ejpmr, 2018,5(3), 523-529

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

NASOPHARYNGEAL CARCINOMA IN TUNISIAN CENTRE: ABOUT 712 CASES
LE CANCER DU CAVUM DANS LE CENTRE TUNISIEN: A PROPOS DE 712 CAS

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Article Received on 17/01/2018 **Article Revised on 07/02/2018** **Article Accepted on 28/02/2018**

SUMMARY

Purpose: The current retrospective study detail the various epidemiological, clinical, therapeutic and prognostic factors of nasopharyngeal carcinoma (NPC) in the center of Tunisia. **Materials and Methods**: The study concerned 712 patients with confirmed NPC treated between 1995 and 2013 in department of radiation oncology Hospital Farhat Hached of Sousse and the medical center Ibn Khaldoun Hammam Sousse. Survival rates were calculated using the Kaplan Meier method, and the differences were compared with the log rank test. Multivariate analysis was performed with the Cox regression model to identify independent factors. **Results:** The median age at presentation was 47 years, the most common presenting symptom was a palpable neck lump (70, 9%) and the median duration of symptoms was 7, 2 months. The predominant histological type was undifferentiated carcinoma (UCNT). According to the classification TNM 2010, the tumors are divided into T1 in 43.3% of cases, T2 in 25%, T3-T4 in 30, 6%. 7, 3% of patients was metastatic at presentation (bone metastasis 90, 3%). the 5-year overall survival, recurrence-free survival and metastasis-free survival were, respectively, 60.3%, 89.2% and 80.1%. **Conclusion:** In our series were noted good results in terms of local control and overall survival. The treatment is mainly based on the multimodal chemotherapy and radiotherapy association. High radiation doses are associated with excellent local control at the cost of late toxicities which become more important for the young population.

KEYWORDS: Nasopharyngeal carcinoma; Radiotherapy; Chemotherapy; Prognostic Factors.

INTRODUCTION

The NPC attracts special attention among all other head and neck cancers for marked difference in geographical distribution : South East Asia is a high risk region for NPC especially southern regions of China, where the malignancy is observed in middle-aged individuals, an intermediate rates are observed in several populations in North Africa and in the Middle East.[1] An association with Epstein Barr virus (EBV) is well established in these populations. Also it is characterized by the predominance of undifferentiated types histological. High-dose radiation therapy with chemotherapy is the primary treatment of NPC, both for the primary tumor site and the cervical lymph nodes.

The purpose of this report is to describe epidemiological, clinical, therapeutic and prognostic factors of nasopharyngeal carcinoma.

MATERIALS AND METHODS

This is a descriptive retrospective study from 1995 to 2013, including 712 cases of nasopharyngeal carcinoma treated at the radiotherapy department, Hospital Farhat Hached of Sousse and the medical center Hammam Sousse Ibn Khaldoun. All patients had histological confirmed nasopharyngeal cancer. For the realization of this work we have developed an information sheet including all necessary elements in our study.

The Statistical Package for the Social Sciences (SPSS) program was used for statistical analysis. Survival rates were calculated using the Kaplan Meier method, and the differences were compared with the log rank test. Multivariate analysis was performed with the Cox regression model to identify independent factors.

RESULTS

Characteristics of patients are detailed in Table 1.There was a male preponderance (sex-ratio: 2.4). The mean age at diagnosis was 47 years (Ranging from 08 to 85 years). The predominant histological type was undifferentiated type (UCNT) in 95.1% of cases. The cervical lymph nodes were the most common revealing sign (70.9%), Paraneoplastic syndrom was present in 4.2% of cases; 7.3% of our patients had distant metastases at the time of diagnosis, of which 90.3% were bones metastases.

Neoadjuvant chemotherapy followed by radiotherapy was used in 60.8% of patients. Only 16.2% of patients had been treated by concomitant chemo radiotherapy.

Rradiotherapy was delivered by a cobalt machine (Gamma ray) for the majority of patients. Only 36 patients were treated with three-dimensional radiotherapy via a linear accelerator. Radiotherapy with a dose> = 70 Gy was delivered in 82,8%.

Survival and prognostic factors

The median follow-up time 42 months (range 2.0- 198 months), with 6.7% patients lost follow-up. The 5-year overall survival(OS), disease-free survival (DFS) and local-recurrence free survival(LRFS) were 60.3%, 71% and 98.2% respectively (figure 1,2,3).

In univariate analysis (Table 2) we focused on patients treated with curative intent (n=594), the 5-year OS of T1 and T4 were 67, 7% and 57, 9%, p = 0.001. The 5-year OS rate for patients treated with exclusive radiotherapy was 56, 8%, it was 74, 7% for patients treated with concomitant chemo radiotherapy. This rate was 70, 1% for patients treated with neoadjuvant chemotherapy and radiotherapy.

Multivariate analysis

Cox regression multivariate analysis(Table 3) showed that age, delay of consultation, the TNM classification (especially lymphe node involvement), treatment modalities, radiotherapy doses were significant factors (P < 0.05).

Failure pattern

There were 162 patients (22.7%) failed during follow up, with 83 in local-regional, 79 in distant metastasis. The median failure times were 23 months (6–150 months) and 10 months (1–72 months) for local-regional recurrence and distant metastasis. Regarding loco-regional recurrence, there were 60 cases of recurrence in the nasopharynx and 23 cases of lymph node recurrence. The survival rate at 05 years for patients who presented loco-regional recurrence was 29.3%.

The most common site of metastasis was bone (56 patients, 71%); other sites included liver (n = 16) and lung (n = 7). The 3-year survival after the onset of metastasis was 52%.

Late toxicities

The most common late toxicities were xerostomia, neck fibrosis and hearing loss, with incidence of 78.6%, 68.8% and 40.1% respectively. 7 patients (1,6%) had developped osteoradionecrosis. 3,2% of patients presented endocrine disorders.

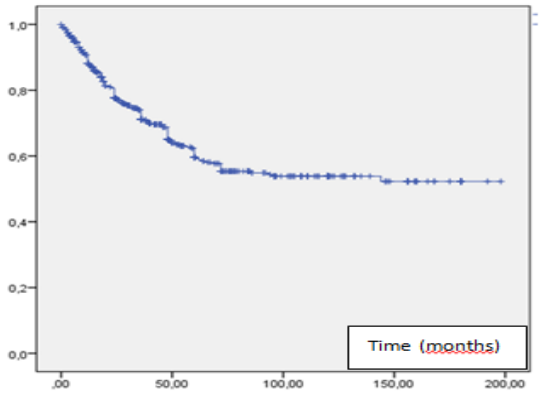

Figure 1: The Overall Survival.

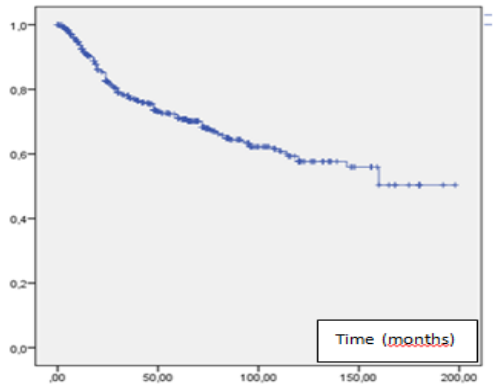

Figure 2: Disease-free-survival.

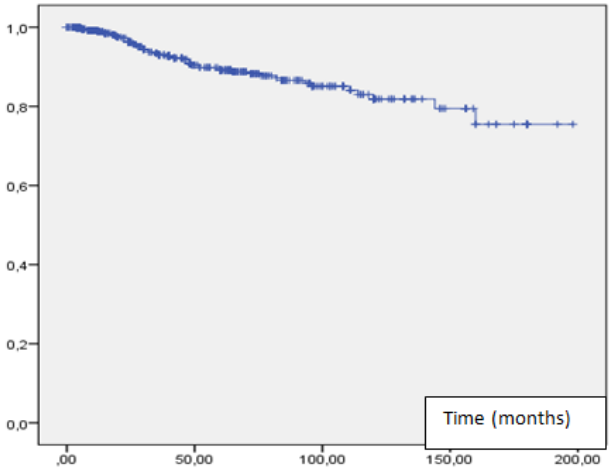

Figure3: Local-recurrence-free survival

Table 1: The characteristics of patients.

	Number	Percentage
Gender		
Male	503	71
Female	209	29
Age (years)		
<20	78	11
20-50	356	50
>50	278	39
Symptoms/signs		
Cervical nodes	505	70,9
Otologic signs	438	61,5
Rhinologic signs	434	60,9
Neurologic signs	401	56,3
Ocular signs	46	6,4
Histopathology		
Undifferentiated NPC	677	95
Moderately differentiated NPC	13	1,8
Poor differentiated NPC	11	1,6
Other	11	1,6
T classification(2010)		
T1/T2/T3/T4	303/178/108/123	42,5/25/15,2/17,3
N classification(2010)		
N0/N1/N2/N3	173/177/219/143	24,3/24,8/30,8/20,1
Treatment		
Exclusive Radiotherapy	130	18,3
Concomitant chemo-radiotherapy	115	16,2
Neoadjuvant chemotherapy-radiotherapy	433	60,8
Chemotherapy exclusive	34	4,7

Table 2: prognostic Factors.

Factors	Overall Survival at 5 years (%)	p
Age <20 years 20-50 years >50 years	 79,6 71,6 57,7	<0,001
Delay of consultation <= 6 months >6 months	 72,8 59,9	0,004
involvement of cranial nerves Invasion No Invasion	 42,1 69,8	 0,001
T stage (TNM 2010) T1/T2/T3/T4	 67,7/81,9/61,2/57,9	<0,001
Therapeutic sequence Radiotherapy exclusive Neoadjuvant chemotherapy-radiotherapy Concomtant cheomo-radiotherapy	 56,8 70,1 74,7	0,012

Table 3: Multivariate Analysis.

Pronostics Factors	P
Age <50 years	<0,001
Delay of Consultation	0,001
TNM Classification	<0,001
Lymphe node involvement	0,003
Treatment Modalities	0,003
Radiotherapy Dose	0,0001

Table 4: Overall Survival (review of literature)

Series	Number	5 years overall-survival (%)
Sanguineti 1997[14]	378	48
Heng1999[31]	677	56,6
Siti Azrin 2014[32]	159	38
Baillet 1996[37]	100	42
Liu 2003[38]	83	83
Chow 2002[39]	172	62
Yeh 2005[33]	849	59,3
Lee2005[40]	2687	75
Yan 2013[41]	185	78
Kimura 2011[-]	525	67,6
Janka 2012[15]	126	49,7
Xu 2010[42]	1706	67,6
Lee 1992[22]	5037	52

DISCUSSION

In this study, we collected 712 cases of nasopharyngeal carcinoma in Tunisian center. That represented 7.7% of all tumors treated in our department. According to the Northern Tunisia cancer registry, the incidence of nasopharyngeal carcinoma is 1.9 per 100 000 population in 2006.[2] The nasopharyngeal carcinomas are rare in most countries of the world particularly in Europe and North America (incidence less than 1/100 000 / year).[3][4][5]

Zones of high incidence are located in East Asia, mainly in southern China.[3][1][6] In the region of Canton, the incidence reached 30-80 / 100000 / year.[7] In 2008, 2000 cases were registered in Malaysia corresponding to the highest national incidence in the world.[8]

There are also intermediate incidence zones (of the order of 4 to 8/100 000 / year).[9] The classic example is that of North Africa. Particularly this cancer has a bimodal distribution with two incidence peaks between 15 and 25 and a second at 50 years.[9][10] In Tunisia, nasopharyngeal cancer is the first head and neck cancer for women[11] and the second after laryngeal cancer for men.[1] Because of the anatomical structure and the deep location of the nasopharynx, the first signs are willingly late.[12] The most common circumstance of discovering is the presence of cervical lymphadenopathy (70.9% of cases in our series) which is the case for other series in percentages from 41 to 76%[13][14][15] After an endoscopic examination performed in all patients, the posterior wall

was the most frequently involved (52.6%) which is consistent with the literature where the most common site of origin is the side wall of the nasopharynx, in particular the fossa of Rosen- müller[12], followed by the posterior superior wall.[16] The assessment of locoregional extension was represented by a CT scan of the nasopharynx in 98.5% of cases and Magnetic Resonance Imaging in 4.2% of patients.

The assessment of extension at distance was performed in 100% of patients and was represented by a chest X-ray, abdominal echography and bone scintigraphy in 98% of patients. PET-scanner is more and more practiced for the detection of distant metastases. In an Australian series of 2011, the use of PET-scanner has changed the therapeutic treatment either by detecting occult distant metastases (8%), or by modifying the node classification (25%).[17] PET-scanner can replace conventional imaging exams in the extension assessment, so, The association of MRI of the nasopharynx + PET-scanner is desirable for the initial extension assessment.[18] The PET-scanner is, moreover, in increasing use for the evaluation of the response to treatment, but the limiting factor for its use remains its poor availability so far.

Therapeutic modalities

Radiotherapy is the primary therapeutic modality because of the radiosensitivity and curability of this cancer. The combination with chemotherapy showed overall and metastasis free survival improvement.[19][20]

Radiotherapy

It has been reported about the old series published in the literature of the therapeutic results of radiotherapy alone very different depending on the stage and extent of

tumor. Local control and overall survival rates were excellent for localized tumors (T1, T2), respectively 90-80%.[21][22] If locally advanced tumors (T3, T4) or mass cervical lymph node (N2, N3), the local control rate after radiotherapy alone were mediocre, in the range of 10 to 40% depending on the series.[21][23] Therefore, combination chemotherapy and radiotherapy in advanced tumors is required in the treatment of nasopharyngeal carcinomas. The dose per fraction and total irradiation dose was a source of a large variation in the literature.

In our study, the survival rate increases with the increase of the dose delivered to the tumor.

A Chinese work published in 2014, including 868 patients treated with intensity modulated radiotherapy (IMRT), noticed a significant difference in disease-free survival for patients treated with radiation dose <= 65.6 Gy (77.9%) and those treated with a dose> to 65,6Gy (92.7%).[24]

Intensity-modulated radiotherapy (IMRT) improves tumor coverage with a sparing of organs at risk and has become the new standard of care for nasopharynx cancer and should be offered to all patients subject to the availability of the technique.

The conventional dose with standard fraction (1.8 to 2 Gy per session, 5 sessions per week) is 70 Gy on the macroscopic tumor and 45-60 Gy on the prophylactic treatment areas. The IMRT is often performed with an integrated boost-type fraction (dose supplement on the macroscopic target volume with different dose levels per fraction).[25]

Chemotherapy

In our study, neoadjuvant chemotherapy with 3 cures followed by radiotherapy was the most used treatment modality (60.8%), The most commonly used chemotherapy regimen was "adriamycin-cisplatin" in 85.5% of cases. This choice is made on the basis of randomized studies showing a significant survival benefit in favor of combination chemotherapy and radiotherapy.[26][27][28] Zhang et al[29] showed that induction chemotherapy containing taxanes improves metastasis free survival by 10%. In our series overall 5-year survival for patients treated with radiotherapy alone was 50%. This rate is 64.5% for patients treated with neoadjuvant chemotherapy followed by radiotherapy with a significant difference.

A meta-analysis of nasopharyngeal carcinomas, contains eight randomized trials, showed the benefit of the combination of chemotherapy and radiotherapy in terms of overall survival (6% at 5 years) and disease-free survival (10% at 5 years).[30]

The impact was clear and prominent during concomitant administration of these two therapeutic modalities.

After the interim analysis of Intergroup 0099 study[25], which showed better survival in favor of the chemo radiotherapy compared with radiotherapy alone (67% against 37%, 5-year overall survival). Concomitant chemoradiotherapy was considered the cornerstone of the standard treatment for locally advanced nasopharyngeal carcinoma.

In our study, 115 patients underwent concomitant chemo-radiotherapy. The "adriamycin-cisplatin" protocol was used in 44.3% of patients, the only cisplatin used in 53% of cases. Overall survival at 5 years was 70.5% for this group of patients, metastasis-free survival and recurrence-free survival were respectively, 84.5%, 88.9%.

The results of overall survival in our series is 60.3% at 5 years which is comparable to those reported in the literature (Table 4):

Prognostic factors influencing the survival were age, delay of consultation, especially tumor and lymph node extension and treatment modalities. These prognostic factors are similar to other literature series.[31][32][33][34][35]

The analysis of treatment failures showed particularly low incidence of local recurrence of 8.4% and metastasis rate of 18.4%.

The recurrence-free survival and metastasis-free survival at 5 years were respectively 98.2% and 80.1%.

Since the majority of our patients were treated with two-dimensional radiotherapy, high percentages of the toxicities were screnned. Currently with the advent of new radiotherapy techniques (IMRT, VMAT ...) the rate of late toxicity is significantly reduced.[36][24]

CONCLUSION

Nasopharyngeal cancer is a relatively common tumor in our country.

In our series, despite the tumor scalability were noted good results in terms of local control and overall survival.

The treatment is mainly based on the multimodal chemotherapy and radiotherapy association, treatment failures are mainly metastatic.

High radiation doses are associated with excellent local control at the cost of late toxicities which become more important for the young population.

The hope is, however, represented by the spread of new radiation techniques conformal intensity modulated, that can provide the solution to problems of toxicity while retaining excellent local control rates.

REFERENCES

1. Boussen H, Ghorbal L, Naouel L, Bouaouina N, Gritli S, Benna F, et al. Nasopharyngeal cancer (NPC) around the Mediterranean area: Standard of care. Crit Rev Oncol Hematol, 2012; 84(1): 106–9.
2. Ben Abdallah M, Ben Ayoub WH. Registre Cancers NORD-TUNISIE ; Données, 2004 – 2006. 2012; 1–128.
3. "Globacan 2012, 1.0." Cancer Incidence and Mortality Worldwide", 2012.
4. Chan a. TC, Gregoire V, Lefebvre J-L, Licitra L, Hui EP, Leung SF, et al. Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2012; 23(7): vii83-vii85.
5. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev, 2006; 15(10): 1765–77.
6. Kimura Y, Suzuki D, Tokunaga T, Takabayashi T, Yamada T, Wakisaka N, et al. Epidemiological analysis of nasopharyngeal carcinoma in the central region of Japan during the period from 1996 to 2005. Auris Nasus Larynx. Elsevier Ireland Ltd., 2011; 38(2): 244–9.
7. Fleury B, Biston MC, Montbarbon X, Pommier P. Cancers du cavum de l'adulte. Cancer/Radiotherapie. Elsevier, 2010; 14(1): S23–33.
8. GLOBOCAN 2008 Cancer Incidence, Mortality and Prevalence Worldwide in, 2008.
9. Boussen H, Bouaouina N, Mokni-Baizig N, Gamoudi A, Chouchane L, Benna F, et al. Les carcinomes du nasopharynx: Données actuelles. Pathol Biol., 2005; 53(1): 45–51.
10. Bouaouina N, Kabbaj O, Bouzouita K, Boussen H GH, Harrabi I et al. Le cancer du cavum de l'enfant. Cancer radiother, 2000; (S4): 162s.
11. H. Karray-Hakim, W. AyadiI LF-BL. Mise au point sur les marqueurs du virus d'Epstein Bar utilisés pour le diagnostic primaire du cancer du cavum et la détection de rechute ou métastases après traitement BURDEN A. 2009; 1–5.
12. Rivera S, Keryer C, Busson P, Maingon P. Les carcinomes du nasopharynx: De la biologie à la clinique. Cancer/Radiotherapie, 2005; 9(1): 55–68.
13. Petersson F. Nasopharyngeal carcinoma: A review. Semin Diagn Pathol, 2015; 32(1): 54–73.
14. Sanguineti G, Geara FB, Garden a S, Tucker SL, Ang KK, Morrison WH, et al. Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of local and regional control. Int J Radiat Oncol Biol Phys., 1997; 37(5): 985–96.
15. Čarman J, Strojan P. Nasopharyngeal carcinoma in Slovenia, 1990-2003 (results of treatment with conventional two-dimensional radiotherapy). Reports Pract Oncol Radiother, 2012; 17(2): 71–8.
16. Barnes L, Eveson JW, Reichart P, Sidransky D. Pathology and Genetics of Head and Neck Tumours. WHO Classif Tumour, 2005;(9): 163–75.
17. Law A, Peters LJ, Dutu G, Rischin D, Lau E, Drummond E, et al. The utility of PET/CT in staging and assessment of treatment response of nasopharyngeal cancer. J Med Imaging Radiat Oncol, 2011; 55(2): 199–205.
18. Ng SH, Chan SC, Yen TC, Chang JTC, Liao CT, Ko SF, et al. Staging of untreated nasopharyngeal carcinoma with PET/CT: Comparison with conventional imaging work-up. Eur J Nucl Med Mol Imaging, 2009; 36(1): 12–22.
19. Song Y, Wang W, Tao G, Zhou X. Survival benefit of induction chemotherapy in treatment for locally advanced nasopharyngeal carcinoma – A time-to-event meta-analysis. Oral Oncol. Elsevier Ltd., 2015; 51(8): 764–9.
20. Sanguineti G, Bossi P, Pou A, Licitra L. Timing of Chemoradiotherapy and Patient Selection for Locally Advanced Nasopharyngeal Carcinoma. Clin Oncol, 2003; 15(8): 451–60.
21. Noël G, Vignot S, Mazeron JJ. Les traitements des cancers du nasopharynx : revue de la littérature, 2002; 59–84.
22. Lee a W, Foo W, Thaw M. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: overall survival and patterns of failure. int J Radiat Oncol Biol Phys, 1992; 23(1): 261–70.
23. Licitra L, Bernier J, Cvitkovic E, Grandi C, Spinazzé S, Bruzzi P, et al. Cancer of the nasopharynx. Crit Rev Oncol Hematol, 2003; 45(2): 199–214.
24. Sun X, Su S, Chen C, Han F, Zhao C, Xiao W, et al. Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities. Radiother Oncol. Elsevier Ireland Ltd., 2014; 110(3): 398–403.
25. Jardel P, Thariat J, Blanchard P, Elloumi F, Toumi N, Bensadoun R-J, et al. Prise en charge des cancers du cavum (rhinopharynx). Bull Cancer. Elsevier, 2014; 101(5): 445–54.
26. Glisson BS, Sanguineti G, Tucker SL, Ph D, Garden AS, Ang KK, et al. Induction Chemotherapy followed by Radiotherapy Results of a Matched Cohort Study, 1997; 3–10.
27. Hareyama M, Sakata K, Shirato H, Nishioka T, Nishio M, Suzuki K, et al. A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. Cancer, 2002; 94: 2217–23.
28. Al-Saraf M., Le Blanc M.,Giri P.G.S et al. Superiority of five year survival withchemo-radiotherapy vs radiotherapy in patients with locally advanced nasopharyngeal cancer. Inter- group(0099) (SWOG 8892, RTOG 8817, ECOG 2388) phase 111 study. Oncol, 2001; 20: 2279.
29. Zhang L-N, Gao Y-H, Lan X-W, Tang J, OuYang P-Y, Xie F-Y. Effect of taxanes-based induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: A large scale

propensity-matched study. Oral Oncol. Elsevier Ltd., 2015; 51(10): 950–6.
30. Baujat B, Audry H, Bourhis J, Chan ATC, Onat H, Chua DTT, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: An individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol. Elsevier, Jan 1, 2006; 64(1): 47–56.
31. Heng DMK, Wee J, Fong KW, Lian LG, Sethi VK, Chua ET, et al. Prognostic factors in 677 patients in Singapore with nondisseminated nasopharyngeal carcinoma. Cancer, 1999; 86: 1912–20.
32. Siti-azrin AH, Norsa B, Naing NN. Five-Year Survival and Median Survival Time of Nasopharyngeal Carcinoma in Hospital Universiti Sains Malaysia, December, 2007; 2014; 15: 6455–9.
33. Yeh S-A, Tang Y, Lui C-C, Huang Y-J, Huang E-Y. Treatment outcomes and late complications of 849 patients with nasopharyngeal carcinoma treated with radiotherapy alone. Int J Radiat Oncol, 2005; 62(3): 672–9.
34. Teo P, Shiu W, Leung SF, Lee WY. Prognostic factors in nasopharyngeal carcinoma investigated by computer tomography--an analysis of 659 patients. Radiother Oncol, 1992; 23(2): 79–93.
35. Liu W, Tang Y, Gao L, Huang X, Luo J, Zhang S, et al. Nasopharyngeal carcinoma in children and adolescents - a single institution experience of 158 patients. Radiat Oncol, 2014; 9(1): 274.
36. Peng G, Wang T, Yang K, Zhang S, Zhang T, Li Q, et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol. Elsevier Ireland Ltd., 2012; 104(3): 286–93.
37. Baillet F, Simon JM, Rozec C, Ronchin P, Salemkour M, Diana C, et al. Radiothéapie de 100 cancers du cavum. bull Cancer/Radither, 1996; 1–5.
38. Liu M-T, Hsieh C-Y, Chang T-H, Lin J-P, Huang C-C, Wang A-Y. Prognostic factors affecting the outcome of nasopharyngeal carcinoma. Jpn J Clin Oncol, 2003; 33(10): 501–8.
39. Chow E, Payne D, O'Sullivan B, Pintilie M, Liu FF, Waldron J, et al. Radiotherapy alone in patients with advanced nasopharyngeal cancer: comparison with an intergroup study. Is combined modality treatment really necessary? Radiother Oncol, 2002; 63(3): 269–74.
40. Lee AWM, Sze M, Au JS, Leung S, Leung T, Chua DT, et al. Treatment results for nasopharyngeal carcinoma in the modern era: The Hong Kong experience. Int J Radiat Oncol Biol Phys, 2005; 61(4): 1107–16.
41. Yan Z, Xia L, Huang Y, Chen P, Jiang L, Zhang B. Nasopharyngeal carcinoma in children and adolescents in an endemic area: A report of 185 cases. Int J Pediatr Otorhinolaryngol. Elsevier Ireland Ltd., 2013; 77(9): 1454–60.
42. Xu L, Pan J, Wu J, Pan C, Zhang Y, Lin S, et al. Factors associated with overall survival in 1706 patients with nasopharyngeal carcinoma: Significance of intensive neoadjuvant chemotherapy and radiation break. Radiother Oncol. Elsevier Ireland Ltd, 2010; 96(1): 94–9.