Successful Treatment of Melanoma Metastatic to the Left Atrium Using External Beam Radiation Therapy

By William J. Magnuson, MD [2] and John B. Halligan, MD [3]

The successful treatment of a patient with primary nasal melanoma metastatic to the lung, pulmonary vein, and left atrium using radiation therapy is described. The patient was effectively treated with a conventional external beam radiation fractionation scheme (rather than a more commonly used hypofractioned regimen) that was utilized to minimize risk of arterial embolus of the tumor or rupture of a vessel wall. A post-treatment CT demonstrated a significant decrease in the caliber of the right pulmonary vein and tumor thrombus. The patient never developed cardiac valvular dysfunction or acute life-threatening massive embolism of tumor from the atrium. Unfortunately, the patient experienced clinical decline secondary to the massive progression of intra-abdominal disease and subsequently died from multiple liver metastases and liver failure. Numerous studies and this case report demonstrate that radiation therapy can be very effective in the treatment of malignant melanoma, especially when only small volumes of disease need to be treated and adequate total doses are used. Therefore, radiation therapy appears to play an important yet underutilized role in the treatment of metastatic melanomas.

The incidence of melanoma has increased significantly in the past two decades, while mortality has remained stable or has decreased.[1,2] As the incidence of melanoma increases, so does the incentive to discover novel and more efficacious methods of treatment. Effective palliative therapies should not be overlooked, however. Delaney et al recently reported that 23% of melanoma patients will have an indication for radiotherapy during their illness.[3] Radiation therapy is applied to less than 3% of all cases, largely because of the long-held notion that melanomas are universally resistant to radiation therapy.[4]

Radiation therapy has a well-established role for patients with incurable, metastatic melanoma. The major indications include treatment of dermal, subcutaneous, lymph node, bone, and brain metastases and spinal cord compression. The effects of palliative radiation are often easily seen because only relatively slight tumor shrinkage is required for symptomatic relief. Symptoms of mass effect, pressure, and bleeding from metastases in various sites benefit from palliative radiation. Seegenschmiedt et al found median survival in stage IV melanoma treated with radiotherapy was only 7 months.[5] While cardiac extension into the right atrium of tumors that invade the vena cava, such as Wilms tumor and renal cell carcinoma, is fairly common, and metastatic melanoma to the pericardium or myocardium is occasionally seen, extension of any tumor from the pulmonary vein into the heart is extremely rare. We report on a patient with stage IV melanoma with a bulky right lung lesion extending along the pulmonary vein into the left atrium palliatively treated with external beam radiation therapy. FIGURE 1

Computected tomography scan of patient’s chest when he was first diagnosed with intracardiac extension of disease.

Case Presentation

In 2005, a 63-year-old Filipino American male without previous disease or family history of cancer...
was diagnosed with a primary nasal cavity melanoma and underwent resection and postoperative radiation therapy that consisted of 6,600 cGy to the nasal cavity via a multifield 3D conformal technique completed in September 2005. The patient was asymptomatic until December 2007, when he contracted what was thought to be a lower respiratory infection that subsequently failed to respond to antibiotic therapy. In February 2008 the patient underwent a chest CT scan which demonstrated multiple pulmonary nodules, including a large right infrahilar mass in the right lower lobe that abutted the mediastinum and extended through the pulmonary vein into the left atrium. The tumor thrombus was approximately the diameter of the aortic arch and at least 4-5 cm in length, occupying a large portion of the left atrium (Figure 1).

Computed tomography (CT)-guided lung biopsy confirmed metastatic melanoma. Subsequent magnetic resonance imaging (MRI) showed multiple small (7 mm and 3 mm) enhancing lesions in the supratentorial and infratentorial brain consistent with metastatic disease. Review of systems revealed only cough of 2 months’ duration and intermittent hemoptysis. The patient denied any weight loss, decrease in energy, shortness of breath, or neurologic symptomatology. The only finding appreciated on physical examination was diminished breath sounds in the right lung base.

At that time it was believed that the malignancy in the patient’s pulmonary vein and left atrium would ultimately cause the patient to die before his asymptomatic brain metastases would become manifest. He was referred to a university medical center cardiothoracic surgery service, but was deemed to be inoperable and referred back to our service. The lesion was found to be increasing in size and threatening the tricuspid valve (Figure 2). Palliative radiotherapy was offered owing to the inoperability of the tumor, and because systemic chemotherapy was not likely to yield a significant response. Palliative radiation therapy is typically given with hypofractionated regimens of 400 cGy × 5, 300 cGy × 10, or 250 cGy × 15 fractions to minimize patients’ time on treatment, given their limited survival time. In addition, because of the broad shoulder on the cell-survival curve, larger fraction sizes have been considered optimal for patients with malignant melanoma.

There also was concern about abrupt tumor death with larger fraction sizes resulting in an arterial embolus of tumor or rupture of vessel wall with severe acute sequelae in a patient who at that time had an excellent performance status. Therefore, a conventional external beam radiation fractionation scheme (180 cGy per fraction to 4500 cGy) was planned to minimize risk and achieve the palliative goal. A four-field box technique was used with 18 MV X-rays because of the central location of the tumor. Only the immediately perihilar and atrial volumes were targeted, to spare the normal lung and esophagus. No attempt was made to include the entire bulky mass in the more peripheral lung volume. Daily cone beam CT was used for localization.

The patient began treatment in March 2008 and tolerated the treatment remarkably well,
successful treatment of melanoma metastatic to the left atrium using external beam radiation therapy

published on physicians practice (http://www.physicianspractice.com)

large axillary or ilioinguinal nodal metastases (but with a satisfactory life expectancy) can be treated with 55-60 Gy, with similarly impressive local/regional control rates[21] Patients with incurable disease and previously resected disease (melanomas at least 1.5 mm thick, clinically detectable nodal disease or patients with previously resected disease) of 88%, surpassing results from previous trials of a similar nature. A recent Australian study of two palliative regimens of whole-brain radiotherapy doses for metastatic melanoma also demonstrated improved intracranial control for patients treated at 2 Gy per fraction twice daily to 40 Gy, compared with 4-Gy fractions given once daily to 20 Gy.[19] These findings demonstrate that if the proper total dosages are employed, the term radioresistant need not apply to malignant melanoma and that larger fraction sizes may not be necessary. For patients with resectable local-regional disease, Ang and colleagues from M. D. Anderson Cancer Center achieved excellent complete and partial response rates with six fractions of 6 Gy given twice per week.[20] The study demonstrated an overall 5-year local-regional control rate for patients with high-risk disease (melanomas at least 1.5 mm thick, clinically detectable nodal disease or patients with previously resected disease) of 88%, surpassing results from previous trials of a similar nature. However, a review of adjuvant treatment of melanoma by Chang and colleagues from the University of Florida showed no difference between 6-Gy fractions to 30 Gy and 2-Gy fractions to a median of 60 Gy, with similarly impressive local/regional control rates[21] Patients with incurable disease and large axillary or ilioinguinal nodal metastases (but with a satisfactory life expectancy) can be

Discussion

In the 1930s, when the model of grading tumor radiosensitivity by histologic type obtained recognition, malignant melanoma was quickly labeled as radioresistant.[6] While early retrospective data proposed little responsiveness to radiation delivered at a low dose per fraction, it is now well documented that melanoma cells are radioresponsive irrespective of fractionation schedule if sufficient total doses of radiation are given.[7-9] Furthermore, recent radiobiological studies have shown great heterogeneity of malignant melanoma tumor cells, which may account for the extensive differences of radiosensitivity found in human xenografts.[10,11] The spectrum of clinical responses and in vitro assays of cultured cells illustrates that melanomas have a wide range of sensitivities to radiation. Generally speaking, melanomas tend to be less sensitive to radiation than common epithelial carcinomas.[12] Nevertheless, this level of increased resistance does not validate the reputation for radioresistance often ascribed to melanoma in accepted texts. The resolution of this discrepancy has come from in vitro studies demonstrating that melanoma cells are moderately less susceptible to radiation only at lower doses.[12] These results suggested that using greater doses per fraction would result in superior outcomes. This belief has been supported by several clinical studies that have used higher doses per fraction (≥ 4 Gy) and achieved high response rates in an assortment of primary and metastatic sites in patients receiving regional irradiation.[13-15] However, in the only prospective randomized trial (Radiation Therapy Oncology Group 83-05) that compared a greater fraction size (800–3,200 cGy; biologically effective dose [BED] acute 57.6 Gy, BED late 117 Gy) with conventional fraction size (250–5,000 cGy; BED acute 62.5 Gy, BED late 92 Gy), no significant difference in either complete response or partial response was detected.[16] Studies by Overgaard and Sause have found that the total radiation therapy dose may be the best prognostic factor for metastatic melanoma.[17,18] A recent Australian study of two palliative regimens of whole-brain radiotherapy doses for metastatic melanoma also demonstrated improved intracranial control for patients treated at 2 Gy per fraction twice daily to 40 Gy, compared with 4-Gy fractions given once daily to 20 Gy.[19] These findings demonstrate that if the proper total dosages are employed, the term radioresistant need not apply to malignant melanoma and that larger fraction sizes may not be necessary. For patients with resectable local-regional disease, Ang and colleagues from M. D. Anderson Cancer Center achieved excellent complete and partial response rates with six fractions of 6 Gy given twice per week.[20] The study demonstrated an overall 5-year local-regional control rate for patients with high-risk disease (melanomas at least 1.5 mm thick, clinically detectable nodal disease or patients with previously resected disease) of 88%, surpassing results from previous trials of a similar nature. However, a review of adjuvant treatment of melanoma by Chang and colleagues from the University of Florida showed no difference between 6-Gy fractions to 30 Gy and 2-Gy fractions to a median of 60 Gy, with similarly impressive local/regional control rates[21] Patients with incurable disease and large axillary or ilioinguinal nodal metastases (but with a satisfactory life expectancy) can be...
effectively treated with a lower dose per fraction (eg, 50 Gy in 25 fractions) to decrease the risk of neuropathy or limb edema.[20]

The size of the metastatic lesion has been shown to be predictive of response, as lesions of 1 cc volume or less respond almost universally to radiation.[22] Furthermore, a study by Overgaard et al showed that tumors < 3 cm in size and > 5 cm in size had 79% and 21% complete response rates, respectively. Likewise, in the RTOG study, lesions > 5 cm had a complete response rate of only 20%. A study by Bentzen et al showed that the radiation sensitivity of melanoma cells varies within the same individual according to the site of biopsy, depending on whether the neoplasm is from the primary site, regional nodes, or distant metastases.[23] The study showed that metastatic deposits were by and large less responsive to radiation than their primary lesions, signifying that tumor development may result in the evolution of a radiation-resistant tumor phenotype.

When put in the perspective of other palliative uses of radiation therapy, the response of radiated malignant melanomas that have metastasized to the brain or bone is virtually identical to the response observed following treatment of other types of disseminated neoplasms that are generally regarded as radiosensitive.[12,24] The most frequent sites of metastatic melanoma are skin, subcutaneous tissue, and lymph nodes, comprising 50% of metastases.[20] The lung is the next most frequent site of occurrence, followed by the liver, brain, and bone.[25]

Seegenschmiedt et al analyzed prognostic factors and survival in patients with metastatic melanoma treated with external beam radiotherapy. The investigators found that in patients with soft tissue, skin, and/or lymph node metastases (UICC [International Union Against Cancer] stage IV), the median survival time was 7 months.[5] Patients with solitary metastases had a median survival time of 8 months, while those with multiple metastases had a median survival time of 4 months.[5] Finally, patients treated for bone metastases had a median survival time of 6.6 months, compared with 5.3 months for those treated for CNS metastases and 3.6 months for patients treated for pulmonary metastases.[5] Our patient’s survival time was similar to these described outcomes.

After the results of the randomized RTOG study are grouped with the findings of elective radiation therapy, it becomes apparent that malignant melanomas are not resistant to radiation therapy. Furthermore, the results of these studies clearly demonstrate that radiation therapy can be very effective, especially when only small volumes of disease need to be treated and adequate total doses are used. Therefore, radiation therapy appears to play an important yet underutilized role in the treatment of metastatic melanomas. Regardless of the effectiveness of radiation therapy to control disease locally, increases in survival will necessitate use of more successful systemic agents. Only then will the effects of refined local treatment improve our ability to increase survival and quality of life for patients with melanoma.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:


Successful Treatment of Melanoma Metastatic to the Left Atrium Using External Beam Radiation Therapy


25. Habernalz HJ, Fischer JJ: Radiation therapy of malignant melanoma: Experience with high
Successful Treatment of Melanoma Metastatic to the Left Atrium Using External Beam Radiation Therapy

Source URL:

Links: