

## **Malignant melanoma management and COVID-19 pandemic: update**

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### **Introduction**

The safety and management of cancer patients in the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID) pandemic is paramount. Most cancer centres have planned for contingencies. At the height of the pandemic, several scientific associations developed guidelines or recommendations to aid oncologists in their clinical practice [1]. The NICE guidelines include a series of measures to minimize face-to-face contact, e.g., offering telephone or telemedicine consultations (in particular for follow-up visits), using home delivery services for medicines and using local services for blood tests [2].

The risk of severe complications and death from COVID-19 is highest in patients who are older or who have comorbidities including immunosuppression, diabetes, cancer, or cardiopulmonary disease [3]. The prevalence of these risk factors is high in older patients who typically present with non-melanoma skin cancer. Hence, the various international committees have proposed triaging and or delaying definitive local treatments [4, 5].

At this moment, it is difficult to predict when the current outbreak will end and there is the potential for a second wave of cases over the winter period. Moreover, learning from past outbreaks and pandemics, suggests that complete eradication of a pathogen after its emergence is rarely achieved. We could see COVID coming back as an endemic cause of seasonal pneumonia with the potential to overwhelm current health- system capacity. Therefore, postponing cancer treatments might be associated with some risks, the impact on waiting times and patient outcomes [6] and competing patient- level and system- level priorities.

Hence, it is desirable that oncologists, if possible, should avoid delaying any curative interventions (systemic treatments, radiation, and surgery). There is increasing emphasis on avoiding the “distraction effect” of the pandemic i.e. risk of shifting focus away from standard clinical care to COVID-19 only care [7]. The risk to develop COVID-19 disease in the setting of oncological patients can be stratified into three scenarios: a) to prevent a patient with advanced skin cancer who is COVID-19 negative to be exposed to viral infection; b) to prevent a patient with advanced skin cancer who is COVID-19 positive to infect the health professionals; c) to prevent a patient with advanced skin cancer COVID-19 positive to infect other patients.

Adoption of proactive management and containment measures, including adherence to the international guidelines (a tiered approach to categorize patients into different priority levels to receive active cancer therapy), can help to protect healthcare workers and patients from possible contamination and enable us to choose the best therapeutic strategy for the patients [1, 8, 9].

Therefore, we sought to update the guidance for management of malignant melanoma (MM) patients in radiotherapy departments taking into consideration the risk patients face from both cancer and from infection.

### General advice

- **Alterations in MDT functioning:** 1) One specialist for each discipline can be physically present at the MDT; 2) The room identified to hold the meeting allows to have at least 1.5 meters of distance among the participants; 3) All other participants take part through a dedicated platform that guarantees the audio-video participation of members and sharing of radiological images, photographic documentation and medical records.
- Switch from face to face outpatient clinic appointments to telephone/ video-based outpatient consultations where possible.
- Consider delivery of systemic therapies in COVID free hubs or at home and home delivery of oral treatments to avoid breaking shielding.
- These service changes underpin how the recommendations 1 and 7 of NICE NG161 on communicating with patients and modifications to usual service that can be introduced in practice for staff and patients.
- Use the RCR Skin Cancer Forum to seek advice from colleagues.
- Clearly record all changes in standard management in the patient record and document discussion with the patient / family.

### Management

The melanomas could potentially be divided into 3 categories to guide surgical treatment decisions [10, 11] as per **table** below.

Risk group	Types of skin cancers	Suggested treatment decision
<b>Low</b>	Melanoma in situ	Wide local excision may be postponed for at least 3 months
<b>Intermediate</b>	T1 melanomas with clear margins after biopsy, T1 melanomas with close margins, T1b, T2 melanomas	Wide local excisions should be done Sentinel lymph node biopsies (SLNB) should be reviewed on a case-by-case basis and may be postponed
	pT2b-pT3b melanoma	Prioritize SLNB
<b>High</b>	Invasive, thick and ulcerated melanoma (T3, 4) Recurrent melanomas	Weigh against patient risks and standard treatment is to be prioritized

## **Radical radiotherapy**

- Malignant melanoma (MM) is not reliably radiosensitive therefore radiotherapy is rarely used in definitive setting. The exceptions include patients unfit for surgery, or inoperable mucosal melanomas. Where definitive radiotherapy is used, modified fractionation should be considered.
- Lentigo maligna (LM), Lentigo maligna melanoma (LMM) and melanoma in situ should be considered for deferred treatment in 2-3 months. If considering radiotherapy, hypo-fractionated regimens are preferable, where possible, to reduce the number of patient visits to hospital. This will reduce the risk of exposure to the virus for both patient and staff and the overall burden to radiotherapy departments

## **Adjuvant radiotherapy – primary site**

- Adjuvant radiotherapy is rarely used apart from situations where postoperative margins are inadequate and further surgery is either contraindicated or the patient declines it. Each case should be carefully assessed to balance the risk of exposure to COVID-19 virus against the risks of local recurrence.
- Patients with closely excised MM at high risk of recurrence should be considered for further surgery or adjuvant radiotherapy.

## **Adjuvant radiotherapy – nodal basin**

- Adjuvant radiotherapy to involved nodal basins with high risk features (i.e. extracapsular spread, multiple or large nodes, recurrence after previous nodal surgery) reduces the risk of local recurrence, but there is no survival benefit. Many of these patients will now be candidates for adjuvant systemic therapy rather than radiotherapy. Therefore, adjuvant nodal radiotherapy is not offered routinely for regional nodal metastases from cutaneous melanoma primary, apart from those patients who are not suitable for adjuvant systemic treatment. However, it should be considered in regional metastases from mucosal primaries. Each case should be carefully assessed to balance the risk of exposure to COVID-19 virus against the risk of regional recurrence.

## **Adjuvant systemic treatment**

- Consider adjuvant therapy for patients with stage IIIc and III d melanoma
- PD-1 inhibitor monotherapy is recommended for patients starting immunotherapy, reserving combination immunotherapy for patients with higher-risk disease
- Consider six-weekly adjuvant pembrolizumab for patients with BRAF wild-type melanoma
- Patients with a BRAF mutation should be advised adjuvant BRAF/MEK inhibitors. Consider encorafenib and binimetinib due to the lower chance of symptoms mimicking COVID-19 infection

## **Palliative treatment**

### ***Palliative radiotherapy***

- Palliative radiotherapy should only be delivered where the benefits clearly outweigh current risks.
- Currently palliative radiotherapy is regarded as priority 4, where “*alleviation of symptoms would reduce the burden on other healthcare services*”. Consider using single fraction or shorter fractionated schedules, depending on the clinical scenario.
- Metastatic spinal cord compression may be priority 2 (“*urgent palliative radiotherapy in patients with malignant spinal cord compression who have useful salvageable neurological function*”). Departments should consider how they will deliver radiotherapy to NMSC patients who are Covid-19 positive, or suspected on clinical grounds.
- In oligometastatic intracranial/ extracranial disease, consider stereotactic radiotherapy. Further guidance is included in RCR document *Guidance for Stereotactic Radiosurgery (SRS) During COVID-19 Pandemic*: <https://www.rcr.ac.uk/sites/default/files/stereotactic-radiosurgery-srs-covid19.pdf>. SABR is being rolled out across England to further reduce the burden on other treatment modalities and reduce travel for patients [12].
- For palliative radiotherapy consider 20Gy in 4# instead of 20Gy in 5#, 30Gy in 8# instead of 30 in 10# or single fraction of 8-10 Gy (e.g. in bleeding or fungating skin nodules) [13].

Close liaison between medical oncologists specialising in melanoma and clinical / radiation oncology colleagues is particularly important at this time. Symptomatic patients may be helped by palliative radiotherapy if they are not suitable for or not responding to SACT.

### ***Palliative systemic treatment***

Individuals with cancer, especially those who are receiving systemic anticancer treatments, are deemed to be at an increased risk of mortality from COVID-19. However, there is emerging evidence to suggest that cancer plus COVID-19 mortality is principally driven by advancing age and the presence of other non-cancer comorbidities.

Immunotherapy has been postulated to protect from infection as its immune mechanism is similar to those involved in the immune response against viral infections [14]. Other considerations for use of immunotherapy are: systemic steroids used for immune mediated toxicity could hamper the immune response against the virus, The interstitial pattern of immune mediated pneumonitis mimics COVID pneumonia making it difficult to differentiate between the two [15]. A recent meta-analysis of clinical trials of critically ill patients with COVID-19 has shown lower 28-day all-cause mortality with use of systemic corticosteroids, compared with usual care or placebo [16].

In a UK wide prospective cohort study, Lee et al have concluded that withholding effective cancer treatments from many cancer patients during the pandemic runs the risk of increasing cancer morbidity and mortality, much more so than COVID-19 itself. They have

reported no significant effect on mortality for patients treated with immunotherapy, hormonal therapy, targeted therapy and radiotherapy use [17]. Similar reassuring findings have been reported from Italy [18].

- Decision regarding combination vs single-agent immunotherapy should be tailored to patient fitness, tolerance and ability to handle side-effects.
- A combination of ipilimumab 1 mg/kg and nivolumab 3 mg/kg every 3 weeks for four infusions, with following consideration for single-agent nivolumab therapy, is associated with lower incidences of immune-mediated toxic reactions
- Single-agent immunotherapy should be discussed for patients with no brain metastasis. Consider the lowest frequency dosing scheme of available regimens (e.g. Nivolumab 480 mg intravenous every 4 weeks or pembrolizumab 400 mg intravenous every 6 weeks)
- BRAF/MEK inhibitors should be considered for patients with BRAF V600-mutated melanoma and brain metastasis
- In some patients best supportive care may be the most appropriate management.

#### Other resources of advice

- BAD <http://www.bad.org.uk/healthcare-professionals/covid-19>
- BAOMS [https://www.baoms.org.uk/professionals/omfs\\_and\\_covid-19.aspx](https://www.baoms.org.uk/professionals/omfs_and_covid-19.aspx)
- BAPRAS <http://www.bapras.org.uk/docs/default-source/covid-19-docs/corona-virus---melanoma---final-version-2.pdf?sfvrsn=2>
- Melanoma Focus Coronavirus/COVID-19 Information for Healthcare Professionals <https://melanomafocus.com/members/coronavirus-info-professionals/>

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