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RESEARCH ARTICLE

PROGNOSTIC FACTORS AND FAILURE PATTERNS IN NON METASTATIC NASOPHARYNGEAL CARCINOMA AFTER VOLUMETRIC MODULATED ARC THERAPY, A RETROSPECTIVE STUDY

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Abstract

Purpose : The aim of this study was to identify the key failure patterns and prognostic factors of relapsed Nasopharyngeal carcinoma (NPC).

Patients and Methods : Between January 2013 and December 2017, so during 5 years, a total of 101 patients with NPC were diagnosed and treated with radiotherapy (RT) or concurrent chemo radiotherapy at Military Teaching Hospital Mohamed V (MTHM V) of Rabat, Morocco. The sex ratio was 2,6 and the median age was $42,95 \pm 16,362$ years. Regarding anatomo-pathological aspect, the undifferentiated carcinoma has been the most frequently, noticed in 93,1 %. The treatment received was based on neoadjuvant chemotherapy followed by concomitant chemo radiotherapy (RCC) in 79,2 % of patients, a RCC from the outset in 12,8 % of cases, and a neoadjuvant chemotherapy followed by radiotherapy in 8 % of cases. All patients were treated with VMAT technique with a prescribed doses levels of 69,96, 59.4 and 54 Gray in 33 sessions.

Results : There were just 3 patients with incomplete follow-up, but complete follow-up information was available for 98 patients with a median follow-up time of $45,37 \pm 17,31$ months. The overall survival (OS) and the relapse free survival (RFS) rate after 5 years was 82,3 % and 76,8% respectively. Among the 101 patients, 21 (20,8 %) relapsed with the time to relapse was $22,6 \pm 10,3$ months. The loco regional relapse founded in 5 patients (5%) and metastases to the distant organ were found at 16 patients (15,8 %). Overall survival after 4 years of relapse changes according to seat of relapse. There OS at 4 years for locoregional relapse and for distant metastases was estimated at 83% and 7,3% respectively.

Conclusion : This report reviews NPC recurrence data after primary treatment. Rates of local and distant relapse were comparable with those previously reported and the majority of recurrences occurred within the first five years. The prognosis after relapse varied with nodal status, seat of relapse as well as the remission duration after treatment.

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Introduction:-

Nasopharyngeal carcinoma (NPC) is a challenge in oncology. Due to the deep-seated anatomic location and proximity of NPCs to critical structures, radical surgical resection is extremely difficult [1]. However, radiotherapy has undergone several different periods of development, and it was not until the advent of mega-voltage machines that a 5-year overall survival (OS) rate of 25% was first achieved, which marked the first major breakthrough in the treatment of NPC and established radiotherapy as the primary modality of choice for NPC [2]. Since that time, progressive improvements in the treatment outcomes of patients with NPC have been achieved. Initially, in the 1970-1980s, conventional radiotherapy alone resulted in similar outcomes in both the endemic and non-endemic areas, with 5-year OS rates of 48%–52%, a cumulative local failure rate of 20%, a cumulative regional failure rate of 14%, and a cumulative distant metastasis rate of 19% [3, 4]. During the 1990s, rapid technological advances in imaging methods, computerized planning systems, and radiotherapy facilities and the accumulation of radiobiological knowledge that enabled schedule, dose, and fractionation optimization led to better outcomes after radiotherapy, with 5-year OS rates of 65%–74%, a cumulative local failure rate of 12%, a regional failure rate of 5%, and a distant metastasis rate of 16% [5, 6]. However, local relapse and distant metastasis remained the two major causes of failure. Intensity modulated radiotherapy (IMRT) was introduced in the 2000s and represented a major breakthrough in the radiotherapeutic management of NPC. Due to the dosimetric advantages of IMRT combined with the use of magnetic resonance imaging (MRI) guided tumor volume delineation and concurrent chemotherapy, local control rate in NPC patients has improved significantly [7, 8]. However, cancer relapse is still the leading cause of cancer-related deaths in patients with NPC. The most common cause of death after radiotherapy is distant metastasis, followed by nasopharyngeal and cervical recurrence [9]. Although much is known on the treatment and prognostic factors for this cancer, there is few of systematic studies on patterns of relapse and long-term outcomes after relapse occurs.

The aim of this study was to identify the key failure patterns and prognostic factors of relapsed NPC.

Materials and Methods:-**Patient cohort:**

Between January 2013 and December 2017, so during 5 years, a total of 101 patients with NPC were diagnosed and treated with radiotherapy (RT) or concurrent chemoradiotherapy at Military Teaching Hospital Mohamed V of Rabat, Morocco. Of these 101 patients, sex ratio was 2,6 (men predominance) and complete followup information was available except for 3 patients. The median age was 42,95±16,362 years. Pathology classification is based on the World Health Organization (WHO) with type I representing squamous cell carcinoma, type II representing non-keratinizing carcinoma and type III representing undifferentiated carcinoma (UCNT). In our cohort, 93,1 % of patients presented a type 3 carcinoma.

Image assessment and criteria for staging parameters:

All patients benefited from cervico-facial CT scan with or without MRI, and an extensional assessment with bone scan and thoracoabdominal CT for locally advanced forms. Then, TNM distribution was obtained with classification of the American Joint Committee on Cancer (AJCC) 2010. Almost all patients were locally advanced at the time of diagnosis : Stage I : 1,0 %, Stage II : 10,9 %, stage III : 45,5 %, stage IVa : 32,7 % and stage IVb : 9,9 %.

Initial treatment methods for NPC:

The treatment was in curative intent in all our patients, it consisted of neoadjuvant chemotherapy followed by concomitant chemoradiotherapy (RCC) in 79,2 % of patients, a RCC from the outset in 12,8 % of cases, and 8% of patients received neoadjuvant chemotherapy followed by exclusive radiotherapy. All patients were treated with radical radiotherapy based on IMRT according to the VMAT technique for the entire course. Target volumes were delineated slice-by-slice on treatment planning CT scans with MRI fusion imaging using an individualized delineation protocol. The prescribed doses levels were 69.96, 59.4 and 54 Gray, with 5 fractions per week in 33 sessions. All targets were treated with the simultaneous integrated boost technique moderately accelerated. During the study period, concurrent chemoradiotherapy was recommended for stage III to IVa-b disease. Concomitant chemotherapy consisted of cisplatin (80–100 mg/m²) given on weeks 1, 4, and 7 of radiotherapy or cisplatin (30-40 mg/m²) given weekly. The patient and tumor characteristics are well-summarized in Table1

Follow up:

Treatment responses and toxicity were assessed in each patient every week during treatment, every 3 months during the first 2 years after treatment, and then every 6 months during the following 3 years. Endoscopy, computed tomography (CT), or MRI scans of the head and neck were also performed every 3 months in the first year and annually thereafter. Additional tests were performed when indicated to evaluate local or distant failure. The last follow-up time was 1th May 2019.

Table 1:- Patient, tumor and treatment characteristics.

Characteristics		Number	Pourcentage
Gender	Man	73	72,3%
	Women	28	27,7%
Age	Average	42,95 ± 16,36	
Diagnosis delay	Médian	6 (4-12)	
Clinical (signs)	Rhinologic	49	48,5%
	Nodes	62	61,4%
	Otological	53	52,5%
	Neurologic	38	37,6%
Histology	EC MD	3	3%
	EC 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%
Stage	I	1	1%
	II	11	10,9%
	III	46	45,5%
	IVA	33	32,7%
	IVB	10	9,9%
Therapeutic protocol	NEO CMT + RT	8	8%
	NEO CMT + RCC	80	79,2%
	RCC	13	12,8%

EC: Epidermoid carcinoma, MD : moderately differentiated, UCNT: undifferentiated carcinoma of nasopharyngeal, NEO: neoadjuvant, CMT: chemotherapy, RT : radiotherapy, RCC: concomitant chemoradiotherapy.

Statistical analysis:

All analyses were performed using SPSS version 16.0. The actuarial rates were estimated using the Kaplan-Meier method, and the survival curves were compared using the log-rank test. The following endpoints (measured from the start of treatment to the first defined event) were estimated: local relapse free survival (LRFS), nodal relapse-free survival (NRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and OS. The OS was calculated from the date of the histological diagnosis until the date of the last visit or death and the RFS was calculated from the date of the histological diagnosis until the date of the last visit or the date of relapse.

Multivariate analyses with the Cox proportional hazards model were used to test for independent prognostic factors by backward elimination of the insignificant explanatory variables. The Cox proportional hazards model was also used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). Host factors (age and sex) were included as covariates in all tests. Two-tailed P values < 0.05 were considered statistically significant.

Results:-

Frequency and characteristics of recurrence after initial treatment for NPC:

At the end of the study, there were just 3 patients with incomplete follow-ups, but complete follow-up information was available for 98 patients with a median follow-up time of $45,37 \pm 17,31$ months. The overall survival (OS) rate after 5 years was 82,3 % and the Relapse Free Survival (RFS) after 2 and 5 years was 85,6 % and 76,8% respectively (Fig 1 and 2).

Among the 101 patients, 21 (20,8 %) relapsed. The median time to relapse was $22,6 \pm 10,3$ months. The median age of patients at relapse was $46,71 \pm 13,71$ years with sex ratio was 2 (men predominance). All patients who relapsed were initially locally advanced with 9 (42,8%) stage III ,7 (33,3%) stage IVA, and 5 (23,9%) stage IVB.

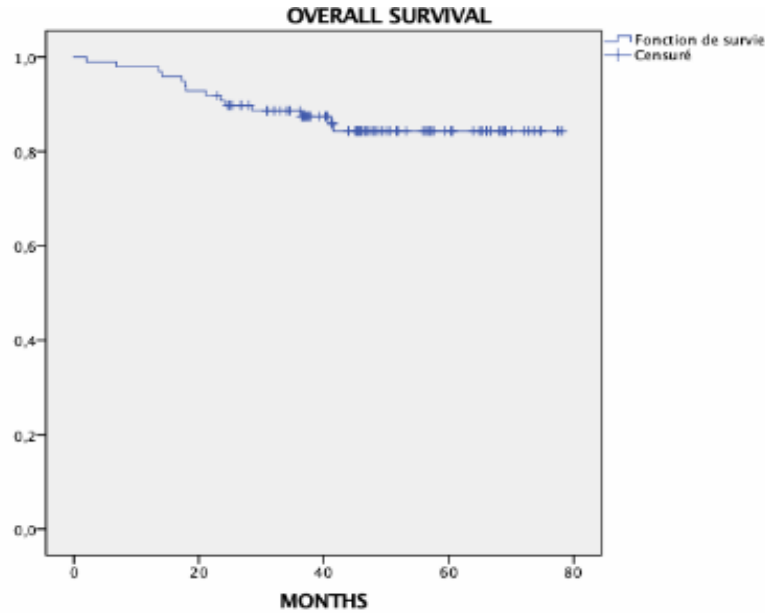


Figure1: Kaplan-Meier overall survival curve.

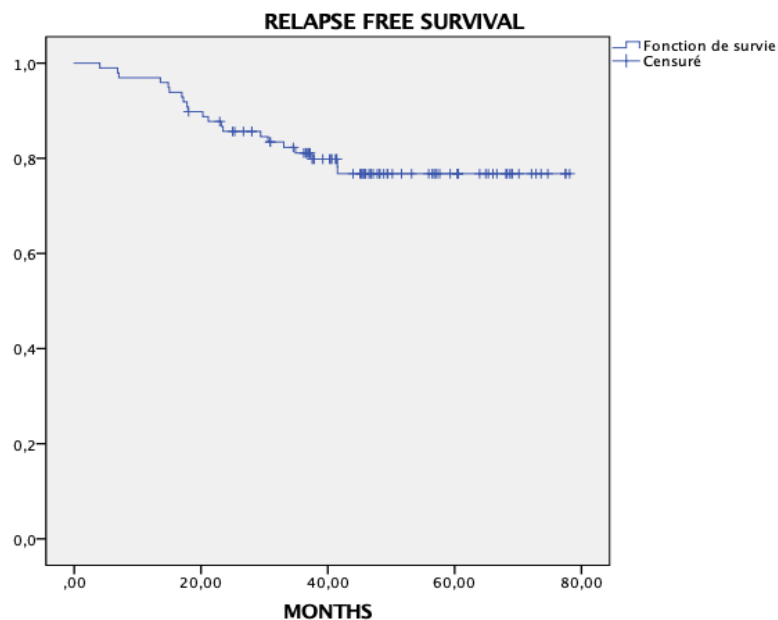


Figure 2:- Kaplan-Meier Relapse-Free Survival Curve.

The anatomic sites of the relapses were combined into two groups: distant (lung, liver, bone and others) versus loco regional sites (nasopharynx or neck nodes). In this series for loco-regional relapse founded in 5 patients (5%), we found 3 local relapses in the nasopharynx, 1 regional nodal relapse and 1 both local and nodal relapse. Metastases to the distant organ after initial treatment were found at 16 (15,8 %) patients. Knowing the most frequent sites of distant metastases is important in the follow-up examinations of NPC patients.

In our study, bone was the most common site of relapses, occurring in 7 (43,75%) as the single initial site of metastasis. Further patient percentages for the first site of relapse included 2 (12,5%) for single lung, 2 (12,5%) for single liver, and 5 (31,25%) in multi-organ sites (including both bone and visceral metastases).

Salvage therapy was proposed for all our patients. Local recurrences were treated with chemotherapy and reirradiation, one of them received stereotactic radiotherapy. Nodal relapses were treated with chemotherapy and surgery and distant metastasis with chemotherapy.

Prognostic factors: multifactorial analysis:

Our final analysis examined the prognostic factors for the predictive value of survival rate.

Table 2 presents the relative importance of each single factor, unadjusted for other factors by Cox regression analysis.

Using univariate analysis, we found that sex, age (<40 years vs ≥ 40 years) and histology (grade 1–2 vs grade 3) were not associated with survival rates when metastasis occurred in patients with NPC ($P > 0.05$). The dominant factors that correlated with survival rates were: (1) nodal status (N1-2 vs. N3, $P = 0.049$), (2) metastatic sites (distant recurrence vs local recurrence, $P = 0.014$), (3) remission duration (less than or greater than 24 months, $P = 0.028$). When these factors were analysed in multivariate analysis, we found that nodal status (N1-2 vs. N3, $P = 0.025$) was an important prognostic factor.

Table 2:- Univariate and multivariate analysis of the different risk factors.

variables		Relapse		Univariate analysis			Multivariate analysis		
		No (n=80)	Yes (n=21)	OR	CI 95%	P value	OR	CI 95%	P value
Age (year)	Average	41,96 $\pm$ 16,93	46,71 $\pm$ 13,71	0,981	0,951-1,013	0,238			
Gender	Man	59(73,8)	14(66,7)	1,405	0,499-3,955	0,520			
	Women	21(26,3)	7(33,3)	Ref					
Diagnosis delay (mois)		7,79 $\pm$ 6	8,90 $\pm$ 7,37	0,975	0,908-1,047	0,486			
Histology	UCNT	75(93,8)	19(90,5)	1,579	0,284-8,777	0,602			
	Autres	5(5,3)	2(9,5)	Ref					
Therapeutic protocol	NEO CMT +RT	8(10)	0(0)	10 ⁹	0	0,999	37x10 ⁸	0	0,999
	NEO CMT +RCC	65(81,25)	15(71,4)	2,5	0,720-8,677	0,149	5,162	1,104-24,146	0,999
	RCC	7(8,75)	6(28,6)	Ref					
Spreading		49,06 $\pm$ 5,67	48,15 $\pm$ 3,57	1,038	0,933-1,155	0,492			
Stage	I	1(1,3)	0(0)	Ref					
	II	48(60)	9(42,9)	0	0	0,999			
	III	0(0)	0(0)						
	IVA	31(38,8)	12(57,1)	0	0	0,999			
T	T1	9(11,3)	4(19)	Ref					
	T2	28(35)	4(19)	3,111	0,643-15,049	0,158	2,193	0,401-11,979	0,365
	T3	15(18,8)	4(19)	1,677	0,332-	0,535	1,123	0,183-	0,900

					8,368			6,908	
	T4	28(35)	9(42,9)	1,383	0,342-5,590	0,649	0,506	0,098-2,619	0,417
N	N0	11(11,8)	1(4,8)	Ref					
	N1	20(25)	3(14,3)	0,680	0,056-6,547	0,680	0,508	0,044-5,801	0,586
	N2	44(55)	12(57,1)	0,333	0,039-2,845	0,315	0,154	0,016-1,436	0,101
	N3	5(6,3)	5(23,8)	0,091	0,008-0,995	0,049	0,058	0,005-0,704	0,025

Ref : reference variable

The OS after 4 years of relapse changes according to seat of relapse, so this OS for loco regional relapse and distant metastases was estimated at 83 % and 7,3 % respectively (Fig 3).

In addition, the remission duration was also an important prognostic variable. OS changes from patients who relapsed before and after 24 months, like we can clearly see in the curves (Fig 4).

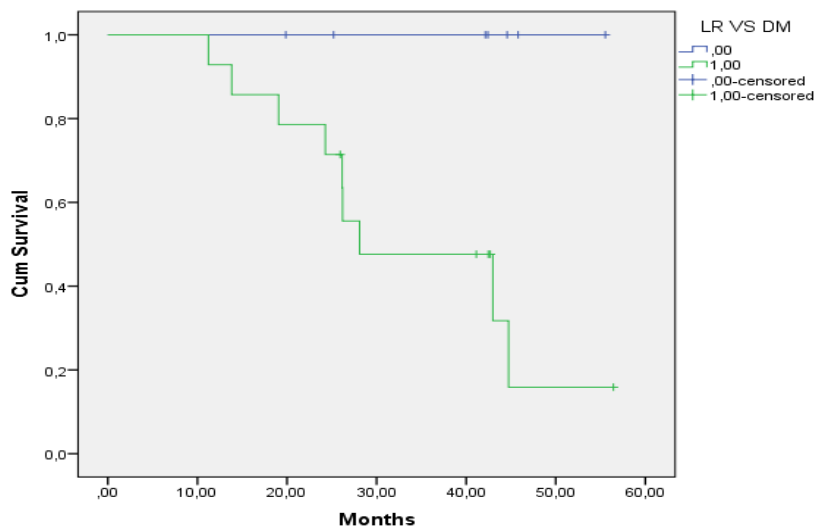


Figure 3:- Overall survival curve according to seat of relapse.

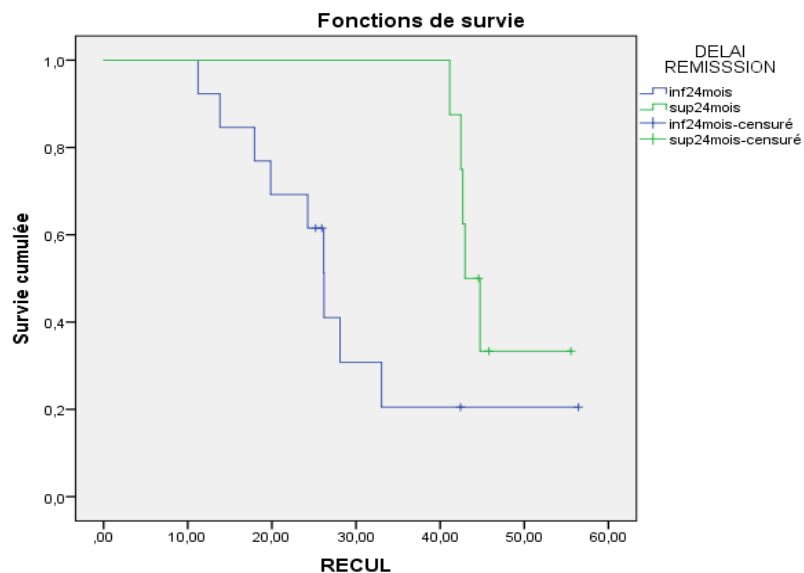


Figure 4:- Overall survival curve according to remission duration.

Discussion:-

Local recurrences and distant metastases are the main causes of treatment failures in NPC. With advances in imaging technology and the advent of modern radiation techniques, local control has substantially improved and distant metastases have become the predominant pattern of treatment failure [10].

In this study, all relapses occurred within the 5 first years following initial treatment. Thus, if patients have no recurrence within 5 years, they are much less likely to have a recurrence at all. This finding is consistent with previous studies [11]

Our local recurrence rate of 5% after a median follow-up of 45,37 months is comparable to other studies [12]. The rate of local and / or loco regional recurrence varies according to the series ranging from 18 to 35% [2, 13, 14, 15]. These rates do not generally exceed 10% in case of IMRT [3]. This indicates that local recurrences remain the greatest challenge.

The treatment results in patients with locally recurrent NPC are unsatisfactory, with a 5-year actuarial local control rate ranging from 15% to 37.8% [17, 18]. In our study, loco regional recurrences are in good control after reirradiation or surgery for nodal relapse except for one patient who refused reirradiation because of blindness risk.

NPC comprises an heterogeneous group of tumors as defined by their morphologic appearances and molecular genetic characteristics. The development of distant metastases represents the most important prognostic indicator in patients diagnosed with NPC. In this series, the rate of distant metastases was 15,8% (16/101), which is very close to the majority of series for example in a study of Clinical features and prognostic factors in patients with nasopharyngeal carcinoma relapse after primary treatment, the rate of distant metastases was 16,5% [19]. Another study published in 2016 interesting prognostic factors and failure patterns in non metastatic nasopharyngeal carcinoma after intensity modulated radiotherapy [20], the 5-year LRFS and DMFS rates of 94.6% and 82.6%, confirmed that distant metastasis has surpassed local relapse to be the major cause of failure in NPC in the IMRT era, whereas our previous data from the conventional radiotherapy era demonstrated that both local relapse and distant metastasis were the major causes of failure in NPC, with 5-year LRFS and DMFS rates of 85% and 81%.

A number of studies have confirmed that IMRT has improved local control but not distant control in NPC [21, 22, 23]. Thus, most of the parameters that influence distant control have not been altered by the introduction of IMRT. Therefore, among distant relapse bone was the first and most frequent distant metastatic site occurring in 33,3% of the patients. We further examined whether specific organ metastasis at the time of presentation had a prognostic significance for NPC patients. Our results revealed that among patients with distant metastases, the site of involvement did not appear to have an impact on survival. The presence of bone, liver and lung metastasis, as well as multi-organ metastases, did not demonstrate a statistically significant correlation with survival time.

Compared with patients with local recurrence, our finding supports previous observations that patients with a distant recurrence have a significantly poorer prognosis than patients with a local recurrence with ($p=0,014$). In our study, OS in local recurrences patients was much better than those with distant metastases.

The remission duration was also an important prognostic variable. We made a comparison between the two groups (intervals of relapse-free ≤ 24 months and >24 months. The differences in the survival curves were significant between the two groups ($p=0,028$). Similarly, in a study by Lee, recurrence in patients with long latency had a significantly better survival than patients with short latency [24]. However, the reason for the relatively better prognosis for a patient with long relapse-free intervals after primary treatment is unclear.

Conclusion:-

This report reviews NPC recurrence data after primary treatment. Rates of local and distant relapse were comparable with those previously reported, and the majority of recurrences occurred within the first five years. The prognosis after relapse varied with nodal status, seat of relapse as well as the remission duration after treatment. Local recurrences had a better prognosis than distant recurrences, while distant metastases to the bone had a similar prognosis with those to liver and multi-organ involvement. So, the main type of failure for NPC in the IMRT era was distant metastasis. The Sex, age, tumor size and pathology did not seem to impact the survival time in patients with recurrence. Despite these significant findings, there were some limitations because a retrospective design consists of complications such as lead-time and length time biases.

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:

The authors declare any conflicts of interest here

Author's Contribution:

Khalid Hadadi and Maroa Belemlih 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, H.S, and H.M, designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

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