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TUMOR EXTENT AS A DETERMINING FACTOR IN RADIOTHERAPY OF GLIOBLASTOMAS

by

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In spite of improvements in radiotherapy equipment and techniques in recent years, we are unable to cure the great majority of highly malignant gliomas of the brain. For establishing the cause of failures we have two propositions to consider: (1) that the highly malignant glioma is biologically so constructed that it is radioresistant at a dose level tolerated by normal brain tissue, and (2) that our treatment techniques may inadequately irradiate all the tumor tissue present. This paper is concerned with the second aspect.

Some years ago, while working at the Royal Marsden Hospital, I was engaged in the treatment of a large number of patients with brain tumors. These patients formed part of a controlled study to determine the value of postoperative irradiation for intracranial gliomas (PENMAN 1954). A number of these patients, mostly with astrocytic gliomas, grades III and IV, died shortly after admittance for radiation therapy and usually before an adequate amount of treatment could be given. Thirty such cases came to autopsy and formed the basis of a study undertaken by CONCANNON and myself to compare the estimated size of the tumor to be irradiated with its true extent. A full report of this study has been published earlier (1960). The complete clinical notes, roentgenograms, and the preserved brains of these patients were available for study. Localization of

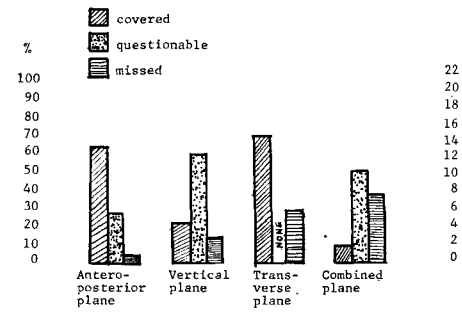


Fig. 1. Graphic representation of the number and percentage of tumors adequately included, questionably included and missed in the volume irradiated; each plane considered separately and then for all planes combined.

the tumor and estimation of its size for the purpose of radiation therapy was based primarily on contrast roentgenologic examinations. In addition, the clinical and operative findings were taken into account. The size and localization of the tumors as indicated by these studies were compared with the actual size and location as shown at post mortem examination. We modified BULL & ROVIT's classification (1957) of the result of roentgenologic localization of brain tumors more adequately to suit the purpose of the radiation therapists. This is important since probably an appreciable part of the tumor will be underdosed or missed completely if any portion of the tumor lies outside the area delineated by the radiologist.

Our classification of results in the roentgenologic diagnosis of brain tumours is as follows:

1. *Excellent:* the tumor accurately and completely localized.

2. *Good:* major portion of the tumor localized; less than 20 % of tumor outside but closely adjacent to the area delineated by the radiologist.

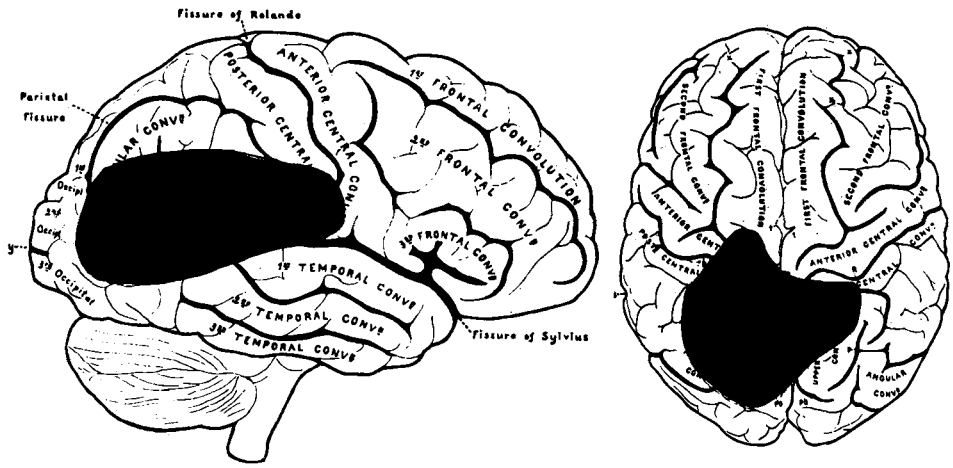
3. *Poor:* more than 20 % of the tumor outside the indicated volume; tumor distantly removed from the area indicated; study inadequate to demonstrate tumor or localize tumor.

The roentgenologic diagnostic accuracy in the 29 patients for whom roentgenograms were available was as recorded below:

Excellent	4 cases	13.8 %
Good	11 cases	37.9 %
Poor	14 cases	48.3 %

In almost half the number of cases, the roentgenologic localization was so poor that at least 20 % of the tumor or more was outside the volume indicated by the roentgenologic examination.

A review of the time interval between the contrast studies and the death of



a b

Fig. 2. Diagrams of tumor extent in a patient: as determined prior to therapy (a) and at autopsy (b).

the patients showed that 50 % of them had died within 30 days of the study being performed and all within 78 days, so that it is unlikely that the tumor had extended at all between the time of the study and death. Conversely, it is unlikely that the radiation therapy given to some of these patients had decreased the size of the tumor materially in this group of patients since only 6 completed the planned course of therapy.

Our treatment policy at that time was to irradiate patients with malignant gliomas through medium-sized portals in the hope of being able to deliver a large dose to a relatively small volume. The desired dose was 5 500 to 6 000 R to be delivered in 6 to 7 weeks. As a rule two lateral portals measuring 10 cm×8 cm and a superior portal measuring 10 cm×6 cm were employed so that a cylinder of tissue approximately 8 cm×8 cm×10 cm was included in the high dose volume. The volume however, was adjusted to include the tumor as indicated by the roentgenologic examination described above.

In 21 of these patients, who died so quickly after admission to our hospital, radiation therapy had either been planned or commenced, and in these patients we were able to compare the extent of the planned treatment volume with the actual extent of the tumor in the post mortem specimen. We chose as the actual tumor volume that needed to encompass the gross extent of the tumor surrounded by a 1 cm zone of grossly normal tissue around the tumor as a minimum margin of safety. Microscopic extension of the tumor, although almost certainly present

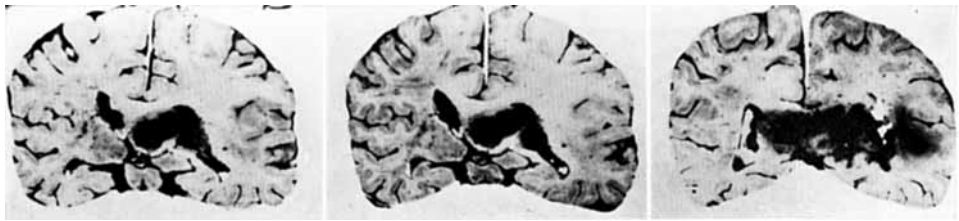


Fig. 3. Sections of the brain of the same patient as in fig. 2 to show the extent of the tumor.

to a large extent, was neglected in the study since this could only increase the degree to which we failed to cover the tumor adequately. We also assumed that the setting up of the treatment fields would have been entirely accurate in order to optimize the conditions of tumor coverage. Isodose curves for the planned fields were plotted in the antero-posterior, vertical and transverse planes and the gross tumor extent in each dimension as determined at post mortem examination of the brain was compared with the isodose curve for the corresponding plane. Our results were analyzed as follows.

Tumors were considered adequately covered by the treatment plan if in each plane the gross extent of the tumor and the 1 cm zone around it was included within the isodose curve. Tumor coverage was considered questionable if there was the possibility that a portion of the tumor or its surrounding margin was outside the irradiated volume. The tumor was considered missed if a portion of the tumor or of the 1 cm margin was definitely not within the treated zone. The result of our analysis was that out of the 21 patients with completed treatment plans, the tumor was covered adequately in only two. Tumor coverage was questionable in 11 and a portion of the tumor was definitely missed in 8.

Fig. 1 is a bar diagram of these findings for each plane separately and all planes combined and it will be seen that particularly in the vertical plane and the transverse plane, the planned volume was inadequate and that in the vertical plane, coverage was questionable in a large number of patients. Leaving aside the question of microscopic infiltration, even a study such as ours of the gross pathology confirms the well known fact that gliomas spread beyond the confines of an anatomic area such as a lobe of the brain and that the highly malignant gliomas are almost invariably larger and more extensive than was suspected in the clinical and roentgenologic examination. Laterally placed tumors extended mainly in an antero-posterior direction; more centrally placed tumors not infrequently spread across the midline (9 patients), and two patients in this series had an unsuspected second glioma, in the same hemisphere in one of the patients and on the opposite side in the other.

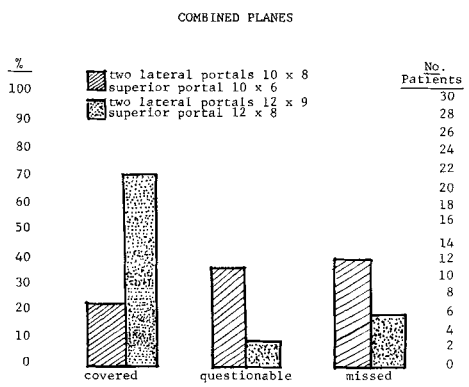


Fig. 4. Graphic comparison of results for medium field versus large field technique for all planes combined.

A diagram of the suspected lesion in a patient considered to have a unilateral parieto-occipital tumor is shown in Fig. 2. Examination of the fixed brain disclosed that the tumor extended massively into the opposite hemisphere (Fig. 3).

Since most of the treatment plans were for the medium-sized fields described above, we next made a study of the tumor coverage which would have been obtained in the 30 patients with this technique and compared this with the results which we might have achieved by a large field technique. For the purpose of this study, the medium field technique was again defined as two lateral 10 cm$\times$ 8 cm portals and a superior 10 cm$\times$6 cm portal, whereas large fields were defined as two lateral 12 cm$\times$9 cm portals and a superior 12 cm$\times$8 cm portal. The same conditions were applied to this study as in the analysis of the portals actually used. It will be recognized that the medium-sized field technique gives us a high volume cylinder of approximately 8 cm$\times$8 cm$\times$10 cm, whereas the large volume technique gives us a cylinder of 9 cm$\times$10 cm$\times$12 cm a volume almost double. The result is graphically presented in Fig. 5. This figure shows that, had the larger fields been used, the tumor would have been adequately covered in nearly three-quarters of the patients instead of less than one-quarter where the smaller portals were used. Those in whom the tumors were missed would have been reduced from more than one-third to one-fifth and those in whom coverage was questionable would have been reduced from one-third to one-tenth. Even so, one-fifth of the tumors would have been missed, and this leads me to believe that in this group of highly malignant gliomas the whole intracranial content has to be irradiated.

It must be stressed that this is a highly selected group of patients since all of them died soon after admission and almost all of them had extremely malignant tumors. Clearly these patients may have had larger and more rapidly growing tumors than others who would have survived for longer periods of time.

We conclude that with our present method of localization and knowledge of spread of gliomas there is no place for small or medium volume radiation therapy in the treatment of the highly malignant tumors. I believe that if there is to be hope of success the whole of the intracranial contents has to be irradiated. This study does not answer the question whether roentgen therapy can be effective for these tumors with large volume irradiation. I believe the question answered here is that radiotherapy is unlikely to be effective if smaller volumes are treated. Such failure could be caused solely through inadequate coverage of the tumors.

Acknowledgements

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SUMMARY

Failure to cure highly malignant gliomas may be due to an underestimate of the tumor extent. Twenty-one patients were planned for irradiation (chosen target volume as a rule 10 cm×8 cm×8 cm) but death occurred before effective therapy was given. When the treatment plan was compared with the tumor extent in the autopsied brain, only two out of the twenty-one patients were found to have had adequate tumor coverage. If the target volume had been doubled (12 cm×10 cm×9 cm) one-fifth of the patients would still have had inadequate tumor coverage. We conclude that the whole brain should be irradiated for glioblastomas.

ZUSAMMENFASSUNG

Ein Misserfolg in der Behandlung hochmaligner Gliome mag auf eine fehlerhafte Beurteilung der Ausbreitung des Tumors beruhen. Strahlenbehandlung wurde für 21 Patienten planiert (Feldgrösse meistens 10 cm×8 cm×8 cm) aber die Patienten starben bevor die Radiotherapie effektiv durchgeführt werden konnte. Bei Autopsie des Gehirns in diesen 21 Fällen zeigte es sich, dass die Behandlungsplanung nur in zwei Fällen den ganzen Bereich des Tumors umfasste. Falls die Feldgrösse verdoppelt wäre (12 cm×10 cm×9 cm) so würde man in einem Fünftel der Fälle immernoch eine unzureichende Tumorbestrahlung erreicht haben. Es erscheint in Fällen von Glioblastom, dass das ganze Gehirn bestrahlt werden sollte.

RÉSUMÉ

L'échec du traitement de gliomes très malins peut être dû à une sous-estimation de l'étendue de la tumeur. L'auteur a établi le plan de traitement de vingt et un malades (le volume cible choisi éait en règle de 10 cm × 8 cm × 8 cm); mais ces malades sont décédés avant d'avoir reçu un traitement efficace. La comparaison du plan de traitement avec l'extension de la tumeur dans le cerveau autopsié a montré que le volume irradié n'englobait convenablement la tumeur que chez deux malades sur les vingt et un. Si on avait doublé de volume cible (12 cm×10 cm×9 cm) un cinquième des malades auraient encore eu un volume d'irradiation inadapté. L'auteur conclut qu'il faudrait irradier le cerveau entier pour les glioblastomes.

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