Superficial Radiotherapy For Cutaneous Melanoma

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Cutaneous melanoma is a lethal malignancy that remains a therapeutic challenge despite an expanding number of advanced treatment options. The only highly effective therapy is early detection and complete surgical excision of local disease. In patients presenting with more advanced melanoma, surgery can be combined with systemic therapies and/or radiation.

Radiotherapy in the treatment of melanoma is likely underutilized owing to a historic misperception that all melanomas are radioresistant. More recent work suggests that melanomas show a range of sensitivity to radiation, and growing evidence supports use of this modality in select patients.

Radiation Therapy

Radiotherapy utilizes ionizing radiation to damage DNA and subsequently arrest cancer cell growth. When treating internal targets with radiotherapy, high-energy X-rays in the megavoltage range (4–16 MV) are typically used. In treating primary, recurrent, or metastatic disease in the skin, it is possible to use superficial radiotherapy to minimize collateral tissue damage and increase the therapeutic index. Superficial radiotherapy uses lower-energy superficial or orthovoltage X-rays (10–500 kV) or electron beams, as these forms of radiation have limited tissue penetration. With superficial radiotherapy, the majority of the energy is deposited within a shallow treatment volume near the body’s surface, and underlying structures are spared. In particular, electrons allow rapid dose fall-off beyond skin depth, thereby limiting the amount of radiation delivered to deeper structures. In the past, Grenz ray machines were used as a source of superficial “soft X-radiation,” however, they are now virtually non-existent in the US.

Use of superficial radiotherapy is limited, in part, by its effect on adjacent normal tissues. Typically, radiosensitive tumor cells exhibit a steep dose-response curve compared to normal cells, which can recover from small doses of radiation. This difference allows prolonging life cannot be underestimated. One of the most dreaded sequelae of advanced melanoma is metastasis of the tumor to the brain. Although brain metastasis is generally associated with a poor prognosis, some patients respond well, and a few can manifest durable responses to systemic therapy and/or radiotherapy. In this issue, Drs. Ashwatha Narayana, Anna Pavlick, and John Golfinos at New York University Medical Center describe their use of radiotherapy and radiosurgery in the treatment of melanoma brain metastasis.

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From the Editors

Melanoma is often incorrectly perceived as a radiation-resistant tumor. Although curative therapy usually relies on surgical interventions, circumstances may arise where surgical intercession is not ideal, convenient, or even possible. In such situations, other modes of therapy such as topical immunomodulation, cryotherapy, or radiation therapy may provide alternatives, which in select cases may prove curative.

In this issue of The Melanoma Letter, Drs. Isaac Brownell, Nancy Lee, and Alice Ho at Memorial Sloan-Kettering Cancer Center explore the uses of superficial radiotherapy in treating certain types of melanoma. The technique can serve as an adjuvant therapy to regional lymph node basins in select patients at high risk for regional recurrence, as a palliative therapy for disseminated inoperable disease, and in select cases, as a primary therapy for lentigo maligna and lentigo maligna melanoma as well as unresectable in-transit metastases. On page 3 Dr. Reinhard Dummer details the experience of European clinicians using superficial radiotherapy to treat LMM.

While curative therapy for melanoma remains of paramount importance, the value of palliative therapy and treatments aimed at prolonging life cannot be underestimated. One of the most dreaded sequelae of advanced melanoma is metastasis of the tumor to the brain. Although brain metastasis is generally associated with a poor prognosis, some patients respond well, and a few can manifest durable responses to systemic therapy and/or radiotherapy. In this issue, Drs. Ashwatha Narayana, Anna Pavlick, and John Golfinos at New York University Medical Center describe their use of radiotherapy and radiosurgery in the treatment of melanoma brain metastasis.

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for the use of fractionated radiotherapy, where the total therapeutic dose of radiation needed to treat the tumor is divided into multiple, small, “conventional” dose fractions administered over time. Conventionally fractionated radiotherapy has less impact on surrounding normal tissues and is better tolerated than low-fraction, high-dose (“hypofractionated”) regimens.

Melanoma and Radiotherapy

Unlike highly radiosensitive tumors, melanomas often have a dose response to radiation that is similar to late-responding normal tissues. Because melanoma cells may effectively recover from the damage caused by conventional-fractionation radiation doses, higher doses per treatment may be needed to achieve cytotoxicity. Therefore, hypofractionated dosing regimens are often selected. Most treatment centers opt for hypofractionated regimens that are effective in controlling melanoma yet relatively well tolerated. There is still debate in the field regarding the potential efficacy of conventional-fraction radiotherapy,6 and further studies are needed to explore this issue.

The National Comprehensive Cancer Network (NCCN) guidelines on melanoma treatment support the use of radiation for palliation of disseminated inoperable disease and also as an alternative treatment for unresectable in-transit metastases in local dermal lymphatics.7 While radiation is becoming more common in the treatment of isolated or limited (oligometastatic) internal organ disease, it is infrequently the treatment of choice for in-transit metastases.

In addition to the NCCN indications, several retrospective series demonstrate the efficacy of adjuvant radiotherapy to regional lymph node basins in select patients at high risk for regional recurrence.4,6,8 This application is often limited to patients with high-risk clinical and pathologic features, as the increased local control must be balanced against the risks of complications such as lymphedema or fibrosis, and the fact that overall survival is probably not improved. Radiation, along with systemic therapies, is also a second-line consideration for the treatment or palliation of any melanoma where surgery is not feasible.

For inoperable cutaneous lesions, superficial radiation is a potential therapeutic option.

Superficial Radiation for Select Melanomas

Only in exceptional circumstances is a surgical treatment approach impossible and thus replaced by superficial radiotherapy as the primary treatment for cutaneous melanoma (Table 1). There are also situations where postoperative superficial radiation can be considered (Table 2). In evaluating a patient for radiation, the treatment volume, dosage, and fractionation scheme should be tailored to the individual’s tumor properties, predicted recurrence risk, and surrounding anatomy. Potential late adverse effects such as fibrosis, chronic radiation dermatitis, and radiation-induced carcinomas should also be considered. Prior radiation exposure is also a consideration, as reirradiation is often poorly tolerated.

Radiation for Lentigo Maligna and Lentigo Maligna Melanoma: Superficial radiotherapy is a second-line treatment option for lentigo maligna (LM). LM is an intraepidermal proliferation of malignant melanocytes that presents as a slowly enlarging pigmented macule, often on chronically sun-damaged skin in elderly patients. When a focus of the tumor invades the dermis, the lesion is called a lentigo maligna melanoma (LMM). LM and LMM are often large and have a predilection for the use of fractionated radiotherapy, where the total therapeutic dose of radiation needed to treat the tumor is divided into multiple, small, “conventional” dose fractions administered over time. Conventionally fractionated radiotherapy has less impact on surrounding normal tissues and is better tolerated than low-fraction, high-dose (“hypofractionated”) regimens.

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Superficial Radiotherapy for Lentigo Maligna Melanoma: Clinical Experience in Europe

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Surgery is the standard first-line treatment approach for primary melanoma. Based on the current recommendations for safety margins, surgery can usually be safely performed without creating disfiguring defects. However, in certain situations, especially in critical localizations such as the periorbital region or the nose, surgery can result in substantial morbidity.

Melanomas on the face are most common in patients of advanced age, who present significant actinic damage. This patient population often suffers from additional co-morbidities that increase the risk of complications during extensive surgical procedures. The most common melanoma type in the population is lentigo maligna melanoma (LMM), which often presents as a large hyperpigmented spot, or macule, that is not well circumscribed.

LMM usually grows intraepidermally for a long time without resulting in any relevant invasion into the dermis. However, it often does extend into the deeper epidermis by proliferating along the hair follicle epithelium.

For LMM in patients of advanced age, superficial radiotherapy using Grenz rays (supersoft x-rays) has been used in Europe for decades. This method was developed in radiotherapy centers in the early decades of the past century. Dermatology departments in Hamburg, Munich, Berlin, Vienna and Zurich defined the treatment protocol for LM, and investigations are still valid today.

The radiodermatitis typically dissipates within 1–5 years status post-radiation therapy is usually quite good to excellent, especially in central regions of the face. In other regions of the face the appearance of hypopigmentation or mild telangiectasia may occur and persist indefinitely.

Based on many positive experiences over the last 80 years, we consider superficial radiotherapy to be a reasonable alternative to surgery for LMM, especially in patients who are over 60 years of age.

References

for the head and neck. Complete surgical excision of such lesions can require extensive reconstruction, impairing the function of facial structures. In elderly patients unable to tolerate large surgical procedures, or in lesions where the anticipated reconstruction would have notable functional and cosmetic impact, superficial radiotherapy can be considered as primary treatment. Other non-excisional treatment alternatives to consider for unresectable LM include cryotherapy and immunotherapy with topical imiquimod cream.

Retrospective studies suggest that local recurrence rates for LM or LMM treated by superficial radiotherapy compare favorably to surgical treatment approaches, but no controlled prospective trials have been conducted. Anecdotally and in our experience, the treatment is tolerated well, shows low morbidity, and results in acceptable cosmetic outcomes. However, there is insufficient evidence to gauge its ultimate impact on rates of disseminated disease, overall survival, or comparative cosmetic outcomes.

Similar to LM, other subtypes of cutaneous melanoma may present in clinical contexts where surgery is impossible or inadvisable. These patients may also be considered for superficial radiotherapy.

When treating a cutaneous melanoma with radiation, the treatment field includes the area of the lesion plus a margin of clinically uninvolved skin. The appropriate size of the safety margin for radiotherapy of melanoma is debatable. For LM, some authors recommend a margin of at least 1 cm, as they have observed recurrences at the edge of the radiotherapy field when less than 1 cm was used. When planning radiation treatments for pigmented lesions, especially LM, the lesion can be examined with a Wood’s lamp to better delineate the clinical border. If there are questions about the extent of involvement, scouting skin biopsies can be considered to better define the lesion margins. Histological depth of the tumor should guide treatment depth. In LM, involvement of adnexal structures such as hair follicles would warrant a deeper treatment volume. When defining the extent of the disease,
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photographic documentation and close communication between the dermatologist, dermatopathologist and radiation oncologist can help in designing the optimal treatment volume.

Radiation for In-Transit Metastases: Another potential use of superficial radiotherapy for primary treatment is in controlling in-transit melanoma metastases. The first-line treatment for isolated or limited numbers of local cutaneous metastases is complete surgical excision. But when the lesions are too extensive to excise, alternative approaches such as intralesional chemotherapy or superficial radiotherapy can be considered. While radiation will occasionally control in-transit metastases, the primary goal for this therapy is palliation of fungating or bleeding cutaneous lesions. If the cutaneous metastases are anatomically restricted to a limb, hyperthermic isolated limb perfusion or infusion should also be considered as an alternative treatment approach.

Postoperative Radiation: Superficial radiotherapy may also have a benefit as an adjuvant therapy to surgery in select cutaneous melanomas. Just as systemic adjuvant therapy should be considered for patients with cutaneous melanoma at high risk for distant metastases, postoperative radiation can be considered for locally advanced disease with features that portend increased locoregional recurrence risk. A number of disease characteristics have been associated with increased local recurrence rates, and have been suggested as relative indications for postoperative superficial radiation (Table 2). These include excisions with close or positive margins where further surgery is not possible, head and neck location, mucosal melanoma, recurrent disease, thickness > 4mm, neurotropic or desmoplastic histopathology, ulceration, and satellitosis. Whenever possible in patients with unresectable LMM, the areas of invasion should be identified and surgically excised prior to treating the residual macular lesion with radiation or another alternative modality.

Some non-controlled case series suggest postoperative radiotherapy can reduce rates of local recurrence in high-risk melanoma lesions. There is no convincing evidence that this treatment significantly reduces distant metastases or increases overall survival rates. It is important to note that not every patient with one of the aforementioned high-risk features will benefit from radiotherapy, and the potential benefit must be weighed against the potential risks. The epidermis and hair follicles are highly proliferative and are therefore sensitive to radiation. Thus, acute erosive radiation dermatitis and permanent alopecia often accompany superficial radiotherapy. Moreover, the patients are subjected to the time and cost associated with multiple treatments, although these inconveniences are reduced with hypofractionated radiation regimens. Late adverse effects such as atrophy, fibrosis, and ulceration are minimized due to limited dermal penetration of superficial radiation. However, even superficially irradiated patients are at increased long-term risk of developing non-melanoma skin cancers within the treatment field. Monitoring the treatment area for disease recurrence and new malignancies is an important part of the regular ongoing skin surveillance in melanoma patients who receive radiation.

Conclusions

It is now well accepted that deep-penetrating megavoltage radiation therapy has a role in the palliation of metastatic melanoma, especially in treating isolated brain lesions. A growing body of evidence also suggests that superficial radiotherapy is effective at improving locoregional control for unresectable LM and as a postsurgical adjuvant in locally advanced disease. Superficial radiation produces favorable cosmetic outcomes and few long-term adverse events. While this treatment modality has great promise, and while there is evidence to suggest that superficial radiotherapy is a reasonable alternative to surgery for LM or LMM, no randomized trials have evaluated its efficacy or risks in the treatment of cutaneous melanoma. Controlled, prospective multicenter studies are needed to standardize treatment protocols, identify patient populations that would most benefit, and evaluate the impact on disease-free and overall survival as well as cosmesis.

References

Melanoma brain metastases are the third most common type of brain metastasis after lung and breast cancer. They develop in a high proportion of advanced melanoma cases; they are clinically seen in 10 to 30 percent of patients with systemic melanoma, and in one autopsy series, incidence was as high as 50 to 73 percent. The median time to development of brain metastasis from the time of initial diagnosis is approximately 3.5 years.

Types of Treatment
Melanoma brain metastases exert a profound effect on the quality and length of survival, and despite the best current management, they represent the direct cause of death in 60 to 70 percent of affected patients.

The treatment options for these patients include best supportive care, whole brain radiation therapy, stereotactic radiosurgery, conventional surgery, chemotherapy, or a combination of the above. Because a majority of the patients have or will soon develop widely disseminated disease, treatment is dictated by the need to achieve immediate short-term palliation and the desire for durable symptom-free remission. The median survival of patients with symptomatic brain metastases is approximately one month without treatment and two months with corticosteroid administration (Table 1).

<table>
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<th>Treatment</th>
<th>Median survival (months)</th>
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<td>Whole brain Radiotherapy</td>
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Table 1. Median survival based on treatment, from the largest published series on melanoma brain metastases
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In a retrospective study from Cleveland Clinic, overall survival with surgery alone was 4.8 months compared to 8.8 months with surgery and WBRT. Three large retrospective series using WBRT following surgery showed a median survival of 8.9 months. To date, no prospective trials exist confirming WBRT results in the postoperative setting in melanoma.

Randomized studies have found that different radiation schedules using WBRT did not make an appreciable difference. The Radiation Therapy Oncology Group (RTOG) has tried five schedules of fractionation varying from 20 Gy in one week to 40 Gy in 4 weeks in three randomized trials using WBRT for brain metastases. All the regimens were similar in improvement in neurological function (50 percent), duration of improvement (9–12 weeks), time to progression (10 weeks), survival (15–18 weeks), and/or the quality of palliation. However, no sub-group analysis was done based on the site of primary disease, so the benefit of WBRT fractionation in melanoma remains unclear.

Stereotactic radiosurgery (SRS), a targeted therapy procedure that uses special equipment to position the patient and precisely deliver a large radiation dose to a tumor but not to normal tissue, is an alternative to surgery for patients with limited brain metastases. The rationale for SRS in brain metastases includes the spherical shape of most small (<3cm) lesions, which allows for conformal dose distribution; pseudocapsule of the lesions, which allows tight margins; and location predominantly at the gray-white matter junction, a relatively non-eloquent region that can permit delivery of single large doses. Generally a dose of 15–22 Gy at the 50–80 percent isodose line is administered in a single session to the contrast-enhancing lesion.

Results of large SRS studies have shown a radiological response rate of 80 to 90 percent in all metastases and median survival of 9–12 months, indicating the effectiveness of this therapy. However, the treatment result in melanoma is less encouraging than for other cancers. In a series of 106 patients with 221 melanoma metastases treated with SRS alone in Marseille, France, the median survival was 5.1 months, with metastasis-free survival of 3.7 months. The radiological responses were complete in 14 percent and partial in 42 percent of the cases. In another series of 103 patients with 151 metastases treated with SRS alone or in addition to WBRT at M.D. Anderson Cancer Center (MDACC) in Houston, the one-year local control and overall survival were 49 percent and 25 percent respectively.

Eighty-five percent of all patients developed new brain metastases at 1 year. At Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City, the median survival in 49 patients with 92 melanoma brain metastases treated with SRS alone was 6 months. The prognosis was better in those with a solitary lesion, lesions smaller than 2 cm, and those who received ≥18 Gy; however, even these patients fared worse compared to those with other cancers, indicating a less than satisfactory response to single fraction radiation.

Hypofractionated stereotactic radiotherapy: Patients with limited brain metastases who are not suitable candidates for either surgical resection or SRS due to the lesions’ location or size can be treated with hypofractionated stereotactic radiotherapy while avoiding WBRT up front. At MSKCC, 20 patients were treated with a dose of 30 Gy in 5 fractions using 2 fractions per week to the lesion alone with a tight margin. The one-year control rate was 70 percent and the median overall survival was 8.5 months. The complete response, partial response, and stable disease were 15, 30, and 45 percent respectively in this study, with 15 percent steroid dependency, indicating a new option for these patients.

Chemotherapy: The role of chemotherapy has traditionally been minimal in the treatment of melanoma brain metastases. However, over the last few years, Temozolomide has shown some activity among the agents that have been studied. In a small phase II trial from the Cytokine Working Group, 31 patients, mostly asymptomatic and chemo-naïve with a good performance status, were treated with WBRT and Temozolomide. In this study, three radiological responses were seen, including one complete response. Median survival was 6 months. The role of Temozolomide with SRS alone in melanoma is now being addressed in clinical trials.

Conclusion

The results of therapy for melanoma brain metastases remain unsatisfactory when compared to other cancers. A small but selective group of patients do benefit from aggressive therapy with surgery or SRS. The role of WBRT either as adjuvant or as the only treatment at this time is not clear. The preliminary results of hypofractionated SRS seem to be comparable to both surgery and SRS in terms of local control and morbidity; the technique merits further trials. Better systemic control still remains the optimal way to prevent brain metastases at this time.
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References


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