Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Sep 30; 10(B):2307-2312.
https://doi.org/10.3889/oamjms.2022.10438
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Oncology*

Assessment of Response to Chemoradiation and Radiation Therapy in Patients with Nasopharyngeal Carcinoma

Sebastian Ario Susanto[1]*, Yussy Afriani Dewi[2], Raden Ayu Hardianti Saputri[2]

[1]Medical Education Study Program, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia; [2]Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia

Edited by: Ksenija Bogoeva-Kostovska
Citation: Susanto SA, Dewi YA, Saputri RA. Assessment of Response to Chemoradiation and Radiation Therapy in Patients with Nasopharyngeal Carcinoma. Open-Access Maced J Med Sci. 2022 Sep 30; 10(B):2307-2312. https://doi.org/10.3889/oamjms.2022.10438
Keywords: Nasopharyngeal Carcinoma; Chemoradiotherapy; Head-and-neck cancer
***Correspondence:** Sebastian Ario Susanto, Medical Education Study Program, Faculty of Medicine, Universitas Padjadjaran/Hasan Sadikin General Hospital, Bandung, Indonesia.
E-mail: sebastian18001@mail.unpad.ac.id
Received: 17-Jun-2022
Revised: 01-Sep-2022
Accepted: 20-Sep-2022

Funding: Self-funded
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: Nasopharyngeal carcinoma (NPC) is a head-and-neck cancer that develops in the epithelial lining of the nasopharynx. The provision of radiotherapy and chemoradiation therapy in NPC can be evaluated by assessing the tumor response.

AIM: The present study aims to determine the response in patients with nasopharyngeal carcinoma (NPC) to radiotherapy and chemoradiation therapy.

METHODOLOGY: The study design is a retrospective bivariate analytic study from the Otorhinolaryngology-Head and Neck Society Head-Neck Surgical Oncology data registry program for the period of 2016−2021 at Dr. Hasan Sadikin General Hospital, Bandung. A total sample of 447 patients with NPC was used, and data were processed with descriptive and bivariate analytical tests. The variables used were patient characteristics and tumor response to radiotherapy and chemoradiation therapy. The tumor response was obtained based on the results of the examination at least 3 months after the administration of therapy and categorized according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).

RESULTS: Three hundred and eighty-three NPC patients (252 men and 131 women) underwent chemoradiation or radiation therapy, and their tumor response had been evaluated. Most patients were diagnosed at Stages III and IV and treated by chemoradiation. In total, 314 of 383 patients (82%) achieved CR (complete response), 50 patients (13.1%) achieved PR (partial response), 11 patients (2.9%) had PD (progressive disease), and 8 (2.1%) patients had SD (stable disease). There is no statistically significant difference in the type of therapy response when correlated with the each of the variables; age, sex, and educational level ($p > 0.05$). There is a statistically significant difference in the type of therapy response among different clinical stage groups ($p < 0.0001$).

CONCLUSION: Most nasopharyngeal carcinoma patients in the study had a complete response (82%) for either chemoradiation or radiotherapy alone. Age, sex, and education level have no significant effect on therapy response. On the other hand, the response to therapy is significantly correlated to the clinical stage of the disease.

Introduction

Nasopharyngeal carcinoma (NPC) is a head-and-neck cancer arising from the mucosal surface of the nasopharynx, the upper part of the pharyngeal cavity. It exhibits squamous differentiation [1], [2], [3]. In 2020, NPC had an estimated incidence of 133,354 cases of global morbidity, with an estimated number of deaths reaching 80,008 [4]. Nasopharyngeal carcinoma is endemic in South China and Southeast Asia and has a higher incidence in the developing countries, including Indonesia [5], [6]. Nasopharyngeal carcinoma is Indonesia's most common head-and-neck cancer and had 19,943 new cases diagnosed in 2020 [7], [8].

Nasopharyngeal carcinoma is sensitive to radiotherapy and chemotherapy [9]. As a primary modality in NPC patients, radiotherapy tends to show good outcomes in early-stage NPC patients (Stages I−II), characterized by a high level of local-regional tumor control. Advanced tumors (Stages III−IV) require more intensive therapy in the form of chemoradiation [10]. Therapy evaluation is done to assess the tumor response. Several response criteria can be used; one of them is the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), which evaluates the anatomical changes in tumor burden through the size changes in the target lesion. The RECIST 1.1 criteria categorize tumor response into four types: Complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) [11].

In West Java, research on tumor response in patients with NPC has never been conducted. This study aims to determine the tumor response in NPC patients in West Java, Indonesia. The data of the response therapy are expected to help provide evaluation data for treatment in NPC patients in West Java.

Methods

This research was conducted in January 2022 using a descriptive and retrospective bivariate analytic study design. This study uses secondary data in the form of a data registry. The sample population was NPC patients recorded in the Otorhinolaryngology-Head and Neck Society Head-Neck Surgical Oncology data registry program for the period of 2016−2021 at Dr. Hasan Sadikin General Hospital, Bandung. The sample size of the data taken in this study is the same as the total population. Inclusion criteria included NPC patients diagnosed based on histopathological results and evaluated at least 3 months after therapy, with complete data.

The variables used were age, sex, education level, clinical stage, type of therapy, and tumor response in NPC patients to chemoradiation or radiotherapy alone. The 8th edition of the American Joint Committee on Cancer Staging (AJCC) standard was used to determine the disease stage, while the tumor response was examined using the RECIST 1.1 criteria.

The responses assessment was carried out using a computed tomography scan measuring the longest diameter of the non-nodal lesion and the short axis of the lymph node. Target lesions are all measurable lesions up to two per organ and five in total, selected on baseline scan. All other lesions or sites are recorded as non-target lesions. Measurable lesions were defined as lesions with a longest diameter ≥ 10 mm and lymph nodes with a short axis ≥ 15 mm.

Following the RECIST 1.1 criteria, the outcomes are then divided into four types of therapy response: Complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). Complete response is defined as the disappearance of all lesions, both target and non-target, except lymph nodes. All lymph nodes must be < 10 mm short axis. Partial response is defined as a ≥ 30% decrease in the sum of the longest diameters of target lesions compared with baseline. Stable disease is when neither partial response nor progressive disease occurs. Progressive disease is defined as ≥ 20% and ≥ 5 mm increase in the sum of the target lesion measurements compared with the smallest sum recorded; the appearance of one or more new lesions; or unequivocal progression of non-target lesions.

The statistical analysis data were processed using Microsoft Excel 2016 program for the descriptive method and the Statistical Package for the Social Sciences (IBM SPSS) Statistics version 25.0 program (USA) for the analytical method. Results are displayed in table form.

Age is numerical data presented with mean, median, standard deviation, and range, whereas sex, education, clinical stage, therapy, and response are categorical data and presented with frequency and percentage. For numerical data >2, groups of p-values were tested with the one-way ANOVA test if the data were normally distributed with the alternative of the Kruskal–Wallis test if the data were not normally distributed. For categorical data, the p-value is calculated using the Chi-squared (χ^2) test with the alternative test of Kolmogorov–Smirnov and Fisher's exact if the requirements of the χ^2 are not met. The cutoff significance of p-value is 0.05.

This study was conducted under the ethical guidelines of the Helsinki Declaration and was approved by the Padjadjaran University Research Ethics Commission no. 1025/UN6.KEP/EC/2021 and permission by the Health Research Ethics Committee of Hasan Sadikin Hospital LB.02.01/X.2.2.1/790/2022. The committee waived the requirement for individual informed consent because the patient medical data and follow-up data were extracted retrospectively.

Results

There were 447 NPC patients in the Otorhinolaryngology-Head and Neck Surgery Department, at Dr. Hasan Sadikin General Hospital, during 2016−2021. Of those 447, 383 patients met the inclusion criteria, with a median age of 50 years and age range 13−83 years. There were 252 males (65.8%) and 131 female patients (34.2%). The patient's educational background consisted of elementary school (17%), junior high school (17%), high school (57.7%). diploma degree (2.1%), and bachelor's degree (4.4%). About 1.8% of patients did not or had not attended school (Table 1).

Table 1: Characteristics of nasopharyngeal carcinoma patients undergoing therapy and evaluation of response to therapy (n = 383)

Variable	n = 383
Age	
Mean ± SD	48.82 ± 13.353
Median	50.00
Range (minimum–maximum)	13.00–83.00
Sex	
Male	252 (65.8)
Female	131 (34.2)
Education	
Uneducated	7 (1.8)
Primary school	65 (17.0)
Junior high school	65 (17.0)
Senior high school	221 (57.7)
Diploma	8 (2.1)
Bachelor	17 (4.4)
Clinical stage	
Stage I	6 (1.6)
Stage II	42 (11.0)
Stage III	68 (17.8)
Stage IVA	212 (55.4)
Stage IVB	55 (14.4)
Therapy	
Radiotherapy	5 (1.3)
Chemoradiation	378 (98.7)
Response	
CR	314 (82.0)
PR	50 (13.1)
PD	11 (2.9)
SD	8 (2.1)

CR: Complete response, PR: Partial response, PD: Progressive disease, SD: Stable disease, SD: Standard deviation.

In clinical staging, NPC patients are dominated by advanced carcinoma. NPC patients with Stages I and II were 6 (1.6%) and 42 (11%) people, respectively, while the patients who experienced NPC Stages III and IV were 68 (17.8%) and 267 (69.8%), respectively, with 212 patients with IVA and 55 IVB (Table 1). Therefore, chemoradiation is the most often used therapy due to the higher number of advanced-stage patients. All Stages II–IV patients were given chemoradiation, whereas five of the six Stage I patients were given radiotherapy and one is given chemoradiotherapy. In total, 378 (98.7%) patients received chemoradiation and 5 (1.3%) received radiation therapy only.

Patients showed various tumor responses. In total, 314 of 383 patients (82%) achieved CR, 50 patients (13.1%) achieved PR, 11 patients (2.9%) had PD, and 8 (2.1%) patients had SD. Each response group showed a different mean, median, and age range. The variable age was tested using the Kruskal–Wallis test for the analysis because the data were not normally distributed. The statistical tests found that the p-value of the age variable in response groups was greater than 0.05 ($p > 0.05$). (Table 2). Thus, it can be concluded that there is no statistically significant difference when correlating the type of therapy response with the age.

The variables in the sex and education group were tested using the χ^2 test. The statistical tests found that there was no statistically significant difference when correlating the type of therapy response with the sex and education level.

All of the six patients with Stage I disease exhibit CR. In Stage II patients, a CR was observed in 37 out of 42 patients (88.1%), a PR in 4 patients (9.5%), and SD in 1 patient (2.4%). In Stage III patients, 64 out of 68 patients revealed CR (94.1%) and 4 patients (5.9%) showed PR. The response in Stage IVA patients was CR in 183 out of 212 patients (86.3%), PR in 24 patients (11.3%), PD in 2 patients (0.9%), and SD in 3 patients (1.4%). For patients with Stage IVB, 24 out of 55 patients (43.65%) had CR, 18 patients (32.7%) had PR, 9 patients (16.4%) had PD, and 4 patients (7.3%) had SD. With regard to the clinical stage, it was seen that the response to therapy was significantly correlated to the clinical stage ($p < 0.0001$).

Discussion

In this study, the research subjects had an age range of 13–83 years, with a median age of 50 years. There are more male patients than female patients, with a ratio of 2:1. This result is similar to a study conducted by Saputri (2019), showing that NPC patients in West Java, in general, have a median age of 45 years, and the number of male patients is more than females with a ratio of 1−2:1 [12]. A different interplay between environmental, genetic, and viral causes of NPC may cause a higher age group in this study [13]. The male predominance of NPC patients cannot be fully explained. Still, it may be caused by differences in the prevalence of exposure to risk factors such as smoking and occupational carcinogenic exposure. Other hypotheses suggest an intrinsic effect, such as the protective effect of estrogen [14].

Most of the educational background of patients undergoing therapy and evaluation of response is high school. It differs from Handayani's (2020) research, where most NPC patients have an elementary school educational background. The patient's educational background and socioeconomic conditions can affect the choice of the patient's medical treatment decisions [15]. Patients may refuse therapy due to a lack of funds or a fear of the treatment's side effects and seek alternative options [16].

This study found that most patients were diagnosed at clinical Stages III and IV. Similar results were found in the study by Adriana who showed 84.9% of Stage III and IV patients, and the study in Ethiopia showed 86.2%. Studies in endemic areas show 80−90% of Stage III and IV cases [17], [18]. This could indicate the

Table 2: Bivariate analysis between each of the patient's characteristics and type of the therapy response

Variable	Response				p
	CR (n = 314)	PR (n = 50)	PD (n = 11)	SD (n = 8)	
Age					
Mean ± SD	49.15 ± 13.460	47.64 ± 12.784	45.27 ± 15.363	48.25 ± 10.660	0.744
Median	50.50	50.00	47.00	46.00	
Range (minimum–maximum)	16.00–83.00	13.00–71.00	16.00–66.00	32.00–65.00	
Sex					
Male	207 (82.1)	33 (13.1)	6 (2.4)	6 (2.4)	0.820
Female	107 (81.7)	17 (13.0)	5 (3.8)	2 (1.5)	
Education					
Uneducated	5 (71.4)	2 (28.6)	0	0	0.720
Primary school	50 (76.9)	12 (18.5)	2 (3.1)	1 (1.5)	
Junior high school	54 (83.1)	9 (13.8)	2 (3.1)	0	
Senior high school	183 (82.8)	25 (11.3)	6 (2.7)	7 (3.2)	
Diploma	7 (87.5)	0	1 (12.5)	0	
Bachelor	15 (88.2)	2 (11.8)	0	0	
Clinical stage					
I	6 (100)	0	0	0	0.0001**
II	37 (88.1)	4 (9.5)	0	1 (2.4)	
III	64 (94.1)	4 (5.9)	0	0	
IVA	183 (86.3)	24 (11.3)	2 (0.9)	3 (1.4)	
IVB	24 (43.6)	18 (32.7)	9 (16.4)	4 (7.3)	

CR: Complete response, PR: Partial response, PD: Progressive disease, SD: Stable disease, SD: Standard deviation, * Significant at $p \leq 0.05$.

difficulty of early diagnosis due to the vague symptoms that arise in the early stages [19]. Education programs on signs and symptoms of early-stage nasopharyngeal carcinoma are essential so that people can recognize and come at an earlier stage. In addition, information about procedures, costs, and health insurance can persuade people to go to public health care. The fact that this study takes place in Dr. Hasan Sadikin General Hospital, Bandung, a top referral hospital in West Java, may also account for the high number of patients assigned at Stages III and IV.

Most of the patients were given chemoradiation therapy. The majority of Stage I patients were given radiotherapy. All patients with Stages II–IVB were given chemoradiation. This follows the clinical guidelines for NPC released by the European Society for Medical Oncology (ESMO) which states that Stage I NPC patients can only be given radiotherapy. In contrast, Stage II patients can be given radiotherapy or chemoradiation. Patients with Stages III and IV are advised to receive chemoradiation therapy. Intensive systemic treatment such as chemoradiation is needed to treat patients with NPC in Stages III and IV due to the predisposition to distant metastases as one of the primary causes of treatment failure and death in NPC patients [20]. Various studies also have shown that giving chemoradiation to NPC patients exhibits a higher survival rate than giving only radiotherapy [17], [21], [22].

Nasopharyngeal carcinoma patients given therapy were then evaluated with RECIST 1.1 criteria. These criteria assess the anatomical changes in tumor burden through the size changes in the target lesion and divide the response to therapy into four types: CR, PR, PD, and SD. Patients in the study showed all four types of responses, with the majority showing a good response with CR (82%), followed by PR (31.1%), PD (2.9%), and SD (2.1%). These results show a higher CR value compared to the study by Liang (2019), which only showed 48.1% CR, 48.9% with PR, 2.8% with SD, and 0.3% with PD [23]. The high CR demonstrates the high effectiveness of therapy in research subjects.

The association between age, sex, educational level, and clinical stage with therapy response was investigated in this study. Each response group showed a different age result, and both the sex and status of education groups show variations in response to therapy. The results found that these three variables had no statistically significant association with the tumor response ($p > 0.05$). On the contrary, the bivariate analysis results found that the clinical stage has a statistically significant association with the tumor response ($p < 0.0001$). Stage IVB patients have lower CR percentage than patients with Stage IVA and Stage III in advanced NPC.

The same result was found in the research conducted by Li (2017). About 83.3% of CR patients were assessed after 3 months of therapy. This study found that response was not significantly associated with the age and sex of the patient but significantly affected by the clinical stage. This may be because age, sex, and education level do not directly determine the quality of the tumor or affect the treatment given. For clinical stages, tumor spread may affect the outcome of therapy response in NPC patients. This research also found that Stage I and II patients had a higher percentage of CR than Stage III and IV patients [24], [25]. Peng (2017) also found more PR in Stages III–IVB NPC patients with neoadjuvant chemotherapy and concurrent chemoradiation [26].

The limitation of this study is the lack of more detailed data regarding the therapy given to the research subjects, such as the dose and type of radiotherapy and chemotherapy given. This can provide a better understanding of the impact of treatment on the response to the treatment.

Conclusion

Age, sex, and education level have no significant association with response therapy, while the clinical stage has a significant association with response therapy.

Recommendation

The public needs to know the signs and symptoms early to be treated in the early stages. More comprehensive data collection in therapy on NPC patients should be completed for further research.

Data availability statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Padjadjaran University Research Ethics Commission no. 1025/UN6.KEP/EC/2021 and permission by the Health Research Ethics Committee of Hasan Sadikin Hospital LB.02.01/X.2.2.1/790/2022.

Credit Authorship Contribution Statement

SS participated in the design of the study, performed the statistical analysis, and drafted the

manuscript. YD participated in supervising the design of the study, the acquisition of data, and helped to draft the manuscript. RS participated in supervising its design and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgment

Our gratitude goes to Dr. Hasan Sadikin General Hospital, Bandung, for allowing us to obtain the necessary data, and Mrs. Vita who helped us analyze the statistical data in this study.

References

1. Mohammed MA, Abd Ghani MK, Hamed RI, Ibrahim DA. Review on nasopharyngeal carcinoma: Concepts, methods of analysis, segmentation, classification, prediction and impact: A review of the research literature. J Comput Sci. 2017;21:283-98. https://doi.org/10.1016/j.jocs.2017.03.021
2. Watkinson JC, Gilbert RW. Stell and Maran's textbook of head and neck surgery and oncology, 5th edn. Ann R Coll Surg Engl. 2013;95(3):231. https://doi.org/10.1308/rcsann.2013.95.3.231
3. Simo R, Robinson M, Lei M, Sibtain A, Hickey S. Nasopharyngeal carcinoma: United Kingdom national multidisciplinary guidelines. J Laryngol Otol. 2016;130(S2):S97-103. https://doi.org/10.1017/S0022215116000517
   PMid:27841121
4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
   PMid:33538338
5. Forman D, Bray F, Brewster DH, Mbalawa CG, Kohler B, Piñeros M, *et al*. Cancer incidence in Five Continents. Vol. 10. Lyon, France: IARC Scientific Publication; 2013. p. 164.
6. Mahdavifar N, Ghoncheh M, Mohammadian-Hafshejani A, Khosravi B, Salehiniya H. Epidemiology and inequality in the incidence and mortality of nasopharynx cancer in Asia. Osong Public Health Res Perspect. 2016;7(6):360-72. https://doi.org/10.1016/j.phrp.2016.11.002
   PMid:28053841
7. Adham M, Kurniawan AN, Muhtadi AI, Roezin A, Hermani B, Gondhowiardjo S, *et al*. Nasopharyngeal carcinoma in Indonesia: Epidemiology, incidence, signs, and symptoms at presentation. Chin J Cancer. 2012;31(4):185-96. https://doi.org/10.5732/cjc.011.10328
   PMid:22313595
8. International Agency for Research on Cancer. Global Cancer Statistics 2020. Indonesia: International Agency for Research on Cancer; 2021. Available from: https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf [Last accessed on 2021 Jan 30].
9. Shah JP, Patel SG, Singh B. Jatin Shah's Head and Neck Surgery and Oncology E-Book. Edinburgh, London: Elsevier Health Sciences; 2012.
10. Kamran SC, Riaz N, Lee N. Nasopharyngeal carcinoma. Surg Oncol Clin. 2015;24(3):547-61. https://doi.org/10.1016/j.soc.2015.03.008
    PMid:25979399
11. Nishino M. Tumor response assessment for precision cancer therapy: Response evaluation criteria in solid tumors and beyond. Am Soc Clin Oncol Educ Book. 2018;38:1019-29. https://doi.org/10.1200/EDBK_201441
    PMid:30231378
12. Hardianti RA, Dewi YA, Utami RD. Risk factor of nasopharyngeal carcinoma Dr. Hasan Sadikin general hospital Bandung. Int J Nasopharyngeal Carcinoma. 2019;1(3):110-1. https://doi.org/10.32734/ijnpc.v1i03.2065
13. Chang ET, Ye W, Zeng YX, Adami HO. The evolving epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2021;30(6):1035-47. https://doi.org/10.1158/1055-9965.EPI-20-1702
    PMid:33849968
14. Xie SH, Yu IT, Tse LA, Mang OW, Yue L. Sex difference in the incidence of nasopharyngeal carcinoma in Hong Kong 1983-2008: Suggestion of a potential protective role of oestrogen. Eur J Cancer. 2013;49(1):150-5. https://doi.org/10.1016/j.ejca.2012.07.004
    PMid:22892061
15. Handayani R, Dewi YA, Madani DZ. Prevalence of nasopharyngeal carcinoma patients in departement of ORL-HNS Hasan Sadikin general hospital 2010-2017. Int J Nasopharyngeal Carcinoma. 2020;2(1):1-3. https://doi.org/10.32734/ijnpc.v2i01.3191
16. Wildeman MA, Fles R, Herdini C, Indrasari RS, Vincent AD, Tjokronagoro M, *et al*. Primary treatment results of nasopharyngeal carcinoma (NPC) in Yogyakarta, Indonesia. PLoS One. 2013;8(5):e63706. https://doi.org/10.1371/journal.pone.0063706
    PMid:23675501
17. Adriana R, Dewi YA, Samiadi D, Candra EW. Survival analysis of nasopharyngeal carcinoma in Hasan Sadikin hospital. Int J Nasopharyngeal Carcinoma. 2019;1(1):3-6. https://doi.org/10.32734/ijnpc.v1i1.952
18. Beyene ET, Ketema SG, Alebachew AN, Saleh MY, Gebremariam TA. Descriptive epidemiology of nasopharyngeal carcinoma at Tikur Anbessa hospital, ethiopia. BMC Cancer. 2021;21(1):540. https://doi.org/10.1186/s12885-021-08311-8
    PMid:33980204
19. Ruback MJ, Galbiatti AL, Arantes LM, Marucci GH, Russo A, Ruiz-Cintra MT, *et al*. Clinical and epidemiological characteristics of patients in the head and neck surgery department of a university hospital. Sao Paulo Med J. 2012;130(5):307-13. https://doi.org/10.1590/S1516-31802012000500007
    PMid:23174870
20. Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, *et al*. Nasopharyngeal carcinoma: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(4):452-65. https://doi.org/10.1016/j.annonc.2020.12.007
    PMid:33358989
21. Sun XS, Liu SL, Luo MJ, Li XY, Chen QY, Guo SS, *et al*. The association between the development of radiation therapy, image technology, and chemotherapy, and the survival of patients with nasopharyngeal carcinoma: A cohort study from 1990 to 2012. Int J Radiat Oncol Biol Phys. 2019;105(3):581-90. https://doi.org/10.1016/j.ijrobp.2019.06.2549
    PMid:31319091
22. Qiu WZ, Huang PY, Shi JL, Xia HQ, Zhao C, Cao KJ. Neoadjuvant chemotherapy plus intensity-modulated radiotherapy versus

concurrent chemoradiotherapy plus adjuvant chemotherapy for the treatment of locoregionally advanced nasopharyngeal carcinoma: A retrospective controlled study. Chin J Cancer. 2016;35(1):1-9. https://doi.org/10.1186/s40880-015-0076-9

PMid:26739148

23. Liang SB, Zhang N, Chen DM, Yang XL, Chen BH, Zhao H, *et al*. Prognostic value of gross tumor regression and plasma Epstein barr virus DNA levels at the end of intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma. Radiother Oncol. 2019;132:223-9. https://doi.org/10.1016/j.radonc.2018.10.010

PMid:30366725

24. Li WF, Zhang Y, Liu X, Tang LL, Tian L, Guo R, *et al*. Delayed clinical complete response to intensity-modulated radiotherapy in nasopharyngeal carcinoma. Oral Oncol. 2017;75:120-6. https://doi.org/10.1016/j.oraloncology.2017.10.020

PMid:29224808

25. Amin MB, Edge SB, Greene FL. AJCC Cancer Staging Manual. Vol. 8. New York: Springer; 2017.

26. Peng H, Chen L, Li WF, Guo R, Mao YP, Zhang Y, *et al*. Tumor response to neoadjuvant chemotherapy predicts long-term survival outcomes in patients with locoregionally advanced nasopharyngeal carcinoma: A secondary analysis of a randomized phase 3 clinical trial. Cancer. 2017;123(9):1643-52. https://doi.org/10.1002/cncr.30520

PMid:28001301