

## Review

# Lentigo Maligna - A Scientometric Analysis of Mainstream Scientific Knowledge

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## REZUMAT

### *Lentigo maligna – analiza scientometrică a fluxului principal de cunoaștere științifică*

**Introducere și obiective:** S-a realizat o analiză scientometrică de tipul „qualitative data analytics” a fluxului principal de cunoaștere științifică pentru a identifica tendințele actuale ale cercetării asupra lentigo maligna (LM).

**Material și metodă:** În urma analizei bazei de date SCOPUS au fost selectate 338 articole publicate între anii 2004-2014, având ca temă lentigo maligna. Criteriile de selecție au fost reprezentate de cuvintele cheie specifice. Materialele au fost procesate în două fișiere: într-unul au fost introduși termenii cheie menționați de autor în baza unui algoritm specific și a anului de publicare; au fost evaluate și abstractele articolelor respective. Datele astfel obținute au constituit baza pentru două tipuri de analiză scientometrică.

**Rezultatele:** Rezultatele analizei se concretizează în „norul cuvintelor cheie” precum și evoluția în timp a acestora. Suplimentar, s-a obținut o imagine detaliată asupra construcțiilor conceptuale ale publicațiilor, cu un nivel suplimentar de profunzime în raport cu simpla analiză a termenilor cheie. Markerii imunohistochimici precum și markerii histologici de prognostic rămân insuficient evaluați.

**Concluziile studiului:** Analiza scientometrică asupra publicațiilor referitoare la LM reflectă lipsa dinamicii în acest domeniu de interes. Perspectivele moderne în ceea ce privește aprecierea prognosticului acestei leziuni sunt slab exprimate și necesită creșterea efortului de cercetare în această direcție.

**Cuvinte cheie:** lentigo maligna, cuvinte cheie, analiză scientometrică

## ABSTRACT

**Introduction & Objectives:** A scientometric analysis of the type "Qualitative data analytics" of the main stream scientific knowledge to identify current trends of research on lentigo maligna (LM) was performed

**Materials & Methods:** Subsequent to the SCOPUS database analysis, 338 articles on LM published between 2004 and 2014 were selected. The selection criteria were represented by specific key words. The publications were processed into 2 files: key terms indicated by either the authors or SCOPUS based on a software specific algorithm and depending on the publication's year; abstracts of the respective papers. Following the data processing procedures, the acquired data constituted the basis for the 2 types of scientometric analysis.

**Results:** The outcome of the analysis resided into a "cloud of keywords" as well as its evolution in time. Additionally, the review resulted in a detailed picture of the conceptual construction of the available data, with an extra-layer of scientific depth when compared to a simple analysis of key terms. The increasingly acknowledged immunohistochemistry and histology prognostic markers remain insufficiently assessed.

**Conclusions:** The scientometric analysis on LM related publications emphasized a lack of reliable research dynamics in this field of expertise. The modern prognostic perspectives related to this pathology are poorly reflected and require further scientific interest.

**Key words:** lentigo maligna, key words, scientometric analysis

## INTRODUCTION

Lentigo maligna (LM) is a type of melanocytic proliferation, the term being used by clinicians and pathologists for melanoma in situ on chronically sun damaged skin (1) in case that the lesion is confined to the epidermis. The pathology in question is classified as lentigo maligna melanoma (LMM) when it invades the dermis (2), over a protracted period of time (3). They both represent a subtype of malignant melanocytic proliferation according to the World Health Organization criteria (4). Once the dermis is invaded, the prognosis of the lesion is similar to that specific for other types of melanoma (5). Most LM patients display a slowly enlarging pigmented macula or patch which tends to occur in middle aged and older individuals (6), with a slight female preponderance (2).

The preferred method for diagnosing LM is excision (7), secondary to dermatoscopy (8) and biopsy (9). Distinguishing LM from a background of increased melanocytes on chronically sun damaged skin in a small biopsy specimen remains one of the most serious diagnostic challenges for dermatopathologists (10). Histology shows proliferation of atypical melanocytes at the epidermal-dermal junction in small nests or single cells (11).

Immunohistochemical studies are essential in highlighting the extent of the melanocytic proliferation (11). Cytogenetic abnormalities have been documented both in cultured cell lines derived from

LM as well as by fluorescence in situ hybridization performed on LM biopsies (12, 13). This condition constitutes a therapeutic challenge for surgeons due to its location in aesthetically important areas as well as to the difficulty in determining the correct margins (14). Surgical excision is the preferred LM treatment while the modern therapeutic approaches include the "spaghetti" technique described in 2011, Mohs micrographic surgery and stage geometric excision using the Wood lamp (15). A variety of other therapies are represented by radiotherapy, laser ablation and the use of topical immune system modulators. These treatment alternatives have been used with variable success rates in patients with extended lesions who were not viable candidates for surgery (10, 15).

This scientometric analysis, which involved 3 different software solutions, benefited from a rather high degree of innovation within the current academic practice. Both utility and possible limitations of such an approach derive from the fact that this type of analysis is based on a reliable quantitative data assessment.

## MATERIALS & METHODS

The scientometric qualitative data analysis was performed based on the mainstream scientific knowledge represented by articles recorded in the SCOPUS Elsevier database. The purpose of the trial was represented by the identification of current LM

research trends as well as the testing of the relevance of various descriptive analysis' methodologies. While considering the SCOPUS database, a total of 338 English written articles were filtered using the LM term selection criteria during a 10 year time interval (2004-2014). Based on this criterion, 2 specific files were exported for Excel processing: key terms indicated by either the authors or SCOPUS based on a software specific algorithm and depending on the publication year; abstracts of the respective papers. Subsequent to the processing procedures, the acquired data constituted the basis for the 2 types of scientometric analysis.

The quantitative characteristics of the texts in question were suggested in the first instance by the key terms that described the analyzed articles. A useful methodological note was represented by the level of significance for this type of analysis. The resulting "word cloud" contained and particularly highlighted the high frequency encountered key terms. Consequently, the word size and color intensity became directly proportional with the occurrence rate, while the marginal terms and niche research areas (marked by low frequency of occurrence) could be scarcely revealed. Despite these limitations otherwise inherent to the analysis at hand, the potential to establish the general trend characterizing this field of interest remained promisingly high, as it was likely to result in a reliable perspective on both traditionally popular landmarks as well as poorly assessed but yet modern points of view.

Since the key terms within the database have been associated with the publication year, the use of the respective terms time evolution was evaluated. Furthermore, in order to substantiate a complex scientometric assessment, a semantic analysis software tool (Tropes Semantic Knowledge) was applied. The theory behind this software integrated two working models: propositional evaluation of discourse and predicative propositional analysis. This analytical model was based on the need to find a cognitive unit of primary information processing and a syntactic measure, both tools allowing cropping speech features.

Representing more than a "statistics of texts", the semantic analysis of abstracts from the selected papers emphasized a detailed picture of the available manuscripts conceptual construction, with an extra-layer of scientific depth when compared to a simple assessment of key terms. In order to operationally

manage the semantic analysis, the selected abstracts were exported from Excel into separate files, thus resulting into a viable "analysis scenario" described by the Tropes software. The figures in black background contained statistically processed results as synthesized by the Gephi software dedicated to the analysis of networks, while the input used in Gephi was the ontology of terms defined and exported from Tropes software. Specifically, the graphs illustrated the semantic relations between words, thus ensuring the thickness of the link aimed to show the strength of semantic relationships. The size of the nodes indicated the frequency of occurrence in texts.

The connections (lines between nodes) were illustrated with color source. Moreover, the source nodes were related to the beginning of the semantic connection, thus creating a complex network based on which one concept is described by another. The links appeared as visible bonds starting with a specific weight set between 7.1 and 77, while weaker relationships (under 7.1) were not illustrated. These weights reflected the strength of the semantic relations between concepts, which were grouped into classes of networks based on an algorithm of "modularity class". The resulting modular classes were, in this case, themed episodes of text actually constituting groups of concepts coherently discussing a phenomenon or a generic theme.

## RESULTS

The articles' distribution in accordance with the year of production was shown to be relatively uniform, with an average number of 39 articles per year. The "word cloud" emphasized high frequency key terms in a manner in which the word size and color intensity became directly proportional with the specific frequency (**fig. 1**).

The terms that occurred at least 21 times in the total analyzed corpus were represented at the edge of the "word cloud" with the smallest text size, while the terms with up to 312 occurrences were shown at the center of the image with maximum size characters. In order to underline the statistical range of data comprehended in **fig. 1**, only 3.5 % of the key terms within the corpus of articles were included in the "word cloud".

It was observed that setting a lower limit for the frequency range (below 21 appearances) would make the texts become unreadable. For example, through a filter of key terms that appear once in the

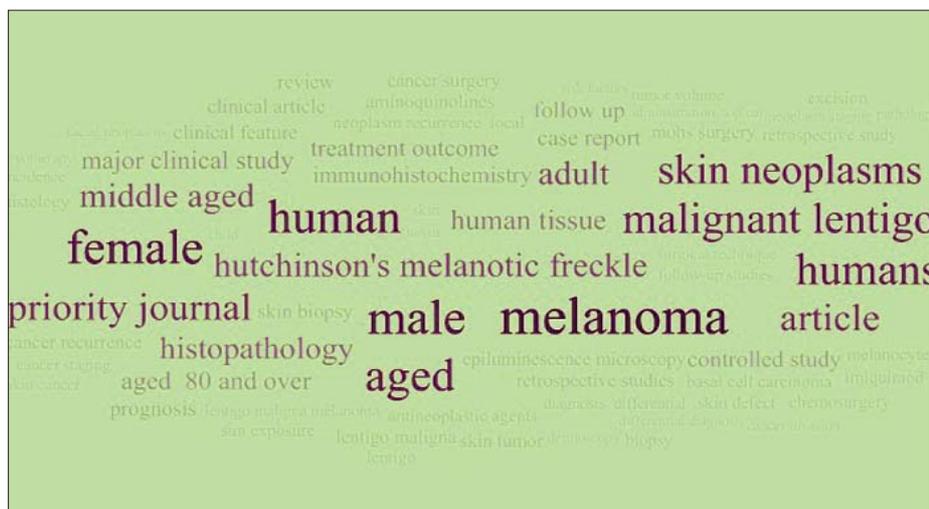
database, a total of 1,222 terms could be identified, while 1,876 terms occurred less than 20 times (therefore not shown in **fig. 1**).

An evidence based perspective of the above mentioned ideas was obtained through a number related frequency translation. The comparison between the classical and the relatively new terms involved in LM scientific analysis largely confirmed the predominance of the first category of notions. On the other hand, it became clear that the new diagnostic

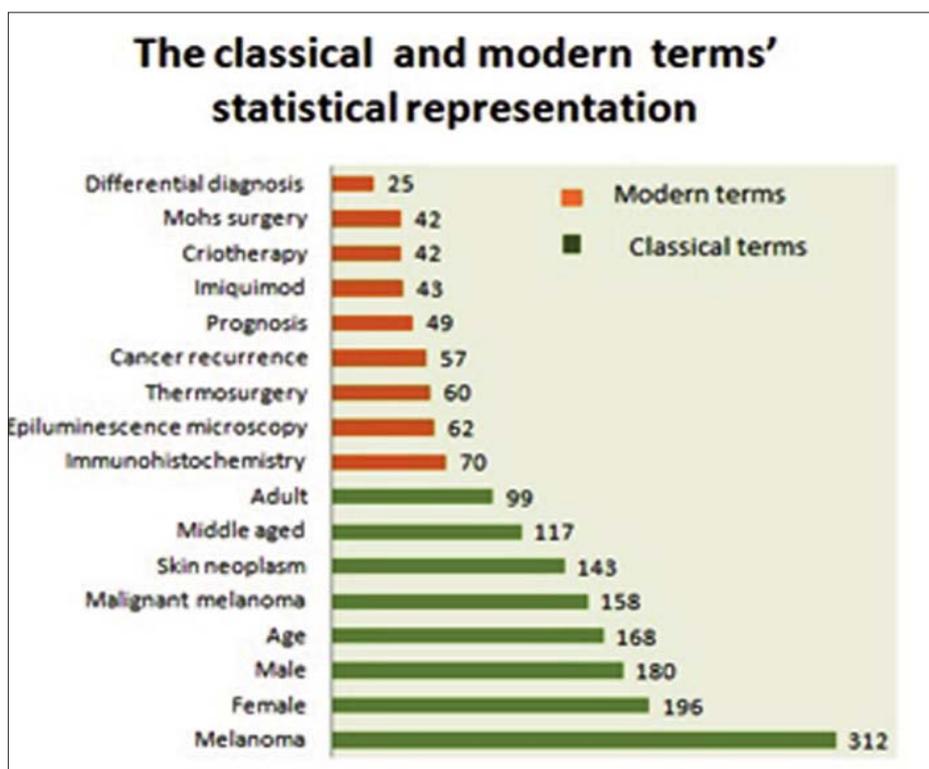
approaches (immunohistochemical markers involved in tumor progression), as well as modern treatment alternatives (“spaghetti” technique, Mohs micrographic surgery and stage geometric excision) are scarcely quoted in the great majority of texts (**fig. 2**).

Most interestingly, the ends of the interval at hand specific for the statistically evaluated classical terms remained more or less the same, without significant variations between 2004 and 2014. From another point of view, a certain dynamics of the

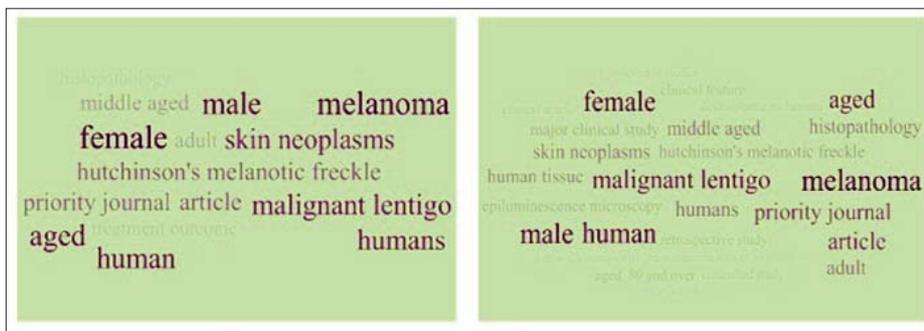
**Figure 1.** The “word cloud” of key words for the 2004–2014 time period



**Figure 2.** The classical and modern terms’ statistical representation



**Figure 3.** The key words analysis focused on the edges of the interval (2004 and 2014)



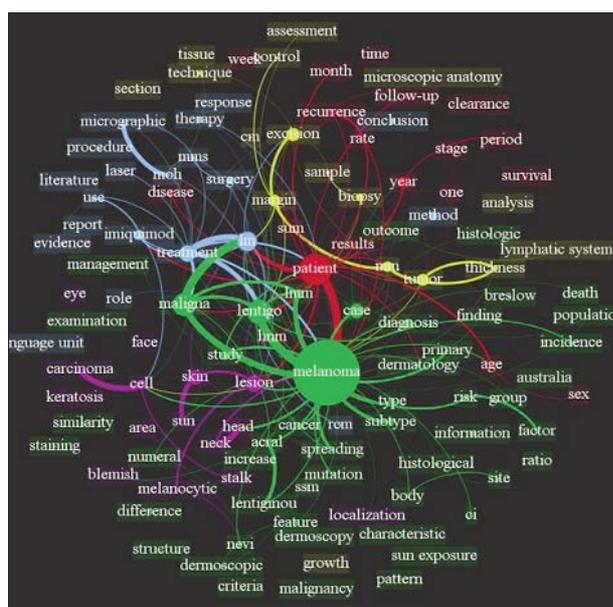
“word cloud” was observed over the years, marked by a promising tendency towards further inquiry into the modern aspects of LM pathology. More precisely, it was noted that the center area of the “word cloud” displayed a rather “frozen” image (systematic concern for the classical keywords), while the periphery of the cloud increasingly incorporated the newly introduced diagnostic, therapeutic and prognostic notions (fig. 3). This phenomenon constitutes solid proof concerning the active involvement of the scientific community in LM related research.

A different outcome of this trial aroused from the completion of a dictionary of terms in which the software identified the word units called "references", thus surpassing the barrier of simply counting notions' frequency. Some scenarios were proposed in regard to references that appeared in the total corpus of texts at least 30

times, thus avoiding the inclusion of insignificant terms. For example, a general map of semantic relations between representative concepts for the studied corpus of articles was designed around the concept of "melanoma" (fig. 4).

As the link specific thickness matched the strength of semantic relationships and the nodes' size indicated the frequency of occurrence in various texts, it might be relevant to quantify the outcomes of a consequently definite diagnosis and correct treatment. Among the available publications, the interest was consistently focused on the recurrence and survival rates, oncologic outcomes and follow-up profile (fig. 5).

Among the specific terms for medical procedures, a central place was occupied by classical approaches such as tumor biopsy, control of the resection margins, tumor depth evaluation (Clark and Breslow indexes) and sentinel node puncture. The modern therapeutic modalities such as Mohs



**Figure 4.** Conceptual network map based on the Tropes' defined relations



**Figure 5.** Patient focused automatically identified modular class

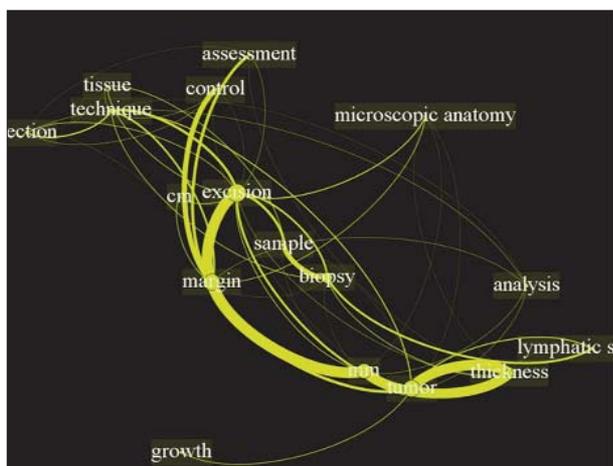


Figure 6. 'Surgical treatment' sub-network map

micrographic surgery or stage geometric resection using Wood lamp did not materialize into center-pieces of the network (fig. 6).

## DISCUSSION

The described lack of a high dynamic trend concerning key terms suggests persistent clinical and diagnostic obstacles. On the other hand, this aspect may reflect the absence of progress in the global scientific community regarding this field of pathology. Practically speaking, it is rather insufficient that only a few studies supported the idea of newly introduced reliable diagnostic and treatment methods. In fact, the actual viability of the modern approaches largely depends on their implementation into widely acknowledged current practice. Interestingly enough, during the specific extremes of range (2004/2014), drawing a parallel between the relatively "frozen" image characterizing the center of the key terms' based "word clouds" and the substantial changes reflected in the peripheral area of the clouds in question can be considered as relevant. Further more from this perspective, it becomes obvious that most of the key terms located in the central area remain more or less constant. At the same time, it could be considered essential to notice the newly used key terms from the periphery of the cloud emerging over the last few years.

Despite the fact that the recently developed diagnostic and treatment modalities continue to be rather rarely discussed in the overall published literature when compared to the classical terms, their potential has been consistently underlined. For instance, the "spaghetti" surgical technique described

by Gaudy Marqueste et al. in 2011 was described as rather revolutionary therapeutic approach. Basically, the respective technique allows an accurate delineation of the surgical margins of LM lesions to be outlined, thus providing a low rate of multiple excisions and tissue sparing in functional or aesthetically valuable areas. Naturally, the viability of the method will be determined by long term studies involving large series of cases (14).

When LM progresses to LMM, the pathological analysis is expected to assess histological markers with prognostic significance such as Clark invasion level, Breslow index, mitotic index, intra-tumor lymphocytic infiltration and vascular permeation aspects of tumor ulceration. In view of an accurate diagnosis, histological parameters should be considered along with local or distant metastasis (16). The majority of statistical reports highlighted the prognostic clinical factors such as gender, location, age, hormonal status, race and immunologic context. Most of them were generously represented in the center of the "word cloud" for the entire time range (2). Precisely because these issues were constantly addressed for a long time in almost all researches, it was concluded that gender significantly impacts survival differences at 5 years (up to 10-20 times higher survival rate in women), while old age (over 80) also constitutes an unfavorable prognostic factor (2).

When talking about immunohistochemistry, several markers of melanocyte differentiation are constantly used, each of them displaying its own set of advantages and limitations. Although not quite a novelty, this pathology technique was characterized by distinctively spectacular outcomes but suffered from little application in daily practice (7).

The general immunohistochemical markers of cellular differentiation are represented by Vimentin and S-100 while the melanocytic specific markers are HMB-45, MART-1/Melan-A, MITF, TRP2 and MAGE. Last but not least, the aberrant markers are constituted by citokeratins, CEA, EMA, GFAP, actin and desmin (17, 18).

Additionally, immunohistochemical markers for tumor progression include the molecules involved in key points of the cellular proliferation and migration (inter/intracellular signaling and cellular adhesion) processes, together with extracellular matrix degradation (18). Tumor proliferation markers behave differently in relation to tumor progression, meaning that during cellular proliferation, some of them may

be up- (cyclin A, B1, D1, D3, E, Ki67, PCNA, telomerase, Cdk2, mdm2 and p21) (19) or down-regulated (p15, p16, p27) (20).

An interesting perspective is related to immunohistochemical of cellular migration, including those of cellular signaling and adhesion. Each of these may be, at their own turn, up- (EGFR, c-Myc, N-ras, Transferrin receptor, N-cadherin, MCAM, ICAM-1, ALCAM, A4 $\beta$ 1, Av $\beta$ 3 and CD44v6) (21, 24) or down-regulated (c-Kit, PTEN,  $\beta$ -catenin, E-cadherin and VCAM-1) (22). The proteases involved in the degradation of extracellular matrix undergo an up-regulated phenomenon as the tumor progresses (MMP1, MMP2, MMPa, MMP13, TIMP1, TIMP3, MT1-MMP, EMMPRIN and cathepsin B, D, H and L) (22-29).

Obviously, the sole existence of these new approaches is not nearly enough, as it must be backed by well-designed basic research projects resulting into relevant publications reliably explaining their impact on cancer specific recurrence and survival. The persistently small share of available data in this field of interest, largely showed by the reduced frequency of representative key terms among the corpus of articles, suggests its constantly low practical applicability. The published manuscripts generally reflect the scientific concerns in this field. Based on these premises, there is definitely a need for more advanced research aimed to explore this promising diagnostic niche. Ideally, during a future scientometric assessment on this topic, the relatively new terms should be revealed as larger and located more centrally within the “word cloud” as well as the specific networks of modularity classes.

## CONCLUSIONS

Generally speaking, there is a continuous concern about lentigo maligna, reflected in the predominantly increasing publications emerging in this field of research during the recent years. Unfortunately, although there are emphasized newer aspects with regard to diagnostic abilities, therapeutic attitude and prognostic assessment of such lesions, the widely displayed tendency of scientific development still leans towards the re-assessment of the classical theories concerning diagnosis and prognostic markers.

The new treatment alternatives refer to more complex surgical techniques that target a more accurate evaluation of tumor invasion’ margins, together with an improved tumor resection and non-

surgical modalities (cryotherapy, electrocautery, topical immunomodulator, radiotherapy and laser). Furthermore, a superior evaluation of the invasive and metastatic potential of such lesion is achieved by the thorough use of immunohistochemical markers. Although these features are indeed supported by a series of well-conceived studies, they are not constantly appreciated during the daily medical care, a drawback largely reflected by the insufficient number of recent publications in this field.

These aspects may be considered as underlining the general perception of the techniques in question as genuinely innovative methods requiring further evidence-based confirmation. While attempting to summarize the previously discussed issues highlighted by the keywords’ scientometric analysis, it might be established the persistent absence of highly dynamic research profile in this field of interest. Consequently, the future research efforts and tendencies are due to focus on the new LM approaches, thus possibly turning them into reliable diagnostic and treatment centerpieces.

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