

RESEARCH ARTICLE

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MANAGEMENT OF THE NASOPHARYNGEAL CANCER IN THE ONCOLOGY DEPARTMENT OF THE UHC/JRA (MADAGASCAR)

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ARTICLE INFO

Article History:

Received 10th July, 2019

Received in revised form

03rd August, 2019

Accepted 27th September, 2019

Published online 16th October, 2019

Key Words:

Chemotherapy,
Madagascar,
Nasopharyngeal cancer,
Radiotherapy

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ABSTRACT

Nasopharyngeal cancer (NPC) is uncommon in Sub-Saharan Africa, particularly in Madagascar. Radiotherapy is the main definitive treatment of this cancer. In our country, most patients did not have access to treatment because the radiotherapy machine did not exist during the study period. The aims of this study were to report the cases of NPC seen in the oncology department of the University Hospital Center Joseph Ravoahangy Andrianavalona (UHC/JRA) during the period from January 2009 to December 2013, to discuss the proposed treatments and to demonstrate the value of radiation treatment in the management of the patients. This was a descriptive and retrospective review of patient folder. Ninety seven cases of head and neck (H&N) cancer were recorded; we have studied 7 patients with NPC. The annual incidence was 0.3%. The ages of the patient were between 20 to 62 years old and the sex ratio 1.33. Nasal obstruction and epistaxis were the first troubles recognized by the patients. Our patients did not screen for viral investigation. Six patients had T4 and N2 classification AJCC and one patient with metastasis. Only chemotherapy was done for the cure. Cisplatin-Fluorouracil (CDDP-FU) and Adriblastina-Cisplatin (AC) were used. The recurrences appeared within the six months after the last cycle of chemotherapy and death within the year of the patient management. The oncology department of the UHC/JRA found a big challenge to treat the patients who needed radiation. They only gave chemotherapy to their patients. The outcome of this type of treatment is clearly questionable in the management of the NPC in advanced stage.

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Citation: Tovo Harivony, Tika, L., Randriamalala, NCR, Razakanaivo, M. and Rafaramino, F. 2019. "Management of the Nasopharyngeal cancer In The Oncology Department Of The Uhc/Jra (Madagascar)", *International Journal of Development Research*, 09, (10), 30377-30381.

INTRODUCTION

NPC is distinguished from other cancers of the upper aerodigestive tract by its epidemiology, pathology, clinical presentation and treatment. Ninety percent of the cases are undifferentiated carcinoma nasopharyngeal type (UCNT) (Lester, 2007). The etiological factors are Epstein Barr Virus (EBV), environmental risk factors such as diet and alcohol-smoking, and genetic susceptibilities (Nicholls *et al.*, 1997; Vokes *et al.*, 1997 and Polesel *et al.*, 2011). It is a relatively rare cancer and it accounts for only about 2% of upper respiratory cancers and 0.6% of all cancers, with the exception of a certain population group where the prevalence of the disease is considerably high (Nicholls *et al.*, 1997). The risk is high among Cantonese living in the central region of Guangdong in southern China. Intermediate risk is observed in south-east Asia (Thailand, Vietnam, Malaysia or the Philippines), but also in the Middle East, northern Africa and

the Mediterranean, Alaska and Greenland. It is a rare tumor in Europe and North America, the annual incidence in men and women in the United States is respectively 0.5 and 0.2 per 100,000 inhabitants (Vokes *et al.*, 1997). The anatomical characteristics of the nasopharynx condition the local evolution of the tumors as well as their symptomatology but especially the therapeutic management. The most common telltale clinical signs are otological, rhinological or neurological signs. Later, one or more high cervical lymphadenopathies can be found in the sub-digastric or spinal high territory (posterior triangle of the neck) with uni or bilateral distributions. Concurrent chemoradiotherapy with cisplatin is the standard treatment for NPC. It significantly improves patient survival (Rabti *et al.*, 2006). Intensity-Modulated Radiation Therapy (IMRT) techniques are used routinely in the irradiation of NPC. But depending on the equipment available to the center, the primary tumor can be irradiated using a linear accelerator or a teletherapy device. The prescribed dose varies between 65 Gy and 70 Gy. A

prophylactic dose of 45 to 50 Gy is delivered to the region at risk of tumor and lymph node swarmed. In case of nodal invasion, a supplement of 15 to 20 Gy in 1.5 to 2 weeks is necessary. A local control rate around 80% is observed for small tumors classified as T1 / T2a, and a local control rate of 55-72% for intermediate and locally advanced T2b / T3 / T4 tumors treated with supplement dose external beam radiotherapy to the total dose at least 70 Gy (Peter *et al.*, 2006 and Mazon and Grimard, 1999). Patients with UCNT have better survival (50% at 5 years) than those with squamous cell carcinoma (36%). There are more deaths by metastatic evolution in UCNT (46.7% versus 17%) and many more deaths by local evolution in squamous cell cancers (Baillet *et al.*, 1996). Brachytherapy is used in addition to external radiotherapy, for small volume tumors but also stereotaxic radiotherapy with 18 to 24Gy at high dose rates or 15 Gy in 3 fractions (Peter *et al.*, 2006 and Peter *et al.*, 2004). The thickness of the tumor should not exceed 10 mm and only the respective tumors of the sphenoid or wound after external radiotherapy or chemotherapy. Brachytherapy provides a total dose of 72.5 to 75 Gy at the level of the primary tumor. Table I shows better control of T3 tumors treated with brachytherapy boost (Mazon *et al.*, 2003 and Chang *et al.*, 1996). According to the anatomical constraint and logistics, brachytherapy is very little used for the treatment of the cancer of nasopharynx, however, it retained an important place in the re-irradiations of this region.

Table 1. Result at 5 years obtained for NPC treated by boostbrachytherapy Curado *et al.*

From 1970 to 1994	Number of cases	Specific survival	Overall survival
T1-T2			
Brachytherapy	92	82%	78%
No brachytherapy	56	53%	43%
		p=0.0001	p=0.0001
T3			
Brachytherapy	20	74	74
No brachytherapy	26	60	46
		p=0.25	p=0.08
T1-T3			
Brachytherapy	112	81	78
No brachytherapy	82	56	44
		p=0.0001	p=0.0001

Chemotherapy alone has been shown to be effective only in recurrent and metastatic cases (Rabti *et al.*, 2006). The combination chemotherapy protocol with taxane, platinum and fluorouracil has become standard in advanced H&N cancers in induction (Vermoken *et al.*, 2007 and Posner *et al.*, 2007). The objectives of our study were to report the cases of NPC seen in the oncology department of UHC/JRA during the period from January 2009 to December 2013, to discuss the proposed treatments and to demonstrate the value of radiation treatment in the management of the patients.

PATIENTS AND METHODS

This study was performed in the department of oncology of the University Hospital Center Joseph Ravoahangy Andrianavalona, Madagascar. This was a retrospective study during four years from January 1st, 2010 to December 31st, 2013. All patients with tumor located in the nasopharynx with histological evidence were included. We excluded the files where the diagnosis was confirmed but the patient had abandoned with incomplete data in the folder and the

hematological malignancies type of lymphomas. The parameters studied were: gender, age, risk factor, circumstances of discovery, histological type, AJCC (American Joint Committees on Cancer) staging, treatment and outcomes.

RESULTS

Over the four-year period, the oncology department of UHC/JRA had registered 97 patients diagnosed with cancers in the H&N region with a male predominance and an average age of 52 years. Seven patients had NPC including four men and three women. The average age of the patients was 44.4 years ranging from 20 to 62 years.

Patient 1: It was a 48-years-old woman who was seen for the first time on June 10th, 2010 for squamous cell carcinoma of the nasopharynx. She had discovered her illness by the appearance of pain in her throat. She did not have a particular risk factor. On clinical examination, she had a nasal voice, a bulged palate and a bilateral cervical lymphadenopathy. The cervical CT scan had classified his tumor T4N2MX. The Computed Tomography of Chest, Abdomen and Pelvis (CT CAP) did not find any metastatic localization. The oncology staff proposed him chemoradiation. She could not have it for financial reasons. Chemotherapy was then offered as an alternative. She had received 4 cycles of Paclitaxel followed by 2 cycles of AC. A clinical tumor regression of 50% was observed, then a progression at 3 months after the last cycle. At the last news, the patient died 13 months after the start of her care.

Patient 2: It was a 20-years-old man who had squamous cell carcinoma of the nasopharynx, first seen on June 28th, 2011. His illness started with repeated epistaxis. He did not have a particular risk factor. The clinical course was epistaxis and bilateral cervical lymphadenopathy. Due to a lack of financial means, he had not been able to do a CT scan. Clinically the tumor was classified T3N2MX. In front of this pecuniary problem, the oncology staff had proposed a chemotherapy type AC. One cycle had been administered, and then the patient was lost to follow-up.

Patient 3: It was a 54-years-old woman seen for the first time on June 20th, 2012 for squamous cell carcinoma of the nasopharynx. Her illness began with a nasal obstruction. She had a risk factor for chewing tobacco. The clinical course was marked by increased nasal obstruction and cervical mass syndrome with bilateral lymphadenopathy. She could not do a CT scan for financial reason. She had been clinically classified T3N2MX. The oncology staff had offered heran induction chemotherapy with Taxane-Platinum-Fluorouracil (TPF) followed by chemoradiation. She was only able to receive CDDP-FU, in total 4 cycles. Clinical examinations showed tumor stability. A progression of the tumor was noted 4 months after the last cycle. The patient died 18 weeks later in a context of poor performance status and dyspnea.

Patient 4: It was a 62-years-old man who had presented squamous cell carcinoma of the nasopharynx, seen in the oncology department on March 12nd, 2013. His illness had started 12 months before with a trailing nasal obstruction and epistaxis. During his consultation he had a swelling of the left side up to the orbital region with left blindness, nasal obstruction and epistaxis. The clinical course was marked by

this syndrome of significant left facial mass, cervical and mandibular lymph node bilateral. The H&N CT scan had classified his disease T4N2MX (Figure 1). The chest X-ray was normal. Abdominal ultrasound revealed hepatic nodules suggestive of secondary metastasis. Definitely it was classified T4N2M1. The oncology staff had proposed him a best supportive care (BSC). The evolution was marked by the tumor progression with the death of the patient in the month following his hospitalization.

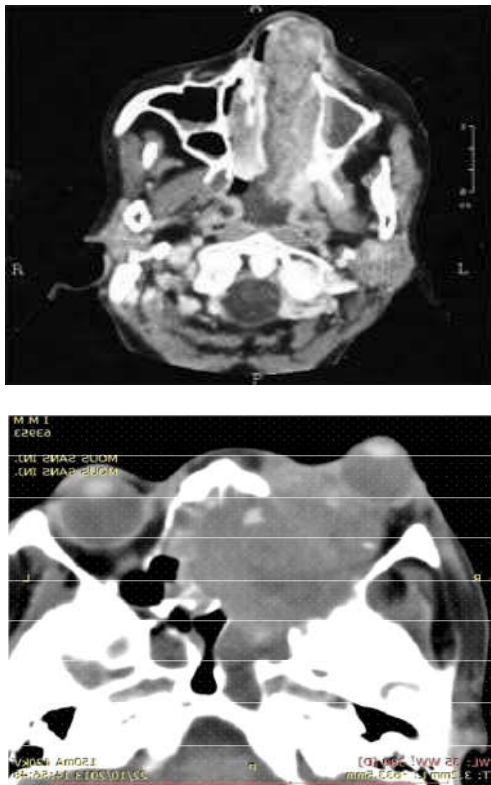


Figure 1. CT scan of patient 4 showing a nasopharyngeal tumor classified T4

Patient 5: It was a 20-years-old woman diagnosed with UCNT. She was seen for the first time on November 05th, 2013. Her illness began five months ago with nasal obstruction and repeated epistaxis, followed by a facial mass syndrome with nasal and maxillary swelling and right exophthalmia. She had no particular antecedent. The clinical examination found this mass syndrome and the presence of a multiple cervical lymph node bilateral. The H&NCT scan had classified her tumor T4N2MX. The CT CAP was not done. The oncology staff had proposed an induction chemotherapy type TPF followed by chemoradiation. For lack of financial means, she was then offered a chemotherapy type AC. She had received one cycle. The clinical evolution was bad with poor performance status. The family had asked to leave the hospital. A medical letter had been written to her doctor to recommend a supportive care. At the last news the patient died 8 months after the last cycle of chemotherapy.

Patient 6: It was a 52-years-old man who had a UCNT. He had been registered in the oncology department on September 18th, 2010. His illness began with cervical swelling. He was a smoking patient. On clinical examination, he had right cervical lymphadenopathy. The H&N CT scan had classified his tumor T2N2MX. The CT CAP was not done. The oncology staff had offered him chemoradiation. Due to a lack of means, he had received a chemotherapy type CDDP-FU. A clinical tumor

regression of 25% was observed, then a stability at the end of the four cycles of chemotherapy. A tumor progression was noticed five months after the end of the chemotherapy. The patient was unable to resume chemotherapy and was lost to follow-up.

Patient 7: It was a 55-years-old man who had squamous cell carcinoma of the nasopharynx. He was seen for the first time in the oncology department on February 10th, 2011. The circumstances of discovery of his illness were nasal obstruction and swelling of the face. The clinical examination found a large swelling of the right side with exophthalmia, cervical and supraclavicular lymph nodes. His risk factors were smoking and chewing tobacco. The only tests he could do were the chest X-ray and abdominal ultrasound that were normal. It had been clinically classified T4N2MX. The oncology staff had offered a palliative chemotherapy type CDDP-FU. He had received 2 cycles. The clinical outcome was aworsening of the general deterioration of the patient and the death after the second cycle of chemotherapy.

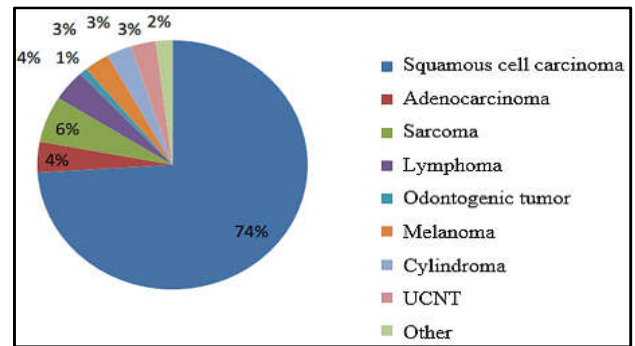


Figure 2. Distribution of H&N cancers according to the pathological result

Parameters studied: From 2010 to 2013, the oncology department has registered 97 cases of cancers of the H&N region. The NPC had an annual incidence rate of 1-2 cases per year or 5% of H&N cancers. The sex ratio was 1.33. The average age was 44.4 years old with two young adults aged 20 and a maximum age of 62 years old. Forty-two percent of our patients were smokers with smoked tobacco and chewing tobacco. None of our patients were alcoholics. No patient had been able to benefit from viral particle testing or viral serology for EBV. All patients initially had nasal obstruction. The trailing epistaxis was revealing in three patients. One patient had noted latent throat pain and one patient had early cervical mass syndrome likely to be lymph node. For three patients, the progression of the disease was towards the appearance and the evolution more or less rapid cervical lymph node and facial mass syndrome.

Table 2. Chemotherapy regimens received by patients treated in the oncology department

Patient	Decision of oncology staff	Received treatment
Patient 1	Chemoradiation	4 cycles of Paclitaxel and 2 cycles of AC
Patient 2	Chemotherapy type AC	1 cycle of AC
Patient 3	Chemoradiation	4 cycles of CDDP-FU
Patient 4	Best Supportive Care	Best Supportive Care
Patient 5	Induction chemotherapy type TPF followed by chemoradiation	1 cycle of AC
Patient 6	Chemoradiation	4 cycles of CDDP-FU
Patient 7	Chemotherapy type CDDP-FU	2 cycles of CDDP-FU

The swelling reached the neck on both sides and at the level of the face. There was a nasal deformity and an exophthalmia. Blindness was found in one patient. Among the seven patients, five had squamous cell carcinoma and two UCNT. Figure 2 shows the distribution of H&N cancers according to the pathological result. Squamous cell carcinoma accounted for about 74% of all cancers of the H&N region including nasopharyngeal location. UCNT represented 3%. Six out of seven patients arrived in the oncology department with a tumor classified at least T3 according to the AJCC classification. A bilateral cervical lymphadenopathy N2 was also present in seven patients. And a patient was metastatic from the outset during his first consultation. The treatment was based on chemotherapy that was either AC or CDDP-FU. Table II shows the chemotherapy regimens received by patients treated in the oncology department. The evolution of the disease was towards a death which occurred in the year following the diagnosis. The progression for patients who had chemotherapy was observed in the six months from the end of the last cure. This was preceded by either a low tumor regression of 25 to 50% and a short-term partial stability of 3 to 5 months.

DISCUSSION

In Africa, there are about 5000 new cases per year of NPC, but most of them are in the North of the continent where the incidence is estimated at 2.1% of cancers. The histological type UCNT predominated. The incidence of this cancer is very high in high-risk countries like South China and Maghreb countries. Sub-Saharan Africa, including Madagascar, is a low-risk area for NPC (Parkin *et al.*, 2003 and Curado *et al.*, 2007). Our study did not reflect the incidence or actual frequency of this cancer in Madagascar. Only a few case reports were found for some African countries. Their estimates were in line with other low-risk countries for NPC (Buraima *et al.*, 2009 and Ouoba *et al.*, 1997). In our cases, the incidence of this cancer compared to the oncology patient registry was estimated to be less than 1%, which was consistent with the literature. In 25% of cases, the age of onset of NPC was around 25 years. In the black population in the United States, this age was around 10 to 19 years old (Parkin *et al.*, 2003). But cancer could appear at much older ages. In our study we had an extreme at 62 years old. There had been two 20-year-old patients, one with squamous cell carcinoma and one with UCNT. Which corresponded to the literature data on the peak of occurrence of this tumor. The role of the EBV in the carcinogenic mechanism of NPC is now clearly established. No patient had viral serology, either before or during treatment. The only known risk factors were tobacco. In addition, there was no family history of NPC in our patients. The classic clinical signs indicative of a tumor process located at the level of the nasopharyngeal are an erythematous otitis, deafness, headache, later other trailing signs appear as nasal obstruction and epistaxis. Our patients had almost all presented these signs. Indeed, these signs were too often ignored by these patients or went unnoticed in consultation (Vokes *et al.*, 1997 and Wei and Sham, 2005). In our study, three patients had chemotherapy type CDDP-FU. Two patients had AC and one had a single paclitaxel course followed by AC. Multidrug therapy based on cisplatin is effective for squamous cell carcinoma and UCNT cancers. For these patients, the oncology staff had proposed either chemoradiation or induction chemotherapy followed by chemoradiation. CDDP-FU was found to be among the oldest protocols used in H&N cancers in general and NPC. Used in induction, this protocol provided

an objective response of 94% and a complete remission of 84% in an Asian study, however this same study had announced that only the patients with an early stage responded while the stages T3 and T4 did not respond and partially left residual lesions before radiotherapy. The complete response in a Spanish study was 40% and the partial response was 45%, with a 22-month survival rate. They mainly compared this protocol and marked its superiority over the Bleomycin-Epirubicin-Cisplatin (BEC) protocol (Atichartakarn *et al.*, 1988 and Bernal *et al.*, 1989). The AC protocol was also used in the oncology department. CHU et al had demonstrated that there was no benefit from this concurrent therapy with radiotherapy compared to radiotherapy alone for advanced stages, it only affected the incidence of tumor progression and relapse but not overall survival (Chua *et al.*, 1998). Currently, the TPF protocol, which has become a standard in induction of H&N cancers, is also beginning to be tested in NPC. This protocol is feasible but acute and late toxicity requires the use of conformational radiotherapy (Djemaa-Bendjazia *et al.*, 2012). This protocol had been proposed by the oncology staff but the patients could not do it because of financial means. Regardless of the chemotherapy protocols, it provided even small but significant benefits for overall survival and progression-free survival. This benefit was observed especially when administered concurrently with radiotherapy (Baujat *et al.*, 2006). Induction chemotherapy also had its place, it provided 80% local control despite recurrence and secondary metastases (Garden *et al.*, 1990). In total, the oncology department had patients with stages III and IV. The lack of financial means had forced him to propose only palliative treatments with questionable issue. In addition, these financial problems could not allow to have the best chemotherapy regimens. Since 2009, Madagascar had no longer a radiotherapy machine in public hospitals. It had used a telecobalt that is equivalent to a 4 MeV 2D linear accelerator. This type of machine is totally suitable for low income countries. Currently the technological evolutions are very fast, the techniques evolved from cobalt to mono and multi energetic accelerators, 2D to 3D and IMRT. Aggressive chemotherapy is complementary to conformational techniques to limit toxicity and have the best dosimetry. Indeed, in the 1950s and 1960s, when cobalt was commonly used, studies had already shown that local recurrence was not dependent on tumor stage but on volume and radiation dose (Chu *et al.*, 1984). Radiation therapy has been shown to improve local and locoregional control even when used alone (Sanguinete *et al.*, 1997). But it was no more effective than chemoradiation with cisplatin, especially for stage II, III and IV tumors that were the preserve of most patients. Improving the treatment of NPC would require radiotherapy and chemotherapy, as several clinical trials have shown with new drugs and new radiotherapy techniques (Chow *et al.*, 2002; Al-Sarraf *et al.*, 1998 and Karen, 1998).

Conclusion

The oncology department of the UHC/JRA found a big challenge to treat the patients who needed radiation, because the only radiotherapy machine in Madagascar has stopped functioning since 2009. They only gave chemotherapy to their patients. The outcome of this type of treatment is clearly questionable in the management of the NPC in advanced stage. To improve the management of this cancer, the creation of a radiotherapy public center must be performed as soon as possible.

Conflicts of interest: None.

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