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Delayed adverse effects after irradiation of gliomas: clinicopathological analysis*

Riccardo Soffietti, Rossella Sciolla, Maria Teresa Giordana, Ezio Vasario[1] & Davide Schiffer
II Neurological Clinic,[1]Department of Radiotherapy, University of Torino, Italy

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Summary

Out of 107 pts. treated with radio- and chemotherapy for low and high grade gliomas (TD: 45–65Gy), 3 cases developed pathologically documented radionecrosis (coagulative necrosis with minimal or no persistent tumor). Clinico-therapeutic modalities were analyzed for all cases and biologically equivalent doses were calculated according to NSD, ED and btu formulas. All cases of radionecrosis fell into the group of doses close to 60Gy/30fx./42d. and NSD=1758, ED=1340 and btu=1161. Isodose curve reconstruction on planes corresponding to histological sections of brains with radionecrosis demonstrated that doses received by areas of necrosis were higher than the calculated mid-plane doses in two cases. Clinical and autoptic incidence of radionecrosis were 2.8% and 10% respectively. High doses of steroids during RT seemed to offer some protection against radionecrosis, while number of chemotherapy cycles did not influence the risk of radionecrosis. A higher autoptic rate of irradiated gliomas is needed in order to obtain a better understanding of a number of unresolved problems.

Introduction

The most serious hazard following irradiation of the CNS for both extracranial and intracranial tumors is delayed radionecrosis. Pathologically, it is characterized by coagulative necrosis with vessel wall alteration (1, 2); clinically, the picture is that of a neurological deterioration with a large mass or diffuse abnormality on CT-scan (3).

Few Authors have reported on the incidence of radionecrosis after treatment of gliomas (4, 3, 5), owing mainly to the difficulty of differentiating between radiation necrosis and recurrent tumor on CT-scans (6) and to the low re-operation and autopsy rate (3). Recently, some Authors (7, 8) tried to get a better understanding of CNS radiation tolerance by analyzing treatment modalities of reported radionecroses.

The role of steroids during radiotherapy, the possible potentiating effect of chemotherapy and the importance of preexisting pathological conditions (hypertension, diabetes, etc.) in inducing CNS radiation damage remains unclear (9).

This paper has a twofold purpose: 1) To determine the incidence of pathologically documented radionecrosis in a population of patients irradiated for gliomas and followed until death or for an adequate period of time. 2) To analyze the relationship between the incidence of radionecrosis and clinico-therapeutic parameters.

Material and methods

Out of 125 cases treated between 1975 and 1981 with radio- and chemotherapy, we considered a sub-

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Address for offprints: R. Soffietti, II Neurological Clinic, University of Torino, Via Cherasco 15, 10126 Torino, Italy.

group of 107 who had received at least 45Gy. Patients were followed until death or for a minimum of 3 years (time necessary to demonstrate 74% of CNS radionecroses, according to Kramer et al.) (10). Histological diagnosis was available in 98 cases (63 glioblastomas, 5 gliosarcomas, 18 anaplastic astrocytomas, 4 anaplastic oligodendrogliomas, 4 well-differentiated astrocytomas, 4 oligodendrogliomas). 9 cases were not operated upon, but had a clinico-radiological aspect strongly suggesting a malignant glioma. All cases were treated by ^{60}Co through bilateral opposing portals, large enough to cover the entire cranial content (85 cases) or restricted to the tumor bed (22 cases). The tumor dose was calculated through the midsagittal plane of the skull at the central axis of the treatment field. 89 cases reived conventional radiotherapy (5 to 7 weeks for most patients) with daily fractions (1.6–2.0 Gy each). In 11 cases the radiosensitizer Misonidazole (1–1.5 gm/m^2) was given twice a week in association with daily fractions of 2 Gy. Superfractionation (2 daily fractions of 1 Gy each) was used in 7 cases. Total radiation doses were 45–65Gy. Mono- or polichemotherapy was given to all but one patient (BCNU; CCNU; Streptozotocin; Procarbazine; MeCCNU-Procarbazine; BCNU-Methylprednisolone; Hydroxiurea; CCNU-VM26-5Fluorouracil; Ftorafur).

4 patients were re-operated upon for recurrence.

30 autopsies were performed and the brains fixed in buffered formalin. Serial coronal slices 1 cm thick were embedded in paraffin; 10μ thick section were processed for routine pathological examination. Dose distribution on coronal planes corresponding to the histological sections was obtained by the computerized system for radiotherapy "RT-Plan" of General Electric. The different dose fractionation schemes were reduced to a common denominator using the Nominal Standard Dose (NSD) formula ($TD=NSDxN^{0.24}xT^{0.11}$) (11), the Equivalent Dose (ED) formula ($TD=EDxN^{0.377}xT^{0.058}$) (12) and the Brain Tolerance Unit (btu) formula ($TD=btu\ xN^{0.45}xT^{0.03}$) (8).

All cases were divided into four groups, according to steroid dose (dexamethasone) during radiotherapy (1) no steroids; 2) < 150 mg; 3) > 150 and < 300 mg; 4) > 300 mg, including cases receiving high doses of methylprednisolone, 400 mg/m^2/d. over 14 days), and in three groups according to number of chemotherapy cycles (1) < 5; 2) >5 and < 10; 3) > 10;). Distribution of pathologically proven radionecroses in the different groups was statistically evaluated by the χ^2 test for the trend (13).

Results

Radionecrosis with minimal or no persistent tumor was pathologically documented in 3 out of 30 autopsied patients, whose clinical and therapeutic parameters are illustrated in Table 1-Fig. 1a. Histo-

Table 1. Delayed radionecroses.

a) Clinical parameters

Case	Sex-age	Diagnosis at surgery	Latency to radionecrosis	Aspect at CT-scan	Tumor at autopsy
1	M; 69	GBL	13 mo.	contralateral, diffuse low density area, without contrast enhancement	minimal
2	F; 41	GBL	11 mo.	*	no tumor
3	M; 39	GBL	11 mo.	homolateral, low density area, with contrast enhancement	minimal

* The last CT-scan was performed more than one mo. before death, which occured after a sudden clinical deterioration.

b) Therapeutic modalities

Case	Tumor dose (Gy); fractions; time (days);	Radiation field (cm)	No. chemotherapy cycles	Steroid dose during RT	Radiation dose to radionecrosis
1	55.27; 27; 37;	18 x 15	10 BCNU	148 mg	55.27-57.78
2	58.90; 31; 46;	18 x 12	5 Procarbazine	0	61.80-64.70
3	63; 35; 70;*	18 x 18	7 Polichemother.	0	69.30-72.45

* Case 3 received Misonidazole (total dose: 210 mg)during RT. Radiotherapy was interrupted for 21 days because of severe leucopenia.

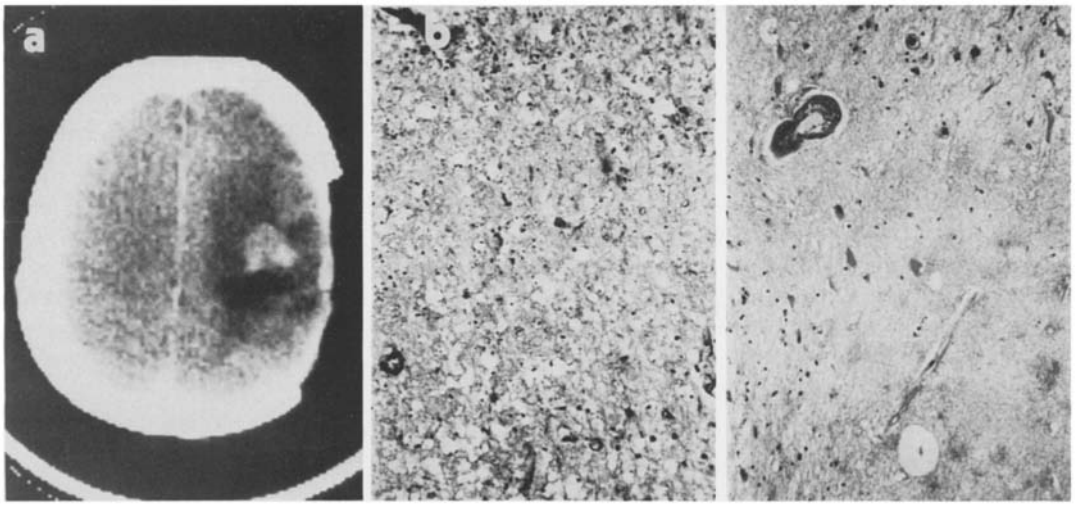

Fig. 1. a) Case 3. CT scan at progression, showing a contrast-enhanced mass with a surrounding area of low attenuation; b) Case 3. Coagulative necrosis of the parenchyma. HE, 200x; c) Case 3. Vessel wall degeneration and sparse reactive astrocytes. HE, 200x.

logical aspect was typical, with coagulative necrosis (Fig. 1b), spongionecrosis, macrophage areas and severe vascular damage (Fig. 1c). The white matter was involved in all cases, the cerebral cortex in only one. Necrosis was in peritumoral position in two cases and contralateral in one; all three cases had been treated by very large fields. Isodose curve reconstruction on coronal histological sections showed that radionecrotic areas had received doses ranging from 55.27 to 72.45 Gy (Fig. 2).

In one further case (anaplastic astrocytoma at surgery) no tumor was found at autopsy, but the white matter was severely damaged (edema, spongiosis, hyalinization of vessel walls, but no clearcut picture of coagulative necrosis). Clinically, the patient, who had received 60.32Gy, progressively deteriorated over a 7 month period, while the CT-scan failed to show a recurrence or any other abnormality.

Pathologically documented radionecroses account for 2.8% of clinical cases (3 out of 107 cases) and 10% of autopic cases (3 out of 30 autopsies). All three cases survived more than 1 year after surgery: the percentage of death with radionecrosis was 7.6% between 12 and 18 months (2/26) and reached 12.5% between 18 and 24 months (1/8).

Cases with radionecroses had received a tumor dose of more than 5.5Gy, but in only two the tumor dose was in the upper range of doses received by the entire pupulation ($\geq$ 60 Gy)

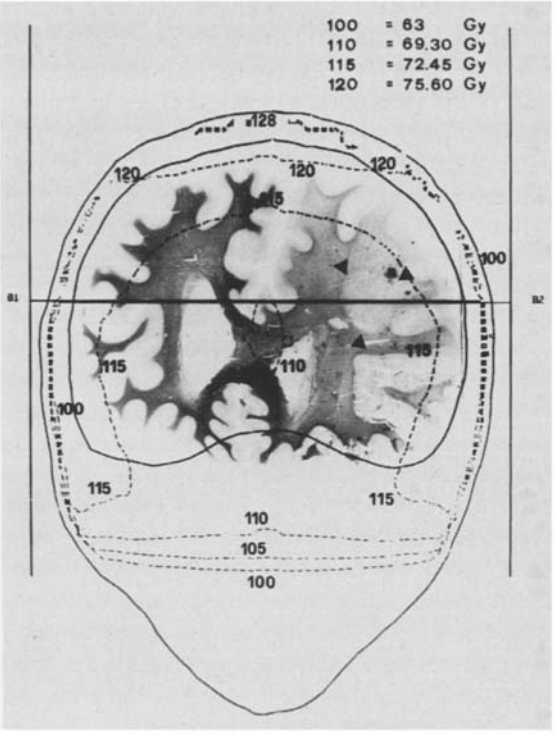

Fig. 2. Case 3. Dose distribution on the coronal histological section. Luxol Fast Blue B for myelin. (arrows: area of radionecrosis).

Table 2. Distribution of cases according to NSD, ED and btu values.

NSD	RDN treated cases	ED	RDN treated cases	btu	RDN treated cases	corresponding convetional fractionation
⩽ 1562	0/41	⩽ 1209	0/41	⩽ 1056	0/43	NSD = 1562 ED = 1209 btu = 1056 } 50Gy, 25 fx., 35d.
1563–1666	0/24	1210–1253	0/11	1057–1078	0/7	NSD = 1666 ED = 1253 btu = 1078 } 60Gy, 35 fx., 49d.
1667–1758	3/58 NSD of RDN (1682, 1684, 1695)	1254–1340	3/51 ED of RDN (1289, 1293, 1294)	1079–1161	3/53 btu of RDN (1120, 1120, 1125)	NSD = 1758 ED = 1340 btu = 1161 } 60Gy, 30 fx., 42d.
> 1758	0/4	> 1340	0/4	> 1161	0/4	

NSD, ED and btu values for radionecreses (RND) and total irradiated population are shown in Table 2.

No case with radionecrosis had suffered from hypertension or diabetes. All three of them had received steroid doses of less than 150 mg during radiotherapy. When considering all treated patients, the trend toward a lower incidence of radionecrosis at higher steroid doses has a slight statistical significance ($p < 0.05$), but there is no significance when survivals of more than one year only are considered. No significant correlation was found between the number of chemotherapy cycles and the incidence of radionecrosis.

In one out of four re-operated cases, histological evidence of tumor regrowth was accompanied by severe damage of normal nervous tissue.

Discussion

Clinico-radiological characteristics of our cases of radionecrosis are similar to those reported elsewhere (3,5). Clinically, a strong suspicion had arisen only in case 1 (low density area contralateral to the tumor on the CT scan). When an enhancing mass is found at the tumor site (e.g.: case 3), a differential diagnosis between recurrence and radionecrosis cannot be made (6); in addition, after radiation doses of more than 60Gy, contrast enhancement in radionecroses can be a common finding (e). PET could probably achieve a better differentiation (14).

As most radiation-induced changes are closely adjacent to the tumor (1, 2), it seems that sparing the normal nervous tissue during tumor irradiation is virtually impossible. On the other hand, as radiation damage can sometimes occur at a distance from the tumor (e.g.: case 1), and glioblastomas most frequently recur within a 2 cm margin of the primary site (15), a reduction of radiation doses on the non strictly peritumoral normal nervous tissue seems advisable, as already proposed by Shapiro (16).

Our incidence of pathologically documented radionecroses (3/107 = 2.8%) is slightly lower than the reported 3% of Mikhael (3), 4% of Marsa et al. (4), and 5% of Marks et al. (5). The low number of radionecroses among our cases could be accounted for by a number of factors, such as:

1) The relatively low rate of histological verifications after radiotherapy: only 31% of irradiated patients were re-operated upon or autopsied. In fact, a strong clinico-radiological suspect of radionecrosis had arisen in at least one further case (low density area contralateral to the tumor on the CT scan), but was not histologically documented).
2) The already mentioned exception to radionecroses of autoptic cases where a large radionecrosis coexisted with either a small, active tumor or a large, histologically quiescent one.
3) The fact that cases such as the one we described (progressive neurological deteriotation, without CT scan abnormality or clearcut necrosis at autopsy) escape classification either as radionecroses or as tumor progressions even on histological examination.

On the other hand, autoptic incidence of radionecrosis was 10% (3/30), and Marks et al. (5) mention-

ed an even higher rate (4/18). This stresses the need for a higher autoptic rate among conventionally irradiated patients, but also suggests that the actual incidence of radionecrosis could be higher than generally recognized. This seems particularly true for long-surviving patients (our incidence was maximal between 18 and 24 months) which presently can reach up to 30% at 18 months after the best known therapies (surgery + RT + BCNU, according to BTSG studies) (17).

A further problem in the correct evaluation of the real incidence of radionecrosis is that a differentiation between severely altered normal nervous tissue and widely damaged residual tumor can be almost impossible (2, 18), even when wholebrain histological sections are available. As a consequence, differential diagnosis between delayed adverse effects of irradiation and a recurrent tumor is, in our opinion, very unreliable when based on small biopsies, eventhough multiple.

According to Marks et al. (5), frequency of radionecrosis is similar for high and low grade gliomas. In our cases, all radionecroses were originally glioblastomas, but we cannot say anything regarding the incidence of radionecrosis among well differentiated gliomas, because of the very low number of such tumors treated at our Institution.

Keeping in mind the importance of size fraction in the induction of both brain and spinal cord radiation damage (12, 19, 20, 21), biologically equivalent doses for treatment schedules of all cases were calculated, using not only the NSD, but also the ED and btu formulas, which give particular importance to number of fractions in comparison to total time. Below values of NSD = 1666, ED = 1253 and btu = 1078 (corresponding to 60Gy/35fx/49d.) no necrosis was found. This treatment seems safer than 60Gy/30fx./42d. (Table 2). The generally held opinion (22, 3, 7, 5) is that risk of radionecrosis increases with very high doses; we cannot contribute to the problem, owing to the low number of patients treated with doses in excess of 60Gy, 2Gy/fx. (4 cases). However, by isodose curve reconstruction on planes corresponding to the coronal histological sections, radiation doses absorbed by areas of radionecrosis where higher than the calculated mid-plane doses in two instances (case 1, 3) (Table 2). This also stresses the need of calculating the actual dose distribution within the brain in order to obtain reliable dose-effects correlations (5).

The role of steroids during radiotherapy is controversial. It has been suggested (1) that high doses offer protective action against radiation damage, which seems to be confirmed by our findings. This could be due to management of the edema which seems to make peritumoral tissue of malignant gliomas more vulnerable to irradiation. Aristizabal et al. (23) reported a high incidence of radionecrosis in patients with hypercortisolism, treated for pituitary adenomas. Controlled studies on numerous cases of both highly edematous tumors (e.g.: malignant gliomas) and less edematous ones (e.g.: low grade gliomas) are essential if a definition of the problem is to be obtained.

Number of chemotherapy cycles did not seem to influence the risk of radionecrosis. However, radionecroses are generally observed in long-surviving patients, who usually receive the heaviest chemotherapy. As drug-induced pathological changes in irradiated cases are recognized with extreme uncertainty (2, 24), the role of chemotherapy in the development of delayed radiation damage remains to be defined.

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