

# Survival and Prognostic Factors in Patients with Malignant Melanoma: Statistical Analysis of 466 Cases Treated between 1998 and 2014

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Received date: June 23, 2017; Accepted date: July 25, 2017; Published date: August 01, 2017

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### Abstract

The aim of this study is to analyse how patient's or melanoma's characteristics influence the prognosis. Therefore, we retrospectively reviewed and analysed our database, selecting 466 patients with most complete data. At diagnosis, average age is 55 years; most melanomas are in stage lb, mean thickness amounts to 2.14 mm, with gradual reduction over the time. Ulceration is detected in 24% of cases, being associated with augmented thickness and reduced survival. Mostly, the number of mitosis per mm<sup>2</sup> is >1 and nodal infiltration is present in mild form. Women have more frequently primitive melanomas of the limbs; men often develop primitives on the trunk. In the head and neck district we find the highest percentages of advanced nodular melanomas. The sentinel node is positive in about 20% of cases. Elderly patients, despite lower lymphatic involvement rates, show worst prognosis. Univariate estimates on the likelihood to have positive SNs linked to individual prognostic factors demonstrate the importance of high thickness, nodular type, advanced age, presence of ulceration and absence of regression. Mean number of excised nodes during CLND is around 17. At deadline, mortality is 13.48%, overall survival at 1, 3 and 5 years is 99, 93 and 88% respectively. Survival improved among time (88 vs. 95% at 3 years, 83% vs. 90% at 5 years). Analysis of survival indicates advanced stage at diagnosis, high thickness, nodular type, head and neck location, male sex and advanced age as negative prognostic factors. The presence and quality of nodal involvement strongly affects survival: Positive nodal biopsy patients show 30% lower OS5y values, mostly in case of macroscopic tumor burden.

**Keywords:** Malignant melanoma; Solid tumors; Leukaemia; Lentigo maligna

#### Introduction

Malignant melanoma accounts for about 5% of skin cancers, but is the most lethal. It originates from melanocytes, pigment producing cells deriving from neural crest that should be retrieved all around the body. Currently, in Western countries, melanoma shows the fastest growing incidence between all malignant tumors in men and is second only to lung cancer in women. From 1950 to 2000 it has been estimated an overall incidence increase of about 300% and despite screening efforts mortality has not significantly decreased [1]. The highest incidence is found in Australia and New Zealand, the lowest in Japan. Its occurrence seems to be related to several factors, both genetic and environmental, in particular to ultraviolet rays of medium intensity (UVB) exposure.

# **Patients and Methods**

Our Institute is a reference center for patients with melanoma, dealing with a population of about 600000 people, here an average of 80 Sentinel Node Biopsies (SNB) are performed every year and about 1.600 patients are in follow-up. We have realized a retrospective review of patients undergoing SNB after melanoma excision during 16 years and selected 466 patients with most complete data.

During the study period, the criteria for the execution of SNB have been: Tumor thickness (Breslow)  $\geq 1$ mm, or in melanomas <1 mm the presence of ulceration or 1 mitosis/mm<sup>2</sup>. We used both colloidal mapping with 99 Technetium (99mTc) and vital dye (Patentblau V, Guerbet, Roissy Cdg, France) injection, in order to accurately and quickly identify the SN, that was subsequently treated according to EORTC protocol, with semi-serial histological sections (200 µm), and considered positive even after immuno-histological detection of isolated tumor cells.

# Age and sex

Mean age at diagnosis is 55.6 years (SD16), with a minimum of 5 and a maximum of 86 years (Table 1). This is in accordance with other observations, which set average age at diagnosis at 57 years, almost a decade before most solid tumors [2]. Rather rare in children, it does not spare any age group and is second only to leukaemia for potential life year's loss [3].

52.8% of patients in this series are men and 47.2% women. Primary melanoma location shows a sex-specific distribution, preferentially affecting limbs among women and trunk among men.

Sex	Head and neck	Trunk	Limbs	Not specified	Total
F	15	60	142	3	220 (47.21 %)
м	21	120	98	7	246 (52.79%)
Total	36	180	240	10	466

Table 1: Gender of patients by location.

Melanomas of the trunk tend to be more precocious (average onset 53 years) compared to those of the head and neck district (average onset 64 years). In fact, melanomas of the head and neck are associated with chronic patterns of sun exposure, while those of the trunk to young age sunburns [4,5].

The greater the age of the patient, the more advanced is the stage at diagnosis (Table 2) the OS5y strictly depends on the stage at diagnosis, since most stage I patients can expect a prolonged disease-free survival (DFS) and even the healing, while those with more advanced lesions are more likely to die of metastatic disease [6]. The poorest prognosis of elderly patients could therefore be ascribed to diagnosis carried out in a more advanced stage.

Stage	Median age	IQR	Average age
In situ	52.18	30.92	50.95
1	53.91	22.94	54.26
2	62.15	21.23	58.73
3	59.07	25.17	56.71
4	61.6	17.58	62.16

Table 2: Median age, IQR and average age by diagnosis.

#### Stage

The majority of patients are in stage IB at diagnosis (Table 3). In fact, melanoma is unique between all cancers: a spot on the skin surface that can be self-relieved [7]. Thanks to awareness programs and population screening, a growing number of melanomas are diagnosed at an early stage [8].

Stage	Frequency	%
In situ	9	1.93
1	229	49.1
2	107	23
3	92	19.7
4	6	1.29
Unknown	23	4.94
Total	466	100

Table 3: Stage at diagnosis.

Melanoma occurs in a more advanced stage among men than among women and among older patients compared to the younger

ones. In the head and neck and trunk districts, stage at diagnosis is significantly more advanced than in the limbs (p<0.001), according with the findings of other larger series [6].

# Histotype

In 122 cases we could not trace precise data on histology, among the remaining 344 patients we notice the prevalence of SSM, followed by NM (Table 4). In the category "other" we have grouped 5 cases of lentigo maligna, 14 of acral lentiginous melanoma and 9 of nevoid melanoma.

This is consistent with the general remarks, which point out the SSM as the most common histological subtype and the NM as the second [9]. As age increases also the proportion of NM increases, but not significantly (Table 5).

Histotype	Frequency	%
SSN	215	62.5
NM	101	29.36
Others	28	8.14
Total	344	100

**Table 4:** Histological types.

Histotype	<50 years	50-65 years	>65 years	Total
SSM	78	68	69	215
NM	28	27	46	101

Table 5: Histotype by age.

#### Other histological characteristics

The average thickness amounts to 2.14 mm (SD 2.23 mm). As expected, different histological types have very distant values of average and median thickness (Table 6).

Histotype	Median	IQR	Mean
SSN	1.2	1.5	1.59
NM	2.8	2.22	3.51
Others	1.2	0.8	1.98
Total	1.42	1.57	2.14

 Table 6: Median and mean thickness and IQR according to the histotype.

By Kernel Density Estimation (KDE), we have confirmation that NMs have a higher probability of being thicker at presentation (Figure 1). Breslow thickness and nodular type are independent factors significantly associated to positive SNB [10]. The box plot chart for stage shows that the median values increase with stage and presence of wide variability, confirmed by numerous outliers towards higher values in the II and III stage (Figure 2).

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Figure 1: Kernel density according to histotype.



Worth noting the progressive decrease of thickness over time: the median value decreases by 1.75 mm in the first sub-period (1998-2003) to 1.20 mm in the last (2010-2014). This is due to increasingly early diagnosis, effect of population awareness campaigns.

Ulceration is a powerful independent prognostic factor, which is necessarily analysed during histopathological examination [6]. Defined as absence of intact epidermis overlying a significant portion of the primary melanoma, its incidence increases together with thickness [11]. The presence of ulceration corresponds to a decrease of survival rates in all thickness categories; it is the only primitive melanoma related characteristic that can modify the prognosis of the disease with nodal involvement [12]. Among our patients ulceration is mostly absent (Table 7). Data on tumor growth pattern are incomplete; in any case the clear predominance of melanomas in Vertical Growth Phase (VGP) is noticeable (Table 8). Even if data concerning regression are largely incomplete, they show a trend in line with literature, that is regression is present only in a minority of patients (Table 9). In this regard, we should remember that, after first being considered as a risk factor and later as a protective factor, current research report conflicting results about the significance of regression and its link with the SN state [13].

Ulceration	Frequency	%
Present	110	23.61
Absent	309	66.31
Missing	47	10.09
Total	466	100

Table 7: Ulceration.

Type of growth	Frequency
Vertical	178
Horizontal	16
Mixed	14
Missing	258
Total	466

# Table 8: Type of growth.

Regression	Frequency
Absent	240
Present	79
Missing	147
Total	466

# Table 9: Regression.

The Tumor Infiltrating Lymphocytes (TILS) are a type of white blood cells that are found in tumors; implicated in the killing of cancer cells, their presence is often associated with better clinical outcomes. It seems that the host response represented by the presence of TILS has a favourable impact on survival, although some experts suggest a possible overestimation of the influence of this factor on prognosis [14]. Currently, the intratumoral lymphocytic infiltrate in malignant melanoma is classified as brisk (marked), non-brisk (slight) or absent; in our experience lymphocytic infiltration is mostly present and nonbrisk (Table 10). Among all patients there have been three cases of multifocal melanoma.

Nodal Infiltration	Frequency
Absent	45
Brisk	83
Non-brisk	178
Missing	160
Total	466

Table 10: Nodal infiltration.

Although the mitotic rate is a continuous variable, the threshold that delineates an increased metastatic risk is at least 1 mitosis/mm<sup>2</sup>. It is the strongest prognostic factor after primary tumor thickness and the vast majority of our patients exceed that threshold [15].

## Nodal status

At histology 20.17% of SNs show metastatic deposits, which are more than twice in NM patients (35.64%) compared to SSM patients (15.81%) (p<0.001), reflecting the natural evolution of the disease [16].

Interestingly, the percentage of positive SNs has increased over time, although variation is not statistically significant. This can perhaps be attributed to the increased sensitivity of histological parameters, which currently lead to consider positive a SN even in the presence of isolated tumor cells identified through immunohistochemistry. Analysis of data shows the fundamental relationship between thickness and SN positivity: Setting the cut-off at 1 mm, we find a 5.6% of positive SNBs for lesser thicknesses and a 26,07% of positive SNBs for greater thicknesses (p<0.001). This relationship, as well as logic, is well known since long time, although the exact thickness below which virtually no nodal involvement should be expected is not established [17,18].

After logistic regression to estimate the effect of thickness on the SN positivity, using the Roc curve [19] it is possible to calculate the optimal cut-off point between thickness and positivity of the SNB, obtaining a value of 1.665 (1.30-1.99, I.C. 95%) (Figure 3).



In presence of ulceration, positive SNB stands at 30.28% vs. 17.32% in case of its absence (p<0.001). Again, this is in line with what already highlighted by other authors: the presence of ulceration is considered as a predictive factor for SN positivity and should be an additional reason to execute SNB [20].

Using a logit (or logistic regression) model to estimate the probability of having a positive SNB linked to individual prognostic factors (univariate estimates), we can point out the influence of high thickness, nodular histology, advanced age, absence of regression and presence of ulceration (Table 11). The amount of nodal involvement has been considered as macroscopic tumor burden when >1 mm and as microscopic tumor burden when  $\leq 1$  mm, in presence of few (10-30) or even isolated metastatic cells.

	Odds ratio	Standard Error	P>Z	95% CI
Breslow<1 mm	Ref.	-	-	-
Breslow ≥ 1 mm	5.95	2.44	0	2.66-13.29
Other histotypes	Ref.	-	-	-
SSM	1.21	0.4	0.568	0.63-2.29
NM	3.61	1.23	0	1.85-7.03
<50 years	Ref.	-	-	-
50-65 years	0.74	0.2	0.271	0.43-1.27
>65 years	0.83	0.22	0.484	0.48-1.41
Presence of regression	Ref.	-	-	-
Absence of regression	3.5	1.59	0.006	1.44-8.51
Absence of ulceration	Ref.	-	-	-
Presence of ulceration	2.07	0.53	0.005	1.25-3.43

Table 11: Univariate logit estimates for positive SNB.

Among the 94 patients with positive SNB, 69.15% show a macroscopic and 30.85% a microscopic tumor burden (Table 12). The presence of macroscopic tumor burden seems associated with worst-disease free survival and melanoma specific survival [21].

SNB	Frequency	%
Negative	366	78.54
Macroscopic tumor burden	65	13.95
Microscopic tumor burden	29	6.22
Missing	6	1.29
Total	466	100

Table 12: Nodal status.

The mean number of nodes removed during the Completion Lymphadenectomy (CLND) has been 17.37. The average number of positive nodes has been 1.91 for stage III and has risen up to 3.25 for stage IV. With regard to the importance of SN tumor load, we observe at CLND among patients with microscopic tumor burden a 17.24% of positive non-sentinel nodes, a value that rises up to 21.54% among patients with macroscopic tumor burden. Focusing on the relationship between histotype and nodal positivity, NMs manifest their major aggressiveness with an average value of 2.23 positive nodes at CLND compared to 1.55 of the SSMs. In approximately 6% of patients with negative SNB, a Therapeutic Lymphadenectomy (TLND) has later been required, because of the clinical occurrence of lymphatic spread.

# Analysis of Survival

To measure the fraction of patients living for some time after treatment, we have excluded 57 non-resident individuals, for whom no follow-up information has been available and then used the Kaplan-Meier estimator for specific cause. At the end of follow-up (31 December 2014), of the 409 considered individuals, deaths have been

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55, accounting for 13.48% of the sample. Overall Survival (OS) shows a trend in line with international literature [22], being OS1y 99%, OS3y 93% and OS5y 88%. Analysing survival in the three sub-periods, there has been a clear improvement between the first and the following two (OS3y 88% vs. 95%, OS5y 83% vs 90%) (Figure 4). This finding should be seen in the context of a better multidisciplinary and targeted management of patients.





Looking at survival in the two sexes, a constant advantage emerges for women over men (Figure 5). This difference seems minimal 1 year after diagnosis, becoming more and more evident at 3 and 5 years (OS3y 96% vs. 90%, OS5y 91% vs. 86%). Female patients with melanoma generally show significantly longer survival rates, as other case series also point out [23]. Women are more likely than men to have thin, non-ulcerated melanomas localized on the limbs, all favourable prognostic factors [24,25]. Male sex is considered an independent risk factor affecting OS in melanoma patients [26]. No significant differences in survival rates between first and second stage can be seen up to 5 years after diagnosis, when the worst prognosis of stage II clearly emerges (OS5y 97% vs. 90%). For patients with stage III at diagnosis, survival at 1 year was 96% at 3 years 70% and at 5 years 62% (Figure 6). These observations are consistent with other literature [22]. The small number of patients with metastatic melanoma at diagnosis does not allow valid statistical analysis, but according to the AJCC estimates, OS5y for stage IV would be 5-16%.



Younger patients, particularly younger than 50 years, show a survival advantage throughout the entire follow-up (Figure 7).



Indeed, advanced age is associated with a worse prognosis. Younger age, despite primary melanoma often presents aggressive features at diagnosis (high mitotic rate, ulceration), goes together with a better prognosis, suggesting a different biology [27].

Increasing age is associated with a decreased incidence of SN involvement at multifactorial analysis (Figure 8).



Despite this, elderly patients have higher five years mortality rates compared to young patients [28]. NM has a significantly worse prognosis than SSM (OS5y 0.72 vs. 0.90), as earlier reported [29].

In our series, thin melanomas (<1 mm) show a noticeable (11%) advantage in 5 years survival rates, compared to thick melanomas (>1 mm) (Figure 9).



Head and neck melanomas have an aggressive behaviour, leading to poorer prognosis than trunk and limbs ones [30,31]. That is already evident 1 year after diagnosis, and increases at 5 years (OS5y 74% vs 89% and 90%) (Figure 10). SN status substantially influences survival rates (OS5y 96% vs. 67% for negative vs positive SNB) (Figure 11). Similar reports emerge from other larger series [22].



Distinguishing positive SNB patients on the amount of nodal tumor burden, survival estimates show a substantial overlapping of values until three years, when the better prognosis of microscopic burden emerges (80% vs. 73%) and amplifies at 5 years (75% vs. 62%) (Figure 12). The debate on the importance of nodal tumor burden is more topical than ever, it is not actually part of the staging procedure, but its impact on prognosis is remarkable. Recently, such classification evolved, with the new category of minimal tumor burden, for SN metastatic amounts  $\leq$ 0.1 mm or  $\leq$ 0.2 mm [32]. There is an on-going trial, which aims to define the smallest SN involvement requiring CLND, the MINITUB trial organized by the EORTC Melanoma Group. Anyway, until the prognostic value of very small amounts will not be proved by long follow up clinical trials, it is probably prudent to treat patients regardless of tumor burden as positive at SNB [33].





# Discussion

Proper surgical management is critical for optimal diagnosis, staging and treatment of primary cutaneous melanoma. The goals of surgery include: Histological confirmation of diagnosis, which ideally is established through an excisional biopsy with simple free margin, management of regional nodes, local recurrences, in transit or distant metastases, optimal functional and aesthetic results. An excisional biopsy including 1 to 2 radial mm of normal skin and subcutaneous fat is the optimal technique to remove suspected lesions, without compromising further potential staging manoeuvres. In fact, SNB is potentially less accurate after wide excision. In case of melanoma at histology, therapy continues in the context of the so-called two-stepsurgery, through a surgical scar revision by widening of the excision margins [34]. That should be quickly carried out, possibly within six weeks after the first biopsy [35]. Not performing wide excision after biopsy leads up to 40% of local recurrence. The extent of resection margins during scar revision depends on the primary melanoma Breslow, as stated by the 2017 NCCN guidelines: 0.5-1 cm margin for in situ melanomas, 1 cm margin if  $\leq 1$  mm thick, 1-2 cm margin if 1.01-2 mm thick and 2 cm margin for any thicker melanoma. It is mandatory to remove all subcutaneous tissue until the muscle fascia, in order to avoid any risk of disease diffusion.

Melanoma cells often spread through the lymphatic system, but physical and radiological examination of regional nodes is often not conclusive. There are specific patterns of lymphatic diffusion according to the location of the primary melanoma and skip metastases are not described. One node within a lymphatic basin is supposed to be the first involved in case of metastatic spread, the so called sentinel node. If this node is negative at histology, the entire basin is considered disease-free [36]. The SNB is a minimally invasive technique developed to identify patients with subclinical nodal metastases at higher risk of recurrence, which could potentially benefit from a CLND or a systemic adjuvant therapy. If negative, avoids an unnecessary Elective Lymph Node Dissection (ELND). Furthermore, the procedure is usually carried out under local anaesthesia, with very low morbidity and quick return to work and normal activities [37]. The lymphatic mapping is especially helpful to define the lymphatic flow of areas with ambiguous or multiple drainage, as trunk, head and neck. The decision whether or not analyse regional nodes relies on the recurrence risk. The probability to detect metastatic deposits at SNB increases with the thickness of the primitive melanoma [38-40] providing important prognostic information. In fact, overall survival, disease-specific survival and relapse free survival are significantly longer in patients with negative nodes [41].

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Relevant studies suggest lymphatic mapping with SNB as prognostic tool, further prospecting a survival advantage for patients with intermediate thickness melanoma and microscopic nodal involvement assigned to SNB and if necessary CLND, compared with those managed by simple observation [42,43]. Thus, the most common current approach to any amount of lymphatic disease consists of a CLND regardless of the importance of nodal involvement [33]. This attitude can lead to an overtreatment and the opportunity to perform less aggressive nodal dissections should be evaluated case by case, as for instance axillary lymphadenectomies limited to the first and second level in selected patients [44]. This also considering the doubts about the real impact on survival of CLND compared to simple observation stated in some series [42,45] in this regard we will await the results of the clinical trial MSLT-II.

ELND does not seem to confer any benefit in terms of survival, but involves an increase in costs and morbidity, therefore it is not currently practiced [46]. TLND is still the recommended approach in case of clinical or cytological (FNAB) involvement of regional nodes. There is some evidence that CLND after positive SNB offers survival benefits over TLND. SNB is not associated with significant OS benefits, however, it is related with higher rates of DFS/RFS [47].

#### Conclusion

Our work examined a homogeneous cohort of melanoma patients, with particular reference to the main features of the disease and the major prognostic factors, thus focusing on the SN status, which is to date the most important one. In our opinion, until prospective randomized clinical trials will assess the negligibility of very small amounts of disease in the SN, is safer to treat patients regardless of tumor burden as positive. As for most neoplastic diseases, best therapeutic approach to melanoma is surgery: Healing can solely be achieved by prompt and radical surgical treatment, carried out if possible in dedicated centres, on the basis of the letter scientific evidences.

Despite the remarkable increase of melanoma incidence, mortality rates have been steady in the last decades, due to information and screening campaigns, early resection of suspicious lesions, patient's selection by SNB, development of new adjuvant therapies and careful follow-up. Malignant melanoma implies still nowadays high mortality and disability costs, featuring an important research area, with the aim of improve prognosis and quality of life of people that face such diagnosis.

# Funding, Ethical Standards and Consent

No funding was received. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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Informed consent was obtained from all individual participants included in the study.

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