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RESEARCH ARTICLE

DIAGNOSTIC, THERAPEUTIC AND EVOLUTIONARY CHARACTERISTICS OF NASOPHARYNGEAL CANCER MANAGED WITH VMAT IN DEPARTMENT OF RADIOTHERAPY, MOHAMED V MILITARY TEACHING HOSPITAL - RABAT IN MOROCCO

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Abstract

Purpose: The aim of this study was to report the experience of Military Teaching Hospital Mohamed V (MTHM V) in the management of NPC treated with volumetric modulated arc therapy (VMAT)

Materials and Methods: This is a retrospective study conducted between January 2013 and December 2017. All patients with a nasopharyngeal cancer were included. Patients who had distant metastasis at the time of diagnosis were excluded. The volumetric arc therapy modulation of intensity (VMAT) is the technique radiotherapy used in all our patients.

Results: one hundred and one (101) patients with nasopharyngeal cancer were treated in our department. The average age was 42.95±16.36. The predominant histological type is undifferentiated carcinoma (UCNT) in 93 % of cases. Tumors were classified according to the American Joint Committee on Cancer (AJCC) classification of 2010 in Stage I : 1%, Stage II in 10.9%, Stage III in 45.5%, Stage IVa in 32.7% and stage IVb in 9.9%. The treatment consisted of neoadjuvant chemotherapy followedby concomitant radio chemotherapy (RCC) at 79.2 % of patients, an RCC immediately in 12.8 % of cases and 8 % of patients received neoadjuvant chemotherapy followed by exclusive radiotherapy. The therapeutic tolerance was good with 16.8% of acute radiomucite Grade 3, 8.9% of acute dermatitis Grade 3 and no complication Grade 4. The overall survival was 98.8% and 84.8% at 2 and 5 years respectively, and the PFS was 85.6% and 76.8% at 2 and 5 years, respectively. N3 and time to relapse were significant in multivariate analysis for OS. Neoadjuvant chemotherapy and N3 were significant in multivariate analysis for PFS.

Conclusion: volumetric modulated arc therapy with concurrent chemoradiotherapy with additional neoadjuvant chemotherapy has good response and outcomes. Our findings are in good accordance with other series but further large studies are warranted to improve prognostic of this potentially curable malignancy.

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Introduction:-

Nasopharyngeal carcinoma (NPC) is the predominant tumor type arising in the nasopharynx. It differs from other head and neck squamous cell carcinomas in epidemiology, histology, natural history, and response to treatment.

Worldwide, there are around 86 000 incident cases and 50 000 deaths annually [1-3]. NPC displays a distinct racial and geographic distribution, which is reflective of its multifactorial etiology [1]. The incidence of nasopharyngeal carcinoma demonstrates a marked geographical variation. It is rare in the United States and Western Europe, with an incidence of 0.5 to 2 cases per 100,000 [2, 4]. By contrast, nasopharyngeal carcinoma is endemic in Southern China, including Hong Kong, where the incidence may reach 25 cases per 100,000 per year. Intermediate-risk regions include Southeast Asia, North Africa and the Middle East, and the Arctic. Populations that migrate from areas of high to low risk retain an elevated risk, although this risk typically diminishes in successive generations [4]. The major etiological factors for endemic nasopharyngeal carcinoma are genetic susceptibility, early-age exposure to chemical carcinogens, and Epstein-Barr virus (EBV) infection.

NPC has very good response to radiation and cure is promise, especially if early detected. Radiotherapy is the backbone treatment strategy for NPC. But about 70% of the patients with NPC present with stages III or IV are at risk to suffer from local or/and regional recurrence or distant metastases after radiotherapy [5]. However, the treatment of advanced NPC often requires a combination of chemotherapy and radiation therapy. The National Comprehensive Cancer Network and European Society for Medical Oncology recommend concurrent chemoradiotherapy with or without adjuvant chemotherapy (AC) as the standard basic treatment for stage II–IVB patients. However, AC is mainly used in patients with residual disease or those with advanced disease due to the lower compliance rate, especially after concurrent chemoradiotherapy. Interestingly, neoadjuvant chemotherapy plus concurrent chemoradiotherapy has been commonly used in stage II– IVB NPC patients in many centers because the considerable response rate is high. Nevertheless, this combined treatment was recommended as level 3 evidence in the latest version of guidelines [6].A pooled data analysis of two-Phase III studies has shown that the addition of neoadjuvant chemotherapy to RT significantly improves the disease-specific survival of stage II–IVB NPC patients but that no improvement in overall survival (OS) is observed [7].

The intensity modulated radiotherapy (IMRT) of head and neck cancer has been demonstrated often to produce greater dose distributions in terms of improved tumor exposure and lower doses to normal tissues. Three randomized trials have compared IMRT to conventional radiotherapy in the treatment of NPC [8]. Although local control rates with IMRT have improved with the advent and widespread adoption of IMRT.

The aim of this study was to report the experience of Military Hospital Teaching Mohamed V in the management of NPC treated with volumetric modulated arc therapy (VMAT)

Materials and Methods:-

This is a retrospective study spread over 5 years, conducted within radiotherapy department of the MTHM V in Rabat between January 2013 and December 2017. All data was collected via the records patient clinics. These data were then examined, coded and entered into an electronic database and validated by the study's principal investigator.

All patients benefited from a pre-therapeutic assessment including a physical examination, biochemical and hematologic assessments, a biopsy- proven fiber optic nasopharyngoscopy and histological evidence, combined with a nasopharyngeal and neck CT scan with or without MRI to assess the loco regional extension of the disease. Patients with locally advanced disease at the time of presentation received additional extension assessment including thoraco-abdominal CT scan and bone scintigraphy. Patients who had distant metastasis at the time of diagnosis were excluded. The seventh edition of the system of classification of the American Joint Committee on Cancer (AJCC) has been used for staging the diseases.

The VMAT is the technique radiotherapy used in all our patients. The simulation scanner is made with a 5-point mask, the Contouring target volumes is performed on a CT scan injected after registration on the diagnostic MRI. The nasopharyngeal gross tumor volume (GTV NP) and the neck lymph nodes (GTV NN) were

determined from the results of imaging, clinical and endoscopic. The high-risk CTV (CTV HR) covers the GTV NP and the GTV GG with a margin of 5-10mm while excluding the non-infiltrated anatomical barriers, the intermediate risk CTV NP (CTV IR NP) covers the CTV HR NP plus a margin of 5mm while including areas at risk of microscopy. The CTV GG Intermediate (CTV GG IR) covers CTV GG HR plus the nodal regions of the level II, III, IVa and back pharyngeal necks as well as the underlying and overlying levels of the levels reached. A third node level at low risk (LR) may be added including the remaining neck levels. A further 3 to 5mm margin is added to target volumes to form the PTV.

The radiotherapy was administered with a VMAT technique in simultaneous integrated boost (SIB) moderately accelerated using 2 to 3 arcs with 3 levels of high risk dose (HR) receiving 69.96 Gy, intermediate risk (IR) : 59.4 Gy and low risk (LR) : 54 Gy , with 5 fractions per week in 33 sessions . The treatment plan is validated by the radiation oncologist and the medical physicist; priority is given to critical neurological structures, followed by target tumor volumes and organs of intermediate importance. Radiation therapy has been used alone or in combination with weekly cisplatin chemotherapy. Induction chemotherapy was administered to patients with locally advanced disease and different regimens were used based on cisplatin, anthracycline and 5-FU.

The biological monitoring and clinical courses of treatment patients had weekly for treating acute complications that may arise and ensure good compliance to treatment.

A near the end of the treatment the monitoring continued on schedule following: every 3 months for the first 2 years, every 6 months the 3rd, 4th and 5th year , then annually , it included a physical examination, particularly of the head and the neck . A nasofibroscopy and head and neck MRI were performed periodically to evaluate response, detect relapses and documenting the late complications.

The data in our series were collected using a well-structured checklist containing the important parameters of the study. Data collection included patient data (age at diagnosis and sex). The data also included clinical presenting symptoms (rhinological, otological, neurological and lymph node), duration of symptoms (months) and other clinical data such as TNM classification and stage of illness according to the seventh edition of the AJCC of 2010 and histological type according to the classification of the World health Organization, the primary treatment modalities (radiotherapy, chemotherapy, both), and the complications during the treatment, and monitoring data: the time of the last consultation, the date and site of relapse (local, loco regional or distant) and date of death.

The acute and late toxicities of radiotherapy were classified according to common endpoint criteria for adverse reactions (CTCAE Version 3 .0). Only grade 3 or higher toxicities have been recorded and reported.

Statistical analysis of the data was performed by SPSS 23 for MAC (SPSS, Inc., Chicago, IL, USA). The overall survival rate (OS) and survival without relapse (PFS), has been calculated and analyzed with the Kaplan-Meier method. OS was calculated from the date of histological diagnosis to the date of the last visit or death and PSF was calculated from the date of histological diagnosis to the date of the last visit or date of loco regional or distance relapse.

Results:-

During the period of the study spread over 5 years, 101 patients with nasopharyngeal cancer were treated in the radiotherapy department in the MTHM V by the VMAT type radiotherapy. The average age was 42.95±16.36; the sex ratio was 2.6 with a male predominance. The average consultation time was 6 months (4-12). The revealing signs were lymph node in 61.4%, otological in 52.5 %, rhinologic in 48.5 % and neurologic in 37.6 %. The predominant histological type is undifferentiated carcinoma (UCNT) in 93 % of cases. Tumors were classified according to the American Joint Committee on Cancer (AJCC) classification of 2010 in Stage I : 1%, Stage II in 10.9%, Stage III in 45.5%, Stage IVa in 32.7% and stage IVb in 9.9% , The distribution according to the T was as follows: T1: 12.9%, T2: 31.7%, T3: 18.8%, T4: 36.6% and the status lymph node was N0: 11.9%, N1: 22.8%, N2: 55.4%, N3 : 9.9%.

The treatment was referred curative in all patients; it consisted of neoadjuvant chemotherapy followed by concomitant chemoradiotherapy (RCC) at 79.2 % of patients, an RCC immediately in 12. 8 % of cases and 8 % of patients received neoadjuvant chemotherapy followed by exclusive radiotherapy (Table 1).

The therapeutic tolerance was good with 16.8% of acute radiomucite Grade 3, 8.9% of acute dermatitis Grade 3 and no complication Grade 4. Late complications were as following: skin fibrosis in 12.9%, lockjaw in 6.9%, Grade 3 hyposialia in 19.8%, and asialia in 2% of cases, hearing lose were found in 15,8% of patients (Table 2).

With a median follow-up of 45.37 ± 17.31 months, 3 % of patients were lost sight of, the overall survival was 98.8% and 84.8% at 2 and 5 years respectively. The mean Time to relapse was 22,6 ± 10,3 months, and the PFS was 85.6% and 76.8% at 2 and 5 years, respectively (Table 3 and Fig 1, 2, 3, 4).

Different prognostic factors were included in a univariate and multivariate analysis (table 4, 5, 6). For OS: relapse delay was significant in univariate analysis, and N3 and time to relapse were significant in multivariate analysis. For PFS: stage III, N2 and stage (I and II vs III and IV) were significant in univariate analysis, and neoadjuvant chemotherapy and N3 were significant in multivariate analysis.

Discussion:-

Nasopharyngeal carcinoma is the predominant tumor type arising in the nasopharynx, it differs from other head and neck squamous cell carcinoma and requires particular attention.

The incidence of this carcinoma shows a clear geographical variation and suggests a multifactorial etiology. It is mainly associated with an interaction of several factors; such us Epstein-Barr virus (EBV) infection, the high intake of preserved smoked foods, and genetic predisposition [1].

In most low-risk regions, the disease incidence increase with age; while in high incidence areas, there is a bimodal distribution noted with a minor peak observed among adolescents and young adults and a larger later peak around 50 to 59 years of age and declines thereafter [2]. Median age in our population was 42,95 ± 16,36 years which is compared to the other parts of intermediate-risk regions of North Africa. The incidence of nasopharyngeal carcinoma is two to threefold higher in males compared with females [3]. the sex ratio found in our series was 2.6.

Diagnosis of NPC is often delayed until it manifests by spreading to surrounding structures. Common symptoms reported are headache, nasal obstruction, ear symptoms, and neck swellings [1]. Cranial nerves III, IV, V, and VI are most commonly affected because of para cavernous sinus tumor invasion [9].Our cases reported neck swellings (61.4%), ear symptoms (52.5%), nasal symptoms (48.5%), and cranial involvement (37.6%).

NPC has a tendency to show early lymphatic and hematogenous spread [10-12]. Lymph node metastases at presentation are present in 75 to 90 % of cases and are bilateral in more than 50 percent. In our study we found neck lymph node metastases as the first presenting symptoms in 80.1% of cases.

The World Health Organization (WHO) classifies nasopharyngeal carcinoma into the three histopathologic types [13]. Non keratinizing undifferentiated carcinoma (WHO type III) is the commonly subtype; which is strongly associated with EBV and has a more favorable prognosis than other two subtypes. In our series, we found majority of cases (93%) being undifferentiated subtype III carcinomas.

NPC has mainly treated with radiation therapy (RT) because it is a radiosensitive tumor and because its anatomic location limits a surgical approach. Due to both loco regional control and survival benefit, concurrent chemo radiotherapy has emerged as the standard of care at least for locally advanced stages of nasopharyngeal cancer since the report of the Intergroup 0099 trial in 1998 by Al-Sarraf et al [14], and the confirmation of their results by several subsequent randomized trials and meta analyses [15-20]. Besides, the main advantage of neoadjuvant chemotherapy is early eradication of micro-metastasis, which consequently improves OS by reducing the distant metastasis rate.

Cisplatin is the most effective agent in this setting. However, carboplatin has a more favorable toxicity profile than cisplatin and appears to have similar efficacy [21]. In our cases carboplatin was used in less than 15% of the concurrent chemo radiotherapy due to low glomerular filtration rates. The current standard regimen for concurrent cisplatin is either 100 mg/m2 on days 1, 22, and 43 or a weekly dose of 30 to 40 mg/m2. Weekly schedule was administered for all our patients because it can be given more readily in ambulatory.

However, IMRT can improve target volume coverage and sparing of organs at risk, resulting in excellent dosimetric advantages compared to other radiation techniques in nasopharyngeal cancer [22-24], which theoretically should

lead to reduced late toxicity, especially in terms of xerostomia by sparing dose to one or both parotid glands and improved outcomes [8, 25, 26].

In the present study we show encouraging relapse free survival local control (5-year RFS 76,8%) and overall survival (5-year OS 84,8%%) with acceptable acute and limited late toxicities (grade 3 xerostomia: 16,8%) using VMAT combining neoadjuvant chemotherapy, concurrent chemotherapy or both. Furthermore, our results are in good harmony with other IMRT-series [2T-33] describing similar results regarding outcome and toxicity. However, more careful patient selection for sparing of one or both parotid glands seems required and should be weighed against target coverage as highlighted by serious reports on intraparotideal recurrences [34].

Table 1:- Characteristics of the population.

Characteristics		Number	Percentage
Gender	Man	73	72.3%
	Women	28	27.7%
Age	Average	42.95+ / _16.36	
Diagnosis delay	Median	6 (4-12)	
Clinical	Rhinologic syndrome	49	48.5%
	Neck lymph node	62	61.4%
	Otologic syndrome	53	52.5%
	Neurologic syndrome	38	3 7.6%
Histology	SCC moderately differentiated	3	3%
	SCC low differentiated	4	4%
	UCNT	94	93%
T	T1	13	12.9%
	T2	32	31.7%
	T3	19	18.8%
	T4	37	36.6%
N	N0	12	11.9%
	N1	23	22.8%
	N2	56	55.4%
	N3	10	9.9%
STADE	I	1	1%
	II	11	10.9%
	III	46	45.5%
	IVA	33	32.7%
	IVB	10	9.9%
Therapeutic protocol	NEO CMT + RTH	8	8 %
	NEO CMT + RCC	8 0	79.2 %
	RCC	13	12.8 %
	EXCLUSIVE RT	0	0 %

SCC: Squamous cell carcinoma
UCNT: Undifferentiated carcinoma of nasopharyngeal type
NEO CMT: neoadjuvant chemotherapy
RTH: radiotherapy
RCC: concurrent chemoradiotherapy

Table 2:- Late complication.

Late complication		Nombres	Percentage
Fibrosis		13	12.9 %
Lockjaw		7	6.9 %
Hyposialia	**Grade 3**	20	19.8%
	Grade 4	2	2%
Radionecrosis	**Bone**	0	0%
	Brain	0	0%

Hearing lose	16	15,8%

Table 3:- Follow up.

Following time		45.37 ± 17.31 (average)
Lost from seen		3 (3%)
Time to relapse		43.86 ± 18.02 (average)
Relapse		21 (20.8 %)
Relapse seat	**Locoregional**	5 (5%)
	Distant	16 (15.8%)
Survival	**OS**	OS at 2 years : 98.8% OS at 5 years : 84.8%
	PFS	PFS was at 2 years: 85.6% PFS was at 5 years: 76.8%

OS: overall survival
PFS: relapse free survival

Table 4:- Univariate analysis of OS and PFS.

	Univariate analysis			
Variables	OS		PFS	
	P Value	95% IC	P Value	95% IC
AGE	0,261	-	0,233	-
Gender	1,000	-	0,587	-
Diagnostic delay	0,512	-	0,375	-
Protocol	0,887	-	-	-
Induction chemotherapy	0,495	-	0,229	-
Staging	0,737	-	-	-
Stage	0,998	-	0,437	-
T	0,726	-	0,459	-
N	0,765	-	0,120	-
Relapse delay	<0,001	1,07-1,24	-	-
Relapse before 2 years	<0,001	12,12-276,84	-	-
Stage III	0,710	-	0,054	0,97-17,31
N2	0,398	-	0,037	1,11-35,99
Stage I, II vs Stage III, IV	-	-	0,032	0,173-0,923

Table 5:- Multivariate analysis of OS.

Variables	P Value	95% C. I	
		Lower	Upper
Relapse delay	0,004	1,062	1,377
Induction chemotherapy	0,116	-	-
LR relapse vs distant relapse	0,091	-	-
N0	0,193	-	-
N1	0,118	-	-
N2	0,529	-	-
N3	0,042	0,002	0,901

LR: locoregional

Table 6:- Multivariate analysis of PFS.

Variables	P Value	95% C. I	
		Lower	Upper
Stage I, II vs Stage II, IV	0,999	-	-
Induction chemotherapy	0,030	0,044	0,855
N0	0,262	-	-
N1	0,190	-	-

N2	0,157	-	-
N3	0,055	0,968	17,506

Fig 1:- Overall survival (OS) curve.

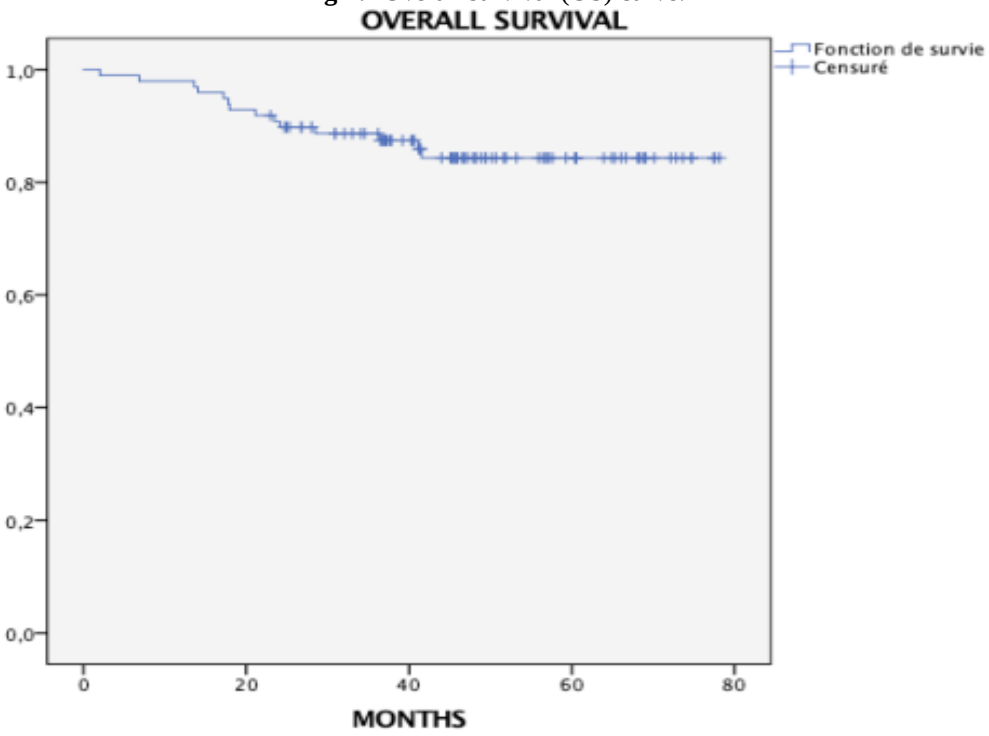


Fig 2:- Progression free Survival (PFS) curve.

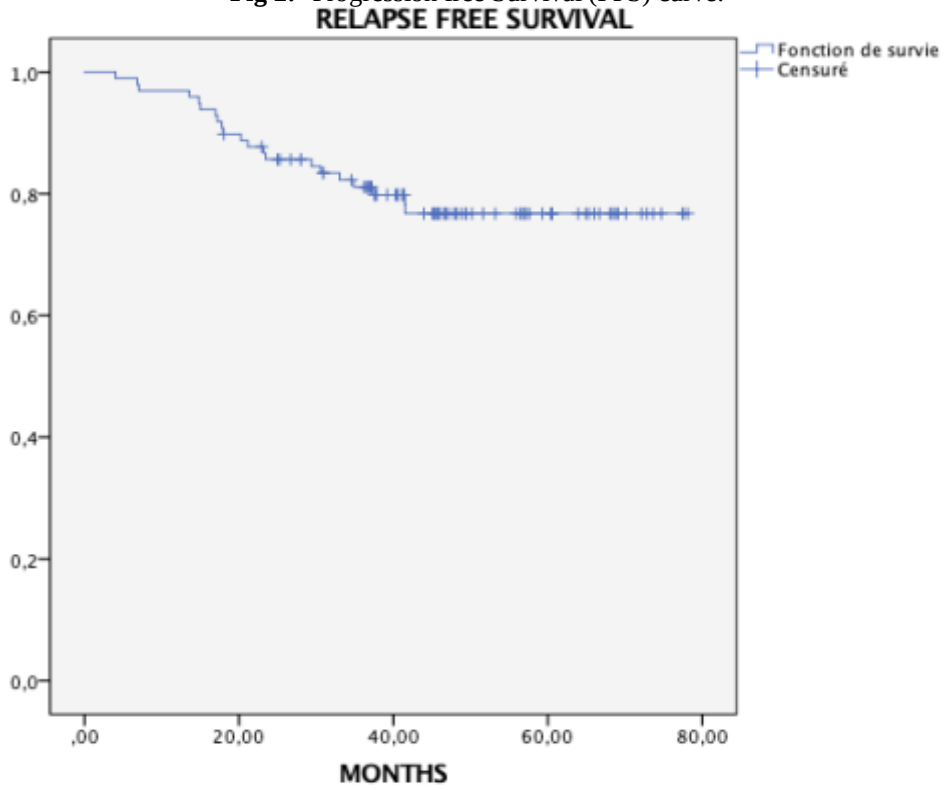


Fig 3:- Survival curve by stage.

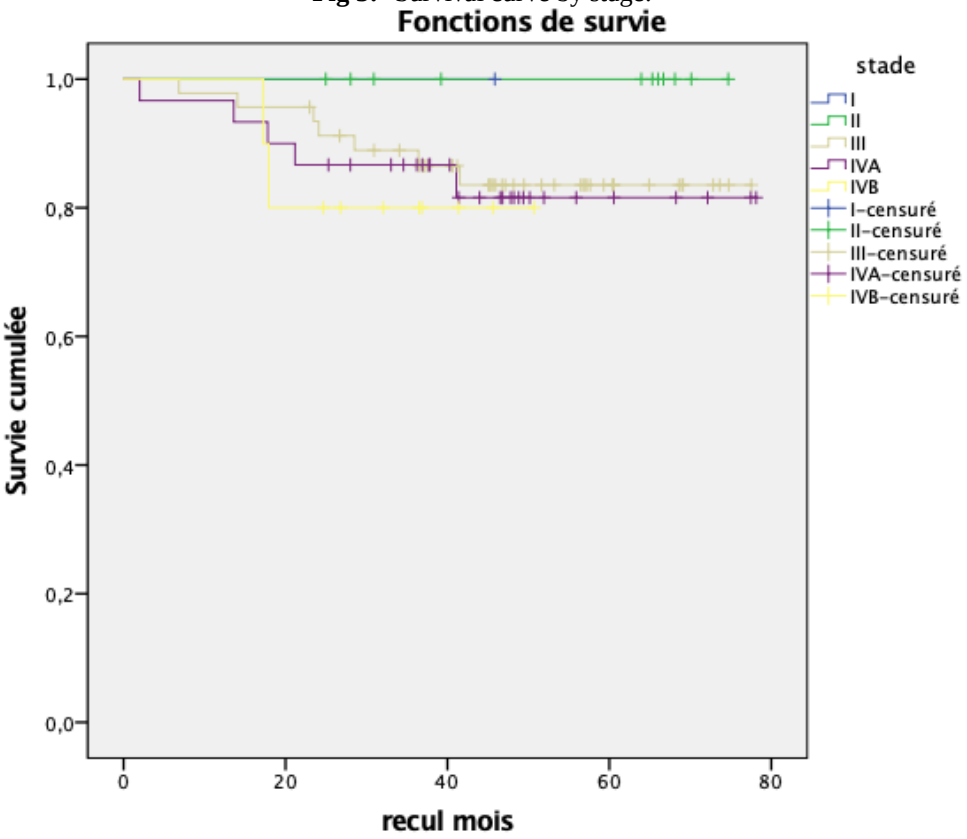
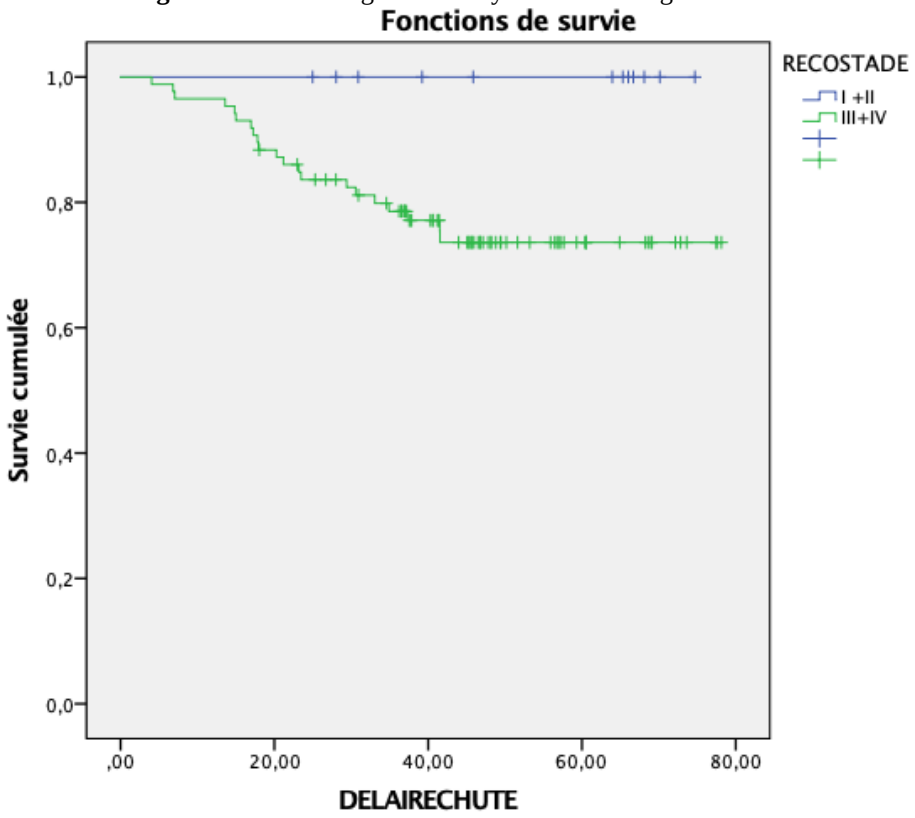


Fig 4:- Localized Stage vs Locally Advanced Stage Survival.



Conclusion:-

IMRT according to the VMAT technique with concurrent chemo radiotherapy with or without additional neoadjuvant chemotherapy has good response and outcomes with acceptable rates of acute and limited rates of late toxicity in patients with nasopharyngeal cancer. Our findings are in good accordance with other series but further large studies are warranted to improve prognostic of this potentially curable malignancy.

Abbreviations list:

NPC: Nasopharyngeal carcinoma
EBV: Epstein-Barr virus
AC: adjuvant chemotherapy
RT: radiotherapy
OS: overall survival
PFS: relapse free survival
IMRT: intensity modulated radiotherapy
VMAT: volumetric modulated arc therapy
AJCC: American Joint Committee on Cancer
GTV: gross tumor volume
NP: nasopharyngeal
HR: high-risk
IR: intermediate risk
LR: risk
SCC: Squamous cell carcinoma
UCNT: Undifferentiated carcinoma of nasopharyngeal type
NEO CMT: neoadjuvant chemotherapy
RCC: concurrent chemoradiotherapy

Ethics approval and consent to participate:

Informed consent (verbal) was obtained from all participants. This study was submitted to and approved by research and ethics committee of military teaching hospital Mohamed V

Competing interests:

We (authors) declare that we have no conflict of interest.

Authors' Contribution:

K.H and M.H, performed research and share the first position in this manuscript; A.M and EM analyzed data statistically and drafted the manuscript; M.H and M.B., collected the clinical data; M.E, K.A, K.H, H.S, N.Z and H.M, designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

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