rate after MAL-PDT seems to be acceptable compared to other treatment options, especially when we take the cosmetic outcome into consideration.
Introduction

Non-melanoma skin cancer
Skin cancer can be divided into melanoma skin cancer, non-melanoma skin cancer and a few other rare groups. NMSC is again divided in basal cell carcinoma and squamous cell carcinoma, which account for 75% and 20% of NMSC, respectively. The incidence of NMSC has risen steadily with 3-8% a year since the 1960s.(1;2)

Basal Cell carcinoma

Epidemiology
Basal cell carcinoma is the most common skin tumour in Caucasians. The growth rate of BCC is very slow and it very seldom metastasizes, even though it is regarded as a malignant tumour since it rarely goes into spontaneous regression. People with fair skin complexion, red or fair hair, or light eye colour are more prone to BCC. The role of pigmentation is clearly shown by the fact that people of coloured origin have a much lower incidence of BCC. Increased sun light and UV exposure seems to increase the risk of BCC, and there is also a correlation between incidence and age. The highest incidence rates are reported in Australia and the lowest in Finland. There used to be a higher incidence for men compared to women, 2:1, but this is changing. For people under the age of 50, women now have a higher incidence rate, and the overall incidence rate is closing on 1:1. There also seems to be an increase in incidence for both genders and also for younger people.(3;4)

Classification
There are several different ways of classifying BCC. The two main forms have been based on the histopathological growth patterns and on the histological differentiation. A total of 14 morphological subtypes and 12 miscellaneous variants have been described, while the WHO lists 10 variants. There is no universal classification system that is agreed upon today, but growth pattern seems to be biologically the most significant parameter. Therefore a simplified
morphological classification system is generally used, which is clinically more reproducible and useful. It has also been common to divide the subgroups into indolent-growth or aggressive-growth pattern, or low- and high risk BCC.\(^{(5-8)}\)

Nodular BCC (≈50%); It is the most common BCC and appears like a pearly pink papule, often with telangiectasia. Tumour cells grow as round masses within the dermis, they have sharp contours and a nodular appearance. There is peripheral palisading of the nuclei, and there may be surrounding retraction artefacts. Often central degeneration or necrosis is present, giving it a cystic appearance. There is variable cell differentiation and size. Nodular BCC has a continuous basement membrane and the cells are surrounded by stroma that can show a myxoid change. Nodular BCC can be seen both in sun-exposed and sun protected skin.

Micronodular BCC (≈15%) is a subtype of nodular BCC. It presents itself with small nodules, that are by definition smaller than <0.15mm diameter. The lesion often has an uneven border and the surrounding stroma shows myxoid or collagenized morphology. These lesions seem to have a higher rate of recurrence.

Pigmented BCC (≈2% in Caucasians) is also a subtype, most commonly found in nodular BCC and a few in superficial BCC. They have melanocytes in the tumour and melanophages in the stroma.\(^{(5-7)}\)

Superficial BCC (≈15%); Round or oval shaped lesions with a well defined, pearly border. There are slit-like retractions to the palisading of basal cells. Superficial BCC were previously called superficial multifocal BCC. Here the BCC cells grow down from the epidermis into the superficial layer of the dermis. Down growths are interconnected, but separated by normal dermis, giving it a multifocal appearance. Superficial BCC have a continuous basement membrane. They are most often seen on the trunk and limbs, and can be seen in both sun exposed and sun protected skin.\(^{(5-7)}\)

Infiltrative or Morpheic BCC (10-20%); Tumour has a scaly surface and reddish colour and the size varies. The border is irregular with pointed projections. It also lacks a pearly border. There is often no palisading, or it is not well
developed. The surface can either be elevated or depressed. The stroma is not as myxoid as with the nodular BCC, and it is frequently fibrotic, but not to the extent of morpheaform BCC. Loss of basement membrane around individual cells is a sign of progression to a more aggressive state. Lesions may infiltrate the subcutis or even muscle and other adjacent structures. Morpheaform or sclerosing BCC (1-5%); this is a subtype of infiltrative BCC, characterized by the presence of stromal fibrosis, which make it appear like white- or yellow fibrotic scar tissue. They rarely ulcerate or bleed. The cell groups are poorly demarcated, and there is widespread invasion into the dermis and subcutaneous tissue. It is seen mostly in sun exposed skin.(5-7)

Mixed BCC (10-15%); as the name gives away, is a combination of the above lesions. One third of nodular BCC have a superficial BCC component, while a combination of superficial BCC and infiltrative BCC also occurs.(5-7)

**Pathogenesis**

BCC originates from the basaloid epithelia. They are pluripotent progenitor cells. When the basal cell nevus syndrome was mapped, only a few chromosomal regions had loss of heterozygoicity, one of them being on chromosome 9q22-31, which contains the PTCH suppressor gene. Damage to PTCH is one of three things that causes disturbances in the SHH –pathway, including damage to SMO and GLi-1 which are both enzymes further down the SHH signalling pathway. Alterations in the SHH pathway causes unregulated cell proliferation, and thereby is one of the main causes of BCC, both in basal cell nevus syndrome and sporadic BCC.

Bcl-2, a protein that inhibits apoptosis, has been found in sporadic BCCs. Enhanced expression of Bcl-2 has been shown in both nodular BCC and superficial BCC. This makes the cells more susceptible to the mutagenic effect of UV-light, and to further damage. Enhanced expression of p53, without the accompanying increase in p21 expression, suggests mutagenesis of p53 appears. Mutations in p53 cause reduced ability to repair DNA and for the cell to undergo apoptosis, and has been identified in 40% of BCCs. Especially in infiltrative- and morpheaform BCC.
The main predisposing risk factor for the development of BCC is ultraviolet light exposure and it is the reason for 72% of mutations to the p53 gene. UVB causes C→T and CC→TT transition mutations which directly damage DNA and RNA. The reason cytosine is the nucleotide that is mutated, is unknown. UVA is 10000 less mutagenic than UVB, but natural radiation consists of a much greater quantity UVA, thereby making it significant to some degree. It causes damage by increasing the oxidative stress on the cells.(4;5;9-11)

**Risk Factors**

Skin type 1, fair or red hair, blue or green eyes and freckling as a child, are risk factors BCC. Severe or frequent sunburn as a child also seems to predispose for BCC, in contrast to that in adults. Australians of British origin born in Britain, have a lower incidence of BCC than Australians of British origin born in Australia. It seems like the overexposure to UV light in childhood or in adolescence is the critical factor for development of BCC as an adult. There is a modest increase in risk for BCC for psoriasis patients treated with oral psoralen and UVA (PUVA). Tanning bed exposure has so far not shown an increase in risk. Patients with renal failure, diabetes mellitus or HIV infection are particularly prone to superficial BCC, in contrast to immunosuppressed patients who are prone to infiltrative BCC. Transplant patients have a 10-100 times increased risk of BCC. A few hereditary and genetic conditions have a greater risk of acquiring BCC. They include xeroderma pigmentosa, nevoid basal cell syndrome, albinism and Bazex’s syndrome. Smoking has been hypothesized to lead to the development of BCC, but no association has been proven. Arsenic acid, used in some medications in the early 20th century for acne, syphilis, depression and lethargy, tends to accumulate in the skin and causes a high incidence of skin cancer, including different types of BCC, Bowen’s and SCC. Also, radiation, x-rays, scars and thermal burns have all proved to increase the risk of BCC.(4;5;10-12)
Nevoid Basal Cell Carcinoma Syndrome

Epidemiology
NBCCS, also known as Gorlin’s syndrome, is an autosomal dominant illness, although 30-50% cases are sporadic. The prevalence is reported to be at least 1/57000. In 90% of all cases, loss of heterozygosis is found on chromosome 9q22-31, the PTCH gene. Furthermore, 30% have mutations on p53. Both situations are discussed above.(5;13)

Clinical presentation
NBCCS is characterized by several features, and basal cell carcinoma is the most prominent one. The commonest sites for lesions are on the face, back and chest, and they usually classify as superficial- and nodular BCC. The BCCs may number from only a few to a thousand and they seem to become more aggressive after puberty. Radiotherapy causes proliferation and later invasion of the BCCs. Palmar and sometimes plantar pitting is also common. The pits are 1-2mm in diameter, and asymmetric. Another characteristic feature is cysts of the skin and jaws, 5 being the average number. The cysts are particularly prone to recurrence following surgery. Calcifications of the Falx cerebri and of the diaphragma sellae are other prominent findings, including bifid ribs and spina bifida of the vertebrae and frontal bossing. Fibroma of the heart has also been observed at a fairly higher incidence than in the general population.(5;13)

Actinic Keratosis and Squamous cell carcinoma

Actinic keratosis
Actinic keratosis, also known as solar keratosis, is closely related to UVB exposure. It affects fair-haired and fair-skinned people, and the incidence is highest in Caucasian populations who live close to the equator. In recent years the relationship between actinic keratosis and the development of squamous cell carcinoma has been closely investigated. The atypical cells in AK and SCC are alike, but AK will stop developing and as many as 25% go into spontaneous remission, if sun exposure is limited or stopped. On the other hand 40% of SCC arise de novo, while 60% originates from AK. Only 1% of
untreated AK-lesions develop to SCC, on average this gives patients with untreated actinic keratosis a risk rate of 8-20% of developing SCC. AK can be divided into 6 histological subtypes; hypertrophic, atrophic, Bowenoid, lichenoid, pigmented and acantholytic. Overlapping occurs.(14-16)

**Clinical presentation**
Actinic keratosis has a sandpaper like surface and is often more readily diagnosed by palpation. The colour can vary from skin-colour to yellowish-black to red-brown. The shape can be round or irregular, and the border between dysplastic and normal keratinocytes can be both well- or illdefined. AK can be a papule or a macula, scaly or keratotic. The size is usually between 1 - 3mm in diameter, but can become much larger. (14-16)

**Transformation into Squamous cell carcinoma**
UVB is the main cause of AK formation, although other oncogenes also play a role. UVB causes thymidine dimer formation in DNA and RNA, resulting in gene mutations and neoplastic transformation. Neoplastic keratinocytes are often present in AKs and can be found in as many as 90% of SCC. The most important mutations are found in the telomerase gene and the p53 tumor suppressor gene. Telomerase is linked to apoptosis, while p53 is responsible for DNA protection, repair and proofreading. Mutations in these genes cause uncontrolled proliferation and growth of damaged keratinocytes. DNA aneuploidy has been found in both AK and SCC, and an increase in aneuploidy has been associated with the transformation from AK to SCC. There is lots of data available, and there clearly seems to be a continuum form atypical neoplastic cells to SCC that penetrates the dermis, but all the links have not been found or understood properly yet.(14-16)
**Treatment modalities**

**Surgical excision**
This is the most common treatment modality for NMSC. The treatment consists of excising the tumour together with a margin of normal tissue. The tissue can then later be analyzed histologically to determine whether the whole tumour has been removed. The normal risks of surgery are present, including bleeding and infection. The cosmetic outcome can be less good than other modalities, but surgical excision has a cure rate of 95% for BCC and 92% for SCC. It is most reliable in treating low risk tumours. (2;17)

**Mohs micrographic surgery**
MMS is the gold standard in treatment of NMSC, with 5 year recurrence rates of 1% for BCC and 3% for SCC. It’s usually used for tumours greater than 2cm in diameter, aggressive subtypes, recurrent tumours or tumours on cosmetically sensitive locations. The surgeon removes sections of tumour and analyzes piece by piece microscopically, mapping the margins of the tumour. This is done until there are no more tumour cells left. The result is greater conservation of healthy tissue and margin control. Like with all surgery, bleeding and infections may occur. (2;17)

**Curettage and electrodessication**
Curettage is first preformed on the tumour, followed by electrodessication which destroys remaining tumour cells around the margins by inducing necrosis. This cycle is repeated two to three times. Margins cannot be analyzed after the procedure. C&ED is mostly used on primary superficial BCC and some nodular BCC smaller than 1,5cm diameter. Cure rates for primary BCC and SCC are 92% and 96%, respectively, but these numbers are significantly reduced for; recurrent tumours, tumours bigger than 2cm diameter, infiltrating tumours and tumours in high risk locations. Development of a white scar is common, and quite often hypertrophic scars are also seen.(2;17)
Cryosurgery
This treatment is gradually being replaced by other modalities. The reason for this is due to a generally poorer cosmetic outcome compared to newer modalities and even surgery. The method also does not permit analysis of the margins. The procedure is applied by spraying the tumour with liquid nitrogen at -196.5°C over two freeze–thaw cycles lasting 30 seconds each. Tumour cells freezing and vascular stasis cause necrosis. The ideal tumour temperature of minus -50 to -60°C can be monitored by thermocouples. Overall cure rate for BCC is 93% and for SCC it is 96%. Scaring is not uncommon, including hypertrophic scarring and hypopigmentation.(2;17)

Radiotherapy
Radiotherapy is best used in cases with older patients who cannot tolerate surgery proficiently, or with tumours in areas which would result in unnecessary disfiguration if treated with surgery. It is also used when histological analysis show unclear margins after surgery. The treatment consists of x-rays or electron beams concentrated at the tumour. It is not recommended for patients under 50 years of age, because of the danger of developing melanoma cancer. The cosmetic result is also often poorer for younger patients. Overall cure rates are 90-93% for smaller tumours of BCC and SCC. It is important to note that radiotherapy is contraindicated with Gorlin’s syndrome and a few other genetic disorders.(2;17)

Topical 5-Fluorouracil
5-FU is a chemotherapy agent that causes cell necrosis by inhibiting DNA synthesis. Because it is limited by its ability to penetrate deeper lesions, 5-FU is seldom used. Cure rates are also reported to be lower than for other modalities, but combination methods may have a better outcome. 5-FU is applied twice daily for 6 weeks on superficial BCC, but may need treatment for as long as 10-12 weeks. Some patients experience severe local skin reactions.(2;17)
**Interferon**
This is a new treatment used when surgery is not recommended, and has reportedly had complete response rates of 50-80%. Treatment consists of 3 injections per week over 3 weeks. Interferon induces apoptosis via CD-95 ligand-receptor and stimulation of IL-2 and IL-10.(2)

**Imiquimod**
Imiquimod is used on superficial BCC, small nodular BCC and carcinoma in situ. It activates Th-1 cell mediated immunity and secretion of cytokines through by binding to Toll-like receptors 7 and 8, giving a cytotoxic effect. Imiquimod has also been shown to stimulate NK-cells, proliferation of B-lymphocytes and activation of Langerhans cells. It also induces Fas receptor mediated apoptosis. Treatment is generally applied once daily, 5 times a week, for 6 weeks with superficial BCC. This results in a clearance rate of 88%. Treatment once a day, 5 to 7 times a week, for 6 to12 weeks applied to nodular BCC, gives a clearance rate 71-76%.(2;17)

**Photodynamic Therapy**

**General principles**
Photodynamic therapy is a relatively new treatment modality and has gradually developed into today’s form over the last 20 years. PDT destroys tumour cells selectively, and has a very low toxicity. It can easily be used in combination with other modalities and generally has excellent results for cosmetic outcome. Cosmetic outcome with PDT has been fairly superior to both cryosurgery and normal surgical excision. The two main components of this treatment are a photosensitizer and light. For this reason the treatment depends on the accessibility of light to the area being treated and the delivery mode of the photosensitizer to the desired location. The PS can either be given systemically or by topical application, lastly being the most common mode used on non-melanoma skin cancer. PS has the ability to selectively accumulate in tumours. One of the reasons for this is that tumours have increased proliferation rate, also other characteristics of tumour cells and the
photosensitizers play a role here. Techniques like; removing crusts on tumours by curettage, and increasing application time, both increases penetration of the compound and the efficiency of the treatment. Light activates the photosensitizers by exciting it to a triplet state. This compound state transfers its energy readily, creating cytotoxic singlet oxygen and reactive oxygen species, which causes cell death. Mechanisms of cell death through apoptosis, necrosis and autolysis have all been described after treatment with PDT.(1;18-20)

**Light source**
Different light sources have been used, with almost equal effect. The gold standard now is a lamp with a broad illumination field, either a filtered light source or a LED. What is important is that the spectral output of the light matches the excitation peaks of the photosensitizer, thereby causing it to excite the photosensitizer more efficiently. Another factor to consider is the light’s ability to penetrate the tissue. Red light, \( \lambda \geq 600 \text{nm} \), is generally used because it has the deepest penetration of the skin, while matching with a high peak of the absorption spectrum of MAL.(19;20)

**Topical Photosensitizers; 5-aminolevulinic acid (ALA) vs. methyl aminolevulinate (MAL)**
In Europe, Australia and New Zealand Metvix is approved for the treatment of actinic keratosis, superficial- and nodular basal cell carcinoma. In the United States, ALA and Metvix have been approved for the treatment of actinic keratosis. Research has shown that MAL has better tissue penetration and tumour selectivity than ALA, because of its increased lipophilic structure. The incubation time is only 3 hours for MAL, opposed to 4-6 hours for ALA, when treating BCC. This may also contribute to MAL being reported as less painful than ALA, including that it is presumed that ALA stimulates peripheral nerve endings.(1;18-20)
Introduction to the study

A research group at the Research Institute, affiliated to the Norwegian Radium Hospital (DNR), has been working with PDT since the late 70ies. Sustained work on ALA-based PDT started in 1991. ALA is a compound that is hydrophilic, and tissue penetration was inadequate for topical application. A more lipophilic substance was desired and in 1995, a patent on lipophilic ester derivates of ALA was filed by the group. This was followed by animal trials, and a clinical phase I study, which were primarily conducted at DNR and by 1997-98 these trials were finished. Because of very promising results, in parallel to classical phase II studies conducted worldwide, the Norwegian group were authorized to conduct a compassionate-use study protocol, which is a phase II study carried out on patients where results and adverse effects are registered. Permission was granted after review by The National Committee for Research Ethics in Norway and the Norwegian medicines agency (Statens legemiddelverk). From 1997-2002 this Compassionate-use study was conducted at the Norwegian Radium Hospital. All patients, all lesions, treatment characteristics and results were registered in a database, until Metvix was fully approved in 2002 (first in the EU in 2001, and then in Norway in 2002). A total of almost 12000 lesions were registered and treated, where of ⅔ being Basal cell carcinoma. This database was reviewed in 2008, and data was updated when a follow-up time of more than 5 years was available. This has been the main inclusion criteria for this study. The study consists of 424 patients, with 2479 lesions, where of 1857 BCC, 601 AK and the rest being either Bowen or SCC.
Materials and Method
In this study we have researched through the journals of all the patients registered in the compassionate-use study. We have updated the original database to 2008, so that we have a minimum 5 year follow-up of every single lesion in the new, updated database.

Our inclusion criteria for the study have been:

- At least 5 years must have passed form the baseline date (the date the lesion was registered by us), until the last follow-up date.
- Lesions that were included were basal cell carcinoma and actinic keratosis. The basis for the diagnosis was either clinical, by cytology or by histology.
- Patients that either are immune suppressed in the follow-up of kidney, heart or other organ transplant, or have been treated with arsenic medication, are all registered in the updated database, but not included in this study and their numbers are not represented at all. The Gorlin patient population is also registered, but have been excluded from this material as well, in order to have a more homogenised population.

Of the 12000 lesions in the original database, there was a major dropout, due to:

- death – 200 patients of the original total of more than 3000
- not followed-up because of too big geographic distance to treatment facility
- insufficient capacity at the clinic and the patient had too few lesions to be prioritized for continued treatment
- they have had other major illness causing them to discontinue follow-up.

Standard treatment of BCC consists of two treatment sessions, with the second treatment usually occurring after one week or within a 3 month period of the first session. This however does not always suit the patient or the practitioner. Therefore we have defined that; if there has been a second treatment, and the second treatment has been within one year of the first treatment, it counts as the first treatment with the date of the “second” treatment being the baseline date. Even though we have this relatively broad definition for first treatment, the majority of lesions that have had two treatments counted as the initial treatment, have had their second treatment within the usual three months. Superficial BCC and nBCC thin were generally treated once. While nBCC thick
and infiltrative BCC had the standard two session first treatment. AK thin was generally treated in only one session, while AK medium and thick were treated twice.

A small number of SCC and Bowen’s disease have been treated with PDT within this compassionate use study. These tumours are not within the inclusion criteria, but the lesions’ true histological nature has first been properly discovered by biopsy result at a later date. Some recurrent AKs have first proven to be a SCC after the third or fourth biopsy. Retrospectively MAL-PDT turned out to be quite effective in the treatment of Bowen’s disease. A total of 17 studies have later been conducted, and Bowen’s disease is now included in the treatment indications after showing the best treatment results of all NMSCs.(19;21)

The patient population that has been treated for NMSC at the Norwegian Radium Hospital went through a prehospital selection. They were referred by dermatologists from Oslo and the area around. The lesions were broadly considered as “difficult to treat”, with lesions in locations that were less fit for surgery, cryosurgery or other modalities. Many of them had previously been treated extensively. A rough estimate suggests that 10% of these patients were referred directly to surgery and 10% directly to radiotherapy, while the rest were referred to PDT. This has not been a specific selection, but has depended on the referral from the dermatologist, and upon the doctor who has made the judgement on which treatment modality is most suitable. Also worth noting is that; in 2002 one of the doctors left the clinic, halving the manpower. At that time the clinic was forced to phase out and refer patients with the least problems, meaning the patients with the fewest and easiest to treat lesions, and leaving the more problematic and hard to treat lesions.

The main bulk of the treatment procedure was mapped out in the phase I studies, for example application time, substance concentration etc. However, some improvements of the procedure were added along the way. For example the tissue penetration was a known limiting factor. A curettage technique reducing thickness of the lesion in order to reduce the penetration depth of both MAL and light had already been introduced. Around the year 2000 they added the multiple puncture technique, which consists of giving a series of small punctures to the bottom and the periphery of the lesion, together with curettage. This was done to further enhance the tissue penetration of MAL.
All our data is produced and all the work is done at the DNR skin clinic. All patients were in a regular follow-up and treatment programme at this unit, and no patients were requested to come back for a reassessment especially for this study. No data is collected from other dermatological clinics or from any general practitioners. All lesions are treated and followed-up for 5 years or more at the Radium hospital by senior consultants Trond Warloe and Ana Solèr.

The statistics for this paper are done by PhD Even Angell at the Research Institute of the Norwegian Radium hospital. The confidence intervals for the proportions showing complete response were calculated using the Wilson score method without continuity correction. The confidence intervals in this material can easily be compared, to see if there is statistical significance. If two confidence intervals overlap, there is no statistical significant difference between the two parameters that one is comparing. This will be used extensively in the “Results” section.(22)
**Results**

CR is the cumulative “Complete Response Rate” over 5 years. This means the percentage of lesions successfully treated with no recurrence within 5 years of last treatment. In general, most lesions were treated in one or two sessions within one year, as defined in materials and methods. However, some lesions had a recurrence and were retreated with PDT. These lesions were followed, and those who were successfully reported, with a subsequent full 5 year follow-up, are represented in the group CR6. This group is included in the cumulative CR group.

As seen in table 1, the overall cure rate for the group, including sBCC, nBCC thin and nBCC thick, is 79%. Within the group there is a falling tendency, having best results for sBCC with 84% down to nBCC thick with 65%. If we look at the confidence intervals for BCC using the criteria discussed in materials and methods, we can see that there is a statistical significance that the results for sBCC are better than for nBCC, both thin and thick, and also vs. infiltrative BCC. But the difference between nBCC thin and thick is not significant, since the confidence intervals are overlapping. There is only a slight overlap, so we can say that there is a pretty clear trend that nBCC thin has better treatment results than nBCC thick. The treatment for thin nBCC is significantly better than for infiltrative BCC. The difference is not significant for thick nBCC vs. infiltrative BCC, but again there is an apparent trend.

A similar tendency can be seen for AKs as for BCCs. The overall complete response rate for AKs is 62%. AK thin has a CR of 63% and medium AK has a CR of 56%. AK thick does not seem to follow the expected trend, having a CR of 69%. This is probably due to the relatively small number of lesions treated within this group, 35 compared to 427 for AK thin and 139 for AK medium. If we look at the 95% confidence interval and compare the groups, we can only say that there is a trend towards a reduced complete response rate from thin to thick AK, but there is not a statistically significant difference.

Within the CR6 group the results are inversely proportional to the CR group. This is valid for both BCCs and AKs, except for infiltrative BCC and thick AK, which are considered to be the lesions difficult to treat. Again the small number of lesions in this category are a defining factor. Only one lesion extra in each
group would bring the percentage up greatly. It may also mean that if an infiltrative BCC first reoccurs, it should be retreated by another modality.

Avr. no. of Treatm. is the average number of treatments per lesion. As expected this characteristic has a rising trend from sBCC having the fewest treatments per lesion with 1.3, up towards infiltrative BCC having 2.3 treatments per lesion. For AK we observe the same trend, with 1.5 treatments per lesion for thin AK and 1.7 for medium AK. Again there is an exception for AK thick, as commented above.

In table 2 we have the group “To surg/rad” which means lesions that have been referred to surgery or radiation therapy, after failing treatment with PDT. The physical criterion for a referral is that the lesion is non-responding to the original treatment session, meaning that less than 50% of the lesion has healed. Other reasons for referral to surgery or radiotherapy are changed characteristics like size, increased thickness or infiltration grade. There is an increasing percentage with increasing lesion thickness and infiltration grade for both BCC and AK, except for AK thick which again might be due to the small number of lesions. The number of treatment failures is lowest with the sBCC and AK thin, with 1.1% and 0.9% respectively. While for infiltrative BCC; as many as 13% are referred to surgery or radiotherapy. Looking at the confidence interval we can state that these differences are significant for sBCC and nBCC thin compared with nBCC thick and infiltrative BCC. There is not significantly fewer failure referrals for sBCC compared with nBCC thin, neither for nBCC thick compared to infiltrative BCC. But there seems to be a trend in both cases.

The group “To PDT” consists of lesions followed for 5 years or longer, but have had a recurrence and then been retreated and the subsequent follow-up period has been less than 5 years. These lesions are generally partial responding, meaning more than 50% reduction of lesion size and thickness. The partial success in the treatment of the lesion has been interpreted in the direction, that the lesion has the potential to be successfully treated with a new round of PDT. This group represents the majority of lesions that have not obtained complete response.
In the “Missing” group the lesion has either not been retreated or is lost in the follow-up. The remaining lesion area could be small compared to the initial lesion, and considered not necessary to retreat. In other circumstances the remaining non-repsonding area could be part of a larger treatment field and retreated within a different adjacent area and thereby renamed. In addition, due to late arrival of biopsy reports, some lesions were converted from one category to another.

PDT treatment has shown great results for “Cosmetic outcome”. Our results, presented in table 3, are well above 90% of all lesions with a complete response rate falling into the categories “Excellent” or “Good”. Overall BCC scores a 98.1% and overall AK scores a 99.2%, even Infiltrative BCC scores a 94.3% if we look at the “Excellent” and “Good” categories combined.

The “Fair/Poor” category is characterized by hypopigmentation, fibrosis or a white depression scare. On average only 1.9% of BCCs and 0.8% of AK develop this problem. Infiltrative BCC has the highest rate of unsatisfactory cosmetic outcomes, 5.7%, which accounts for 5 of 87 lesions, assumable because of more extensive curetage prior to treatment.

A certain number of lesions needed more than one treatment session. Table 4 contains the distribution of the number of treatment sessions for each lesion category, before the lesion has become completely responding. This table represents only the completely responding lesions with a 5 year or more follow-up.

As commented above, for table 1, the thin lesions for both BCC and AK clearly need fewer treatment sessions than the thicker and infiltrative lesion types. For complete responding sBCC, 92% were treated only once to obtain a 5 year sustained CR. However, if we consider all sBCC treated, only 79% obtained a 5 year CR for the first treatment session (data not shown).

For infiltrative BCC, considered as a difficult to treat lesion, we only achieved a 52% sustained CR, and out of these lesions only 60% had a one session treatment.

Another interesting aspect is the treatment results, put in context with size and location, which we have represented in table 5. To obtain a sufficient number
of lesions to perform statistical analysis, some subgroups have been added together. The new groups are; All BCC (includes sBCC, thin and thick nBCC as previously), sBCC, nBCC (thin and thick added together), All AK (includes thin, medium and thick AK as previously), and thin and medium AK.

There is a clear tendency that lesions located on the head are harder to treat than on the extremities and trunk/neck. This is valid in all categories and sizes of lesions, either statistically significant, or in groups with few lesions, a clear tendency. Looking at the “All BCC” group, there is a significantly worse complete response rate for the treatment of <10mm and 10-29mm treating head, compared to extremities or trunk/neck. The same accounts for the groups sBCC and nBCC. Because of few lesions in the ≥30mm groups, we get very wide confidence intervals, and so we do not have a difference that is significant. Looking at All AK there is statistical significance if we compare treatment for the groups <10mm head to trunk/neck, and if we compare 10-29mm head to extremities. Looking at the thin and medium AK we have the same relationship.

Looking at the results within a subtype, for a single location and comparing the size, there is a clear tendency that there are better results for <10mm than 10-29mm, and better results for 10-29mm than for ≥30mm in all the variations. There is only a significantly better complete response for <10mm than the 10-29mm in the group All BCC head. But if we compare <10mm with ≥30mm, there are statistically significantly better results for All BCC; head, extremities and trunk/neck, sBCC; trunk/neck, and nBCC; trunk/neck, as well as for All AK; head, and Thin and medium AK; head. It should also be noted that for All BCC, sBCC and nBCC trunk/neck 10-29mm has significantly better results than ≥30mm.

An interesting and important aspect of the study is appearance of recurrence as a function of time. The Kaplan Meier plots give a graphic representation of the longitudinal development of recurrence. There is an artefact in graph 1 and 3, because of our definition that all retreatment within a year count as the first treatment. From the first graph we see that sBCC has fewer recurrences than nBCC thin, which again has fewer recurrences than nBCC thick. The curve for nBCC thick is steep until 2 year follow-up, and then somewhat flattens out,
while nBCC thin which is less steep, flattens out after 2 to 3 years follow-up. This indicates that the 2 to 3 first years of follow-up are important in determining a lesions further development. The second graph represents the lesions that have failed treatment and been referred to either surgery or radiotherapy. The artefact from the first graph is not present here. Generally there is an expected higher percentage of the thicker lesion groups that have been referred to, which is confirmed in this plot. The number of failures does not seem to increase notably after 2 years of follow-up, neither for nBCC thick, thin or sBCC. From this we can deduce that at least a 2-3 year follow-up for these subtypes of BCC is indicated, to be sure of treatment success.

Reviewing the graphs 3 and 4, for AK, we have the same relationships as for BCC, again with exception for AK thick. In table 3 we also have the artefact caused by our “one year first session”. For AK thin and medium there is quite a constant reduction in CR until year 3-4, while they flatten somewhat out from 4-5. This indicates that AK has a stable recurrency potential for quite a long time, and therefore one can not determine the true treatment result safely until at least 4 years have passed. For graph 4 we can see that fewer AKs end as failures, than BCCs. Also for AK there are virtually no new referrals to surgery or radiotherapy after the 2nd year of treatment. There is no artefact in this graph.
Discussion
A 5 year follow-up is the standard follow-up period for cancer treatment; hence we have reassessed our clinical material at this time. This study represents the first 5 year follow-up for treatment of basal cell carcinoma and actinic keratosis with MAL-PDT, which is natural since this unit at the Norwegian Radium hospital was the first treatment facility using the actual photosensitizer. In opposition to traditional clinical studies where the lesions would be clearly defined in size, location and type, our study on the contrary, represents the outcome of a regular treatment situation for lesions and patients.

There have been several multicenter, randomized and open studies of MAL-PDT. If we compare the results, there have been complete response rates varying from around 70% to mid 90%, all depending on the different treatment methods and groups of lesion characteristics. Some studies have only used single session treatments, while others have consequently used double session treatments. There is also variation in whether or not curettage has been performed. One must also take into account the difference in patient population; from a standard to the difficult to treat lesions. Another defining factor has been the follow-up times, which in these studies have varied from 3 to 36 months. An analysis of 12 different trials with variations as mentioned above, calculating the weighted average for the complete response for a total of 826 sBCC and 208 nBCC, showing a complete response rate of 87% and 53%, respectively. Newer studies have brought the weighted average for complete response rate for nBCC up to 71%.(20)

An interesting open, uncontrolled study on a difficult to treat population compared clinical complete response rate to histological complete response rate. They performed a two session first treatment within a week on both sBCC and nBCC, and then had a follow-up after 3 months. Recurrent lesions were retreated. The follow-up time was 36 months. The result for clinical CR for sBCC was 92% and for nBCC it was 87%, while the histological CR for sBCC was 85% and for nBCC it was 75%. The histological results are of course a more accurate representation of complete rate, and it correlates well with our results. From this we can deduce that a 5 year follow-up may be long enough to determine whether or not the lesion we are dealing with is a true- or a false
clinical complete response. The patient population/lesion characteristics, with treatment method and results for this study seems to be comparable to our study, confirming the validity of our results.(20;23)

Comparing our results for the treatment of BCC with MAL-PDT to other modalities, the 5 year complete response rates for Mohs micrographic surgery is better than 98% for primary BCC and 96% for recurrent BCC, and is considered the gold standard for BCC treatment. For excision surgery, the 5 year CR rate is 95% for primary BC and 83% for recurrent BCC, while for Curettage and Electrodesiccation the CR is 92% for primary but only 60% for recurrent BCC. For radiotherapy the 5 year CR is 91% for primary BCC and 90% for recurrent. Finally, cryosurgery has been reported with a 92% CR rate in a 5 year study, but several comparative studies has shown a cryosurgery CR rate of as low as 61%. Comparative studies of MAL-PDT to cryosurgery on BCC lesions show no significant difference in the complete response rate for the two treatment modalities. In all of these reviews the lesion type was not specified, but the CR rate has been calculated separately for primary and recurrent BCC. Most of these studies show cure rates better than ours, however the lesion material is not always comparable.(2;24)

In the same manner, the results for MAL-PDT treatment on AK have produced quite varying results. In a European multicenter study, consisting of 193 patients with 699 lesions, MAL-PDT was compared to cryosurgery. The lesions that were not located to the head were treated with a single session, and the rest with a double session. Their results for the PDT group were 69%, at 3 months follow-up. Such a short follow-up period is inconclusive. There have been numerous studies, mainly phase III comparing cryosurgery to MAL-PDT in single and dual session. Generally, MAL-PDT seems to have better results, but the follow-up time in all these studies is also limited, and thereby an eventual the comparison to our study is not well funded as demonstrated in our Kaplan Meier plots. A German study comparing MAL-PDT with cryosurgery, has demonstrated a 3 year CR of 87.5% for AK, but when we look at the literature, the general recurrence rate for 3 years follow-up on AK has been reported to be as high as 30%, correlating quite well with our results.(20;25)
An Australian study looking at MAL-PDT treatment on BCC found that lesions on the scalp/face, the so called H-zone, had worse treatment results compared to trunk/neck. The difference was statistically significant, 54% vs. 88% (p=0.009), after a 2 year follow-up. Again this correlates well with our results, where face/scalp has been significantly harder to treat than extremities and trunk/neck for several parameters, for both BCC and AK. For other treatment modalities lesions in the H-zone also have higher recurrence rate for BCC. The same relationship also accounts for increasing lesion size. This is probably applicable to AK as well. In conclusion, we consider our cure rate for lesions located on the extremities and trunk/neck to be satisfactory, and the results for head seem to follow the same patterns previous studies.(17;20;26)

Looking at cosmetic outcome, it is usual to combine the “Excellent” and “Good” group. Two studies important studies present a cosmetic outcome of 84% and 85% for MAL-PDT treatment on nBCC. For AK the cosmetic results have been reported to vary form 96% to 97%. Our results coincide perfectly for AK, but we have a somewhat stronger result for BCC. The judgement of cosmetic outcome is not a easy measurable science, but when we compare our results with surgery (84-33%), cryosurgery (81%, significantly worse than PDT and surgery ), radiation (63%) and C&ED (91%) we can clearly see that this is PDTs most beneficial aspect.(2;20)

Another feature that should be commented upon is that the multiple puncture technique has greatly increased the effect of treatment on the tougher lesions like thick nBCC and infiltrative BCC. This has however not become apparent within our 5 year follow-up, but becomes more apparent when we looked at a 3 or 4 year follow-up (data not shown). This is not absolutely stated yet, so the results will be updated and presented at a later date.

An interesting aspect doing scientific work within this field has been the histopathological heterogenic composition in these lesions, valid both for BCC and AK. This feature may explain that some of these lesions are more treatment resistant than originally thought and histological subgroup has to be taken into account in the treatment of NMSC. In the literature the percentage of mixed lesions has been found to be 10-15 percent, as mentioned in the introduction.
### Table 1

<table>
<thead>
<tr>
<th>General</th>
<th>Pasients</th>
<th>Lesions</th>
<th>CR</th>
<th>CR: 95% Confidential int.</th>
<th>CR6</th>
<th>Avr. no of Treatm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-13: All BCC</td>
<td>252</td>
<td>1857</td>
<td>78,6 %</td>
<td>76,7 %</td>
<td>80,4 %</td>
<td>4,0 %</td>
</tr>
<tr>
<td>11: sBCC</td>
<td>174</td>
<td>1047</td>
<td>83,8 %</td>
<td>81,4 %</td>
<td>85,9 %</td>
<td>2,8 %</td>
</tr>
<tr>
<td>12: nBCC thin</td>
<td>173</td>
<td>635</td>
<td>74,0 %</td>
<td>70,5 %</td>
<td>77,3 %</td>
<td>5,0 %</td>
</tr>
<tr>
<td>13: nBCC thick</td>
<td>95</td>
<td>175</td>
<td>64,6 %</td>
<td>57,2 %</td>
<td>71,3 %</td>
<td>7,4 %</td>
</tr>
<tr>
<td>14/16: BCC infiltrative</td>
<td>65</td>
<td>87</td>
<td>51,7 %</td>
<td>41,4 %</td>
<td>61,9 %</td>
<td>2,3 %</td>
</tr>
<tr>
<td>21-23: All AK</td>
<td>159</td>
<td>601</td>
<td>61,6 %</td>
<td>57,6 %</td>
<td>65,4 %</td>
<td>3,7 %</td>
</tr>
<tr>
<td>21: AK thin</td>
<td>142</td>
<td>427</td>
<td>62,8 %</td>
<td>58,1 %</td>
<td>67,2 %</td>
<td>2,1 %</td>
</tr>
<tr>
<td>22: AK medium</td>
<td>63</td>
<td>139</td>
<td>56,1 %</td>
<td>47,8 %</td>
<td>64,1 %</td>
<td>8,6 %</td>
</tr>
<tr>
<td>23: AK thick</td>
<td>24</td>
<td>35</td>
<td>68,6 %</td>
<td>52,0 %</td>
<td>81,4 %</td>
<td>2,9 %</td>
</tr>
<tr>
<td>30: SCC</td>
<td>7</td>
<td>12</td>
<td>16,7 %</td>
<td>4,7 %</td>
<td>44,8 %</td>
<td>0,0 %</td>
</tr>
<tr>
<td>40: Bowen</td>
<td>6</td>
<td>9</td>
<td>88,9 %</td>
<td>56,5 %</td>
<td>98,0 %</td>
<td>11,1 %</td>
</tr>
</tbody>
</table>

Avr. no of Treatm. is the average number of treatments per lesion.

### Table 2

<table>
<thead>
<tr>
<th>Treatment results</th>
<th>CR</th>
<th>To surg/rd</th>
<th>Surg /Rad: 95% Conf.int.</th>
<th>To PDT</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-13: All BCC</td>
<td>78,6 %</td>
<td>2,4 %</td>
<td>1,8 %</td>
<td>3,2 %</td>
<td>17,8 %</td>
</tr>
<tr>
<td>11: sBCC</td>
<td>83,8 %</td>
<td>1,1 %</td>
<td>0,7 %</td>
<td>2,0 %</td>
<td>14,4 %</td>
</tr>
<tr>
<td>12: nBCC thin</td>
<td>74,0 %</td>
<td>2,5 %</td>
<td>1,6 %</td>
<td>4,1 %</td>
<td>21,6 %</td>
</tr>
<tr>
<td>13: nBCC thick</td>
<td>64,6 %</td>
<td>9,1 %</td>
<td>5,7 %</td>
<td>14,3 %</td>
<td>24,6 %</td>
</tr>
<tr>
<td>14/16: BCC infiltrative</td>
<td>51,7 %</td>
<td>12,6 %</td>
<td>7,2 %</td>
<td>21,2 %</td>
<td>33,3 %</td>
</tr>
<tr>
<td>21-23: All AK</td>
<td>61,6 %</td>
<td>1,5 %</td>
<td>0,8 %</td>
<td>2,8 %</td>
<td>29,6 %</td>
</tr>
<tr>
<td>21: AK thin</td>
<td>62,8 %</td>
<td>0,9 %</td>
<td>0,4 %</td>
<td>2,4 %</td>
<td>30,0 %</td>
</tr>
<tr>
<td>22: AK medium</td>
<td>56,1 %</td>
<td>3,6 %</td>
<td>1,5 %</td>
<td>8,1 %</td>
<td>30,9 %</td>
</tr>
<tr>
<td>23: AK thick</td>
<td>68,6 %</td>
<td>0,0 %</td>
<td>0,0 %</td>
<td>9,9 %</td>
<td>20,0 %</td>
</tr>
<tr>
<td>30: SCC</td>
<td>16,7 %</td>
<td>75,0 %</td>
<td>46,8 %</td>
<td>91,1 %</td>
<td>8,3 %</td>
</tr>
<tr>
<td>40: Bowen</td>
<td>88,9 %</td>
<td>11,1 %</td>
<td>2,0 %</td>
<td>43,5 %</td>
<td>0,0 %</td>
</tr>
</tbody>
</table>
### Table 3

<table>
<thead>
<tr>
<th>Cosmetic outcome</th>
<th>Excellent</th>
<th>Good</th>
<th>Fair/Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11-13: All BCC</strong></td>
<td>55.9 %</td>
<td>42.3 %</td>
<td>1.9 %</td>
</tr>
<tr>
<td>11: sBCC</td>
<td>55.9 %</td>
<td>41.9 %</td>
<td>2.2 %</td>
</tr>
<tr>
<td>12: nBCC thin</td>
<td>58.9 %</td>
<td>40.1 %</td>
<td>1.0 %</td>
</tr>
<tr>
<td>13: nBCC thick</td>
<td>44.4 %</td>
<td>52.9 %</td>
<td>2.6 %</td>
</tr>
<tr>
<td>14/16: BCC infiltrative</td>
<td>40.0 %</td>
<td>54.3 %</td>
<td>5.7 %</td>
</tr>
<tr>
<td><strong>21-23: All AK</strong></td>
<td><strong>57.1 %</strong></td>
<td><strong>42.1 %</strong></td>
<td><strong>0.8 %</strong></td>
</tr>
<tr>
<td>21: AK thin</td>
<td>55.6 %</td>
<td>43.6 %</td>
<td>0.8 %</td>
</tr>
<tr>
<td>22: AK medium</td>
<td>57.0 %</td>
<td>42.1 %</td>
<td>0.9 %</td>
</tr>
<tr>
<td>23: AK thick</td>
<td>75.9 %</td>
<td>24.1 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>30: SCC</td>
<td>66.7 %</td>
<td>33.3 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>40: Bowen</td>
<td>62.5 %</td>
<td>37.5 %</td>
<td>0.0 %</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Avr. no of Treas</th>
<th>1. Treat</th>
<th>2. Treat</th>
<th>3. Treat</th>
<th>≥4 Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11-13: All BCC</strong></td>
<td>1.4</td>
<td>87.5 %</td>
<td>9.5 %</td>
<td>2.3 %</td>
<td>0.8 %</td>
</tr>
<tr>
<td>11: sBCC</td>
<td>1.3</td>
<td>91.6 %</td>
<td>7.0 %</td>
<td>0.9 %</td>
<td>0.6 %</td>
</tr>
<tr>
<td>12: nBCC thin</td>
<td>1.5</td>
<td>85.7 %</td>
<td>10.2 %</td>
<td>3.6 %</td>
<td>0.4 %</td>
</tr>
<tr>
<td>13: nBCC thick</td>
<td>1.9</td>
<td>62.8 %</td>
<td>25.7 %</td>
<td>8.0 %</td>
<td>3.5 %</td>
</tr>
<tr>
<td>14/16: BCC infiltrative</td>
<td>2.3</td>
<td>60.0 %</td>
<td>26.7 %</td>
<td>8.9 %</td>
<td>4.4 %</td>
</tr>
<tr>
<td><strong>21-23: All AK</strong></td>
<td>1.5</td>
<td>85.1 %</td>
<td>13.2 %</td>
<td>1.6 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>21: AK thin</td>
<td>1.5</td>
<td>86.9 %</td>
<td>11.9 %</td>
<td>1.1 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>22: AK medium</td>
<td>1.7</td>
<td>80.8 %</td>
<td>16.7 %</td>
<td>2.6 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>23: AK thick</td>
<td>1.5</td>
<td>79.2 %</td>
<td>16.7 %</td>
<td>4.2 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>30: SCC</td>
<td>2.0</td>
<td>0.0 %</td>
<td>0.0 %</td>
<td>100.0 %</td>
<td>0.0 %</td>
</tr>
<tr>
<td>40: Bowen</td>
<td>2.1</td>
<td>75.0 %</td>
<td>12.5 %</td>
<td>0.0 %</td>
<td>12.5 %</td>
</tr>
<tr>
<td>CR: 95%</td>
<td>CR</td>
<td>Confidence int.</td>
<td>No of lesions</td>
<td>CR: 95%</td>
<td>CR</td>
</tr>
<tr>
<td>---------</td>
<td>----</td>
<td>----------------</td>
<td>---------------</td>
<td>---------</td>
<td>----</td>
</tr>
<tr>
<td>11:13: All BCC</td>
<td>&lt; 10 mm</td>
<td>70 %</td>
<td>64.0 %</td>
<td>218</td>
<td>92 %</td>
</tr>
<tr>
<td></td>
<td>10-29 mm</td>
<td>55 %</td>
<td>48.3 %</td>
<td>224</td>
<td>84 %</td>
</tr>
<tr>
<td></td>
<td>&gt;=30 mm</td>
<td>45 %</td>
<td>38.4 %</td>
<td>29</td>
<td>70 %</td>
</tr>
<tr>
<td>11: BCC</td>
<td>&lt; 10 mm</td>
<td>73 %</td>
<td>63.3 %</td>
<td>113</td>
<td>80 %</td>
</tr>
<tr>
<td></td>
<td>10-29 mm</td>
<td>63 %</td>
<td>50.4 %</td>
<td>97</td>
<td>80 %</td>
</tr>
<tr>
<td></td>
<td>&gt;=30 mm</td>
<td>47 %</td>
<td>35.8 %</td>
<td>15</td>
<td>70 %</td>
</tr>
<tr>
<td>12:8:13: nBCC</td>
<td>&lt; 10 mm</td>
<td>68 %</td>
<td>59.4 %</td>
<td>103</td>
<td>87 %</td>
</tr>
<tr>
<td></td>
<td>10-29 mm</td>
<td>63 %</td>
<td>46.0 %</td>
<td>137</td>
<td>73 %</td>
</tr>
<tr>
<td></td>
<td>&gt;=30 mm</td>
<td>43 %</td>
<td>21.4 %</td>
<td>14</td>
<td>70 %</td>
</tr>
<tr>
<td>21:23: All AK</td>
<td>&lt; 10 mm</td>
<td>64 %</td>
<td>55.1 %</td>
<td>117</td>
<td>85 %</td>
</tr>
<tr>
<td></td>
<td>10-29 mm</td>
<td>65 %</td>
<td>48.1 %</td>
<td>228</td>
<td>79 %</td>
</tr>
<tr>
<td></td>
<td>&gt;=30 mm</td>
<td>41 %</td>
<td>30.8 %</td>
<td>78</td>
<td>67 %</td>
</tr>
<tr>
<td>21:22: Thin or moderate AK</td>
<td>&lt; 10 mm</td>
<td>63 %</td>
<td>54.4 %</td>
<td>115</td>
<td>88 %</td>
</tr>
<tr>
<td></td>
<td>10-29 mm</td>
<td>66 %</td>
<td>49.1 %</td>
<td>215</td>
<td>79 %</td>
</tr>
<tr>
<td></td>
<td>&gt;=30 mm</td>
<td>42 %</td>
<td>31.2 %</td>
<td>77</td>
<td>67 %</td>
</tr>
</tbody>
</table>

Confidence intervals for the proportions with complete cases were calculated using the Wilcoxon rank sum method without bootstrap correction.

(Reeves AG, Statistics in Medicine 17: 857–872, 1998.)
Kaplan Meier plots

BCC: All recurrences

BCC: Surg/Rad

AK: All recurrences

AK: Surg/Rad
Reference List


