

Diagnostic, Therapeutic and Evolutionary Characteristics of Nasopharyngeal Cancer in Morocco

Elamin Marnouche^{1*}, Mohammed Elmarjany¹, Rachid Razine², Abdelhak Maghous³, Issam Lalya¹, Khalid Andaloussi¹, Amine Bazine¹, Noha Zaghba¹, Khalid Hadadi¹, Hassan Sifat¹ and Hamid Mansouri¹

¹Department of Radiotherapy, Mohamed V Military Hospital, Rabat, Morocco

²Department of Public Health, Laboratory of Biostatistics, Clinical Research and Epidemiology, School of Medicine and Pharmacy of Rabat, Rabat, Morocco

³National Institute of Oncology, Rabat, Morocco

Abstract

Background: Nasopharyngeal carcinoma (NPC) is a radiosensitive and radio curable cancer, the radiation therapy (RT) is the mainstay of treatment with significant improvement in survival of patients. The aim of this study was to report the experience of Military Hospital Mohamed V in the management of NPC and their results.

Materials and methods: 83 no metastatic NPC patients managed at the radiotherapy department of Military Hospital Mohammed V of Rabat in Morocco, between January 2005 and December 2009, were included for investigation of their demographic, histological, therapeutic and follow-up characteristics. Statistical analysis of the data was carried out by the SPSS for Windows.

Results: The mean age was 44.5 ± 12.5 years with sex ratio 4:1. At diagnosis, rhinologic symptoms represented the most common clinical presentation, reported by 56 (67, 5%) patients. Almost ninety percent (n=74) of patients presented UCNT histology. Most of the patients (85.5%) presented a locally advanced disease; stage III and IV. Therefore, forty patients (48.2%) were treated by concurrent chemoradiotherapy and 35 patients (42.2%) received induction chemotherapy. With a mean follow up of 70 ± 32 months, twenty nine patients (34.9%) died, 6 (7.2%) presented local or locoregional relapse. While 11 (13.2%) patients presented distant recurrences. The five years overall survival (OS) was 68% ranging from 91% for both stage I and II, 79.3% for stage III to 40% for stage IV. The five years disease free survival (DFS) was 81.1%, whereas distant failure free survival (DFFS) was 84.1%. In multivariate analysis, the disease stage according to the seventh edition of the AJCC system was an independent prognostic factor.

Conclusion: Our outcomes in NPC are similar to the literature. Patients' survival is directly impacted by the disease staging which is the most important prognostic factor. We hope to improve these results with the recent acquisition of volumetric-modulated arc therapy machines.

Keywords: Nasopharyngeal carcinoma; Radiotherapy; Concomitant radio-chemotherapy

Abbreviations: NPC: Nasopharyngeal Carcinoma; OS: Overall Survival; DFS: Disease Free Survival; DFFD: Distant Failure Free Survival; AJCC: American Joint Committee on Cancer Staging System; TNM: Tumor Node Metastasis; RT: Radiation Therapy; IMRT: Intensity Modulated Radiotherapy; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; 5FU: 5 Fluoro Uracil; WHO: World Health Organization; IQR: Interquartile Range; EBV: Epstein Barr Virus; L-FFR: Local Failure-Free Rate; UCNT: Undifferentiated Carcinoma of Nasopharyngeal Type.

Background

Nasopharyngeal carcinoma (NPC) is a cancer arising from the nasopharynx epithelium. Within the boundaries of the nasopharynx, the tumor epicenter is frequently seen at the fossa of Rosenmuller, from where the tumor invades adjacent anatomical spaces or organs [1]. It differs from other head and neck squamous cell carcinomas in epidemiology, histology, natural history and response to treatment.

Nasopharyngeal carcinoma is an uncommon cancer in the most parts of the world and demonstrates a marked geographical variation. The age-adjusted incidence rate (per 100,000 people per year) among men ranges from 0.6 in the United States and Japan to 5.4 in Algeria, 5.8 in the Philippines, 11.0 in Singapore, 17.2 among Eskimos, Indians and Aleuts in Alaska to 17.8 and 26.9 in Hong Kong and Guangdong Province in Southern China, respectively [2-4]. In Morocco, there

is a few data about incidence coming from several cities such as Casablanca (3, 74 per 100,000 men/year versus 0, 88 per 100,000 women/year in 2004) [5] or rabat (3, 3 per 100,000 men per year versus 1, 8 per 100,000 women per year in 2005) [6]. The male-to-female incidence ratio is 2:1 to 3:1. [7]. A bimodal age distribution is observed in low-risk populations (such as Europe and North America). The first peak incidence arises between 15 to 25 years of age, with the second peak at 50 to 59 years of age [8-10]. In high-risk populations (including Southeast Asia, North Africa, Eskimos) [11,12], the peak incidence occurs in the fourth and fifth decades of life [8].

Since it is a clinically occult site, patients may remain asymptomatic for a prolonged period. The majority of patients has a locally and/or regionally advanced disease because of this asymptomatic period or, in some cases, due to a missed diagnosis [13,14]. Diagnosis of

*Corresponding author: Elamin Marnouche, Department of Radiotherapy, Mohamed V Military Hospital, Rabat, Morocco, Tel: 212665096287; E-mail: elaminmarnouche@gmail.com

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nasopharyngeal carcinoma is made by biopsy of the primary tumor or Fine-needle aspiration of a suspicious neck mass. The staging workup is performed, as disease staging according to the American Joint Committee on Cancer staging system AJCC is considered as the most important prognostic factor.

The development of radiation therapy (RT) revolutionized the management of nasopharyngeal carcinoma with the advent of megavoltage machines; the review by Moss [15] in 1965 showing 25% of patients alive at 5 years marked the first major breakthrough and established the role of RT as the primary modality of choice [16]. The adjunction of concurrent chemotherapy has more improved survival [17]. Recent development in RT techniques with Intensity-modulated radiotherapy (IMRT) further improved tumor coverage and organs at risk sparing.

The aim of this study was to report the experience of Military Hospital Mohamed V in the management of NPC.

Methods

This was a retrospective analytic study of 83 no metastatic NPC patients treated at the radiotherapy department of Military Hospital Mohammed V of Rabat in Morocco, between January 2005 and December 2009. Informed verbal consent was obtained from all patients to access and use their patient data. This study was submitted to and approved by research committee of military teaching hospital Mohamed V.

Patients were investigated by physical examination, fiberoptic examination, head and neck computed tomography CT, Magnetic resonance imaging MRI was not used currently, chest X-ray and abdominal ultrasound or thoracic and abdominal CT. Bone scan was performed if clinically indicated and for patients with locally advanced disease. The seventh edition of the AJCC system was used for disease staging.

All patients were treated by 3D radiotherapy technique using lateral opposing cervicofacial fields that encompassed the primary tumor and the upper neck nodes in one volume with a matching lower anterior cervical field for the lower cervical lymphatics in order to deliver a "prophylactic dose" 50 Gy, 2 Gy/fraction with a first lateral treatment fields reduction "spine off" at 40 Gy and electron therapy was used to complete dose in this area to respect spinal cord tolerance. Then, treatment fields were reduced again to reach 70 Gy in primary tumor and, if technically possible with photons X 6 MV, in pathologic cervical lymph nodes. If not, electron therapy was used to complete the dose in cervical lymphadenopathies. Regarding organs at risk, especially critical structures, we tried to respect tolerance's threshold. However, radiation technique capabilities and disease stage (mostly locally advanced disease) were the main limitations. All patients were well informed of radiation risk in term of late toxicities.

The radiation treatment was used alone or with concurrent chemotherapy based on weekly cisplatin. Induction chemotherapy was administered for patients with locally advanced disease and different regimens were used based on cisplatin, anthracycline and 5FU.

The patient's follow-up continued according to the following schedule: every 3 months for the first 2 years, every 6 months for the 3th, 4th and 5th years and then annually. Physical examination especially head and neck was performed in every visit. CT scan and fiberoptic examination were performed periodically to evaluate the response, to detect relapse and to assess late effects.

Data was collected using a well-structured checklist containing the important study parameters. The record collection included the patient related data (age at diagnosis and gender). Data included also clinical presenting symptoms (rhinologic, otologic, neurologic and lymph node syndromes), duration of symptoms (months) and other clinical data such as TNM classification and stage of disease according to the AJCC seventh edition 2010 and the histological type according to the world health organization WHO classification 1978. The type, the modalities of primary treatment (radiotherapy, chemotherapy, both), the date and the sites of relapse (local, loco regional, distant metastases), the follow up data, the death date and the date of last follow-up visit were also recorded.

Statistical analysis of the data was carried out by the SPSS 20 for Windows (SPSS, Inc., Chicago, IL, USA). Qualitative variables were presented as number and percentages. Quantitative variables were presented as mean \pm standard deviation for variables with normal distribution and as median and interquartile range (IQR) for variables with skewed distributions. Khi2 test was used to compare qualitative variables. The survival rate was analyzed with the Kaplan-Meier method.

Results

Eighty three patients were treated in our department. Table 1 summarizes their clinical, para clinical, histological characteristics and treatment modalities.

The mean age was 44.5 ± 12.5 years with sex ratio 4:1. At diagnosis, the rhinologic symptoms represented the most common clinical presentation (67, 5%). Otologic symptoms and adenomegaly were present respectively in 50 (60.2%), 44 (53%) patients. The median symptoms duration before histologic diagnosis was 8.9 months [7-12]. According to the former WHO classification, almost ninety percent of patients presented UCNT histology.

Most of patients (85.5%) presented a locally advanced disease (stage III and IV). Therefore, chemotherapy was usually administrated (concomitant or induction chemotherapy). Induction chemotherapy was delivered in 3.1 ± 0.52 cycles.

With a mean follow up of 70 ± 32 months, twenty nine patients (34.9%) died, 6 (7.2%) presented local or locoregional relapse. While 11 (13.2%) patients presented distant recurrences, half of them occurred in bone. The mean duration of recurrence was 23.6 ± 17.28 months. Forty six (55.4%) patients were healthy and 8 (9.6%) patients were lost to follow up. We tried to contact all patients who were lost to follow-up by phone and by sending correspondence letter without response.

The five year overall survival (OS) was 68% ranging from 91% for both stage I and II, 79.3% for stage III to 40% for stage IV (Figures 1 and 2). The five year disease free survival (DFS) was 81.1% (Figure 3) whereas distant failure free survival (DFFS) was 84.1%.

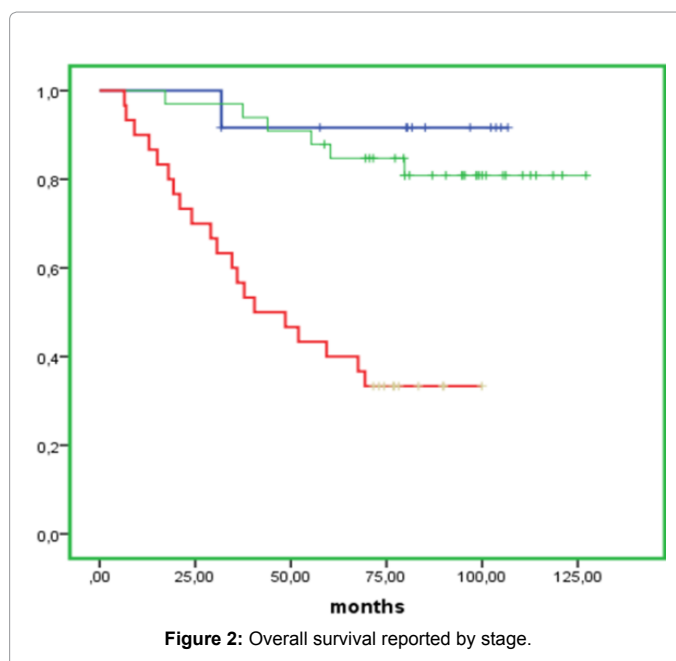
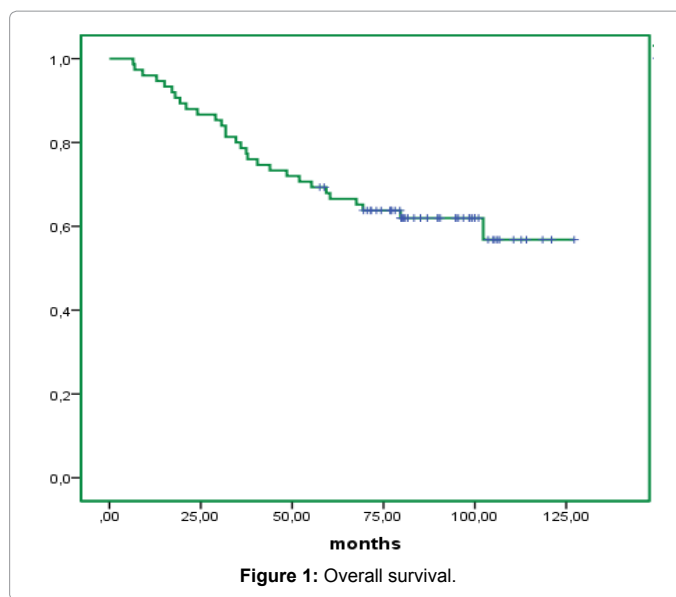
In univariate analysis shown in Tables 2 and 3, the TNM stage impacted significantly OS ($p=0.002$), DFS ($p=0.001$) and DFFS ($p=0.002$). T-category influenced significantly OS ($p=0.012$) and DFS ($p=0.022$) whereas N- category influenced significantly both DFS ($p=0.019$) and DFFS ($p=0.001$). Induction chemotherapy as treatment modality was a significant factor for both DFS ($p=0.001$) and DFFS ($p=0.018$). Moreover, duration between induction chemotherapy and radiotherapy also influenced statistically DFS ($p=0.028$) and DFFS ($p=0.04$). For OS, TNM stage was an independent prognostic factor in multivariate analysis ($p=0.002$). However, Multivariate analysis was not

performed for DFS and DFFS because of the relatively small number of events.

Item	Results
Age °	44.5 ± 12.5
Gender \$	
Men	96 (83.1)
Women	14 (16.9)
Clinical review \$	
Lymph node syndromes \$	
Unilateral	36 (43.4)
Bilateral	8 (9.6)
Otologic syndrome \$	50 (60.2)
Neurologic Syndrome \$	16 (19.3)
Rhinologic syndrome \$	56 (67.5)
Time between initial symptoms and diagnosis* (months)	8.9 [7-12]
Histology \$	
Type (I)	0
Type (II)	9 (10.8)
Type (III)	74 (89.2)
Para clinical review \$	
Cervicofacial CT	83 (100)
Nasopharyngeal MRI	7 (8.4)
Chest X ray	78 (94)
Abdominal ultrasound	74 (89.2)
Thoracic and abdominal CT	11 (13.3)
Bone scan	55 (66.3)
Stage \$	
I	7 (8.4)
II	5 (6)
III	38 (45.8)
IV	33 (39.7)
Treatment modalities \$	
Radiotherapy alone	7 (8.4)
Concurrent Chemoradiotherapy	40 (48.2)
Induction chemotherapy followed by Concurrent chemoradiotherapy	35 (42.2)
Induction chemotherapy regimen	
Cisplatin, anthracycline, 5FU	7 (20)
Cisplatin, anthracycline	23 (65.7)
Cisplatin, 5FU	5 (14.3)
Duration between induction chemotherapy and radiotherapy° (days)	43.24 ± 20.31

°Quantitative variable presented as mean ± standard deviation
 * Quantitative variable presented as median and interquartile range
 \$ Qualitative variable presented as number (n) and percentage (%): n (%).

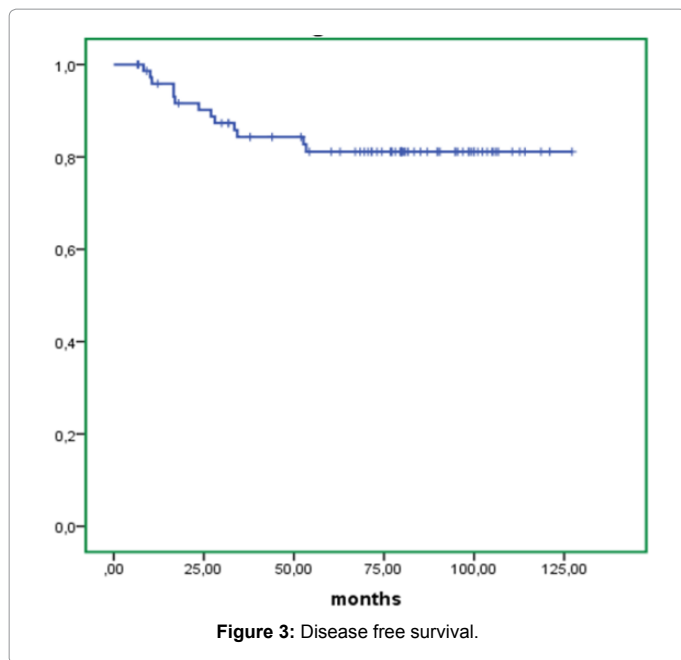
Table 1: Clinical, para-clinical, histological, therapeutic characteristics of patients.



	OS			DFS			DFFS		
	p	OR	95% IC	p	OR	95% IC	p	OR	95% IC
TNM stage	0.002	0.38	0.2-0.70	0.001	5.79	2.17-15.41	0.002	4.64	1.8-12
T category	0.012	0.56	0.36-0.88	0.022	2.10	1.11-3.98	0.34	-	-
N category	0.24	-	-	0.019	2.87	1.2-7	0.001	15	3.09-72
Parapharyngeal space involvement	0.054	-	-	0.18	-	-	0.26	-	-
Gender	0.98	-	-	0.83	-	-	0.76	-	-
Histology	0.55	-	-	0.99	-	-	0.99	-	-
Induction chemotherapy	0.06	-	-	0.001	13.9	2.8-69.4	0.018	5.6	1.34-23.4
Induction chemotherapy regimen	0.9	-	-	0.69	-	-	0.7	-	-
Time between induction chemotherapy and radiotherapy	0.054	-	-	0.028	1.04	1.04-1.07	0.04	1.04	1.02-1.07
Time between initial symptoms and diagnosis	0.12	-	-	0.81	-	-	0.4	-	-

°Quantitative variable presented as mean ± standard deviation.
 *Quantitative variable presented as median and interquartile range. \$ Qualitative variable presented as number (n) and percentage (%).

Table 2: Univariate analysis for factors influencing overall, disease free, distant failure free survival.



Late toxicities	Frequency (%)
Trismus	39.4 (n=33)
Hyposialia (grade3)*	38.5 (n=32)
Cervical fibrosis	19.3 (n=16)
Otologic disorders	61.5 (n=48)

*According to CTCAE v3.0

Table 3: Proportion of late toxicities.

Five women (17.2%) died versus 24 (82.8%) men. Forty percent of women who died were under 40 years of age versus 60% but it was not statistically significant.

Discussion

Chemoradiotherapy is the mainstay of NPC treatment. It improved significantly survival rates which decreased with disease stage. We found that the five years overall survival was 68%, ranging from 91% for stage I and II to 40% for stage IV. The TNM stage remained the most important prognostic factor.

The five years OS was 68%; 91% for both stage I and II, 79,3% and 40% for stage III and stage IV respectively ; whereas Five-years OS rates from series ranged from 36% to 58% [18-23]. Lee et al. found in a retrospective study including 2687 patients, a five years OS rate of 75% with 75% and 58% for stage III and IV respectively [16]. In the same study, they reported DFFS of 81% versus 84.1% in our institution.

The TNM staging is the most important prognostic factor. In general, advanced T-category is associated with worse local control and overall survival whereas advanced N-category predicts an increased risk of distant metastasis and a worse survival. In multivariate analysis, TNM stage was an independent prognostic factor (p=0.002) impacting overall survival. In univariate analysis, T-category influenced significantly OS (p= 0.012) and DFS (p=0.022) whereas N- category influenced significantly both of DFS (p=0.019) and DFFS (p=0.001).

In addition to T and N categories, pre- and post-therapy Epstein Barr virus (EBV) DNA levels have a prognostic significance: higher levels confer a worse prognosis, stage for stage [24-27]. Five-years survival

rates according to tumor node metastasis (TNM) stage grouping and pretherapy EBV DNA levels from one case series are as following: Stage I, II disease, low DNA (<4000 copies/mL)-91%, Stage I, II disease, high DNA (≥ 4000 copies/mL)-64%, Stage III, IV disease, low DNA-66%, Stage III, IV disease, high DNA-54% [26]. As the research of EBV DNA is not a standard of a work up in the NPC, we did not perform EBV DNA levels in the routine practice.

Parapharyngeal space extension may be associated to distant metastasis. Cheng et al. [28] found parapharyngeal space extension to be the key factor in distant metastasis even in N1 and N2 NPC. However, Teo et al. [29] did not find parapharyngeal space involvement to be an independent significant prognostic factor in a study of 903 patients. In this study, we did not find that the parapharyngeal space involvement affects the occurrence of distant metastasis (p=0, 26). These contradictory findings may be attributed to the varying definitions of parapharyngeal space and the incidence in the different series.

Another prognostic factor to consider is the gross volume of the primary tumor (GTV-P). Although it is highly correlated to T-stage, considerable variability in tumor volume exists within the same T-stage, and evidence increasingly suggests that tumor volume as an independent significant factor can better predict prognosis than T-category as specified by AJCC [29-32]. In a study of 308 patients staged with MRI, Sze et al. [32,33] showed that those with GTV-P of <15 cm³ had significantly higher L-FFR than those with a value of ≥ 15 cm³ (97% vs. 82% at 3 years; p<0.01). Multivariate analysis confirmed GTV-P to be a strongly significant factor independent of T-category by the 1997 fifth edition of the AJCC; the risk of local failure increased by 1% for every 1-cm³ increase in volume.

Most series found significantly better prognosis for females and younger patients [34]; in this study, five women (17.2%) died versus 24 (82.8%) men. Forty percent of women who died were under 40 years of age versus 60% but it was not statistically significant.

Depending on the degree of differentiation, nasopharyngeal carcinoma was categorized into three pathological subtypes, on the basis of WHO criteria, as follows: (I) squamous cell carcinoma, (II) no keratinizing carcinoma, and (III) undifferentiated carcinoma (UCNT: undifferentiated carcinoma of nasopharyngeal type) [35]. In the current World Health Organization (WHO) pathologic classification, [36] released in 2005, types II and III were combined into a single category of non-keratinizing carcinoma. A third category, the basaloid squamous carcinoma, was added. Of note, the former WHO classification remains quite commonly used. Although not all studies found histology to be an independent prognostic factor, [37,38] many found no keratinizing and undifferentiated carcinomas to be more radiosensitive and offer better prognosis than keratinizing squamous cell carcinoma [39-41]. We found that histology did not affect overall survival (p=0.55).

The role of induction chemotherapy followed by either RT alone or concurrent chemoradiotherapy is unclear. The MAC-NPC meta-analysis included data from 1039 patients included in six trials [17]. There was a statistically significant improvement in progression free survival (47 versus 39 percent at 5 years, HR 0.81, 95% CI 0.69-0.95). However, the difference in overall survival was not statistically significant (57 versus 55 percent at 5 years, HR 0.96, 95% CI 0.80-1.16). In a multicenter phase III trial conducted by Sun Yat-sen University at 10 centers in China, 480 patients with stage III-IVB, node-positive disease were randomly assigned to sequential chemotherapy with three cycles of docetaxel, cisplatin, and fluorouracil (TPF) followed by concurrent cisplatin plus RT, or to concurrent cisplatin plus RT

alone without adjuvant chemotherapy [42]; Failure-free survival at three years was significantly better in those receiving induction TPF compared with concurrent chemoradiotherapy alone (80 versus 72 percent, HR 0.68, 95% CI 0.48-0.97). The three-year overall survival rate was also significantly better in those receiving induction TPF (92 versus 86 percent, HR 0.59, 95% CI 0.36-0.95). Distant metastases were significantly reduced, and local regional failure was lower, although not significantly, in the induction arm [42]. We found that induction chemotherapy influenced DFS ($p=0.001$) and DFFS (0.018) in univariate analysis. Moreover, time between induction chemotherapy and radiotherapy also influenced statistically DFS ($p=0.028$) and DFFS ($p=0.04$). In theory, induction chemotherapy may control micrometastases earlier and facilitate RT planning by downstaging locally advanced tumors, especially for large T4 lesions, advanced nodal disease, or when delivery of a full course RT is challenging due to close proximity to critical structures [43]. Therefore, it seems reasonable that time between induction chemotherapy and RT could have an effect on survival. Induction chemotherapy was typically given 3 weeks prior to the initiation of RT [44].

Intensity-modulated radiotherapy (IMRT) has supplanted conventional radiotherapy in the treatment of NPC in an increasing number of institutions throughout the world. In centers where modern radiation technology is available, IMRT is the preferred method. Briefly, this technique caters for delivery of tumoricidal doses to gross tumor and subclinical disease, while minimizing doses to adjacent normal tissues. The recent improvement in disease control and survival in patients with nasopharyngeal carcinoma is partly attributable to IMRT [1]. A review of 1593 patients who were treated at a single institution with progressive radiotherapy techniques (2D radio therapy, 3D radiotherapy, and IMRT) over two decades (1994 to 2010) also showed increased disease-specific and overall survival in individuals who received IMRT [45]. In a randomized study by Peng and colleagues, IMRT contributed to an absolute improvement in 5-years loco regional control of 7.7% compared with conventional 2D radiotherapy. [46]

The relatively small number of patients was the main limitation of this study. However, we did this choice to have a sufficient follow-up time. A lack of reporting toxicities (grading) was also noted. Therefore more rigors will be needed and procedures will be established to correct this lack of reporting.

Conclusion

Our results in NPC management are similar to the literature. Patient's survival is directly impacted by the disease staging which is the most important prognostic factor. We hope to improve these results with the recent acquisition of volumetric-modulated arc therapy machines.

Competing Interest

The authors declare that they have no competing interests.

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Authors' Contribution

E.M. and M.E. performed research and share the first position on article; E.M., R.R and A.M, analyzed data statistically; E.M. and A.M., collected the clinical data; K.A, A.B., I.L., 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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