Surgical treatment of single brain metastasis

Evaluation of results by computerized tomography scanning

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From July, 1977, through December, 1978, a series of 33 patients with solitary brain metastases underwent surgical resection and postoperative radiation therapy at Memorial Sloan-Kettering Cancer Center. Sequential computerized tomography (CT) scanning was performed to determine the incidence of local recurrence and new brain metastases. The cause of death was identified by clinical follow-up study. The median survival for the entire group was 8 months, with a 1-year survival of 44%. Of the patients with no evidence of systemic cancer at the time of craniotomy, 81% lived 1 year. Local recurrence was noted in one patient known to have subtotal removal of tumor, and three patients developed carcinomatous meningitis. Of the 20 patients who died, four died within 30 days following surgery; three died of causes related to the central nervous system (CNS); and 13 (65%) succumbed to systemic cancer. These data show that recurrence in the CNS following surgery and radiation therapy for single brain metastasis is low, and that serial CT scanning provides a much better measure of the effectiveness of treatment of this complication of cancer than survival times. It is suggested that results of CT and neurological examination be used as indices when comparing different modes of therapy for brain metastases. Significant further improvement in survival of these patients is dependent on control of systemic cancer.

KEY WORDS • solitary brain metastasis • surgical treatment • computerized tomography

METASTASIS of cancer to the brain is common, and autopsy data from our institution indicate that the incidence of this complication is increasing. This apparent increase is most likely due to longer survival times in patients with cancer, and, consequently, longer periods at risk resulting from control of disease outside the central nervous system (CNS) by chemotherapy and radiation therapy. Clinically, this hypothesis is supported by the increased incidence of brain metastases noted in patients with oat-cell carcinoma of the lung, and with some sarcomas.

Among patients with intracranial metastases, those with solitary brain tumors represent an important group, comprising almost one-half of patients with parenchymal brain metastases. The treatment of these patients has been controversial. Both surgical excision followed by radiation therapy, and whole-brain irradiation alone, are currently considered standard forms of treatment. Surgery has the advantages of providing accurate histological diagnosis, eliminating the primary cause of chronic edema of the surrounding brain, and accomplishing rapid decompression of the brain in acutely deteriorating patients. Surgical excision is also the only method of eradicating radioresistant tumors. The superiority of surgical excision prior to radiation therapy in radiosensitive neoplasms, however, has yet to be proven by a randomized, controlled trial. Two major factors presently complicate such an undertaking. Our own experience indicates that the biggest problem in attempting to randomize treatment, especially when craniotomy may be involved, arises from the fact that both the patients and referring physician prefer treatment to be on an individual basis. In addition, statistical considerations require a very large number of patients to be entered in such a study. Joint participation by many institutions would be required.

In most series, the effectiveness of treatment of single brain metastases is gauged by the length and
TABLE 1
Sites of primary tumor in patients with single brain metastases

<table>
<thead>
<tr>
<th>Site of Primary Tumor</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>lung</td>
<td>12</td>
</tr>
<tr>
<td>skin (melanoma)</td>
<td>7</td>
</tr>
<tr>
<td>kidney</td>
<td>5</td>
</tr>
<tr>
<td>testicle</td>
<td>3</td>
</tr>
<tr>
<td>unknown</td>
<td>2</td>
</tr>
<tr>
<td>breast</td>
<td>1</td>
</tr>
<tr>
<td>adrenal gland</td>
<td></td>
</tr>
<tr>
<td>colon</td>
<td>1</td>
</tr>
<tr>
<td>skeletal muscle (rhabdomyosarcoma)</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>33</td>
</tr>
</tbody>
</table>

Clinical Material and Methods

During the period July, 1977, through December, 1978, 33 patients with solitary brain metastases identified by CT were operated on at Memorial Sloan-Kettering Cancer Center. Seventeen tumors were in the dominant hemisphere and four were in the cerebellum. Table 1 indicates the sites of primary cancer in this group of patients. Lung cancer and melanoma were the two most common cancers encountered in this series; the relative rarity of breast cancer is due to the fact that intracranial metastases from breast cancer are treated primarily by radiation therapy at this institution.

The extent of systemic cancer was evaluated by chest x-ray film, radionuclide bone scans, and liver-spleen scans. Excluding their CNS status, all patients had a projected life expectancy of at least 3 months. Thus, while patients with far advanced systemic malignancy were not operated on, the presence of disease at one or more sites outside the CNS was not taken as a contraindication for craniotomy.

All patients were placed on glucocorticosteroids (dexamethasone, 4 mg every 6 hours, by mouth) prior to surgery. The goal of surgery was complete excision of all tumor identifiable with at least ×4.5 magnification. Such gross total excision was believed to have been achieved in 30 patients. In two patients, surgical resection was incomplete; and in one patient, no tumor was removed. The same steroid schedule was continued during surgery, and, in the 24 patients who received postoperative radiation therapy (3900 rads in 2½ weeks), throughout the treatment period. Steroids were then tapered and discontinued. Four patients underwent surgery after their tumors had failed to respond to radiation therapy. Five other patients did not undergo radiation therapy after surgery.

Computerized tomography scanning was performed within 1 to 2 weeks following craniotomy, after completion of radiation therapy, and at 2- to 3-month intervals thereafter. Neurological examinations were performed at monthly intervals, and performance was evaluated using the Karnofsky scale. Survival curves were plotted by the Kaplan-Meier product-limit method. Differences between subgroups were analyzed statistically by means of the log-rank test. Based on their neurological grade at 2 months after surgery, survival times were computed to evaluate whether patients in better neurological condition lived longer than those in poor neurological condition. Survival was further stratified for the absence or presence of cancer at one or more sites.

Results

Figure 1 illustrates the survival curve for this group of patients. The median survival was 8 months, with a 1-year survival in 44% of the patients. Twenty of the 33 patients had a Karnofsky grade of 80 or more at 2 months, and maintained their neurological status to
within a few weeks of death, or until last follow-up examination. Another eight patients had a Karnofsky rating of 50 to 70 that reflected their preoperative status rather than neurological deterioration following surgery. Two patients had increased neurological deficit after surgery. The survival data show that patients with better neurological grades (80 or more) had a median survival of 1 year, but the difference between the two groups was not statistically significant (Fig. 2). If the extent of systemic cancer is considered, patients who had no evidence of cancer had a 1-year survival of 81%, and no surgical mortality or morbidity (Fig. 3). In the group of patients with evidence of systemic cancer, there was no apparent difference in survival between those patients demonstrated to have active tumor at one other site as compared to those in whom studies showed more than one positive site. The combined median survival in these subgroups was 5 months. The difference, however, in survival between those who had no detectable systemic involvement and those who had obvious tumor outside the CNS is highly significant (p < 0.001).

Four patients died within 1 month following surgery. The causes of death were pulmonary embolus, progressive liver failure from metastatic tumor, pneumonia in a comatose patient with hypernephroma who had failed radiation therapy and who subsequently did not improve following surgical excision of the tumor, and florid growth of multiple intracranial metastases undetected on the preoperative CT scan in a patient with choriocarcinoma. This last patient had had no tumor removed at surgery.

Among the remaining 29 patients, recurrence at the site of the original metastasis was seen in one of the two patients known to have had incomplete surgical removal. This patient, with metastatic hypernephroma involving the scalp, bone, falk, and surrounding dura, underwent two additional craniotomies to remove recurrent tumor, and subsequently died of systemic disease. The residual neoplasm in the second patient, who underwent incomplete tumor resection, disappeared following radiation therapy. Thus, of the 29 patients who could be followed by serial CT scans for more than 1 month (range 2 to 16 months), 28 patients revealed no evidence of tumor at the original site.

Twenty-one of these 29 patients were followed by CT scans for at least 6 months. In one patient, a second metastasis was noted in the posterior fossa after resection of a presumed solitary supratentorial lesion. This second lesion was apparent on a retrospective analysis of the first CT scan, and represents an error in diagnosis. No other new parenchymal brain metastases were noted in this follow-up group. Three patients (two with melanoma, one with lung cancer) developed tumor seeding in the spinal subarachnoid space between 6 and 8 months after surgery. These meningeal relapses were not associated with detectable cancer elsewhere, and were responsible for the death of two patients. One patient with testicular cancer died of CNS superinfection (Candida albicans) after intensive chemotherapy and steroid therapy. Autopsy disclosed multiple fungal abscesses, but no evidence of residual tumor.

Fifteen of the 29 patients who survived for more than 1 month following craniotomy died of progressive cancer involving other systems. In all these 15 patients, serial CT scanning revealed no evidence of recurrence of CNS tumor on follow-up

![Fig. 2. Survival curve by Karnofsky grade at 2 months in 28 patients. Triangles indicate Grades 80 or more (20 patients, 10 alive), and squares indicate Grades 50 to 70 (eight patients, three alive).](image)

![Fig. 3. Survival curve according to extent of disease. Square indicates no systemic cancer (16 patients, 11 alive); open triangle indicates one positive site (chest, bone, or liver: 11 patients, two alive); closed triangle indicates two or more positive sites (six patients, none alive).](image)
studies. Autopsies performed on four of these patients showed no evidence of intracranial tumor. Thirteen patients were still alive and had no evidence of recurrent tumor on CT at the time of statistical analysis.

**Discussion**

In a previous study of treatment of single brain metastases by surgery and radiation therapy, we noted two factors that influenced survival, namely, time of onset of cerebral metastasis, and neurological grade prior to craniotomy. The relation of a third factor to survival (extent of disease) became apparent in that retrospective study only when the data were stratified to include time of onset of cerebral metastasis. The present prospective study, in which a routine extent of disease work-up was included and the patients were followed after treatment by serial CT scan, provides, we believe, additional information in regard to survival of these patients and efficacy of treatment.

The overall median survival of 8 months with a 1-year survival of 44% represents a modest increase over the 6 months shown in the previous study and other reported studies. This apparent improvement, however, may be related to such factors as the small size of the series, and selection of patients. Improvement in detection of patients who have a truly single metastasis and accurate localization of the lesion provided by the CT scan almost certainly played a role. A more concrete finding is the fact that the median survival of patients who had no other detectable evidence of disease at the time of craniotomy is significantly increased. Eleven of these 16 patients are still alive, and the median, therefore, has not been reached; however, it will be at least three times that of patients with detectable cancer at other sites, since 56% of the patients with undetected cancer at other sites are alive at 15 months. This finding relates directly to the observation that the major cause of death in the series as a whole was progression of cancer outside the CNS. With the accrual of more such statistical data bearing on survival of patients with cancer, it should be possible in the relatively near future to predict which patients will benefit most from surgical removal of solitary, and, in some circumstances, multiple metastatic brain tumors.

The most important aspect of this study is the documentation by CT scanning of the results of treatment. Although survival time is obviously important in gauging the impact of treatment of a specific complication (in this case, cerebral metastasis) on a systemic disease, it may not accurately reflect the effectiveness of that treatment. In this series of 33 patients, CT scans in the immediate postoperative period revealed no evidence of residual neoplasm at the operative site in any of the 30 patients in which resection of the tumor was believed to have been achieved. Follow-up scans carried out routinely in the 27 of these 30 patients who lived for more than 1 month showed no recurrent tumor. Of the 13 patients still alive 8 to 16 months following surgery, none has evidence of cerebral neoplasm.

From these data, it seems apparent that surgical removal of all visible tumor followed by radiation therapy is highly effective in the treatment of single brain metastases, and that major gains in survival of similar populations so treated are dependent primarily upon improvement in therapy of disease peripheral to the CNS. In addition, since each series will contain a varied mix of patients in regard to factors known to influence survival, valid comparison between series and various modes of therapy must include objective evidence of tumor relapse, such as that provided by the CT scan.

One of the important questions to be answered in future studies of the treatment of single brain metastases is whether whole-brain irradiation is necessary in those patients in whom total surgical removal of the tumor is believed to have been achieved, and who show no evidence of tumor on postoperative CT scans. Under these circumstances, the use of whole-brain radiation therapy in this and the previous series has been based on three premises, namely: 1) microscopic neoplastic foci may have been left in the tumor bed; 2) small undetected metastases may reside in other portions of the brain; and 3) radiation therapy is more effective in the treatment of microscopic deposits of cancer cells than in larger tumors. Especially in those patients who statistically have a good chance of living for a year or more following craniotomy, the theoretical possibility of sterilizing microscopic foci of tumor by whole-brain radiation therapy must be weighed against the possibilities of delayed complications of such radiation and the future need for palliative radiation of fresh metastases to the meninges and brain. Although the fact that no new tumors outside the operative site were detected in the patients receiving whole-brain radiation therapy in this series may lend support to the rationale of such treatment, an equally plausible explanation is that, with the exceptions previously noted, all the tumors surgically removed represented true solitary metastases. In our opinion, the most important reason for testing this latter hypothesis by limiting radiation therapy to the locale of the tumor bed in a series of patients is the possibility that unnecessary damage to other portions of the brain can be avoided. One patient in this series became blind and another totally deaf, most probably as a result of radiation. In addition, it is our impression that, as patients who have undergone whole-brain radiation therapy live longer, we are seeing an increasing number of patients with dementia with and without demonstrable brain atrophy (hydrocephalus ex vacuo) on CT scanning.

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References


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