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RESEARCH ARTICLE

CEREBRAL RADIONECROSIS IN PATIENTS IRRADIATED FOR CAVUM CANCER: RETROSPECTIVE STUDY OF 15 CASES

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Abstract

Introduction: Cerebral radionecrosis is a rare but a serious complication induced by radiotherapy of the nasopharyngeal cancer. Since nasopharyngeal cancer is common to have skull base infiltration, radiation fields cover inevitably the temporal lobes despite the use of the more advanced intensity-modulated radiotherapy (IMRT). Even though the development of imaging means and the systematic practice of CT and MRI in post-therapeutic monitoring, the diagnosis and treatment of cerebral remain challenging.

Materiel and Method:A retrospective study including fifteen cases of cerebral radionecrosis occurring after radiotherapy of cavum cancer, based on data from 382 irradiated for cavum cancer during the period from January 2017 to January 2022 and who were regularly followed in post-therapeutic monitoring.

Results: The incidence of cerebral radionecrosis in our patients was 3,9%. The average age of patients was 47.5 years (range 28 - 62 years), with a female predominance (sex ratio: 4M/11F = 0.36). All our patients were followed for locally advanced UCNT of the cavum (73% stage IVA and 27 % stage III). 80% of cases have benefited from conformal radiotherapy technique by intensity modulation (VMAT archtherapy). And all cases have had concomitant chemotherapy. Cerebral radionecrosis occurred after an average delay of 31.6 months (11-77 months) from the end of irradiation. The location of the cerebral radionecrosis lesions was temporal in all our patients. Exploring dosimetric data of our patients, we noted that in 58% of cases the dose constraint at the level of the temporal lobe affected by radionecrosis was not respected. Cerebral radionecrosis was initially discovered on MRI of the cavum, a brain MRI was subsequently requested to show areas of cerebral radionecrosis. Spectroscopy was carried out in 33% of patients. Cerebral radionecrosis was treated with corticosteroid therapy in 53% of cases. After a mean follow-up of 19.8 months (2-63 months) the evolution of cerebral radionecrosis in patients irradiated fornasopharyngeal cancer, was marked by radiological stability without the appearance of clinical symptoms in 53% of cases.

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Conclusion: Cerebral radionecrosis of radiation-treated cavum patients could be a devastating complication. Furthermore, the differential diagnosis remains challenging and may require the use of advanced imaging modalities. The intricate relationship between dose parameters and radionecrosis incidence requires large-scale longitudinal studies. Despite the fact that there is no definitive treatment for cerebral radionecrosis, bevacizumab has proven to be an encouraging treatment option.

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Introduction:

Cerebral radionecrosis is a relatively rare but serious iatrogenic complication in patients treated with radiotherapy for cavum cancers, given the diagnostic and therapeutic difficulties posed to radiotherapists. It can jeopardize the functional and vital prognosis of the patient. Its diagnosis has benefited from the development of imaging means and the systematic practice of CT and MRI in post-therapeutic monitoring.

The first case of cerebral radionecrosis occurring after irradiation for intracranial neoplasia was described by Fischer and Holfelder in 1930 [1]. The treatment of cavum cancer, particularly common in our North African context, is essentially based on radiotherapy which provides local control rates. However, radiotherapy of the ENT (ears, nose, throat)sphere, particularly that of the nasopharynx, is not devoid of morbidity and complications which can develop following damage to neighboring structures.

The radiation field inevitably covers the middle and lower region of the temporal lobes of the brain, and the base of the skull due to their proximity to the nasopharynx. In addition, the radiation dose is usually 65 to 70 Gy, which can sometimes exceed the tolerance of brain tissue [2].

Through this retrospective study carried out on patients diagnosed with cerebral radionecrosis during post-therapeutic monitoring of irradiated nasopharyngeal cancer, we report the clinical, radiological, therapeutic and evolving aspects of this complication, by comparing our data with advances in the literature.

Material and Method:

We carried out a retrospective study in the radiotherapy and the radiology departments of the national institute of oncology Sidi Mohamed Ben Abdellah in Morocco. Were included in our study, all patients followed for nasopharyngeal carcinoma authenticated histologically and treated during a period spread from January 2017 to December 2022 in the radiotherapy department and who were in quarterly post-therapeutic monitoring. All cases where medical records could not be used, patients who did not benefit from radiotherapy and patients lost to follow-up were excluded from our study.

The search for data concerning the occurrence of radionecrosis after irradiation of nasopharyngeal cancer was established from the ENOVA database by retrospective analysis of post-therapeutic control consultations providing information on late side effects of radiotherapy, namely cerebral radionecrosis, as well as from the database of the the department of radiology by searching the reports of radiological examinations of patients treated for cavum cancer for the diagnosis of cerebral radionecrosis by entering the key words: cavum MRI, brain MRI and cerebral radionecrosis.

Among the 382 patient files treated for nasopharyngeal cancer during the period of our study, we were able to retain 15 patients who presented with cerebral radionecrosis.

The clinical, paraclinicaland epidemiological data of these patients were entered on an Excel data sheet. The statistical analysis was carried out using SPSS software.

Results:

Cerebral radionecrosis was found in 15 patients among the 382 patients irradiated for nasopharyngeal cancer in the radiotherapy department at the National Institute of Oncology during the study period, an incidence of 3.9%. The

average age of patients who presented with cerebral radionecrosis was 47.5 years (range 28 - 62 years), with a female predominance (sex ratio: 4M/11F = 0.36). 93% of patients had no notable history; a history of poorly controlled diabetes was found in only one patient.

All our patients were treated for undifferentiated carcinoma of the cavum UCNT of the cavum proven histologically and classified according to the 8th TNM edition classification of 2017. All our patients were diagnosed with a locally advanced disease (73% stage IVA and 27 % stage III).

The treatment of cavum cancer consisted of external radiotherapy on the cavum and the cervical lymph node areas, delivered by a linear accelerator either by 3D conformational technique in 3 patients treated in 2017 or by intensity modulation radiotherapy technique (VMAT archtherapy) in 80% of cases. The total dose was either 70 GY with a classic fractionation of 2GY/FR or 69.96 GY (2.12GY/FR) in a hypofractionated protocol with the integrated boost. In all cases our patients benefited from chemotherapy concomitant with radiotherapy based on cisplatin at a dose of 40 mg/m2 weekly.

In 73.3% this concomitant radiochemotherapy protocol was preceded by induction chemotherapy based on cisplatin + adriamycin (3 courses).

Cerebral radionecrosis occurred after an average delay of 31.6 months (11 – 77 months) from the end of irradiation; its discovery was fortuitous (asymptomatic patients) on post-therapeutic control radiological examinations (MRI of the cavum) in 60% of cases. The most common symptom found in our symptomatic patients was headaches in 40% of cases. A severe deterioration of the neurological state was found in only one patient.

Fig 1: Characteristics of patients suffering from cerebral radionecrosis after radiotherapy of nasopharyngeal carcinoma

Patients	Age	TNM	Total radiotherapy dose (Gy)	Dose /fraction	End of RTH delay/Symptoms (Month)	Symptom	Seat
1	60	T3N1MO	70 GY	2GY/FR	14 MONTHS	0	BILATERAL TEMPORAL
2	50	T4N2M0	69.96 GY	2.12 GY/FR	22 MONTHS	0	BILATERAL TEMPORAL
3	58	T4N0MO	70 GY	2 GY/FR	40 MONTHS	STRABISMUS + HEADACHE	RIGHT TEMPORAL AND PONTIC
4	51	T4N3M0	69.96 GY	2.12 GY/FR	54 MONTHS	0	LEFT TEMPORAL
5	31	T4N2M0	69.96 GY	2.12 GY/FR	30 MONTHS	0	RIGHT TEMPORAL
6	28	T3N1MO	69.96 GY	2.12 GY/FR	36 MONTHS	0	RIGHT TEMPORAL
7	47	T4N3M0	70 GY	2 GY/FR	77 MONTHS	0	BILATERAL TEMPORAL
8	61	T4N1M0	69.96 GY	2.12 GY/FR	36 MONTHS	HEADACHE + TINNINESS	RIGHT TEMPORAL
9	62	T3N1MO	70 GY	2 GY/FR	28 MONTHS	0	BILATERAL TEMPORALS
10	33	T4N0M0	69.96 GY	2.12 GY/FR	26 MONTHS	HEADACHES	RIGHT TEMPORAL
11	40	T4N2M0	69.96 GY	2.12 GY/FR	11 MONTHS	STRABISMUS + HEADACHE	LEFT TEMPORAL
12	60	T4N2M0	69.96 GY	2.12 GY/FR	24 MONTHS	HEADACHES	BILATERAL TEMPORAL PARIETO
13	42	T1N2M0	69.96 GY	2.12 GY/FR	14 MONTHS	0	LEFT TEMPORAL
14	46	T4N1M0	69.96 GY	2.12 GY/FR	36 MONTHS	HEADQUARTERS + PARAPERESIA OF THE LEFT MS AND MIDDLE + DIZZINESS	TEMPORAL ANT LEFT
15	44	T4N2M0	69.96 GY	2.12 GY/FR	26 MONTHS	0	TEMPORO POLAR SUP LEFT

National Institute of Oncology, Rabat

Cerebral radionecrosis was initially discovered on MRI of the cavum in all our patients, a brain MRI was subsequently requested to show areas of cerebral radionecrosis characterized by T2 hypersignal, without translation on the diffusion sequence and surrounded by perilesional edema of varying importance (in 80% of cases), the diagnosis was uncertain in 20% of cases, raising the problem of differentiation between cerebral radionecrosis and brain metastasis or progression of the lesion.

The location of the cerebral radionecrosis lesions was temporal in all our patients, specifically in the right temporal lobe in one third of cases, left in one third and bilaterally in the other third of patients. Given the temporal location of radionecrosis, we retrospectively explored the dosimetries of our patients, particularly the dose-volume

histograms, to see if the dose constraint during irradiation of the cavum was respected at the level of the temporal lobes that were subsequently affected by radionecrosis. Note that to validate the radiotherapy treatment plan, the target tumor volume must be covered optimally, which can explain the tolerance of certain dose excesses at the level of the organs at risk according to their priority, particularly if the tumor is large with extension to adjacent organs.

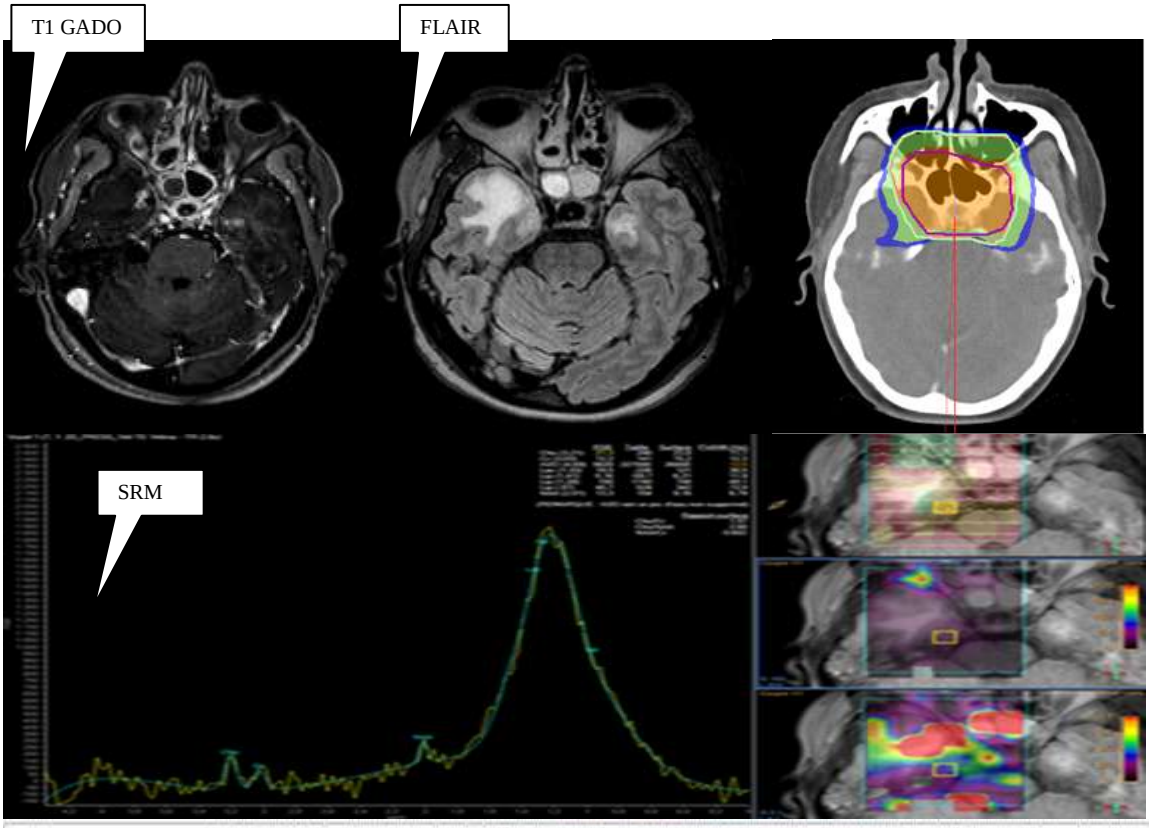
In our patients, we noted that in 58% of cases the dose constraint at the level of the temporal lobe affected by radionecrosis was not respected (theoretically the nearmax dose = D2% should not exceed 70 GY, and the dose received per 0.03 cc of the volume must not exceed 72GY). The nearmax dose was between 70 and 75GY in 52% of patients and the dose received per 0.03cc of the temporal lobe volume was between 72 and 76GY in 66 of the cases.

In addition to temporal localization, pontine lesions and parietal lesions were described in 2 patients.

Additional spectroscopy was carried out in 33% of patients; the appearance was in favor of a fall in N-acetylaspartate (NAA), choline with peak in lipids and lactates, suggesting encephalic radionecrosis in 26%. Spectroscopy made it possible to correct the diagnosis of cerebral radionecrosis in secondary location in a patient in whom doubt about the nature of the brain lesion on brain MRI had previously been raised (peak of NAA and choline).

Cerebral radionecrosis was treated with corticosteroid therapy in 53% of cases, while no treatment was prescribed in the rest of the patients whose lesions were small and asymptomatic. Bevacizumab was proposed to a patient whose radionocrosis lesions were significant in the temporal and pontine region and responsible for hydrocephalus and falcorial involvement, but given the rapid deterioration of the neurological and general condition (Glascow Score GCS=7) of this patient this treatment could not be initiated.

The evolution of cerebral radionecrosis in patients irradiated for nasopharyngeal cancer, with a mean follow-up after the occurrence of the complication of 19.8 months (2-63 months), was marked by radiological stability without the appearance of clinical symptoms in 53 % of cases, radiological regression was noted in 13% of patients while clinical and radiological worsening leading to death was described in only one patient.



Structure	Volume [cm³]	Min. Dose [Gy]	Max. Dose [Gy]	Mean Dose [Gy]	Cold Ref. [Gy]	Volume < [cm³]	Volume < [%]	Hot Ref. [Gy]	Volume > [cm³]	Volume > [%]	% in Volume	Is in SS	Heterogeneity Index	Conformity Index
PTV HR	255.960	48.577	79.636	71.157				**66.460**	242.441	94.72	100.00	yes	1.12	0.75
PTV JR	695.976	38.702	79.636	65.285				56.430	**683.814**	**98.25**	100.00	yes	1.27	0.84
PTV LR	843.366	34.786	79.636	63.921				**51.300**	841.516	99.78	100.00	yes	1.31	0.83
ME	22.161	1.424	40.925	25.625				26.575	**0.030**	**0.14**	100.00	yes	16.87	
TC	28.604	13.045	57.824	35.998				**54.050**	0.030	0.11	100.00	yes	2.00	0.00
CHIASMA	0.762	34.329	61.071	46.821				**58.685**	0.030	3.94	100.00	yes	1.62	0.00
NO GH	0.795	18.023	58.434	42.267				54.825	**0.030**	**3.77**	100.00	yes	2.33	0.00
NO DT	0.906	22.515	59.154	45.309				56.495	**0.030**	**3.31**	100.00	yes	1.81	0.00
PAROTIDE DTE	20.028	11.553	72.073	36.039				31.736	**10.014**	**50.00**	100.00	yes	3.47	0.00
PAROTIDE GH	20.826	14.473	71.903	34.598				**32.188**	10.413	50.00	100.00	yes	3.08	0.00
CAVITE BUCCALE	63.840	25.092	74.846	42.983				40.860	**1.000**	**1.57**	100.00	yes	2.21	0.01
MANDIBULE	69.489	17.211	68.598	35.683				36.603	**1.000**	**1.44**	100.00	yes	2.20	0.00
LARYNX	11.419	23.258	71.021	38.467				45.000	**3.205**	**27.58**	100.00	yes	2.31	0.00
LEVIS+JMH	3.306	3.161	12.437	6.225				**10.809**	0.026	0.77	100.00	yes	2.41	0.00
patient	19683.633	0.018	79.636	10.661							99.69	no	363.34	0.00
LT DT	97.089	1.322	76.956	19.218				**67.526**	1.942	2.00	100.00	yes	24.24	
LT GH	103.257	1.210	76.315	17.194				**64.225**	2.065	2.00	100.00	yes	23.29	

Fig.2: 48 years old female with no neurological symptoms following x round of radiotherapy. End of treatment MRI showed few areas of enhancement surrounding the posterior side of the right sphenoid wing bilaterally with edema on FLAIR. SMR demonstrated an exceptionally high lipid peak (red arrow).

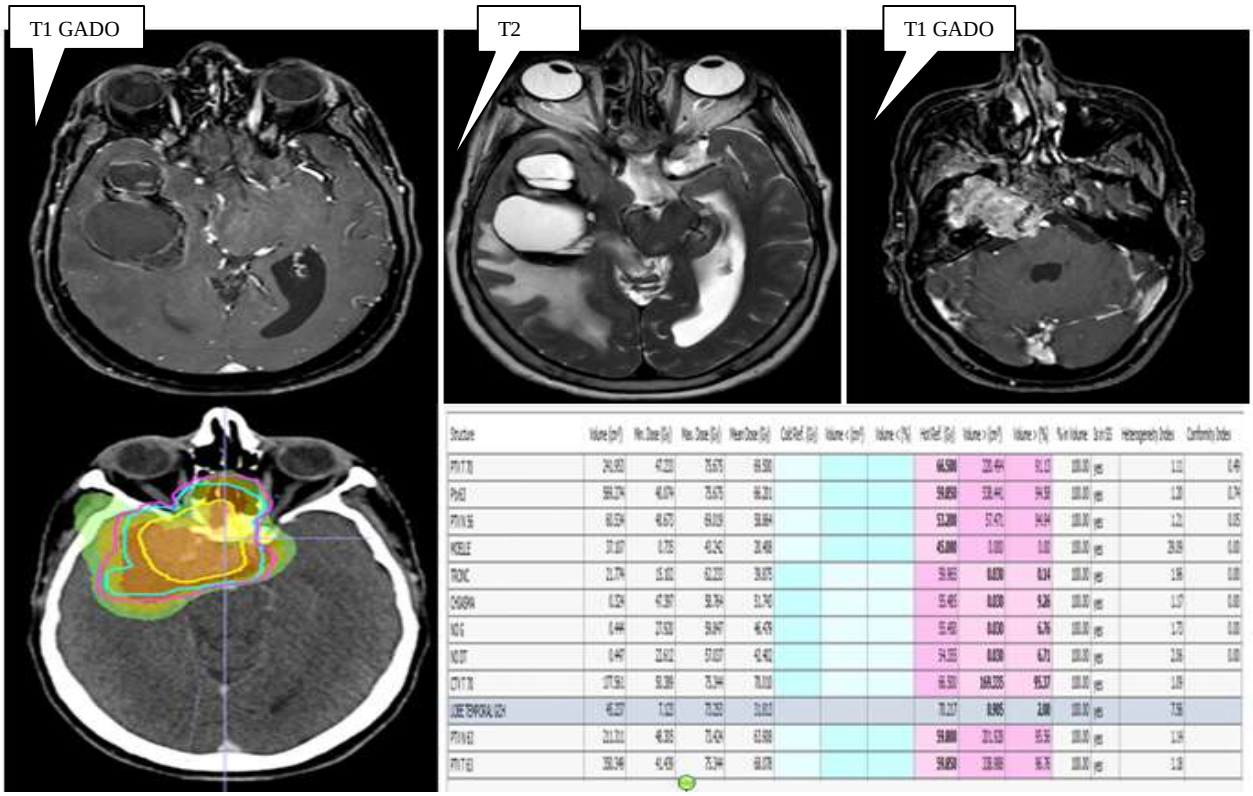


Fig.3: 50 y.o women under radiotherapy collapsed during her treatment session. MRI showed multiple cystic temporal lesion containing a liquid-liquid level , with a thin enhanced margin responsible of a temporal engagement (asterixis). The initial tumor invaded the ipsilateral side of the sphenoidal bone consequently increasing the radiation area on the brain parenchyma on the same side .

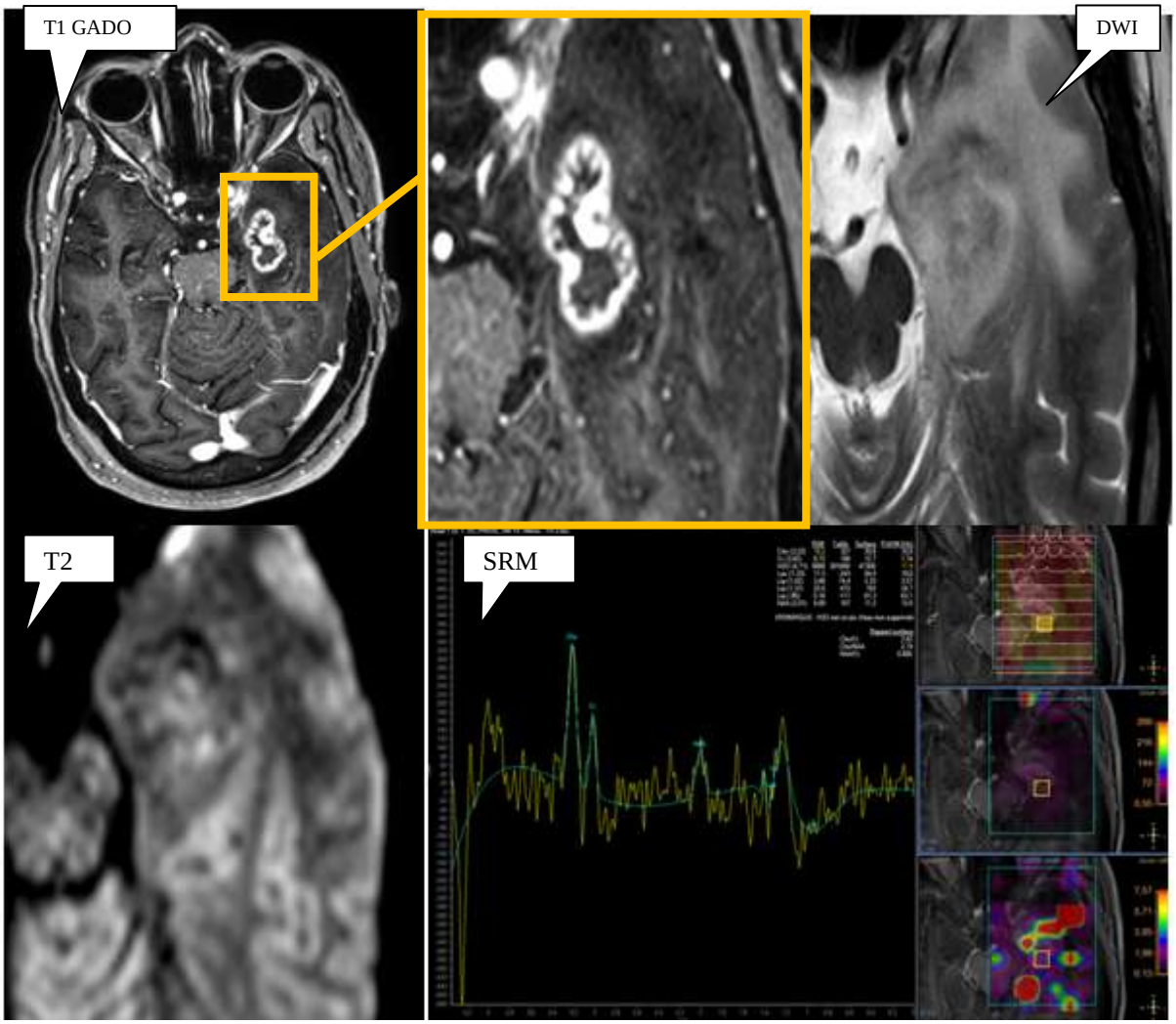


Fig.4: 38 years old man finished radiation for his NPC, a year after he presented intense headache with several episode of convulsions . MRI showed a temporal lesion with peripheral enhancement with a slight internal restriction on DWI sequence and peripheral edema on T2. SRM is showed a inversion of the Cho/NAA ratio and a slight increase of lip

Discussion:

Radiotherapy is a very effective treatment in the management of nasopharyngeal tumors. However, focal cerebral radionecrosis is a potentially disabling late complication of external radiotherapy. Its incidence, probably underestimated, varies depending on the series from 0.95 to 14% [1-3], in our serie the incidence was 3.9% with a female predominance.

In the literature, some factors were involved in the risk of developing cerebral radionecrosis such as the total dose, the duration of irradiation and especially the dose per fraction [4-7], with a major protective role of fractionated regimens [3,10]. Lee et al. [10], demonstrated in 1008 patients then in 1032 patients [3], treated with irradiation for nasopharyngeal carcinoma, that conventional fractionation (2 Gy per fraction) could lead to a risk of necrosis of 5% at ten years. The brain is also more sensitive to the hyper-fractionated-accelerated pattern with a higher incidence of temporal necrosis, which demonstrates the preponderant role of fractionation in the occurrence of cerebral

radionecrosis. Our patients were treated by radiotherapy with external irradiation focused on the cavum and cervical lymph node areas. The total irradiation dose was 70 Gy and the fractionation plan was classic in 26% of patients (five fractions of 2 Gy per week) and hypofractionated by VMAT integrated boost technique in 73% of cases (five fractions of 2. 12 Gy per week).

Even though IMRT could effectively reduce the incidence of cerebral radionecrosis in T1 – T3 patients, the incidence of this complication in T4 patients is still significant and consequently requires regular follow-up. For patients treated with IMRT, the incidence of temporal lobe radionerosis was ranged from 4.6 to 8.5% [16-18].

Other risk factors have been studied such as age with a higher risk in children and the elderly, the presence of vascular comorbidities such as high blood pressure or diabetes as well as the volume of irradiated brain parenchyma [5]. Concomitant platinum-based chemotherapy also seems to increase the risk of cerebral radionecrosis but this has not been formally demonstrated [5,7,14].

In our patients, there were no cardiovascular comorbidities, a history of diabetes was found in only one case, neoadjuvant chemotherapy based on Adriamycin and cisplatin was given to the majority of our cases. as well as concomitant chemotherapy with radiotherapy based on platinum salts 40 mg/m2 weekly in all patients in our series.

Cerebral radionecrosis can occur after a period ranging from six months to 24 years. However, 90% of lesions become symptomatic within five years following irradiation [4, 6], which is consistent with our study which found an average time to discovery of radionecrosis of 31.6 months. The presence of a clinical latency period is explained by the capacity of the brain parenchyma to tolerate chronic alterations without raising intracranial pressure [17].

The clinical symptoms of cerebral radionecrosis are variable, and the presentation can range from headaches to major cognitive disorders. It was demonstrated in a study carried out in patients irradiated for cavum cancer that the severity of cognitive disorders is significantly associated with the volume of radionecrosis, the type of symptoms also depends on the site of the brain lesion [18]. Thus the site most frequently affected by this complication being the temporal lobe is associated with language, memory and behavior disorders. Temporal localization was also described in all patients in our study.

Regarding radiological diagnosis, differentiating between radiological necrosis (RN) and a tumor can pose challenges. Conventional MRI is very sensitive and generally suggests a diagnosis via a T1/T2 mismatch (hyposignal on T1 and hypersignal on T2 with heterogeneous and nodular contrast enhancement). This discrepancy indicates that the majority of the mass observed on T2 represents necrotic tissue, contrasting with the enhanced T1 sequences where the active tumor area is highlighted. Of note, brain metastases from nasopharyngeal cancers are rare and usually lack necrotic features. [19] Additionally, advanced MRI techniques play a crucial role in confirming or refuting the initial diagnosis. [20] Dynamic MRI (including perfusion and diffusion techniques) and spectro-MRI are particularly effective in distinguishing radionecrosis lesions from malignant lesions. Reduced parameters in MRI perfusion with dynamic susceptibility contrast are indicative of radionecrosis. [20] Finally, MRI spectroscopy reveals distinctive features such as increased lesion behavior, moderate lipid peak, or elevated choline/creatine and choline/N-acetylaspartate (NAA) ratios, which suggest metastases. Conversely, radiation-induced injury typically has low levels of NAA, choline, and creatine as well as a relatively high peak lipid. [20] Regarding positron emission tomography (PET), reduced uptake with various radiotracers (such as fluorodeoxyglucose (FDG) indicates necrosis. FDG has been widely studied among these radiotracers, but it shows low specificity [21 , 22, 23].

Stereotactic biopsy is a procedure that provides pathological material and, therefore, a reliable diagnosis but remains an invasive procedure and is not recommended [22,23].
The objective of the treatment of cerebral radionecrosis being clinical cure with a lower risk of morbidity, 4 treatments have been studied in the literature with different and generally average levels of proof of effectiveness, we are talking about: corticosteroid therapy, hyperbaric oxygen therapy (HBOT), antiangiogenics (anti-VEGF), and surgery [24,27].

Used as first-line treatment when neurological signs appear, cortisoids reduce the inflammatory cascade responsible for RN lesions and also reduce the associated cerebral edema. However, their well-known long-term side effects are severe [35,36].

Bevacizumab (Avastin*), which is an anti-VEGF monoclonal antibody, is currently the only treatment that has demonstrated sufficient effectiveness [28-32]. A prospective, randomized, double-blind study, including 14 patients, compared bevacizumab versus corticosteroid therapy; only patients receiving bevacizumab (12 patients at the end of the study) showed clinical and radiological improvement [32]. The meta-analysis by Kahn et al. [33] analyzed in 2021 two prospective studies, 7 retrospective studies and two "case reports", 89 patients in total, all with radionecrosis on brain metastases of different origins. This meta-analysis shows that bevacizumab allows a reduction in the size of the lesion on MRI (48% reduction in T1 and 62% reduction in T2), a reduction in corticosteroid doses and an improvement in symptoms in 98% of patients. The doses were very heterogeneous between 1 and 15 mg/kg/3 weeks, with doses of 5 and 7.5 mg/kg/3 weeks being the most frequently used in these studies. The number of injections varied between 2 and 6.

In the same area, no study has reported a benefit in this indication with another anti-VEGF.

Hyperbaric oxygen therapy is a modality of administering oxygen at a pressure greater than atmospheric pressure (760 mmHg or 1 ATA). The patient is placed in a sealed box which will gradually be pressurized until the internal pressure is greater than atmospheric pressure. The use of very high oxygen pressures makes it possible to recruit effects of oxygen that do not exist or only modestly at atmospheric pressure (oxygen used as a medicine with healing, anti-infectious hemodynamic effects and others) .

In the literature, the use of oxygen therapy associated or not with bolus corticosteroid therapy allows for radiological improvement, followed by stabilization, and clinical improvement. [36.37]

Neurosurgical excision of a radionecrosis lesion is a complex decision, but should always be considered. It makes it possible to establish a definitive diagnosis between recurrence and RN. Its indication is often delicate and must be posed in a collegial manner. [36.38]

Concerning prevention, its role remains essential given the incurable nature of the complication. It consists of sparing brain tissue, particularly the temporal lobes, during irradiation of nasopharyngeal cancer, something which is still not possible given the inclusion of the lower part of the temporal lobes in the target volumes due to their proximity, particularly when it comes to locally advanced tumors. Reducing the total dose is also impossible due to the obligation to give a carcinologically effective dose [3,10], moreover the use of new techniques allowing better precision in radiotherapy, such as conformal radiotherapy with modulation of intensity, and proton therapy, make it possible to administer high doses to the tumor while protecting the organs at risk and thereby reducing the risk of cerebral radionecrosis.

Conclusion:-

Cerebral radionecrosis, mainly temporal, is a serious and irreversible complication of radiotherapy. Its often variable clinical presentation can range from minor to major symptoms. It may be discovered incidentally during radiological follow-up examinations in asymptomatic patients.

MRI is the examination of choice for monitoring patients after radiotherapy. However, the differential diagnosis between brain tumor (exceptional brain metastasis of nasopharyngeal cancers or primary tumor) and radionecrosis is often difficult. Multimodal MRI techniques with perfusion sequences and spectrometry greatly improve the sensitivity and specificity of the examination.

Corticosteroid-based treatment remains the most frequently used, but the possibility of side effects and especially prolonged corticosteroid dependence must be emphasized. The combination of corticosteroid therapy and hyperbaric oxygen therapy also allows a good radiological and clinical response while allowing a progressive reduction of corticosteroids. However, there is nowadays a particular interest in the use of bevacizumab in this indication. Finally, better knowledge of pathophysiology will open up the prospects for better targeted therapies.

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