Management of newly diagnosed single brain metastasis using resection and permanent iodine-125 seeds without initial whole-brain radiotherapy: a two-institution experience

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Object. Whole-brain radiotherapy (WBRT) after resection of a single brain metastasis can cause long-term radiation toxicity. The authors evaluated the efficacy of resection and placement of 125I seeds (without concomitant WBRT) for newly diagnosed single brain metastases.

Methods. In a retrospective review from two institutions (1997–2003), 15 women and 11 men (mean age 55 years) with single brain metastasis underwent gross-total resection and placement of permanent low-activity 125I seeds. Primary systemic cancer sites varied. Patients were monitored clinically and radiographically. With neuroimaging evidence of local recurrence or new distant metastasis, further treatment was administered at the physician’s discretion. By the median follow-up evaluation (12 months), the local tumor control rate was 96%. Distant metastases occurred in three patients within 3 months, suggesting synchronous metastasis, and in six patients more than 3 months after treatment, indicating metachronous metastasis. Treatment in these cases included radiosurgery in seven patients, WBRT in two, and resection together with 125I seed placement in one. Two patients who suffered radiation necrosis required operative intervention (lesion diameter > 3 cm, total activity > 40 mCi). All 26 patients who had been treated using resection and placement of 125I seeds had a stable or an improved Karnofsky Performance Scale score. At the last review, nine of 16 living patients showed no evidence of treatment failure. The median actuarial survival rate was 17.8 months (Kaplan–Meier method).

Conclusions. Permanent 125I brachytherapy applied at the initial operation without WBRT provided excellent local tumor control. Local control and patient survival rates were at least as good as those reported for resection combined with WBRT. Although the authors noted a higher incidence of distant metastases compared with that reported in other studies of initial WBRT, these metastases were generally well controlled with a combination of surgery, stereotactic radiosurgery, and, less often, WBRT. Twenty-four patients (92%) never required WBRT, thus avoiding potential long-term radiation-induced neurotoxicity.

KEY WORDS • single brain metastasis • brachytherapy • iodine-125 seeds • resection • clinical outcome

RAIN METASTASES are a common complication of systemic cancer, comprising the most common type of adult intracranial tumor and occurring in more than 100,000 new cases annually in the US.21,22 The incidence of intracranial metastases in patients with cancer is estimated to range from 15 to 30%.13 At the time of diagnosis, most patients have multiple brain lesions. Those with multiple metastases are usually not candidates for resection but are likely to undergo WBRT, with or without an SRS boost. The median survival of patients with brain metastases approximates 1 month without treatment compared with 3 to 6 months after WBRT.6,18

Although WBRT remains an acceptable option for patients with multiple brain metastases, the optimal treatment for those with surgically accessible single cerebral metastasis is not well defined. Approximately 20 to 30% of patients with brain metastasis have a single brain lesion.7,10 The Radiation Therapy Oncology Group has re-
ported that a subset of patients with single intracranial metastasis, good functional status (KPS score ≥ 70), and controlled systemic disease has a favorable prognosis (that is, a likelihood of long-term survival). Data from previous randomized, prospective studies in these patients have demonstrated median survival rates of approximately 10 months after resection and subsequent WBRT compared with 3 to 6 months after WBRT alone.

Because surgery alone does not always eliminate microscopic disease at the operative site, local control can be improved with adjuvant radiotherapy. After surgical removal, WBRT is beneficial and can significantly decrease the local recurrence rate compared with resection alone. However, potential acute adverse effects (for example, headache and alopecia) and, more important, delayed adverse effects (for example, memory loss and dementia) significantly limit the overall benefit of WBRT. The delayed effects are particularly important for patients with single brain metastasis who can have long-term survival exceeding 1 to 2 years.

Unlike primary brain tumors, metastases minimally infiltrate the brain. Limited residual microscopic disease in the wall of the resection cavity should respond to aggressive local adjuvant treatment delivered to the vicinity of the resection cavity. Brachytherapy with low-activity seeds following resection would seem to provide an ideal option for effectively controlling local disease at the resection site. Data from previous studies on resection and brachytherapy for metastasis have revealed good control of local disease.

In the present study of patients with single brain metastasis, we postulated that gross-total resection and brachytherapy using low-activity permanent seeds would result in excellent local tumor control and avoid the need for initial WBRT and its attendant side effects. After independently adopting this approach at two institutions, we collaborated to conduct a retrospective analysis. We here report the results of tumor resection and placement of permanent 125I seeds (without WBRT) for the management of patients with newly diagnosed single brain metastasis.

**Clinical Material and Methods**

**Patient Population**

We retrospectively reviewed the medical records from 1997 to 2003 for patients who had undergone resection and placement of 125I permanent seeds without concomitant WBRT. The patients had presented to the neurosurgery departments at the University of Cincinnati and University of California, San Francisco, with a single surgically accessible brain metastasis, a KPS score ≥ 70, and controlled systemic disease. In general, these patients had large lesions (median size 3 cm, range 2–6 cm) and were not candidates for SRS (Fig. 1). In this group of 15 women and 11 men (median age 55 years, range 40–74 years), the KPS score ranged from 70 to 90 (median score 90). The primary cancers were lung (12 cases), melanoma (four cases), colon (three cases), breast (two cases), renal (one case), cervix (one case), prostate (one case), ovarian (one case), and unknown (one case). The interval from initial diagnosis of the primary cancer to brain metastasis ranged from 0 to 164 months (median 9 months). Nineteen patients had stable systemic disease (that is, no sites of active disease outside of the brain at the time that brain metastasis was diagnosed), and systemic cancer and brain metastasis were synchronously diagnosed in seven patients. Magnetic resonance images of the brain demonstrated a single brain lesion in all 26 patients; 21 lesions were supratentorial and five were infratentorial.

**Surgical Technique**

After the induction of general anesthesia, patients underwent frameless image-guided resection of the metastatic tumor. The activity of the implanted 125I seeds ranged from 0.55 to 0.92 mCi/seed. The radiation oncologist calculated seed spacing by using computerized 2D planar dosimetry to deliver the prescribed dose to a tissue depth of 5 mm. After cutting a piece of cottonoid to that size, the surgeon placed it within the surgical cavity as a reference. Seeds covered the entire cavity but did not cover the brain tract used to approach deep-seated lesions. Dosimetry calculations took into account the probability of resection cavity collapse, thereby preventing excessive radiation dose at sites of wall abutment. Seed spacing ranged from 6 to 10 mm, the prescribed dose was 15,000 cGy, and 15 to 66 seeds were implanted in each patient. The actual dose at 5 mm from the implant ranged from approximately 120 to 200 cGy.

The 125I seeds were placed in the resection cavity in a circumferential fashion under direct visual guidance; the surgical technique varied slightly between the two institutions. At the University of California, San Francisco, the seeds were placed on the cavity surface and attached with cyanoacrylate (Super Glue). At the University of Cincinnati, the seeds were inserted perpendicularly into the brain parenchyma, protruding 1 to 2 mm into the surgical cavity; layering the resection cavity with Surgicel and Tis-
seal fibrin glue secured the seeds (Fig. 2A). The low-energy emissions of the $^{125}\text{I}$ seeds were shielded by stainless steel bowls during preparation of the seeds in the operating room. After seed implantation, absorption in tissue effectively shields personnel from most radiation exposure. Lead aprons are also effective shields but are not required.

Follow-up Evaluation and Data Analysis

Within the first 24 hours of surgery, a 3-mm-section computed tomography scan of the head was obtained to rule out hemorrhage and to perform 3D dosimetry (Fig. 2B). Patients underwent clinical and neuroimaging (MR imaging with Gd) follow-up evaluations at 3-month intervals. The MR sequences consisted of axial and coronal T$_1$-weighted scans with single-dose Gd enhancement. All imaging studies were reviewed initially by the neuroradiologists during each patient’s visit and later by the multidisciplinary team. We defined local control as stable or absent contrast enhancement with the patient receiving stable or decreasing doses of steroids. Metabolic imaging (for example, fluorodeoxyglucose positron emission tomography) and MR spectroscopy were used to distinguish between tumor recurrence and radiation changes. If neuroimaging revealed local recurrence or new distant metastasis (that is, treatment failure), further treatment was individualized for the patient and could include resection together with $^{125}\text{I}$ seeds, SRS, or WBRT. Our treatment strategy for recurrence was surgery if accessibility was not an issue in the case of one lesion, SRS in the case of two to six lesions, and WBRT in the case of six or more lesions.

Survival was calculated from the time of resecting the brain metastasis, and actuarial survival was calculated using the Kaplan–Meier method (Fig. 3).

RESULTS

Adverse Events

In all 26 patients, postoperative Gd-enhanced MR images confirmed gross-total resection, as indicated by complete elimination of the enhancing lesion. The surgery-related mortality rate was 0%. One patient (3.8%) experienced deep vein thrombosis and pulmonary emboli during the perioperative period. The median postoperative hospital stay was 3 days (range 2–10 days). The KPS score at 1 month after surgery remained the same or improved in all patients; the median KPS score was 90 before and after surgery. Two patients (8%) suffered symptomatic radiation necrosis 6 and 9 months later as manifested by headaches and focal neurological symptoms, which corresponded to the lesion location. These patients underwent surgery, and radiation necrosis was confirmed with histological studies. Both patients had
lesions that exceeded 3 cm in diameter (3.1 and 5 cm) and underwent implantation of more than 60 seeds with a total activity of more than 40 mCi. There was no incidence of seed migration outside the resection cavity in any patient.

**Clinical Outcome**

At the median follow up of 12 months, local tumor control at the surgical site was achieved in 25 (96%) of 26 patients. One patient had a recurrence at the resection site 5 months after treatment and underwent SRS, which resulted in good local control of the disease. Ten patients (38%) suffered new distant metastases within the brain: three presented with single lesions and seven had multiple lesions. Disease recurred in three patients within 3 months of initial resection and was deemed metastasis synchronous with the initially resected lesions. Seven patients had metachronous metastases with recurrences more than 3 months after the initial resection. Treatment for recurrence included resection and placement of $^{125}$I seeds in one patient with a single distant synchronous lesion, SRS in two patients with a single lesion and five patients with multiple lesions, and WBRT in two patients with multiple metachronous lesions.

The follow up ranged from 3 to 34 months (median 12 months). The rate of survival at 1 year was 72%; at 2 years, 46%. The median actuarial survival rate was 17.8 months (Fig. 3). Death was attributed to progressive systemic disease in four patients (40%), brain disease in two (20%), both systemic and brain disease in two (20%), and unrelated causes in two (20%). The cause of death was determined by the treating medical oncologist and confirmed by independent review of both medical records and appropriate imaging studies.

**Discussion**

Data in this two-institution retrospective study showed that the initial use of resection and $^{125}$I seeds in patients with newly diagnosed single brain metastasis safely resulted in excellent local disease control without exposure to the risks of initial WBRT. In the 26 patients with a range of pathological subtypes, 25 (96%) had excellent local disease control, only one (4%) experienced a local recurrence, and nine (35%) had distant recurrences in the brain. In other studies in which investigators used WBRT, disease recurred predominantly at the site of resection. In patients in the present study, the pattern of recurrence differed; that is, treatment with the $^{125}$I seeds was effective in producing local control. However, distant metastases occurred because no initial WBRT was administered.

For local or distant recurrence, patients were successfully treated with other modalities including resection and placement of $^{125}$I seeds in one patient and SRS in seven patients, thus completely avoiding the possible deleterious effects of WBRT. The two patients who underwent WBRT for recurrence had multiple metachronous metastases that were diagnosed more than 3 months after the initial resection and placement of $^{125}$I seeds. The additional metastases in these patients may have been caused by a new post-treatment ‘tumor shower’ of metastatic cells. In that situation, these patients may not have benefited from the initial use of WBRT. Alternatively, these patients might have harbored additional metastases not visualized on neuroimaging that might have benefited from WBRT.

Our results were achieved without exposing patients to the potential long-term adverse effects of WBRT. Although data from prospective studies of patients who have undergone resection and initial WBRT for single lesions have demonstrated decreases in local and distant metastatic recurrences, the median survival and duration of functional independence were not significantly improved. In addition, WBRT is associated with cognitive problems, both as radiation-induced acute and delayed complications. Such complications occur in up to 11% of long-term survivors who undergo WBRT. Side effects—fatigue, alopecia, memory loss, and radiation-induced dementia—negatively affect a patient’s quality of life and raise questions about the value of WBRT.

In the present series of 26 patients, the results also demonstrated that the combined therapy was safe for the management of newly diagnosed single brain metastasis. One patient (4%) experienced perioperative morbidity (deep vein thrombosis) and then pulmonary emboli postoperatively. There were no wound problems or infections. In addition, the 8% incidence of radiation necrosis was comparable with the incidence in reports of other modalities of aggressive local radiotherapy, such as SRS. Note that patients in the present study had relatively large metastatic lesions (median diameter 3 cm, range 2–6 cm). Both patients who experienced symptomatic radiation necrosis had lesions exceeding 3 cm in diameter and total radiation activity greater than 40 mCi, suggesting a dose-dependent risk of radiation necrosis.

Finally, the survival rate achieved with this treatment modality was comparable with those reported for other treatment modalities (Table 1). At the median follow up (12 months), 62% of the patients remained alive, which represents an actuarial survival rate of 17.8 months. This survival rate is comparable with results reported by Patnell et al. and Noordijk et al. for patients who underwent both resection and WBRT. Our analysis was a small single-arm study that included patients with single brain metastasis, good functional status, and controlled systemic disease; thus, the patients had an inherently better prognosis than the general population of patients with brain metastases. A prospective, randomized controlled trial would be needed to compare the efficacy of our protocol with standard resection and WBRT.

The rationale for aggressive local therapy using resection and concomitant brachytherapy (that is, permanent placement of low-activity $^{125}$I seeds) draws from what has so far been discussed regarding the treatment of single brain metastasis. Substantial evidence shows that resection improves survival, postresection radiotherapy improves control of recurrent disease, and recurrence usually occurs locally at the resection site after WBRT. Therefore, an ideal method would deliver maximal therapy locally with resection and radiotherapy while sparing patients with the potential for long-term survival from the untoward effects of WBRT. Of course, WBRT would be available as a future treatment option for metachronous metastases.

Available reports on brachytherapy for brain metastasis are limited. Most cases consist of either temporary high-activity $^{125}$I brachytherapy or permanent low-activity $^{125}$I seeds in patients with recurrent metastasis who have un-
In a retrospective review, Bogart et al. reported that 15 patients with single brain metastasis from non-small cell lung cancer who had undergone resection and permanent placement of 125I seeds; all had controlled systemic disease and good functional status (KPS score ≥ 70). The authors reported a median survival rate of 14 months (median follow up 14 months), an 80% local control rate, and a 20% distant recurrence rate; these outcomes were comparable with those achieved using resection and WBRT. Recently, Rogers and colleagues reported their experience with high-activity 125I brachytherapy via the GiaSite balloon system. Fifty-four patients with single brain metastasis underwent resection followed by the delivery of 6000 cGy without the use of initial WBRT. The authors reported a local control rate of 83%, median survival of 40 weeks, and 44% distant recurrence rate. As one might expect with high-activity brachytherapy, the 1-year risk of radiation necrosis was 23%, which was higher than the 8% incidence seen with low-activity 125I seeds in our study.

The use of low-activity 125I seeds following resection has several appealing characteristics. First, this method of adjuvant therapy effectively delivers radiotherapy to the local region, that is, the region with the highest failure rate. Second, low-activity 125I seeds are routinely available to most centers. Seed placement requires no additional procedures like other forms of brachytherapy (for example, high-activity temporary brachytherapy or balloon-based 125I brachytherapy) and adds less than 30 minutes to the operative procedure. Third, placement of 125I seeds is relatively safe both in terms of radiation exposure and surgical risk. In our 26 patients, there was a 0% surgical mortality rate, 4% perioperative morbidity rate, and low risk (8%) of delayed radiation necrosis. There is no need for radiation shielding, and the risk of exposure to healthcare workers and families is minimal. We noted a higher incidence of distant metastases compared with that in studies in which initial WBRT was used. However, distant metastases in our patients were generally well controlled with a combination of surgery, SRS, and, less often, WBRT.

**Conclusions**

We concluded that permanent 125I brachytherapy used at the initial operation without WBRT is an effective option for solitary brain metastases and have adopted this treatment paradigm at our two institutions for select patients. Resection and placement of 125I seeds proved to be a safe procedure that provided excellent control of local disease in our patients with single brain metastasis, good functional status, and controlled systemic disease. Local tumor control and patient survival rates with this treatment modality were comparable to those reported for resection and WBRT or SRS (with or without adjuvant WBRT). Withholding WBRT at resection can avoid potential adverse effects; this procedure can be used later as a treatment for recurrence.

**References**


**TABLE 1**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study Type</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Survival (mos)</th>
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<td>32</td>
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<td>S + WBRT</td>
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<td>12</td>
<td>10 14</td>
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<tr>
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<td>26</td>
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* RS = radiosurgery; S = surgery.
† Overall.‡ At 1-year follow up.