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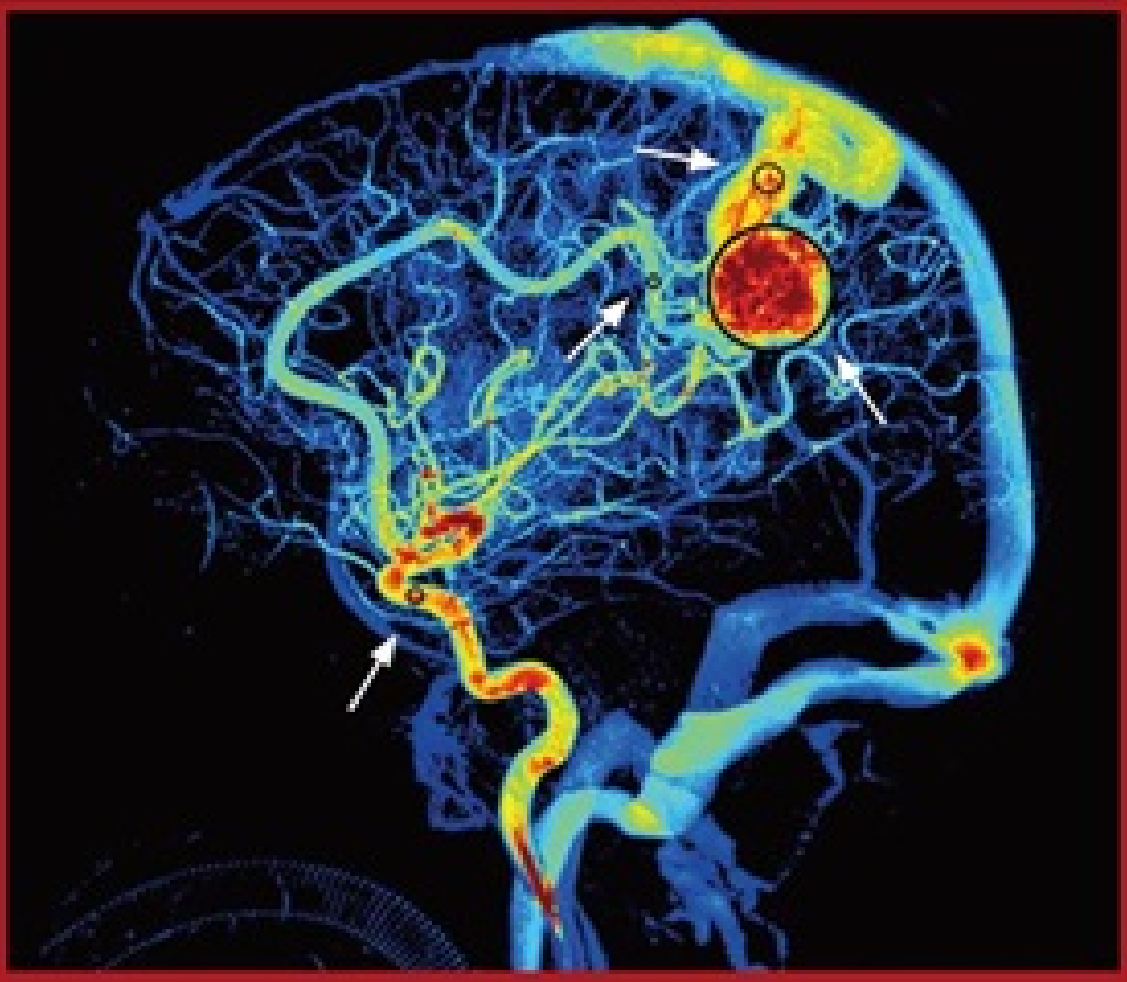

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Local Delivery of Chemotherapy Prolongs Survival in Experimental Brain Metastases from Breast Carcinoma

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Abstract

Despite improved systemic control of metastatic breast cancer, the incidence of brain metastases from breast carcinoma continues to rise, in part because most systemically administered agents have poor central nervous system penetration. Therefore, as a method of optimizing drug delivery into the central nervous system, we studied the safety and efficacy of chemotherapy delivered locally via biodegradable polymers in a mouse model of breast carcinoma metastases to the brain.

The chemotherapeutic agents carmustine (BCNU), carboplatin, and camptothecin were incorporated into controlled release polymers and tested

individually against intracranial challenges of EMT-6 breast tumor in BALB/c female mice. For each drug, four groups were tested: Group 1, empty polymer (no drug); Group 2, external beam radiotherapy (XRT) alone; Group 3, local chemotherapy from biodegradable polymer alone; and Group 4, local chemotherapy and XRT together. Polymers were implanted 5 days after intracranial tumor inoculation; XRT was administered on Days 7 through 9 (300 cGy/d).

BCNU polymer alone (n = 10; median survival time, >200 d; $P < 0.0001$) and BCNU and XRT together (n = 10; median survival time, 41 d; $P = 0.02$) significantly improved survival in mice with intracranial EMT-6 breast cancer in comparison with control animals (n = 20; median survival time, 17 d). Carboplatin and camptothecin, either with or without XRT, and XRT alone did not have any significant effect on survival.

Local delivery of BCNU with biodegradable polymers can significantly prolong survival in a murine model of intracranial metastatic breast cancer. Surgical resection and placement of BCNU polymers into the resection cavity may decrease the incidence of local recurrence of breast cancer metastases with minimal morbidity.

Breast cancer is the second most common cause of central nervous system (CNS) metastases after lung cancer (18,46). Clinically significant intracranial disease is observed in approximately 10 to 20% of patients with metastatic breast cancer (52), and 50% of these patients have solitary intracranial lesions (23,27). Despite multimodality treatment strategies, the prognosis for metastatic breast carcinoma is poor, with several studies showing survival times of only 3 to 4 months for patients who receive radiotherapy (XRT) and systemic chemotherapy for brain metastases (23,38,39,56). Even patients with solitary lesions, the group with the best prognosis, have a median survival of only 14.5 months (41).

Although overall control of metastatic breast cancer will require systemic therapies, the development of strategies to improve local control of metastases in the brain is important for several reasons. First, many patients die as the result of intracranial disease despite aggressive therapy. Patients who present with metastases to the brain from solid tumor are more likely to die as a result of neurological complications than of systemic progression of

their disease (53,65). Second, in chemotherapeutic protocols for breast cancer, many drugs cross the blood-brain barrier poorly, increasing the likelihood of intracranial relapse. Third, improved local control of metastatic disease in the brain may improve the quality of life even if overall survival is unaffected (53). For these reasons, efforts continue to develop strategies to better control local metastatic disease in the brain.

Currently, attempts to control intracranial metastases locally include surgery and stereotactic radiosurgery, with whole brain XRT and chemotherapy used as nonfocal treatment modalities. Isolated metastases to the brain have generally been treated with surgical extirpation plus postoperative whole brain XRT (14,15,24,27,47,48). This treatment strategy also has been used for multiple intracranial metastases (two to five lesions) (4). More recently, stereotactic radiosurgery has been advocated as an alternative to open surgery, with survival rates and local control rates similar to those associated with surgery (2,3,19,55). Nevertheless, despite clearly improved survival with these combination therapies, 31 to 48% of patients with brain metastases develop recurrence of tumor in the CNS, and in two-thirds of these patients, tumors recur at the site of resection (53).

Clearly, current therapies for controlling local recurrence of metastatic breast cancer in the brain are not adequate. For this reason, we explored the use of chemotherapy-impregnated biodegradable polymers as a method of improving the local control of brain metastases without increasing undesirable systemic side effects. Several studies have shown delivery of high-dose carmustine (BCNU) via biodegradable polymers to be safe and effective for primary brain tumors (7-11,54,57,58,61,63). The neurological morbidity of implanting polymers in the brain is minimal, and significant systemic side effects are not observed (9,10). Furthermore, the polymers can be implanted before XRT is administered (9,12,61). The present report describes the role of this novel treatment for CNS metastases stemming from breast cancer.

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MATERIALS AND METHODS

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Study design

First, we developed a murine model for metastatic breast carcinoma to the brain by stereotactically implanting EMT-6 breast tumor cells into the left parietal lobes of BALB/c female mice. Using previously determined maximally tolerated doses of locally delivered chemotherapy in the mouse brain, with and without subsequent XRT (25), we then tested the efficacy of the three chemotherapeutic agents (BCNU, camptothecin, and carboplatin), with and without XRT.

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Tumor line

The EMT-6 breast carcinoma cell line was obtained from the DCT Tumor Repository (NCI-Frederick Cancer Research and Development Center, Frederick, MD). The cells were maintained in Dulbecco's modified Eagle's medium containing 10% fetal calf serum and penicillin / streptomycin in humidified incubators gassed with 5% carbon dioxide. Cultured tumor monolayers were harvested with 0.025% trypsin, were counted, and were resuspended in medium before intracranial implantation.

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Animals

BALB/c female mice, 6 to 12 weeks old, were obtained from Harlan Sprague-Dawley (Indianapolis, IN). These animals were allowed free access to Baltimore city water and rodent chow. They were housed and treated in accordance with the policies and principles of laboratory care of the Johns Hopkins University School of Medicine Animal Care and Use Committee.

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Chemotherapeutic agents

BCNU and carboplatin (*cis*-diammine-1,1-cyclobutane-dicarboxylate platinum [II]) were obtained from Bristol-Myers-Squibb (Princeton, NJ). Sodium camptothecin was obtained from the National Cancer Institute (Bethesda, MD).

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Polymers

Poly[1,3-bis(carboxyphenoxy)propane-*co*-sebacic-acid]-anhydride, with a 20:80 molar ratio, was supplied by Guilford Pharmaceuticals Corp., Baltimore, MD. Poly[1,3-bis(carboxyphenoxy)propane-*co*-sebacic-acid]anhydride polymers containing BCNU, carboplatin, or camptothecin were prepared as described previously (25). The polymers were disc-shaped (1.5 mm in diameter, 0.5 mm in height, and 5 mg in weight).

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Tumor inoculation

The surgical site was shaved and prepared with 70% ethyl alcohol and iodine-containing solution. After a midline incision, a 2-mm burr hole was made 2 mm posterior to the coronal suture and 2 mm lateral to the sagittal suture. The animals were then placed in a stereotactic frame, and the tumor cells were delivered over 3 minutes by a 26-gauge needle inserted to a depth of 3 mm. The site of injection was in the center of the burr hole. Thus, subsequent local therapy through the burr hole was centered on the tumor bed. The needle was then removed, and the site was irrigated with 0.9% saline solution and was closed with sutures.

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Histological studies

Three animals were killed 5 days after tumor inoculation to ascertain the size of the tumor before polymer implantation. The brains were removed, fixed in 10% formalin, blocked in paraffin, sectioned in a coronal plane in 10-μm sections, and stained with hematoxylin and eosin.

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Polymer placement

The surgical incision used for injecting the tumor was re-opened 5 days later. No gross tumor was visible. A single polymer was inserted in the cortex entirely below the level of the inner table of the parietal bone. This corresponds to the location of the tumor inoculation 5 days previously. After hemostasis was obtained, the placement site was irrigated and closed with sutures.

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Radiotherapy

For radiation treatment, the animals were restrained in ventilated plastic centrifuge tubes with their heads positioned a fixed distance from the collimated 137-Cs source of a laboratory irradiator (Mark I irradiator, Model 68; J.L. Shepard and Associates, San Fernando, CA). Radiation was delivered at a dosage of 300 cCy per day (single fraction) for 3 consecutive days (total dose, 900 cCy) on Days 7 through 9 after initial inoculation. Previous studies with this radiation dosage in identical mice have demonstrated that the dose is well tolerated clinically (25), with mild to moderate histological changes observed 100 days after therapy. In addition, this dose has shown modest efficacy in prolonging survival in intracranial metastasis models, approximating the response of patients with brain metastases to radiation.

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Development of the tumor model

Groups of five mice received intracranial injections of one of the following amounts of EMT-6 tumor cells: 1,000; 10,000; 50,000; or 100,000 cells. The cells were injected stereotactically into the left parietal lobe as described above. Survival was assessed and autopsies were performed whenever possible. Survival curves were prepared for each dose of tumor cells, and the maximal dose that gave a median survival of 15 to 20 days with 100% mortality was chosen for subsequent efficacy trials.

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Efficacy studies

Each drug was tested in an independent experiment in the intracranial EMT-6 model. The doses of polymer-delivered chemotherapy and XRT had been determined in toxicity studies (25). All animals initially underwent tumor implantation. Group 1 received blank polymer on the 5th postoperative day and no XRT (control group, 20 animals). Group 2 received polymer containing the maximally tolerated dose of chemotherapy on Day 5 and no XRT (maximal local chemotherapy group; 10 animals received 20% BCNU polymer, 10 animals received 1.0% carboplatin polymer, and 10 animals received 10% camptothecin polymer). Group 3 received empty polymer on Day 5 and XRT (300 cGy/d) on Days 7 through 9 (XRT group, 20 animals). Group 4 received chemotherapy-loaded polymer on Day 5 and XRT on Days 7 through 9 (combination therapy group; 10 animals received 10% BCNU and XRT, 10 animals received 0.5% carboplatin polymer and XRT, and 10 animals received 10% camptothecin polymer and XRT). To avoid duplication and to minimize the number of animals required, the experiments were run concurrently with Groups 1 (control) and 3 (XRT alone) having extra animals and used in efficacy testing for all three drugs.

Previous toxicity studies (25) had demonstrated that the maximally tolerated dose of BCNU and of carboplatin was reduced when administered with concurrent XRT. For this reason, animals in Group 2 of the BCNU experiment received 20% loaded polymer whereas those in Group 4 received 10% loaded polymers. Similarly, for carboplatin, Group 2 animals received 1% polymers whereas Group 4 animals received 0.5% polymers. For camptothecin, 10% loaded polymers were tolerated with (Group 4) or

without (Group 2) XRT. No additive toxicity was observed with camptothecin and XRT, so the maximal dose with concurrent XRT did not need to be reduced.

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Outcome analysis

For all efficacy studies, survival was the primary end point. All animals were monitored for any signs of neurotoxicity, and selected animals underwent autopsies to confirm that the cause of death was intracranial tumor burden. In previous studies in our laboratory using these models, animals that were moribund (tachypneic, with no spontaneous movement) or paralyzed uniformly died within 24 hours. For this reason, animals reaching this condition were humanely killed. This represented a minority of the deaths reported. The distribution of the intervals until death was determined using the method of Kaplan and Meier (40). Two nonparametric statistical analyses, the Mann-Whitney *U* test and the Kruskal-Wallis test, were used to compare survivals between the groups. Statview Version 4.51 (Abacus Concepts Inc., Berkeley, CA) was the software used for statistical analysis.

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RESULTS

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Development of tumor model

Escalating doses of EMT-6 tumor cells were stereotactically implanted into the left parietal lobe to define the optimal tumor model. Median survival decreased with increasing tumor inoculation (Table 1). An inoculum of 50,000 tumor cells provided a desired median survival of 17 days (range, 15-20 d) and was chosen for further trials. A histological evaluation 5 days after tumor inoculation (at the time of polymer implantation) showed a microscopic foci of tumor cells. No tumor dissemination was present.

No. of Cells in Intracranial Challenge	Median Survival (d)	Interquartile Range[a] (d)
1000	23	20–30
10000	20	18–20
50000	16	16–20
100000	14	14–16

[a] The interquartile range represents the range of days between the deaths of 25 and 75% of the animals in the group.

Determination of the Optimal Size of Intracranial Tumor Inoculation for the EMT-6 Intracranial Solitary Brain Metastasis Model

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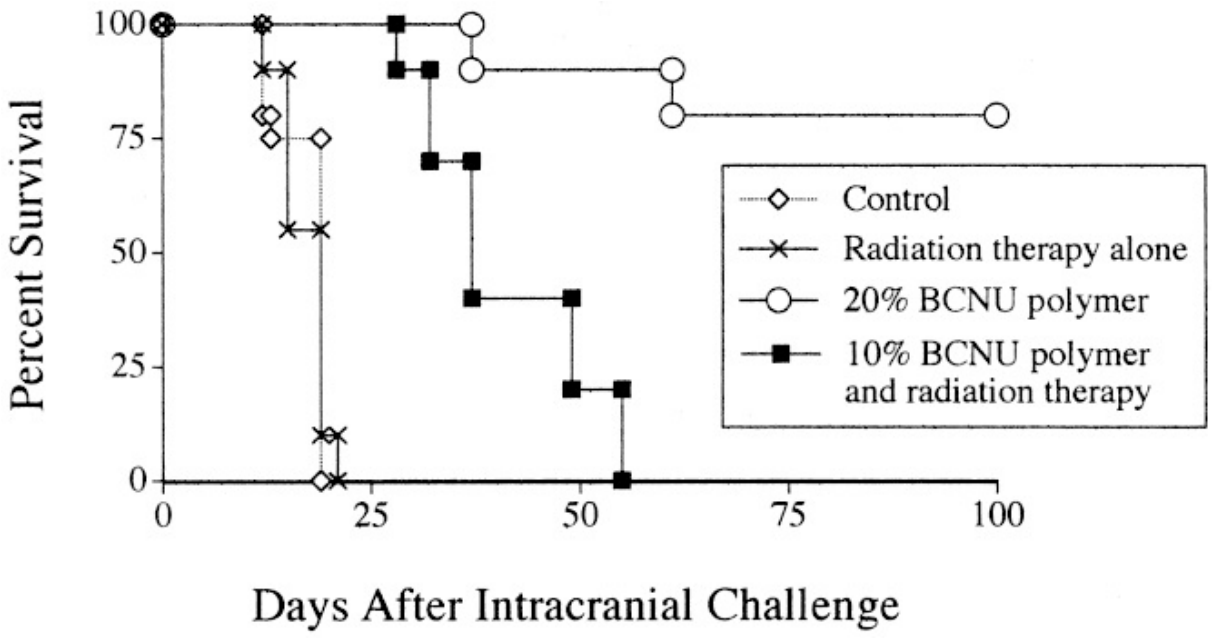
Efficacy of BCNU-loaded polymer

BCNU polymer, both with and without XRT, significantly prolonged survival in the EMT-6 breast carcinoma model (Fig. 1). Mice receiving blank polymer (control) had a median survival of 17.3 days (range, 12-19 d). Animals receiving XRT alone had a median survival of 17.1 days (range, 12-21 d). Mice receiving 10% BCNU-loaded polymer with XRT had a median survival of 41 days (range, 28-55 d; $P = 0.0217$ versus control). Median survival was not reached in animals receiving 20% BCNU-loaded polymer ($P < 0.0001$ versus control); 70% of the animals were alive at 200 days after tumor challenge.



Kaplan-Meier survival curve demonstrating efficacy of BCNU, delivered locally by biodegradable polymer, in treating solitary brain metastases after intracranial injection of EMT-6 breast cancer. Blankpolymer control (◊) shows that the tumor is fatal; XRT alone (x) is ineffective; high-dose (20%) BCNU polymer (○) is very effective, with 70% of the animals alive 200 days after tumor challenge (P < 0.0001 versus control); 10% BCNU polymer plus XRT (•) prolongs median survival (41 versus 17 d for control; P = 0.0217) but fails to afford long-term survival.

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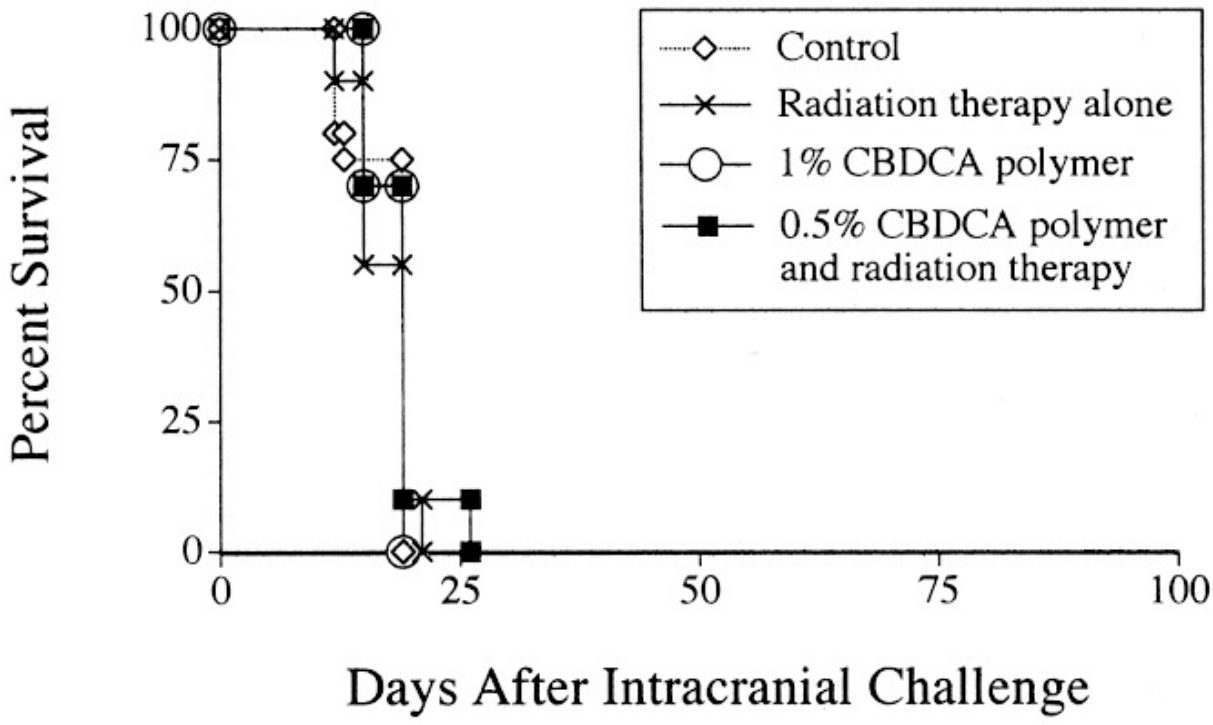
Efficacy of carboplatin-loaded polymer

Figure 2 shows treatment of intracranial EMT-6 breast carcinoma with carboplatin-loaded polymer, with and without XRT. No survival advantage was observed. Animals receiving 0.5% carboplatin-loaded polymer with XRT had a median survival of 18.5 days (range, 15-26 d; $P = 0.91$ versus control). Animals receiving 1% carboplatin-loaded polymer alone had a median survival of 18 days (range, 15-19 d; $P = 0.96$ versus control).



Kaplan-Meier survival curve demonstrating efficacy of carboplatin (CBDCA), delivered locally by biodegradable polymer, in treating solitary brain metastases after intracranial injection of EMT-6 breast cancer. Blankpolymer control (◊) shows that the tumor is uniformly fatal; XRT alone (x), 1% carboplatin polymer (○), and 0.5% carboplatin polymer plus XRT (•) are ineffective in prolonging survival.

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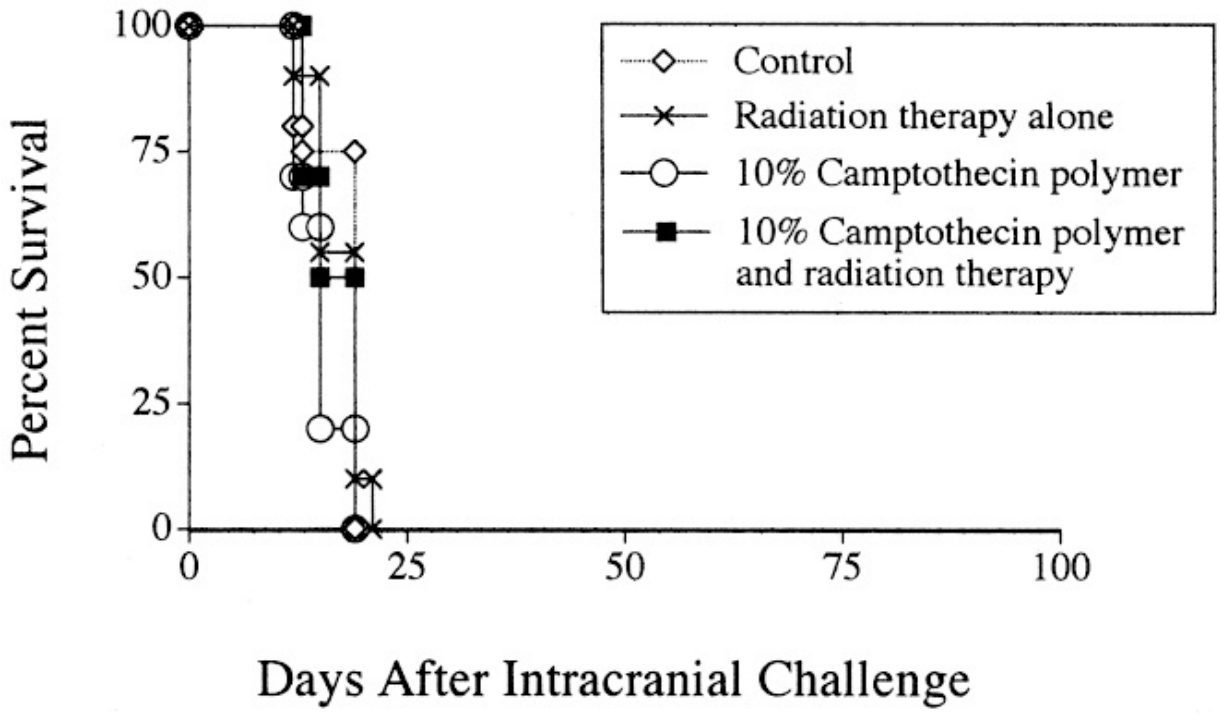
Efficacy of camptothecin-loaded polymer

Figure 3 shows the treatment of intracranial EMT-6 breast carcinoma with camptothecin-loaded polymer, with and without XRT. No survival advantage was observed. Animals receiving 10% camptothecin-loaded polymer with XRT had a mean survival of 16.4 days (range, 13-19 d; $P = 0.93$ versus control). Animals receiving 10% camptothecin-loaded polymer alone had a mean survival of 14.7 days (range, 12-19 d; $P = 0.8$ versus control).



Kaplan-Meier survival curve demonstrating efficacy of camptothecin, delivered locally by biodegradable polymer, in treating solitary brain metastases after intracranial injection of EMT-6 breast cancer. Blankpolymer control (◊) shows that the tumor is fatal; XRT alone (x), 10% camptothecin polymer (○), and 10% camptothecin polymer plus XRT (•) are ineffective in prolonging survival.

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DISCUSSION

With this study, we demonstrated that controlled delivery of chemotherapy from biodegradable polymers alone or with concurrent XRT significantly prolonged survival time in a murine model of intracranial metastatic breast carcinoma. Treatment with high-dose locally delivered BCNU led to a 70% long-term survival rate in a tumor model that is uniformly fatal if untreated.

The incidence of breast cancer continues to increase, and it has become the second most common cause of cancer death among women in the United States (18,46). In recent years, much effort has been placed in using multimodality treatment in the hope of improving survival. As a result, combination chemotherapy, XRT, and hormonal therapy have improved control of systemic disease (33,35-37,42). Despite improved systemic control, however, the incidence of brain metastases in patients with advanced breast carcinoma is increasing (5,6,38,39,49) and may be attributed to at

least two factors. First, many chemotherapeutic agents have poor penetration across the blood-brain barrier, thus increasing the likelihood of intracranial relapse (60). Moreover, tumor sanctuary sites in the central nervous system have been described for both small-cell lung carcinoma (1) and testicular cancer (31) and may serve as a paradigm for how CNS metastatic disease evades systemic anticancer therapies. Second, CNS dosing regimens are associated with significant systemic toxicity and patients are sometimes unable to receive adequate cytocidal therapy to the brain (5,6). For patients with good response to systemic therapy, the only obstacle to long-term survival may be control of the CNS metastases.

Currently, therapies for patients with brain metastases from breast cancer are aimed at controlling local disease and include surgery (53), stereotactic radiosurgery (2,3), and whole brain XRT (15,17,24), used alone or in combination (21,27,32). Some patients receive systemic chemotherapy, immunotherapy, and hormonal therapy (32,33,49,51,56). However, even with aggressive multimodality protocols, prognoses remain poor (23,38,39,56). Promising new therapies for breast cancer have been introduced during the last few years. Taxanes (paclitaxel and docetaxel) (22,28,50), vinorelbine (a novel vinca alkaloid) (45), amonafide, and several elliptinium derivatives (35) have all shown initial promising activity in limited clinical trials. Furthermore, therapy with monoclonal antibodies to breast cancer-related antigens (62), antiangiogenesis agents, and steroid hormone modulators is also under development. The majority of new strategies being used for metastatic breast carcinoma, however, although promising in systemic disease control, may not specifically address the issue of CNS disease and potential relapse. Several studies have suggested that breast carcinoma patients with metastases (6,16,46,65) may have better prognoses than patients with lung or other primaries. For these patients, local drug delivery, such as the one detailed in this article, may be particularly important.

A new therapy for primary CNS malignant neoplasms has recently been developed and it may be useful for secondary CNS neoplasms as well (7,57,58,63). Local delivery of chemotherapy in animal models directly into the CNS via implantable drug-laden polymers has been shown to provide an advantage over systemic administration of anticancer drugs (59,63,64). This technology makes it possible to achieve very high local concentrations of the

desired cytotoxic agent without systemic toxicity and circumvents the restrictions of drug penetration across the blood-brain barrier. The use of surgically implanted BCNU biodegradable polymers for gliomas has now been extensively investigated clinically in Phase I and II protocols (9,10) and Phase III placebo-controlled trials (11,61).

In determining the role for local chemotherapy in treating primary brain tumors, animal models have been successful in predicting clinical efficacy in human trials (11,61,63). In theory, experimental intracranial tumor models more closely resemble metastases than primary brain tumors, because tumor infiltration into the surrounding brain, as observed with primary tumors, is difficult to mimic in a laboratory setting. For this reason, an animal model for breast cancer brain metastases was developed and used to test efficacy. Intracranial models of lung carcinoma, melanoma, renal cell carcinoma, and colon adenocarcinoma have been previously established (25), and together, these five subtypes represent the great preponderance of the histopathologies of metastatic brain lesions.

In the present study, three chemotherapeutic agents were selected, each of which has unique properties that make it ideal for local polymer delivery. BCNU, an alkylating agent, was chosen for local delivery because it has a large number of binding sites and therefore may be especially effective at the high doses achieved by local delivery (26). Carboplatin is an alkylating agent that is water-soluble. Although less neurotoxic than cisplatin, systemic use is still associated with severe marrow toxicity, making carboplatin also in ideal candidate drug for administration via polymer (43,44). Camptothecin is a topoisomerase I inhibitor that exerts its antitumor effect via a mechanism distinct from that of carboplatin or BCNU. Therefore, it may have efficacy against tumors that are resistant to alkylating agents. It is ineffective when administered systemically for brain tumors but potent when administered intracranially via polymers (64).

BCNU polymer alone (20% loading by weight) was the most effective in this breast carcinoma brain metastasis model. BCNU polymer has also shown efficacy in models of brain metastases from renal cell cancer and melanoma (25). When administered with this same XRT protocol, BCNU polymer was effective in a colon carcinoma and a lung carcinoma brain metastasis model

as well. Breast carcinoma is the only model in which BCNU polymer was more effective than the combination of BCNU with XRT. Considering that this particular breast tumor, EMT-6, did not respond to XRT alone, we think that the increased efficacy of the BCNU polymer alone in comparison with BCNU polymer plus XRT is caused by the higher loading dose (20%) of the BCNU polymer that can be tolerated if no XRT is administered. A dose response effect is demonstrated, with the 20% polymer group exhibiting longer survival than the 10% polymer group, even though the 10% polymer group animals received XRT. Neither carboplatin nor camptothecin prolonged survival in this model. In previous studies, carboplatin polymer prolonged survival in mice with brain metastases from either melanoma or colon adenocarcinoma. Locally delivered camptothecin was effective against melanoma brain metastases only if administered in conjunction with XRT (25). Thus, locally delivered BCNU was the most effective of the three agents tested in these five experimental brain metastasis models; carboplatin was also effective in some of the models.

Several potential reasons exist for the superior results achieved with locally delivered BCNU. First, locally delivered BCNU has been shown to achieve therapeutic concentrations as far as 4 cm from the polymer surface 24 hours after surgical placement in primate brains (29). Effective doses have also been seen in the contralateral hemisphere. These experiments were performed with loading doses identical to the ones used in the present study. Thus, BCNU's efficacy in this model may be explained by the large volume of brain that is exposed to effective concentrations (29). Second, depending on the site in the body from which the metastatic EMT-6 is harvested, the EMT-6 cells have shown varying sensitivity to alkylating agents. Although the cells in this model are directly injected rather than hematogenously spread, varying sensitivity to alkylating agents (BCNU and carboplatin, in this case) has been previously reported with this tumor line (34). It is unexpected that the EMT-6 cells in this model were not sensitive to camptothecin, because camptothecin has shown in vitro efficacy against mammary carcinoma cell lines (30).

The potential role for local BCNU therapy in treating brain tumor metastases is two-fold. Local chemotherapy could be used in addition to surgery and XRT to decrease local recurrence rates. In lung cancer brain metastases,

local recurrence rates as high as 24% have been reported after surgery and XRT (13). Local chemotherapy might also be used in place of XRT after complete surgical resection of single brain metastases when only microscopic disease exists in the brain. This situation is modeled by our Group 2, in which maximal medical therapy is delivered to a microscopic tumor focus (no gross tumor visible). In this model, BCNU polymer was very effective in preventing death caused by growth of this small residual tumor. One major aim of XRT after surgical resection is to treat microscopic residual disease in the tumor bed. Local chemotherapy may achieve this goal while sparing the patient the risks of XRT, including dementia (20,21), and it may also be used to decrease dosing of any future systemic therapy administered after XRT. Finally, local chemotherapy may be useful in patients with recurrent brain metastases who have received maximal XRT. On the basis of the data presented in this article, clinical trials have been initiated to address these issues.

This model has several strengths. First, it is rigorous and uniformly fatal if the tumor is not treated. Second, the microscopic foci of tumor present at the time of polymer placement or XRT models the microscopic residual tumor remaining after complete macroscopic tumor resection in patients. Direct injection of tumor cells rather than hematogenous spread was chosen to generate a single locus of tumor. This models the 50% of brain metastasis patients who have single lesions and perhaps the additional 20% who have two lesions each who might still be surgical candidates (4). It is not a good model for patients with widespread or disseminated brain metastases. These types of patients, however, rarely come to surgery and would not be good candidates for local therapy.

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CONCLUSION

In conclusion, local delivery of BCNU via biodegradable polymers significantly improves survival in an intracranial model of metastatic breast carcinoma. Combined intracranial BCNU polymers and XRT also significantly affect tumor growth, and it seems that local chemotherapy can be administered safely before the administration of XRT. Because the

majority of patients with intracranial metastases already receive XRT, that polymer can be administered safely before XRT in animal models may prove important in future clinical trials. This novel treatment strategy for metastatic breast carcinoma may represent an adjunct to controlling intracranial metastases with minimal added morbidity. Furthermore, the use of intracranial biodegradable polymers with newer chemotherapeutic agents and biological therapies may add to the armamentarium available for the treatment of this disease.

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REFERENCES

1. Abner A: Prophylactic cranial irradiation in the treatment of small-cell carcinoma of the lung. **Chest** 103[Suppl 4]:445S-448S, 1993.
Cited Here...
2. Alexander E III, Moriarty TM, Davis RB, Wen PY, Fine HA, Black PM, Kooy HM, Loeffler JS: Stereotactic radiosurgery for the definitive,

noninvasive treatment of brain metastasis. **J Natl Cancer Inst** 87:34-40, 1995.
Cited Here...
3. Alexander E, Moriarty TM, Loeffler JS: Radiosurgery for metastases. **J Neurooncol** 27:279-285, 1996.
Cited Here...
4. Bindal RK, Sawaya R, Leavens ME, Lee JJ: Surgical treatment of multiple brain metastases. **J Neurosurg** 79:210-216, 1993.
Cited Here...
5. Boogerd W, Dalesio O, Bais EM, van der Sande JJ: Response of brain metastases from breast cancer to systemic chemotherapy. **Cancer** 69:972-980, 1992.
Cited Here...
6. Boogerd W, Vos VW, Hart AAM, Baris G: Brain metastases in breast cancer: Natural history, prognostic factors and outcome. **J Neurooncol** 15:165-174, 1993.
Cited Here...
7. Brem H: Polymers to treat brain tumors. **Biomaterials** 11:699-701, 1990.
Cited Here...
8. Brem H, Langer R: Polymer-based drug delivery to the brain. **Sci Med** July/August:52-61, 1996.
Cited Here...
9. Brem H, Ewend MG, Piantadosi S, Greenhoot J, Burger PC, Sisti M: The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: Phase I trial. **J Neurooncol** 26:111-123, 1995.
Cited Here...
10. Brem H, Mahaley MS Jr, Vick NA, Black KL, Schold SC Jr, Burger PC, Friedman AH, Ciric IS, Eller TW, Cozzens JW, Kenealy JN: Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. **J Neurosurg** 74:441-446, 1991.
Cited Here...
11. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G: Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas: The Polymer-Brain Tumor Treatment Group. **Lancet** 345:1008-1012, 1995.

Cited Here...
12. Brem H, Tamargo RJ, Olivi A, Pinn M, Weingart JD, Wharam M, Epstein JI: Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain. **J Neurosurg** 80:283-290, 1994.
Cited Here...
13. Burt M, Wronski M, Arbit E, Galicich JH: Resection of brain metastases from non-small cell lung carcinoma: Results of therapy. **J Thorac Cardiovasc Surg** 103:399-411, 1992.
Cited Here...
14. Cairncross JG, Posner JB: The management of brain metastases, in Walker MD (ed): *Oncology of the Central Nervous System*. Boston, Martinus Nijhoff Publishers, 1983, pp 341-379.
Cited Here...
15. Cairncross JG, Kim JH, Posner JB: Radiation therapy for brain metastases. **Ann Neurol** 7:529-541, 1980.
Cited Here...
16. Carty NJ, Foggitt A, Hamilton CR, Royle GT, Taylor I: Patterns of clinical metastases in breast cancer: An analysis of 100 patients. **Eur J Surg Oncol** 21:607-608, 1995.
Cited Here...
17. Coia LR: The role of radiation therapy in the treatment of brain metastases. **Int J Radiat Oncol Biol Phys** 23:229-238, 1992.
Cited Here...
18. Cresanta JL: Epidemiology of cancer in the United States. **Prim Care** 19:419-441, 1992.
Cited Here...
19. Davey P, O'Brien PF, Schwartz ML, Cooper PW: A Phase I/II study of salvage radiosurgery in the treatment of recurrent brain metastases. **Br J Neurosurg** 8:717-723, 1994.
Cited Here...
20. DeAngelis LM, Delattre J, Posner J: Radiation induced dementia in patients cured of brain metastases. **Neurology** 39:789-796, 1989.
Cited Here...
21. DeAngelis LM, Mandell LR, Thaler HT, Kimmel DW, Galicich JH, Fuks Z, Posner JB: The role of postoperative radiotherapy after resection of single brain metastases. **Neurosurgery** 24:798-805, 1989.

Cited Here...
22. Dieras V, Fumoleau P, Bourgeois H, Misset JL, Azli N, Pouillart P: Taxoids in combination chemotherapy for metastatic breast cancer. **Anticancer Drugs** 7:47-52, 1996.
Cited Here...
23. Distefano A, Yong Yap H, Hortobagyi GN, Blumenschein GR: The natural history of breast cancer patients with brain metastases. **Cancer** 44:1913-1918, 1979.
Cited Here...
24. Egawa S, Tukiyama I, Akine Y, Kajiura Y, Yanagawa S, Watai K, Nomura K: Radiotherapy of brain metastases. **Int J Radiat Oncol Biol Phys** 12:1621-1623, 1986.
Cited Here...
25. Ewend MG, Williams JA, Khosrow T, Tyler B, Babel KM, Anderson RC, Pinn ML, Brat DJ, Brem H: Local delivery of chemotherapy and concurrent external beam radiotherapy prolongs survival in metastatic brain tumor models. **Cancer Res** 56:5217-5223, 1996.
Cited Here...
26. Fleming ID, Brady LW, Cooper MR, Cooper MR: Basis for major current therapies for cancer, in Murphy GP, Lawrence W, Lenhard RE (eds): *American Cancer Society Textbook of Clinical Oncology*. Atlanta, American Cancer Society, 1995, pp 96-134.
Cited Here...
27. Flowers A, Levin VA: Management of brain metastases from breast carcinoma. **Oncology** 7:21-26, 1993.
Cited Here...
28. Fumoleau P, Chevallier B, Kerbrat P, Dieras V, Azli N, Bayssas M, Van Glabbeke M: Current status of Taxotere (docetaxel) as a new treatment in breast cancer. **Breast Cancer Res Treat** 33:39-46, 1995.
Cited Here...
29. Fung LK, Ewend M, Sills A, Sipos EP, Thompson R, Watts M, Colvin OM, Brem H, Saltzman WM: Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide and paclitaxel from a biodegradable polymer implant in the monkey brain. **Cancer Res** 58:672-684, 1998.
Cited Here...

30. Furuya Y, Ohta F, Ito H: Apoptosis of androgen-independent mammary and prostate cell lines induced by topoisomerase inhibitors: Common pathway of gene regulation. **Anticancer Res** 17:2089-2093, 1997.
Cited Here...
31. Gerl A, Clemm C, Kohl P, Schalhorn A, Wilmanns W: Central nervous system as sanctuary site in patients treated with chemotherapy for metastatic testicular cancer. **Clin Exp Metastasis** 12:226-230, 1994.
Cited Here...
32. Glass JP, Foley KM: Brain metastases in patients with breast cancer, in Harris JR, Lippman ME, Marrow M, Hellman S (eds): *Diseases of the Breast*. Philadelphia, J.B. Lippincott Co., 1996, pp 769-778.
Cited Here...
33. Grohn P, Heinonen E, Klefstrom P, Tarkkanen J: Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in Stage III breast cancer. **Cancer** 54:670-674, 1984.
Cited Here...
34. Holden SA, Emi Y, Kakeji Y, Northey D, Teicher BA: Host distribution and response to antitumor alkylating agents of EMT-6 tumor cells from subcutaneous tumor implants. **Cancer Chemother Pharmacol** 40:87-93, 1997.
Cited Here...
35. Hortobagyi GN: Overview of new treatments for breast cancer. **Breast Cancer Res Treat** 21:3-13, 1992.
Cited Here...
36. Hortobagyi GN: Multidisciplinary management of advanced primary and metastatic breast cancer. **Cancer** 74[Suppl 1]:416-423, 1994.
Cited Here...
37. Hortobagyi GN, Buzdar AU: Locally advanced breast cancer: A review including the M.D. Anderson Experience, in Ragaz J (ed): *High-risk Breast Cancer: Therapy*. Berlin, Springer-Verlag, 1991, pp 382-415.
Cited Here...
38. Kamby C: The pattern of metastases in human breast cancer: Methodological aspects and influence of prognostic factors. **Cancer Treat Rev** 17:37-61, 1990.
Cited Here...
39. Kamby C, Soerensen PS: Characteristics of patients with short and long survivals after detection of intracranial metastases from breast cancer. **J**

Neurooncol 6:37-45, 1988.
Cited Here...
40. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. **J Am Stat Assoc** 53:457-481, 1958.
Cited Here...
41. Leavens ME, Moser RP, Obbens EA, Iwata KI: Surgical treatment of metastatic brain tumors. **Cancer Bull** 38:39-42, 1986.
Cited Here...
42. Maher EJ: The use of palliative radiotherapy in the management of breast cancer. **Eur J Cancer** 28:706-710, 1992.
Cited Here...
43. Olivi A, Ewend MG, Utsuki T, Tyler B, Domb AJ, Brat DJ, Brem H: Interstitial delivery of carboplatin via biodegradable polymers is effective against experimental glioma in the rat. **Cancer Chemother Pharmacol** 39:90-96, 1996.
Cited Here...
44. Olivi A, Gilbert M, Duncan KL, Corden B, Lenartz D, Brem H: Direct delivery of platinum-based antineoplastics to the central nervous system: A toxicity and ultrastructural study. **Cancer Chemother Pharmacol** 31:449-454, 1993.
Cited Here...
45. O'Reilly S, Kennedy MJ, Rowinsky EK, Donehower RC: Vinorelbine and the topoisomerase 1 inhibitors: Current and potential roles in breast cancer chemotherapy. **Breast Cancer Res Treat** 33:1-17, 1995.
Cited Here...
46. Parker SL, Tong T, Bolden S, Wingo PA: Cancer statistics, 1996. **CA Cancer J Clin** 46:5-27, 1996.
Cited Here...
47. Patchell RA, Cirruncione C, Thaler HT, Galicich JH, Kim JH, Posner JB: Single brain metastases: Surgery plus radiation or radiation alone. **Neurology** 36:447-453, 1986.
Cited Here...
48. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio R, Markesbery WR, Macdonald JS, Young B: A randomized trial of surgery in the treatment of single metastases to the brain. **N Engl J Med** 322:494-500, 1990.
Cited Here...

49. Paterson AH, Agarwal M, Lees A, Hanson J, Szafran O: Brain metastases in breast cancer patients receiving adjuvant chemotherapy. **Cancer** 49:651-654, 1982.
Cited Here...
50. Ravdin PM, Valero V: Review of docetaxel (Taxotere), a highly active new agent for the treatment of metastatic breast cancer. **Semin Oncol** 22:17-21, 1995.
Cited Here...
51. Rosner D, Nemoto T, Lane WW: Chemotherapy induces regression of brain metastases in breast carcinoma. **Cancer** 58:832-839, 1986.
Cited Here...
52. Salvati M, Capoccla G, Orlando ER, Fiorenza F, Gagliardi FM: Single brain metastases from breast cancer: Remarks on clinical pattern and treatment. **Tumori** 78:115-117, 1992.
Cited Here...
53. Sawaya R, Ligon BL, Bindal RK, Hess KR: Surgical treatment of metastatic brain tumors. **J Neurooncol** 27:269-277, 1996.
Cited Here...
54. Sipos EP, Brem H: New delivery systems for brain tumor therapy. **Neurol Clin** 13:813-825, 1995.
Cited Here...
55. Somaza S, Kondziolka D, Lunsford LD, Kirkwood JM, Flickinger JC: Stereotactic radiosurgery for cerebral metastatic melanoma. **J Neurosurg** 79:661-666, 1993.
Cited Here...
56. Sparrow GEA, Rubens RD: Brain metastases from breast cancer: Clinical course, prognosis and influence of treatment. **Clin Oncol** 7:291-361, 1981.
Cited Here...
57. Storm PB, Brem H: The treatment of brain tumors with drug-impregnated biodegradable polymers, in Kornblith PL, Walker MD (eds): *Advances in Neuro-Oncology II*. Armonk, Futura Publishing Co., 1997, pp 435-445.
Cited Here...
58. Tamargo RJ, Brem H: Drug delivery to the central nervous system: A review. **Neurosurg Q** 2:259-279, 1992.
Cited Here...

59. Tamargo RJ, Myseros JS, Epstein JI, Yang MB, Chasin M, Brem H: Interstitial chemotherapy of the 9L gliosarcoma: Controlled release polymers for drug delivery in the brain. **Cancer Res** 53:329-333, 1993.
Cited Here...
60. Toner GC, Pike J, Schwartz MA: The blood-brain barrier and response of central nervous system metastases to chemotherapy. **J Neurooncol** 7:21-24, 1989.
Cited Here...
61. Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, Unsgaard G, Kuurne T: Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: A randomized double-blind study. **Neurosurgery** 41:44-49, 1997.
Cited Here...
62. Waldmann TA: Monoclonal antibodies in diagnosis and therapy. **Science** 252:1657-1662, 1991.
Cited Here...
63. Walter KA, Tamargo RJ, Olivi A, Burger PC, Brem H: Intratumoral chemotherapy. **Neurosurgery** 37:1128-1145, 1995.
Cited Here...
64. Weingart JD, Thompson RC, Tylar B, Colvin OM, Brem H: Local delivery of the topoisomerase I inhibitor camptothecin sodium prolongs survival in the rat intracranial 9L gliosarcoma model. **Int J Cancer** 62:605-609, 1995.
Cited Here...
65. Zimm S, Wampler GL, Stablein D, Harza T, Young HF: Intracerebral metastases in solid-tumor patients: Natural history and results of treatment. **Cancer** 48:384-394, 1981.
Cited Here...
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