Cureus Open Access Case Report DOI: 10.7759/cureus.27

CyberKnife® Treatment of Metastatic Malignant Melanoma as Part of a Multimodality Therapy

William T. Brown[1], Fahed Fayed[2], Xiaodong Wu[3], James M. Hevezi[4], Irene Monterroso[5], James G. Schwade[6]

1. Miami Cyberknife; University of Miami Miller School of Medicine, Miami, FL 2. CyberKnife Center of Miami; Radiation Oncology Department, University of Miami Hospital & Clinics, Miami, FL 3. CyberKnife Center of Miami; University of Miami Miller School of Medicine, Miami, FL 4. Austin CyberKnife Center, Austin, TX 5. CyberKnife Center of Miami, Miami, FL 6. CyberKnife Center of Miami; University of Miami Miller School of Medicine, Miami, FL

Corresponding author: William T. Brown, brow5417@bellsouth.net
Disclosures can be found in Additional Information at the end of the article

Abstract

Metastatic malignant melanoma is an incurable disease with a median survival of 8.5 months and a probability of surviving five years after the diagnosis of less than 5%. To date, no systemic therapy has meaningfully changed these survival end points. A case of metastatic melanoma treated with combined modalities including image-guided robotic radiosurgery with CyberKnife® (Accuray Incorporated, Sunnyvale, CA, USA), and has an overall survival of 14 years is presented.

Categories: Radiation Oncology
Keywords: melanoma, radiotherapy, cyberknife, sbrt, malignant melanoma, hypo-fractionated radiotherapy

Introduction

Melanoma is a disease with poor outcomes. Surgical resection is often curative in early, limited-stage disease; however, no effective treatment exists for metastatic melanoma. This is particularly of concern when one considers the increasing incidence of melanoma both in the USA [1] (*Fig 1*) and worldwide [2]. To date, no treatment has led to any significant prolongation in overall survival (OS) for patients with metastatic melanoma. Herein, we report a case treated with hypofractionated focal radiation delivered by CyberKnife® radiosurgery (SRS), which allows the administration of higher doses with five times less adjacent tissue irradiation compared to 7 to 13 beam-treatments or arc irradiation and far less when compared to conventional fractionated radiotherapy. The higher tumor dose deliverable with SRS should theoretically increase the probability of local control with less late complications.

Published 05/26/2011

Radiotherapy

Melanoma is generally believed to be resistant to radiation therapy. However, radiation therapy has been successful in select circumstances: as primary therapy for ocular [3] as adjuvant therapy for post-surgical regional lymph node metastases [4] and finally, as palliation to sites of symptomatic/painful metastases [5]. Recent studies are increasingly advocating the utility of radiation therapy in advanced melanoma. A retrospective study of 84 patients with 114 individually treated tumor lesions showed that higher-dose radiotherapy (>30 Gy) to metastatic lesions not involving the CNS provided significant palliation and prolonged survival [6]. As conventional fractionated radiotherapy can be associated with significant morbidity based on the

How to cite this article
Brown W T, Fayed F, Wu X, et al. (2011-05-26 02:24:31 UTC) CyberKnife® Treatment of Metastatic Malignant Melanoma as Part of a Multimodality Therapy. Cureus 3(5): e27. DOI 10.7759/cureus.27

dose and irradiation site, the limits of its use are constantly undergoing revision. Retrospective reviews of patients treated by higher doses have demonstrated local control. These studies indicate that melanoma is not resistant to higher doses of radiotherapy, and support the use of high doses in a selective manner. CyberKnife radiosurgery (SRS) is particularly useful for the delivery of the higher focal doses required while sparing the nearby organs at risk [7-8] .The technique has been previously described [9].

Briefly, CyberKnife can deliver beams from 1600 or more different directions, a capability that allows it to target lesions precisely. Often 80 to 125 beams of radiation are used in each treatment plan. Using multiple beams of radiation can limit the dose to adjacent structures. The treatment can also be non-Isocentric, which means it does not rely on one point in the tumor and can deliver beams of radiation to any area of the tumor. SRS couples anatomic targeting accuracy and reproducibility with high doses of precise ionizing radiation, thereby maximizing the cell-killing effect on the target(s) while minimizing the probability of radiation-related injury in adjacent normal tissues. Theoretically, when delivered in five fractions versus three fraction schemes there is a higher kill rate; a lower complication rate and the therapeutic ratio is higher. By treating with an ablative dose we then recommend adjunctive chemotherapy.

The system relies on a robotic arm to track gold seed markers (fiducial) implanted in the tumor, which can be tracked through image guidance technology and a real-time respiratory tracking system. A single gold fiducial placed transthoracically under CT guidance into the center of the tumor is visualized with low-energy (kV) X-rays, fluoroscopy and CT used for geometric verification at the time of dose delivery. (Illustration 1). During the treatment, two orthogonally-placed X-ray units in the room and light emitting diodes (LEDs) placed on the patient's chest are coordinated the respiration, and therefore the target is robotically tracked in real time. Certain especially X-ray-opaque tumors may be tracked without the need for a gold marker. Treatment time can be 1 to 1 1/2 hours. Based on CT and PET/CT imaging, higher doses of radiation appear to improve local control compared to conventional fractionated radiation [10]. Metastasectomy may prolong survival in select circumstances. Should CyberKnife be able to ablate the metastatic lesion without surgery needs further investigation.

Case Presentation

July 1996, a 62-year-old gentleman presented with a bleeding and itching lesion on the posterior aspect of his right shoulder. The family history was non-contributary. The primary lesion was several inches below the collar line on the upper back. Diagnostic biopsy revealed a desmoplastic malignant melanoma of at least Clark’s IV. Following an extensive preop work-up that was negative for metastatic disease, a wide excision with axillary sentinal node biopsy was performed. Pathology revealed the lesion to be 5 mm. in depth without node involvement. Antineoplastic therapy was not begun at this time.

Three years later, July 14, 1999, a chest X-ray demonstrated two pulmonary nodules, a 1.6-cm ·mass in the right lower lobe (RLL) and a 0.9-mm mass In the left upper lobe (LUL). July 26, 1999, a fine needle aspiration (FNA) biopsy of the right lung lesion was positive for malignant melanoma. On August 18, 1999, a VATS wedge resection of the RUL nodule was performed followed on September 8, 1999, by the VATS wedge resection of the LUL nodule. Margins of both metastatectomies were reported as free of malignant cells.

The patient subsequently received interferon for one year from September 20, 1999, to October 19, 2000.

A new lesion was found on April 13, 2000, in the RLL, which was detected to be increasing in size. May 9, 2000, a PET/CT scan was negative but on September 19, 2000, another PET/CT demonstrated the tumor as hypermetabolic by FDG uptake. October 24, 2000, a VATS wedge resection of the RLL nodule was performed.

Between January 4, 2001, and April 4, 2001, a RUL nodule was found to have increased in size from 6 mm to 10 mm. The new lesion was treated with an 18-month course of granulocyte macrophage colony-stimulating factor (GM-CSF) from January 24, 2001 to July 8, 2002. However, a July 2001 chest CT scan demonstrated two new nodules: 1-cm RUL nodule, and a 8-mm RLL nodule, respectable.

February 18, 2002: resection of the two previous nodules along with a new mediastinal mass was carried out via open thoracotomy. The patient continued on the GM-CSF therapy [11-12].

August 4, 2003: the patient was diagnosed with a right pulmonary artery embolism, which turned out to be secondary to a tumor growing into the right pulmonary artery, and he was started on chemotherapy consisting of Cisplatin, Vinblastine, and DTIC, (six courses from September 2003 to March 2004). The patient responded to the therapy with resolution of the mass.

July 19, 2005: Two new lesions were identified. A parasternal masses of 1.7-cm size and a subcarinal mass of 2.8-cm. It was recommended that he be treated with CyberKnife and chemotherapy. He received 3400 cGy to 100% isodose line and 2550 cGy to the 75% isodose line, to a tumor volume of 6699 mm3, delivered using a 20-mm collimator, 78 non-zero beams, delivered in three fractions. He tolerated the treatment well but did experience a little esophagitis, Grade I, with no other complaints. He completed treatment with higher dose radiosurgery by CyberKnife to the metastasis in the mid-mediastinum on August 12, 2005. He had a complete response to the high dose radiosurgery (SRS course one, mid-mediastinum).

October 2005: a new metastatic melanoma to the subcarinal area of his mediastinum was identified. Again, CyberKnife was indicated. The planned dose was 2400 cGy in three fractions to the 72% isodose line, delivering a 3333.33 cGy to 100% isodose line. A 15-mm collimator was used. Inverse treatment planning was used to deliver the dose covering the planning target volume (PTV), which measured 9 cc. One hundred thirty-four (134) non-zero beams were utilized in three paths. He responded with complete resolution (SRS course two, subcarinal).

PET/CT scans of January 17, 2006, demonstrated interval resolution of lymphadenopathy and FDG activity involving mediastinal lymph nodes that were also present on a prior study of August 5, 2005. No suspicious lesion in this region was found but there were multiple small millimetric lymph nodes in the left supraclavicular and infraclavicular regions with above normal FDG signal that were suspicious for metastatic disease. We followed these metastases in his neck, and they increased in size and become hypermetabolic.

April 3, 2007: PET/CT involving a whole body scan indicated stable left supraclavicular nodules unchanged in size since prior study. Although persistent FDG activity was identified, it did appear to have improved compared to the prior study. Postoperative FDG activity probably corresponded to a precarinal lymph node which was likely inflammatory and reactive in nature. No new evidence or other suspicious activity for malignancy or metastatic disease throughout the remainder of the body was encountered.

A PET/CT scan March 24, 2008, when compared to studies of October 29, 2007, demonstrated that the metastatic melanoma in his left neck, supraclavicular area had enlarged from 1.6 cm to 2.3 cm, and had become more hypermetabolic with SUV 9.1.

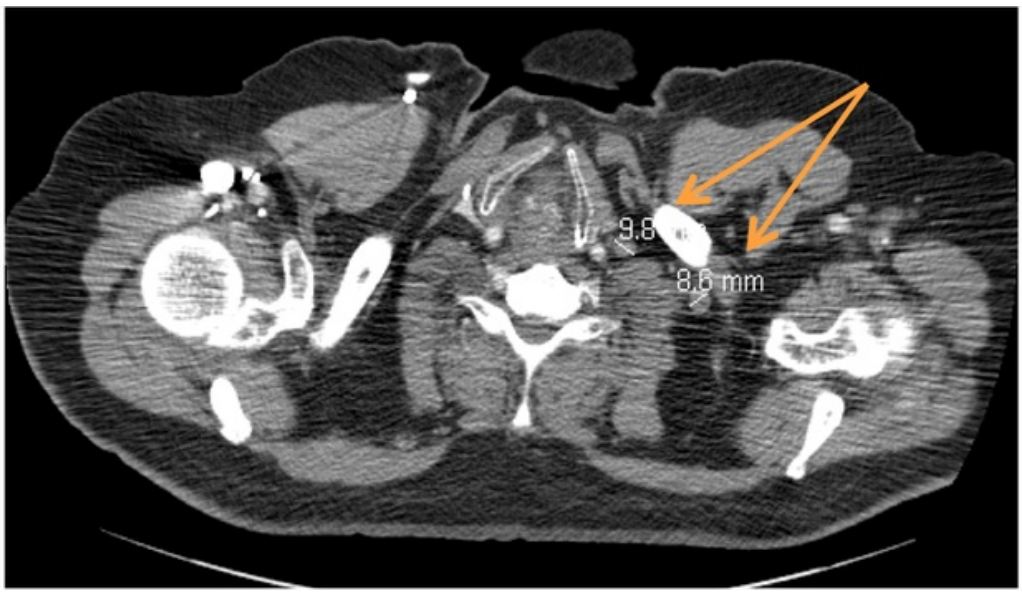

FIGURE 1:

Pre-CyberKnife CT scan 3/24/2008 demonstration supra-clavicular cluster of left neck lymph nodes metastatic melanoma by fine needle biopsy; fiducial will be placed for synchrony

May 1, 2008: He started his third course of high-dose SRS using a 10-mm collimator in three stages giving 3600 cGy to the 70% isodose line covering the lesions which measured 2.234 cc. A total of 124 beams were used by inverse planning and treatment. Maximum dose to the larynx was 639.02 cGy over the course of the treatment. He was treated by fiducial-aided respiratory tracking.

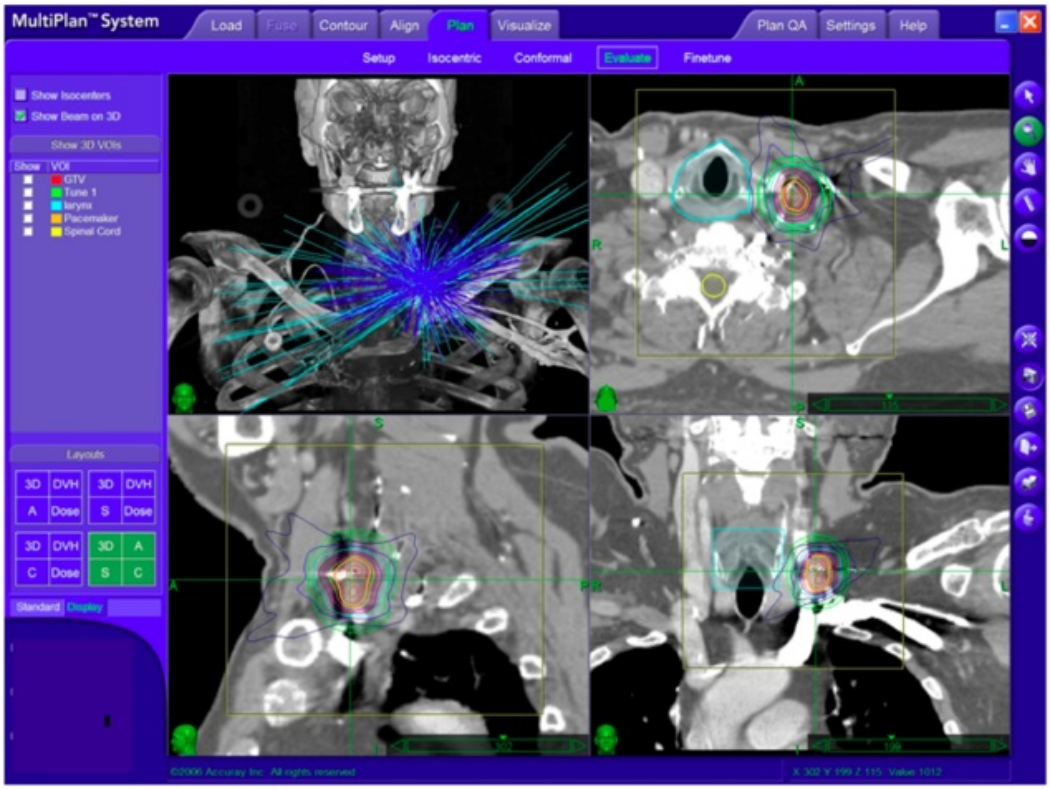

FIGURE 2: CyberKnife planning

May 2008 left neck metastatic melanoma lymph node treated to12 Gy x 3 fractions, 70% IDL

Subsequently the patient experienced a complete resolution of the neck lesions (SRS course three, left neck).

June 10, 2008: CT of neck with contrast showed that the previous cluster of abnormal lymph nodes present in the left neck were no longer identifiable, while those in the right posterior triangle appeared unchanged from previous exam.

Location	Date Treated	Collimator mm	GTV cc	Isodose Line %	Dose Gy	Fx #	Beams	Results
Mediastinum	Aug-05	20 mm	6.6 cc	75%	25	3	78	CR
Subcarinal	Oct-05	15 mm	9 cc	72%	24	3	134	CR
Left Neck	May-08	10 mm	2.234 cc	70%	36	3	124	CR

TABLE 1: CyberKnife treatment of three separate metastatic melanoma masses

CR= complete response. GTV=gross tumor volume. Fx # = fraction number. % isodose line=percentage of isodose used for delivery of radiation.

Follow up imaging with CT and PET suggested a complete response of the treated lesions.

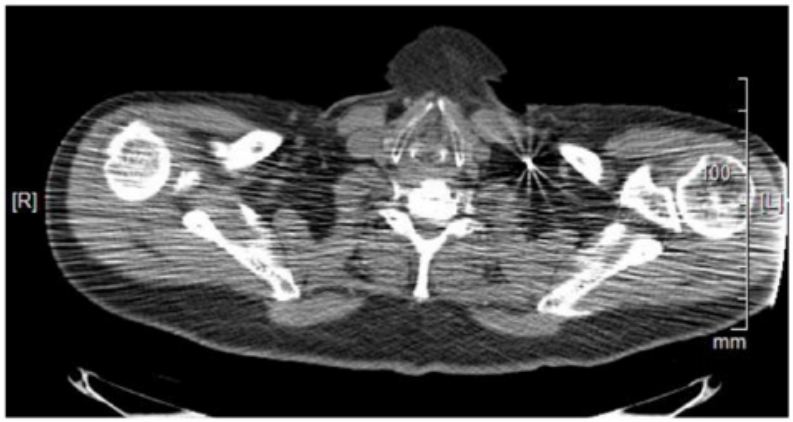

FIGURE 3: Post CyberKnife

11/18/2008 note fiducial negative nodes complete response

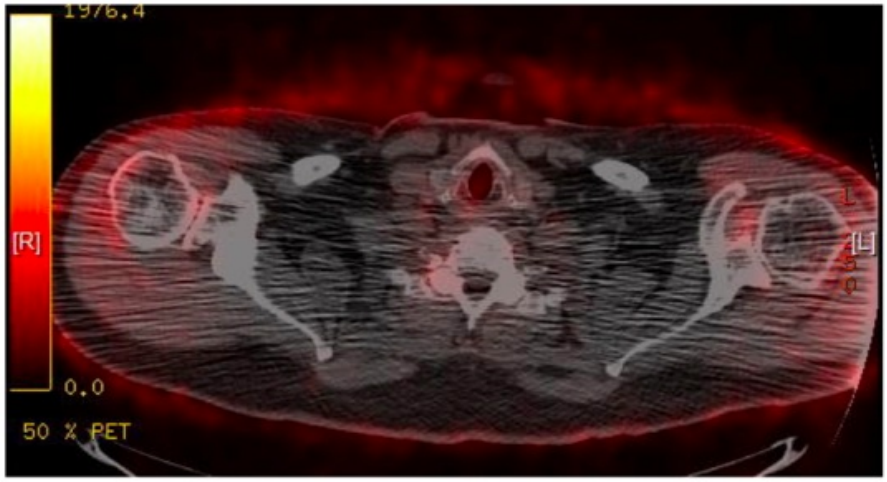

FIGURE 4: Negative PET scan 11/18/2008

November 26, 2008: elevated PSA was noted. A prostate biopsy was positive for prostate carcinoma, which the patient elected not to treat. As of March 2011 this now 77-year-old patient, who had survived 14 years and eight months with metastatic melanoma, continued on chemotherapy as well as both intravenous and oral high dose vitamin C.

Discussion

Resection of metastases is commonly performed for patients whose primary disease is controlled and for whom the metastatic burden is such that all disease can be resected safely. However, some metastasis involves vital structures that prohibit resection. Non-resectional therapies, such as stereotactic body radiation therapy, are being used in centers for patients with oligometastases. Historically radiation therapy has been used in a palliative manor in treatment of metastatic disease. We treat the tumor with ablative intent (curative) and then referrer to medical oncology for adjunctive chemotherapy with curative intent. Because the tumor is never resected with these non-operative interventions, histopathological evaluation of tumor margins for the presence of residual tumor is impossible, and as such, tumor response after each of these therapies is largely based on imaging. The key to successful treatment is early detection of recurrent disease. Therefore, following initial treatment, we obtain PET/CT scans every three months. As soon as a new focus is identified, we initiate treatment. In the past, re-irradiation was limited due to toxicity from wide field radiation, but with modern age guided focal radiotherapy, we can safely re-irradiate and obtain local control.

To date, computerized tomography and computerized tomography-positron emission tomography remain the most readily available modalities for assessment of therapeutic efficacy, and to this end, strict imaging survey and familiarity with the expected imaging characteristics of the treated tumor will aid in recognition of unexpected findings, specifically those of incomplete therapy and/or tumor recurrence. Patients were followed every three months using PET/CT imaging for the first two years, then every four to six months for the remainder of a total of five-year follow-up. Our initial assessment was based on Response Evaluation Criteria in Solid Tumors (RECIST). Any response that was readily assessed using RECIST rules as complete response (CR), partial response (PR), or stable (S) was considered as local control (LC), unless progressive disease (PD) was detected on the subsequent imaging study.

In lung tumor patients treated by high ablative doses, fibrotic or ground glass changes matching the high-dose isodose distribution were considered pneumonitis or treatment effects as opposed to disease progression, especially when PET imaging showed no corresponding hypermetabolism. Yet, the frequency of radiographic changes resulting from inflammation and fibrosis in the surrounding parenchyma complicated the local control evaluation. In those cases where the local control was equivocal in this evaluation, we compared the post-images to the planning FDG-PET/CT scans, and compared the overlying treatment dose distribution. This was correlated in nearly all instances by stable or gradually improving characteristic changes in serial studies. If a progressive nodular enlargement, reappearing or enlarging opacities after shrinkage or disappearance, or increasing standardized uptake value (SUV) on FDG-PET within the lesion (PTV) raised suspicions of tumor recurrence, this prompted a pathological exploration.

It has come into focus that associations of adjunctive chemotherapy or targeted therapies and radiation may be used for optimized treatment of limited metastatic disease and that irradiation of the primary tumor may be recommended in the context of metastatic disease. Adjunctive chemotherapy is usually given after surgery where all detectable disease has been removed, but where there remains a statistical risk of relapse due to occult disease, it is recommended following ablative radiosurgery. Adjuvant chemotherapy after resection of Stage II-IIIA non-

small-cell lung cancer is now the standard of care based on the results of several international phase III studies using platinum-based regimens.

Conclusions

Metastatic melanoma is increasing in incidence, yet there is no effective therapy for its cure. The most likely success will be in the context of multimodal combination therapeutics. Image-guided robotic radiosurgery with CyberKnife may play an important role in future treatment because of its ability to deliver high doses of radiation with limited toxicity. The treatment should be individualized based upon tumor location, tumor volume, pathology and nuclear grade. Clinical trials will be needed to confirm the findings of this case study.

Additional Information

Disclosures

Conflicts of interest: The authors have declared that no conflicts of interest exist.

Acknowledgements

All authors contributed to drafting the manuscript and all authors reviewed and approved the final manuscript.

References

1. Jemal A, Siegel R, Ward E, et al.: Cancer statistics. CA Cancer J. Clin. 2008, 58:71-96. 10.3322/CA.2007.0010
2. Garbe C, Leiter U: Melanoma epidemiology and trends. Clin. Dermatol. 2009, 27:3-9. 10.1016/j.clindermatol.2008.09.001
3. Bellett RE, Mastrangelo MJ, Laucius JF, Bodurtha AJ: Randomized prospective trial of DTIC (NSC-45388) alone versus BCNU (NSC-409962) plus vincristine (NSC-67574) in the treatment of metastatic malignant melanoma. Cancer Treat Rep. 1976, 60:595-600.
4. Stevens MF, Hickman JA, Langdon SP, et al.: Antitumor activity and pharmacokinetics in mice of 8-carbamoyl-3-methyl-imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (CCRG 81045; M & B 39831), a novel drug with potential as an alternative to dacarbazine. Cancer Res. 1987, 47:5846-5852.
5. Middleton MR, Grob JJ, Aaronson N, et al.: Randomized Phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J. Clin. Oncol. 2000, 18:158-166.
6. Tsao H, Sober AJ: Melanoma treatment update. Dermatol. Clin. 2005, 23:323-333. 10.1016/j.det.2004.09.005
7. Jacquillat C, Khayat D, Banzet P, et al.: Final report of the French multicenter Phase II study of the nitrosourea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. Cancer. 1990, 66:1873-1878.
8. Jacquillat C, Khayat D, Banzet P, et al.: Chemotherapy by fotemustine in cerebral metastases of disseminated malignant melanoma. Cancer Chemother. Pharmacol. 1990, 25:263-266. 10.1007/BF00684883
9. Avril MF, Aamdal S, Grob JJ, et al.: Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a Phase III study. J. Clin. Oncol. 2004, 22:1118-1125. 10.1200/JCO.2004.04.165
10. Bedikian AY, Weiss GR, Legha SS, et al.: Phase II trial of docetaxel in patients with advanced cutaneous malignant melanoma previously untreated with chemotherapy. J. Clin. Oncol. 1995, 13:1895-2899.
11. Einzig AI, Hochster H, Wiernik PH, et al.: A Phase II study of taxol in patients with malignant melanoma. Invest. New Drugs. 1991, 9:59-64. 10.1007/BF00194546
12. Einzig AI, Schuchter LM, Recio A, et al.: Phase II trial of docetaxel (Taxotere) in patients with metastatic melanoma previously untreated with cytotoxic chemotherapy. Med. Oncol. 1996, 13:111-117. 10.1007/BF02993861