Therapy-Induced Morphological Alterations in Brain Tumors

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Abstract: Routine therapeutic options for tumors of the brain or spinal cord comprise surgery, radiation and/or chemotherapy, all of which are associated with several possible complications. The most important consequences of brain tumor therapy are hemorrhage, acute brain swelling with external herniation of parts of the brain, CSF leaks, and coagulopathies. The anatomical location of surgical manipulation may have additional special effects, like diabetes insipidus following pituitary or adjacent base of the brain surgery. New techniques of radiotherapy applied in neuro-oncology such as "gamma knife" (stereotactic radiosurgery), intracavital brachytherapy, three dimensional conformal radiation, are also associated with iatrogenic changes in the brain. Pathologic changes induced by various radio-therapeutic modalities are discussed in this review, with special emphasis on terminology, timing and the importance of pathologic examination for assessing the tumor response to therapy, signs of peritumoral tissue damage and tumor recurrence. Therapy-induced secondary neoplastic lesions are also discussed.

Keywords: Brain tumor, glioma, necrosis, radiation, therapy.

INTRODUCTION

Gliomas are the most common intracranial tumors. In the US, every year approximately 15,000 patients die of glioblastoma [1]. The incidence rate of all primary non–malignant and malignant brain and central nervous system tumors is 16.5 cases per 100,000 person–years (9.2 per 100,000 person–years for non–malignant tumors and 7.3 per 100,000 person–years for malignant tumors). The rate is higher in females (17.2 per 100,000 person–years) than males (15.8 per 100,000 person–years) [1]. More than half of these brain tumors are malignant. Despite modern diagnostics and treatments, the median survival time does not exceed 15 months [2, 3]. Diffuse gliomas remain a particularly challenging clinical management problem. Despite a close to 150-year-long history of the scientific approach to the study and classification of brain tumors there still are fundamental hiatuses in our understanding of their biological behavior as it is obviously shown by frequent changes of the WHO categories of brain tumors [4, 5].

Therapy of brain tumors has made only sporadic advances. Even drugs directed against newly identified targets like matrix metalloproteinases or angiogenesis-related targets fail to increase survival duration and, anti-angiogenic drugs have been shown to increase glioma invasiveness, finally leading to gliomatosis cerebri [6, 7]. It is a fascinating coincidence to see that a major change towards the first breakthrough in chemotherapy of malignant gliomas (the "Stupp protocol" involving Temozolomide [8]) occurred as we are approaching the 125th anniversary of the first operation for glioma of the brain, performed on November 25, 1884, by Dr. Rickman Godlee (later Sir Rickman) under the direction of Dr. Hughes Bennett [9].

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An understanding of the pathology of brain tumors plays a crucial role in management of affected patients [10]. It is well recognized that even state-of-the art pathology is only a futile mental exercise without proper imaging data, which today allow a heretofore inconceivable precision of tumor localization [11], as well surgical or radiosurgical resection of lesions [12-14]. In parallel with this unprecedented revolution in neuroimaging molecular genetic analysis of brain tumors continue to shed light on "*subhistological*" features of CNS neoplasia that now often determine proper treatment [15-20]. These new diagnostic approaches have opened new avenues for individual patient-tailored therapy [20-22]. Simultaneously, however, trials of combinations of old and new agents are still going on [23].

While these novelties are being ushered into neuro-oncology there are still numerous serious practical problems. For example there are numerous tumor entities posing formidable challenges to neuro-oncologists due to the fact that there are no available and convincing prospective studies [5]. Just to give one example: it might be a nightmare for those involved to decide about the pros and cons related to radiation therapy of an ependymoma (Gr. III.) in a 4-y-old child. To complicate the issue further it is far from straight forward to make a difference between therapy-induced cellular atypia and *bona fide* biological progression of the same tumor in case of its 3rd biopsy. It is left to the reader to think through the problems of sampling and limitations of immunohistochemistry (IHC) in a stereotactic piece of tissue from such a case.

It is not surprising that conflation of brain tumor with malignant disease characterizes the typical mindset. Gliomas tend to be highly infiltrative and hence totally impossible to eradicate [5-7, 16-19]. Furthermore, it is textbook evidence that many histologically indisputably benign tumors can be lethal, because in these cases there is too much of a 'not very

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evil item' (object) in a non-compliant, tight, vitally confined space [17-18].

Iatrogenic effects brought about by treatment of CNS neoplasia may also increase intracranial pressure. It is because treatment may result in local tissue destruction, edema, distortion and shift of intracranial contents (herniation). Hence clinical signs and symptoms that are often brought about by chemo- and/or radiotherapy of intracranial tumors may closely mimic those produced by tumors affecting the brain: raised intracranial pressure and the onset of epilepsy [24]. This well-known fact calls for the awareness that is required in differential diagnostics of tumors and effects of tumor therapy and should always allow the maximum flow of information between clinicians and pathologists, but unfortunately it is not always the case. The limits set by eloquent regions and the treacherous infiltrating nature of almost all glial tumors their recurrence after surgery is the rule and this almost always is accompanied by biological progression (i.e., progressive dedifferentiation, increasing grade due to accumulation of genetic abnormalities [5, 17, 18, 24]).

The majority of standard chemotherapy regimens act at the level of DNA or DNA replication [15]. Even the recently introduced and most promising agent, Temozolomide, is a DNA alkylating agent [15]. Covalent addition of adducts to the DNA helix or cell-cycle-dependent inhibition of DNA replication have been both part of the brain tumor treatment armory long enough to realize that they may have long term effects not only on tumor cells but also on brain adjacent-to-tumor (BAT). These effects are often displayed in cytological and/or histological features [24]. Similarly, the other fundamental approach to eliminate tumors, i.e., radiation has long been applied to brain neoplasia [14]. Progress in the molecular biology of brain tumors will play a pivotal role in not only the development of new drugs directed at novel targets but also in the more efficacious use of conventional treatment modalities [10]. Hence familiarity with the morphology of therapy-induced changes remains an essential part of surgical neuro-oncopathology. New drugs as well as emerging new radiation methodologies (e.g., "gamma-knife") induce changes that qualitatively do not differ at the level of conventional histopathology from those that had been in use for over 30 years [24]. Important are the alterations, which are brought about by the various combinations of these treatment regimens, particularly when some adjuncts applied interfere directly with tumor blood flow or angiogenesis [10].

Brain tumor treatment inevitably comprises treatment of increased intracranial pressure. Steroids have been know to be fortunately effective in this regard, however in some cases, such as primary CNS lymphomas, steroids may induce tumor alterations (endothelial and tumor cell apoptosis) which may intrinsically interfere with proper diagnosis of the neoplastic process ("ghost tumor" phenomenon) [26].

This review will not cover the acute manifestations that may follow surgery or embolization. Neither can it dwell on the complexity of chemotherapy-associated leukoencephalopathy nor on the many potential toxic effects of therapy on the peripheral nervous system. We will focus on the effects of radiotherapy on tumors and host tissue instead, with some new observations from gamma knife treated neoplasms. Radiation induced lesions remain in constant focus since their relatively high frequency, difficulties in their differential diagnosis and treatment.

RADIATION INJURY OF BRAIN AND TUMOR TISSUE

The original idea behind radiotherapy (RT) was that since radiation damages DNA it will interfere with cell divisions [14, 27]. Since endothelial cells are the most actively dividing elements in adult brain it is not surprising that radiation induced non-tumorous brain injuries, which are a common complication of radiation therapy, have been for long associated with vascular response and endothelial reactions. There seems to be a common acceptance of the three-tired classification of radiation injuries, i.e., (i). acute; (ii) "early delayed"; and (iii) "late delayed". "Early delayed" is often referred to as subacute radiation injury [17, 18, 27-29]. To the present authors it seems logical to stick to the golden nomenclature of standard pathology and when referring to the time course of radiation induced lesions we suggest the use of the classic terminology (which we will do), i.e., *acute*, *subacute* and *chronic*. Although this suggestion may not meet a broad acceptance initially, with the advent of new radio-therapy techniques (stereotactic radiosurgery, "Gamma knife" and linear accelerators [LINAC]) it makes sense to apply a uniform terminology and the classic time course seems to describe all lesions, including those induced by the afore mentioned new RT methodologies. It is also noteworthy that the loose terms "early" and "late" (not to mention the hardly definable "delayed") may often refer to morphological changes which are already present in much earlier phases of lesions' development. "Delayed" radionecrosis cases have been reported within a markedly broad time-frame: from a few months to almost 20 years and it is now a basic statement that its development is strictly dose- and delivery dependent [30-32]. Their clinical evidence is highly dependent on the localization and size of the lesions and these parameters fundamentally changed with the new delivery techniques: we must face the evaluation (both by imaging or histology) of heretofore untreated brain regions with highly unusual forms and intensities of radiation [24, 25].

It is also well documented, both experimentally and clinically, that the transient lesions (acute and most of subacute lesions) are closely related to the disruption of the blood-brain barrier (BBB) with consequent albumin transfer and accumulation of vasogenic edema [11,14,17,18,24,25]. Traditionally the chronic lesions ("late delayed") are mostly irreversible, and they have a much higher risk of permanent neurological deterioration that often leads to the patients' death.

The salient features of chronic radiation injury include blood vessel damage and tissue necrosis. It has become obvious that the new delivery forms of highly focused radiation (stereotactic fractionated radiosurgery, LINAC, proton beam, intensity modulation radiotherapy) have the same effect on neoplastic tissues, although due to a fundamentally different dose distribution the time course of development of frank tissue necrosis has become much shorter [25]. This is probably the most important reason why

we suggest reversion to the standard terminology of systemic pathology.

It seems to be logical to assume that all these changes are related to acute, subacute and chronic changes and injuries of the elements comprising various-sized blood vessels. The most immediate responder is the endothelium and its early reaction can only be detected experimentally. It most likely is a continuous process which eventually results in ischemia/hypoxia and irreversible cellular/tissue death.

Endothelial cells (ECs) first become activated and appear as plump, "edematous", or simply thickened inner lining of blood vessels. Depending on the radiation dose, ultimately EC may undergo single *cell necrosis* or *apoptosis.* During both steps ECs and the perivascular elements are bound to discharge into the tissue numerous cytotoxic-vasoactive substances, such as tumor necrosis factor, interleukins, and various growth factors. Vascular endothelial growth factor released from EC may actually have a protective role and it is being tested as a new approach for the treatment of radionecrosis [33].

Mediators of inflammation, cytokines and growth factors released from EC may promote further vascular wall damage, intravascular coagulation and inflammation in the vessel wall and adjacent tissue. Pathologically one may recognize thrombosis, lumen obstruction, fibrinoid necrosis of the vessel wall. These changes may have multiple consequences: (**i**). Vascular obstruction results in coagulation and eventually colliquation necrosis with or without red blood cell extravasation (hemorrhage); (**ii**) Vascular damage leads to edema, inflammation plus the cytotoxic substance release causes oligodendroglial dropout (apoptosis) thus demyelination; (**iii**) The cellular damage activates microglia and astroglia thus phagocytosis ("gitter cells", siderophages, lipid laden phagocytic elements; (**iv**) Those cells that survive (suffer "*only*" sublethal damage) can multiply and result in vascular proliferation, glial cell abnormalities, pleomorphism (Fig. **1B**) and (fortunately rarely) tumorous transformation [17,18,24,25,28,29].

It is of outmost importance to emphasize that the complete battery of these morphological alterations does not necessarily present itself fully in biopsies. Several elements (e.g., various forms of inflammatory cellular insudation) are rapidly evolving and are only transient. In our own material we have witnessed the presence of T cells, PMLs (neutrophils) rarely eosinophils, particularly in areas adjacent to the most striking lesions, but these elements appear quite unexpectedly and very much depending on the sampling site [34]. When evaluating these phenomena one should remember that during surgical manipulation neutrophilic invasion is often present and is brought about by mechanical irritation of the tissue ("sterile, surgical inflammation") [35]. It is also often overlooked that within the same lesion signs of "cellular agony" ('degeneration') and signs of adaptive response or abortive repair may simultaneously be present (endothelial mitoses and vessel-wall 'hyalinization'). Finally it cannot be overemphasized that the exact timing, doses (fractionation) and all relevant clinical data are necessary for proper evaluation of such material. It is way over the aim of this review to analyze the interactions of various chemotherapeutics and RT and all possible morphological "delicatessen" that may result from concomitant therapeutic regimens, but in case the clinicians do not give all the data (in our practice that is sadly frequent an event) the morphological opinion might be totally false.

OVERVIEW OF THE RADIATION INDUCED, NON-NEOPLASTIC MORPHOLOGICAL CHANGES

Macroscopic Changes

Data on the *acute* alterations are almost impossible to collect due to the fact that these lesions practically are never

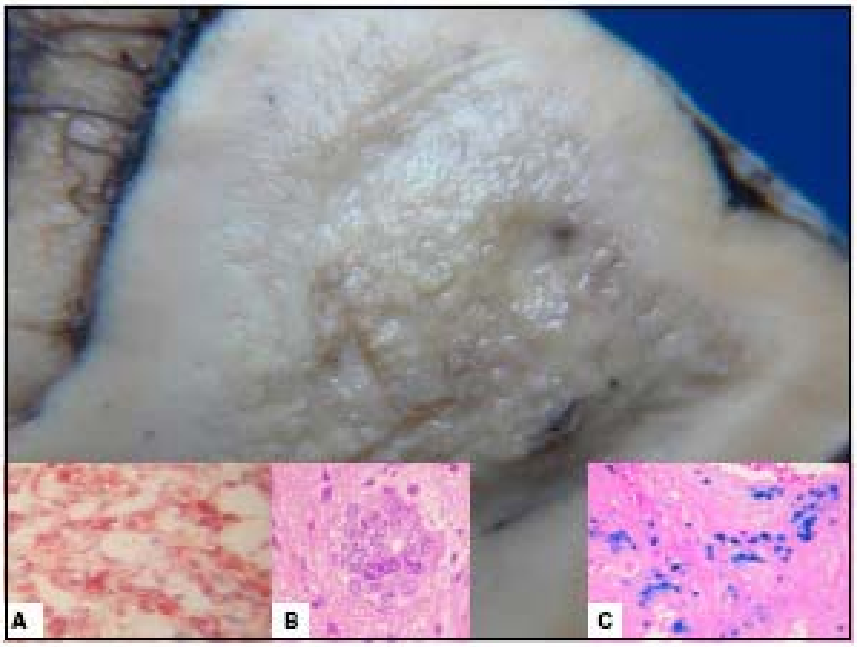

Fig. (1). Metastatic lesion treated by gamma-knife. Note cortical-subcortical necrosis without sharp demarcation. The tissue is rich in lipid-debris (**A**: Oil Red O), bizarre, multinucleated and vacuolated cells (**B**: HE) and focal deposition of hemosiderin (**C**: Prussian blue).

biopsied; in the *subacute* phase chances are that grossly no pathognomonic signs are present, although slight discoloration (grayish white homogeneous appearance of the white matter) and indistinct separation of the cortex and subcortical white matter may evolve. This change is a rather early event in cases treated with stereotactic radiosurgery (Fig. **1**). It is again fundamental to note that the appearance of the resected area will rapidly change as fixation takes place and most pathologists are not familiar with the gross features of fresh specimens. The *chronic* (frankly necrotic and partially "repaired") damage is often visible as an ill-defined, mostly soft, edematous area which may or may not be variegated by hemorrhagic discoloration (Fig. **1**). Consistency of the lesion(s) depends on the relative dominance of coagulation and gliosis, mesenchymal proliferation (hyalinization, "scar" formation). In cases of markedly focused, high energy radiation-induced chronic lesions (micro)cystic transformation may be present [18, 24].

Ever since the introduction of computerized tomography (CT) as an imaging tool it has been widely documented that radiotherapy may induce the development of large fluid filled, smooth-walled cavities, erroneously called cysts. These cavities are actually pseudocysts, since, strictly speaking, they do not have a pre-formed, anatomically defined capsule. Their walls are comprised of gliomesenchymal scar tissue with or without neoplastic elements [18, 36]. Whether or not tumor is still present at these sites is importantly affected by the intrinsic radiosensitivity of the tumor itself. Cerebellar neuroblastoma, primary lymphoma, pineal or suprasellar germinoma may be eradicated completely. The actual amount of mesenchymal elements is highly unpredictable and regionally very heterogeneous.

Microscopic Changes

Systematic data on the *acute* changes in the human brain are not available. When comparing *subacute* and *chronic* histological and/or cytological features it becomes evident that irrespectively of the time period that elapses between treatment and the sampling basically the same events take place and there is considerable overlap, moreover, mixing of morphological alterations depending on the location, dose, mode of RT, precise location and the presence or absence of residual, primary or metastatic neoplasm [18, 24, 36, 37]. Hence it seems to be advisable to keep some time frames, like up to 1 week (acute), between 8 days and 3 months (subacute) and after 3 months chronic lesions may be separated. The actual appearance, both radiographically and in terms of pathomorphology will be quite variable as determined by individual sensitivity (age, genetic background, idiosyncratic characteristics, effects of new therapeutic modalities, etc) and individual therapy (dosage, fractionation, combination of different modalities, etc).

It is because of the emphasis being laid on tailored therapy that the historical categories (i.e., *early delayed*, *late delayed*) need to be revised and at least attempts be made to unify and well define certain terminological criteria. Simultaneously with the realization how different individual malignant tumors can be within the same histopathologic category, and together with the intrinsic propensity of glial neoplasms to regional heterogeneity it is becoming more-and-more apparent that therapy that tries to comply with the tumor's individual molecular and biological make-up will induce similarly heterogeneous tissue response. Therefore it seems to be practical to list the changes in order of the tissue elements which are most commonly affected.

Endothelial cells (ECs) may become swollen, plump and sometimes vacuolated after RT. This may be present together with thinning, karyopyknosis, karyorrhexis. The latter often actually corresponds to apoptosis, which is much easier to detect with electron microscopy. The blood vessels, particularly small arteries and arterioles, often become thickened, homogeneous and increased eosinophilia of the

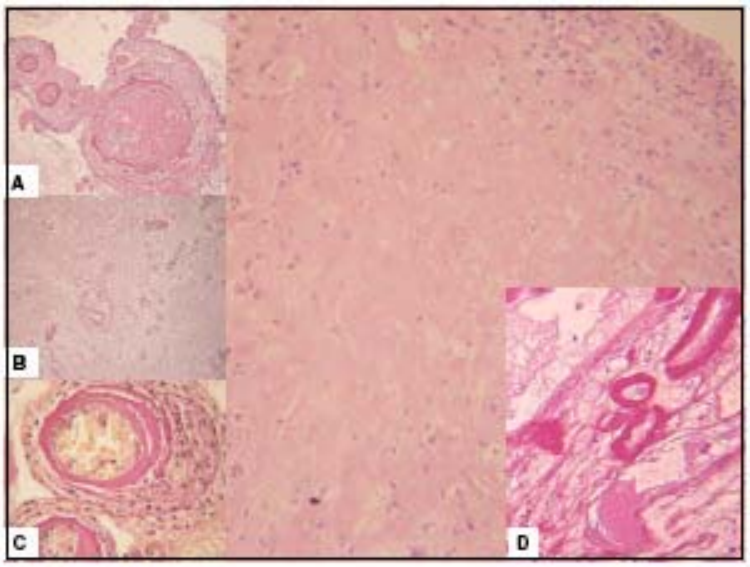

Fig. (2). The superficial necrotic area in the brain is bordered by inflammatory cells (Upper right hand corner). Chronic ("late delayed") radiation necrosis is typically accompanied by severe vascular changes. (**A**) Perivascular fibrosis and fibrin/platelet thrombosis. (**B**) Abortive vasocorona comprised of highly abnormal blood vessels. (**C**) Fibrinoid necrosis of the vessel wall with perivasculitis. (**D**) Fibrinoid necrosis, accumulation of collagen fibers and various degrees of thrombosis.

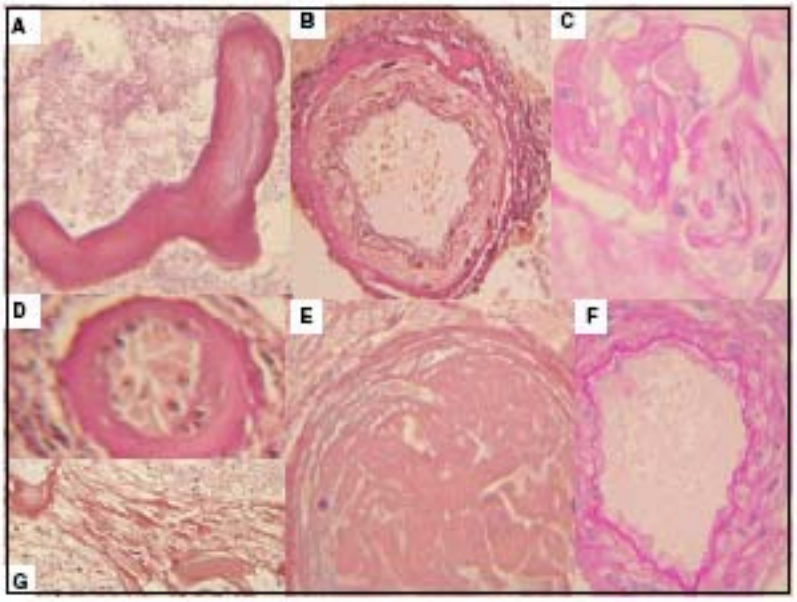

Fig. (3). Pathognomonic vascular changes in chronic ("late delayed") type radionecrosis. (**A**) fibrosis and fibrinoid insudation with complete obliteration (Trichrom). (**B**) Fibrin deposition in the adventitial layer with simultaneous multiplication of the internal elastic lamina (Elastic-vG). (**C**) Angiomatoid vascular proliferation (PAS). (**D**) Smudgy vascular contour and endothelial luminal obstruction (HE). (**E**) Thrombotic occlusion of an abnormal vascular channel (vG). (**F**) intense perivascular cellular reaction, most of these cells are macrophages (PAS). (**G**) Collagen deposition that extends into the neuropil.

wall may be accompanied by a proliferative reaction of perivascular cellular elements plus deposition of macrophages. Lipidization, evident in Oil-Red-O stained specimens (Fig. **1A**), perivascular mixed inflammatory infiltration and siderophages are not uncommon (Figs. **1-3)**. Immunohistochemical stains with antibodies to smooth muscle actin, laminin, collagen type IV and CD68 may be useful. Other classical histochemical stains, like elastica-van Gieson and Gömöri reticulin help to outline the perivascular changes.

Radiation induced changes may affect the tumor's intrinsic, newly formed vessels and brain vessels in the vicinity (BAT= brain adjacent-to-tumor) or even further away. Quite characteristically fibrinous insudation

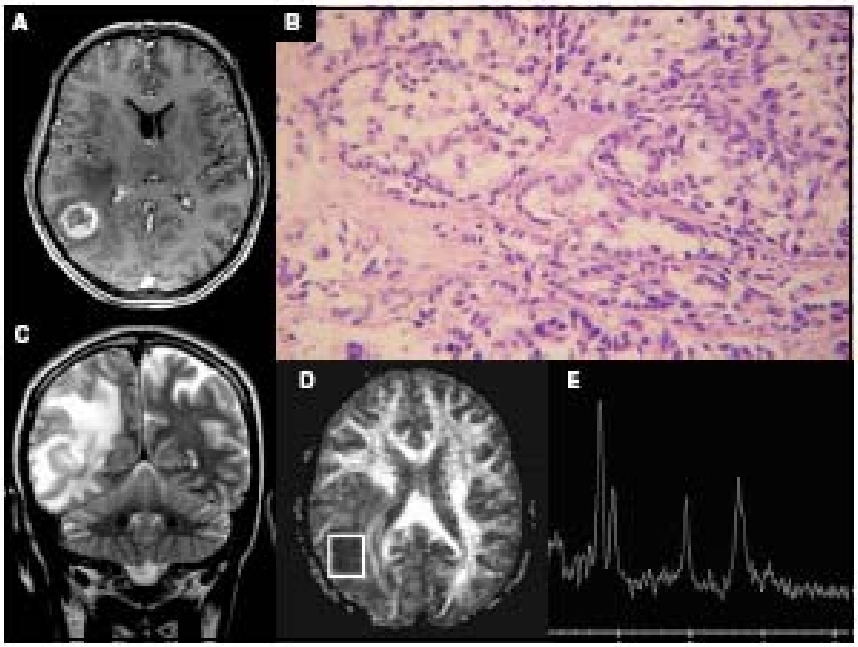

Fig. (4). Residual/recurrent metastatic cancer following gamma-knife treatment. T1 weighted MR image (**A**), T2 weighted MR image (**C**) and Fractional Anisotropy MR image (**D**) map of the recidive process. The conventional MR findings are highly reminiscent of chronic ("late delayed") radiation necrosis. The true nature of the lesion is portrayed by 1H-MRS spectroscopy. (**E**) The elevated cholin peak indicates increased membrane metabolism and hence neoplastic cells. This was eventually validated by histology (**B**).

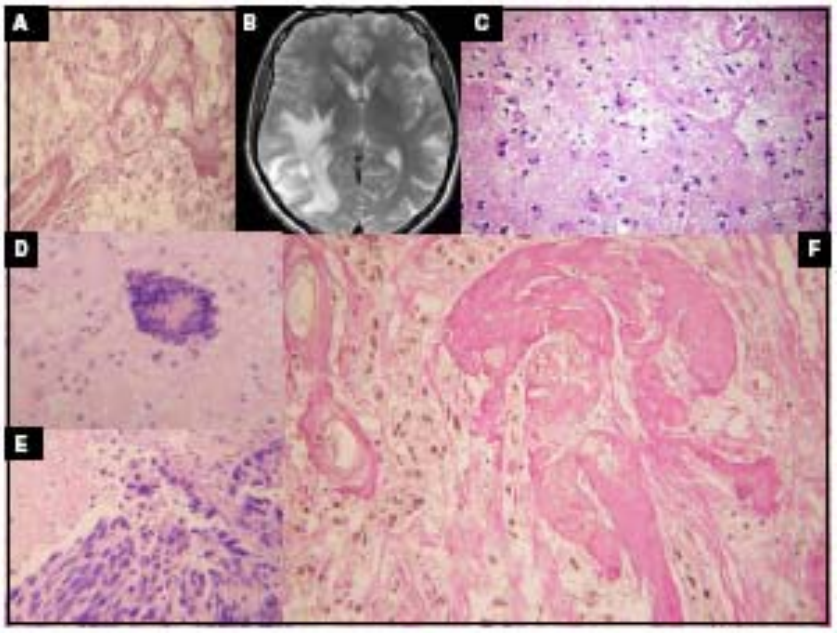

Fig. (5). (**A**) Fibrillary perivascular transformation within a necrotic area (Trichrom). (**B**) T2 weighted MR image that indicated chronic ("late delayed") radionecrosis. (**C**) Radionecrosis in the periphery of the lesion (HE). (**D**) Bizarre giant cell in the vicinity of radionecrosis (HE). (**E**) rather viable residual/recurrent metastatic cancer [the primary was in the lung (HE)]. (**F**) chronic ("late delayed") type radionecrosis that validates part of the original MR diagnosis. There is vascular proliferation with simultaneous fibrosis/necrosis/thrombosis (Elastic-van Gieson).

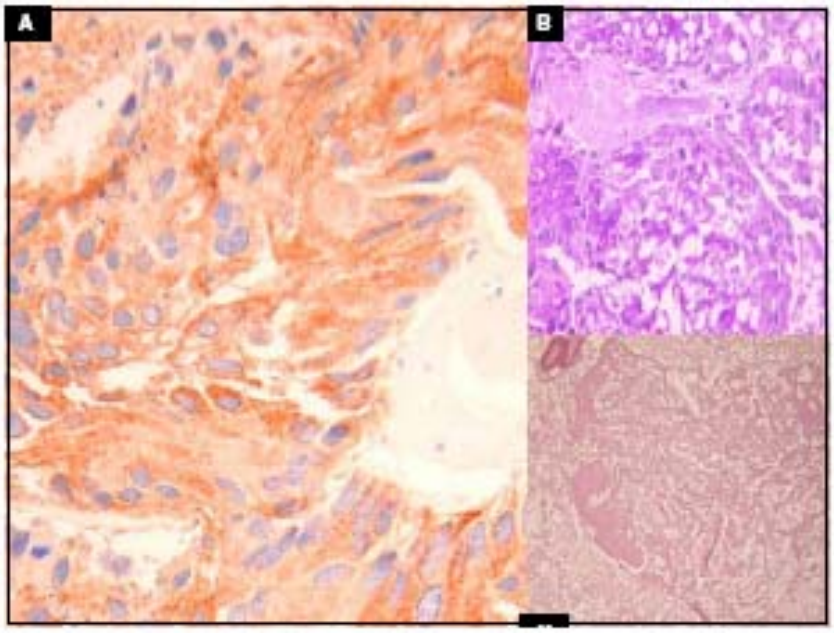

Fig. (6). Residual/recidive metastatic pulmonary mucinous adenocarcinoma after gamma-knife treatment. (**A**) Immunohistochemistry, strong CK7 decoration. (**B**) PAS after digestion shows mucin within the tumor cells. (**C**) Parts of the tumor had been successfully treated, i.e., extensive tumor necrosis (Trichrom).

("fibrinoid necrosis") of the vessel walls occurs but fibrin is often deposited in the extracellular space (neuropil) as well (Figs. **2-7**). Endothelial proliferation may obliterate the lumen that results in ischemic necrosis, which is also a common consequence of the frequently evolving thrombi in the diseased blood vessels. Immunohistochemistry with the antibodies to CD34 and CD31 will highlight the proliferating endothelium. It is also strikingly decorated by antibodies to nestin which in our practice sometimes proves to be more sensitive in these altered specimens than CD34.

Changes affecting the neuropil are common after radiation treatment. In conventional RT cases demyelination may be present relatively far from the actual targeted area (this again will be dependent of the site of actual sampling). Gamma knife treatment is a much more focused irradiation that more likely produces coagulative necrosis of all tissue

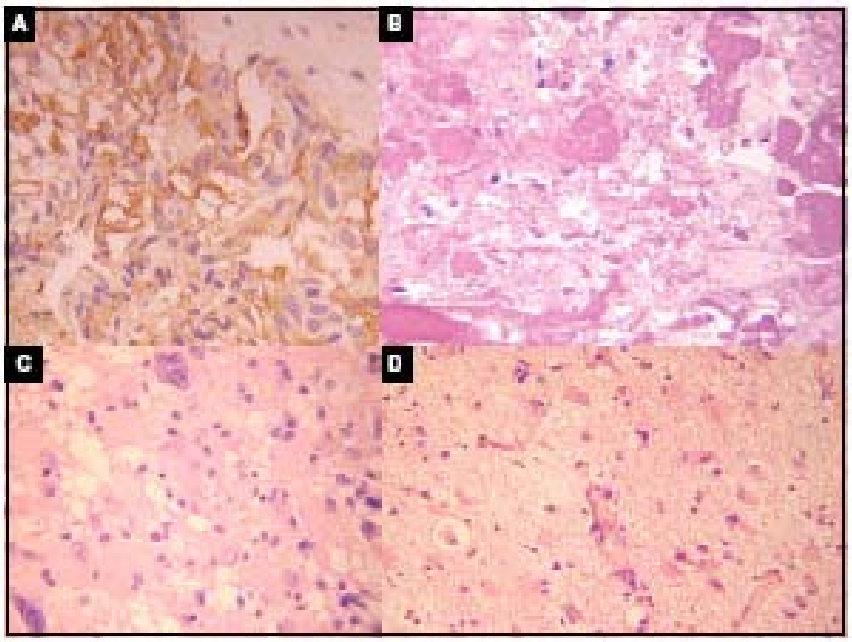

Fig. (7). Recurrent (residual) metastatic cancer within the area of gamma-knife treatment. (**A**) Immunohistochemistry with EMA polyclonal antibody decorates tumor cells. (**B**) There is extensive vascular proliferation, although most lumina are obliterated by thrombi (HE). (**C**) There is considerable pleomorphism within the adjacent brain that may easily be mistaken for astrocytic neoplasm (HE). (**D**) Further towards the periphery of the lesion astrocytic reaction becomes less bizarre and gemistocytic figures tend to dominate (HE).

components. In our series of metastatic tumors we often encountered lakes of fibrin and necrotic debris without residual carcinoma (Fig. **6C**). These changes were accompanied by severe edema and not infrequently the radiological image mimicked recurrent tumor that could not be confirmed histologically. The common appearance of brain tissue after radiation is vacuolated, early on paucicellular tissue with some myelin breakdown and sparing of axons. Special stains (Klüver-Barrera) and IHC may help in precise categorization. Eventually various degrees of reactive astrogliosis follow that may culminate in cavitation and dense fibrillary gliosis. It is very important to keep in mind that reactive glial elements may become very pleomorphic with marked anisonucleosis, and hyperchromasia (Fig. **7C**, **D**).

Changes which affect tumor proper are determined by the size of the neoplastic focus, type of the tumor and the time lag between treatment and sampling. Those changes described above for brain or BAT are common in tumors as well. The common therapeutic interventions may induce striking tumor cell apoptosis or necrosis. The distinction of apoptosis from necrosis may necessitate additional studies and is only of academic interest, and limited clinical significance.

Repeated biopsies pose the problem of differentiating reactive astrocytes from residual or recurrent glial tumor cells and of particular significance is the determination of possible biological progression (i.e., increase in grades) of the original glial neoplasm. Obviously Ki-67 antigen demonstration (Mib-1 antibody) is of little help since both processes involve cells that are not in the G0 phase of the cell cycle. It is rather common to observe a bizarre change of the immunophenotype of metastatic cancerous cells as a result of combined and repeated therapy.

Due to the unusual changes which are brought about by RT and in particular by combined RT and chemotherapy differentiation of reactive changes from residual or recurrent tumor might pose a rather difficult, often even frustrating challenge for the pathologist [18,24,25,36,37]. Recent advances in imaging techniques have considerably helped in solving this problem [38-40] although even acute hemorrhage may complicate the situation in cases of chronic radiation injury [41]. In accordance with reported data in our experience MR spectroscopy often proved to be a highly reliable tool in solving this dilemma (Figs. **4**, **5**) [32-34]. Our initial experiences with diffusion weighted MR imaging are promising similarly to data recently reported [34, 40, 42].

Interstitial changes may include deposition of calcospherites that may look like psammoma bodies but calcification and ferrugination may also involve blood vessels as well. These sometimes affect the targeted area and may also be brought about in more distant foci.

It is rare that patients who had been treated for malignant glioma live long enough to undergo extensive white matter damage and due to white matter loss the evolution of hydrocephalus [18, 25, 36]. These have been described in cases of radiation therapy of head and neck cancer, carcinoma of the larynx or radiation therapy of sellar tumors. There are reports on cortical consequences of delayed radiation therapy-related changes, like bizarre, bilobated ganglion cells and pseudolaminar necrosis, but we have not encountered such cases. The cortical changes, which occurred in gamma knife treated tumors that eventually were biopsied or when the areas became possible to analyze following autopsy, included neuronal pyknosis, “red neurons”, chromatolysis, and other minor nonspecific, secondary, regressive morphological alterations.

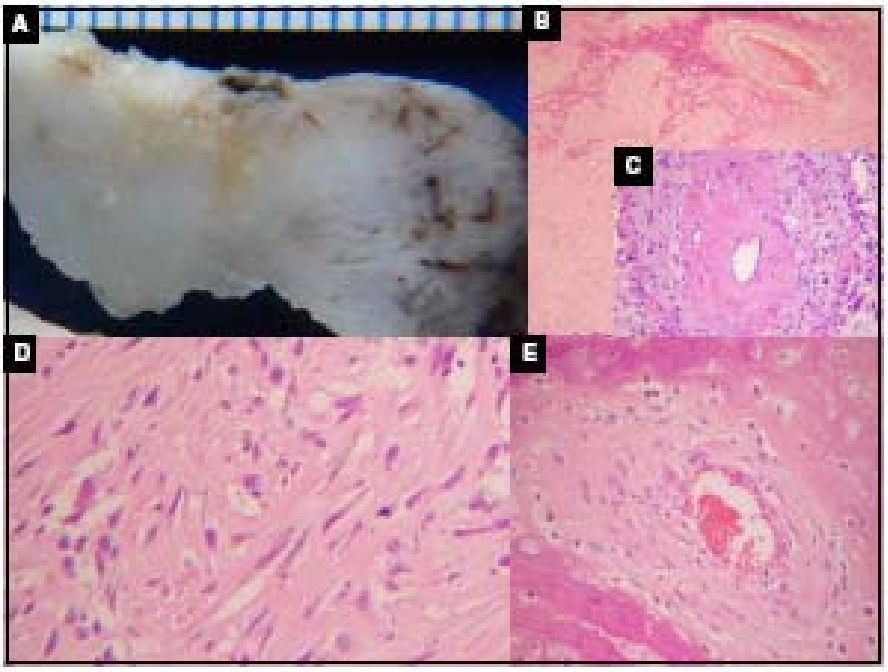

Fig. (8). Whole brain radiation therapy for a Gr. III. oligoastrocytic tumor. Five years later the tumor recurred and proved to be a radiation-induced sarcoma with neoplastic osteoid. (**A**) gross picture of the specimen from the 2nd operation; firm, homogeneous tissue with focal necroses. (**B**) Lattice of neoplastic osteoid that is laid down around blood vessels (HE). (**C**) Radiation damage of the vessel wall that also shows osteoid-like areas (HE). (**D**) sarcomatous change in the vicinity of osteoid (HE). NB. Most of the spindle cells stained positively with smooth muscle actin antibody. (**E**) Higher magnification of the pleomorphic perivascular elements with gradual transformation into osteoid (HE).

NEOPLASTIC SEQUELAE OF RT: SECONDARY TUMORS

DNA damage is one of the crucial sequelae of radiation treatment and may induce activation of cell cycle checkpoints to pause cell division (thus providing time for DNA repair). Alternatively it may activate DNA repair pathways, and if the latter fail apoptosis often ensues that eliminates damaged cells. The ultimate purpose of these responses is the preservation of genetic integrity. Passage through subsequent generations of genetic abnormalities is a key element in tumor evolution and obviously is important in the development of chemo/radio-resistance. For this to happen, however, a cell with damaged DNA has to survive and reproduce.

Those cells – regardless of their exact location, i.e., intra- or extracranially – that survive radiation damage and can even multiply are considered to be responsible for the evolution of secondary malignancies following RT of a primary tumor. These in our practice can be classified as radiation induced meningiomas, radiation induced secondary gliomas, radiation induced sarcomas and gliosarcoma induced by radiation within the area of earlier diagnosed low grade glioma. In addition to "conventional" gliosarcoma we also have seen a case in which the sarcomatous component obviously originated from perivascular elements and in addition to a fibrosarcoma like fusiform cellular component also produced "malignant" osteoid, hence could be classified as radiation induced osteosarcoma (Fig. **8**). It is worth noting at the start that focused radiotherapy (i.e., gamma knife treatment) is considered of less importance in this respect. All our cases occurred after application of traditional – often repeated – radiotherapy. Recently we encountered a radiation induced meningeal sarcoma, sarcomatous change within a glioblastoma and an malignant peripheral nerve sheath tumor affecting the small nerve roots located in the vicinity of the lamina cribrosa.

Although RT induced sarcomata have been amply documented [24, 26], these changes are important because their potential to evolve must be kept in mind particularly during evaluation of repeated biopsies. It is a rather wise rule of thumb that comparison of previous biopsies should be a routine part of evaluation of the second or third, etc. specimens. It is rather common that a comparative analysis brings about clinically important details both retrospectively and prospectively *vis-á-vis* grading, prognosis, personalized (tailored) chemotherapy and combined therapeutic modalities.

CONCLUSIONS

1. It seems to be more practical to use the standard pathology terminology when classifying therapy induced histopathological changes, including those which typify RT. Acute, subacute and chronic lesions are less confusing particularly if there was a general agreement on the associated time-frames.
2. Vascular changes (damage) are the leading pathogenetic alterations and these may take a highly unpredictable form in any phase, mostly depending on the actual form (energy, focus, source, and format) of radiation. Depending on the dominance of proliferative and/or regressive changes (endothelial activation, mitoses, multilayering *vs* apoptosis,

necrosis, thinning) tissue necrosis will follow which always starts as coagulation but may eventually liquefy. Proliferation may often result in angioma-like neovascularization that needs to be differentiated from residual vessels of glioblastoma multiforme.

3. The use of state-of-the-art imaging, particularly MR spectroscopy may be of fundamental help in differentiating residual/recurrent tumor from reactive tissue.

4. Additional studies based on prospective tissue analysis is an absolute must in order to fully understand the possibly adverse effects of new treatment modalities on the brain.

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ABBREVIATIONS

BAT = Brain adjacent-to-tumor

CNS = Central nervous system

CT = Computerized tomography

EC = Endothelial cell

IHC = Immunohistochemistry

LINAC = Linear accelerators

MR = Magnetic resonance

RT = Radiotherapy

WHO = World Health Organization

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