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ORIGINAL ARTICLE

Operational classification of cutaneous squamous cell carcinomas based on unsupervised clustering of real cases by experts

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Abstract

Background: There is currently no staging system for cutaneous squamous cell carcinoma (cSCC) that is adapted to decision-making and universally used. Experts have unconscious ability to simplify the heterogeneity of clinical situations into a few relevant groups to drive their therapeutic decisions. Therefore, we have used unsupervised clustering of real cases by experts to generate an operational classification of cSCCs, an approach that was successful for basal cell carcinomas.

Objectives: To generate a consensual and operational classification of cSCCs.

Methods: Unsupervised independent clustering of 248 cases of cSCCs considered difficult-to-treat. Eighteen international experts from different specialties classified these cases into what they considered homogeneous clusters useful for management, each with freedom regarding clustering criteria. Convergences and divergences between clustering were analysed using a similarity matrix, the K-mean approach and the average silhouette method. Mathematical modelling was used to look for the best consensual clustering. The operability of the derived classification was validated on 23 new practitioners.

Results: Despite the high heterogeneity of the clinical cases, a mathematical consensus was observed. It was best represented by a partition into five clusters, which appeared a posteriori to describe different clinical scenarios. Applicability of this classification was shown by a good concordance (94%) in the allocation of cases between the new practitioners and the 18 experts. An additional group of easy-to-treat cSCC was included, resulting in a six-group final classification: easy-to-treat/complex to treat due to tumour and/or patient characteristics/multiple/locally advanced/regional disease/visceral metastases.

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For affiliations refer to page 618.

Conclusions: Given the methodology based on the convergence of unguided intuitive clustering of cases by experts, this new classification is relevant for clinical practice. It does not compete with staging systems, but they may complement each other, whether the objective is to select the best therapeutic approach in tumour boards or to design homogeneous groups for trials.

INTRODUCTION

At least four different staging systems mostly derived from head and neck tumours are available for cutaneous squamous cell carcinomas (cSCCs)[1–4] but none of them are universally accepted. The European and US therapeutic guidelines are not based on TNM or other classifications.[5] These current classifications are unable to adequately identify patients at high risk of disease progression.[6] Furthermore, the practical decisions in tumour boards are not based on these classifications but rather on a holistic assessment of each situation. Therefore, there is an urgent need for an operational classification of the cSCCs, (1) for case discussion in tumour boards and decision-making, (2) to design clinical trials to compare therapeutic strategies in homogeneous subgroups and (3) to inform guidelines.

Building an operational classification of cSCCs is challenging for many reasons. It encompasses highly heterogeneous situations ranging from common cSCCs in locations where surgery could cause some mutilation, to highly destructive tumours that are considered inoperable. The views and treatment recommendations of medical oncologists, surgeons, radiation oncologists and dermatologists, all potentially involved in patient management, are diverse and difficult to harmonize. Finally, it is challenging to select the most relevant criteria for classification among the hundreds available, some being relative to the tumour itself (size, number, location in high-risk areas, histological features, nodal or distant metastases and the number of previous recurrences), others being linked to prior treatments, treatment options, clinician preferences and skills and patients characteristics (age, general status, comorbidities, but also fear, desires and willingness to cooperate).

Independent clustering of real cases by experts is an original approach based on the 'perceived similarity' between cases and the natural ability of the human brain to recognize patterns, allowing the identification of 'unconscious consensual patterns'. This method has been successfully used by the EADO to generate an operational staging system of basal cell carcinomas (BCCs).[7,8] The EADO objective in this new study was to use a similar approach for cSCCs to converge on a consensual simple and operational classification. As most cSCCs are easy to manage and cured by surgery, we decided to focus on a subgroup of cSCCs that clinicians identified as difficult-to-treat (DTT) regardless of their reasons for considering them as such.

METHODS

Working hypotheses

We hypothesized (1) that experts were unconsciously able to translate the heterogeneity of DTT-cSCCs presentation into a few dominant situations to drive their therapeutic decisions, (2) that these situations were likely to be similar for most experts independently of their specialty (dermatologists, medical oncologists, H&N surgeons, plastic surgeons, dermato-surgeons and radiation oncologists). An overview of the study design is shown in Figure 1.

Phase 1. Independent clustering of real cases

As described in a previous study for BCCs,[7] each expert was presented with a set of real-life patient cases and was asked to cluster them, with the aim of grouping together all cSCCs cases that he/she considered close according to the criteria he/she considered as relevant. Each expert had to perform the clustering alone, 'blinded' to the other experts. The clustering was unsupervised, and each expert was free to choose his/her criteria for classifying the cases with two restrictions: the clustering had to be useful for the clinical management, and the total number of clusters had to be between two and nine, 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 and to find a limited number of clusters that best represented consensus. According to French law, Institutional Review Board approval was not required for this non-interventional study.

Case selection

Patient cases of cSCCs considered to be DTT for any reason by dermatologists/oncologists/surgeons practicing in referral skin cancer centres were collected from 12 centres of the EADO. Each case was recorded on a dedicated website on a standardized one-sheet document, anonymized and blinded with one to five images of the lesion (including radiological images, if relevant) and a standardized case report (Figure 2). The latter included demography, age, sex, ECOG status, comorbidities including

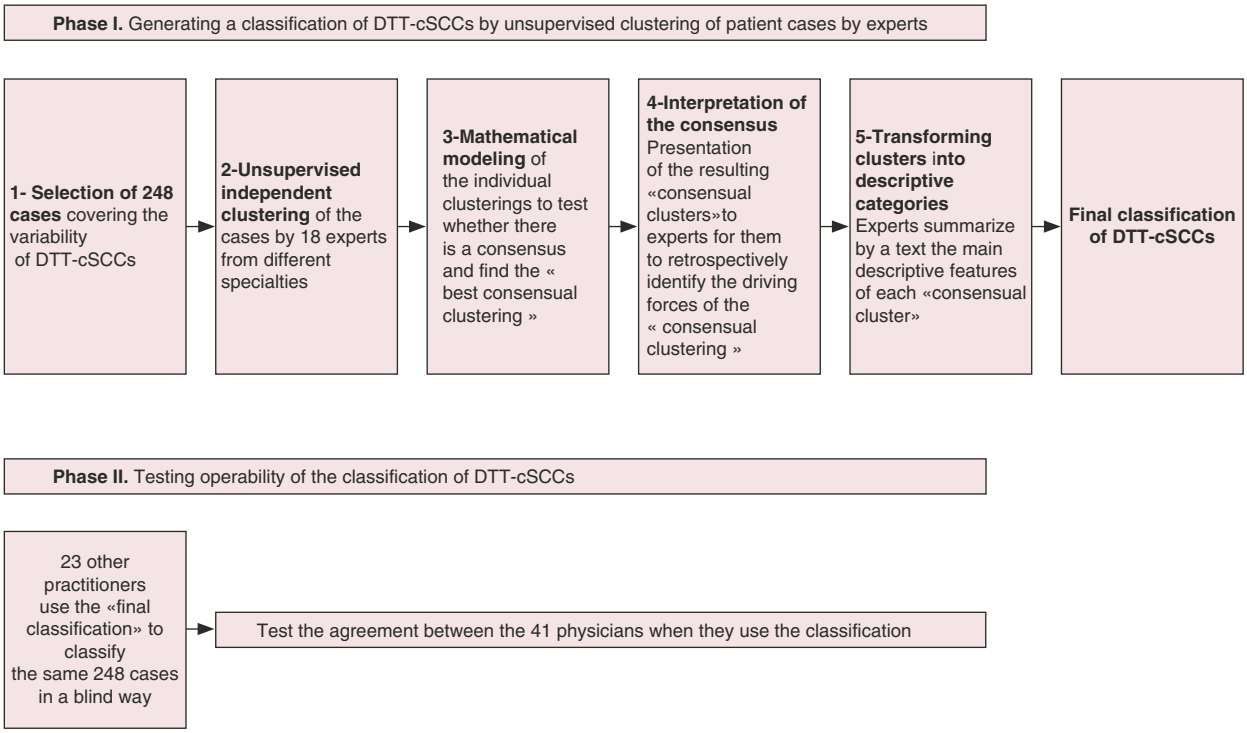


FIGURE 1 General design of the study.

immunosuppression, total number of cSCCs, tumour location, tumour history (including recurrences and previous treatments) and finally the reasons for which this cSCC had been considered 'difficult-to-treat' by the treating physician (see Table S1 for a comprehensive description of the cases). One of the experts (KP) was responsible for overseeing the selection of cases, to ensure that the variability of DTT-cSCCs in the practice was well represented in the case collection.

Experts

Eighteen internationally recognized experts familiar with DTT-cSCCs, from nine countries in Europe, the United Kingdom, the United States and Australia, and from different specialties, participated in the experiment: Seven dermatologists (NB, AS, MCF, KP, RM, RD and AH), four dermato-oncologists (JJG, CG, CGM and JM), two medical oncologists (AG and PA), one H&N surgeon (MP), two dermato-surgeons (RK and STA) and two radiation oncologists (LT and AR).

Independent blind clustering of DTT-cSCC cases by each expert

The 18 experts independently partitioned 248 cases into clusters according to the general principle described above.

Statistical analysis and identification of a consensual clustering

A similarity matrix between all DTT-cSCCs cases was built. If two DTT-cSCCs patient cases were found together in the same cluster from one partition proposed by a given expert, the similarity between the two cases increased by 1. Therefore, maximum similarity between two cases reached 18 for cases found together in a cluster in the 18 partitions, while minimum similarity was 0 if 2 cases were never found together in one cluster, whatever the expert. A side-by-side comparison of the clustering of each pair of experts was performed using the Bcubed statistic.[9–11] Three types of algorithms were tested: K-means approach,[12] hierarchical clustering[13] and DBSACN clustering.[14] For each algorithm, the best values for the hyperparameters were obtained based on the silhouette score metric.[15] Nonlinear multidimensional scaling (MDS)[16] allowed visualization of similarities between cases in 2D plots.

Using the consensual clustering to make an operational classification of cSCCs

The resulting consensual partition generated by the model was presented a posteriori to the same panel of 18 experts. All the pictures of cases classified together in the consensual clusters, as well as the mean, median and distribution of all the clinical variables of that cluster, were provided to

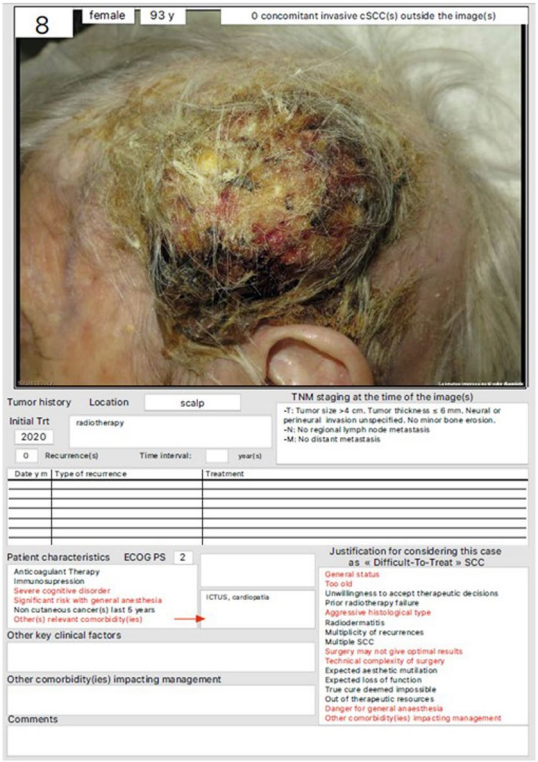


FIGURE 2 Example of a standardized case report sheet submitted to the experts.

the experts. The experts were asked to try to understand the reasons why cases ended up together in each consensual cluster. They were requested to agree on a simple definition of the common characteristics of each consensual cluster, in order to transform the consensual clustering into an understandable classification that could be used by any other practitioner.

Phase 2. Testing the operability of the resulting classification of cSCCs

To verify that the group definitions of the newly generated classification were understandable and usable by other clinicians, a validation phase was organized. Twenty-three physicians familiar with cSCCs, different from the 18 experts, coming from seven different countries (Italy, France, Germany, Spain, Poland, UK and the USA) and different specialties (two medical oncologists, five radiation oncologists, two surgeons and 14 dermatologists) were asked to classify the same 248 DTT-cSCCs cases using the new classification. This test was performed on a dedicated website. Their agreement was evaluated by the percentage of cases that remained in the cluster they had been initially assigned to.

A contrast criterion was used to characterize the distribution of votes across clusters for each case with a maximum value when all observers assigned the case to the same cluster and a minimum value when votes were evenly distributed across groups.

RESULTS

A total of 248 cases of DTT-cSCCs were submitted for clustering (described in Table S1). The majority of experts (16 out of 18) generated a classification into seven to nine groups while two experts defined three and six groups, respectively.

Clustering agreement between experts

The relative distance between the clustering patterns of the different experts is shown in Figure 3a and Figure S1 and does not seem to be influenced either by specialty or nationality.

Identification of a consensual clustering

According to the silhouette score metric,[15] the hierarchical clustering algorithm with a separation in five clusters came out best. The similarity between cases within each cluster and between clusters is illustrated by multidimensional scaling (MDS) and dendrogram representation (Figure 3b,c).

'A posteriori' interpretation of the consensual clusters resulting from the mathematical model

When the five consensual clusters of DTT-cSCCs generated by the model were presented to the panel of 18 experts, there was an agreement in considering that these clusters corresponded to five distinct patterns of clinical situations sufficiently distinct and standardized that their characteristics could be described in a few words (Figure 4), thus making a five group classification usable by other practitioners. The five clinical situations were the following: (1) cSCC complex to treat due to tumour and/or patient characteristics, (2) multiple tumours, (3) locally advanced cSCC, (4) cSCC with regional metastases, that is, either nodal or cutaneous metastases distant from the primary tumour and (5) cSCC with visceral metastases.

Cutaneous metastases can be observed in a variety of clinical scenarios and three different situations can be roughly distinguished in clinical practice: (1) small size cutaneous metastases in the surrounding of the primary tumour site, which can be easily removed by surgery and could be classified in the easy-to-treat group or group 1 according to the overall clinical situation; (2) cutaneous metastases not amenable to surgery, in the setting of a locally advanced tumour, that would rather fit into group 3; (3) cutaneous

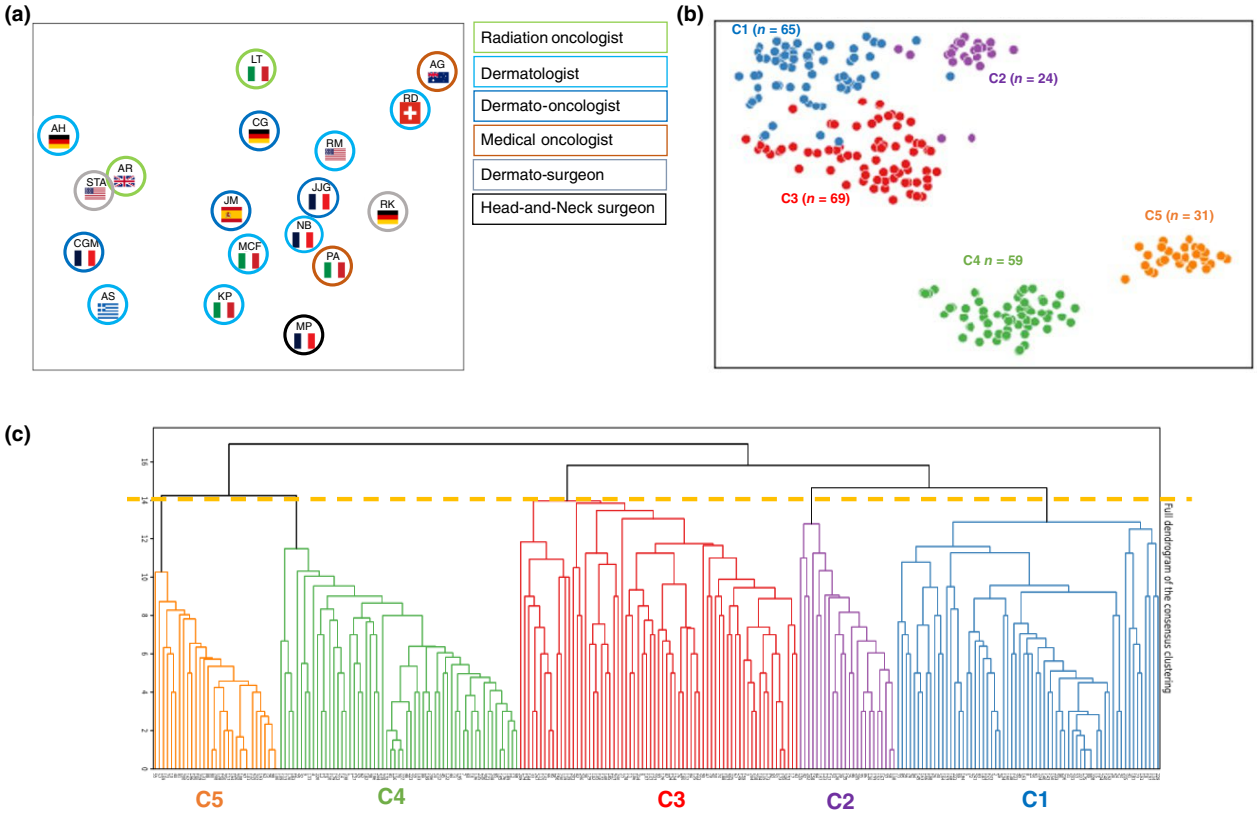


FIGURE 3 (a) Divergence and convergence between experts represented by the relative distance between experts on a two-dimension representation. Each dot represents one expert, its colour codes for the expert's specialty, the letters are the expert's ID and the flag is for the expert's origin. The closer the dots are, the more similar the expert's partitions are. (b) Consensual clustering from the similarity matrix. 2D projection of the cases based on the similarity matrix and the TNSE algorithm. Each dot stands for a case, its colour represents the consensual cluster (C) to which it belongs. This plot helps visualize the similarity between cases, as initially expressed by the similarity matrix. The more cases are similar in the matrix, the closer is their position on the graph. Each colour represents a single group from the consensual clustering. (c) Dendrogram illustration of the consensual clustering obtained with the hierarchical clustering. The colours represent the clusters (C). Each leaf represents a patient's case. The yellow dashed line shows the optimal cut-off level for this clustering.

metastases distant from the primary tumour which are more representative of a regional disease and would therefore be classified in group 4.

Testing the operability of the classification

The agreement between the 23 experts of the validation group in classifying the cases was rather high: a majority of experts agreed on 94% of the cases. However, 15 cases (6%) received distributed votes, nearly equally divided between two groups, and six cases (2%) were split over three groups. Out of these 21 cases, agreement raised to 96%.

The overall agreement (concordance in the group assignment of cases between the validation group of 23 new practitioners and the 18 initial experts) was 90%. There was no clear dominant group assignment for only 15 out of 248 cases which can therefore be considered 'ambiguous' in this classification. The most frequent ambiguities were between group 1 ('complex to treat due to tumour and/or patient characteristics') and group 3 ('locally advanced cSCC') (7 cases) and between group 1 ('complex to treat due to tumour and/or patient characteristics') and group 2 ('multiple cSCC') (8 cases) (Table 1).

DISCUSSION

Using unsupervised case clustering by experts, we generated a simple and understandable categorization of DTT-cSCCs into five well-defined groups, confirming our previous experience with the classification of DTT-BCCs.[7,8] An additional group of easy-to-treat cSCCs, which were not part of this experiment since they are easily managed by surgery and do not require therapeutic discussion, was added to the classification a posteriori in order to cover the full spectrum of cSCCs.

Interestingly, our study shows that the experts analysed the highly variable clinical situations of DTT-cSCCs in a very simple way: visceral metastatic disease, nodal disease and three types of local disease suggesting that the overall assessment is the main driver of their decisions. This may explain why complex classifications such as AJCC, UICC, Bringham and Women's Hospital[1–4] are used for risk

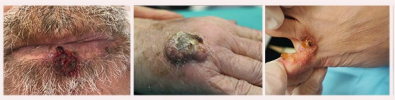
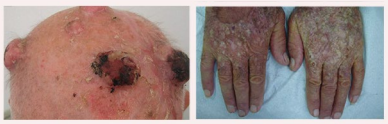
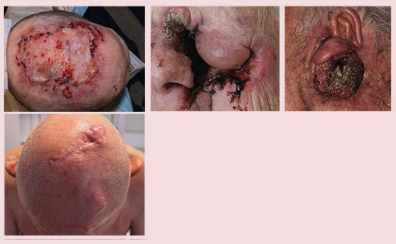
	Stage	Characteristics		Illustrative pictures	Classification group
Common cSCC	I	**Easy to treat cSCC**	cSCC (TN0M0) easily manageable None of the other groups characteristics **Surgical excision recommended*		Not included in the experiment
	IIA	**Complex to treat**	cSCC (TN0M0) complex to treat due to tumor and/or patient characteristics* **Surgery is likely to be curative but functional or cosmetic consequences and/or other factors (general status, immunosuppression, comorbidities, tumor history..) may lead to therapeutic discussion including radiotherapy with curative intention and/or medical treatments*		**Group 1** *n* = 65
	IIB	**Multiple tumors**	Multiple cSCCs (TN0M0) when the number is the main problem for management, whatever the background (genetics, immunosuppression…) **Multimodal approach with either surgery/ radiotherapy/systemic therapy* ***when the characteristics of at least one cSCC, is the main problem and not the number itself, patients must be classified in other relevant groups according to the most problematic cSCC*		**Group 2** *n* = 24
Advanced cSCC	IIC	**Locally advanced without regional metastases**	Locally advanced cSCC (TN0M0) **surgery and/or radiotherapy are unlikely to be curative indication for systemic therapy / radiotherapy/ palliative care according to patient's performance status*		**Group 3** *n* = 69
Metastatic cSCC	III	**Regional metastases**	cSCC with regional metastases either nodal or cutaneous metastases distant from the primary (TN+M0) whatever the severity and number of cSCC **Multimodal approach with either surgery/ radiotherapy/systemic therapy*		**Group 4** *n* = 59
	IV	**Distant metastases**	cSCC with distant metastases (TNM+), whatever the severity and number of cSCC **Multimodal approach with systemic therapy, radiotherapy or palliative care according to patient's performance status*		**Group 5** *n* = 31

FIGURE 4 Six-group classification derived from the interpretation of the five consensual clusters and the addition of the easy to treat group. Each definition is the best formulation found by the experts to describe the common points between cases in each given consensual cluster. The numbers indicate the number of cases initially included in each consensual cluster.

TABLE 1 Concordance in the allocation of cases between the 18 initial experts and the 23 other practitioners using the five-group classification.

		Other practitioners (*n* = 23)						
		Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**Total nb of cases**	**Concordance**
Experts (*n* = 18)	Group 1	**55**	8	2	0	0	65	**85%**
	Group 2	1	**20**	3	0	0	24	**83%**
	Group 3	7	2	**59**	0	1	69	**86%**
	Group 4	0	0	0	**59**	0	59	**100%**
	Group 5	0	0	0	2	**29**	31	**94%**
Total nb of cases		63	30	64	61	30	248	

classification and prognosis while decision-making is predominantly based on the NCCN guidelines[17] in the United States and the EADO-EDF-EORTC-ESTRO guidelines of cSCC in Europe.[18] The complexity of these different classifications may explain why they are not universally implanted in clinical practice. We have not yet evaluated the prognostic value of this classification, but such a low granularity assessment of the overall situation (visceral metastases/regional disease/locally advanced/multiple/complex to treat due to tumour and/or patient characteristics (i.e. location, tumour history, comorbidities and immunosuppression)) is likely to be prognostic. In this regard, it should be noted that the conventional staging systems have a low prognostic value.[6]

The main advantage of this pattern recognition-based classification is the independent clustering methodology which ensures that the different categories of cSCCs are meaningful to the practice as they are mathematically extracted from real-life scenarios. A consensual clustering was not granted upfront between experts from different countries and specialties given the heterogeneity of cSCCs and the multiplicity of potential criteria for classification.

The proximity of clustering between experts does not appear to be driven by their specialties or their nationalities, demonstrating that this intuitive clinical categorization transcends the medical specialties. All experts who have to make a therapeutic decision for problematic cSCCs probably use a similar approach based on an overall assessment of the situation through pattern recognition, a universal mode of analysis in the human brain,[19] that is now being used in machine learning.

There was a strong agreement in the cases classification between the 18 experts who contributed to the generation of the classification and 23 other clinicians, demonstrating that the classification was self-explanatory. Disagreement in cases classification was more frequent between group 1 (complex to treat due to tumour and/or patient characteristics) and group 3 (locally advanced), probably due to a different interpretation of the wording 'locally advanced' tumour, and between group 1 (complex to treat due to tumour and/or patient characteristics) and group 2 (multiplicity of cSCCs as the main problem for management) probably due to a semantic ambiguity in the interpretation of 'the main problem for management' in complex cases.

It must be underlined that the value of a classification depends more on its clinical relevance than on the absence of overlap between groups. In this regard, using numeric criteria such as lesion size and tumour thickness, for instance, is an easy way to ensure a repeatable and standardized division into categories but may have a very low clinical relevance. Conversely, using a classification by clinical scenarios, which allows for a more global assessment of a situation, may be less repeatable and standardized, simply because it encompasses the complexity and uncertainty[20] of the situation, but is still highly relevant for decision making.

While surgery is the gold standard for the 'easy-to-treat' group, curative radiotherapy and/or medical treatments can be discussed as an alternative to surgery for group 1. Groups 2–5 require multimodal treatment with either surgery, radiotherapy or systemic therapies.

Compared to the usual staging systems based on a complex combination of different 'objective' numerical variables, including TNM derived from H&N tumours, this new classification based on 'subjective assessment' of the clinical situations is certainly a progress in the classification of cSCCs with immediate potential applications in tumour boards and the selection of patients for clinical trials.

To what extent other variables such as pathological subtypes, tumour thickness, perineural invasion and kinetics of the tumour, could provide useful additional information remains to be determined, in order to build a composite staging system. Improving this new staging system and assessing its prognostic value in real-life settings and therapeutic applications will be the next steps of our project.

AFFILIATIONS

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

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 can be found online in the Supporting Information section at the end of this article.

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