

IRRADIATION OF BRAIN METASTASES

H. C. BERRY, R. G. PARKER and A. J. GERDES

CHAO et coll. (1954) first published the results of irradiation of brain metastases in 38 patients; 'symptomatic relief' was obtained in 24 (64%). However, the benefits of palliative therapy for patients with brain metastases have been questioned since these patients often have disseminated disease (CUSHING 1932, LANG & SLATER 1964, STORTEBECKER 1954, TAVERAS 1959). Assessment of palliation has proved to be a most difficult task. A surgical criterion for success has been 'increased survival for at least six months without further disability' (LANG & SLATER 1964, SIMIONESCU 1960, STORTEBECKER 1954). Amelioration of signs or symptoms has been reported as the criterion for radiation success (CHU & HILARIS 1961, NISCE et coll. 1971). However, ultimately it is the functional, subjective or objective improvement of the patient that determines whether a significant palliative result has been achieved.

It is the purpose of this report to review the clinical findings, results and implications of the radiation treatment of brain metastases in 124 patients with attention toward palliative results.

Submitted for publication 1 April 1974.

Table 1*Site of the primary tumor in 124 patients with brain metastases*

Primary tumor site	No. of patients	Per cent
Bronchus	37	30
Breast	21	17
Unknown	21	17
Genitourinary tract	14	11
Gastrointestinal tract	8	6
Melanoma	7	6
Other	16	13

Materials and Methods

From August 1964 to April 1973, 119 patients with intracranial metastases were accepted for whole brain irradiation. An additional five patients received partial brain irradiation. The types of primary tumors are presented in Table 1. The largest group of 37 patients (30 %) had bronchogenic carcinoma. The second largest groups each containing 21 (17 %) were mammary carcinoma and unknown primary site. Eighty-nine (72 %) of the patients had metastases at other sites in addition to having intracranial metastases. Seventy-two (58 %) of the primary neoplasms were of a poorly differentiated histologic grade. Forty-three (35 %) of the patients were female. The intracranial metastases were responsible for the initial sign or symptom of disease in 31 (25 %) of the patients. Forty-five (39 %) of the patients had an interval of over 12 months between

Table 2*Presenting signs and symptoms in 124 patients with brain metastases*

Symptom and sign	No. of patients	Per cent
Cranial nerve deficit	54	44
Headache	52	42
Mental change	51	41
Motor deficit	50	40
Convulsion	31	25
Papilledema	31	25
Visual change	31	25
Cerebellar signs	30	24
Nausea/vomiting	24	19
Sensory deficit	13	10

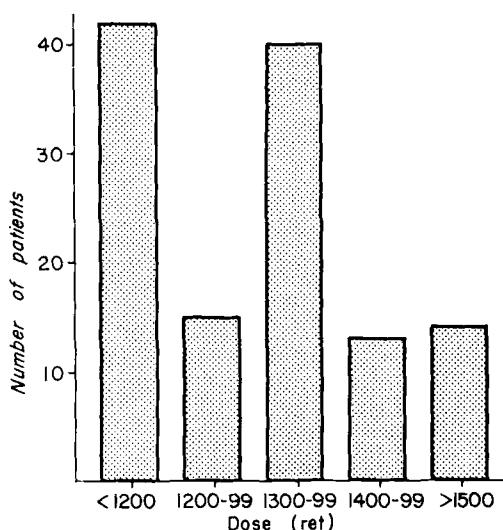


Fig. 1. Dose distribution in ret according to Ellis' formula.

the diagnosis of the primary neoplasm and the diagnosis of intracranial metastasis.

The presenting signs and symptoms are listed in Table 2. Cranial nerve deficit, headache, mental change and motor deficit were most common, each being present in about 40 per cent of the patients. The diagnosis of intracranial metastasis was established by brain scan in 76 patients (61%), by arteriography in 25 (20%), microscopically in 22 (18%) and on clinical grounds in 29 patients (23%). Clinically, the intracranial metastases were considered multiple in 53 (44%), were supratentorial in 82 patients (66%), subtentorial in 24 patients (19%) and both sub- and supratentorial in 17 (14%).

Radiation therapy. One hundred and seventeen (96%) of the patients received supervoltage irradiation (^{60}Co or 8 MeV photons) and in all but five of the 124, the whole brain was irradiated. Treatment was incomplete in eight patients and interrupted in two. Many different patterns of application were utilized in this retrospective investigation. However, the two most commonly used were 3 000 rad/10 Rx/2 weeks or 4 000 rad/20 Rx/4 weeks.

According to ELLIS' calculations (1969), 42 (34%) of the patients received NSD doses of less than 1 200 ret, 15 (12%) between 1 200 and 1 299 ret, 40 (32%) between 1 300 and 1 399 ret, 13 (10%) between 1 400 and 1 499 ret and 14 (11%) received over 1 500 ret (Fig. 1). Sixty-three (51%) of the patients were on steroids during irradiation and 31 (25%) were on maintenance chemotherapy. Twenty-nine (23%) patients had a neurosurgical procedure be-

Table 3*Functional classification of patients with brain metastases*

Class	Definitions
I	Intellectually and physically able to work; neurologic findings minor or not present.
II	Intellectually intact and physically able to be at home, although nursing care may be required; neurologic finding present but not a major factor.
III	Major neurologic findings requiring hospitalization and medical care and supervision.
IV	Requires hospitalization and is in serious physical and neurologic state.

fore or concomitant with irradiation. Eight (6 %) patients were reirradiated when symptoms or signs recurred.

The patients were functionally classified before irradiation according to ORDER et coll. (1968) (Table 3). The term intellectually intact in Class II means that the patient is oriented and able to engage in ordinary conversation.

Improvement is defined as an increase in posttreatment functional status of at least one class over the pretreatment classification. The breakdown of patients according to their functional class and treatment received is presented in Table 4. Sixty-three (50 %) of the patients were in Class II before irradiation. Surgery indicates attempted resection and not simple needle biopsy or shunt placement.

The uncorrected cumulative survival of the entire group of 124 patients is given in Fig. 2. The cumulative survival was 60 per cent at three months from

Table 4*Distribution of patients according to functional class and treatment received*

Treatment	Class			
	I	II	III	IV
Surgery and irradiation	2	9	10	1
Irradiation	14	54	31	3
Total	16	63	41	4

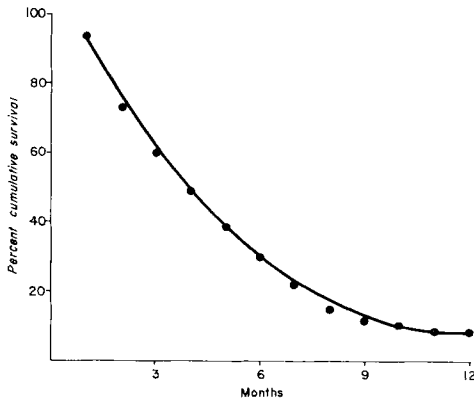


Fig. 2. The cumulative survival of 124 patients treated with whole brain irradiation for brain metastases.

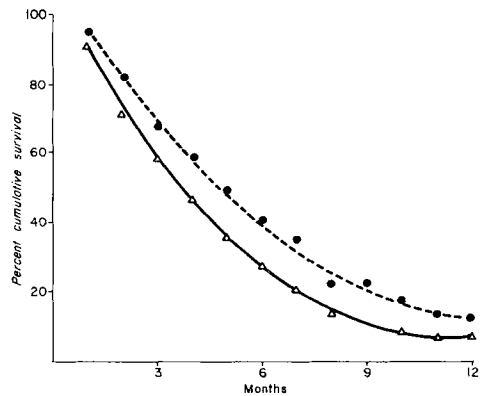


Fig. 3. The difference in survival favoring the group of 22 patients undergoing neurosurgical resection plus irradiation was not statistically significant. ● surgery and irradiation, △ irradiation only.

the first day of irradiation, 49 per cent at four months, 30 per cent at six months and 9 per cent at one year. The mean survival of our patients was 4.7 months. Ten patients survived 13 months or more. In the sub-group of 22 patients who had definitive surgery followed by irradiation, the cumulative survival is 68 per cent at three months, 41 per cent at six months and 14 per cent at 12 months respectively (Fig. 3). These differences in survival apparently favoring the surgery plus irradiation group over the irradiation only group are never with more than 15 per cent gap and are closer than in those reported by MONTANA et coll. (1972). Due to patient selection, these groups are possibly not comparable. For example, the patients in the surgery plus irradiation group were more often (90%) thought to have a solitary intracranial metastasis than were the patients in the irradiation only group (49%). However, the differences in survival although unidirectional are not statistically significant. The overall survivals for the single against multiple metastases groups average 4.7 and 4.8 months, respectively. This is also in agreement with MONTANA et coll.

In assessment of therapy response, 19 (15%) patients did not improve with treatment and 20 (16%) patients deteriorated during irradiation. Seventy-nine (63%) of the patients improved subjectively or objectively and 52 (41%) improved functionally as measured by the classification of ORDER et coll. (1968). The subjective and objective improvements graphically paralleled each other with 41 (55%) of the 79 improved patients maintaining their subjective or objective improvement through the three-to-six-month time interval posttreat-

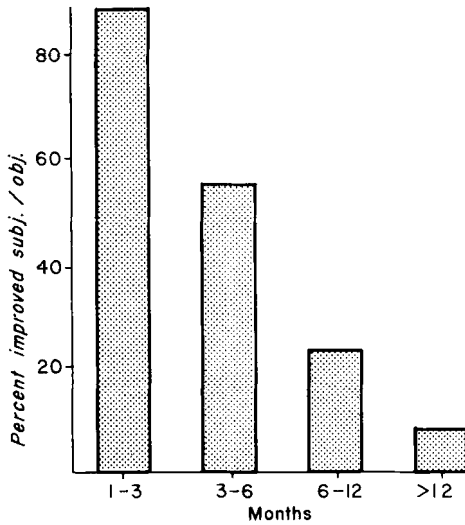


Fig. 4. Duration of subjective or objective improvement, post-irradiation of 79 patients.

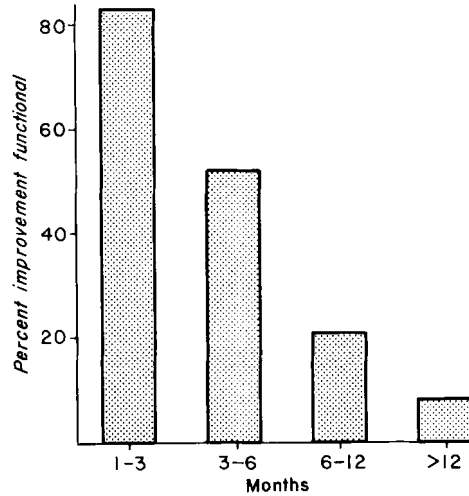


Fig. 5. Duration of functional improvement of 51 patients postirradiation.

ment. Six (8%) of the 79 improved patients remained improved over 12 months (Fig. 4). Twenty-six (52%) of those 51 patients functionally improved remained in a higher functional status through the three-to-six-month postirradiation period (Fig. 5). The mean survival of this group was 6.6 months. A ratio of duration of improvement to duration of survival, the 'palliative index' was calculated for this group (ORDER et coll. 1968). The index was 92 per cent at one to three months, 74 per cent at three to six months and 57 per cent at six to twelve months (Table 5). In 15 (44%) of the 34 patients whose brains were examined postmortem, there were multiple cerebral metastases, in 12 (35%) only a solitary metastasis was demonstrated and in seven patients (21%), no tumor was identified. Four (12%) patients in this group of 34 had preirradiation histologic proof of intracranial metastasis and none of the seven (21%) patients without tumor identified at autopsy were biopsied before irradiation.

Discussion

The facts that 72% of our patients had other metastases in addition to intracranial metastases; bronchogenic carcinoma and mammary carcinoma were the most common primary sites; 44 per cent clinically and 47 per cent postmortem

Table 5*Comparison of both the duration of survival and improvement in patients with functional improvement*

Time, months	Duration of improvement (%)	Survival (%)	'Palliative index' improvement/survival (%)
1-3	83	90	92
3-6	52	70	74
6-12	21	37	57
> 1 yr	8	14	57

had multiple metastases; the majority of metastases were supratentorial; and the most common presenting signs and symptoms were cranial nerve deficit, headache, mental change and motor deficit, further support previous reports (ASK-UPMARK 1956, BERESFORD 1969, CHAO et coll. 1954, CHU & HILARIS 1961, CUSHING 1932, GALLUZZI & PAYNE 1956, GLOBUS & MELTZER 1942, HINDO et coll. 1970, LANG & SLATER 1964, MONTANA et coll. 1972, NISCE et coll. 1971, ORDER et coll. 1968, SIMIONESCU 1960, VIETH & ODOM 1965). The fact that 58 per cent of the intracranial metastases were from poorly differentiated primary tumors is not unexpected. However, this point has not been emphasized in the recent literature on whole brain irradiation. Also, it is of interest that 39 per cent of our patients had an interval of over 12 months between the diagnosis of the primary tumor and the diagnosis of intracranial metastases.

The results in terms of length of survival, per cent of functional improvement and palliative index are similar to recent publications (CHU & HILARIS, HINDO et coll., MONTANA et coll., NISCE et coll., ORDER et coll.). For the group of patients receiving whole brain doses less than 1 200 ret, the average survival was 4.2 months compared to the group receiving over 1 500 ret whose average was 3.6 months. However, this data does not necessarily allow a conclusion that the 1 200 ret level gives overall results equivalent to the 1 500 ret level. Six patients received 1 000 rad in a single increment and their average survival was 3.3 months. Two were retreated once and one was retreated twice, each time receiving 1 000 rad in a single increment. The longest survivor in the single dose group lived eight months and was the individual receiving two retreatments. The (single 1 000 rad) treatments were well tolerated in every instance. Steroid coverage was not routinely used in these patients. There was no correlation between the use of steroids and survival in the entire group, possibly due to patient selection.

Average survival of the group of 63 (51 %) on steroids was 4.3 months against 5.0 months for the remainder not receiving steroids. These figures would agree with recent publications (HINDO et coll., ORDER et coll.) stating that adjunctive therapy with steroids does not seem to significantly influence the palliation rate but may make the critically ill patient more suitable for irradiation.

Of the patients receiving concomitant chemotherapy other than steroids, only 5 (4 %) were on agents known to be clinically effective against intracranial metastases. All of these patients had either leukemia or lymphoma, had a positive temporal response to whole brain irradiation and would have been expected to respond even without specific chemotherapy. Therefore, it cannot be assumed that the results in this group of patients are necessarily due to chemotherapy rather than to irradiation.

Regarding additional measures of quality of survival, 63 per cent of the patients noted subjective and objective improvement which was sustained for three to six months in 55 per cent of the group.

Of the 7 patients without intracranial metastases at autopsy, all but one had widespread metastatic disease in addition to the diagnosis of intracranial metastases, 2 had positive brain scans and the remaining 5 had various cranial nerve abnormalities with (4) or without (1) other signs or symptoms supporting the clinical diagnosis of intracranial metastases. Of this group of 5 clinically diagnosed patients, 3 experienced definite neurologic improvement concomitant with the course of whole brain irradiation, leaving 2 patients in whom the preirradiation diagnosis of intracranial metastases could be seriously raised. False positive brain scans, incorrect clinical diagnosis, location miss at the time of autopsy slide sectioning or more hopefully, intracranial tumor eradication secondary to irradiation could explain the lack of tumor in these 7 patients.

Patients with untreated intracranial metastases have been shown to have a mean survival of two months and a median survival of one month (LANG & SLATER 1964). Reports of surgical treatment indicate apparent improvement in survival statistics over untreated patients (HAAR & PATTERSON 1972, LANG & SLATER 1964, STORTEBECKER 1954, VIETH & ODOM 1965). However, the post-operative mortality has ranged from 11 to 41 per cent in several reports (HAAR & PATTERSON 1972, LANG & SLATER 1964, RASKIND et coll. 1971, RICHARDS & MCKISSECK 1963, SIMIONESCU 1960, STORTEBECKER 1954, VIETH & ODOM 1965). Radiation therapy has not been associated with these high mortality rates.

The difference in survival observed in this series between the group of patients treated with surgery plus irradiation and the group treated with irradiation alone is not significant. Considering the cost and potential morbidity and mortality associated with the surgical treatment of intracranial metastases, it is felt reasonable to rely on whole brain irradiation alone for the palliation of these patients.

SUMMARY

A series of 124 patients with intracranial metastases, treated by irradiation, has been reviewed, retrospectively and prospectively, and the results are reported. Worthwhile palliation was obtained in 79 (63 %) of the total number of patients with functional improvement documented in 52 (41 %). The uncorrected mean survival was 4.7 months. The addition of surgery to irradiation did not improve results significantly in this series. Therefore, surgical removal should be performed on special indications such as rapidly progressing increase in intracranial pressure unresponsive to steroids or shunt, or if the etiology of the intracranial lesion is uncertain.

ZUSAMMENFASSUNG

Eine Serie von 124, strahlenbehandelten Patienten mit intrakraniellen Metastasen wurde retrospektiv und prospektiv zusammenfassend behandelt und es wird über die Ergebnisse berichtet. Eine wertvolle Palliation wurde bei 79 (63 %) von allen Patienten mit nachweisbarer funktioneller Verbesserung bei 52 (41 %) erzielt. Die unkorrigierte mittlere Überlebenszeit betrug 4,7 Monate. Zusätzliche Chirurgie neben der Bestrahlung verbesserte bei dieser Patientenserie nicht signifikant die Ergebnisse. Deshalb sollte eine chirurgische Entfernung nur bei besonderen Indikationen wie rasch fortschreitendem gesteigertem intrakraniellen Druck, der nicht auf Steroide oder einen Shunt reagiert, oder bei Unklarheit der Ursache der intrakraniellen Schädigung vorgenommen werden.

RÉSUMÉ

Les auteurs ont fait une analyse rétrospective et prospective d'une série de 124 malades atteints de métastases intra-crâniennes traitées par irradiation et présentent les résultats. Ils ont obtenu un résultat palliatif satisfaisant chez 79 malades (63 %) du nombre total de malades avec une amélioration fonctionnelle objective chez 52 malades (41 %). Le taux de survie moyen non corrigé était de 4,7 mois. L'association d'interventions chirurgicales à l'irradiation n'a pas amélioré de façon significative les résultats de cette série. C'est pourquoi l'exérèse chirurgicale devrait être faite dans des indications spéciales, telle que l'augmentation rapidement progressive de l'hypertension intra-crânienne non améliorée par les stéroïdes ou par la dérivation ou bien dans les cas où la nature de la lésion intra-crânienne reste incertaine.

REFERENCES

- ASK-UPMARK E.: Metastatic tumors of the brain and their localization. *Acta med. scand.* 154 (1956), 1.
- BERESFORD H.: Melanoma of the nervous system. *Neurology* 19 (1969), 59.
- CHAO J., PHILLIPS R. and NICKSON J.: Roentgen-ray therapy of cerebral metastases. *Cancer* 7 (1954), 682.
- CHU F. C. H. and HILARIS B.: Value of radiation therapy in the management of intracranial metastases. *Cancer* 14 (1961), 577.
- CUSHING H.: *Intracranial tumors*. First edition, p. 105. Charles C. Thomas, Springfield,

Illinois 1932.

- ELLIS F.: Dose, time and fractionation: a clinical hypothesis. *Clin. Radiol.* 20 (1969), 1.
- GALLUZZI S. and PAYNE P.: Brain metastases from primary bronchial carcinoma. *Brit. J. Cancer* 10 (1956), 408.
- GLOBUS J. and MELTZER T.: Metastatic tumors of the brain. *Arch. Neurol. Psychiat. (Chic.)* 48 (1942), 163.
- HAAR R. and PATTERSON R.: Surgery for metastatic intracranial neoplasm. *Cancer* 30 (1972), 1241.
- HINDO W., DETRANA F., LEE M.-S. and HENDRICKSON F.: Large dose increment irradiation in treatment of cerebral metastases. *Cancer* 26 (1970), 138.
- LANG E. and SLATER J.: Metastatic brain tumors: Results of surgical and nonsurgical treatment. *Surg. Clin. N. Amer.* 44 (1964), 865.
- MONTANA G., MEACHAM W. and CALDWELL W.: Brain irradiation for metastatic disease of lung origin. *Cancer* 29 (1972), 1477.
- NISCE L., HILARIS B. and CHU F. C. H.: A review of experience with irradiation of brain metastasis. *Amer. J. Roentgenol.* 111 (1971), 329.
- ORDER S., HELLMAN S., VON ESSEN C. and KLIGERMAN M.: Improvement in quality of survival following whole brain irradiation for brain metastases. *Radiology* 91 (1968), 149.
- RASKIND R., WEISS S., MANNING J. and WERMUTH R.: Survival after surgical excision of single metastatic brain tumors. *Amer. J. Roentgenol.* 111 (1971), 323.
- RICHARDS P. and MCKISSECK W.: Intracranial metastases. *Brit. J. Med.* 1 (1963), 15.
- SIMIONESCU M.: Metastatic tumors of the brain: A follow-up study of 195 patients with neurosurgical considerations. *J. Neurosurg.* 17 (1960), 361.
- STORTEBECKER T.: Metastatic tumors of the brain from a neurosurgical point of view: follow-up study of 158 cases. *J. Neurosurg.* 11 (1954), 84.
- TAVERAS J.: Radiotherapy of brain tumors. *Clin. Neurosurg.* 7 (1959), 200.
- VIETH R. and ODOM G.: Intracranial metastases and their neurosurgical treatment. *J. Neurosurg.* 23 (1965), 375.