



# The role of radiation therapy in the management of cutaneous malignancies.

## Part II: When is radiation therapy indicated?

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### Learning objectives

After completing this learning activity, participants should be able to understand the indications and contraindications to radiation therapy in treatment skin cancers, appropriate clinical scenarios, and margins necessary to treat a variety of skin cancers; and clinicians will be able to confidently recommend and incorporate radiation therapy in the treatment of skin cancers when indicated, thus improving patient care.

### Disclosures

#### Editors

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Radiation therapy may be performed for a variety of cutaneous malignancies, depending on patient health status, tumor clinical and histologic features, patient preference, and resource availability. Dermatologists should be able to recognize the clinical scenarios in which radiation therapy is appropriate, as this may reduce morbidity, decrease risk of disease recurrence, and improve quality of life. The second article in this 2-part continuing medical education series focuses on the most common indications for radiation therapy in the treatment of basal cell carcinoma, cutaneous squamous cell carcinoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi sarcoma, angiosarcoma, cutaneous lymphoma, melanoma, undifferentiated pleomorphic sarcoma, and sebaceous carcinoma. (J Am Acad Dermatol 2021;85:551-62.)

**Key words:** angiosarcoma; basal cell carcinoma; cutaneous lymphoma; cutaneous squamous cell carcinoma; dermatofibrosarcoma protuberans; Kaposi sarcoma; Merkel cell carcinoma; melanoma; pleomorphic dermal sarcoma; radiation therapy; sebaceous carcinoma; undifferentiated pleomorphic sarcoma.

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## INTRODUCTION

Radiation therapy (RT) may be performed for a variety of cutaneous malignancies, depending on patient health status, tumor clinical and histologic features, patient preference, and resource availability. Recent guidelines have better defined the indications for RT in particular clinical scenarios. Table I summarizes the most common indications for RT in the treatment of basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC), dermatofibrosarcoma protuberans (DFSP), Merkel cell carcinoma (MCC), Kaposi sarcoma (KS), angiosarcoma, cutaneous lymphoma, melanoma, undifferentiated pleomorphic sarcoma, and sebaceous carcinoma.<sup>1-8</sup>

## INDICATIONS FOR RADIATION THERAPY

### Basal cell carcinoma

Most BCCs are successfully treated with surgical methods. Primary RT is favored in poor surgical candidates and in tumors that cannot be excised without resulting in significant morbidity, impaired function, or poor cosmesis (Fig 1).<sup>1</sup> This is especially important in cosmetically sensitive areas, such as those near the eyelid, nose, or ear.<sup>1</sup> Similarly, tumors of the lip, oral commissure, or cheek requiring full-thickness resection may also be managed effectively with RT.<sup>9</sup> The National Comprehensive Cancer Network recommends adjuvant RT for BCC with substantial perineural involvement (nerve  $\geq 0.1$  mm in caliber or  $>3$  nerves  $<0.1$  mm) or for positive margins after Mohs micrographic surgery (MMS) or complete circumferential peripheral and deep margin assessment (CCPDMA) if clear margins cannot be achieved.<sup>1</sup> It may also be used for locally advanced disease extending into the cranial cavity.<sup>1</sup> Small, low-risk BCCs may be treated with a 0.5-cm radiation field margin beyond the clinically apparent tumor, while high-risk BCCs should have a wider margin of 1 to 1.5 cm.<sup>10</sup>

Although numerous treatment options for BCC exist, there are few high-quality analyses comparing different modalities. Surgery is considered the most efficacious treatment due to lower rates of recurrence.<sup>11</sup> Two meta-analyses reported a 5-year recurrence rate of 8.7% for primary BCCs and 10% for recurrent BCCs treated with definitive RT.<sup>12,13</sup> More recent retrospective analyses showed a combined 5-year recurrence rate of 4% to 16% for primary and recurrent BCCs.<sup>14-17</sup> RT has increased efficacy in primary, small ( $<2$  cm), and less deeply invasive tumors.<sup>14,15</sup> The efficacy of treating BCCs with RT is directly related to the clinician's ability to delineate tumor margins.<sup>18</sup> Scouting biopsies may be considered in tumors with ambiguous borders.<sup>18</sup> One retrospective analysis reported a 5-year recurrence rate of 39%

within a microscopically positive margin excision compared to only 9% in patients who received adjuvant RT.<sup>19</sup> Approximately 20% to 30% of incompletely excised tumors recur without adjuvant RT.<sup>10</sup>

### Cutaneous squamous cell carcinoma

While surgery is effective for treating cSCC, definitive RT may be desirable in poor surgical candidates.<sup>2</sup> The National Comprehensive Cancer Network panel recommends adjuvant RT for cSCC with positive margins following MMS or CCPDMA when clear margins cannot be attained.<sup>2</sup> Adjuvant RT is also recommended in cSCC with substantial perineural involvement (invasion of large caliber nerve  $\geq 0.1$  mm or invasion of nerve below dermis), as disease recurrence tends to occur along the affected nerves (Fig 2).<sup>20-22</sup> The proximal course of the local nerves should be irradiated in substantial or clinically evident perineural involvement in addition to involvement of named nerves of the head and neck.<sup>2</sup> Adjuvant RT is indicated in the postoperative period for nodal metastases to the head and neck, unless the patient has 1 small ( $\leq 3$  cm) node with no extracapsular extension.<sup>2</sup> RT may be used for large or multifocal lesions, multiply recurrent disease, or advanced disease extending into the cranial cavity (Fig 3).<sup>2</sup> Most cSCCs are treated with a 1- to 1.5-cm radiation field margin.<sup>10</sup> When postoperatively treating nodal metastases, low-dose radiation (2 Gy per fraction) are used to minimize radiation-related sequelae in a healing operative bed.<sup>9</sup>

Data regarding RT for cSCC are mostly limited to retrospective studies. These studies have demonstrated a 5-year recurrence rate of 4% to 7% for primary low-risk cSCC treated with RT.<sup>16,23-25</sup> One metanalysis showed a similar 5-year recurrence rate of 6.7% for primary cSCC treated with RT compared to 10% for recurrent cSCC.<sup>26</sup> Certain high-risk features include diameter  $>2$  cm, thickness  $>2$  mm, invasion  $>6$  mm or beyond the fat, poor differentiation, recurrence, location on the ear or lip, or immunosuppressed host.<sup>2</sup> Retrospective studies of patients with high risk and metastatic cSCC treated with RT had significantly higher recurrence rates of 17% to 54%.<sup>27-31</sup> One retrospective review demonstrated a significantly worse disease-specific survival in patients with cSCC metastatic to the parotid gland treated with RT alone compared to surgery plus adjuvant RT (47% vs 72%, respectively).<sup>32</sup> Another showed a significantly increased 5-year disease-free survival rate in patients with cSCC of the head and neck and nodal metastases when treated with surgery plus adjuvant RT compared to surgery alone (73% vs 54%, respectively).<sup>31</sup> Adjuvant RT improves local control and disease-free survival, but fails to show a survival benefit.<sup>33-37</sup>

*Abbreviations used:*

RT:	radiation therapy
BCC:	basal cell carcinoma
cSCC:	cutaneous squamous cell carcinoma
DFSP:	dermatofibroma sarcoma protuberans
MCC:	merkel cell carcinoma
KS:	kaposi sarcoma
MMS:	Mohs micrographic surgery
CCPDMA:	complete circumferential peripheral and deep margin assessment
CTCL:	cutaneous T-cell lymphoma
PCBCL:	primary cutaneous B-cell lymphoma
UPS:	undifferentiated pleomorphic sarcoma

Common radiation schedules used for the treatment of basal and squamous cell cancers are shown in Table II.<sup>38</sup>

### Dermatofibrosarcoma protuberans

The preferred treatment for DFSP is wide local excision to the fascia or MMS.<sup>3</sup> In poor surgical candidates, definitive RT is not typically used as first-line treatment.<sup>3</sup> Imatinib mesylate is an Food and Drug Administration approved treatment for unresectable, recurrent, and/or metastatic DFSP in adults that is preferred over radiation in nonsurgical candidates.<sup>3</sup> For recurrent disease where further resection is not feasible, RT alone may be used if not performed previously and would then be preferred over imatinib mesylate.<sup>3</sup> Adjuvant RT is performed when margins are positive following CCPDMA or MMS or after disease recurrence and further resection is not feasible.<sup>39-42</sup> The radiation field is widely extended beyond the surgical margins when clinically feasible, approximately 3-5 cm.<sup>3</sup> However, adjuvant RT is not necessary if surgical margins are clear.

The combination of surgery plus adjuvant RT provides excellent local control. A retrospective review of 53 patients with primary or recurrent DFSP treated with surgery plus adjuvant RT had a recurrence rate of 4% at a median of 6.5 years and disease-specific survival of 93% at 10 years.<sup>43</sup> In a series of 13 patients who received surgery plus adjuvant RT and 1 patient who received RT alone, 86% of patients remained disease-free at a median follow up of 10.5 years, including the patient who received RT alone.<sup>40</sup>

### Merkel cell carcinoma

The first-line treatment for MCC is excision with CCPDMA to the fascia or pericranium with 1- to 2-cm margins followed by expeditious initiation of adjuvant RT.<sup>4</sup> In certain cases, MMS has been used. Adjuvant RT is performed postoperatively whether negative or positive margins are obtained following CCPDMA or MMS.<sup>4</sup> It is preferable to start adjuvant RT within

4 weeks after surgery or as soon as the area is healed. The excision site, in-transit tissue, and draining nodal basins are irradiated to account for subclinical disease unless the primary tumor is ≤1 cm, negative post-operative margins are obtained, no lymphovascular invasion is noted, sentinel lymph node biopsy is negative, and the patient is immunocompetent.<sup>4</sup> Definitive RT is reserved for patients who are poor surgical candidates.<sup>4</sup> Wide radiation field margins of 5 cm should be used around the primary site.<sup>4</sup>

RT is not considered a replacement for surgery, however, it can result in 75% to 80% field control in most patients.<sup>10</sup> One multivariate analysis of patients with MCC treated with definitive RT alone showed a significantly improved disease-specific survival at 5 years versus no treatment (73% vs 54%).<sup>44</sup> Data to support adjuvant RT for MCC in specific clinical scenarios are few; however, it is recommended as it decreases disease recurrence and improves disease-specific survival.<sup>4,45,46</sup> Several small retrospective studies reported better outcomes in MCC patients treated with surgery +/- adjuvant RT compared to definitive RT +/- chemotherapy.<sup>47-52</sup> Similarly, a large retrospective study showed a significantly increased overall survival for MCC treated with surgery +/- adjuvant RT compared with definitive RT alone among patients with stage I/II disease (overall survival 76 vs 25 months) and stage III disease (overall survival 30 vs 15 months).<sup>51</sup> One randomized control trial of patients with stage I MCC showed a significant decrease in the risk of regional recurrence in patients treated with surgery followed by adjuvant RT compared to surgery alone (0% vs 16.7%).<sup>53</sup> Therefore, surgery followed by adjuvant RT is currently recommended.

### Kaposi sarcoma

While KS is a radiosensitive disease, a limited number of asymptomatic lesions that do not impair function may be safely managed with observation alone.<sup>5</sup> Definitive and palliative RT is reserved for the short-term management of patients with advanced cutaneous disease in which systemic therapy is not feasible (Fig 4).<sup>5</sup> RT may be used for local disease control until systemic treatment may be initiated.<sup>5,54</sup> Total skin electron beam RT is a therapeutic option for widespread, multifocal disease. Special considerations for treating KS with RT include the development of acute painful reactions to the palmar and plantar surfaces; therefore, treatment should be approached cautiously by treating one extremity at a time.<sup>5,55-57</sup> Lymphedema is a common complication of KS that may be exacerbated by RT.<sup>5</sup> This may lead to a delay in wound healing, delayed response to treatment, and an increased risk of soft-tissue infection.<sup>5</sup> Consequently, referral to a lymphedema specialist is recommended.<sup>5</sup>

**Table I.** Indications for the treatment of cutaneous malignancies with radiation therapy

Cutaneous malignancy	Definitive radiotherapy	Adjuvant radiotherapy	Palliative radiotherapy
Basal cell carcinoma	Nonsurgical candidates	Substantial perineural involvement*	Advanced/incurable disease, cutaneous metastases
	Advanced disease extending into cranial cavity	Positive margins after CCPDMA or MMS <sup>†</sup>	
Cutaneous squamous cell carcinoma	Nonsurgical candidates	Positive margins after CCPDMA or MMS <sup>†</sup>	Advanced/incurable disease, cutaneous metastases
	Advanced disease extending into cranial cavity	Substantial perineural involvement <sup>‡</sup>	
Dermatofibrosarcoma protuberans	Nonsurgical candidates	Postoperatively for nodal metastases to the head and neck <sup>§</sup> Multiply 11recurrent disease	
		Positive margins after CCPDMA or MMS <sup>†</sup> Disease recurrence <sup>†</sup>	Advanced/incurable disease, cutaneous metastases
Merkel cell carcinoma	Nonsurgical candidates	Postoperatively whether negative or positive margins <sup>  </sup>	Advanced/incurable disease, cutaneous metastases
Kaposi sarcoma	Nonsurgical candidates		
Angiosarcoma	Nonsurgical candidates	For limited operable disease	Widespread/multifocal disease
Cutaneous lymphoma	Extensive scalp involvement		
	Localized primary cutaneous B-cell lymphoma		All other cutaneous lymphomas
Melanoma	Cutaneous T-cell lymphoma		
	Large facial lentigo malignas not amenable to surgery	Postoperatively for desmoplastic melanoma Lymph node metastases	Unresectable nodal, satellite, or in-transit disease Cutaneous metastases
Undifferentiated pleomorphic sarcoma		Postoperatively whether negative or positive margins	
	Nonsurgical candidates	Positive margins after CCPDMA or MMS <sup>†</sup>	Advanced/incurable disease, cutaneous metastases
Sebaceous carcinoma		Postoperatively for nodal metastases	

CCPDMa, Complete circumferential peripheral and deep margin assessment; MMS, Mohs micrographic surgery.

\*>3 small nerves <0.1 mm or large nerve involvement ≥0.1 mm in caliber.

<sup>†</sup>when further resection is not feasible.

<sup>‡</sup>large nerve ≥0.1 mm or invasion of nerve below dermis.

<sup>§</sup>Unless patient has one small (≤3 cm) node and no extracapsular extension.

<sup>||</sup>Unless primary tumor ≤1 cm, no lymphovascular invasion, negative margins, negative sentinel lymph node biopsy, and patient is immunocompetent.

Data on the efficacy of RT in treating KS mostly consists of retrospective series and case reports, with few prospectively designed trials. One retrospective study of HIV-negative patients treated with RT showed complete response in 54% of KS lesions, partial remission in 38%, and nonresponse in 8% with a median duration of local control of 19.5 months.<sup>58</sup> Another study showed complete response in 91.4% of HIV-related KS lesions, partial remission in 6.7%, and nonresponse in 0.51% at a range of 1 to 46 months after RT.<sup>59</sup> For classic KS, 1 retrospective study of 771 lesions demonstrated a favorable cure rate of 98.7% at 13.5 years following treatment.<sup>59</sup> While RT is effective in treating KS, the risk of developing subsequent KS lesions persists even after complete remission as HHV-8 is not eradicated.<sup>5</sup>

### Angiosarcoma

The treatment of choice for angiosarcoma is surgery, with or without adjuvant RT, due to its high rates of subclinical extension and local recurrence. Definitive RT alone is considered inadequate for potentially curable disease and should be avoided in radiation-induced angiosarcoma.<sup>6</sup> Definitive RT is only performed in poor surgical candidates or for those with extensive scalp involvement (Fig 5).<sup>6</sup> Adjuvant RT may be used in patients with limited, operable disease to reduce the risk of local recurrence.<sup>6,10</sup> No randomized control trials have been performed to compare therapies, but retrospective series suggest that adjuvant RT combined with surgery, improves local control and overall survival.<sup>60,61</sup> One retrospective



**Fig 1.** Radiotherapy of basal cell carcinoma. **A**, A 64-year-old man with significant lower extremity pitting edema with multifocal BCCs of the right lower leg at the site of a burn from molten iron sustained 45 years ago. **B**, Four weeks into treatment with dose of 55 Gy in 20 fractions (radiation field outlined in black). Full response is expected 4 weeks following completion of therapy.

review of 67 patients with angiosarcoma showed an improved 5-year disease-free survival when treated with surgery followed by adjuvant RT +/- chemotherapy compared to surgery +/- chemotherapy (43% vs 17%).<sup>6</sup> Due to limited data, the role of adjuvant RT is currently unclear and not routinely recommended.

### Cutaneous lymphoma

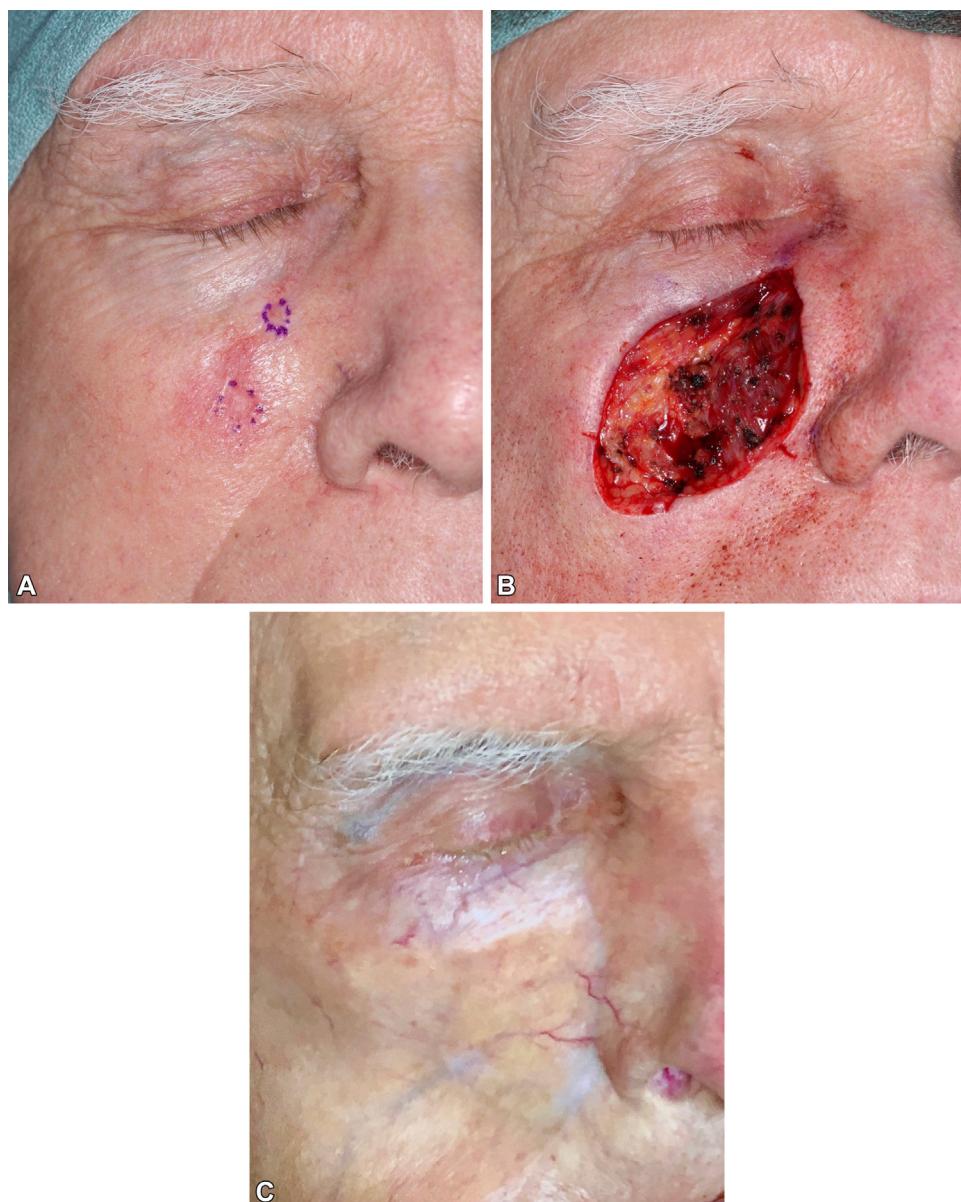
Radiation may be used to treat cutaneous lymphomas as a sole therapy or multimodal regimen as lymphocytes are exceedingly radiosensitive.<sup>62</sup> RT is a treatment for cutaneous T-cell lymphoma (CTCL), CD30<sup>+</sup> lymphoproliferative disorders, and primary cutaneous B-cell lymphomas (PCBCL).<sup>63</sup> Treatment is generally considered palliative with the exception of PCBCL and CTCL, which may be treated definitively.<sup>63</sup> Total skin electron beam radiation involves treatment of the entire cutaneous surface while a patient is standing on a rotating platform.<sup>63</sup> This may be used in the management of patch, plaque, or tumor stage CTCL.<sup>63</sup> Most cutaneous lymphomas may be managed with a dose of 24-30 Gy using a 6-9 MeV electron beam, however, newer prospective studies displayed tolerability and efficacy of low doses of RT using a 12 Gy regimen.<sup>7,62</sup> Individual tumors may require an additional dose of 4-12 Gy.<sup>7</sup> A circumferential and deep radiation margin of 1-2 cm is used when treating cutaneous lymphomas to provide a durable response and minimize toxicity.<sup>7</sup> Lower doses of RT allow for fewer side effects and

opportunity for subsequent treatments if initial response is not adequate. A dose of 4 Gy may be employed for relapsed disease.<sup>7</sup> Figure 6 demonstrates the successful treatment of multifocal CTCL following RT.

Radiation is an effective therapy for both PCBCL and CTCL. One retrospective study of patients with PCBCL treated with RT showed 100% complete response and 87.1% overall survival at 10-years.<sup>64</sup> Another retrospective study showed that low-dose RT  $\leq$  12 Gy was as effective as RT >12 Gy for indolent PCBCL, with complete response achieved in 100%.<sup>65</sup> Likewise, RT of 4 Gy in 2 fractions was found to be effective in managing symptoms of primary or recurrent disease among patients with PCBCL plaques and tumors, with complete response in 72%.<sup>66</sup> In 1 study, CTCL plaques and tumors were effectively treated with 8-12 Gy of electron beam radiation in 1-2 fractions, with complete response demonstrated in 92% of treated patients.<sup>66</sup>

### Melanoma

The standard treatment of localized melanoma is wide local excision. Melanoma is considered a relatively radioresistant skin cancer. Definitive RT may be offered for nonsurgical candidates or in cases where surgery would result in significant morbidity such as a large facial melanoma *in situ*, lentigo maligna (LM) type, in an elderly patient.<sup>8,67</sup> This is more common in Europe, where an estimated 13% to 17% of dermatologists use RT for LM in patients older than 70 years of age.<sup>68,69</sup> Adjuvant RT is recommended in patients with desmoplastic melanoma with factors associated with high risk of local recurrence, such as location on the head or neck, extensive neurotropism, pure desmoplastic histologic subtype, positive margins following excision and further resection is not feasible, or for recurrent disease.<sup>8</sup> Adjuvant RT may be used to treat high risk, resected regional disease, however it is not associated with improved disease-free survival or overall survival.<sup>8</sup> Factors associated with increased risk of regional recurrence include: gross or histologic extracapsular extension of melanoma in macroscopically involved nodes, including  $\geq 1$  parotid node,  $\geq 2$  cervical or axillary nodes,  $\geq 3$  inguinal or femoral nodes,  $\geq 3$  cm cervical or axillary nodes, and/or  $\geq 4$  cm inguinal or femoral nodes.<sup>8</sup> Definitive or palliative RT may be considered for unresectable nodal, satellite, or in-transit disease or for residual local, satellite, or in-transit disease after a prior treatment.<sup>8</sup> For metastatic melanoma outside of the brain, a hypofractionated schedule of 30 Gy in 5 fractions over 3 weeks may be used.<sup>38</sup> For metastatic melanoma of the brain and otherwise adequate

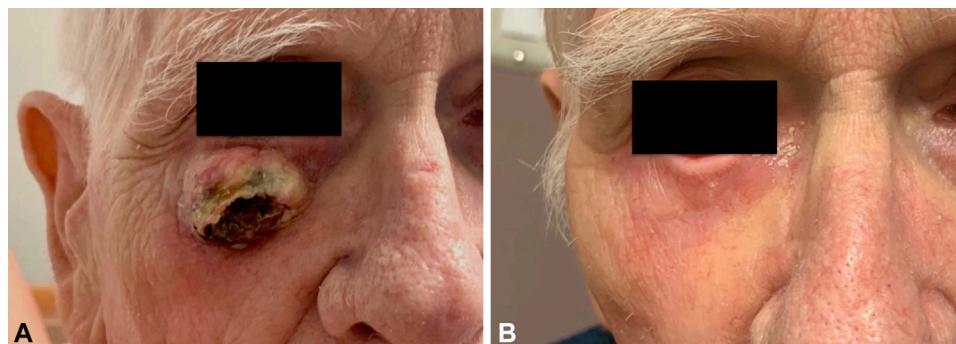


**Fig 2.** Adjuvant radiotherapy of cutaneous squamous cell carcinoma. **A**, An 87-year-old man with multiply recurrent cSCC of the right cheek with significant perineural invasion previously treated with surgical resection, partial right maxillectomy, and right parotidectomy. **B**, Immediately following surgical resection with MMS, right infraorbital nerve resection, and infraorbital foramen resection with clear margins obtained. **C**, Nine years following reconstruction with advancement flap and adjuvant radiation at a dose of 60 Gy in 30 fractions to the right cheek. *cSCC*, Cutaneous squamous cell carcinoma; *MMS*, Mohs micrographic surgery.

disease control, stereotactic radiosurgery should be considered.<sup>38,70</sup> Inoperable, invasive melanomas require a 2 cm margin while LM should have a radiation field margin of 1 to 1.5 cm.<sup>10</sup>

Local control of melanoma can be improved with adjuvant RT as illustrated in a retrospective analysis of patients with desmoplastic melanoma treated with excision plus adjuvant RT, especially in those with residual positive margins, Breslow depth >4 mm, or

locations on the head and neck.<sup>71</sup> Of note, there is a potential for increased toxicity when combining RT with systemic therapies, especially at higher doses of radiation.<sup>72</sup> BRAF and MEK inhibitors may lead to increased toxicity when used with RT, thus, these therapies should be held at least 3 days before and after fractionated RT.<sup>73</sup> Evidence of adverse reactions between RT and immunotherapy have not been shown.<sup>74</sup>



**Fig 3.** Palliative radiotherapy of cutaneous squamous cell carcinoma. **A**, A 76-year-old man with severe dementia with a painful and bleeding 3.5 cm cSCC of the right cheek. **B**, Three months following radiation at a dose of 44 Gy in 10 fractions. *KS*, Kaposi sarcoma.

**Table II.** Common radiation schedules for the treatment of basal and squamous cell cancers

Clinical scenario	Possible fractionation schedule	Total dose (Gy)	Total duration (days)
Most patients, most tumors	4 Gy × 10 fractions	40	12-14
	3 Gy × 15 fractions	45	19-21
	2.5-2.7 Gy × 20 fractions	50-55	26-28
Large treatment field with favorable cosmetic outcome desired or near the eye	2 Gy × 30 fractions	60	42-44
	2 Gy × 35 fractions	70	49-51
Elderly patient with tumor ≤ 1 cm	5 Gy × 8 fractions	40	10-12
Elderly patient with medical comorbidities	8 Gy × 4 fractions	32	4-7
Elderly patient in poor health (palliative)	20 Gy × 1 fraction	20	1

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### Sarcoma

Pleomorphic dermal sarcoma and undifferentiated pleomorphic sarcoma (UPS), previously referred to as malignant fibrous histiocytoma, are spindle cell neoplasms existing within a clinicopathologic spectrum.<sup>75-77</sup> Pleomorphic dermal sarcoma and superficial UPS arise from the dermis and invade subcutaneous fat, with or without lymphovascular or perineural invasion. Management includes CCPDMA or MMS. However, UPS in the deep tissues of the head/neck, extremities, or trunk is more aggressive, with an increased risk of metastasis and a 50% 5-year survival rate.<sup>75-77</sup> Thus, optimal treatment includes surgery plus adjuvant RT, regardless of whether surgical margins are clear. Due to the rarity of these tumors, evolving nomenclature, and limited data available, consensus guidelines on the treatment have not been established.

### Sebaceous carcinoma

The primary treatment of sebaceous carcinoma is CCPDMA or MMS. Definitive RT is used in nonsurgical candidates. The dosage ranges from 50 to 70 Gy in 2 Gy fractions with a 2 cm margin for extra-ocular lesions and varying margin, depending on adjacent anatomy for periocular tumors as RT of

the upper eyelid increases the risk for ocular toxicity, such as conjunctivitis, keratitis, and cataracts.<sup>78,79</sup> Local anesthetic eye drops with steroids are applied prior to inserting eye shields and patients wear an eye patch for 1 to 2 hours following RT each day. Adjuvant RT is used for incompletely excised tumors or for perineural invasion. Additionally, RT may be used palliatively for metastatic or incurable disease. Adjuvant RT to the regional nodal basin may be performed instead of complete lymph node dissection in patients with positive sentinel lymph node biopsy. Regional RT is also used after therapeutic lymphadenectomy for clinically evident nodal metastases.

Few studies have reported RT use in the treatment of sebaceous carcinoma. One study of patients with periocular sebaceous carcinoma treated with 39 Gy of RT resulted in 100% complete response and 57% disease-free survival at 5 years.<sup>80</sup> In another study, patients treated with 50 to 66.6 Gy of RT demonstrated an 80% 5-year overall survival rate and 93% local progression-free rate.<sup>78</sup> Treatment of patients with periorbital sebaceous carcinoma invasive to the parotid gland with surgery +/- adjuvant RT, including those with metastatic disease, resulted in a local recurrence



**Fig 4.** Radiotherapy of Kaposi Sarcoma. **A**, A 90-year-old woman with KS of the medial lower portion of the right leg associated with significant pruritus and pain. **B**, Three months after treatment with a dose of 20 Gy in 5 fractions with relief of symptoms. *KS*, Kaposi sarcoma.



**Fig 5.** Angiosarcoma. **A**, A 75-year-old woman with high-grade angiosarcoma of the forehead and frontal scalp with 4.5 mm of invasion. No lymphovascular or perineural invasion was noted. **B**, Following resection to the periosteum and reconstruction with skin graft one month later. **C**, Two and a half years following adjuvant radiation at a dose of 66 Gy in 33 fractions with no evidence of recurrence.

rate of 29% at 2 years compared to 83% in patients treated with surgery alone.<sup>81</sup>

## CONCLUSION

Radiation therapy has shown to be a safe and effective treatment for a variety of cutaneous

malignancies in select cases. The decision to initiate RT should be tailored to both patient and tumor after careful consideration. A thorough understanding of the indications for RT in specific clinical scenarios in addition to its strengths and limitations optimizes patient care and safety.



**Fig 6.** Radiotherapy of cutaneous T-cell lymphoma. **A**, 65-year-old man with tumor stage CTCL of the right medial lower leg before radiation. **B**, Following treatment with a dose of 45 Gy in 15 fractions. **C**, Same patient with tumor stage CTCL of the right lateral lower leg before radiation. **D**, Following treatment with a dose of 45 Gy in 15 fractions. **E**, 70-year-old man with tumor stage CTCL with large cell transformation of the left dorsal hand and fifth finger before radiation. **F**, Five months following treatment with a dose of 60 Gy in 2 fractions with 1 cm bolus. *CTCL*, Cutaneous T-cell lymphoma.

#### Conflicts of interest

None disclosed.

#### REFERENCES

1. National Comprehensive Cancer Network. Basal Cell Skin Cancer. Version 1, 2020. Accessed March 1, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/nmsc.pdf](https://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf)
2. National Comprehensive Cancer Network. Squamous Cell Skin Cancer. Version 2, 2020. Accessed March 1, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/squamous.pdf](https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf)
3. National Comprehensive Cancer Network. Dermatofibrosarcoma Protuberans. Version 1, 2020. Accessed March 1, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/dfsp.pdf](https://www.nccn.org/professionals/physician_gls/pdf/dfsp.pdf)
4. National Comprehensive Cancer Network. Merkel Cell Carcinoma. Version 1, 2020. Accessed March 1, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/mcc.pdf](https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf)
5. National Comprehensive Cancer Network. AIDS-Related Kaposi Sarcoma. Version 3, 2020. Accessed March 1, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/kaposi\\_blocks.pdf](https://www.nccn.org/professionals/physician_gls/pdf/kaposi_blocks.pdf)

6. Mark RJ, Poen JC, Tran LM, Fu YS, Juillard GF. Angiosarcoma. A report of 67 patients and a review of the literature. *Cancer*. 1996;77(11):2400-2406.
7. National Comprehensive Cancer Network. Primary Cutaneous Lymphomas. Version 1, 2021. Accessed March 1, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/primary\\_cutaneous.pdf](https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf)
8. National Comprehensive Cancer Network. Melanoma: Cutaneous. Version 1, 2021. Accessed March 1, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf)
9. Guadagnolo A, Ang K, Ballo M. In: Cox J, Ang K, eds. *Radiation Oncology*. 9th ed. Mosby; 2010.
10. Veness M, Richards S. Radiotherapy. In: JL B, JV S, L C, eds. *Dermatology*. 4th ed. Elsevier; 2018:2392-2402.
11. Bath-Hextall FJ, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev*. 2007;1(1):CD003412.
12. Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol*. 1989;15(3):315-328.
13. Rowe DE, Carroll RJ, Day CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol*. 1989;15(4):424-431.
14. Silverman MK, Kopf AW, Gladstein AH, Bart RS, Grin CM, Levenstein MJ. Recurrence rates of treated basal cell carcinomas: part 4: X-ray therapy. *J Dermatol Surg Oncol*. 1992;18(7):549-554.
15. Zagrodnik B, Kempf W, Seifert B, et al. Superficial radiotherapy for patients with basal cell carcinoma: recurrence rates, histologic subtypes, and expression of p53 and Bcl-2. *Cancer*. 2003;98(12):2708-2714.
16. Cognetta AB, Howard BM, Heaton HP, Stoddard ER, Hong HG, Green WH. Superficial x-ray in the treatment of basal and squamous cell carcinomas: a viable option in select patients. *J Am Acad Dermatol*. 2012;67(6):1235-1241.
17. Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer*. 1997;76(1):100-106.
18. Tward JD, Anker CJ, Gaffney DK, Bowen GM. Radiation therapy and skin cancer. In: Natanasabapathi G, ed. *Modern Practices in Radiation Therapy*. InTech; 2012:207-246.
19. Cameron MC, Lee E, Hibler BP, et al. Basal cell carcinoma: contemporary approaches to diagnosis, treatment, and prevention. *J Am Acad Dermatol*. 2019;80(2):321-339.
20. Sapir E, Tolpadi A, McHugh J, et al. Skin cancer of the head and neck with gross or microscopic perineural involvement: patterns of failure. *Radiother Oncol*. 2016;120(1):81-86.
21. McNab AA, Francis IC, Benger R, Crompton JL. Perineural spread of cutaneous squamous cell carcinoma via the orbit: clinical features and outcome in 21 cases. *Ophthalmology*. 1997;104(9):1457-1462.
22. Gluck I, Ibrahim M, Popovtzer A, et al. Skin cancer of the head and neck with perineural invasion: defining the clinical target volumes based on the pattern of failure. *Int J Radiat Oncol Biol Phys*. 2009;74(1):38-46.
23. Abbatucci JS, Boulier N, Laforge T, Lozier JC. Radiation therapy of skin carcinomas: results of a hypofractionated irradiation schedule in 675 cases followed more than 2 years. *Radiother Oncol*. 1989;14(2):113-119.
24. Hernández-Machín B, Borrego L, Gil-García M, Hernández BH. Office-based radiation therapy for cutaneous carcinoma: evaluation of 710 treatments. *Int J Dermatol*. 2007;46(5):453-459.
25. Schulte KW, Lippold A, Auras C, et al. Soft x-ray therapy for cutaneous basal cell and squamous cell carcinomas. *J Am Acad Dermatol*. 2005;53(6):993-1001.
26. Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol*. 1992;26(6):976-990.
27. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. *Int J Radiat Oncol Biol Phys*. 2004;60(2):406-411.
28. Jol JAD, van Velthuysen MLF, Hilgers FJM, Keus RB, Neering H, Balm AJM. Treatment results of regional metastasis from cutaneous head and neck squamous cell carcinoma. *Eur J Surg Oncol*. 2003;29(1):81-86.
29. Taylor BW, Brant TA, Mendenhall NP, et al. Carcinoma of the skin metastatic to parotid area lymph nodes. *Head Neck*. 1991;13(5):427-433.
30. DelCharco JO, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Mendenhall NP. Carcinoma of the skin metastatic to the parotid area lymph nodes. *Head Neck*. 1998;20(5):369-373.
31. Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. *Laryngoscope*. 2005;115(5):870-875.
32. Audet N, Palme CE, Gullane PJ, et al. Cutaneous metastatic squamous cell carcinoma to the parotid gland: analysis and outcome. *Head Neck*. 2004;26(8):727-732.
33. Stevens DM, Kopf AW, Gladstein A, Bart RS. Treatment of Bowen's disease with Grenz rays. *Int J Dermatol*. 1977;16(5):329-339.
34. Ampil FL, Hardin JC, Peskind SP, Stucker FJ. Perineural invasion in skin cancer of the head and neck. a review of nine cases. *J Oral Maxillofac Surg*. 1995;53(1):34-38.
35. Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia II. Perineural invasion. *J Am Acad Dermatol*. 2005;53(2):261-266.
36. Cottel WI. Perineural invasion by squamous-cell carcinoma. *J Dermatol Surg Oncol*. 1982;8(7):589-600.
37. Balamucki CJ, Mancuso AA, Amdur RJ, et al. Skin carcinoma of the head and neck with perineural invasion. *Am J Otolaryngol*. 2012;33(4):447-454.
38. Garner W, McGovern S, Ballo M. Radiation oncology in skin cancer treatment. In: MacFarlane D, ed. *Skin Cancer Management: A Practical Approach*. 2nd ed. Springer; 2021:311-326.
39. Suit H, Spiro I, Mankin HJ, Efird J, Rosenberg AE. Radiation in management of patients with dermatofibrosarcoma protuberans. *J Clin Oncol*. 1996;14(8):2365-2369.
40. Williams N, Morris CG, Kirwan JM, Dagan R, Mendenhall WM. Radiotherapy for dermatofibrosarcoma protuberans. *Am J Clin Oncol Cancer Clin Trials*. 2014;37(5):430-432.
41. Ballo MT, Zagars GK, Pisters P, Pollack A. The role of radiation therapy in the management of dermatofibrosarcoma protuberans. *Int J Radiat Oncol Biol Phys*. 1998;40(4):823-827.
42. Hamid R, Hafeez A, Darzi M, Zaroo I, Rasool A, Rashid H. Outcome of wide local excision in dermatofibrosarcoma protuberans and use of radiotherapy for margin-positive disease. *Indian Dermatol Online J*. 2013;4(2):93-96.
43. Castle KO, Guadagnolo BA, Tsai CJ, Feig BW, Zagars GK. Dermatofibrosarcoma protuberans: Long-term outcomes of 53 patients treated with conservative surgery and

- radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013;86(3):585-590.
44. Sridharan V, Muralidhar V, Margalit DN, et al. Merkel cell carcinoma: a population analysis on survival. *J Natl Compr Cancer Netw.* 2016;14(10):1247-1257.
45. Veness MJ, Perera L, McCourt J, et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. *ANZ J Surg.* 2005;75(5):275-281.
46. Clark JR, Veness MJ, Gilbert R, O'Brien CJ, Gullane PJ. Merkel cell carcinoma of the head and neck: is adjuvant radiotherapy necessary? *Head Neck.* 2007;29(3):249-257.
47. Liang E, Brower JV, Rice SR, Buehler DG, Saha S, Kimple RJ. Merkel cell carcinoma analysis of outcomes: a 30-year experience. *PLoS One.* 2015;10(6):e0129476.
48. Hui AC, Stillie AL, Seel M, Ainslie J. Merkel cell carcinoma: 27-year experience at the Peter MacCallum Cancer Centre. *Int J Radiat Oncol Biol Phys.* 2011;80(5):1430-1435.
49. Boyle F, Pendlebury S, Bell D. Further insights into the natural history and management of primary cutaneous neuroendocrine (Merkel cell) carcinoma. *Int J Radiat Oncol Biol Phys.* 1995;31(2):315-323.
50. Siva S, Byrne K, Seel M, et al. 18F-FDG PET provides high-impact and powerful prognostic stratification in the staging of merkel cell carcinoma: a 15-year institutional experience. *J Nucl Med.* 2013;54(8):1223-1229.
51. Wright GP, Holtzman MP. Surgical resection improves median overall survival with marginal improvement in long-term survival when compared with definitive radiotherapy in Merkel cell carcinoma: a propensity score matched analysis of the National Cancer Database. *Am J Surg.* 2018;215(3):384-387.
52. Shaw JHF, Rumball E. Merkel cell tumour: clinical behaviour and treatment. *Br J Surg.* 1991;78(2):138-142.
53. Jouary T, Leyral C, Dreno B, et al. Adjuvant prophylactic regional radiotherapy versus observation in stage I merkel cell carcinoma: a multicentric prospective randomized study. *Ann Oncol.* 2012;23(4):1074-1080.
54. Nobler MP, Leddy ME, Huh SH. The impact of palliative irradiation on the management of patients with acquired immune deficiency syndrome. *J Clin Oncol.* 1987;5(1):107-112.
55. Singh NB, Lakier RH, Donde B. Hypofractionated radiation therapy in the treatment of epidemic Kaposi sarcoma - A prospective randomized trial. *Radiother Oncol.* 2008;88(2):211-216.
56. Hauerstock D, Gerstein W, Vuong T. Results of radiation therapy for treatment of classic Kaposi sarcoma. *J Cutan Med Surg.* 2009;13(1):18-21.
57. Kirova YM, Belembaogo E, Frikha H, et al. Radiotherapy in the management of epidemic Kaposi's sarcoma: a retrospective study of 643 cases. *Radiother Oncol.* 1998;46(1):19-22.
58. Tombolini V, Osti M, Bonanni A, et al. Radiotherapy in classic Kaposi's sarcoma (CKS): experience of the Institute of Radiology of University "La Sapienza" of Rome. *Anticancer Res.* 1999;19(5C):4539-4544.
59. Caccialanza M, Marca S, Piccinno R, Eulisse G. Radiotherapy of classic and human immunodeficiency virus-related Kaposi's sarcoma: results in 1482 lesions. *J Eur Acad Dermatol Venereol.* 2008;22(3):297-302.
60. Schlemmer M, Reichardt P, Verweij J, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. *Eur J Cancer.* 2008;44(16):2433-2436.
61. Pawlik TM, Paulino AF, McGinn CJ, et al. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. *Cancer.* 2003;98(8):1716-1726.
62. Specht L, Dabaja B, Illidge T, Wilson LD, Hoppe RT, International Lymphoma Radiation Oncology Group. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the international lymphoma radiation oncology group. *Int J Radiat Oncol Biol Phys.* 2015;92(1):32-39.
63. Shikama N. Local radiation for cutaneous T-cell lymphoma other than mycosis fungoides and Sézary syndrome. *Chin Clin Oncol.* 2019;8(1).
64. De Felice F, Grapulin L, Pieroni A, et al. Radiation therapy in indolent primary cutaneous B cell lymphoma: a single institute experience. *Ann Hematol.* 2018;97(12):2411-2416.
65. Akhtari M, Reddy JP, Pinnix CC, et al. Primary cutaneous B-cell lymphoma (non-leg type) has excellent outcomes even after very low dose radiation as single-modality therapy. *Leuk Lymphoma.* 2016;57(1):34-38.
66. Neelis KJ, Schimmel EC, Vermeer MH, Senff NJ, Willemze R, Noordijk EM. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. *Int J Radiat Oncol Biol Phys.* 2009;74(1):154-158.
67. Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. *Br J Dermatol.* 2002;146(6):1042-1046.
68. Tio D, Prinsen CAC, Dréno B, Hoekzema R, Augustin M, van Montfrans C. Variation in the diagnosis and clinical management of lentigo maligna across Europe: a survey study among European Association of Dermatologists and Venereologists members. *J Eur Acad Dermatol Venereol.* 2018;32(9):1476-1484.
69. Mahendran RM, Newton-Bishop JA. Survey of UK Current practice in the treatment of lentigo maligna. *Br J Dermatol.* 2001;144(1):71-76.
70. Chang EL, Selek U, Hassenbusch SJ, et al. Outcome variation among "radioresistant" brain metastases treated with stereotactic radiosurgery. *Neurosurgery.* 2005;56(5):936-944.
71. Strom T, Caudell JJ, Han D, et al. Radiotherapy influences local control in patients with desmoplastic melanoma. *Cancer.* 2014;120(9):1369-1378.
72. Kroese SGC, Fritz C, Hoyer M, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: a systematic review. *Cancer Treat Rev.* 2017;53:25-37.
73. Anker CJ, Grossmann KF, Atkins MB, Suneja G, Tarhini AA, Kirkwood JM. Avoiding severe toxicity from combined BRAF inhibitor and radiation treatment: consensus guidelines from the Eastern Cooperative Oncology Group (ECOG). *Int J Radiat Oncol Biol Phys.* 2016;95(2):632-646.
74. Bang A, Wilhite TJ, Pike LRG, et al. Multicenter evaluation of the tolerability of combined treatment with PD-1 and CTLA-4 immune checkpoint inhibitors and palliative radiation therapy. *Int J Radiat Oncol Biol Phys.* 2017;98(2):344-351.
75. Winchester D, Lehman J, Tello T, et al. Undifferentiated pleomorphic sarcoma: factors predictive of adverse outcomes. *J Am Acad Dermatol.* 2018;79(5):853-859.
76. Soleymani T, Aasi SZ, Novoa R, Hollmig ST. Atypical fibroxanthoma and pleomorphic dermal sarcoma: updates on classification and management. *Dermatol Clin.* 2019;37(3):253-259.
77. Miller K, Goodlad JR, Brenn T. Pleomorphic dermal sarcoma: adverse histologic features predict aggressive behavior and allow distinction from atypical fibroxanthoma. *Am J Surg Pathol.* 2012;36(9):1317-1326.

78. Hata M, Koike I, Maegawa J, et al. Radiation therapy for primary carcinoma of the eyelid: tumor control and visual function. *Strahlentherapie und Onkol.* 2012;188(12):1102-1107.
79. Owen JL, Kibbi N, Worley B, et al. Sebaceous carcinoma: Evidence-based clinical practice guidelines. *Lancet Oncol.* 2019;20(12):e699-e714.
80. Azad S, Choudhary V. Treatment results of high dose rate interstitial brachytherapy in carcinoma of eye lid. *J Cancer Res Ther.* 2011;7(2):157-161.
81. Deo SVS, Shukla NK, Singh M, Jha D, Khanna P, Kallianpur A. Locally advanced sebaceous cell carcinoma (T3) of eyelid: incidence and pattern of nodal metastases and combined modality management approach. *Orbit.* 2012;31(3):150-154.