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POSITION STATEMENT

# Position statement on classification of basal cell carcinomas. Part 1: unsupervised clustering of experts as a way to build an operational classification of advanced basal cell carcinoma based on pattern recognition

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## Abstract

**Background** No simple classification system has emerged for 'advanced basal cell carcinomas', and more generally for all difficult-to-treat BCCs (DTT-BCCs), due to the heterogeneity of situations, TNM inappropriateness to BCCs, and different approaches of different specialists.

**Objective** To generate an operational classification, using the unconscious ability of experts to simplify the great heterogeneity of the clinical situations into a few relevant groups, which drive their treatment decisions.

**Method** Non-supervised independent and blinded clustering of real clinical cases of DTT-BCCs was used. Fourteen international experts from different specialties independently partitioned 199 patient cases considered 'difficult to treat' into as many clusters they want (≤10), choosing their own criteria for partitioning. Convergences and divergences between the individual partitions were analyzed using the similarity matrix, K-mean approach, and average silhouette method.

**Results** There was a rather consensual clustering of cases, regardless of the specialty and nationality of the experts. Mathematical analysis showed that consensus between experts was best represented by a partition of DTT-BCCs into five clusters, easily recognized *a posteriori* as five clear-cut patterns of clinical situations. The concept of 'locally advanced' did not appear consistent between experts.

**Conclusion** Although convergence between experts was not granted, this experiment shows that clinicians dealing with BCCs all tend to work by a similar pattern recognition based on the overall analysis of the situation. This study thus provides the first consensual classification of DTT-BCCs. This experimental approach using mathematical analysis of independent and blinded clustering of cases by experts can probably be applied to many other situations in dermatology and oncology.



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## Conflict of interest

This work was presented during the 15th EADO Congress 24-27 April 2019, Paris, France. Dr. Grob reports personal fees from BMS, MSD, Novartis, Roche, Amgen, Pierre Fabre, Sanofi, Merck, Pfizer and Sunpharma, outside the submitted work. Dr. Guminski reports non-financial support from Sun Pharma, during the conduct of the study, and non-financial support from Sun Pharma and personal fees from Regeneron, BMS, Merck KgA and Sanofi, outside the submitted work. Dr. Malvehy reports grants and personal fees from Sunpharma corp. and grants from Roche, outside the submitted work. Dr. Basset-Seguin reports personal fees from Sun Pharma, during the conduct of the study, and personal fees from Novartis, BMS, Galderma, Leo Pharma and from Pierre Fabre, outside the submitted work. Dr. Bertrand has nothing to disclose. Dr. Fernandez-Penas reports personal fees from Roche and Sun Pharma, during the conduct of the study and personal fees from Sanofi, Lilly, Janssen, Novartis, Abbvie, UCB, Merck, Amgen, MSD and Leo, outside the submitted work. Dr. Kaufmann reports grants from Janssen, Lilly,MSD, Novartis, Regeneron, and from Roche, outside the submitted work. Dr. Zalaudek reports personal fees and other support from Sunpharma, Novartis Oncology, MSD and Sanofi Genzyme, outside the submitted work. Dr. Gaudy-Marqueste reports personal fees from BMS, non-financial support from Janssen, BMS and from Pierre Fabre, and personal fees from Roche, outside the submitted work. Dr. Fargnoli reports personal fees from Roche, personal fees from Sunpharma, during the conduct of the study, and grants and personal fees from Almirall, grants and personal fees from Leo Pharma, personal fees from Janssen, grants and personal fees from Novartis, personal fees from Lilly, grants and personal fees from Sanofi, personal fees from UCB, grants and personal fees from Abbvie, personal fees from Celgene, personal fees from Pierre Fabre, grants and personal fees from Galderma, personal fees from Mylan, and personal fees from Medac Pharma, outside the submitted work. Dr. Tagliaferri reports a patent TIMER applicator pending. B. Fertil has nothing to disclose. Dr. Del Marmol has nothing to disclose. Professor Stratigos reports personal fees and/or research support from Novartis, Roche, BMS, Abbvie, Sanofi, Regeneron and Genesis Pharma, outside the submitted work. Dr. Garbe reports grants and personal fees from BMS, personal fees from MSD, grants and personal fees from NeraCare, grants and personal fees from Novartis, personal fees from Philogen, grants and personal fees from Roche, and grants and personal fees from Sanofi, outside the submitted work. Dr. Peris reports personal fees from Roche and Sun Pharma, during the conduct of the study, and personal fees from Abbvie, Allmiral, Biogen, Lilly, Celgene, Galderma, Leo Pharma, Novartis, Pierre Fabre, Sanofi, Sandoz, and Janssen, outside the submitted work.

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## Introduction

Basal-cell carcinomas (BCCs) are one of the most frequent cancers, and most of them are easy to manage by surgery with an excellent prognosis. Distant or regional metastases are extremely rare. However, very complex situations can result either from the natural course of aggressive subtypes of BCCs and/or from a succession of therapeutic compromises responsible for multiple recurrences, which may end up in destructive loco-regional diseases. These cases used to be managed mainly by palliative strategies by various specialists, including dermatologists, plastic surgeons, radiotherapists, and medical oncologists, and never drew interest for classification. A neologism 'locally advanced BCC' (LA-BCC) was recently introduced for the trials with hedgehog inhibitors (HHI)[1,2] representing these severe non-metastatic cases.

There is a need for a staging or at least a categorization of these tumors. Unlike most other solid tumors, the TNM classification applied to skin cancers[3] does not fit BCCs since they do not follow the three-step process of tumor, nodal involvement, and distant metastases extension. Even though they rarely metastasize, BCCs can however have a fatal outcome at the end of a slow but ineluctable destructive process.

Classifying LA-BCCs is challenging for many reasons. First 'advanced' has no clear definition. It is encompassing highly heterogeneous situations from common BCCs in a location where surgery will create some mutilation, to highly destructive BCCs judged inoperable. Second, there are no definite prognostic markers available, and PFS and OS are not meaningful for BCCs, which are not really measurable by RECIST criteria, and can destroy large anatomic areas without affecting survival.


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Third, the views and treatment recommendations of oncologists, surgeons, radiotherapists, and dermatologists are not easy to reconcile. Finally, it is difficult to select the most relevant criteria for classification among the many available. Some are linked to the tumor itself such as the size, number, location in high-risk areas, poorly defined borders, aggressive histology, and number of prior recurrences. Others are linked to treatment options, and each BCC may be considered more or less appropriate for surgery, radiotherapy, or systemic treatment depending on the tumor itself, on prior treatments, on doctor preference and skills, on patient age and comorbidities, not to forget patient opinion, fear, desires and choices.

Our objective was to generate an operational classification of the advanced forms of BCC for the daily practice. We wanted to avoid an arbitrary choice of criteria, as well as a point of view from a single angle of practice (surgery, radiotherapy, systemic therapy, and so on). We thus designed an innovative study based on the independent blind clustering of real patient cases by several experts, whose convergences and divergences were analyzed by a mathematical model. Herein we present the resulting consensual categorization.

## Methods

### Working hypotheses

Although the medical community was so far unable to agree on an operational classification of DTT-BCCs due to a high heterogeneity of cases, we hypothesized that experts were however probably unconsciously able to translate and simplify the high heterogeneity of DTT-BCCs into a few dominant patterns, in order to drive their therapeutic decisions. Our second hypothesis was that these dominant patterns of situations were likely to be similar for most experts despite apparently different point of views of different specialists (dermatologists, oncologists, surgeons). Indeed this simplification is de facto strongly relevant to the practice, whatever the specialty (Fig. 1).

### Independent clustering of real cases

'Independent clustering of real cases' is a method to identify these 'unconscious consensual patterns of BCCs' without being polluted by sterile expert discussions. It is based on the 'perceived similarity' between cases and the natural ability of the human brain to pattern recognition. The more experts accept that two cases can be classified together; independently of the personal factors they take into account to analyze the two cases, the more these two cases are likely to belong to the same pattern of DTT-BCCs. In addition, step by step, this is a way to define consensual patterns of BCC that best approach the real unconscious classification of experts.

Practically, each expert was presented a series of patient cases and was asked to group them into clusters, with the objective to put in a same cluster all the BCC cases which he/she considered close according to the criteria he/she considered as relevant. Each expert had to do his/her clustering alone, 'blinded' from the other experts. Clustering was unsupervised, leaving each expert to choose his/her own criteria for his/her own partition of the cases. There were only two restrictions: (i) the clustering had to be useful for the practical classification of these cases, leaving to each expert his/her own definition of 'usefulness'; and (ii) the final number of clusters had to be between 2 and 10, in order to end up with an operational classification, which would not be the case if there were too many groups. A mathematical model was used to find the convergence between the different individual clustering patterns, to find a limited number of clusters best representing consensus. We previously tested this strategy on the cases from BOLT study[2] with eight experts in three teams and confirmed the feasibility (presented at 14th EADO meeting Marseille 2015). According to the French law, Institutional Review Board approval was not required in the setting of this non-interventional study.

### Cases selection

In order to circumvent ambiguity in the definition of the word 'locally advanced', we addressed these tumors with a more practical definition, i.e. 'difficult-to-treat' BCCs (DTT-BCCs), as defined by the practitioners themselves.

Patient cases considered 'difficult to treat' for any reason by the dermatologist trained in cancers of EADO were collected from 11 centers of the EADO group. Each case was recorded on a dedicated website on a standardized one-sheet document

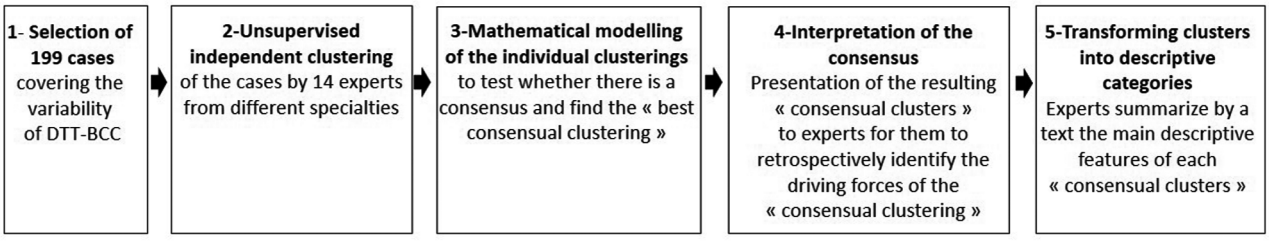


**Figure 1** General design of the study.


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anonymized and blinded with 1–5 pictures of the lesion (and radiography, if relevant) and a standardized case report (Fig. 2). The latter included demography, ECOG status, number of other BCC, past treatments with dates, histopathological subtype, major treatments which can interfere with surgery, other comorbidities, and finally the reasons for which this BCC had been considered 'difficult-to-treat' by the treating physician. An independent expert (KP) was responsible for the selection of cases, completing recruitment when all the variability of DTT-BCC in the practice was considered represented in this collection of cases.

### Experts

Fourteen internationally recognized experts familiar with DTT-BCC, from six countries in Europe and Australia and from different specialties, participated in the experiment in a dedicated two-day meeting: six dermatologists (NB, PF, VD, IZ, AS, MCF), four dermato-oncologists (JJG, CG, CGM, JM), one oncologist (AG), one plastic surgeon (BB), one dermato-surgeon (RK), and one radiotherapist (LT).

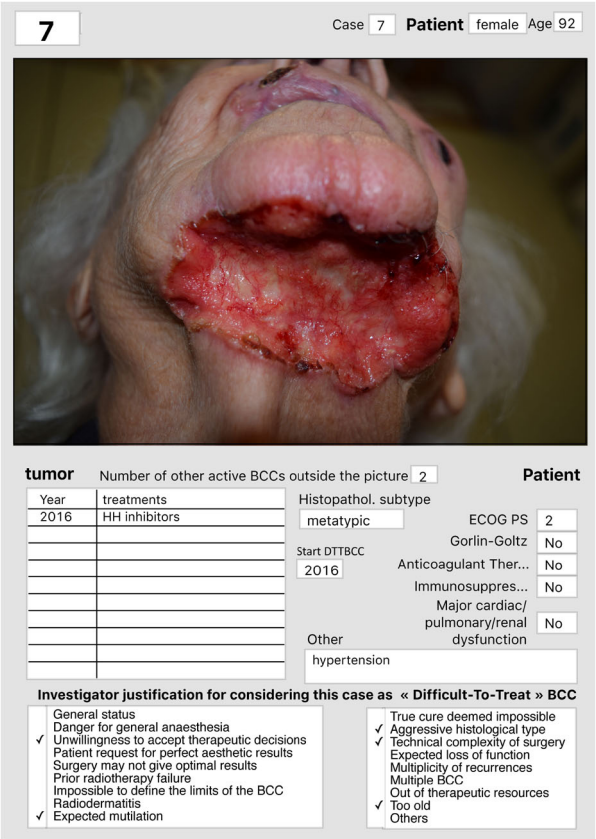


**Figure 2** Example of a standardized case report sheet submitted to the experts.

### Independent blind clustering of DTT-BBC case by each expert

They independently partitioned the 199 cases into clusters according to the general principle described above. Additionally, the experts had to quote the difficulty of treatment for each case on a 1–5 Likert scale (DTT-score) and to define each case as 'locally advanced', yes or no.

### Statistical analysis and identification of a consensual clustering

A similarity matrix between all DTT-BCC cases was built. If two DTT-BCC patient cases were found together in the same cluster from one partition proposed by a given expert, the similarity between two cases increased by 1. Therefore, maximal similarity between two cases reached 14 for cases found together in a cluster in the 14 partitions of experts, while minimal similarity was 0, when two cases were never found together in one cluster, whatever the expert (Fig. 3).

The K-means approach[4] was used to determine the consensual clusters, with the number of clusters, K, varying from 4 to 10 (maximal number of groups authorized in the expert partition). The silhouette method[5] was used to find the optimal K, which is the lowest number of clusters representative of the consensus. Non-linear multi-dimensional scaling (MDS)[6] allowed visualization of similarities between cases in 2D and 3D plots. The comparison of partitions, in other words the comparison of experts, was achieved by means of the BCubed statistic[7–9] and also visualized by MDS.

### Interpretation by the group of experts of the consensual clusters identified by mathematical analysis

The resulting consensual partition generated by the model was *a posteriori* presented to the same panel of 14 experts. For each consensual cluster, the panel had access to (i) all the pictures of cases; and (ii) the mean, median and distribution of all clinical variables of this cluster, including number of BCCs/case, age, sex, ECOG, history of surgery, radiotherapy, mean score of difficulty in treatment and main reasons for considering BCC as DTT-BCCs. The experts were collectively asked to identify the major features that best characterized the cases in each given consensual cluster. They were requested to come to an agreement on a simple text best describing each consensual cluster and on the selection of a few pictures that best illustrate each cluster. Finally, the group of experts was asked to sort the different consensual clusters according to an increasing severity scale, if possible.

## Results

A total of 199 cases of DTT-BCCs were submitted for clustering (described in Table S1).

### Identification of a consensual clustering

According to the average silhouette method, the analysis of the 14 individual partitions showed that the optimal number K of


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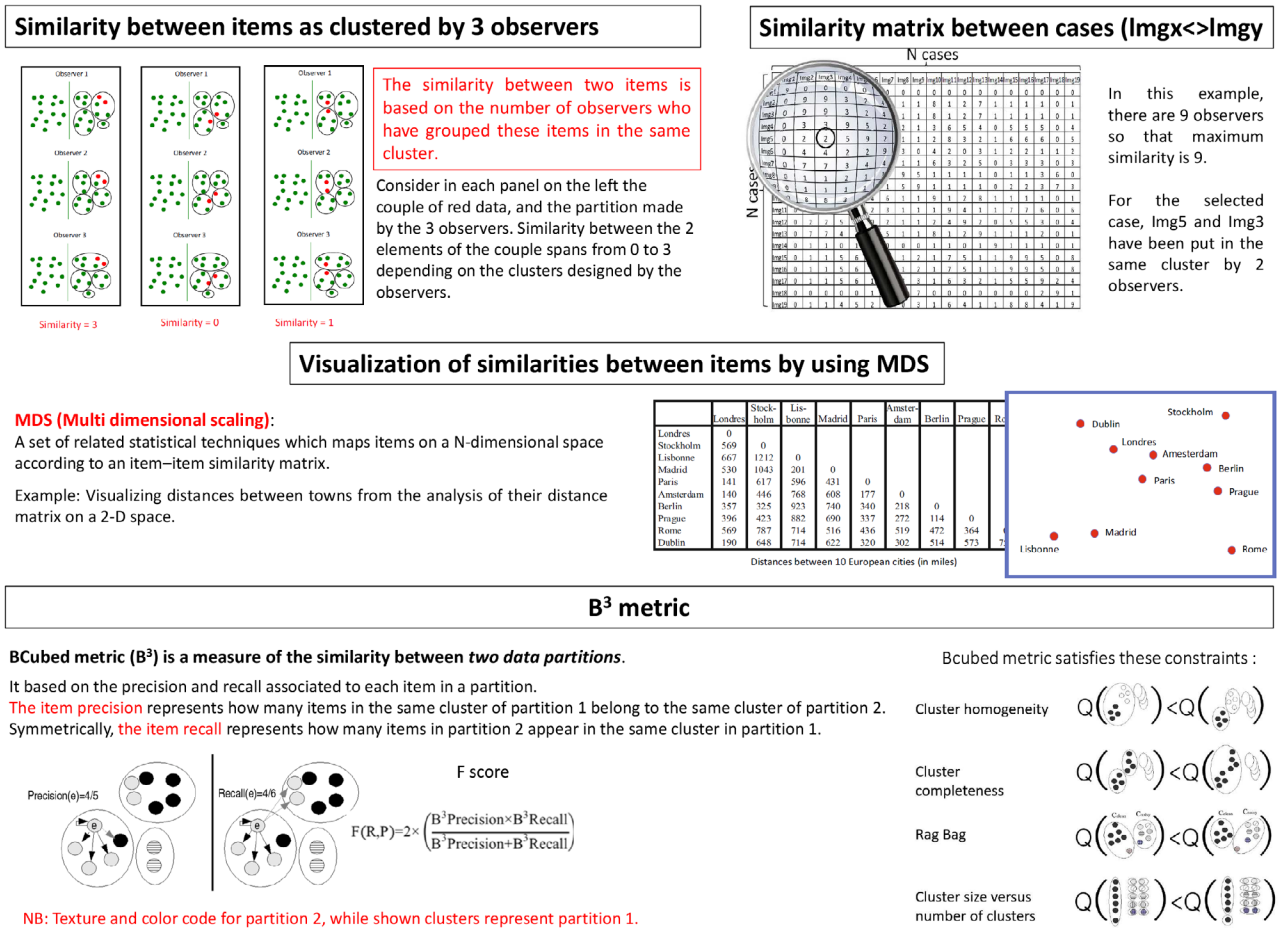


**Figure 3** Comprehensive explanation of the statistical models.

consensual clusters was 5. Similarity between cases within each cluster and between clusters is illustrated by multi-dimensional scaling (Fig. 4).

### Divergence and convergences between experts

The relative distance between the clustering patterns of the different experts show a rather close clustering pattern for a group of 11 experts and more distant patterns for three experts (CG, MCF,VD). Interestingly, the specialties of the experts did not appear to drive the proximity between experts, since the radiotherapist, oncologist and surgeon were all in the main group, and the three most distant were two dermatologists and an onco-dermatologist. In addition, of interest is the fact that the only two experts coming from the same center (JJG and CGM), independently provided the closest pattern of partition (Fig. 5).

### Interpretation "*a posteriori*" of the consensual clusters resulting from the mathematical model

When the five consensual clusters of DTT-BCC generated by the model were presented to the panel of 14 experts, they easily agree that these five clusters were five distinct patterns of clinical situation, easy to describe in a few words and to illustrate by a few representative pictures (Fig. 6). They were also able to agree on a ranking of the five consensual clusters from 1 to 5, from the less to the most severe disease pattern.

### Relation between the concepts of 'locally advanced' and 'difficult-to-treat BCC'

The probability that an expert was considering a BCC as 'advanced' increased with the mean DTT score (Fig. 7). Many BCCs considered as really difficult to treat (score≥3) were not considered 'LA-BCC' by 50% of the experts, and a number of


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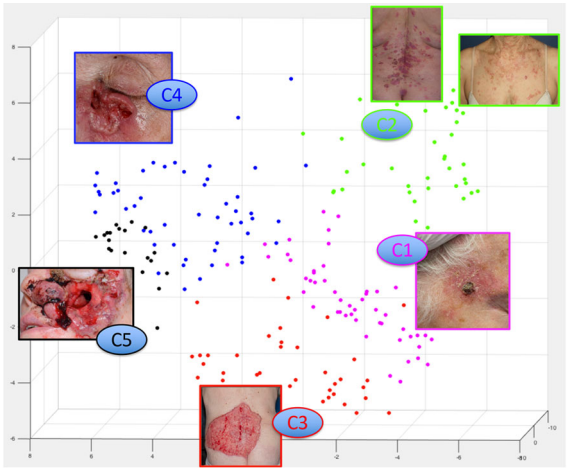


**Figure 4** Three-dimensional scaling for assessing similarity between cases and within consensual clusters (C). Each dot stands for a case, its color represents the consensual cluster it belongs to. A picture representative of the group is used as illustration. This plot helps visualizing the similarity between cases, as initially expressed by the similarity matrix. Clusters appear well separated, even in this low dimensional representation. Values on the axes are the arbitrary unit.


**Figure 5** Divergence and convergence between experts represented by the relative distance between experts on a two-dimensional representation. Each dot represents one expert, its color codes for the expert's specialty, letters are the expert's identification and the flag is for the expert's origin. The closer the dots, the more similar the expert's partitions.

BCC considered 'LA-BCC' by ≥50% of experts had a DTT score <3. The probability that a BCC was considered 'advanced' by the panel increases from cluster 1 to 5, and the score for difficulty of treatment increased from cluster 1 to 5. Interestingly, in cluster 1 and 2, there was a large dispersion of DTT-score and many cases

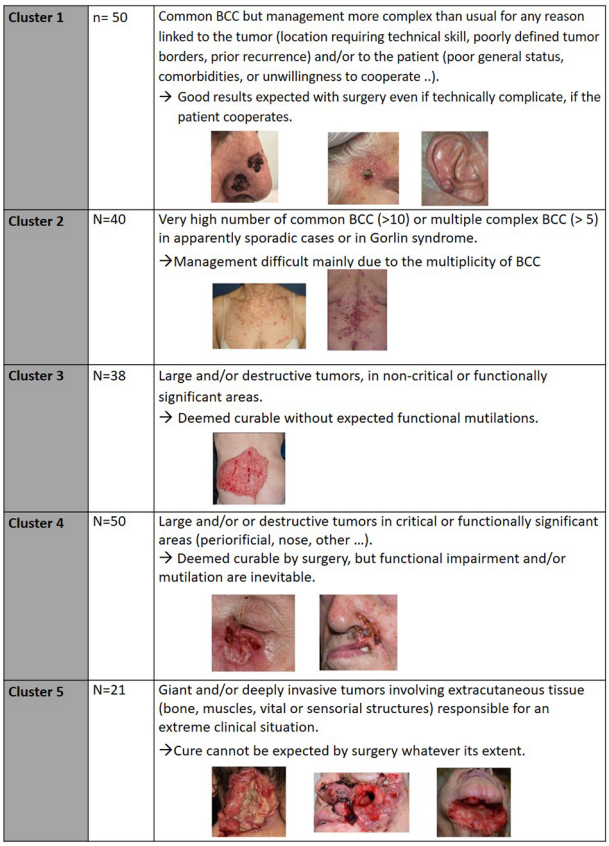


**Figure 6** Description and illustration of the five consensual clusters identified by the mathematical model.

were not called 'LA-BCC' by experts, whereas, in clusters 3, 4 and 5, DTT-score was always high and most cases were labelled LA-BCC.

## Discussion

Using a very original strategy, we were able to generate a simple and understandable categorization of DTT-BCCs in five well-defined groups, based on case clustering by experts. A *a posteriori* analysis of the cases in each of the consensual groups immediately showed that these five groups described distinct clinical patterns or scenarios. A consensual clustering was not granted upfront between experts from different origins. Our results strongly suggest that all experts who have to make a therapeutic decision for problematic BCCs probably use a similar approach based on an overall assessment of the situation by pattern recognition, rather than on the analysis of separate individual criteria. Pattern recognition is a universal mode of analysis in the human brain,[10] which is now used in machine learning.

The independent clustering method is a way to extract the knowledge from experts, when it is difficult to formulate and/or


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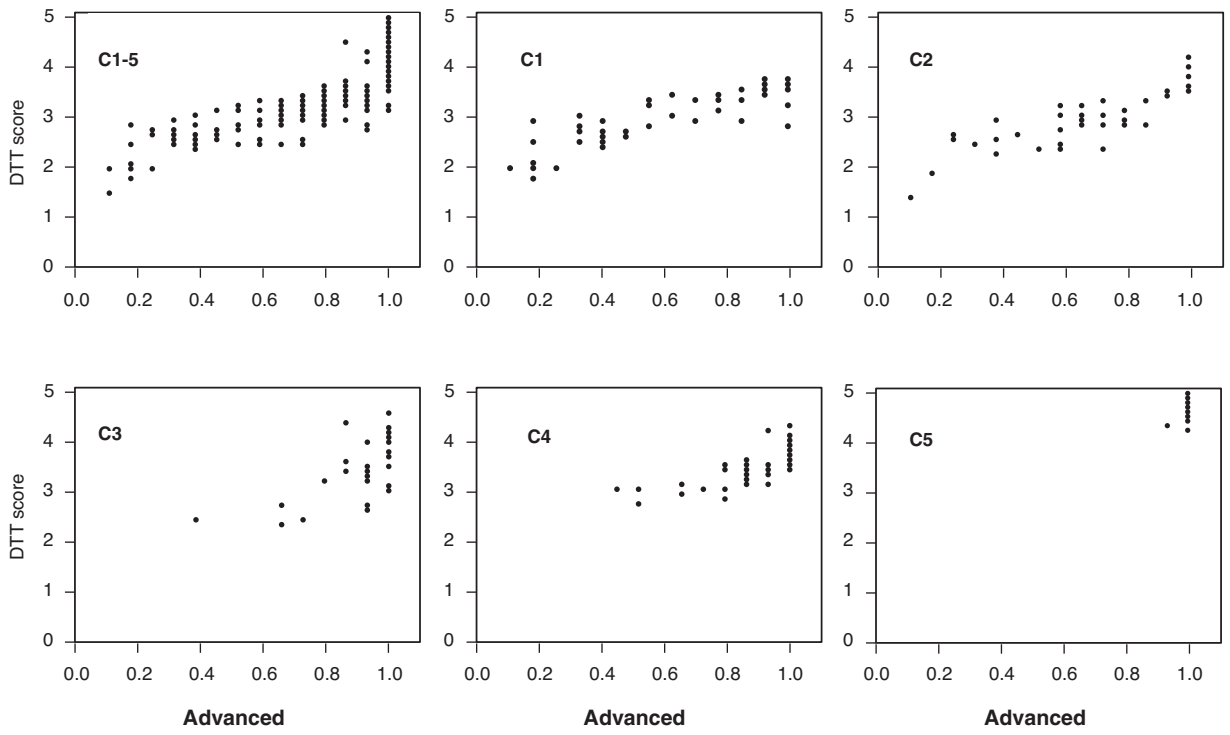


**Figure 7** Probability that a BCC is considered 'locally advanced' (% of experts designing a case as locally advanced) in relation to the mean DTT score (mean assessment of the difficulty in treatment by the 14 experts on a 1–5 Likert scale), for the five clusters C1–C5.

when it is difficult to reconcile apparently different opinions. Interestingly, the results of this mathematical modeling were easily and unanimously accepted by the experts whatever their specialty, although it would probably not have been easy to reconcile their different opinions in a debate starting from zero. The proximity of clustering between experts does not seem to be driven by their specialties (Fig. 5), showing that this intuitive clinical categorization into patterns transcends the medical specialties. Nevertheless, the closest partitions were those of two experts of the same center, suggesting that pattern recognition is influenced by clinical education.

By nature, the result is the best possible consensus from experts. It does not result from an *a priori* choice of some artificial criteria for classification. The criteria were drawn from the analysis of the clustering and not the opposite. This method minimizes biases. Indeed, each expert is valued at the same level, and the classification is influenced neither by the specific impact of a key opinion leader, nor by a specialty lobby. Moreover, it is likely that all DTT-BCCs can be classified in this five patterns categorization, since a very large variability of DTT-BCCs was covered in our experimental sample.

As 'locally advanced BCCs' have never been defined, it is interesting to note that the probability of a BCC being called 'advanced' by the majority of experts are linked to their assessment of difficulty of treatment (DTT score). This study however shows that there is a great variability in what experts call 'locally advanced' BCC, among DTT-BCCs. In this regard, the five patterns described herein may be a more consistent way to classify BCC between physicians than the wording 'locally advanced' or 'non advanced'.

Finally, this study demonstrates that clinicians facing complex and heterogeneous situations agree on a non-formulated but very strong and consistent pattern recognition. Unsupervised independent and blinded clustering of real patient cases is a very interesting method to understand this pattern recognition. This approach can probably be applied to many other situations in oncology and also in dermatology when agreement on classification is complex including inflammatory disorders, for which pattern recognition may be relevant.

## Acknowledgement

The patients in this manuscript have given written informed consent to the publication of their case details.


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## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Main characteristics of the 199 DTT-BCC cases


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