



Management of Primary Skin Cancer During a Pandemic: Multidisciplinary Recommendations

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During the coronavirus disease 2019 (COVID-19) pandemic, providers and patients must engage in shared decision making regarding the pros and cons of early versus delayed interventions for localized skin cancer. Patients at highest risk of COVID-19 complications are older; are immunosuppressed; and have diabetes, cancer, or cardiopulmonary disease, with multiple comorbidities associated with worse outcomes. Physicians must weigh the patient's risk of COVID-19 complications in the event of exposure against the risk of worse oncologic outcomes from delaying cancer therapy. Herein, the authors have summarized current data regarding the risk of COVID-19 complications and mortality based on age and comorbidities and have reviewed the literature assessing how treatment delays affect oncologic outcomes. They also have provided multidisciplinary recommendations regarding the timing of local therapy for early-stage skin cancers during this pandemic with input from experts at 11 different institutions. For patients with Merkel cell carcinoma, the authors recommend prioritizing treatment, but a short delay can be considered for patients with favorable T1 disease who are at higher risk of COVID-19 complications. For patients with melanoma, the authors recommend delaying the treatment of patients with T0 to T1 disease for 3 months if there is no macroscopic residual disease at the time of biopsy. Treatment of tumors \geq T2 can be delayed for 3 months if the biopsy margins are negative. For patients with cutaneous squamous cell carcinoma, those with Brigham and Women's Hospital T1 to T2a disease can have their treatment delayed for 2 to 3 months unless there is rapid growth, symptomatic lesions, or the patient is immunocompromised. The treatment of tumors \geq T2b should be prioritized, but a 1-month to 2-month delay is unlikely to worsen disease-specific mortality. For patients with squamous cell carcinoma in situ and basal cell carcinoma, treatment can be deferred for 3 months unless the individual is highly symptomatic. **Cancer** 2020;126:3900-3906. © 2020 American Cancer Society.

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INTRODUCTION

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, the National Comprehensive Cancer Network (NCCN) and several physician organizations recently have recommended delaying definitive local therapy for many patients with skin cancer. Physicians who were once accustomed to treating skin cancers promptly now must engage in shared decision making with patients to ensure that the marginal benefit of early intervention for skin cancer exceeds the risk of contracting COVID-19 in the clinic setting.

To make informed decisions regarding whether to delay skin cancer treatment during this pandemic, risk assessment of potential COVID-19–associated morbidity and mortality versus primary skin cancer morbidity and mortality is necessary. Physicians also have to consider the temporal issues related to earlier risks from COVID-19 infection versus the later risks of skin cancer progression. Because skin cancer is more common than all other cancers combined,¹ the magnitude of patients who may be at risk of complications of COVID-19 cannot be overemphasized.¹

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In this article, we have summarized current data regarding COVID-19 infection and mortality rates and reviewed the literature assessing how delays in primary skin cancer management may influence cancer-related outcomes. These data will help physicians and patients to interpret skin cancer treatment recommendations recently published by the National Comprehensive Cancer Network (NCCN), the American College of Mohs Surgery (ACMS), and the joint recommendations from the British Association of Dermatologists (BAD) and the British Society for Dermatological Surgery (BSDS). We also have provided multidisciplinary recommendations for the timing of local therapy for patients with early-stage skin cancers during the COVID-19 pandemic that build on the recently published guidelines from medical societies. These recommendations were reached after discussion with experts from dermatologic surgery, radiation oncology, and infectious disease from 11 leading institutions in the United States. These opinions focused on the management of primary, nonanogenital early-stage skin tumors in presumed COVID-19–negative patients and did not address the management of regional or distant metastases from skin cancer or drug therapy (eg, chemotherapy or immunotherapy). These recommendations may be useful for patients and clinicians in any future scenario in which a treatment delay is being considered.

COVID-19 Infection: Factors Associated With Severe Complications and Death

Currently, there are >250,000 cases of COVID-19 in the United States and the number of cases is expected to rise considerably.¹ 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.² In the United States, admission rates to the intensive care unit appear to increase with age: 4.7% to 11.2% for individuals aged 55 to 64 years, 8.1% to 18.8% for individuals aged 65 to 74 years, and 10.5% to 31.0% for individuals aged 75 to 84 years. Mortality rates also increase with age: 0.1% to 0.2% for individuals aged 20 to 44 years, 0.5% to 0.8% for individuals aged 45 to 54 years, 1.4% to 2.6% for individuals aged 55 to 64 years, 2.7% to 4.9% for individuals aged 65 to 74 years, 4.3% to 10.5% for individuals aged 75 to 84 years, and 10.4% to 27.3% for individuals aged ≥ 85 years.² Data are similar in other countries. In China, mortality rates were reported to be approximately 8% in patients aged 70 to 79 years and 14.8% for patients aged ≥ 80 years.³ Chinese patients with COVID-19 had higher death rates if they had

cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6.0%), or cancer (5.6%).⁴ Patients in Italy and other countries also were found to be more likely to die of COVID-19 if they had comorbidities.⁵ Approximately 48% of deaths in Italy occurred in patients with ≥ 3 medical comorbidities, 25% to 26% occurred in patients with 1 to 2 comorbidities, and 1% occurred in patients with no preconditions.⁵ These statistics are important to consider because the median age of diagnosis is 60 to 69 years for melanoma,⁶ 66 years for basal cell carcinoma (BCC),⁷ 75 to 79 years for Merkel cell carcinoma (MCC),⁸ and 78 to 80 years for squamous cell carcinoma.^{9,10} Immunosuppressed patients are up to 70 times more likely to develop skin cancer, and the prevalence of diabetes and cardiopulmonary disease is relatively high in the older patient population most at risk for skin cancer. Assessing the patient's comorbid disease burden and risk of COVID-19–associated intensive care unit admission and mortality is important to triage patients for early versus delayed skin cancer treatment.^{11,12}

In addition to understanding the patient's risk of COVID-19 complications if they contract the disease, physicians also must carefully consider the oncologic risks of postponing skin cancer treatment on a case-by-case basis. Untreated skin cancer may progress to a more advanced stage, potentially increasing the risk of cancer-specific mortality. Reviewing outcomes by clinical stage can help with shared decision making regarding whether to delay treatment (Table 1).¹³⁻¹⁵ The following section summarizes the available data concerning the impact of treatment delays for skin cancers with the highest to lowest rates of metastases. We also have summarized recently published advisory statements for skin cancer treatment during the COVID-19 pandemic and provided multidisciplinary recommendations to assist providers. Clinical judgement is critical in making decisions, especially for patients with symptomatic lesions or those lesions occurring in high-risk locations.

Merkel Cell Carcinoma

MCC is a primary skin cancer with a propensity for regional and metastatic spread, similar to cutaneous melanoma.¹⁶⁻¹⁸ Unlike melanoma, the primary tumor growth of MCC is more often rapid and therefore warrants prompt treatment with wide local excision with or without adjuvant radiotherapy.¹⁹⁻²¹ Although to our knowledge there are few studies to date reporting on the outcomes of a treatment delay in the definitive surgical management of patients with MCC, an Australian retrospective study examined the impact of treatment

TABLE 1. Summary of Oncologic Outcomes by T Classification for Merkel Cell Carcinoma, Cutaneous Melanoma, and Cutaneous Squamous Cell Carcinoma

Clinical T Classification ^a	Merkel Cell Carcinoma ^b	Cutaneous Melanoma ^c		Squamous Cell Carcinoma ^d
	5-Year OS	5-Year DSM	10-Year DSM	10-Year DSM
T1	T1: 56% (54%-58%)			T1: 0.2% (0%-0.5%)
T1a		1%	2%	
T1b		1%	4%	
T2	T2-T3: 41% (39%-44%)			T2a: 0.2% (0%-0.5%)
T2a		4%	8%	T2b-T3: 22% (13%-34%) ^e
T2b		7%	12%	
T3				
T3a		6%	12%	
T3b		14%	19%	
T4	T4: 32% (25%-39%)			
T4a		10%	17%	
T4b		18%	25%	

Abbreviations: DSM, disease-specific mortality; OS, overall survival.

^aSquamous cell carcinoma classification was performed using Brigham and Women's Hospital staging; otherwise, the eighth edition of the American Joint Committee on Cancer staging system was used.

^bClassified according to Harms et al¹³ (2016). Survival outcomes listed were for patients with lymph node–negative disease.

^cClassified according to Gershenwald et al¹⁴ (2017).

^dClassified according to Karia et al¹⁵ (2014).

^eT3 tumors classified according to Brigham and Women's Hospital staging and the eighth edition of the American Joint Committee on Cancer staging system are very rare, with a DSM rate of 100% noted at 10 years.¹⁵

delay for patients treated with either definitive or adjuvant radiotherapy and demonstrated that delays in treatment were associated with deleterious outcomes.²² Five of 11 patients (45%) who were referred for adjuvant radiation developed progressive disease before initiating radiotherapy, with a median time from surgery to disease progression of 30 days (range, 2-48 days). All 5 patients with disease progression had negative surgical margins. Sites of disease progression included the surgical bed (3 patients) and/or the regional lymph nodes (3 patients). Two of 8 patients (25%) who were referred for definitive radiotherapy experienced disease progression prior to the initiation of radiotherapy at a median of 44 days from their biopsy date. Although to our knowledge 1 study reported that a treatment delay of >30 days versus ≤30 days from diagnosis to definitive surgery was not found to be affect oncologic outcomes on univariable analysis in a cohort of 240 patients, the median treatment delay and range in each cohort were not reported.²³ The data should be interpreted with caution given the unpredictable natural history of this disease.

Summary recommendations

Two physician societies have offered treatment recommendations for patients with MCC. The NCCN recommends that treatment not be delayed, with the possible exception of tumors measuring <1 cm that are diagnosed in elderly and/or frail patients.²⁴ The BAD and BSDS recommend prioritizing treatment.²⁵

TABLE 2. Summary Recommendations for the Local Treatment of Patients With Skin Cancer

Type of Cancer	Recommendations ^a
Merkel cell carcinoma	<ul style="list-style-type: none"> • Prioritize treatment • Can delay treatment for approximately 1 mo for patients with favorable T1^b disease who are at high risk of COVID-19 complications
Cutaneous melanoma	<ul style="list-style-type: none"> • Can delay treatment for patients with T0-T1 disease for 3 mo if no macroscopic residual disease is noted at biopsy • Can delay treatment for patients with ≥T2 disease for 3 mo if biopsy margins are negative
Basal cell carcinoma	<ul style="list-style-type: none"> • Can delay treatment for 3 mo unless patients are highly symptomatic
Squamous cell carcinoma	<ul style="list-style-type: none"> • Can delay treatment for patients with Brigham and Women's Hospital T1-T2a disease for 2-3 mo unless there is rapid growth, or patients are symptomatic or immunosuppressed • Prioritize patients with ≥T2b disease, but a 1-mo to 2-mo delay is unlikely to worsen disease-specific mortality

Abbreviation: COVID-19, coronavirus disease 2019.

^aTreatment recommendations assume adequacy of biopsy sampling. Clinician judgment is needed in cases of partial sampling if upstaging is suspected. Recommendations are for patients who are presumed to be negative for COVID-19.

^bFavorable T1 tumors are those measuring <1 cm, with no lymphovascular invasion or immunosuppression.

The definitive treatment of patients with MCC generally should not be delayed (Table 2). In rare cases in which a patient has a favorable T1 tumor (that measuring <1 cm, with no lymphovascular invasion and no

immunosuppression) and has a considerable competing risk of morbidity and/or mortality from COVID-19 (eg, an elderly individual with multiple high-risk comorbidities), a 1-month delay in treatment can be considered because there are data demonstrating that a 1-month delay was not associated with worse oncologic outcomes. Delaying definitive surgery can worsen oncologic outcomes and increases the likelihood that the patient may need adjuvant radiotherapy, which is recommended under normal clinical circumstances by the NCCN for all patients but those with favorable T1 tumors. Daily adjuvant radiotherapy, which typically is delivered over 5 to 6 weeks, would increase the patient's risk of COVID-19 exposure. Use of adjuvant radiotherapy should be decided on a case-by-case basis, examining the risk/benefit ratio. If adjuvant or definitive radiotherapy is needed, moderately hypofractionated radiotherapy can be considered to minimize the number of visits.²⁶ For the palliation of metastatic disease, 8 Gray (Gy) delivered in a single fraction can be used.²⁷

Cutaneous Melanoma

Melanoma causes 6850 deaths per year in the United States,¹ but the mortality risk depends on tumor stage (Table 1).¹³⁻¹⁵ Approximately 90% of melanomas progress through a radial growth phase and can be removed before they develop the potential to metastasize, but 10% of melanomas quickly develop the potential to metastasize.^{28,29}

Several studies have found no association between treatment delays and increased Breslow thickness.³⁰⁻³⁴ In a cohort of 986 patients with cutaneous melanoma who were treated with wide local excision, the timing from biopsy to definitive wide local excision (≤ 14 days, 15-28 days, 29-42 days, 43-91 days, or ≥ 92 days) did not appear to significantly impact disease-free or overall survival on multivariable analysis.³⁵ In contrast, a retrospective study using the National Cancer Data Base (NCDB) presented at the annual meeting of the American Society of Clinical Oncology in 2018 reported significantly worse overall survival for patients with stage I to stage III cutaneous melanoma who experienced a delay of >60 days from diagnosis to definitive surgical management compared with patients treated within 60 days of diagnosis.³⁶ Similarly, another NCDB study reported that delays of ≥ 30 days from biopsy to definitive surgery were associated with worse overall survival for patients with stage I melanoma.³⁷ The mortality risk for patients with stage I disease increased with the number of days from biopsy to surgery as follows: a hazard ratio (HR) of 1.05

for 30 to 59 days (95% CI, 1.01-1.1), a HR of 1.16 for 60 to 89 days (95% CI, 1.07-1.25), a HR of 1.29 for 90 to 119 days (95% CI, 1.12-1.48), and a HR of 1.41 for >119 days (95% CI, 1.21-1.65).³⁷ A key limitation to NCDB studies is the lack of cancer-specific survival data.³⁸

Summary recommendations

Three physician societies have made treatment recommendations for patients with cutaneous melanoma. The NCCN recommends that treatment can be delayed for up to 3 months for patients with T0 to T1 tumors if no macroscopic residual disease is present after biopsy, and treatment can be delayed for up to 3 months among patients with $\geq T2$ disease if biopsy margins are negative.³⁹ The ACMS adopted the NCCN recommendations.⁴⁰ The BAD and BSDS suggest considering delaying treatment of patients with T0 to T1a tumors for 2 to 3 months after biopsy depending on clinical and histological features.²⁵

Our recommendations are consistent with those of the NCCN guidelines.

Cutaneous Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma (cSCC) causes as many deaths in the United States as melanoma.⁴¹ The overall risk of metastasis among patients with cSCC is 3.7% to 5.2%, with 2.8% disease-specific mortality.^{10,42} The risk of metastasis or death is higher for patients with tumors with increased depth of invasion, a large tumor dimension (≥ 2 cm), poorly differentiated disease, perineural invasion of larger nerves (≥ 0.1 mm in dimension), and immunosuppression.^{10,43} For tumors of a higher T classification (Brigham and Women's Hospital [BWH] T2b-T3 disease), the risk of lymph node metastasis is 24% and the risk of disease-specific death is 17%.⁴³

Treatment delay for patients with cSCC is associated with some interval progression in the size of the tumor. In a prospective study of 982 patients with cSCC and BCC who were treated with Mohs surgery, a delay in treatment (median, 2.5 months vs 6.0 months) was found to be significantly associated with tumor growth ($P < .0001$).⁴⁴ Limitations of the study included that the original assessment of lesion size was reported by the patient using a questionnaire, and long-term oncologic outcomes were not reported. In another cohort of patients with cSCC and BCC, a treatment delay of >1 year was correlated with the Mohs defect doubling in size (adjusted odds ratio, 2.0; 95% CI, 1.3-3.1).⁴⁵

Although treatment delays for patients with cSCC are associated with some interval enlargement of the

tumor, to our knowledge there are no data demonstrating a statistically significant association between treatment delay and an increased risk of disease-specific mortality, although this association is well documented for patients with mucosal SCC of the head and neck. In those patients, mortality was found to significantly increase with treatment delays of >46 to 52 days, although this study did not include any patients with cSCC.⁴⁶ One study of patients with invasive cSCC found that a long treatment delay (>18 months) was associated with a clinical tumor size >2 cm (odds ratio, 4.18; 95% CI, 2.45-7.13 [$P < .001$]).⁴⁷ Although a tumor size >2 cm has been well established as a prognostic factor associated with worse disease-specific mortality,^{42,48} the study did not report oncologic outcomes. cSCC tumor-specific factors found to be associated with a statistically significantly increased risk of distant metastasis included increased tumor thickness (HR, 4.79; 95% CI, 2.22-10.36 [$P < .01$]), immunosuppression (HR, 4.32; 95% CI, 1.62-11.52 [$P < .01$]), ear location (HR, 3.61; 95% CI, 1.51-8.67 [$P < .01$]), and increased horizontal size (HR, 2.22; 95% CI, 1.18-4.15 [$P < .05$]).⁴⁹

Summary recommendations

Three physician societies have made recommendations for the treatment of SCC. The NCCN states that treatment can be delayed, but clinicians should consider excision if the tumor poses a risk of metastasis or debilitating disease progression within 3 months. Adjuvant radiotherapy should be avoided unless there is extensive pNI or N2 disease.²⁴ The ACMS states that treatment can be postponed for 3 months in patients with cSCC in situ and small, well-differentiated cSCC. Patients with enlarging, symptomatic, or ulcerating tumors; those with perineural involvement; those with poorly differentiated tumors; and those with patient-specific risk factors (eg, an immunocompromised state) should be prioritized.⁴⁰ The BAD and BSDS suggest deferring treatment for patients with cSCC in situ and small, well-differentiated cSCCs. Patients with the same factors as listed in the ACMS guidelines should be prioritized.²⁵

Patients with cSCC in situ can have their treatment delayed for 3 months. For cSCC, patients with BWH T1 to T2a disease can have treatment delayed for 2 to 3 months given the very low risk of disease-specific mortality associated with these tumors (Table 1).¹³⁻¹⁵ Patients with tumors that are rapidly enlarging or symptomatic or who are immunosuppressed can be prioritized, balancing the competing risk of COVID-19 complications. Patients with BWH \geq T2b disease should be prioritized because

their oncologic outcomes are considerably worse (Table 2). These patients should be evaluated for delayed treatment on a case-by-case basis, weighing patient-specific and tumor-specific factors. Although a treatment delay of 1 to 2 months may result in clinical disease progression with regard to the size of the tumor, this progression is unlikely to translate into higher disease-specific mortality. For older patients, the added risk of COVID-19 exposure may outweigh the marginal benefit of the earlier treatment of cSCC because younger senior citizens (those aged 65-74 years) still have a 28.6% to 43.5% risk of hospitalization with COVID-19 and older senior citizens (those aged 75-84 years) have a 31.1% to 70.3% risk.²

For treatment with definitive radiotherapy,⁵⁰ the provider should strongly consider delaying treatment and/or using hypofractionation to decrease the number of clinic visits.⁵¹ The recently published American Society for Radiation Oncology (ASTRO) clinical practice guidelines for skin cancers provide dose and/or fractionation recommendations for hypofractionated radiation to minimize the number of clinic visits.⁵¹ For hypofractionated radiation (2.1-5 Gy per fraction) in the definitive setting, we recommend delivering a biologically effective dose (BED) assuming an α/β ratio of 10 (BED₁₀) of 56 Gy to 88 Gy, which is consistent with ASTRO guidelines.⁵¹ Acceptable hypofractionated dose regimens for patients with lesions measuring <2 cm in dimension as per the NCCN guidelines that also meet ASTRO BED₁₀ guidelines include 40 Gy in 10 fractions over 2 weeks (BED₁₀ of 56 Gy) and 50 Gy to 55 Gy in 15 to 20 fractions over 3 to 4 weeks. For larger tumors, hypofractionated treatment can be delivered to 50 Gy to 55 Gy over 3 to 4 weeks.⁵¹ In the postoperative setting, we recommend delivering hypofractionated radiotherapy with a BED₁₀ of 56 Gy to 70.2 Gy to the tumor bed.⁵¹ A dose of 50 Gy over 4 weeks is an acceptable option as per the NCCN that also meets ASTRO guidelines (BED₁₀ of 62.5 Gy). Delays in initiating adjuvant radiotherapy after definitive surgery may be associated with worse outcomes for patients with high-risk tumors and need to be balanced against the patient's risk of COVID-19 complications. Although delays in initiating adjuvant radiotherapy are associated with worse outcomes in patients with mucosal SCC of the head and neck, to our knowledge the data are limited regarding the impact of such delays for cSCC. The ASTRO clinical practice guidelines are a helpful resource for evidence-based recommendations regarding treatment indications and acceptable dose and/or fractionation regimens for radiotherapy for cSCC.⁵¹

The clinician must use his or her judgement in evaluating each tumor, considering factors such as predicted

tumoral growth, upstaging, increased morbidity of treatment, and risk of evolution into a symptomatic lesion when determining the appropriate timing for treatment.

Basal Cell Carcinoma

BCCs are at low risk of significant progression⁵² and mortality as a result of a treatment delay due to the slow natural history of this malignancy. Although to our knowledge no studies to date have investigated the effect of treatment delay on disease-specific mortality for BCC, a retrospective study found that a mean treatment delay of 70 days (range, 21-155 days) was associated with a median diameter increase of 0.5 mm and a median area increase of 4.71 mm².⁵³ Delaying treatment for >1 year was associated with a doubling of the Mohs defect size.⁴⁵

Summary recommendations

Three physician societies have made recommendations for the treatment of patients with BCC. The NCCN recommends delaying treatment during the COVID-19 pandemic.²⁴ The ACMS recommends a treatment delay of 3 months unless the patient is highly symptomatic.⁴⁰ The BAD and BSDS recommend that treatment be deferred for 3 to 6 months unless the patient is highly symptomatic.²⁵

Treatment of BCC tumors can be deferred for at least 3 months unless the patient is highly symptomatic. For patients who are treated with definitive radiation, we recommend hypofractionated radiotherapy using the dose and/or fractionation regimens described for patients with cSCC. The recently published ASTRO clinical practice guidelines for skin cancer discuss radiotherapy for patients with BCC.⁵¹

Rare Tumors

Other rare and potentially aggressive cutaneous tumors, such as sarcomas (eg, angiosarcoma, undifferentiated pleomorphic sarcoma, atypical fibroxanthoma, leiomyosarcoma), adnexal carcinomas, and sebaceous carcinomas should be prioritized for earlier treatment. The treatment of patients with dermatofibrosarcoma protuberans without high-risk features (eg, fibrosarcomatous changes, deep lesion, or high-grade tumor) can be deferred for several months given the relatively slow rate of growth and a low likelihood of lymph node and/or distant metastases.⁵⁴ NCCN guidelines recommend delaying the treatment of patients with dermatofibrosarcoma protuberans if there are no high-risk features.²⁴

Conclusions

Providers must balance the tumor-specific risks of treatment delays with patient-specific risks of COVID-19

community exposure to identify those skin cancers that warrant treatment during this time. For the majority of patients at higher risk of COVID-19–related morbidity and/or mortality, the risk of contracting COVID-19 likely outweighs the benefits of early treatment for their skin cancer. Clinician judgement is critical in making these treatment decisions.

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