Nasopharyngeal cancer in non-endemic areas: impact of treatment intensity within a large retrospective multicenter cohort

P. Bossi[1,2], A Trama[3], A Bernasconi[3], S. Grisanti[1], I. Mohamad[4], I. Linares Galiana[5], E. Ozyar[6], P. Franco[7], S. Vecchio[8], P. Bonomo[9], B. Cirauqui Cirauqui[10], M. El-Sherify[11], S. Ursino[12], A. Argiris[13], J. Pan[13], C. Wittekindt[14], E. D'Angelo[15], L. Costa[16], M. Buglione[16], JM. Johnson[13], M. Airoldi[17], R. Mesia Nin[18], C. Resteghini[2], L. Licitra[2,19], E. Orlandi[20]

On behalf of the Nasopharyngeal Cancer Portal Group of Investigators

Running title: Impact of treatment on the outcome in non-endemic NPC

1. Medical Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health-Medical Oncology, University of Brescia, ASST-Spedali Civili, Brescia, Italy.
2. Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.
3. Research Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.
4. Department of Radiation Oncology, King Hussein Cancer Center, Amman, Jordan.
5. Radiation Oncology Department, Hospital Duran i Reynals, Institut Català d'Oncologia (ICO), Radiobiology and Cancer Group, ONCOBELL Program, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain.
6. Department of Radiation Oncology, Acibadem University School of Medicine, Istanbul, Turkey,
7. Department of Oncology, Radiation Oncology, University of Turin, Italy.
8. Medical Oncology, IRCCS San Martino, IST National Cancer Institute and University of Genova, Genova, Italy.
9. Radiation Oncology Unit, Azienda Ospedaliero-Universitaria Careggi, Viale Morgagni 85, 50134, Florence, Italy.
10. Medical Oncology Department, Institut Català d'Oncologia, Badalona Applied Research Group in Oncology (B-ARGO), Hospital Germans Trias i Pujol, Badalona, Spain.
11. Radiation Oncology Department, Kuwait Cancer Control Centre, Kuwait.
12. Department of Radiation Oncology, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy.
13. Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA, United States.

14. Department of Otorhinolaryngology, Head and Neck Surgery, Medical Faculty, Justus-Liebig University Giessen, Giessen, Germany.
15. Radiation Oncology Unit, University Hospital of Modena, Italy.
16. Radiation Oncology Unit, Department of Medical and Surgical Specialties, Radiological Science and Public Health, ASST Spedali Civili of Brescia, University of Brescia, Brescia, Italy.
17. Medical Oncology, Città della Salute e della Scienza, Torino, Italy.
18. Medical Oncology Department, Catalan Institute of Oncology - Badalona, B-ARGO Group, IGTP, Barcelona, Spain.
19. Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy.
20. Radiotherapy 2 Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

Corresponding Author: Paolo Bossi, paolo.bossi@unibs.it
Address: Piazzale Spedali Civili, 1 - 25123 Brescia, Italy
Ph +390303998969

Abstract

Background

Recommendations for managing nasopharyngeal carcinoma (NPC) patients in non-endemic areas are largely derived from studies conductedt in endemic areas. We aimed to analyze the impact of treatment approaches on survival in this patients' setting

Methods

In an international, multicenter, retrospective study, we analyzed clinical data of consecutive NPC patients diagnosed between 2004 and 2017 in 36 hospitals of 11 countries. Treatment was categorized as non-intensive (NIT), including radiotherapy (RT),three-dimensional conformal RT or intensity modulated RT,IMRT), alone or concomitant radio-chemotherapy (RT-CT), and intensive (IT) including RT-CT preceded by induction and/or followed by adjuvant chemotherapy (CT). We fitted Cox proportional hazard models for both overall and Epstein Barr-Encoded RNA (EBER) status-specific analyses. The impact of IT on overall survival (OS) and disease-free survival (DFS) was adjusted for all the available potential confounders.

Findings

Overall, 1021 and 1113 patients were eligible for OS and DFS analyses, respectively (501 and 554 with EBER status available). In the whole group, 5-year OS and DFS were 84% and 65%, respectively. The use of NIT was associated with a risk of death or recurrence 1·37 times higher than patients receiving IT. Patients underwent NIT and induction CT + concurrent 3DRT-CT had a risk of death or recurrence 1·5 and 1·7 times higher than patients treated with induction CT + concurrent IMRT-CT, respectively. The IT did not impact OS in neither EBER+ nor EBER- patients; however, IT showed better DFS in EBER+ but not in EBER- patients.

Interpretation

This study represents, the largest data analysis on NPC patients in low-incidence areas. Among IT approaches, induction CT followed by concurrent IMRT-CT achieved the highest DFS rate, confirming the possible role of this approach in advanced EBER+ disease. The benefit of IT on DFS was restricted to EBER+ patients, suggesting that additional therapy offers no advantages in EBER- cases.

Funding: none

Background

Nasopharyngeal carcinoma (NPC) has unique epidemiological and histological features. The global age-standardised incidence rates (ASR) are high in Southern China and Southeast Asia (5-10 per 100,000), whereas it is much lower in most countries of the world including Europe (1-2 per 100,000).[1,2] In regions where NPC is endemic, non-keratinising subtypes makes up most cases which are invariably associated with Epstein-Barr virus (EBV) infection. In non-endemic areas, keratinising cancer is more common than in endemic regions and the role of EBV is much less pronounced.[3,4] Epidemiological data about EBV-associated NPC are limited in non-endemic areas. An increase of EBV-related NPC subtype has been reported across genders and ethnicities in the United States leading to speculation of an increased role of EBV as a risk factor for NPC in this area.[5] However, the prevalence and prognostic significance of EBV-related NPC in non-endemic countries is not well-established because of the limited evidence.[6-7]

The efficacy of different treatment strategies is mostly derived from prospective clinical trials and large retrospective series involving NPC patients in endemic areas.[8] This data has been extrapolated to further guide treatment decisions in the non-endemic setting. In addition, whether treatment strategies defined in endemic areas can be also effectively applied in EBV negative NPC remain to be established.

We conducted a multicenter collaborative study to analyze the impact of clinical characteristics and treatment strategies on the clinical outcomes of NPC patients treated in non-endemic countries. In this study, we report on the effectiveness of the intensive treatment (IT) on NPC outcomes overall and by EBV-status in non-endemic areas. By IT we mean additional chemotherapy to the standard chemoradiation; whether it is in the form of induction or adjuvant chemotherapy.

Materials and methods

We performed a multicenter retrospective observational study in non-endemic NPC areas (i.e. crude incidence rate ≤ 2/100,000 inhabitants) including Europe (Belgium, Germany, Greece, Italy, Netherlands, Spain, and Switzerland), Jordan, Kuwait, Turkey and the USA (Figure 1). All participating hospitals rely on a multidisciplinary management of head and neck cancer patients including those with NPC.

We included all consecutive patients diagnosed with NPC (International Classification of Diseases for Oncology Third Edition [ICD-O-3] topography codes for site of origin C11 and histologic type keratinizing squamous cell carcinoma 8071/3; non-keratinizing carcinoma 8072/3 and basaloid squamous cell carcinoma 8083/3) diagnosed between 2004 and 2016 and with a minimum follow up of 12 months in 36 hospitals. Data entry started in January 2018 and closed in December 2018.

The following information were recorded: demographic data (age, gender), Eastern Cooperative Oncology Group (ECOG) performance status, Epstein Barr-Encoded RNA (EBER) in tumor specimen and EBV-DNA plasma load before any treatment, data on primary tumor (e.g. clinical stage at diagnosis, treatment strategy etc.), recurrence (site and treatment) and life status.

Stage was defined at cancer diagnosis according to AJCC staging system 7th edition and combined in early (Stage I and Stage II) or advanced (Stage III and Stage IVa, IVb) or metastatic (Stage IVc) to maximize the number of cases available for the survival analyses.

Age at diagnosis was categorized into ≤65 years or >65 years.[9] Treatments were further categorized as follow:

- Non intensive treatment (NIT) including:
    - Radiotherapy (RT) alone, either three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) including static IMRT, volumetric modulated arc therapy, tomotherapy.
    - Concomitant chemotherapy and radiotherapy (CTRT), RT either 3DCRT or IMRT.
- IT treatment (i.e. CTRT plus induction or adjuvant chemotherapy [CT]) which was further detailed in
    - induction CT + CTRT (RT=3DCRT);
    - induction CT + CTRT (RT=IMRT);
    - CTRT (RT=3D) + adjuvant CT;
    - CTRT (RT=IMRT) + adjuvant CT;
    - induction CT + CTRT (RT=IMRT) + adjuvant CT.
- Palliative approaches, consisting in systemic chemotherapy alone or with palliative RT.

Internal consistency checks were performed to verify the reliability of treatment, recurrence and life status dates.

We analyzed patients' characteristics for the whole cohort and per EBER status. As information about EBER were limited, clinical prognostic characteristics (e.g. age, gender, histology, stage, treatment etc.) of patients with and without information about EBER were compared to confirm the absence of selection bias for the group with EBER information.

Ethics approval was obtained from all concerned Institutional Review Boards and the Ethics Committees.

Survival analysis

Overall survival (OS) was defined as the time between the date of treatment end and the date of last follow-up/contact or death. We excluded the time between cancer diagnosis and treatment

completion to account for potential immortal time bias.[10] Disease-free survival (DFS) was defined as the time between the date of treatment completion and the date of first recurrence, last follow-up/contact or death. Both OS and DFS were cut at 5 years and analyzed using Kaplan-Meier survival method. Five-year OS and DFS were estimated for the whole cohort and per EBER status.

Patients were excluded from OS and DFS analysis if they had any of the following: metastasis at cancer diagnosis and/or patients who received palliative care alone, patients with unreliable dates and patients with basaloid squamous cell carcinoma (Appendix 1).

We fitted Cox proportional hazard models for the whole cohort and for EBER-specific analyses.[11] The maximum likelihood bottom-up approach was used to identify the prognostic variables to be considered in the models.[12] This approach starts from a simple model and gradually adds variables only if they significantly increase the likelihood. The different variables are added one at the time until the null model is not rejected. Our objective was to estimate the impact of IT on OS and DFS, adjusted for all the possible confounders. Thus, we started with the model including the treatment variable alone and subsequently added the variables that resulted to have a significant influence on the effect of the treatment on OS and DFS. Variables tested included: gender, histological type, clinical stage, ECOG performance status, age at diagnosis and time-period of diagnosis defined as 2004-2009 *vs* 2010-2016.

We used multiple imputation to minimize missing data in the variables tested, after checking that data were missing completely at random.[13] We tested the collinearity between variables included in the models by the variance inflation factor.[14] Survival statistics were computed using Stata 13® software.

Results

Overall, 1230 cases were registered. After patient's exclusion due to the aforementioned criteria, we considered overall 1021 patients in the analysis for OS and 1113 patients for DFS. Analysis by EBER status included 501 patients for the OS analysis (417 EBER+ and 84 EBER-) and 554 patients for DFS (455 EBER+ and 99 EBER-) (Appendix 1).

Clinical characteristics and treatment strategies are reported in Table 1 for all 1,230 registered cases and stratified according to EBER status. The group of patients with no EBER information did not show any significant clinical and treatment difference compared to the group with EBER information. Briefly, mean age was 50 years and most patients were males and with advanced stage at diagnosis. Age, and stage distributions were comparable across groups whereas the male to

female ratio was 2·8, 2·6 and 1·9 for the whole cohort, EBER+ and EBER- cases, respectively. The majority of NPC patients had a non-keratinizing histology which was more common in EBER+ tumors compared to negative cases (91% vs 70%). Overall, IT were adopted in about half of NPC cases, with a more frequent use in EBER+ patients compared to EBER- cases. IMRT was the most used radiotherapy technique in all subgroups, alone, with concurrent chemotherapy and within IT approaches. Moreover, regardless of the EBER status the most common IT approach consisted of induction chemotherapy followed by concurrent chemo-IMRT.

Table 2 describes treatment strategies by stage for NPC cases for the whole cohort and per EBER status. NPC patients with early disease at diagnosis were treated with RT alone (21%) or CTRT (55%) whereas patients with advanced disease were treated with IT strategies (62%) and CTRT (34%). Considering the EBER status, patients with advanced disease were more frequently treated with IT if EBER+ (70% of the advanced cases); however, 55% of EBER- patients with advanced disease were treated with IT.

Overall survival and DFS by type of treatment (any, IT, NIT) are reported in Figure 2. Five-year OS for the whole cohort was 84% and did not differ by type of treatment. However, 5-year DFS was 65%; it was higher in NPC patients treated with IT (66%) compared to those treated with NIT (63%).

Overall survival and DFS by EBER status and by type of treatment (any, IT, NIT) are reported in Figure 3. Overall survival in EBER+ and EBER- NPC patients did not differ by type of treatment. Disease-free survival in EBER+ NPC patients was higher in those treated with IT compared to those receiving other treatments whereas in EBER- NPC patients the type of treatment had no significant impact.

Table 3 shows the results of the Cox proportional hazard models assessing the impact of the IT on OS and DFS in the whole cohort of NPC patients. Furthermore, the IT was distinguished in "induction + CTRT" and "CTRT + adjuvant", to analyze the prognostic role of each different approach. The results showed that the different IT approach had no independent impact on OS.

Compared to patients treated with induction CT + CTRT (RT=IMRT), the risk of death or recurrence was 1·7 times higher for patients treated with induction CT + CTRT (RT=3DCRT) and 1·5 times higher for patients treated with a NIT approach. NPC patients treated with IT treatment (IMRT or 3DRT) + adjuvant CT had an excess risk of death or recurrence (HR> 1) although this result was not found to be statistically significant.

Table 4 reports the results of the Cox proportional hazard models aimed at assessing the impact of the IT treatment on OS and DFS according to EBER status. The model confirmed that, at the net of confounding factors, the IT did not impact on OS in neither EBER+ nor EBER- NPC patients.

Advanced stage, age (> 65 years old) and years of diagnosis 2004-2009 were significant prognostic factors for treated EBER+ NPC patients.

IT however, showed a positive impact on DFS in EBER+ NPC. In this group, the risk of recurrence was almost 2 times higher (HR=1·8) for patients treated with NIT compared to patients treated with IT. Advanced stage and male gender were other prognostic factors for EBER+ NPC patients. Age > 65 years old was the only significant prognostic factors for EBER- NPC patients.

Discussion

The current study represents, to our knowledge, the largest series of NPC patients collected in non-endemic areas. It focuses on the use and impact of IT, defined as any addition of chemotherapy to concurrent chemoradiation (either in the induction and/or adjuvant setting). We identified that IT was employed twice as much as chemoradiation alone in locally advanced stages. Moreover, it has been more frequently used in EBV+ NPC patients (70% of cases) compared to EBV- cases, in which nearly half of patients (55%) received IT. Interestingly, EBV- patients were more likely to receive adjuvant CT compared to EBV+ cases. This may reflect the influence on oncologists of the well-known Intergroup trial results, which used CTRT followed by adjuvant CT in non-endemic countries.[15]

An important point for further revision is the look for the western countries as non-endemic for EBV-related NPC. Our study showed the prevalence of 82% of EBV in our multicentric unselected study population. Of course, this needs to be more validated on nation-wide scale.

In areas where the disease is endemic, intensification of the treatment has shown to produce increased survival rates, even if the best selection of patients to be offered this approach has not been fully elucidated.[16-17] The application of this approach in non-endemic areas is a matter of debate and real-world data, like ours, could contribute to increase knowledge to better discuss the feasibility and utility of this strategy.

In this regard, the present study supports the use of IT approaches to improve DFS in locally advanced NPC. The use of NIT was associated with a 37% higher risk of relapse or death, reflecting what has been shown in a meta-analysis of studies performed in endemic areas, where the induction plus concurrent chemoradiation option was superior to chemoradiation.[18] However, the IT did not show a clear advantage in terms of OS. The benefit of IT for DFS but not for OS could have different explanations, (1) the main one being the increased use of salvage surgical approaches or of the most conformal techniques of RT for limited locoregional recurrences and (2) the availability of different active systemic therapeutic options also in case of distant recurrences.[19-20]

In the subgroup of patients with known tumoral EBV status, it is interesting to note that the benefit of IT in terms of DFS was restricted to patients with EBV+ NPC. This might reflect a higher chemosensitivity of EBV-related cases, which is mirrored by the physicians' attitude of administering more systemic treatments in this disease subgroup. EBV-related NPC has a high metastasising capacity, due to the peculiar genomic alterations induced by EBV, which promotes distant dissemination by NF-kB signalling pathway.[21-22] Therefore, it is conceivable that a higher number of chemotherapy cycles could have an impact on DFS mainly for EBV+ NPC cases, reducing the risk of distant spread.

Additionally, the study results suggest that EBV- NPC patients would not benefit from an IT approach, suggesting that they should be managed as typical head and neck squamous cell carcinomas (HNSCC) in sites other than nasopharynx, where concurrent chemoradiation alone is the standard of care. In addition, the keratinizing histology is associated with a lower rate of distant metastasis compared to non-keratinizing carcinoma, which is invariably associated to EBV, remarking the most common use of IT in this latter histology.[23-24]. Taking into consideration these data and considering the challenges in designing a randomized trial in a low incidence scenario, one would advocate the use of concurrent chemoradiation in the group of locally advanced EBV-negative NPC, since additional therapy seems to offer no advantages.

We showed that among IT approaches, induction CT followed by CT-IMRT achieved the highest rate of DFS. IMRT is an important milestone in the management of NPC, providing minimal late effects and non-inferior outcomes compared to older RT techniques.[25] Our results are partially aligned with a network meta-analysis performed on 27 trials and 7,940 patients, which showed that in the IMRT era, for OS, PFS, and distant metastasis-free survival (DMFS), induction CT followed by CTRT was the most effective regimen, when compared to CTRT followed by adjuvant CT and CTRT alone.[26] This has been recently confirmed by the results of an individual patient data network meta-analysis. The Authors showed that induction chemotherapy with taxanes followed by concomitant chemoradiotherapy ranked the best treatment in terms of OS over concurrent chemoradiation alone or with adjuvant CT.[27]

Among the other variables considered in our model, we may highlight the role of treatment era in determining a better OS rate. Several factors have probably played a role, including diagnostic advances, better selection of patients, stage migration due to improved disease assessment by radiological imaging, RT technique optimization, improvement in supportive care to avoid severe toxicities, and optimization of salvage therapy for recurrent or metastatic disease.

We acknowledge the limitations of our analysis, mainly consisting of its retrospective nature, and in the voluntary collection of data. In addition, we are aware of the existence of biases in selecting treatment approaches, who were left to the choice of the multidisciplinary group of each center. Therefore, when different treatment options were available according to guidelines, the decision to proceed with an IT vs NIT therapeutic strategy cannot be retrospectively defined. Moreover, no data about acute toxicities are available, due to the retrospective nature of the analysis.
However, this series represent the largest available clinical data defining the outcome of NPC patients coming from non-endemic areas. In the context of rare cancers, the use of retrospective data coming from registries or multicenter data collection represents an opportunity to support the clinical management and drive the therapeutic approaches. [28-29]

In the future, the collection of prospective data coming from Institutions where the disease is not endemic will help in further refining the choice of the treatment approach, also considering other factors influencing prognosis, like circulating EBV DNA and taking into account pre-treatment patient's quality of life, which has been associated with survival in endemic areas.[30]

References

1. Ferlay J, Colombet M, Soerjomataram I et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019; 144(8): 1941-1953.

2. Tang LL, WQ Chen, WQ Xue et al. Global trends in incidence and mortality of nasopharyngeal carcinoma. Cancer Lett 2016; 374(1): 22-30.

3. Stelow EB and Wenig BM. Update From The 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Nasopharynx. Head Neck Pathol 2017; 11(1): 16–22.

4. Lin DC, Meng X, Hazawa M et al. The genomic landscape of nasopharyngeal carcinoma. Nat Genet 2014; 46(8): 866-71.

5. Argirion I, Zarins KR, Ruterbusch JJ et al. Increasing incidence of Epstein-Barr virus-related nasopharyngeal carcinoma in the United States. Cancer 2020;126(1): 121-130.

6. Dogan S, Hedberg ML, Ferris RL, et al. Human papillomavirus and Epstein-Barr virus in nasopharyngeal carcinoma in a low-incidence population. Head & Neck 2014; 36(4): 511-6.

7. Svajdler M Jr, Kaspirkova J, Mezencev R, et al. Human papillomavirus and Epstein-Barr virus in nasopharyngeal carcinoma in a non-endemic eastern european population. Neoplasma 2016; 63(1):107-14.

8. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet 2019; 394 (10192): 64-80.

9. Sommat K, Yit NLF, Wang F, Lim JHC. Impact of comorbidity on tolerability and survival following curative intent intensity modulated radiotherapy in older patients with nasopharyngeal cancer. J Geriatr Oncol 2018; 9(4): 352-358.

10. Yiang X, Kong APS, Luk AOY et al. Validation of Methods to Control for Immortal Time Bias in a Pharmacoepidemiologic Analysis of Renin–Angiotensin System Inhibitors in Type 2 Diabetes. J Epidemiol 2014; 24(4): 267-273.

11. Kleinbaum DG and Mitchel K. Survival Analysis: A self-learning text. Third Edition. Statistics for Biology and Health. Springer Science+Business Media, LLC 2012.

12. Pol D. Empirical problems of the Hierarchical Likelihood Ratio Test for model selection. Syst Biol 2004; 53(6): 949-962.

13. Royston P. Multiple imputation of missing values. The Stata Journal 2004; 4, 3: 227–241

14. Miles J. Tolerance and variance inflation factor. Encyclopedia of statistics in behavioral science. Hoboken, NJ: John Wiley & Sons; 2005.

15. Al-Sarraf M, LeBlanc M, Giri PG et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998; 16: 1310-7.

16. Zhang Y, Chen U, Hu GQ et al. Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma. N Engl J Med 2019; 381: 1124-35.

17. Sun Y, Li WF, Chen NY et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol 2016; 17(11): 1509-1520.

18. You R, Cao Y S, Huang PY et al. The Changing Therapeutic Role of Chemo-radiotherapy for Loco-regionally Advanced Nasopharyngeal Carcinoma from Two/Three-Dimensional

Radiotherapy to Intensity-Modulated Radiotherapy: A Network Meta-Analysis. Theranostics 2017; 7(19): 4825-4835.

19. Prawira A, Oosting SF, Chenet TW al. Systemic therapies for recurrent or metastatic nasopharyngeal carcinoma: a systematic review. Br J Cancer 2017; 117(12): 1743-1752.

20. Ngan KL, Wang L, Lo KW, Lui VWY. Genomic Landscapes of EBV-Associated Nasopharyngeal Carcinoma vs. HPV-Associated Head and Neck Cancer. Cancers (Basel) 2018; 10(7): 210.

21. Meng DF, Sun R, Liu GY et al. S100A14 suppresses metastasis of nasopharyngeal carcinoma by inhibition of NF-kB signaling through degradation of IRAK1. Oncogene 2020; 39(30): 5307-5322.

22. Tham T, Machado R, Russo DP, Herman SW, Teegala S, Costantino P. Viral markers in nasopharyngeal carcinoma: A systematic review and meta-analysis on the detection of p16 INK4a, human papillomavirus (HPV), and Epstein-Barr virus (EBV). Am J Otolaringology 2021; 42(1): 102762.

23. Palazzi M, Orlandi E, Bossi P et al. Further improvement in outcomes of nasopharyngeal carcinoma with optimized radiotherapy and induction plus concomitant chemotherapy: an update of the Milan experience. Int J Radiat Oncol Biol Phys 2009; 74(3): 774-80.

24. Peng H, Chen L, Zhang Y et al. Survival analysis of patients with advanced-stage nasopharyngeal carcinoma according to the Epstein-Barr virus status. Oncotarget 2016; 7(17): 24208-16.

25. Zhang B, Mo Z, Du W, et al. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. Oral Oncol 2015; 51(11): 1041-1046.

26. You R, Cao YS, Huang PY et al. The Changing Therapeutic Role of Chemo-radiotherapy for Loco-regionally Advanced Nasopharyngeal Carcinoma from Two/Three-Dimensional Radiotherapy to Intensity-Modulated Radiotherapy: A Network Meta-Analysis. Theranostics 2017; 7(19): 4825-4835.

27. Petit C, Lee AWM, Carmel A et al. Network-meta-analysis of chemotherapy in nasopharyngeal carcinoma (MAC-NPC): An update on 8,221 patients. ASCO 2020, abstract number 6523.

28. Oing C, K. Oechsle K, Necchi A et al. Impact of primary metastatic bone disease in germ cell tumors: results of an International Global Germ Cell Tumor Collaborative Group G3 Registry Study. Ann Oncol 2017; 28: 576–582.

29. Heppt MV, Roesch A, Weide B et al. Prognostic factors and treatment outcomes in 444 patients with mucosal melanoma. Eur J Cancer 2017; 81: 36-44.

30. Fang FM, Tsai WL, Chien CY, e al. Pretreatment quality of life as a predictor of distant metastasis and survival for patients with nasopharyngeal carcinoma. J Clin Oncol 2010; 28(28): 4384–9.