

## REVIEW

# The Challenges of Melanoma during COVID-19 Pandemic

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## Abstract

Diagnosis, treatment and follow-up of patients with melanoma during COVID-19 pandemic is quite challenging. These patients are often immunocompromised, but, on the other hand, management of this malignant skin cancer should not be delayed. It is necessary to diagnose and stage the melanoma as soon as possible, in an attempt to provide a better prognosis. There are few data regarding the treatment of melanoma during COVID-19 pandemic. However, the general recommendations suggest testing all cancer patients prior administration of the therapy. The *European Society for Medical Oncology* (ESMO) provided guidelines regarding therapy of this skin cancer during COVID-19 pandemic. Every patient is different, and it is always important to evaluate the risks and benefits.

**Keywords:** melanoma, COVID-19 pandemic, immunotherapy, target therapy, ESMO guidelines.

## Rezumat

Diagnosticul, tratamentul și urmărirea pacienților cu melanom în timpul pandemiei COVID-19 este destul de dificilă. Acești pacienți sunt adesea imunodeprimați, dar, pe de altă parte, tratamentul acestui cancer de piele nu trebuie întârziat. Este necesar să diagnosticăm și să tratăm melanomul cât mai curând posibil, în încercarea de a oferi un prognostic mai bun. Există puține date referitoare la tratamentul melanomului în timpul pandemiei COVID-19. Cu toate acestea, recomandările generale sugerează testarea tuturor pacienților cu cancer înainte de administrarea terapiei. *Societatea Europeană pentru Oncologie Medicală* (ESMO) a furnizat ghiduri privind terapia acestui cancer de piele în timpul pandemiei COVID-19. Fiecare pacient este diferit și este întotdeauna important să evaluezi riscurile și beneficiile.

**Cuvinte cheie:** melanom, pandemie COVID-19, imunoterapie, terapie țintită, ghiduri ESMO.

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## INTRODUCTION

In December 2019, several cases of pneumonia of unknown origin were diagnosed in Wuhan, China. Shortly, the scientists discovered a new type of coronavirus. They named it severe acute respiratory syndrome-coronavirus 2, or SARS-CoV-2<sup>1</sup>.

On March 2020, the WHO (*World Health Organisation*) declared COVID-19 infection pandemic, and indicated three priorities for all countries: protection of people at highest risk of severe disease, as patients with comorbidities (for example, cancers), protection of health workers, and supporting all the vulnerable countries in containing infection<sup>2</sup>.

Pandemia with this new coronavirus has a defining impact on medical care. Regarding patients with dermatological conditions, one of the most affected group of patients by this pandemic, are the ones with melanoma, because they are immunocompromised hosts, and are more likely to develop severe forms of infection<sup>3</sup>. On the other hand, melanoma is a serious skin cancer, whose diagnosis and treatment cannot be postponed<sup>4</sup>.

## MANAGEMENT OF MELANOMA AND COVID-19

Melanoma is an aggressive form of skin cancer, with a high mortality<sup>5</sup>. It seems that melanoma is caused by the several genetic mutations (located in the skin, eye, inner ear and leptomeninges)<sup>6</sup>.

As for the epidemiology of melanoma, it affects most frequently caucasians patients, equally males and females. It is important to diagnose this skin cancer early. Metastatic melanoma has often a poor prognosis. This is the reason why staging of melanoma is so important<sup>7</sup>.

Today, the diagnosis of melanoma is based on the staging manual of the American Joint Committee on Cancer, implemented in 2018. Multiple changes have been made to the previous guide: minimal changes in measurements of tumor thickness, removal of mitotic activity, expansion of the regional lymph node (N) categories based on number of positive regional lymph nodes, expansion of metastasis (M) categories based on location of metastasis, and expanded stage groupings in stage III disease to better stratify long term prognosis<sup>8</sup>. Further more, staging correctly the melanoma, provides the best therapy for the patient<sup>9</sup>.

As mentioned previously, it is vital for the patient with melanoma to perform a skin biopsy with histopathological examination, even during pandemic with COVID-19. Diagnosis of this tumor is established by

excisional biopsy<sup>10</sup>. The safety margin, of initial biopsy, is 1-3 mm, around the lesion, and a cuff of subcutaneous fat deep of the tumor<sup>11,12</sup>. Also, an incisional, partial biopsy may be performed instead of complete biopsy. This last method should be avoided as it may inaccurately stage the melanoma, or even negatively affect treatment planning<sup>13</sup>.

Although an excisional biopsy was performed, we should complete removal of the lesion, with a wider and deeper excision, as soon as we get the initial histopathological report of the biopsy. In this case, the histopathological examination is also essential as it must confirm clear margins. The most commonly, a margin of 0.5 cm is adequate: rare, these patients experience recurrence. So, in this situation, we have another example why we cannot delay the complete removal of melanoma<sup>13</sup>.

When it comes to these patients, an important aspect should also refer to the right time to perform sentinel lymph node biopsy. When recommended, it is necessary to be performed before wide excision of the primary melanoma, or in the same operative setting. The purpose is to minimize disruption of the lymphatic channels and optimize the accuracy of lymphatic mapping, as well as identification of the correct sentinel lymph nodule. Thus, this intervention can be delayed, as there is no evidence that influences survival<sup>14,15</sup>.

Any of the patients mentioned before should be tested for COVID-19 if they develop fever, or lower respiratory symptoms, such as dyspnea, hypoxia or cough. However, patients with melanoma should also be tested for other causes of respiratory symptoms: influenza, bacterial pneumonia or others disorders that may mimic symptoms of COVID-19<sup>16</sup>.

Adjuvant therapies are indicated to improve survival: targeted therapies or immunotherapy<sup>17,18</sup>.

Some authors suggest that 70% of patients with melanoma suffer from mutations in genes of key signaling pathways. It seems that mutations produce cell proliferation and malignant phenotype<sup>19</sup>. In fact, these therapies (small molecule inhibitors or antibodies) are directed against mutated proteins<sup>20</sup>. Because, often, in case of melanoma we challenge with mechanisms of resistance to therapy, a synergy between strategies (immunotherapy, targeted therapy, chemotherapy) which target multiple pathways, would be the correct management<sup>20</sup>. Some of the options for these patients are: Nivolumab, Ipilimumab, Vemurafenib+Cobimetinib, Dabrafenib+Trametinib<sup>21</sup>.

During pandemia, the question we should ask is if is indicated to test these patients, treated with immunosuppressive agents. Some authors support the idea that all cancer patients should routinely be tested, 48 to 72 hours prior to administration of the therapy, even if they are asymptomatic or have no knowledge of exposure to COVID-19<sup>22</sup>.

Unfortunately, there are few data regarding treatment of melanoma in case of COVID-19 positive patients. Some guidelines recommend not to discontinue undergoing therapy. However, there is no evidence on how to manage an asymptomatic patient, or a symptomatic one who follows immunotherapy or target therapy<sup>23</sup>.

## ESMO GUIDELINES

Informations provided by The *European Society for Medical Oncology* (ESMO) indicate, for patients who follow chemotherapy, radiotherapy or immunotherapy, to be swabbed for COVID-19, before every treatment session. Furthermore, initiation or continuation of therapy should be discussed for each patient separately, whether it is positive, paucisymptomatic or asymptomatic<sup>24</sup>.

To synthesize, we will highlight the most important aspects related to melanoma management during the COVID-19 pandemic, specified by ESMO. Thus, our high priority patients would be the ones newly diagnosed with invasive primary melanoma, except the skin cancer is incipient (Tis or T1a, and we already performed a wide excision). Also at high risk are post-operative patients, who develop complications. ESMO defines high/medium priority, the patients who accuse new symptoms from treatment, and recommends us trying to manage them by telemedicine, if possible. In case of melanoma survivors, or patients who should have there follow-up only, because they do not have active treatment, maybe the telemedicine would also be a good idea. These patients, together with the ones with dysplastic nevi, represent a low priority<sup>25</sup>.

When it comes to surgery in primary melanoma, there are 3 categories at high priority: curative resection for stage III, surgical management of complications or patients in neoadjuvant studies who had previously planned surgery<sup>25</sup>.

As for high or medium priority, should be mentioned: patients with invasive primary melanoma T1b/higher should benefit from wide excision and sentinel lymph (but, as specified previously, this can be delayed); we should perform wide excision for T1a or lower; As well as resection of oligo-metastatic disease<sup>25</sup>.

ESMO experts consider at high priority, patients who receive adjuvant systemic therapies for stage III melanoma: they should continue therapy if they are part of a clinical trial, providing patient benefits outweigh risks. High or medium priority is represented by patients who follow adjuvant targeted or immunotherapies, with stage III melanoma<sup>25</sup>.

Other recommendations of ESMO refer to advanced melanoma, non-operable stage III or IV. For these patients, systemic therapies should be administered as follows: immunotherapies or targeted therapies for non-operable stage III/IV; patients who are part of a clinical trial should continue the treatment, or course, providing the patient benefits outweigh risks<sup>25</sup>.

Experts also define priorities for radiotherapy for non-operable stage III/IV melanoma. With high priority, are patients with brain metastases, who have indication for stereotactic radiosurgery, threatening lesion or acute spinal cord compression. As for symptomatic metastases, irradiation is considered a high/medium priority. Low priority includes: adjuvant radiotherapy post radical lymphadenectomy and irradiation of asymptomatic, not threatening metastases<sup>25</sup>.

## CONCLUSION

In conclusion, management of melanoma during COVID-19 pandemic is challenging. In most cases, therapy should not be delayed, as progression of the tumor is associated with worse prognosis. However, every case should be discussed separately, and the best decisions should be taken, always balancing the risks with the benefits.

**Compliance with ethics requirements:** The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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