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Management of Melanoma in Elderly Patients over 80 Years

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Melanoma is a malignant tumour with a poorer prognosis in stage III and IV patients. Development of effective therapies for the treatment of advanced melanoma has led to an improvement in survival. Furthermore, the French population is ageing, and treatment of melanoma in this population has several specific limitations. This descriptive, retrospective, single-centre study collected data on the diagnostic and therapeutic management of patients with melanoma of Breslow ≥1 mm or of unknown primary and metastatic spread, at Limoges University Hospital, between 2018 and 2022, and compared the results obtained between 2 groups: under 80 and over 80 years of age; 344 patients were included. The extension work-up was more frequently complete and the sentinel lymph node technique more frequently performed in patients under 80. Wide excision was more frequently in accordance with guidelines in patients over 80. Adjuvant or first-line metastatic treatment was more frequently instituted in patients under 80, but no difference was found as regards the second and third lines, the frequency of adverse events, and the reason for stopping treatment. Our study supports similar management of elderly and young subjects, given the safety profile and efficacy of treatments.

Key words: melanoma; elderly; treatments; initial staging.

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SIGNIFICANCE

Melanoma is a malignant tumour with a poor prognosis in advanced stages. Recently developed new treatments have led to an improvement in survival. Furthermore, France's ageing population is a public health issue. This study collected data on the diagnostic and therapeutic management of patients with melanoma at Limoges University Hospital between 2018 and 2022, and compared the results obtained between 2 groups: under 80 and over 80 years of age. Our study showed similar efficacy and tolerance between older and younger patients, which encourages similar management.

Melanoma is a malignant tumour that accounts for around 4% of all incident cancers and 10% of skin cancers in metropolitan France. There were 15,500 new cases and 1,800 deaths in 2018, representing 1.2% of all cancer-related deaths (1). Its incidence is rising worldwide (2), including in metropolitan France. The prognosis is generally favourable when the tumour is diagnosed at an early stage, but becomes very poor in stage III/IV patients. Nevertheless, recent therapeutic advances (immunotherapy in the form of checkpoint inhibitors and molecularly targeted therapies) have significantly improved overall survival rates.

The ageing of the population is a major public health concern. Individuals over 65 represented 20.5% of the French population on 1 January 2020, and this proportion is increasing steadily (3). In the Nouvelle Aquitaine region, these figures are even higher: 30.6% of the population was over 60 in 2019, and 31.5% in the Haute-Vienne department (3). Elderly people are more vulnerable to cancers, but also to their treatments, which are often the cause of undesirable side effects.

The aim of this study was to describe the management of melanoma in subjects aged 80 or older at Limoges University Hospital, and to compare it with that of patients under 80.

MATERIALS AND METHODS

Study design

This retrospective single-centre, descriptive, and comparative study was performed from clinical data of patients followed for a primary or metastatic melanoma, whose diagnosis and management had been performed between 2018 and 2022 at Limoges University Hospital. Data were extracted from the digital medical records of Limoges University Hospital. The study was approved by the local Ethics Committee (no. 12-2023-04). Each patient included in the study received an information letter concerning the study and was free to refuse inclusion.

Population

Cases eligible in the study were either (*i*) patients with a diagnosis of primary cutaneous melanoma made between January 2018 and December 2022, confirmed by histopathology, with Breslow index ≥1 mm, or (*ii*) patient with metastatic melanoma with unknown primary tumour, diagnosed during the same period of time.

Patients with (*i*) another solid cancer or a malignant blood disease evolving at the time of melanoma diagnosis or management, or (*ii*) Breslow index < 1 mm were excluded.

Statistical analysis

Statistical analysis was performed using Stata 11® software (StataCorp LLC, College Station, TX, USA). The significance

level for all statistical analyses was set at 0.05. The main analysis consisted in comparing the 2 age groups using the χ^2 test or Fisher's exact test, depending on the conditions of application.

Quantitative variables are expressed as mean ± standard deviation and compared between the 2 age groups. Qualitative variables are expressed as numbers and percentages and compared between the 2 groups using the χ^2 test or Fisher's exact test, depending on the conditions of application.

RESULTS

Characteristics of the study population

Of the 344 patients included in the study, 84 were aged 80 years or more at diagnosis and 260 were aged less than 80 years (**Table I**). The mean age in the under 80 group was 62.7 ± 13.4 years and 86.0 ± 5.0 years in the over 80 group. There was a predominance of females in the over 80 group and males in the under 80 group. There were significantly more WHO 0 patients in the under 80 group (91.5%) than in the over 80 group (45.2%). There were almost twice as many melanomas of the head and neck in the over 80s (28.6%) compared with the under 80s (15.4%), and melanomas of the trunk and upper limbs in the under 80s compared with the over 80s. Ocular and mucosal melanomas, as well as melanomas of unknown primary, were rare (5% or less) in both age groups. There was no significant difference between the 2 groups for histopathological type ($p = 0.237$), and superficial spreading melanoma (SSM) was the most frequent melanoma subtype in both age groups. The mean Breslow index was 4.0 mm in the under 80s and 4.9 mm in the over 80s ($p = 0.237$). The median Breslow index was lower in the under 80s (2.2 mm) compared with the over 80s (4.1 mm) ($p < 0.001$). There were more BRAF-mutated melanomas in the under 80s compared with the over 80s, but in most cases the mutation had not been determined.

Table I. Clinical, histopathological, and sociodemographic characteristics of the study population

Factor	Total	< 80 years ($n = 260$)	≥ 80 years ($n = 84$)	*p*-value
Age at diagnosis (years)				
Mean ± SD	68.4 ± 15.5	62.7 ± 13.4	86.0 ± 5.0	
Median	70.9	65.8	84.4	
Gender, *n* (%)				
Male	186	151 (58.1)	35 (41.7)	0.009
Female	158	109 (41.9)	49 (58.3)	
Performance status, *n* (%)				
PS 0	276	238 (91.5)	38 (45.2)	< 0.0001
PS 1	38	12 (4.6)	26 (31.0)	
PS 2	19	6 (2.3)	13 (15.5)	
PS 3	11	4 (1.5)	7 (8.3)	
Location of melanoma, *n* (%)				
Head and neck	64	40 (15.4)	24 (28.6)	
Upper limbs	80	67 (25.8)	13 (15.5)	
Trunk	88	75 (28.8)	13 (15.5)	
Lower limbs	90	61 (23.5)	29 (34.5)	0.001
Mucosa	6	4 (1.5)	2 (2.4)	
Unknown primary	15	13 (5.0)	2 (2.4)	
Ocular	1	0	1 (1.2)	
Histopathological type, *n* (%)				
SSM	156	123 (47.3)	33 (39.3)	
Nodular	78	59 (22.7)	19 (22.6)	
LMM	16	9 (3.5)	7 (8.3)	
ALM	28	18 (6.9)	10 (11.9)	0.237
Other	25	18 (6.9)	7 (8.3)	
Unknown	41	33 (12.7)	8 (9.5)	
Breslow (mm) mean+SD	4.3 ± 4.9	4.0 ± 5.1	4.9 ± 4.0	0.001
Breslow (mm) median	2.7 [1–27]	2.2	4.1	0.001
BRAF mutation, *n* (%)				
Yes	70	62 (23.8)	8 (9.5)	0.01
No	113	78 (30.0)	35 (41.7)	
Not searched	161	120 (46.2)	41 (48.8)	

SD: standard deviation; SSM: superficial spreading melanoma; LMM: lentigo maligna melanoma; ALM: acral lentiginous melanoma.

Extensive work-up performed at diagnosis

The imaging work-up performed at diagnosis (**Table II**) was more often complete in patients under 80 (69.6%) compared with those over 80 (58.3%) ($p < 0.0001$). Incomplete imaging was mostly due to the lack of achievement of lymph node ultrasound. However, patients over 80 (15.5%) were more likely to have had no extension work-up at all (15.5% vs 2.4%) (Table II). For patients for whom it was advisable, the sentinel lymph node technique was performed less frequently in patients over 80 (44.2%) than in those under 80 (78.3%) ($p < 0.0001$) (Table II). When this procedure was actually done, there was no difference between the 2 age groups concerning the positivity of the result.

Treatment

Wide excision was more frequently performed following the 2022 European guidelines (4) in patients over 80 (93.8%) compared with those < 80 (79.8%) ($p = 0.006$) (**Table III**). Adjuvant treatment was initiated more frequently in patients under 80 (97%) compared with those over 80 (81.2%) ($p < 0.001$), with a marked predominance of immunotherapy in both groups. No adjuvant targeted therapy was initiated in patients over 80 (Table III). First-line metastatic treatment following guidelines was more frequently initiated in patients under 80 (96.6%) than in patients over 80 (87.5%) ($p = 0.001$). Most patients

Table II. Imaging work-up carried out at diagnosis

Factor	Total	< 80 years	≥ 80 years	*p*-value
Imaging work-up, *n* (%)				
Complete[a]	230	181 (69.6)	49 (58.3)	
TAP CT+cerebral CT	53	44 (16.9)	9 (10.7)	
TAP CT	31	21 (8.1)	10 (11.9)	< 0.0001
Ultrasound of lymphatic drainage area	6	3 (1.2)	3 (3.6)	
Positron emission tomography	5	5 (1.9)	0	
None	19	6 (2.4)	13 (15.5)	
Sentinel lymph node biopsy, *n* (%)				
Yes	211	177 (78.3)	34 (44.2)	< 0.0001
No	92	49 (21.7)	43 (55.8)	
Not concerned	41	34	7	
Sentinel lymph node result, *n* (%)				
Positive	150	125 (70.6)	25 (73.5)	0.732
Negative	61	52 (29.4)	9 (26.5)	

[a]Full imaging work-up: TAP CT+brain imaging+ultrasound of lymphatic drainage area, or PET+brain imaging.
TAP CT: thorax–abdomen–pelvis computed tomography.

Table III. Treatments

Factor	Total	< 80 years	≥ 80 years	*p*-value
Excision margin, *n* (%)				
Not performed or narrow margins	55	50 (20.2)	5 (6.2)	0.006
Adequate	273	197 (79.8)	76 (93.8)	
Not concerned	16	13	3	
Adjuvant treatment, *n* (%)				
Immunotherapy	101	88 (88.9)	13 (81.3)	0.001
Targeted therapy	8	8 (8.1)	0	
None	6	3 (3.0)	3 (18.8)	
Not concerned	228	160	68	
Metastatic treatment: 1st line, *n* (%)				
Single-agent immunotherapy	35	20 (33.9)	15 (62.5)	
Combination immunotherapy	20	20 (33.9)	0	
Targeted therapy	23	17 (28.8)	6 (25.0)	0.001
Chemotherapy	0	0	0	
None	5	2 (3.4)	3 (12.5)	
Not concerned	261	201	60	
Metastatic treatment: 2nd line, *n* (%)				
Single-agent immunotherapy	11	8 (34.8)	3 (37.5)	
Combination immunotherapy	8	7 (30.4)	1 (12.5)	
Targeted therapy	6	5 (21.7)	1 (12.5)	0.533
Chemotherapy	3	2 (8.7)	1 (12.5)	
None	3	1 (4.3)	2 (25.0)	
Not concerned	313	237	76	
Metastatic treatment: 3rd line, *n* (%)				
Single-agent immunotherapy	4	3 (33.3)	1 (50.0)	
Combination immunotherapy	2	2 (22.2)	0	
Targeted therapy	2	2 (22.2)	0	0.898
Chemotherapy	2	1 (11.1)	1 (50.0)	
None	1	1 (11.1)	0	
Not concerned	333	251	82	

over 80 received single-agent immunotherapy (62.5%), whereas patients under 80 received either single-agent or combination immunotherapy (33.9% each). Targeted therapy for first-line metastatic disease was used to a similar extent (around a quarter of cases) in both age groups, and no patients received chemotherapy. There was no difference between the 2 age groups for second- and third-line metastatic treatment. We can nevertheless observe that a few patients were treated with chemotherapy when there were none in first-line treatment, and one patient over 80 received combination immunotherapy, unused in the first-line treatment in this age group. The number of patients for third-line treatment was small ($n=11$). There was no difference between the 2 age groups concerning the reason for stopping treatment, regardless of the treatment line (Table III).

Adverse events

There was no difference between patients under 80 and those over 80 in the occurrence of adverse effects requiring medical attention following sentinel node surgery. Similarly, there was no significant difference regarding the incidence of stage III or IV treatment-related adverse events in either the metastatic or adjuvant setting (**Table IV**).

Follow-up

There were more complete remissions at 1 and 2 years of follow-up among those under 80 (75.6% and 70.2%, $p=0.03$) compared with those over 80 (56.6% and 46.0%, $p=0.014$) (**Table V**). The difference in outcomes between the 2 age groups was no longer significant at 3 years, notably in terms of death, despite a higher proportion of patients over 80 with disease progression at 1 and 2 years (Table V).

Table IV. Occurrence of adverse events

Factor	Total	< 80 years	≥ 80 years	*p*-value
AE sentinel lymph node, *n* (%)	20	16 (9.0)	4 (11.4)	0.735
Not concerned	131	82	49	
AE stage III or IV adjuvant, *n* (%)	16	13 (13.7)	3 (23.1)	0.31
Not concerned	235	164	71	
AE stage III or IV metastatic 1, *n* (%)	18	15 (28.3)	3 (15.8)	0.56
Not concerned	266	201	65	
AE stage III or IV metastatic 2, *n* (%)	4	3 (16.7)	1 (16.7)	0.98
Not concerned	314	236	78	
AE stage III or IV metastatic 3, *n* (%)	2	2 (22.2)	0	0.822
Not concerned	328	245	83	

AE: adverse effects.

DISCUSSION

Our study provides an overview of the management of melanoma in elderly subjects in our dermatology department, and highlights several differences in comparison with younger patients seen in the same period of time. The characteristics of melanoma in our series aligned with existing literature trends. In patients over 80, melanomas of the head and neck were more frequent and those on the trunk less frequent, which can be explained by differences in sun exposure (5–7). The Breslow index tends to be higher in elderly patients, ranging from 2.3 to 3.7 mm on average depending on the study (7, 8) vs 1.35 mm in younger patients (6). Our study showed a greater difference, with an average Breslow of 4.9 mm in patients over 80 vs 4.0 in younger patients ($p<0.001$). This may be explained in our region by the high number of people with agricultural activity, which results in major

Table V. Follow-up at 1 year, 2 years, and 3 years from diagnosis

Factor	Total	< 80 years	≥ 80 years	*p*-value
1 year follow-up, *n* (%)				
Complete remission	213	170 (75.6)	43 (56.6)	0.003
Partial remission or stability	9	3 (1.3)	6 (7.9)	
Progression	42	28 (12.4)	14 (18.4)	
Death	14	11 (4.9)	3 (3.9)	
Lost to follow-up	23	13 (5.8)	10 (13.1)	
Not concerned	42	34	8	
2 years' follow-up, *n* (%)				
Complete remission	148	125 (70.2)	23 (46.0)	0.014
Partial remission or stability	3	2 (1.1)	1 (2.0)	
Progression	24	15 (8.4)	9 (18.0)	
Death	27	20 (11.2)	7 (14.0)	
Lost to follow-up	26	16 (9.0)	10 (20.0)	
Not concerned	115	81	34	
3 years' follow-up, *n* (%)				
Complete remission	88	72 (58.5)	16 (39.0)	0.12
Partial remission or stability	1	1 (0.8)	0	
Progression	18	12 (9.8)	6 (14.6)	
Death	30	22 (17.9)	8 (19.5)	
Lost to follow-up	27	16 (13.0)	11 (26.8)	
Not concerned	179	136	43	

sun exposure, and by the persistent shortage of dermatologists. In addition, BRAF mutation is associated with young age (9, 10) which is also the case in our study (see Table I). However, we did not find any difference in histopathological type of melanoma, although predominance of lentigo maligna melanoma (LMM) (5) and nodular melanomas in elderly subjects has been reported (6, 11).

In our study, the initial work-up was less often exhaustive in patients over 80, and 15.5% of this age group did not undergo any work-up, compared with only 2.1% of patients under 80 ($p<0.0001$). Few studies have looked at initial work-up practices depending on age; Ciocan et al. (7) showed similar results to our study in 2013, with patients over 70 years of age having an initial work-up less often than those under 70. However, the nature of the initial work-up differed from current recommendations. Similarly, sentinel lymph node biopsy was less frequently performed in our study in patients over 80, a result also reported by Rees et al. (5, 12), particularly when melanoma was located on the head and neck. This can be explained by a more complex surgical procedure with a greater risk of adverse effects in that anatomical region. The main argument put forward for not performing a sentinel lymph node biopsy in elderly patients is their limited life expectancy and the greater likelihood of death from other diseases than from progression of melanoma (13). In addition, the adjuvant situation makes this non-essential procedure questionable in elderly patients. Nevertheless, the current trend towards increased life expectancy is regularly pushing back the age at which this question arises, and improves the consideration of comorbidities and general status rather than calendar age per se.

We did not find any significant difference in sentinel lymph node biopsy positivity, although a few articles showed an inverse relationship between age and sentinel lymph node positivity (14, 15), possibly linked to age-related lymphatic dysfunction.

Surprisingly, we found that excisions not performed or with insufficient margins were more frequent in patients under 80 (20.2% vs 6.2%; $p<0.06$). The literature tends to suggest the opposite: Rees et al. showed that only 58% of patients aged 85 or over had appropriate wide excision and that older age and the location of the melanoma on the face and neck were significantly associated with lower margins (12). Ciocan et al. (7) obtained comparable findings, with 5% of narrow margins in patients under 70 compared with 16.8% in those over 70 ($p<0.001$). This difference may be explained by the higher proportion of surgical treatments performed solely for the patient's comfort in the case of very large and/or symptomatic tumours, but with no adequate margins. In our study, most incomplete surgical excisions were lacking depth, not reaching the fascia, while the lateral margins may have been adequate. In other cases, the patient refused definitive surgical excision, or the surgical treatment was limited by age or overall health status, or by anatomical location of the tumour.

The initiation of adjuvant therapy was more frequent in patient under 80 than in patients over 80 in our study (97% vs 81.2%, $p=0.001$). To our knowledge, no recent study has addressed this issue. Only the study by Ciocan et al. in 2013 found a similar proportion of adjuvant treatment between under 70 and over 70 age groups (7). However, the adjuvant therapy in that study was limited to interferon alpha at the time. This is not directly comparable to the therapies used in our series (immunotherapy and targeted therapy), which are now routinely employed as adjuvant therapy and in metastatic melanoma, in accordance with current guidelines.

Similarly, there are very few recent studies looking at differences in treatment depending on age at a metastatic stage. Bateni et al. studied patients with metastatic melanoma between 2004 and 2015 and showed that patients over 80 were least likely to receive immunotherapy ($p<0.0001$), chemotherapy, or targeted therapy ($p<0.0001$) (14). Moreover, Van Der Kooij et al. (9) reported that patients under 40 years were more often treated with targeted therapy in first line than those over 40, which may be explained by the higher frequency of BRAF mutation in younger patients. In our series, combination immunotherapy was only performed in patients under 80 with metastatic melanoma except in 1 case in second line (see Table III). Furthermore, there was a significant difference between the 2 age groups only for the first line of treatment. Although it was appropriate, more patients over 80 were not treated by immunotherapy in first line (12.5% vs 3.4%, $p=0.001$) and none received combination immunotherapy, whereas 33.9% of those under 80 did. On the other hand, there was no difference between the 2 age groups for the subsequent lines of treatment, either in terms of frequency of initiation or nature of treatment, or for the reason for discontinuation of treatment for any line. The occurrence of grade III or IV adverse events leading to discontinuation of treatment is therefore not over-represented in patients over 80, which is consistent with the literature where safety is described as similar (16–19). More specifically, Reichert et al. (20) studied 60 patients over 80 years old treated with combined immunotherapy, and showed an acceptable safety profile in this elderly population with 63% of immune-related adverse events, including 27% being grade 3 or higher.

Besides, our study showed no difference in the incidence of adverse effects related to the sentinel lymph node biopsy. Very recently, Bobircã et al. (21) observed more lymphoceles and delayed wound healing in patients over 70 ($p=0.004$). Conversely, the cohort study by Solari et al. (22) showed no link between advanced age and the occurrence of post-surgical adverse events, suggesting that age alone is not sufficient to predict the risk of complications.

Several studies (23–27) are in favour of a similar or even lower frequency of adverse events in elderly subjects treated with single-agent immunotherapy or targeted therapy. The same applies to combination immunotherapy in metastatic melanoma. Although it does cause more toxicities than single-agent immunotherapy, it does not appear to cause more adverse events in elderly subjects compared with younger ones (28). In our study, no difference was found between the 2 age groups.

Several studies have shown reduced survival in elderly subjects with melanoma (29–31), probably related to pejorative pathological criteria: high Breslow index, ulceration, high mitotic index, regression, nodular type. In our study, there were fewer complete remissions at 1 and 2 years of follow-up in patients over 80, but similar death rates between the 2 age groups at 3 years of follow-up. These results may be explained by a longer delay in diagnosis in elderly subjects, possibly due to decreased attention to skin changes, impaired vision hindering detection, and lower participation in screening campaigns (32–34).

Our study describes the diagnostic and therapeutic management of melanoma in patients over 80, and the differences in real life compared with younger subjects, an issue that has not been much addressed in the recent literature, despite its growing importance due to the ageing of the population and the development of new therapies. The sizeable number of patients involved was a strength of the study, as were the encouraging results concerning tolerance regardless of age.

Limitations

The limitations of this study are its retrospective and single-centre design, as well as data collection performed by a single examiner. Also, what we observed in part of the region Nouvelle Aquitaine (southwest of France) may not be generalizable to the whole French territory.

Conclusion

In summary, our study provides an overview of the diagnostic and therapeutic management of melanoma in elderly patients and their outcome in a French region. It highlights several specific features of melanoma occurring in elderly patients and shows encouraging results in terms of possibilities of effective treatment and safety. Larger-scale prospective studies are needed to confirm the actual application of guidelines on management and treatment of melanoma in elderly patients, especially in the current context of extending treatment indications, of advanced therapies and growth of an ageing population.

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IRB approval status: This study was approved by the Ethics Committee of Limoges Hospital (no. 12-2023-04). All subjects were free to refuse inclusion in this study.

The authors have no conflicts of interest to declare.

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