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ORIGINAL ARTICLE

Head–neck melanoma: Clinical, histopathological and prognostic features of an Italian multicentric study

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Abstract

Background: Primitive location of melanoma could be a relevant prognostic factor. As regards the scalp, some studies indicate a particularly aggressive biological behaviour for this anatomical localisation.

Objectives: In this multicentric study, data regarding head–neck melanoma (HNM) have been revised.

Methods: The design of the study included two main phases. In this retrospective study, data regarding HNM have been collected and analysed.

Results: In summary, our data suggest that the posterior neck is the area most affected by thicker melanomas. Cheeks and neck melanoma are associated with reduced disease-free years of life and overall survival compared with all other sites of HNM.

For affiliations refer to page 83.
Fabrizio Guarneri and Cataldo Patruno contributed equally.
In memoriam of Prof. Ugo Bottoni.

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Conclusions: This study provides useful information in defining the clinical features of HNM, thus improving diagnosis and treatment strategies.

KEYWORDS
head–neck melanoma, location of melanoma

INTRODUCTION

Melanoma is a skin cancer responsible for over 70% of skin disease deaths.[1] Main prognostic factors in melanoma patients are clinical (age, sex and anatomical localisation) and histopathological (histological subtype, Breslow's thickness, Clark's classification, ulceration, regression, mitotic index, amount of tumour infiltrating lymphocytes, capillary invasion and microscopic satellites and perineural invasion).[2] Primary head and neck cutaneous melanoma (HNM) may affect the scalp, face, ears, and neck, with different frequencies.[3–8] HNM has been associated with a worse overall prognosis compared to cutaneous melanoma in other anatomic sites.[9] In several studies, head and neck localisation has been analysed as a single unit, preventing the tracking of single skin areas.[10] On the other hand, some authors consider scalp and ear HNM to be at higher risk, while others consider scalp and neck.[11,12] As a consequence, clinical implication of the different localisations of HNM has not been accurately defined.

To the best of our knowledge, there are no Italian studies analysing a large number of HNM patients. The aim of this retrospective, multicenter study is to identify significant clinical, histopathological and prognostic factors for HNM. In particular, we analysed the possible prognostic differences among four different subsites within the head and neck area (divided into 10 anatomic areas: cheeks, scalp, anterior neck, ears, temples, forehead, nose, posterior neck, eyelids and lip-chin), and searched for microscopic parameters that might explain the prognostic differences.

MATERIAL AND METHODS

Adult patients (≥18 years) with a known primary HNM treated between 1 January 2000 and 31 December 2018 in 21 Dermatology Centers of Northern (9 Centres), Central (7 Centres) and Southern (5 Centres) Italy were included.

Follow-up was documented through medical records in local databases. The study was performed following the principles defined in the Declaration of Helsinki.

Data collection was carried out following the current legislation regarding the privacy of patients. Patients with missing or incomplete data were excluded from the study. For each patient, data regarding demographics, clinical and histologic features of primary melanoma (site, growth pattern, Breslow thickness and ulceration) were collected. Regarding the localisation of cancer, 10 anatomic areas were considered (cheeks, scalp, anterior neck, ears, temples, forehead, nose, posterior neck, eyelids and lip-chin). Melanoma staging was performed according to the Melanoma Staging System of the American Joint Committee on Cancer.[13] In addition, survival and mortality in relation to some variables, such as age, Breslow thickness, sex and body location, were evaluated. Survival time was calculated on the interval between the first and last visit (or date of death, if known) and represented in Kaplan–Meier curves.

Comparisons between groups of values were performed with Student's t test for independent samples or Mann–Whitney's U test, as appropriate, in the case of quantitative variables. To compare groups of categorical variables, contingency tables were made and analysed by chi-square test or, in case of values of 5 or less, by Fisher's exact test. The Benjamini–Hochberg procedure was used to adjust for multiple comparisons, with a false discovery rate threshold of 0.05.

RESULTS

A total of 1198 adult patients with primary HNM (720 males [60.10%] and 478 females [39.90%]) were visited in the participant Centres in the period considered, but 15 clinical files were not accessible or lost for accidental reasons, and consequently 1183 (98.74%) were included in the study.

At the time of surgical exeresis, patients had a mean age of 65.50 ± 15.95 years (range 3.5–99.83). Lentigo maligna melanoma (LMM) was the most frequent type ($n = 546$, 46.15% of cases), followed by superficial spreading melanoma (SSM; $n = 337$, 28.49%), nodular melanoma (NM; $n = 149$, 12.60%) and acral lentiginous melanoma (ALM; $n = 2$, 0.17%). Other cases of melanoma not falling within aforementioned types were 149 (12.60%). Mean Breslow thickness was 2.06 ± 2.81 mm; in situ melanomas were 33.81%. Ulceration was observed in 14.19% of cases, regression <75% in 5.26% and regression ≥75% in 1.42%. The relative frequencies of tumour stages are shown in Figure 1.

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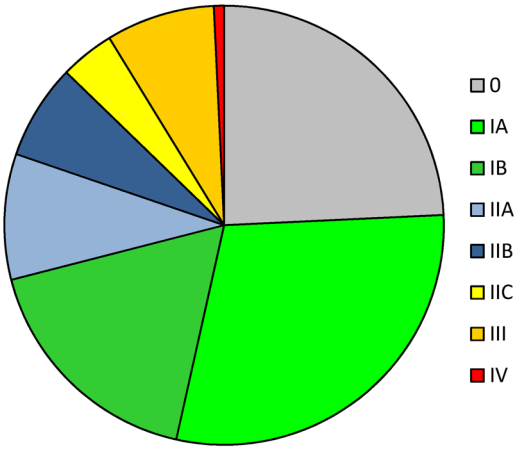

FIGURE 1 Relative frequencies of tumour stages in the study population.

Most HNM was located on cheeks ($n = 383$, 32.38%) and scalp ($n = 200$, 16.91%), while it was rarely observed on posterior neck ($n = 37$, 3.13%), eyelids ($n = 37$, 3.13%) and lips-chin ($n = 26$, 2.20%).

The mean survival time of the 143 patients whose deaths were due to HNM within the study period was 37.15 ± 33.91 months, while the other patients were followed up for a mean time of 40.69 ± 41.12 months.

Based on the Benjamini–Hochberg correction, only values of $p < 0.0098$ were considered significant when comparing subgroups of patients.

As shown in Table 1, melanomas were more frequent in males than in females for all the anatomic sites considered, except cheeks (203 females, 53%) and lip-chin (14 females, 53.85%). However, the difference between males and females was significant only in the case of ears ($p = 0.0027$), scalp ($p < 0.001$) and cheeks ($p < 0.001$).

Stratification by tumour location showed a significantly higher age at the time of surgical treatment for patients with melanoma of nose (mean 71.05 ± 11.76 years, range 39.08–96.92, $p < 0.001$) and cheeks (mean 69.22 ± 14.50 years, range 3.5–96.83, $p < 0.001$), and a significantly lower age for patients with melanoma of anterior neck (55.16 ± 17.56 years, range 13.83-87.83, $p < 0.001$), compared with the rest of the study population.

Stratification by affected area showed some significant differences in the proportions of melanoma types, as shown in Table 2. In detail, LMM was significantly more frequent than other types on nose and cheeks, and significantly less frequent on scalp, ears, posterior, and anterior neck; SSM was significantly more frequent on anterior neck and less frequent on cheeks and nose; NM was significantly less often found on cheeks and nose, and other melanomas occurred significantly more often on posterior neck and less often on cheeks.

Survival data of the study population considered were fragmentary or missing in a relevant number of cases, because many patients who lived far from participating Centers preferred, for logistic reasons, to undergo the majority or all of the follow-up visits in other hospitals, closer to their homeplace. Overall, data of 757 patients were available (death notification and/or at least one follow-up visit) and were used for survival analysis. According to these data, the mean survival time of patients affected by melanomas of cheeks was significantly shorter than that of patients affected by other HNMs (mean time 33.63 ± 40.92 months, range 0–171, $p < 0.001$). As shown in Figure 2, no significant differences of tumour stages were observed between the 757 patients who were included in the survival analysis and the 426 excluded ($p = 0.41$). In the analysis of the subgroup of 143 patients whose death was ascertained within the study period (Table 3), a significantly shorter survival time was observed for those with melanoma of posterior neck (mean 15.33 ± 12.18 months, range 2–37) than for those with other HNMs ($p = 0.004$).

Survival was also evaluated separately for patients with non in situ HNM. In this case, data of 357 patients were available: 101 had melanoma on cheeks, 72 on scalp, 45 on ears, 39 on anterior neck, 26 on temples, 26 on forehead, 18 on posterior neck, 15 on eyelids, 11 on nose and 4 on lips-chin. The Kaplan–Meier survival curves for these patients are shown in Figure 3. While visual analysis apparently suggests that differences between different sites might exist, the log-rank analysis does not allow to reject the null hypothesis in this subpopulation ($p = 0.098$); this result is probably strongly influenced by the overall small number of cases and the high number of censored data.

DISCUSSION

The role of primary anatomic site as a prognostic indicator in cutaneous melanoma has been discussed for decades.[14,15] In our study, we sought to investigate a population of primary cutaneous HNM patients using a large melanoma database, with the purpose of evaluating the effective prognosis weight of the site of primary localisation.

It has already been reported that the frequency of localisation of HNM is variable; indeed, it is 40%–60% for malar area, 14%–49% for occipital scalp, 20%–29% for the neck, 8%–11% for the ear and 3% for the scalp.[16] In another study, approximately 10% to 25% of melanomas were found in the head and neck region,

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TABLE 1 Demographics of patients diagnosed with head–neck melanoma, stratified by anatomic location.

	Sex, *N* (%)				
Area	**Males**	**Females**	***p***	**Age, mean ± SD**	***p***
Cheeks	180 (47.00)	203 (53.00)	**<0.001**	69.22 ± 14.50	**<0.001**
Scalp	150 (75.00)	50 (25.00)	**<0.001**	63.83 ± 14.45	0.08
Anterior neck	87 (59.18)	60 (40.82)	0.83	55.16 ± 17.55	**<0.001**
Ears	84 (73.04)	31 (26.96)	**0.0027**	62.82 ± 17.53	0.06
Temples	57 (67.06)	28 (32.94)	0.17	65.37 ± 14.41	0.94
Forehead	50 (62.50)	30 (37.50)	0.64	69.28 ± 14.03	0.015
Nose	43 (58.90)	30 (41.10)	0.84	71.05 ± 11.76	**<0.001**
Posterior neck	27 (72.97)	10 (27.03)	0.10	60.25 ± 18.92	0.047
Eyelids	20 (54.05)	17 (45.95)	0.45	67.52 ± 13.37	0.44
Lips and chin	12 (46.15)	14 (53.85)	0.14	71.49 ± 19.55	0.06

the most common sites being the occipital scalp and skin of the cheek.[17]

Our data seem to be in accordance with literature[16]; indeed, we found a higher frequency of HNM on cheeks (32,38%) and scalp (16,91%), while it was rarely observed on posterior neck (3,13%), eyelids (3,13%) and lips-chin (2,20%). In our analysis, HNM was more frequent in males than in females for all the anatomic sites, except cheeks and lip-chin. However, the difference between males and females was statistically significant only in the case of ears (73.04% males), scalp (75% males) and cheeks (53% females).

In the literature, the scalp region is most frequently affected in males and is associated with higher Breslow thickness and ulceration rate than in other anatomical sites. The scalp region seems to have a worse prognosis than other head and neck sites, since it more frequently metastasises.[6] This could be the consequence of a late diagnosis due to difficult self-inspection; in fact, scalp cancers are often reported by hairdressers and barbers.[18] Furthermore, the scalp is characterised by intense vascularisation and complex lymphatic drainage; therefore, metastasis more rapidly spreads by blood and lymphatics.[19]

Scalp melanoma is more common in older than in younger patients, and it occurs about 6 times more frequently in males than females. This could also be related to the higher incidence of androgenetic alopecia among males, and the higher ultraviolet damage on the scalp in the elderly.[20]

Distinct dermoscopic features in neck melanomas, according to sun-damaged skin have been reported.[21]

In our study, cheeks and neck location was independently associated with worse outcomes compared to all other anatomic sites. Indeed, follow-up of melanomas of cheeks was significantly shorter than that of other HNMs (mean time 33.63 ± 40.92 months). A significantly shorter survival time was observed for patients with melanoma of posterior neck, compared to other HNM (15.33 ± 12.18 months). This observation highlights the possible unfavourable role of light exposure.

It has been reported that ear and face melanoma have a more favourable course than melanoma of the scalp and neck.[22]

However, survival of patients affected by melanoma of the ear is significantly influenced by ulceration, while in all the other head and neck sites by ulceration and sentinel lymph node positivity.[22]

The nasal region has a high local recurrence rate with significant reduction of disease-free survival (DFS), probably due to its prominent position and constant exposure to sunlight.[23] Another study evinced that the most common tumour site was the face, followed at a considerable distance and in decreasing order of frequency by the scalp, neck, and ears.[24] Face melanoma is more frequent in females (90% of cases as an LMM), while melanoma of the ear and neck is more frequent in men.[20]

Using the Surveillance, Epidemiology, and End Results database, concerning survival differences between patients with HNM and those with melanoma of other sites, scalp and neck melanoma were associated with significantly decreased DFS and overall survival (OS) compared with other areas of the head and neck.[14] A recent study reported that 34% of 27,097 patients presented scalp or neck melanoma.[24]

In our study, patients had a mean age of 65.50 ± 15.95 years at the time of surgical exeresis of HNM. Stratification by tumour location showed a significantly higher age at the time of surgical exeresis for patients with

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TABLE 2 Histopathological characteristics of all head–neck melanomas, stratified by anatomic location.

Area	Type	*N* (%)	*p*	In situ, *N*/ total (%)	*p*
Cheeks	LMM	251 (65.54)	**<0.001**	185/383 (48.30)	**<0.001**
	ALM	0 (0.00)	0.33		
	SSM	74 (19.32)	**<0.001**		
	NM	26 (6.79)	**<0.001**		
	Other	32 (8.36)	**0.0024**		
Scalp	LMM	62 (31.00)	**<0.001**	41/200 (20.50)	**<0.001**
	ALM	0 (0.00)	0.52		
	SSM	68 (34.00)	0.06		
	NM	36 (18.00)	0.011		
	Other	34 (17.00)	0.039		
Anterior neck	LMM	21 (14.29)	**<0.001**	24/147 (16.33)	**<0.001**
	ALM	1 (0.68)	0.11		
	SSM	81 (55.10)	**<0.001**		
	NM	28 (19.05)	0.012		
	Other	16 (10.88)	0.50		
Ears	LMM	39 (33.91)	0.0056	22/115 (19.13)	**<0.001**
	ALM	1 (0.87)	0.054		
	SSM	36 (31.30)	0.48		
	NM	21 (18.26)	0.054		
	Other	18 (15.65)	0.30		
Temples	LMM	37 (43.53)	0.61	22/85 (25.88)	0.10
	ALM	0 (0.00)	0.69		
	SSM	23 (27.06)	0.76		
	NM	13 (15.29)	0.44		
	Other	12 (14.12)	0.66		
Forehead	LMM	41 (51.25)	0.34	30/80 (37.50)	0.50
	ALM	0 (0.00)	0.70		
	SSM	20 (25.00)	0.47		
	NM	8 (10.00)	0.47		
	Other	11 (13.75)	0.75		
Nose	LMM	58 (79.45)	**<0.001**	44/73 (60.27)	**<0.001**
	ALM	0 (0.00)	0.72		
	SSM	7 (9.59)	**<0.001**		
	NM	2 (2.74)	**0.0088**		
	Other	6 (8.22)	0.24		
Posterior neck	LMM	6 (16.22)	**<0.001**	9/37 (24.32)	0.20
	ALM	0 (0.00)	0.80		
	SSM	14 (37.84)	0.20		

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TABLE 2 (Continued)

Area	Type	*N* (%)	*p*	In situ, *N*/ total (%)	*p*
	NM	6 (16.22)	0.50		
	Other	11 (29.73)	**0.0014**		
Eyelids	LMM	22 (59.46)	0.10	14/37 (37.84)	0.62
	ALM	0 (0.00)	0.80		
	SSM	5 (13.51)	0.040		
	NM	3 (8.11)	0.40		
	Other	7 (18.92)	0.24		
Lips and chin	LMM	9 (34.62)	0.23	12/26 (46.15)	0.19
	ALM	0 (0.00)	0.83		
	SSM	9 (34.62)	0.48		
	NM	6 (23.08)	0.10		
	Other	2 (7.69)	0.45		

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.

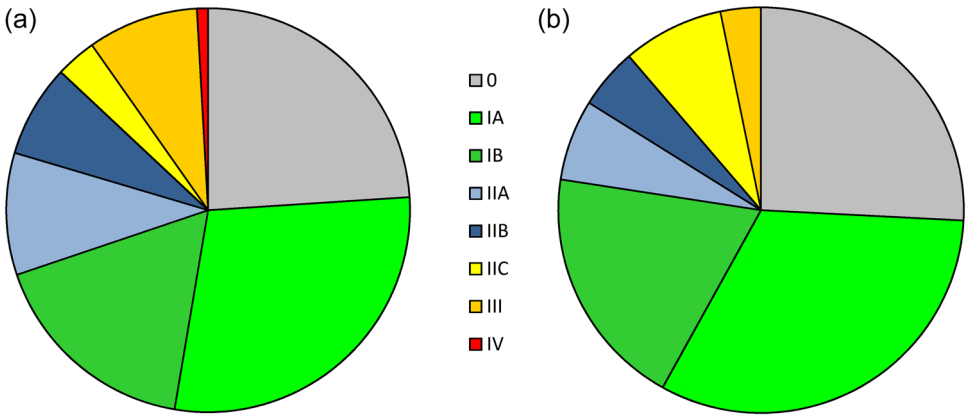

FIGURE 2 Relative frequencies of tumour stages in the 757 patients included in the survival analysis (a) and the 426 excluded (b).

TABLE 3 Survival time of patients whose death was ascertained within the study period ($n = 143$), differentiated on the basis of the location of their head and neck cutaneous melanoma.

Area	No. of patients	Survival time (months), mean ± SD	p
Cheeks	37	46.84 ± 32.17	0.047
Scalp	39	38.87 ± 38.48	0.74
Anterior neck	10	39.11 ± 21.77	0.80
Ears	14	30.71 ± 29.82	0.44
Temples	13	28.46 ± 27.71	0.32
Forehead	7	29.71 ± 40.50	0.54
Nose	7	40.29 ± 55.21	0.89
Posterior neck	6	15.33 ± 12.18	**0.004**
Eyelids	5	22.0 ± 20.54	0.30
Lips and chin	5	41.6 ± 33.25	0.77

Note: SD=standard deviation. Significant *p* values are written in bold.

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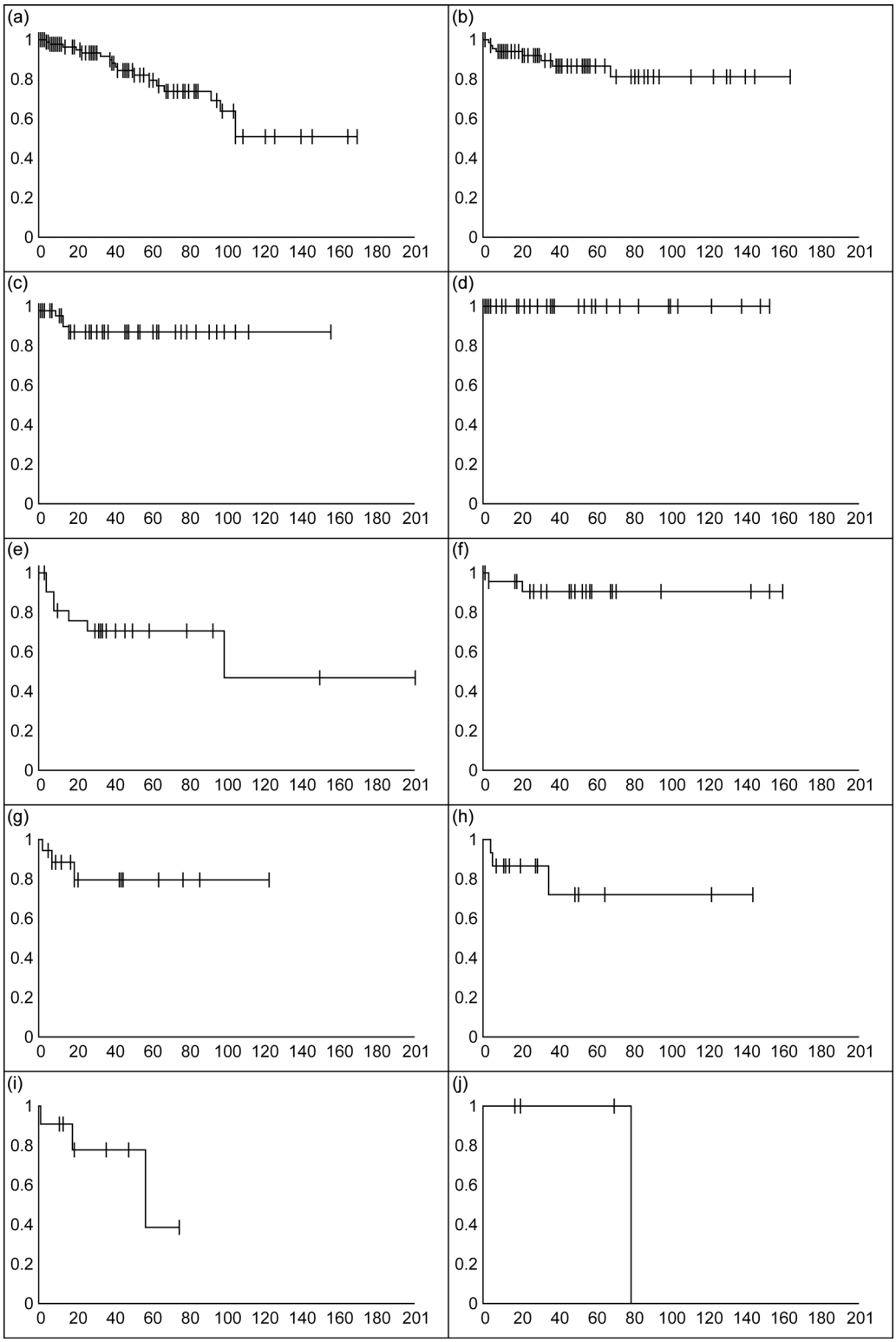

FIGURE 3 Kaplan–Meier survival plots of non in situ head and neck melanomas for which death notification or at least one follow-up visit within the study period is available ($n = 357$), divided by anatomic site. Survival times are expressed in months. (a) cheeks ($n = 101$), (b) scalp ($n = 72$), (c) ears ($n = 45$), (d) anterior neck ($n = 39$), (e) temples ($n = 26$), (f) forehead ($n = 26$), (g) posterior neck ($n = 18$), (h) eyelids ($n = 15$), (i) nose ($n = 11$) and (j) lips-chin ($n = 4$).

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melanoma of nose and cheeks, and a significantly lower age for patients with melanoma of anterior neck.

Ageing is considered as a poor prognostic factor of HNM. Indeed, a linear increase in risk with age has been reported with clinical significance by the age of 65 years.[25] In our study, LMM was the most frequent type of melanoma, followed by SSM, NM, ALM and other types of melanoma.

LMM was significantly more frequent than other types on nose and cheeks, and significantly less frequent on scalp, ears, posterior and anterior neck. Our data seem not to agree with a German study, which showed that the LMM type was preferentially located on the head and neck site.[26]

On the other hand, SMM was significantly more frequent on anterior neck and less frequent on cheeks and nose, while NM was significantly less often found on cheeks and nose. Other melanomas frequently affect the posterior neck and cheeks.

In Aragués's retrospective study of 280 patients, over two thirds of the tumours (36.1%, $n = 101$) were in situ melanomas. Median tumour thickness was 0.4 mm (range, 0–18 mm). The predominant histologic subtype was lentigo maligna, with 172 cases (61.4%), followed by SSM and NM.[27]

Seventy-two patients (25.7%) had stage T3 or T4 melanoma.[27] In our case series, mean Breslow thickness was 2.06 ± 2.81 mm. Indeed, in situ melanomas were 33.81%. Ulceration was observed in 14.19% of cases, regression <75% in 5.26%, and regression >75% in 1.42%. These data seem to confirm those reported in a French study in which HNMs occurred later in life than in other sites.[28] A higher proportion of in situ cases (49.6%), in particular LMM, with mean Breslow thickness 2.18 versus 1.77 mm was found. In a retrospective analysis of 191 HNM, regression was associated with thinner Breslow, decreased rates of sentinel node positivity, and lower recurrence, suggesting that regression may not be a negative prognostic indicator of HNM.[29]

The mean survival time from diagnosis of 143 patients was 37.15 ± 33.91 months and a significantly shorter survival time was observed for patients with posterior neck HNMs. The other patients were followed up for a mean time of 40.69 ± 41.12 months. In a review of the literature, it has been shown that in HNM, the main risk factors associated with a reduction in OS and DFS were age, sex, and anatomical site.[17] Patients over 65 years of age had a lower 5-year survival rate compared with younger patients; males had a worse prognosis than females, and the scalp region had the worst prognosis, also being an independent prognostic indicator.[23–30]

As regards surviving, no significant differences have been highlighted between different sites, in the sub-population considered; this result is probably strongly influenced by the overall small number of cases and the high number of censored data.

The present study has some limitations, owing to its retrospective nature and the use of non-homogeneous databases having been obtained from different centres. Moreover, given the duration of the study period, significant variations in standard staging procedures occurred, making the study population somewhat heterogeneous.

CONCLUSION

To the best of our knowledge, we herein report the largest series of HNM of Italian literature. The posterior neck was the area most affected by thicker melanomas, supporting the literature data. Neck melanoma was associated with reduced survival compared with all other sites of HNM. This agrees with the literature, which suggests that neck, together with cheeks, must be considered the highest-risk area for HNM. Head and neck sites should not be neglected in the dermatological inspection. They must also be photo-protected, especially in certain working conditions. These areas must be checked periodically and doubtful lesions must be promptly removed.

AUTHOR CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: *Study conception and design*: Giusy Schipani and Cataldo Patruno. *Data collection*: Giusy Schipani. *Analysis and interpretation of results*: Fabrizio Guarneri. *Draft manuscript preparation*: Giusy Schipani, Fabrizio Guarneri and Cataldo Patruno. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Not applicable.

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