5. Hershatter B, Halperin E, Cox E. Medulloblastoma: the Duke experience. *Int J Radiat Oncol Biol Phys* 1986, 12, 1771–1777.
6. Silverman C, Simpson J. Cerebellar medulloblastoma: the importance of posterior fossa dose to survival and patterns of failure. *Int J Radiat Oncol Biol Phys* 1982, 8, 1869–1876.
7. Merkel DE, Dressler LG, McGuire WL. Flow cytometry, cellular DNA content, and prognosis in human malignancy. *J Clin Oncol* 1987, 5, 1690–1703.
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, 53, 457–481.
9. Hedley DW, Friedlander ML, Taylor IW, Rugg CA, Musgrove CA. Application of DNA flow cytometry to paraffin-embedded archival material for the study of aneuploidy and its clinical significance. *J Histochem Cytochem* 1981, 31, 1333.
10. Yasue M, Tomita T, Engelhard H, Gonzalez-Crussi F, McLone DG, Bauer KD. Prognostic importance of DNA ploidy in medulloblastoma of childhood. *J Neurosurg* 1989, 70, 385–391.
11. Frederiksen P, Reske-Nielsen E, Bichel P. Flow cytometry in tumours of the brain. *Acta Neuropathologica* 1989, 41, 179–183.
12. Hoshimo T, Nomura K, Wilson CB, Knebel KD, Gray JW. The distribution of nuclear DNA from human brain-tumour cells. *J Neurosurg* 1978, 49, 13–21.
13. Mork SJ, Laerum OD. Model DNA content of human intracranial neoplasms studied by flow cytometry. *J Neurosurg* 1980, 53, 198–204.
14. Sieben G, Calliauw L, Van Oostvelott P, Roels H. The influence of AZQ on the DNA distribution of human cerebral tumours in short-term culture. *Eur J Cancer Clin Oncol* 1985, 21, 217–220.
15. Look AT, Roberson PK, Williams DL, *et al.* Prognostic importance of blast cell DNA content in childhood acute lymphoblastic leukemia. *Blood* 1985, 5, 1079–1086.
16. Shapiro DN, Parham DM, Douglass ME, *et al.* Relationship of tumor cell ploidy to histologic subtype and treatment outcome in children and adolescents with unresectable rhabdomyosarcoma. *J Clin Oncol* 1991, 9, 159–166.
17. Douglass EC, Look AT, Webber B, *et al.* Hyperdiploidy and chromosomal rearrangements define the anaplastic variant of Wilm's tumor. *J Clin Oncol* 1986, 4, 975–981.
18. Look AT, Douglass EC, Meyer WH. Clinical importance of near-diploid tumor stem lines in patients with osteosarcoma of an extremity. *N Engl J Med* 1988, 318, 1567–1572.
19. Look AT, Hayes A, Shuster JJ, *et al.* Clinical relevance of tumour cell ploidy and N-*myc* gene amplification in childhood neuroblastoma: a pediatric oncology group study. *J Clin Oncol* 1991, 9, 581–591.

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Fractionated Stereotactic External Beam Radiotherapy in the Management of Brain Metastases

R.W. Laing, A.P. Warrington, F. Hines, J.D. Graham and M. Brada

24 patients with 28 brain metastases were treated with fractionated stereotactic radiotherapy (SRT). Doses ranged from 10 Gy in two fractions to 20 Gy in two fractions. 13 patients received SRT boost after whole brain radiotherapy (WBRT), 5 were treated with SRT alone and 6 were treated at the time of recurrence following WBRT. The median progression-free survival at the treated site was 18 months and the median survival was 18 months. All patients were treated without admission to hospital. Toxicity of fractionated SRT was minimal and patients treated without WBRT did not suffer significant alopecia. Fractionated SRT offers a non-toxic non-invasive alternative to excision surgery in patients with solitary brain metastases. The optimum fractionation schedule and the role of whole brain irradiation remain to be determined.
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INTRODUCTION

ALTHOUGH WHOLE brain radiotherapy (WBRT) achieves useful palliation of symptoms in 60–80% of patients with brain metastases, approximately 50% of patients die with uncontrolled brain disease [1]. Increasing radiation dose to the whole brain in the presence of multiple lesions [1] or wide field boost to a limited volume of the brain [2] does not improve symptomatic control or survival.

Approximately 40% of patients have solitary brain metastases [3] and radical treatment with excision in addition to WBRT improves local control and survival [4]. Focal irradiation either in the form of brachytherapy or stereotactic external beam radiotherapy (SRT)/radiosurgery can be considered as an alternative to surgical excision. It has been employed to gain local control of small intracranial tumours such as acoustic neuroma [5], or recurrent gliomas [6]. In the treatment of solitary metastases SRT has been used largely as single fraction treatment

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both with dedicated multiheaded cobalt unit (gamma knife) [7] and linear accelerator based systems [8–11]. Initial studies reported effective local control with some toxicity associated with high dose single fractions [8].

We developed a fractionated SRT technique based on a non-invasive method of fixation with the relocatable Gill–Thomas stereotactic frame [12, 13] and have embarked on studies of fractionated SRT in the management of patients with brain metastases. In the evolution of fractionated SRT we performed a phase I dose escalation study using 5 Gy per fraction following conventional whole brain irradiation. This was followed by a phase II study using 10 Gy per fraction to a dose of 20 Gy with or without whole brain irradiation. We report the efficacy and toxicity of these regimens.

PATIENTS AND METHODS

Between April 1989 and June 1992, 24 patients with 28 intracranial metastases were treated with fractionated SRT. The criteria for entry into the SRT study were: radiological evidence of a brain metastasis either biopsy proven or from a histologically verified malignancy, suitable size for SRT (≤ 5 cm) [14], and good performance status (≥ 70 Karnofsky performance score). Patients were aged 20 to 80 years (median 58). 21 patients had a solitary lesion and 1 patient had two lesions and 1 patient had four lesions. The maximum diameter of the metastases ranged from 15 to 52 mm (median 28 mm). The histological diagnosis is shown in Table 1. 10 patients (42%) had non-small cell lung carcinoma and 5 (21%) had breast carcinoma. Twenty-four lesions (86%) were supratentorial and four (14%) were infratentorial.

Patients were immobilised in a Gill–Thomas relocatable frame (Radionics Inc, Burlington, Massachusetts, U.S.A.) adapted for radiotherapy [12, 13]. Tumours were localised by contrast enhanced computed tomography (CT) scanning using a fiducial system described previously [13]. The target volume was defined as the enhancing tumour plus a 2 mm margin; this was encompassed by and prescribed to the 90% isodose. For non-spherical lesions the margin was greater than 2 mm at some points. Twenty-seven lesions were treated with three to five single isocentre non-coplanar arcs [14], and one lesion with six non-coplanar static fields. Treatment was delivered on a 5 MV linear accelerator in routine clinical use, adapted for SRT.

Patients were either treated at first presentation (18 patients) or at relapse after surgery and WBRT (3 patients) or WBRT alone (3 patients). 10 patients were treated as part of a dose escalation programme with 5 Gy per fraction following 30 Gy WBRT given in 10 fractions; 3 received 10 Gy in two fractions, 3 received 15 Gy in three fractions, 3 received 20 Gy in four fractions and 1 patient received 30 Gy in six fractions. Subsequently, the fraction size was increased to 10 Gy, and 14 patients (17 metastases) received 20 Gy in two fractions 4 days apart; 9 after WBRT and 5 without. Patients received corticosteroids during SRT if there was clinical or radiological suspicion of raised intracranial pressure. Four separate clinical groups were identified by the dose of radiation received, the addition of WBRT and a history of relapse prior to SRT.

Table 1. The site of the primary tumour and histology in 24 patients with brain metastases treated with SRT

Primary tumour	Number of patients
Breast (adenocarcinoma)	5
Bronchus (NSCC)	10
Testis (germ cell tumour)	2
Kidney (clear cell carcinoma)	1
Uterus (adenocarcinoma)	1
Salivary gland (adenoid cystic carcinoma)	1
Unknown primary (adenocarcinoma)	2
Colon (adenocarcinoma)	1
Bladder (transitional cell carcinoma)	1

Group 1. WBRT followed by a low dose SRT boost (≤ 15 Gy at 5 Gy/F).
Group 2. WBRT followed by a high dose boost ≥ 20 Gy.
Group 3. SRT 20 Gy in two fractions without WBRT.
Group 4. Treatment at relapse after WBRT with SRT ≥ 20 Gy.

Patients were followed for 1 to 28 months (median 6 months) from the time of SRT. Minimum follow-up for surviving patients was 2 months. 1 patient from abroad was lost to follow-up, and 1 patient died from a pulmonary embolus before completing treatment; both were included in the survival analysis but were censored in the analysis of local control. Systemic treatment for generalised metastatic disease was given after SRT as deemed clinically appropriate. Survival and progression-free survival (PFS) were measured from the date of SRT and calculated by the life-table method [15]. Patients were assessed clinically monthly and then every 2 months and radiologically by CT or MR scans at 6 weeks post SRT and then every 2 months when clinically appropriate. Progression was defined radiologically in 6 patients (see below). In the absence of CT or magnetic resonance (MR) scanning it was defined clinically in 2 patients by progressive neurological deterioration of the pattern of deficit seen at presentation. The radiological response at the latest follow-up investigation was categorised as: complete response (CR)—no evidence of residual tumour, partial response (PR)—product of the maximum perpendicular diameters on transverse scans reduced by ≥ 50%, static disease (SD)—no change or reduction in size < 50%, and progression (PD)—the product of the maximum transverse perpendicular diameters increased by ≥ 25% or new growth within 2 cm of the treatment volume (marginal recurrence). Clinical assessment was also categorised: CR denotes resolution of all neurological symptoms on stable or reducing corticosteroid dose, PR denotes an improvement of neurological symptoms without increase in corticosteroids, no response (NR) as no change in symptoms, and PD as symptomatic progression.

Neurological deterioration or features of raised intracranial pressure in the absence of tumour progression on CT/MR scanning were considered as treatment-related toxicity.

RESULTS

Local control

Following fractionated SRT eight lesions progressed. 2 patients had subsequent surgical resection and the presence of viable tumour confirmed. The median PFS at the treated site was 18 months (Fig. 1). Table 2 details 9-month PFS for the four groups of patients. 2 patients relapsed at the edge of the treatment volume after partial resection of large recurrent metastases followed by SRT. Four other CT/MR scan-confirmed relapses occurred within the treatment volume. There was no significant difference in the local PFS for patients who received ≥ 20 Gy compared to < 20 Gy SRT, or for metastases > 30 mm when compared to ≤ 30 mm in diameter.

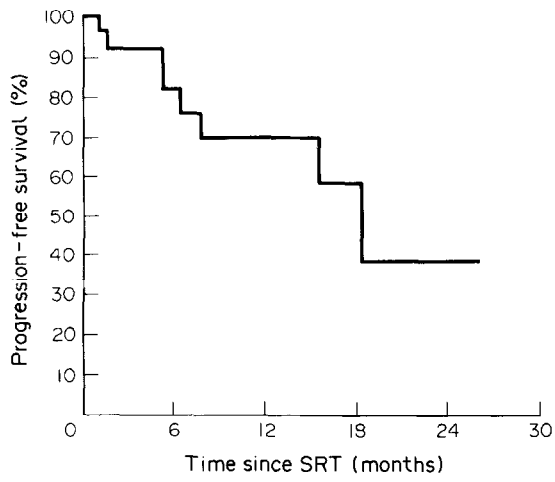

Fig. 1. Actuarial probability of local control at the treated site of 28 lesions treated with fractionated SRT.

Response

The clinical and radiological response is shown in Table 2. Clinical improvement was recorded after SRT in 16 (73%) patients at a median time of 6 weeks (range 2–12 weeks).

Twenty metastases had radiological assessment between 7 and 111 weeks (median 24 weeks) after SRT. Ten (50%) regressed and of these three (16%) were categorised as CR, seven (35%) as PR, four (21%) remained static and six (31%) progressed. In 3 patients brain metastases developed at a distance from the treated volume, one in a patient who did not receive WBRT and two after WBRT.

Survival

10 patients died, and the median survival was 18 months (Fig. 2). 8 patients died due to uncontrolled primary tumour or metastatic disease outside the CNS. 2 patients died as a result of progressive brain metastases.

Toxicity

Patients were treated entirely on an out-patient basis. The acute toxicity was minimal with any of the fractionation schedules. Increase in headache was reported by 1 patient within 1 week of completing treatment which responded to a short course of corticosteroids. When SRT was employed without WBRT there was no significant alopecia. No neurological deterioration occurred that could be attributed to radiation damage. 1 patient died 4 weeks after completing WBRT and SRT boost (20 Gy/2 F). Prior to treatment he had mild hydrocephalus secondary to a large thalamic lesion and on deterioration with headache and herpes zoster infection was admitted to a hospice without further investigation. This patient is assumed to have died of PD although exacerbation due to radiation-induced oedema cannot be excluded.

DISCUSSION

Patients with brain metastases have poor prognosis despite aggressive treatment aimed at the control of brain lesions [16]. This is not only due to poor control of intracranial disease but also due to uncontrolled primary tumour or extracranial metastatic disease. Treatment of brain metastases is, therefore, largely palliative and should be aimed at symptom control with minimal disturbance for the patient. It should be short, non-invasive, without toxicity and given on an out-patient basis. Patients with solitary brain metastases have the most favourable prognosis of the group of patients with metastatic disease in the brain [17–19]. Aggressive local treatment in the form of surgery when added to whole brain irradiation improves survival [4], yet despite such intensive treatment the median survival of patients with solitary metastases is of the order of 40 weeks.

Fractionated SRT using a non-invasive relocatable frame qualifies on many counts as the ideal palliative treatment for solitary brain metastases. It can be given entirely on an out-patient basis, and is well tolerated without acute toxicity and without causing hair loss. However, in the treatment of solitary brain metastases it is necessary to demonstrate that such local treatment is equivalent to surgical excision in terms of survival and local control, as well as producing symptomatic benefit. The symptom control reported in this study is comparable to the neurological improvement seen with other radiotherapy schedules [2, 16]. The survival results of the cohort of 24 patients (28 lesions) with a median PFS at the treated site of 18 months and median survival of 18 months are comparable to the results following surgical excision [4]. As in other studies of treatment of solitary brain metastases the patients were highly selected and such favourable survival results are largely a reflection of overall tumour burden and the overall clinical condition. Nevertheless, such relativity long survival allows for assessment of the adequacy of local tumour control.

Other studies employing single fraction radiosurgery with gamma knife [7] or linear accelerator [8–11] also support the effectiveness of SRT with local control of metastases ranging from 80 to 100%. Unequivocal survival comparison with surgical excision can only be obtained from randomised studies.

The optimum dose/fractionation schedule has not been

Table 2. Response to SRT in 22 evaluable patients (26 lesions)

	Group 1 Low dose SRT + WBRT	Group 2 High dose SRT + WBRT	Group 3 High dose SRT no WBRT	Group 4 SRT at relapse	Total
Number of patients	5	6	5	6	22
Number of metastases	5	6	8	7	26
Radiological response*	0/3	2/3	7/7	1/7	10/20
9 month PFS† (number relapsed)‡	60% (2)	83% (1)	100% (0)	57% (2)	70% (5)
Number of patients with clinical response (CR + PR)	4	4	4	4	16

* Number of lesions responding (radiological PR + CR)/total lesions treated where scans available; † PFS, actuarial progression-free survival at the treated site; ‡ number of patients relapsing before 9 months.

defined. Patients in this study were treated during the evolution of fractionated SRT and three schedules were used. The numbers of patients in each group are small and it is, therefore, difficult to define dose response data particularly with such a heterogeneous group of tumours. However, there is a suggestion that patients receiving doses of 20 Gy or more achieve better local control without increased toxicity and on present evidence we would advocate doses of at least 20 Gy in two fractions.

The linear quadratic formula has been used to determine isoeffective doses for single fraction and fractionated SRT [20]. Sixteen Gy single treatment, 20 Gy in two fractions, and 25 Gy in five fractions appear isoeffective in terms of tumour control. Radiosurgical doses of 16–20 Gy (median 16 Gy) have been used as a boost after WBRT [7], 9–25 Gy (median 16 Gy) for relapse after WBRT [9], and 15–50 Gy (median 22 Gy) as sole treatment [8]. In all the studies the reported local control rate was in excess of 88% although the results are not represented in an actuarial manner.

In a palliative situation, particularly in the treatment of recurrent metastases, hospital visits should be minimised and the fewer fractions used the better. Providing the toxicity is minimal, which would be the case for small lesions, single fraction treatment would be ideal. However, solitary lesions are frequently large and with SRT there is less relative sparing of surrounding normal tissue [14]. In this situation it would be at least theoretically of advantage to give fractionated treatment. Our present policy is to continue treatment with two fractions. This schedule does not significantly increase the financial cost of treatment, as the major cost of planning and simulation remains unchanged when compared to single treatment. To determine the optimum dose for single fraction or fractionated SRT will require large cooperative studies as performed in patients with multiple metastases.

It is assumed that the presence of apparently solitary metastases in the brain is a hallmark of more extensive clinically undetectable disease in the brain. It has, therefore, been a policy to treat such patients with whole brain irradiation [4, 21]. The increased sensitivity of MR scanning allows for more specific selection of patients with true solitary lesions. The influence of whole brain irradiation on subsequent relapse outside the solitary irradiated site is not clear. In the initial phases of the protocol patients were treated with SRT after whole brain irradiation. In the later phases of the study whole brain radiotherapy was selectively avoided. At present, it is not possible to assess the additional value of whole brain radiotherapy in these patients.

Retrospective studies comparing the role of whole brain radiotherapy following surgery give conflicting results. In a non-randomised study of 33 patients the addition of WBRT did not improve the control of intracranial disease or survival [22], while in another study of 85 patients those treated without WBRT had shorter median survival and 60% required subsequent WBRT for symptomatic relapse [21]. The addition of WBRT to single fraction radiosurgery was associated with improved intracranial tumour control when compared to radiosurgery alone [11]. However, this retrospective comparison involved only 17 patients and there was no survival difference between the two groups.

A policy of withholding whole brain irradiation at initial treatment of solitary metastases has a number of advantages. It would avoid alopecia and could subsequently be given only to patients recurring within the brain. The lack of toxicity of 'prophylactic' whole brain irradiation combined with SRT, suggests it would be well tolerated at a later date despite high local radiation doses to small volumes. In a proportion of patients with true solitary metastases and in patients who relapse at extracranial sites, such policy would avoid whole brain irradiation.

In the absence of randomised trials assessing the role of whole brain irradiation in addition to local treatment it is reasonable to treat patients with solitary metastases with a policy of SRT alone. This is particularly true if the solitary nature of the tumour is confirmed on MR imaging.

We conclude that fractionated SRT is an effective, well tolerated and non-invasive form of intensive local treatment of solitary brain metastases which seems equivalent in its efficacy to local neurosurgical excision. It is also effective in the control of symptoms and can be given as a short entirely out-patient-based treatment. Providing the effectiveness is confirmed in other studies, SRT is likely to become the treatment of choice for patients with solitary brain metastases.

1. Kurtz J, Gelber R, Brady L, Carella R, Cooper J. The palliation of brain metastases in a favourable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981, **7**, 891–895.
2. Hoskin P, Crow J, Ford H. The influence of extent and local management of the outcome of radiotherapy for brain metastases. *Int J Radiat Oncol Biol Phys* 1990, **19**, 111–115.
3. Delattre J, Krol G, Thaler H, Posner J. Distribution of brain metastases. *Arch Neurol* 1988, **45**, 741–744.
4. Patchell R, Tibbs P, Walsh J, *et al.* A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990, **322**, 494–500.
5. Flickinger J, Lunsford L, Coffey R, et al. Radiosurgery of acoustic neurinomas. *Cancer* 1991, **67**, 345–352.
6. Laing R, Warrington A, Graham J, Britton J, Hines F, Brada M. Efficacy and toxicity of fractionated stereotactic radiotherapy in the treatment of recurrent gliomas (phase I/II study). *Radioth Oncol* 1993, in press.
7. Coffey R, Flickinger J, Lunsford L, Bissonette D. Solitary brain metastasis: radiosurgery in lieu of microsurgery in 32 patients. *Acta Neurochir* 1991, **52**, 90–92.
8. Sturm V, Kimmig B, Engenhardt R, *et al.* Radiosurgical treatment of cerebral metastases. *Stereotact Funct Neurosurg* 1991, **57**, 7–10.
9. Loeffler J, Kooy H, Wen P, *et al.* The treatment of recurrent brain metastases with stereotactic radiosurgery. *J Clin Oncol* 1990, **8**, 576–582.
10. Adler J, Cox R, Kaplan I, Martin D. Stereotactic radiosurgical treatment of brain metastases. *J Neurosurg* 1992, **76**, 444–449.
11. Fuller B, Kaplan I, Adler J, Cox R, Bagshaw M. Stereotaxic radiosurgery for brain metastases: the importance of adjuvant whole brain irradiation. *Int J Radiat Oncol Biol Phys* 1992, **23**, 413–418.
12. Gill S, Thomas D, Warrington A, Brada M. Relocatable frame for stereotactic external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 1991, **20**, 599–603.
13. Graham J, Warrington A, Gill S, Brada M. A non-invasive, relocatable stereotactic frame for fractionated radiotherapy and multiple imaging. *Radiother Oncol* 1991, **21**, 60–62.
14. Graham J, Nahum A, Brada M. A comparison of techniques for stereotactic radiotherapy by linear accelerator based on 3-dimensional dose distributions. *Radiother Oncol* 1991, **23**, 29–35.
15. Peto R, Pike M, Armitage P, Breslow N, Cox D, Howards S. Randomised clinical trials require prolonged observation on each patient. Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
16. Borgelt B, Gelber R, Kramer S, *et al.* The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1980, **6**, 1–9.
17. Galicich J, Sundaresan N, Arbit E, Passe S. Surgical treatment of single brain metastasis: factors associated with survival. *Cancer* 1980, **45**, 381–386.
18. Sarma D, Weilbaecher T. Long-term survival after brain metastasis from lung cancer. *Cancer* 1986, **58**, 1363–1370.
19. Salerno T, Munro D, Little J. Surgical treatment of bronchogenic carcinoma with a brain metastasis. *J Neurosurg* 1978, **48**, 350–354.

20. Brenner D, Martel M, Hall E. Fractionated regimens for stereotactic radiotherapy of recurrent tumors in the brain. *Int J Radiat Oncol Biol Phys* 1991, **21**, 819–824.
21. Smalley S, Schray M, Laws E, O'Fallon J. Adjuvant radiation therapy after surgical resection of solitary brain metastasis: association with pattern of failure and survival. *Int J Radiat Oncol Biol Phys* 1987, **13**, 1611–1616.
22. Dosoretz D, Blitzer P, Russell A, Wang C. Management of solitary metastasis to the brain: the role of elective brain irradiation following complete surgical resection. *Int J Radiat Oncol Biol Phys* 1980, **6**, 1727–1730.

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Vascular Density and the Response of Breast Carcinomas to Mastectomy and Adjuvant Chemotherapy

Efi Protopapa, George S. Delides and László Révész

Using morphometric analysis of histological preparations, in a retrospective study vascular indices, expressing the extent of vascularisation, were determined for a number of mammary carcinomas. The indices were found to be related to the survival of the patients treated with modified radical mastectomy in combination with pre- and postoperative chemotherapy, the cases with low indices having the shorter survival. The impaired access of the cytotoxic agents to cells in the deficiently vascularised tumours was considered as an explanation. It was concluded that determination of vascular density in tumours may have a prognostic value in regard to the treatment response, and may be helpful in choosing the appropriate treatment.
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INTRODUCTION

STAGING AND histological grading of tumours are most commonly used for the selection of treatment and indication of the prognosis of the neoplastic disease. Despite identical treatment of tumours of the same stage and similar histological classification, frequently greatly varying treatment responses can be observed. These observations can be interpreted as indicating that factors not included in the staging and grading may play an important role in defining the result of treatment. Currently, the characterisation of the factors with predictive value for the tumour treatment response is subject to extensive research [1].

In 1968 Kolstad [2] reported that the results of radiotherapy for cancer of the uterine cervix were closely related to the vascular density in the tumours, as determined by colposcopic measurements. Richly vascularised cases responded to treatment better than cases with a poor vascularisation. These observations were subsequently confirmed by authors who used different morphometric methods for the retrospective evaluation of the vascularity in histological sections of biopsy specimens from cervical carcinomas [3–5]. The vascularity was also found to be related to the radiotherapy response of nasopharyngeal carcinomas [6], carcinomas of the rectum [7] and the bladder [8]. These and some other related observations were discussed in a recent review [9].

The presence of radioresistant cells in extended hypoxic areas, which may occur in the poorly vascularised cases, has been put forward as an explanation for the failure of radiotherapy [2, 10]. In view of the known radiobiological "oxygen effect", the radiosensitivity of cells under hypoxic conditions can be decreased by a factor up to about 3 in comparison to the well oxygenated cells.

It is conceivable that, being less accessible to the blood circulation, the cells in the less well vascularised tumours will show resistance besides radiotherapy, to parenteral or oral treatment with cytostatic drugs. The determination of the extent of vascularisation may, therefore, have a prognostic value also for chemotherapy. In an attempt to investigate this possibility, in a retrospective study we determined the vascular density in a number of mammary carcinomas which were treated surgically in combination with neo-adjuvant chemotherapy, and the vascularity was then related to the survival of the patients. This paper reports the results.

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PATIENTS AND METHODS

Patients

A total of 26 patients with mammary tumours were included in the study, treated at the Metaxas Memorial Cancer Institute in the period between 1978 and 1982. They were selected according to the following criteria: (a) they were premenopausal cases, aged between 35 and 50 years; (b) the tumours were