Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions

S.C. Flohil,[1] C.M. Proby,[3] A.D. Forrest,[3] S. van Tiel,[1] O. Saksela,[4] S. Pitkänen,[4] T. Ahti,[4] R. Micallef[5] and E. de Vries[1,2,6] on behalf of the EPIDERM Group*

[1]Department of Dermatology, Erasmus MC University Center, Rotterdam, The Netherlands
[2]Department of Public Health, Erasmus MC University Center, Rotterdam, The Netherlands
[3]Department of Dermatology, Ninewells Hospital and Medical School, University of Dundee, Dundee, U.K.
[4]Department of Dermatology and Allergology, Helsinki University Central Hospital, Helsinki, Finland
[5]Malta National Cancer Registry, Department of Health Information and Research, Guardamangia, Malta
[6]Comprehensive Cancer Center South, Eindhoven, The Netherlands

Summary

Background Limited data are available on how often basal cell carcinomas (BCCs) are clinically diagnosed without histological confirmation and how they are treated.
Objectives Within the framework of the EPIDERM project, an audit was conducted in four European countries to study the occurrence of clinically diagnosed BCCs without histological confirmation and to investigate how these are treated.
Methods In the Netherlands, Scotland, Finland and Malta studies were performed within different timeframes. Patients with one or more BCC(s) were selected and the number of clinically diagnosed BCCs without histological confirmation and their treatment was investigated by (manually) reviewing the (electronic) patient records and checking the (hospital) pathology databases to find evidence of histological confirmation.
Results In the Netherlands, 1089 patients with a first histologically confirmed BCC developed 1974 BCCs of which 1833 (92·9%) were histologically confirmed and 141 (7·1%) were not. A 4-month retrospective study conducted in Scotland selected 294 patients with 344 BCCs; 306 (89·0%) were histologically confirmed and 38 (11·0%) were not. A 3-month prospective study performed at the same centre in Scotland identified 44 patients who developed 58 BCCs; 44 (75·9%) of these were histologically confirmed and 14 (24·1%) were not. In Finland, there were 701 patients who developed 977 BCCs, of which 807 (82·6%) were histologically and 170 (17·4%) nonhistologically confirmed. In Malta, there were 420 patients with 477 BCCs. Only three (0·7%) of them were clinically diagnosed without histological confirmation. In the Netherlands and Finland, clinically diagnosed BCCs without histological confirmation were most often treated with cryotherapy, whereas in Scotland 5% imiquimod cream was the preferred treatment modality.
Conclusions Although the frequency of clinically diagnosed BCCs without histological confirmation differed between the four European regions (range 0·7–24·1%), this confirms that the burden of BCC in Europe is underestimated when based on data from pathology and/or cancer registries.

Correspondence
Esther de Vries.
E-mail: e.devries@erasmusmc.nl

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Conflicts of interest
None declared.

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Basal cell carcinoma (BCC) is the most common cancer among caucasians and its incidence is increasing worldwide.[1–5] The growing number of patients with a history of BCC and/or multiple BCC, together with the costs related to treatment and follow-up, make this skin cancer an increasingly important public health problem.[6,7]

Most incidence and prevalence rates reported in the literature for BCC are based on data from cancer registries. However, only a few population-based cancer registries register BCC information and most of them only collect the first histologically confirmed BCC per patient.[3,8] The large numbers involved, the high prevalence of multiple BCCs within one

patient on day of diagnosis, the practical problems in coding 'multiple BCCs', the number of cancer registry clerks needed and the difficulties in accessing private clinics all prevent many cancer registries from collecting (additional) BCC information.

Therefore, the exact size of the BCC problem is largely unknown as a significant proportion of patients with BCC develops multiple BCC over time and physicians may treat clinically diagnosed BCC without histological confirmation. In the last decade, the latter has become more common with the introduction of new noninvasive treatments such as photodynamic therapy and 5% imiquimod cream, which often have better cosmetic outcome than standard surgery.[9] Besides a previous Dutch report, there are limited data on how often BCC gets diagnosed and treated without histological verification and whether there are differences across Europe.[10] Lack of histological confirmation impedes registry of BCC in cancer registries and consequently BCC incidence and prevalence data will be lower than experienced by dermatologists.

Within the framework of the EPIDERM project, an audit was conducted in four European countries (the Netherlands, Scotland, Finland and Malta) to investigate the occurrence of clinically diagnosed BCC without histological confirmation.[11]

Materials and methods

The Netherlands

This study has been described before.[10] In short, a retrospective study was performed. All 1290 patients from four participating hospitals with a first histologically diagnosed BCC in 2004 were extracted from Eindhoven Cancer Registry (ECR).[2] These patients were linked to PALGA, the Dutch nationwide network and registry of histo- and cytopathology.[12] The 1290 extracted patients were followed for subsequent histologically confirmed BCCs until 1 November 2010 or date of death, whichever came first. BCC case definition has been described before.[7] Twenty-nine patients could not be retrieved from PALGA, 23 already had a histologically confirmed BCC prior to 2004, 149 had incomplete or missing patients records or were never seen by a dermatologist; therefore 1089 patients were considered eligible for this study. Among these patients, the number of nonhistologically confirmed BCCs and the treatment methods for histologically and nonhistologically confirmed BCCs were registered by manually reviewing the patient records of these individuals between 14 January and 28 March 2011.

Scotland

A 4-month retrospective study and a 3-month prospective study were carried out in the dermatology department of Ninewells Hospital, Dundee, to estimate the proportion of BCCs seen that were clinically diagnosed without histological confirmation and therefore never recorded on a histopathology or cancer registry database. Clinical details in the form of a general practitioner letter are registered in an electronic clinical database (Dermabase, NHS, Tayside, Scotland, UK) for all patients attending the department of dermatology. A Dermabase record is generated after every dermatology appointment and therefore an individual patient may have multiple Dermabase records. This Dermabase record includes a diagnosis recorded either as 'active diagnosis' or 'inactive diagnosis'. In case there were deficiencies in tracking all BCCs using Dermabase, a prospective study was conducted as well, whereby all patients attending a selection of outpatient clinics were audited over a 3-month period.

Four-month retrospective study

Electronic patient records in Dermabase with an active diagnosis of 'basal cell carcinoma' were identified between 1 September and 31 December 2009, representing 310 patients. For each patient, the hospital pathology database was searched from 1 September 2009 until 31 May 2010, allowing five additional months to accommodate delays in surgical treatment. Nine patients were excluded because neither pathology data nor Dermabase letters were available, or because the Dermabase entries represented first appointments that were not attended. Two patients were excluded because the diagnosis of BCC was in fact 'inactive' and five patients because they were recorded under 'basal cell carcinoma' when they had a diagnosis of basal cell papilloma. In total, 294 patients with an active diagnosis of BCC were included in this study. For those with and without evidence of histological confirmation, Dermabase was interrogated to find the method of treatment. No information was collected on the histopathological subtypes and anatomical localization of the included BCCs.

Three-month prospective study

Seventy-seven patients attending dermatology clinics at Ninewells Hospital, Dundee between 11 January and 11 April 2010 and identified as presenting with a BCC were studied. Forty-four of these 77 had one or more BCC(s) correctly diagnosed at that clinic appointment and were included in the audit, whereas the remainder had the initial clinical diagnosis of BCC made prior to the study period and were therefore excluded. For each patient, the pathology database was searched between 10 January and 31 May 2010 to look for receipt of a BCC specimen after the appointment at which the clinical diagnosis of BCC was made. For those with and without evidence of histological confirmation, Dermabase was interrogated to find the method of treatment. No information was collected on the histopathological subtypes and anatomical localization of the included BCCs.

Finland

Between 1 October and 31 December 2009 a retrospective and between 1 January and 31 March 2010 a prospective study was performed at the department of dermatology of the Skin and Allergy Hospital, Helsinki University Central Hospital in Helsinki (the regional centre for dermato-oncology). All

skin cancer patients who visited the department of dermatology during these 6 months were included. During this study period, 701 patients were diagnosed or treated for one or more BCC(s). In June 2010 the hospital pathology database was checked to verify histologically confirmed BCCs, allowing two additional months to accommodate delays in surgical treatment. In the retrospective part of the study the patient records were investigated to find the method of treatment; in the prospective part the method of treatment was recorded after the appointment. No information was collected on the histopathological subtypes and anatomical localization of the included BCCs.

Malta

Between 1 October 2009 and 31 March 2010, all hospitals and clinics both public and private (Mater Dei Hospital, St James Hospital, St Philip's Hospital, Dr Deguara's laboratory, the oncology department and St Mark's laboratory) were visited to collect and count all patients with a BCC between 1 January and 31 December 2009, by going through all hospital pathology databases, patient records, oncology reports and notifications. When a BCC was mentioned in the patient record, oncology report or in a notification, but not found in the pathology database, it was considered a clinically diagnosed BCC without histological confirmation. When a patient presented with multiple BCC on the day of diagnosis, only the localization of one BCC was registered in the Maltese Cancer Registry. If available within the hospital pathology database, the histopathological subtype of the BCC was registered.

Results

The Netherlands

After combining the data from PALGA, ECR and the hospital patient records, 1974 BCCs were diagnosed among 1089 patients.[10] Overall, the patients contributed 6253 person-years of follow-up. The mean ± SD age at date of first histologically confirmed BCC was 65·0 ± 14·0 years. The male/female ratio was 1 : 1. Of the 1974 BCCs, 1833 (92·9%) were histologically and 141 (7·1%) were nonhistologically confirmed (Table 1).

Surgical excision (83·6%) was the most performed treatment modality, followed by cryotherapy (6·1%) and photodynamic therapy (2·8%). This distribution was the same for histologically confirmed BCCs (Table 2). For nonhistologically confirmed BCCs, cryotherapy (65·2%) was the predominant treatment, followed by photodynamic therapy (23·4%), 5-fluorouracil (4·3%) and imiquimod cream (4·3%).

Scotland

Four-month retrospective study

In total, 344 BCCs were recorded in 294 patients: 156 (53·1%) men and 138 (46·9%) women. The mean ± SD age

Table 1 Number of histologically and nonhistologically confirmed basal cell carcinomas (BCCs) in four European regions

Country	Study design	Time period for patient selection	Total number of patients	Total number of BCCs	Histologically confirmed BCCs	Nonhistologically confirmed BCCs	Percentage of nonhistologically confirmed BCCs	Specifics
Netherlands	Retrospective	1 January 2004–31 December 2004	1089	1974	1833	141	7·1	The first 1089 patients with a first histologically confirmed BCC in 2004 were selected in four hospitals and followed until 1 November 2011 or date of death
Scotland	Retrospective	1 September 2009–31 December 2009	294	344	306	38	11·0	All patients with a Dermabase electronic record giving 'active diagnosis' of BCC were selected
	Prospective	11 January 2010–11 April 2010	44	58	44	14	24·1	All patients attending the Monday morning dermatology clinic at Ninewells Hospital were audited. All audited patients with a diagnosis of BCC were selected
Finland	Retrospective/ prospective	1 October 2009–31 March 2010	701	977	807	170	17·4	A 3-month retrospective study and a 3-month prospective study were conducted. All patients with a diagnosis of BCC who visited the department of dermatology were selected
Malta	Retrospective	1 January 200–31 December 2009	420	447	444	3	0·7	All hospitals and clinics in Malta were visited to collect and count all patients with a BCC

Table 2 Dutch study: treatment per basal cell carcinoma (BCC)

Treatment	Total number BCCs (n = 1974), n (%)	Histologically confirmed BCCs (n = 1833), n (%)	Nonhistologically confirmed BCCs (n = 141), n (%)
Surgical excision	1650 (83·6)	1650 (90·0)	–
Mohs micrographic surgery	20 (1·0)	20 (1·1)	–
Cryotherapy	121 (6·1)	29 (1·6)	92 (65·2)
Photodynamic therapy	56 (2·8)	23 (1·3)	33 (23·4)
5-Fluorouracil cream	10 (0·5)	4 (0·2)	6 (4·3)
Imiquimod cream	8 (0·4)	2 (0·1)	6 (4·3)
Diclofenac gel	–	–	–
Curettage	14 (0·7)	14 (0·8)	–
Tretinoin	–	–	–
Radiotherapy	–	–	–
Expectative/not treated	4 (0·2)	2 (0·1)	2 (1·4)
Missing	91 (4·6)	89 (4·9)	2 (1·4)

at date of diagnosis was 70·5 ± 12·4 years. Of the 344 BCCs, 306 (89·0%) were histologically confirmed and 38 (11·0%) were not confirmed histologically (Table 1).

Most BCCs were treated surgically (87·2%), followed by imiquimod cream (4·9%) and cryotherapy (2·3%). All but one histologically confirmed BCC were treated with simple surgical excision or Mohs micrographic surgery. One was treated with radiotherapy. For nonhistologically confirmed BCC, imiquimod cream (44·7%) was the preferred treatment method, followed by cryotherapy (21·1%) and 5-fluorouracil cream (Table 3).

Three-month prospective study

The 44 patients diagnosed with a BCC between 11 January and 11 April 2010 had a total of 58 BCCs. The patients comprised 24 (54·5%) men and 20 (45·5%) women. The mean ± SD age at diagnosis was 71·2 ± 10·7 years. Of the 58 BCCs, 44 (75·9%) were histologically and 14 (24·1%) were not histologically confirmed (Table 1). The mean ± SD number of BCCs diagnosed at the date of appointment was 1·3 ± 0·82 (range 1–5).

Taking the retrospective and prospective audits together, most BCCs were treated surgically (86·8%), followed by imiquimod cream (7·0%) (data not shown). All histologically confirmed BCCs were treated with surgical excision. For BCCs without histological confirmation, imiquimod cream (53·8%) was the preferred treatment, followed by cryotherapy (15·4%) and overall for 10 BCCs it was decided to observe and not to treat because the patients were elderly and frail.

Finland

Among the 701 included patients there were 327 (46·6%) men and 374 (53·4%) women. In total, they developed 977 BCCs during the study period. The mean ± SD age at diagnosis was 72·3 ± 12·8 years. Of the total 977 BCCs, 807 were histologically confirmed (82·6%) and 170 (17·4%) were nonhistologically confirmed (Table 1).

Most BCCs were treated with standard surgical excision (57·1%), followed by cryotherapy (28·4%) and photodynamic therapy (11·8%). For three patients the therapy was missing because they died before they were treated. For histologically confirmed BCC, the distribution was similar. Nonhistologically

Table 3 Scottish 4-month retrospective study: treatment per basal cell carcinoma (BCC)

Treatment	Total number BCCs (n = 344), n (%)	Histologically confirmed BCCs (n = 306), n (%)	Nonhistologically confirmed BCCs (n = 38), n (%)
Surgical excision	300 (87·2)	300 (98·1)	–
Mohs micrographic surgery	5 (1·5)	5 (1·6)	–
Cryotherapy	8 (2·3)	–	8 (21·1)
Photodynamic therapy	–	–	–
5-Fluorouracil cream	5 (1·5)	–	5 (13·2)
Imiquimod cream	17 (4·9)	–	17 (44·7)
Diclofenac gel	1 (0·3)	–	1 (2·6)
Curettage	–	–	–
Tretinoin	–	–	–
Radiotherapy	1 (0·3)	1 (0·3)	–
Expectative/not treated	7 (2·0)	–	7 (18·4)
Missing	–	–	–

Table 4 Finnish study: treatment per basal cell carcinoma (BCC)

Treatment	Total number BCCs (n = 977), n (%)	Histologically confirmed BCCs (n = 807), n (%)	Nonhistologically confirmed BCCs (n = 170), n (%)
Surgical excision	558 (57·1)	558 (69·1)	–
Mohs micrographic surgery	23 (2·4)	23 (2·9)	–
Cryotherapy	278 (28·4)	147 (18·2)	131 (77·1)
Photodynamic therapy	115 (11·8)	76 (9·4)	39 (22·9)
5-Fluorouracil cream	–	–	–
Imiquimod cream	–	–	–
Diclofenac gel	–	–	–
Curettage	–	–	–
Tretinoin	–	–	–
Radiotherapy	–	–	–
Expectative/not treated	–	–	–
Missing	3 (0·3)	3 (0·4)	–

confirmed BCCs were most often treated with cryotherapy (77·1%) and the remainder with photodynamic therapy (22·9%) (Table 4).

Malta

Of the 420 included patients, there were 256 (61·0%) men and 264 (39·0%) women. In total, they developed 447 BCCs. The mean ± SD age at diagnosis was 65·9 ± 13·8 years. Only three (0·7%) of the 447 tumours were diagnosed clinically without histological confirmation (Table 1). The most common site was the head and neck area (n = 256), followed by trunk (n = 67), upper extremities and shoulders (n = 28) and lower extremities (n = 22). This excluded 47 BCCs for which site was not registered. The histopathological subtype was unspecified in 412 (92·2%) BCCs. Of the remainder, 30 BCCs (6·7%) were superficial, while five (1·1%) had infiltrative growth pattern. No detailed information was available on the treatments used.

Discussion

The frequency of clinically diagnosed BCC treated without histological confirmation differed between the four European regions (range 0·7–24·1%), the highest proportion being observed in the small prospective study in Dundee, Scotland. This contrasts with the findings of a previous study in 1997 from Glasgow (3·8%), which suggested that dermatologists rarely treat clinically suspicious tumours without histological proof of diagnosis.[13] Either practice varies significantly across Scotland or (more likely) dermatological practice has changed with the advent and greater availability of nonsurgical treatments such as imiquimod cream and photodynamic therapy. A previous study among French dermatologists found that 14·1% of the clinically suspicious BCCs were not histologically confirmed, which is not dissimilar from the percentages observed in Finland (17·4%) and in the retrospective study performed in Dundee, Scotland (11·0%).[14]

Malta, with < 1%, had the lowest percentage of BCCs diagnosed without histological confirmation. After interviewing the Maltese dermatologists (n = 12) about their practices of treating patients, they all confirmed that it was custom to verify all clinically suspicious BCCs histologically with biopsy and/or surgical excision. In the Netherlands, the number of subsequent clinically diagnosed BCCs without histological confirmation (developed during a mean follow-up period of almost 6 years) was investigated in patients with a prior histologically confirmed BCC. This differs from the study design of the other three European regions in which there was no selection of patients who already had a first, histologically confirmed BCC. Besides dissimilarities in practice and study design, also differences in insurance reimbursements between the European regions may account for the wide variation found in the percentage of clinically diagnosed BCC. However, the latter should not be such a large factor as in all four European regions BCCs do not need histological confirmation for patients to receive insurance reimbursements (based on personal communications with Sari Pitkänen, Rita Micallef and Esther de Vries).

This study confirms an underestimate of the absolute BCC number based on histologically confirmed BCC alone and illustrates that previous studies based on cancer registries and/or pathology databases will have underestimated the true BCC burden. Therefore, health care policy makers (especially in the Netherlands, Scotland and Finland) should incorporate the proportion of BCCs treated without histological confirmation into their calculations (in Malta this seems to be a less of a problem). This is especially important as in all four European regions the ratio of dermatologists to the total population is dramatically low, ranging from 1 to 3·6 per 100 000 inhabitants.[15]

In the Netherlands, Scotland and Finland, the preferred treatment modality for histologically confirmed BCC is standard surgical excision, followed by cryotherapy (the Netherlands and Finland) and imiquimod cream (Scotland). No detailed data were available for Malta; however, it seems that most are surgically excised (based on personal communication). In the Netherlands and Finland, for clinically diagnosed BCC without histology, cryotherapy was the treatment used

most often, followed by photodynamic therapy. In Scotland, imiquimod was the preferred treatment, then cryotherapy.

A limitation of this study was the methodological differences between the substudies performed in the four European regions. The study design was notably different in the Netherlands, where patients with a first histologically confirmed BCC in 2004 from four dermatology departments were followed for subsequent clinically diagnosed BCCs. In Scotland and Finland, the audits were performed at hospital level, while in Malta all hospitals and clinics were investigated for clinically diagnosed BCC. This was possible for Malta because of its small size and contained geographical region. In addition, the cancer registry in Malta recorded all BCCs for which there was a histological diagnosis. Another important variation was the size of the study populations. Although the prospective Scottish study observed the highest percentage of BCC diagnosed clinically without histology, this study also had the smallest study population, which may have inflated the proportion. None the less, the greater proportion of BCCs without histological diagnosis identified in this prospective study compared with the retrospective study from the same department demonstrates the importance of prospective investigation. This potential problem of missed BCCs in retrospective studies was largely avoided by interrogating hospital case notes for all included patients in the other substudies.

A French medical cost analysis study described that when histological confirmation was performed in clinically suspicious superficial BCCs, a diagnosis of BCC was confirmed in 85% of cases.[16] Additionally, a study from the U.S.A. suggested that the positive predictive value of the clinical diagnosis of a BCC is only 80%, and that is when the dermatologist is reasonably confident about the diagnosis.[17] Therefore, the observed percentages of clinically diagnosed BCC without histological confirmation within this study may be an overestimate. These limitations and the differences identified between the substudies from four different European regions suggest that our data are an estimate for the number of clinically diagnosed BCC and may not be representative for Europe as a whole.

In conclusion, limited data are available about the frequency of clinically diagnosed BCCs without histological confirmation and their treatment. Although the percentage of nonhistologically confirmed BCCs differed between the four European regions, our findings confirm that the burden of BCCs is underestimated when based solely on data from pathology records and/or cancer registries.

What's already known about this topic?

- Cancer registry data only include histologically confirmed tumours.
- It is not known how often basal cell carcinomas (BCCs) are diagnosed without histological confirmation nor how these histologically unconfirmed BCC are treated.

What does this study add?

- The frequency of BCC diagnosed without histological confirmation differed widely between four European regions (the Netherlands, Scotland, Finland and Malta), ranging from 0·7% to 24·1%.
- In the Netherlands and Finland, clinically diagnosed BCCs without histological confirmation were most often treated with cryotherapy, whereas in Scotland 5% imiquimod cream was the preferred treatment modality.

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Appendix 1

Other members of the EPIDERM group involved in this study are as follows. Erasmus MC University Medical Center Rotterdam, the Netherlands: Jan Willem Coebergh; First and Second Departments of Dermatology and Venereology, Aristotle University, Thessaloniki, Greece: Dimitrios Ioannides, Dimitrios Kalabalikis, Dimitrios Sotiriadis, Myrto Trakatelli; Dermatology Unit, Hospital Universitario Virgen Macarena, Seville, Spain: Lara Ferrandiz, Andres Ruiz-de-Casas, David Moreno-Ramirez; Department of Dermatology, Sir Paul Boffa Hospital, Floriana, Malta: Sue Aquilina, Lawrence Scerri, Charmaine Apap; Department of Dermatology and Allergology, Helsinki University Central Hospital, Helsinki, Finland: Annamari Ranki; Department of Dermatology, Skin Cancer Center, Charité-Universitätsmedizin Berlin, Germany: Eggert Stockfleth, Martina Ulrich, Birgit Hinrichs, Efthymios Altsitsiadis; Department of Dermatology, University of Modena and Reggio Emilia, Italy: Cristina Magnoni, Chiara Fiorentini; Department of Dermatology and Venereology, Medical University of Warsaw, Warsaw, Poland: Slawomir Majewski; Skin Tumour Laboratory, Medical Research Institute, Ninewells Hospital and Medical School, Dundee, U.K.: Leaca Crawford, Colin Fleming, James Gibbs; Research Group Marketing, Faculty of Business and Economics, Katholieke Universiteit Leuven, Belgium: Efthymios Altsitsiadis.