



Michele R. Sassi. *Grinding the Sesame Seeds, Rajasthan, India*. Photograph, 2007.

The preclinical and clinical data on the radiobiology of melanoma, the current indications for radiation therapy, and the use of radiation for melanoma are reviewed.

Radiation Therapy as Primary and Adjuvant Treatment for Local and Regional Melanoma

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Background: *The role of radiation therapy as primary and adjuvant therapy for localized or locally advanced melanoma is controversial.*

Methods: *To develop evidence-based guidelines, PubMed was searched using the keywords melanoma AND (radiation OR radiotherapy). These references were reviewed and the relevant articles selected. The articles were then reviewed for further references. Because of the paucity of prospective or randomized trials, no attempt was made to classify the quality of the results.*

Results: *No phase III trials of nodal irradiation for prevention of regional recurrence are available. A phase III trial is being completed by the Tasman Radiation Oncology Group. A phase II trial has been completed by the group. Multiple retrospective series have been published. The available data appear to confirm that nodal radiation therapy is effective in preventing nodal recurrence. No dose response or fraction size response was found. According to generally accepted guidelines, radiation therapy should be offered for patients who have nodes greater than 3 cm, more than 3 involved nodes, or extracapsular extension. For radiation therapy for the treatment of metastatic disease, a phase III trial showed that 50 Gy in 2.5-Gy fractions was as effective as 32 Gy in 8-Gy fractions, with 25% complete remission and 35% partial remission. In contrast, the retrospective studies support that larger fraction sizes, at least 4 Gy, are more effective.*

Conclusions: *Adjuvant nodal irradiation appears to be effective for the prevention of nodal recurrence. Radiation therapy can also be effective for treatment of local disease, if surgery is not an option.*

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Submitted November 5, 2007; accepted February 26, 2008.

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Abbreviations used in this paper: TROG = Tasman Radiation Oncology Group.

Introduction

The role of radiation therapy as primary or adjuvant treatment for melanoma is controversial. Melanoma is traditionally considered a radiation-resistant tumor, and preclinical studies support this in part. Clinical studies suggest that radiation therapy is effective, though perhaps not with standard techniques.

This article reviews the preclinical and clinical data on the radiobiology of melanoma and discusses

the current indications for radiation therapy as part of a multidisciplinary treatment approach. The data on the use of radiation in the palliative setting, as primary treatment, and as adjuvant therapy to the nodal regions are reviewed.

Radiobiology of Melanoma: In Vitro and In Vivo Studies

Several preclinical studies investigated the radiosensitivity of melanoma. Cell culture studies showed that melanomas have a wide range of sensitivity to radiation, as do other cell lines.^{1,2} Spheroid studies confirmed the cell culture studies.^{3,4} The radiation sensitivity of human xenografts varied from sensitive to resistant.^{4,5} The alpha:beta ratio from cell culture measurements correlated with the 2-Gy survival fraction (SF2) from in vivo measurements, confirming that there are innate differences in the radiobiology of melanoma cells.⁶ In vivo studies also showed that sublethal doses of radiation therapy increased the subsequent risk of metastases, possibly due to increased hypoxia in the regrowing primary tumor.⁷ In vitro studies also suggest that compared with primary lesions, cells from metastatic lesions are more radioresistant.⁸

Definitive Radiation Therapy for Melanoma Cutaneous Melanoma and Nodal Disease

Clinical studies suggest that larger fractions are needed for the local control of primary cutaneous and nodal melanoma. Danish authors reported on 618 tumors from their own database, combined with reports from the literature.^{9,10} They examined factors such as total dose, dose per fraction, treatment time, and tumor volume. They determined the alpha:beta ratio of melanoma to be 2.5 Gy and an isoeffect formula for dose and fraction size of $ETD_{vol} = D \times [(d + 2.5)/2.5] \times M^{-0.33}$, where ETD is the extrapolated total dose (an isoeffect dose corrected for fraction size), D is the total given dose, d is the fraction size, and M is the mean diameter of the lesion. The ETD for 50% control was estimated at 83 Gy for a tumor 1 cm in diameter. There was a strong association between local control and survival; the 3-year survival rate was 56% for patients with local control and 0% for patients without local control.

The same group then further analyzed their own data using stricter analytic methods on 239 lesions.¹¹ These data suggested an alpha:beta ratio of 0.57, lower than many tumors, which have ratios of around 10. They hypothesized that melanomas respond to radiation similarly to normal late-responding tissues, and therefore larger daily fractions, up to 6 Gy, may be more effective than standard 2-Gy fractions. Control was also related to the size of the tumor, and correcting for size eliminated much of the apparent variability of the sensitivity of melanomas.

Several retrospective trials show a dependence of control on fraction size. Investigators at Ellis Fischel

State Cancer Hospital¹² analyzed 41 lesions from 27 patients. They reported a 37% overall response rate but when regimens using at least 4 Gy were used, the response rate was 67%. Dvorak et al¹³ analyzed the response pattern of 36 patients and also concluded that a larger fraction size (8 Gy) was more successful than standard fractionation or 4-Gy fractionation. A study from the Mallinckrodt Center at Washington University¹⁴ on 67 lesions from 35 patients found no correlation with response and total dose but did find a strong correlation with fraction size. Four complete responses (9%) were seen in 43 lesions treated with fractions less than or equal to 5 Gy compared with 12 complete responses (50%) in 24 lesions treated with fractions greater than 5 Gy. The correlation was seen for cutaneous lesions but not for nodal lesions. Olivier et al¹⁵ reported their experience with 114 lesions on 84 patients. The median dose was 30 Gy (39 Gy biologically equivalent dose, BED). They found that a higher dose correlated with improved freedom from progression and survival. In a report by Strauss et al¹⁶ on radiation used for 83 sites from 48 patients, fractions of 6 Gy to 8 Gy produced the highest response rates (80%). In a study of 31 patients with bulky nodal disease treated with primary radiation therapy, Burmeister et al¹⁷ reported an 84% response rate. They observed a better local control rate with fractions of at least 4 Gy compared with fractions of less than 4 Gy.

Overgaard et al,¹⁸ however, reported a randomized trial of 35 tumors in 14 patients with metastatic or recurrent malignant melanoma. The patients were randomized to high dose-per-fraction radiotherapy: either 9 Gy × 3 or 5 Gy × 8, twice weekly. Among 35 patients, complete and persistent regression was found in 24 (69%) and partial response in 10 (29%) of the tumors. No difference in response was observed between the two treatment regimens. Also, a randomized trial was conducted by the Radiation Therapy Oncology Group (RTOG 83-05) for the primary treatment of measurable metastatic melanoma lesions of either 32 Gy in 4 fractions of 8 Gy or 50 Gy in 20 fractions of 2.5 Gy for the primary treatment of melanoma.¹⁹ Of 131 treated patients, 126 were evaluable, and there was no difference in local control between the two arms. The overall complete remission rate was 24% and the partial remission rate was 35%. An increased rate of grade IV toxicities occurred in the 8-Gy arm (3 vs 0), the majority being skin toxicities. A grade IV skin toxicity was ulceration.

Thus, the preponderance of retrospective data suggests that use of larger doses per fraction results in improved local control rates. However, the only randomized trial using smaller fractions, comparing 8-Gy fractions and 2.5-Gy fractions, showed no difference in response rate.¹⁹ The best conclusion that can be drawn is that for the treatment of gross melanoma at least 2.5-Gy fractions should be used.

Radiation Therapy in the Treatment of Head and Neck Mucosal Melanomas

Salmi and Holsti²⁰ reported on 17 patients with head and neck mucosal melanomas. The patients received 5-Gy fractions to 40, 60, or 80 Gy. Tumors were excised 10 to 14 days after the end of radiation therapy. The degree of tumor kill correlated with dose, and extensive tumor kill occurred only after 80 Gy. There was only 1 complete response.

Wada et al²¹ reported on 31 patients with mucosal head and neck melanoma. Radiation therapy was the primary treatment for 21 patients, and 10 patients received radiation therapy after surgery for gross residual disease. Complete responses were observed in 9 patients (29%) and partial responses were seen in 18 patients (58%). On multivariate analysis, dose fraction size of at least 3 Gy achieved better local control.

Klausner et al²² reported on a trial of concurrent 5-fluorouracil (5-FU) and radiation therapy (4-Gy fractions given twice a week, 8 hours after intravenous 5-FU infusion, to 52 Gy). Among the 30 patients, 10% had a complete response and 60% had a partial response.

Owens et al²³ reported on 48 patients with mucosal head and neck melanomas. Among 20 patients treated with surgery alone, 9 (45%) had local-regional failure, while in 24 patients receiving adjuvant radiation therapy, 4 (17%) had local-regional failure. In a study by Temam et al²⁴ on 69 patients with mucosal head and neck melanomas, 30 patients received surgery alone and 39 received adjuvant radiation therapy. Radiation therapy was given to the large majority of patients as either 50 Gy or 70 Gy in 2-Gy fractions. Although patients receiving radiation therapy tended to have higher stage tumors, the local control rate favored radiation therapy, 62% vs 26%.

Krengli et al²⁵ analyzed the results of 74 patients with upper aerodigestive tract mucosal melanomas. Treatment consisted of surgery in 17 patients (23%), surgery plus radiotherapy in 42 (57%), radiotherapy in 11 (15%), and chemo-immunotherapy in 4 (5%). Definitive radiation therapy was given with a wide range of fraction sizes (median 2.0 Gy, mean 2.4 Gy) and total doses (median 60 Gy, mean 55 Gy). The 6-month disease-free survival rate was 59% for patients treated with surgery alone and 90% for patients treated with surgery plus adjuvant radiation therapy. Among 51 patients with no evidence of disease at 6 months after primary treatment, the 3-year local control rate was 57% for patients treated with surgery alone and 71% for patients treated with surgery and postoperative radiation therapy.

These retrospective data support the use of larger daily fractions for the primary control of melanomas. However, the best local control rates were obtained with the combination of surgery and adjuvant radiation therapy. The effect of fraction size in the adjuvant setting has not been elucidated.

Adjuvant Nodal Radiation Therapy

Hietanen et al²⁶ reviewed 45 patients with Clark level II-V melanoma who received surgery or radiation therapy to the regional nodes for cutaneous melanoma with 51 patients who did not. There was no difference in recurrence in the nodes or in survival between the two groups. Investigators at the University of Florida²⁷ reported on 56 high-risk patients receiving adjuvant nodal irradiation. The majority (49 patients) had head and neck primaries; 27 patients were treated at presentation and 29 were treated at nodal recurrence. The 5-year local control rate was 87%. They found no difference in local control between patients treated to 60 Gy in 2-Gy fractions and 30 Gy in 6-Gy fractions.

In a large series on adjuvant radiation therapy for cutaneous melanomas from The University of Texas M. D. Anderson Cancer Center,²⁸⁻³² radiation therapy was delivered in 6-Gy fractions twice a week to 30 Gy. The latest update is a 2006 review of all sites (cervical, inguinal, axillary).³³ Indications for nodal irradiation included extracapsular extension, 4 or more nodes positive, a lymph node larger than 3 cm, or recurrent nodal disease. A total of 466 patients were reviewed. The 5-year local control rate was 89%. On multivariate analysis, no clinical or pathologic characteristic was identified that correlated with local failure.

O'Brien et al³⁴ reported on results from nodal irradiation for head and neck melanoma patients at the Royal Prince Alfred Hospital in Sydney, Australia. Among 143 patients with 152 neck dissections, 52 received adjuvant radiation therapy (33 Gy in 6 fractions over 18 days) and 100 received no adjuvant therapy. The irradiated patients had more advanced disease: 65% had 2 or more positive nodes and 48% had extracapsular spread compared with 40% and 19%, respectively, in the non-irradiated group. Despite this, there was in-field recurrence in only 6.5% of the irradiated patients compared with 19% in the group receiving no adjuvant therapy.

Burmeister et al³⁵ reported on a Tasman Radiation Oncology Group study (TROG 96-06), a prospective trial of postoperative nodal irradiation for node-positive melanoma patients. A total of 234 patients were enrolled. The radiation was prescribed as 48 Gy in 20 fractions (2.4 Gy per fraction). The in-field recurrence rate was 7%.

Creagan et al³⁶ published the only randomized trial for nodal irradiation in 1978. Eighty-two patients with trunk or extremity melanoma and biopsy-proven nodal metastases at lymphadenectomy were randomized to observation or radiation therapy. The patients were treated with anterior and posterior fields to receive 1.78 Gy daily fractions to 25 Gy, a 4-week break, and then another 25 Gy in 14 fractions. Patients were accrued from January 1972 to July 1977. Eleven patients were eliminated from analysis because they had participated in another trial. Another 6 patients (5 controls and 1

irradiated patient) did not meet the eligibility requirements. Nine patients (1 control and 8 irradiated patients) were ineligible due to protocol violations. The remaining 56 patients (27 irradiated and 29 controls) were included in the analysis. Twenty-four patients were treated at Mayo Clinic, and 3 were treated at other institutions. The median disease-free interval in the radiation arm was 20 months and 9 months in the controls ($P = .07$). The median survival was 33 months in the irradiation arm and 22 months for the controls ($P = .09$). Disease-free interval and survival were improved only for patients with a single positive node. However, after adjustment for covariates such as age and sex, treatment was not significant for either disease-free interval or survival. Three of the 27 patients with radiation therapy recurred in the treatment field, and 1 of 29 control patients recurred in the nodal basin.

TROG is completing a randomized trial of adjuvant radiation therapy, 48 Gy in 20 fractions, for patients with positive node dissections for melanoma.

Investigators at The University of Texas M. D. Anderson Cancer Center³⁷ also studied whether radiation therapy alone is sufficient for local control of the draining lymphatics of cutaneous head and neck melanomas. With a median follow-up of 5 years, the actuarial local control rate for patients with nodes that were not treated surgically was 93%. This suggests that radiation alone may be adequate for treating the at-risk nodes.

Burmeister et al¹⁷ reported on toxicity in their series of combined adjuvant and primary treatment of nodal metastases. No complications occurred in 69% of the patients. The major complication was edema, seen in 23% of the patients. Ballo et al³⁸ reported on toxicity during axillary irradiation among patients at M. D. Anderson Cancer Center. Twenty percent developed clinically significant arm edema.

In summary, the available data suggest that adjuvant radiation therapy increases local-regional control after nodal dissection for cutaneous melanomas. There is no clear daily dose effect on the outcome. Furthermore, for clinically node-negative patients, radiation alone may be sufficient for local control of the nodal basins.

Technical Aspects of Radiation Therapy

Anatomy

Modern radiation therapy techniques allow high-precision treatment of the areas at risk with maximal sparing of normal tissues. This increased precision necessitates accurate definition of the nodal regions. The following descriptions of the nodal risk areas are based on the surgical approach to nodal dissections.

Lower Extremity: The inguinal nodes lie along the femoral artery. They spread laterally along the circumflex vessels and medially along the external pudendal arteries. The lateral border of the nodal basin is the medial edge of the sartorius muscle. The medial border

is the lateral edge of the adductor longus muscle. The superior border is above the inguinal ligament, at a line from the anterior superior iliac crest towards the umbilicus, stopping medially at the level of the pubic tubercle. The deep margin of the supra-inguinal ligament extent is the external oblique aponeurosis. The inferior border, or apex, is where the sartorius muscle crosses over the femoral artery, as the muscle comes superior-laterally to inferior-medially.³⁹

The nodes continue into the pelvis along the femoral artery as it goes under the inguinal ligament and becomes the external iliac artery. Both the external iliac nodes and the obturator nodes should be included in the field. The external iliac nodes are along the iliac vessels and are found within the area bounded by the inguinal ligament inferiorly, pelvic sidewall laterally, the lateral border of the bladder medially, and the iliac bifurcation superiorly. The obturator nodes extend along the obturator artery, which arises from the internal iliac artery near the iliac vein bifurcation, running along the pelvic wall. It exits at the upper aspect of the obturator foramen.³⁹

For treatment planning purposes, one set of recommendations to encompass the external iliac nodes is to include a 7-mm margin around the external iliac vessels; extending the anterior border by an additional 10 mm anterolaterally along the iliopsoas muscle to include lateral external iliac nodes.⁴⁰ An 18-mm strip encompassing the external and internal iliac regions with an 18-mm-wide strip along the pelvic sidewall will encompass the obturator nodes. Another source recommends a 2-cm radial expansion around the external iliac vessels to encompass the iliac nodes.⁴¹

Upper Extremity: The axillary node compartment can be described as an eccentrically shaped pyramid. In the axial plane the compartment is triangular. The chest wall is the medial border, the subscapularis muscle is the posterior border, the latissimus muscle is the posterior-lateral border, and the pectoralis muscle is the anterior border. A coronal section through the axillary compartment is bounded by the axillary vein superiorly, the chest wall medially, and the latissimus laterally.⁴² Dijkema et al⁴³ reviewed CT delineation of the nodes, based on a cadaveric dissection. Their review, as well as that of Mansur et al,⁴⁴ compared the location of the axillary nodes in abduction and adduction. Mansur et al⁴⁴ noted that the lymph nodes are medial to the humeral head when the arm is adducted (arm akimbo) whereas they overlie the humeral head when the arm is abducted (raised 180°). Therefore, in contrast to axillary irradiation during breast irradiation, treating with the arm akimbo may be more appropriate during radiation for melanoma. Madu et al⁴⁵ reviewed the location of the infraclavicular and supraclavicular nodes. The supraclavicular fossa is described as being divided into two compartments: the lesser supraclavicular fossa, which is between the two

heads of the sternocleidomastoid muscle, and the greater supraclavicular fossa at the base of the posterior triangle of the neck. The authors defined the entire supraclavicular fossa as:

- medial = lateral edge of the trachea, excluding the thyroid and thyroid cartilage
- anterior = deep surface of the sternocleidomastoid muscle and deep cervical fascia
- posterolateral = anterior and medial borders of anterior scalene muscle
- posteromedial = carotid artery and jugular vein

The infraclavicular fossa was defined as:

- inferior = subclavian artery
- inferior = most superior border of pectoralis minor muscle at the level of the insertion of the clavicle into the manubrium
- anterior = deep surface of the pectoralis major muscle
- posterior = subclavian-axillary artery

Head and Neck: Delman and Lee⁴⁶ describe the technique for a neck dissection for melanoma. A modified radical neck dissection is the standard operation, clearing the nodes of levels II-V and sparing the spinal accessory nerve, sternocleidomastoid muscle, and the internal jugular vein. Some aspects of their dissection are determined by the results of the sentinel lymph node biopsy. For example, they do not perform a parotid resection unless it is involved clinically or radiographically.

Several radiographic head and neck nodal atlases are available. Poon et al⁴⁷ developed an atlas based on MRI scans of 35 patients with head and neck cancer. They defined 12 neck levels that were more specific to a CT evaluation than are the classical levels I-VI. These levels were based on structures identifiable within the axial CT slices, such as the nasopharynx, thyroid cartilage, ascending ramus of mandible, and inferior to the mandible.

Generally, levels II-V should be included within the radiation portal. However, alterations can be made depending on the location of the primary and expected nodal drainage. A sentinel lymph node biopsy and a PET scan can help direct the definition of the areas at potential risk.

Dose and Fractionation

There is no consensus on dose and fractionation. Pre-clinical studies on the inherent radiosensitivity of melanoma cells led Ang et al²⁸ at The University of Texas M. D. Anderson Cancer Center to employ a high-dose-per-fractionation regimen for adjuvant head and neck irradiation of 6 Gy twice a week for a total of 30 Gy. Other centers followed suit.⁴⁸ However, clinical studies found no advantage for larger per-fraction doses for nodal irradiation,²⁷ including studies that found an advantage for hypofractionation at the primary site.¹⁴

The policy at our center is to use 2 Gy fractions for nodal irradiation in order to reduce the risk of edema and myelopathy. Usually 50 to 60 Gy total dose is given.

Treatment Planning

Prior to 3-dimensional treatment planning, lymph nodes were frequently treated to arbitrary volumes and depths, often using electrons for the supraclavicular and inguinal nodes. CT- or MRI-based treatment planning allows precise treatment planning based on the relation of the nodes to the vascular supply.

Intensity-modulated radiation therapy (IMRT) and other highly conformal treatment methods allow treatment of the complex nodal structures while minimizing the risk of damage to normal structures and, hopefully, reducing the risk of edema. No prospective studies have been done to confirm this. Nonetheless, it is probably advantageous to use IMRT for inguinal/pelvic and head and neck nodes. There can also be advantage in some patients during treatment of the axillary nodes. This can be determined on a case-by-case basis.

Conclusions

Radiation therapy can be used for primary control of melanoma, particularly smaller lesions, and lesions not amenable to surgery. A larger fraction size, at least 2.5 Gy, may increase the probability of response. Nodal irradiation also appears to increase the regional control among patients with node-positive disease. Current recommendations for nodal irradiation include the presence of a node larger than 3 cm, more than 3 positive nodes in the dissection, and extracapsular extension. Standard fractionation and total doses appear to be sufficient. A large randomized trial from TROG will provide definitive information on the role of adjuvant nodal irradiation.

Disclosures

No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.

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