Non-endemic non-keratinizing nasopharyngeal carcinoma: Long-term toxicity following chemoradiation

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Abstract. Chemoradiotherapy (CRT) is considered the standard of care for non-keratinizing nasopharyngeal carcinoma (NK-NPC) worldwide, with improved overall survival, local recurrence-free survival and distant metastasis-free survival rates compared with radiotherapy alone. However, CRT is associated with late toxicities that can diminish a patient's quality of life and increase morbidity and mortality rates. Following the geographical distribution of NK-NPC, research has predominantly been performed on the endemic Asian population of patients. To extrapolate these results, more investigations in non-Asian populations are needed. The present study aimed to analyze the occurrence and severity of late toxicities following CRT strictly in patients with non-endemic NK-NPC. The clinical retrospective study included 36 patients >18 years of age with pathohistologically confirmed NK-NPC who were treated in the Institute of Oncology and Radiology of Serbia (Begrade, Serbia) with CRT during a 5-year period (January 2015 to December 2020). After completing combined treatment with a mean tumor dose of 68.64Gy and a median of 4 cycles of weekly cisplatin (40 mg/m^2), late sequelae were routinely assessed during regular follow-ups and graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer 'Late Radiation Morbidity Scoring Schema'. Overall late toxicities were registered in 83.3% of the patients, mostly at grade ≤2. Neck fibrosis was observed in 69.44% and xerostomia in 58.33% of patients. Late dysphagia was experienced by 2 patients, secondary hypothyroidism by 4 patients and neuropathy by 3 patients. In conclusion, based on the results of the present study, late toxicities can be expected in the majority of patients with non-endemic NK-NPC following CRT. However, late sequelae are of lower grade, with neck fibrosis and xerostomia being the most predominant.

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Introduction

Nasopharyngeal cancer (NPC) is a rare epithelial carcinoma with an extremely uneven geographical distribution. As represented by GLOBOCAN data for 2020, NPC contributes to only 0.7% of the total number of new cancer cases worldwide, and 70% of these cases are diagnosed in Eastern and Southeastern Asia (1). According to the 4th edition of the World Health Organization classification, these carcinomas are divided into three types: non-keratinizing (subdivided into differentiated and undifferentiated), keratinizing and basaloid squamous cell types (2). Non-keratinizing NPC (NK-NPC) has distinct features such as ethnic disparities, radio- and chemosensitivity, metastatic potential and well-proven role of Epstein Barr virus in its pathogenesis (3). Due to its sensitivity to anti-neoplastic treatment, a large proportion of patients, even in advanced stages of disease, could be cured or achieve long-term remission (3).

Late presentation of NK-NPC requires multimodality treatment. Radiotherapy (RT) is a mainstay of the curative-intent approach, with high doses (70 Gy) needed for the eradication of the gross tumor and doses of 50-60 Gy required for regions of microscopic infiltration risk (4). Chemotherapy, in different schemes of application (induction, concomitant and adjuvant) is added. Cisplatin-based concomitant chemotherapy has become a treatment standard when considering data from randomized clinical trials and meta-analyses, which has indicated that combined treatment improves overall survival, local recurrence-free survival and distant metastasis-free survival rates (5-7).

This intensive combined therapeutic approach inevitably leads to numerous toxicities, both acute and late. In contrast to acute toxicities, late sequelae are in general unrecognized, underestimated and often lacking adequate therapy. Nevertheless, their paramount importance comes from a tendency to progress over time, affecting patients' quality of life (QoL), increasing morbidity and even causing mortality. Published literature reporting late morbidity in NK-NPC survivors is scarce, often inconsistent and, following uneven geographical distribution, predominantly driven from the

Asian population of patients with endemic NK-NPC (8-11). Therefore, the present study aimed to analyze the occurrence and severity of late toxicities following CRT in patients with strictly non-endemic NK-NPC.

Materials and methods

Study design. The present clinical retrospective study was conducted at the Institute for Oncology and Radiology of Serbia (Belgrade, Serbia) between January 2015 and December 2020. The Multidisciplinary Tumor Board made treatment decisions for every patient based on current recommendations. Written informed consent was obtained from all subjects, who were fully aware of the planned combined treatment and its potential acute and late toxicities. Information on data publication was included in the consent. Confidentiality was maintained throughout the study with the protection of subjects' personal information. Anonymity was carefully maintained and no disclosure of any personal identifiers was allowed.

Patient characteristics. A total of 36 adult patients were included from our non-endemic region (state of Serbia), all with histologically confirmed, non-metastatic, NK-NPC. Since the Institute for Oncology and Radiology of Serbia is a referral center for Serbia, patients not only from Belgrade but from other regions were also included. Patients treated with palliative intent or previously treated for another malignancy, those with refractory disease or patients with Eastern Cooperative Oncology Group performance score (ECOG PS) ≥2 were excluded (12). Based on local findings upon an ear, nose and throat examination with fiber-endoscopy, a full blood count with biochemical analysis and radiological imaging [multi-slice computed tomography (CT)/magnetic resonance imaging of splanchnocranium/head and neck, lung X-rays and ultrasound of the abdomen], patients were staged according to the seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system up till 2018 and according to the eight edition of the AJCC/UICC staging system onwards (13,14).

RT. Radical RT was planned for every patient with a tumor dose of 70 Gy in 35 fractions, with a standardized fractionation regimen (2 Gy per fraction) and conformal technique. After patient immobilization in a supine position with a thermoplastic immobilization mask, a CT simulation of the head and neck from the vertex to the fifth thoracic vertebra was performed obtaining 2.5-mm thick slices with intravenous iodine contrast.

According to the institutional treatment protocol for the Institute of Oncology and Radiology of Serbia and the International Commission on Radiation Units and Measurements Reports 50, 62 and 83, target volumes were delineated on each slide of the CT simulation (15-17). The gross tumor volume (GTV) was defined by the primary tumor and macroscopic metastatic lymph nodes.

The high-risk clinical target volume (CTV) included the GTV with 5-mm margins, and a tumor dose (TD) of 70 Gy in 35 fractions was prescribed to that volume. Intermediate-risk CTV covered the entire nasopharynx, parapharyngeal space, clivus, base of the skull, pterygoid fossa, posterior half of ethmoidal sinus, inferior sphenoid sinus or the whole sphenoid sinus if the tumor invaded its inferior parts, the posterior edge of the nasal cavity and the maxillary sinuses. A TD of 60-64 Gy in 30-32 fractions was prescribed to this volume. Low-risk CTV encompassed intermediate-risk CTV with prophylactic neck node level I-V and VIIa bilaterally, with a TD of 50 Gy in 25 fractions prescribed. This standardized dose configuration was planned for every patient, respecting the dose constraints on the organs at risk.

To account for the patient motion and set-up error, each CTV was expanded by 3-5 mm, thus obtaining the planning tumor volume. More narrow margins (1-3 mm) were used in situations when the primary tumor was adjacent to a critical neurological structure.

On each slice, organs at risk, including the brain stem, spinal cord, temporal lobes, brain optic nerves, optic chiasm, lens, parotid glands, mandible and temporomandibular joints, were also outlined (Fig. 1). Irradiation was delivered on linear accelerators with integrated multi-leaf collimators and high-energy photons. Adequate patient positioning on the RT machine underwent regular everyday verifications with kV or MV portals and/or cone beam CT.

Everyday patient's positioning on the RT machine demanded a high level of precision, as shown in Fig. 2. Over the study period, RT for treating NPC patients was delivered with the 3D conformal technique up until 2018, and with the intensity-modulated radiation therapy (IMRT) technique afterward, following its implementation in the Institute of Oncology and Radiology of Serbia (Fig. 3).

Faces shown in the top right panel of Figs. 1 and 3 are digital 3D reconstructions obtained from three planes (axial, coronal and sagittal) of RT treatment planning CT, which represents a virtual patient, i.e. a 3D model of a particular patient which is the concept of 3D-conformal RT. Figs. 1 and 3 are presented to depict the extreme proximity of tumor volumes and healthy structures (organs at risk) in patients' radiation plans, as well as localization and volume of skin and subcutaneous tissues included in the irradiated volume.

Chemotherapy. All patients received concurrent cisplatin weekly, with a dose of 40 mg/m^2. The aim was to administer at least 5 or 6 cycles of mono cisplatin a 40 mg/m^2 concurrent with radiation. Neoadjuvant chemotherapy was administered in high-risk patients with locoregional extended disease. In a subgroup of patients who did not start treatment with neoadjuvant chemotherapy, yet were assessed as high risk for local recurrence or distant dissemination upon the completion of CRT, an adjuvant chemotherapy was applied. Neoadjuvant, as well as an adjuvant chemotherapy consisted of cisplatin (80 mg/m^2) with 5-fluorouracil (800 mg/m^2) continuous infusion for 5 days, recycled every 3 weeks for three cycles.

Follow-up and statistical analysis. After combined CRT treatment, patients were followed up every 3 months during the first 2 years, every 6 months from year 2 to year 5, and once a year thereafter. The late toxicities were clinician-reported and graded according to the the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer 'Late Radiation Morbidity Scoring Schema' (18).

Measurements of descriptive statistics are used for interpretation of the parameters of importance. Categorical

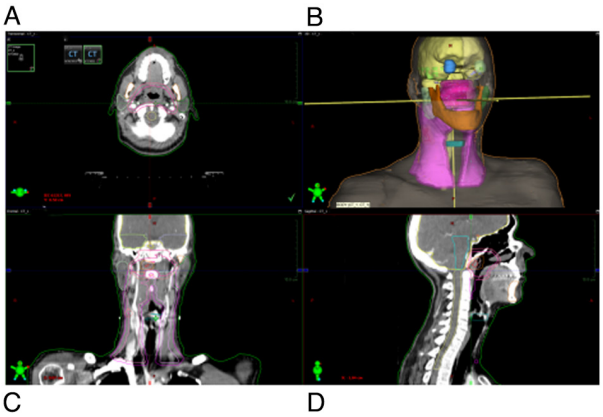

Figure 1. Organs at risk and tumor volume delineation in three planes and in three-dimensional reconstruction on treatment planning CT simulation taken from the vertex to the fifth thoracic vertebra. (A) Axial plane, (B) three-dimensional reconstruction, (C) coronal plane and (D) sagittal plane. Colors representing OAR: Brain, yellow; brainstem, cyan; optic chiasm, light orange; spinal cord, light yellow; temporal lobe left, purple; temporal lobe right, light green; eye globe right, blue; eye globe left, translucent green; mandible, dark orange; parotid gland left, dark green; parotid gland right, mint; glottis, dark cyan. Colors representing tumor volumes: GTVprimary, red; GTVnodal, dark red; CTV50, magenta; PTV50, pink; CTV60, dark magenta; PTV60, dark pink; CTV70, light pink; PTV70, light orange. GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume.

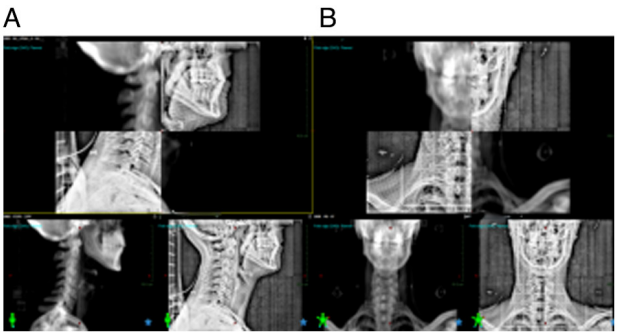

Figure 2. Patient's position verification on linear accelerator with kV portal. (A) Lateral and (B) frontal views.

variables are described using frequencies (percentages), while mean, median, standard deviation and range are used for numeric variables. For testing normal data distribution, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. $P<0.05$ was considered to indicate a statistically significant difference. To compare disease characteristics, treatment details and toxicities, statistical tests were selected based on data type and distribution: The Wilcoxon rank-sum test for continuous variables, and Fisher's exact test for categorical variables. The statistical analysis was performed with the program R [version 4.3.1 (2023-06-16 ucrt) - 'Beagle Scouts'; Copyright© 2023 The R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit)] (www.r-project.org; downloaded: August 21, 2023).

Results

All patients were >18 years old, with a median age of 49.5 years (range, 18-71 years) and with good performance

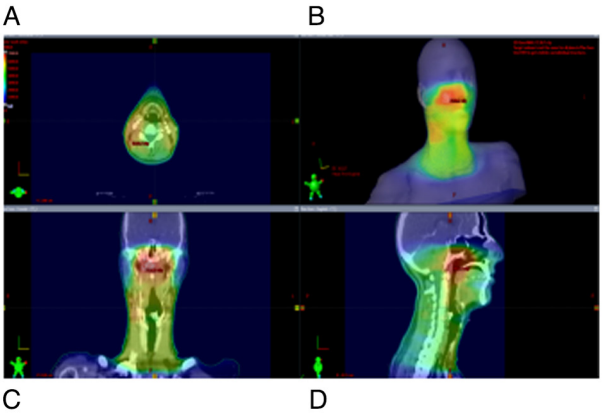

Figure 3. Isodose distribution in the nasopharyngeal carcinoma intensity-modulated radiation therapy irradiation plan on treatment planning CT simulation taken from the vertex to the fifth thoracic vertebra. (A) Axial plane, (B) three-dimensional reconstruction, (C) coronal plane and (D) sagittal plane. Isodose distribution is presented in color wash-out manner with the range of tumor doses from 10 Gy (in blue) to 70 Gy (in red) as seen in the color line on the top left panel.

status (ECOG PS≤1). Of the 36 patients included, 27 were men and 9 were women, with a male/female ratio of 3:1. The majority of patients presented in the advanced stage of disease. Specifically, 47.2% (17 patients) were in clinical stage III and 27.8% (10 patients) were in stage IVA. A total of 25% of the cohort (9 patients) was diagnosed in stage II (Table I).

In 29 patients (80.6%), treatment commenced with induction chemotherapy, and all patients completed three cycles. In the adjuvant setting, 6 patients (16.7%) received chemotherapy, with a median of two cycles. Whether chemotherapy was administered in the induction or adjuvant approach, all patients were scheduled for CRT according to the Multidisciplinary Tumor Board decision based on current treatment protocols.

Over the study period, RT was delivered with IMRT in just over one-third of patients (14 patients; 38.9%). The rest of the patients were treated with 3D conformal RT. The median TD reached was 68.64 Gy, with a range of 44-70 Gy. Out of the 36 patients, 32 (88.9%) received a TD of 70 Gy in 35 fractions. Only 4 patients did not reach the prescribed dose. In 2 of these patients, therapy was terminated earlier due to Covid infection (one after a TD of 62 Gy and the other after a TD of 64 Gy), while 1 patient refused to continue with CRT after manifestation of an acute toxicity of severe grade [mucositis grade III according to CTCAE vs. 4.3 (19)] and reached a TD of 40 Gy. In the fourth patient, the reason for failure to receive the planned TD was the development of neurological symptomatology unrelated to primary disease after a TD of 60 Gy.

In the absence of contraindications, from the start of RT, chemopotentiation was applied with mono cisplatin in the weekly regimen, with a dose of 40 mg/m^2. Six cycles were realized in 3 patients (8.3%). Most of the patients (11 patients; 30.6%) received five cycles. Four cycles of weekly cisplatin were applied in 7 patients (19.4%) and three cycles in another 7 patients (19.4%). Five patients (13.9%) received two cycles of concurrent chemotherapy. The predominant reasons for chemotherapy withdrawal were hematological and non-hematological acute toxicities, namely mucositis grade III,

Table I. Patients and tumor characteristics.

Characteristic	n (%)
Age, years	
Median	49.5
Range	18-71
Sex	
Men	27 (75.0)
Women	9 (25.0)
ECOG PS	
0	26 (72.2)
1	10 (27.8)
Comorbidity	
HTA	6 (16.7)
Heart disease	2 (5.6)
Diabetes mellitus	3 (8.3)
Lung	1 (2.8)
Depression	1 (2.8)
Hepatitis	1 (2.8)
Stage	
II	9 (25.0)
III	17 (47.2)
IVA	10 (27.8)
T stage	
T1	6 (16.7)
T2	10 (27.8)
T3	12 (33.33)
T4	8 (22.2)
N stage	
N0	4 (11.1)
N1	12 (33.3)
N2	17 (47.2)
N3	3 (8.3)

ECOG PS, Eastern Cooperative Oncology Group performance score; HTA, arterial hypertension; T, tumor; N, node.

dermatitis grade III, febrile neutropenia, neutropenia grade III and thrombopenia grade III.

The median number of concomitant cycles was four. In total, 3 patients (8.3%) received only one cycle. Of these, 1 patient withdrew from further therapy after one cycle of cisplatin and a TD of 40 Gy due to severe acute toxicity, namely mucositis grade III, as aforementioned. In another patient, also previously mentioned, CRT was interrupted after one cycle of mono cisplatin and a TD of 60 Gy due to central nervous symptomatology development. In the third patient, further application of concomitant CT was interrupted due to HCV infection activation, but RT was completed to a TD of 70 Gy/35 fractions.

After the completion of CRT, during regular follow-up, late sequelae of any sort were registered in 30 out of the 36 patients (83.3%). No late sequelae of any type were found in 6 patients (16.7%) (Table II).

Table II. Distribution of the late toxicities.

Late toxicity	n (%)
Overall toxicity	30 (83.3)
Neck fibrosis	25 (69.4)
Late xerostomia	21 (58.3)
Late dysphagia	2 (5.6)
Secondary hypothyroidism	4 (11.1)
Secondary neuropathy	3 (8.3)

The most common treatment-related late complication was neck fibrosis, experienced by 25 patients (69.4%) in the form of skin thickening and induration, muscle atrophy and loss of subcutaneous fat. Late xerostomia developed in 21 patients (58.3%). Only xerostomia grade ≤2 with no notable impact on the dietary habits was recorded as follows: Grade 1 in 41.67% of the cases and grade 2 in 16.67%. Only 2 patients (5.6%) developed late dysphagia. As the most serious and potentially life-threatening outcomes of this sequela, no instance of aspiration pneumonia or the need for a feeding tube was recorded. Secondary hypothyroidism as a post-irradiation consequence developed in 4 patients (11.1%) and was easily corrected with synthetic thyroid hormone. Neuropathy was noted in 3 patients (8.3%) in the form of facial numbness, paresthesia and dysesthesia, and palsy of the VII cranial nerve.

All registered late adverse events were statistically analyzed. Due to the sporadic occurrence of late dysphagia, secondary hypothyroidism and secondary neuropathy, no significant associations to patient, tumor or treatment characteristics were found, so the late toxicities that are most likely to affect the majority of patients treated with CRT were focused upon.

Exploring the associations between patient characteristics, no statistically significant difference was found in the frequency of overall late toxicity (P=0.14), neck fibrosis (P=0.37) and late xerostomia (P>0.999) between men and women. In the present study, tumor (T) stage, node (N) stage and clinical stage of disease did not have a significant impact on late toxicity prevalence (Table III).

The results imply that the administration of chemotherapy in different settings, neoadjuvant, concomitant or adjuvant, has no significant effect on the occurrence of post-therapy overall toxicity and late neck fibrosis (Table III). However, late xerostomia occurred significantly more often in patients who received five cycles compared with that in patients who received less than five cycles of weekly cisplatin concomitant with RT (P=0.02). Neoadjuvant and adjuvant chemotherapy applications had no statistically significant influence on its development.

The delivered TD had a substantial impact on the overall late toxicity, neck fibrosis and late xerostomia frequency in the patients (P=0.02, P=0.002 and P=0.02, respectively) when a mean TD of 67.0, 67.15 and 68.1 Gy was reached (Figs. 4-6).

Although in the subgroup of 22 patients treated with 3D conformal RT, a type of late post-therapy effect manifested in 66.7% of patients, late fibrosis in 60.0% and secondary xerostomia in 71.4%, when compared with patients treated with IMRT,

Table III. Overall toxicity, late neck fibrosis and late xerostomia associations with tumor and treatment characteristics analyzed by Fisher's exact test.

Characteristic	Overall toxicity	Late neck fibrosis	Late xerostomia
Male/female	P=0.14	P=0.37	P>0.999
T stage (1-4)	P=0.48	P=0.90	P=0.72
N stage (0-3)	P=0.80	P=0.91	P=0.43
Clinical stage (2-4)	P=0.61	P=0.87	P=0.51
Neoadj.chemo/no neoadj.chemo	P=0.58	P>0.999	P=0.69
3D conformal RT/IMRT	P=0.18	P>0.999	P=0.09
Adj.chemo/no ajd.chemo	P=0.52	P=0.29	P=0.65

T stage, tumor stage; N stage, node stage; adj.chemo, adjuvant chemotherapy; IMRT, intensity modulated radiotherapy.

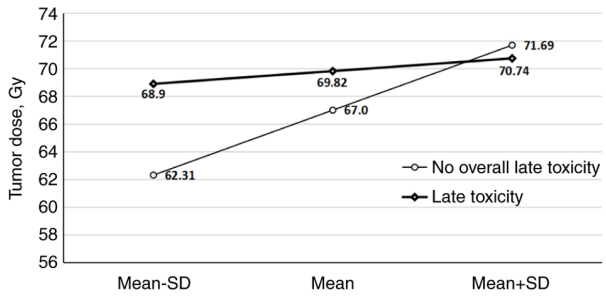

Figure 4. Statistically significant association between reached tumor dose and overall toxicity manifestation (Wilcoxon rank sum test with continuity correction, P=0.02).

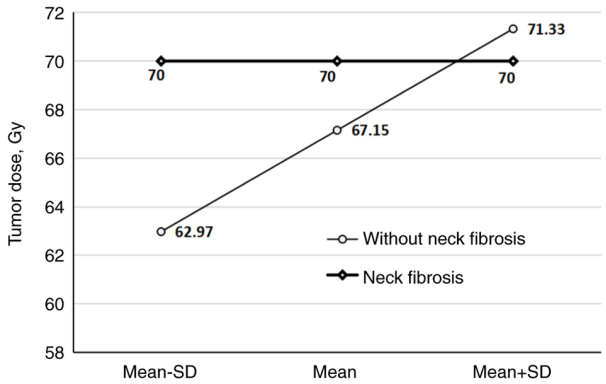

Figure 5. Statistically significant association between reached tumor dose and late neck fibrosis manifestation (Wilcoxon rank sum test with continuity correction, P=0.002).

statistical significance with regard to late toxicity incidence was not reached (P=0.18, P>0.999 and P=0.09, respectively).

Discussion

The last few decades have witnessed immense and accelerated advances in RT techniques and planning systems, as well as the appliance of chemotherapy in various sequencing schemes, along with RT in the management of NPC, thus providing promising outcomes for treated patients (3,6,20). As a result of this, survivorship issues emerge. Treatment-induced

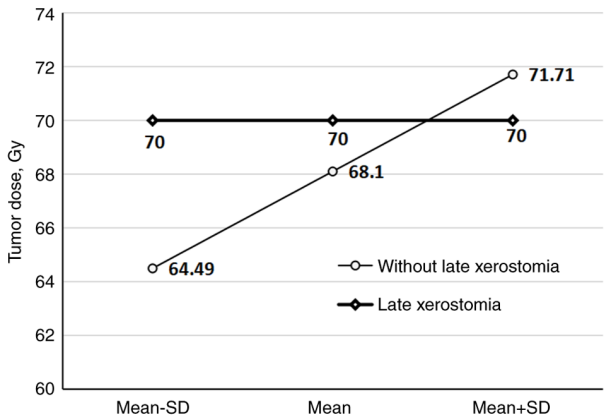

Figure 6. Statistically significant association between reached tumor dose and late xerostomia manifestation (Wilcoxon rank sum test with continuity correction, P=0.02).

late consequences can cause significant morbidity in cancer survivors, diminish their QoL and even, in rare cases, lead to death (9). Specific localization of NK-NPC and notoriously narrow therapeutic margins indicate the possibility of morphological, functional and esthetic damage. Unlike acute toxicities, late sequelae are globally more likely to be unrecognized, underestimated and left without adequate treatment, even though the majority of patients can suffer from one or several toxicities. Published data on this topic tend to be scarce and inconsistent, but also follow the extremely unequal geographical and ethnic distributions of NK-NPC, dominantly obtained from the Asian population of patients (8-11). In such circumstances, results gained from the present retrospective study of patients with non-endemic NK-NPC have to be discussed and compared mainly with results registered in Asian-based studies.

In the present study, a male predominance was found regarding sex distribution, with 75% of patients being men. This is in strong concordance with data from a meta-analysis by Blanchard *et al* (3), which reported 74% of patients being male, and with GLOBOCAN data (1), which imply a male to female ratio of 2-3:1. The median age of 49.5 years is in line with the median age of <50 years reported in some previous studies (3,21). The majority of patients in the current study

presented in the locoregional advanced stage of disease, with 72% in stages III and IVA, due to the aggressive biological behavior of NPC-NK, as shown across the literature (3,8,9,21,22).

Given their immense potential to negatively influence the QoL of NPC survivors, late sequelae are gaining importance within the contemporary scientific community. Much of our knowledge of this relationship is based on clinician-reported records. As it has been accepted that clinicians may inadvertently underestimate symptoms and their severity, oncological interest is shifting to patient-reported outcomes (PROs) (23,24). However, the paucity of data from NPC survivors also affects this aspect of investigation, and only a limited number of clinical trials have included PROs when performing QoL assessments (22). One of the more recent and important investigations was performed by McDowell *et al* (22) in a non-endemic medical center. The study showed that the five highest-scoring items of PROs were problems with dry mouth, mucus, swallowing or chewing, memory, and teeth or gums. Moderate associations between physician-reported adverse events and PROs were seen for dysphagia, xerostomia, dysarthria, voice/speech and aspiration. To overcome short-comings of reporting late post-treatment events, trials dealing with QoL are suggested to incorporated both PROs and clinician-reported adverse events.

In the present clinician-reported study, more than three-quarters of patients developed some form of late toxicity after completion of combined therapy. To the best of our knowledge, there is a paucity of data regarding overall post-treatment toxicities in this particular type of cancer after CRT. Several reasons can be provided in the explanation of this such as heterogeneity of baseline patients characteristics, different study designs, heterogeneity of therapy approaches, rarity of tumor and insufficient reporting. In a study conducted by Lee *et al* (8), in 422 patients treated with 3D conformal RT with a conventional or accelerated fractionation regimen, with or without chemotherapy, the overall toxicity rate was 27%, with a markedly greater rate of 37% in the chemotherapy-based group (16). In another study performed by Zeng *et al* (9), higher overall incidence of one or more late toxicities was registered in 55.8% of patients. Also, the study emphasized that a notably greater frequency of late sequelae was found in patients treated with CRT compared to those treated with RT alone (63.2 vs. 42.0%). Although it is hard to make a comparison among heterogeneous groups of patients and those with different treatments, it could be argued that, among the other aforementioned reasons, differences in ethnicity may play a role in the greater incidence of overall toxicities in the present study compared with the incidence of general toxicities in these studies on the endemic population. No significant impacts of patient and tumor characteristics on overall post-therapy consequences were found in the study, in contrast to findings from the study by Zeng *et al* (9), which found that T and N stage categories were significant factors for late toxicities in general. Previously, Lee *et al* (8) determined that only patient age was a strong significant factor in overall late toxicities, but not T and N tumor stage.

Nearly 70% of patients in the present group developed subcutaneous neck fibrosis as the most frequent late toxicity after CRT treatment. In the study conducted by Huang *et al* (10), secondary neck fibrosis was registered in 71.1% of cases in the group of patients with NPC irradiated using a non-IMRT planning technique; however, in the group of patients irradiated with IMRT, the frequency of this late sequela was considerably lower at 34% (18). It should be underlined no chemotherapy was administered in the study by Huang *et al* (10). Zeng *et al* (9) recorded a neck fibrosis incidence rate of 34.3% in patients treated with IMRT, and a considerably higher rate of 45.1% in the group of patients who underwent combined CRT. In one of the most comprehensive studies coming from a center outside an endemic region, the study conducted by McDowell *et al* (22) reported subcutaneous neck fibrosis in 55% of patients. Again, RT doses were delivered with IMRT in all patients. Although this study informs on physician-reported late toxicities and PROs in patients with NPC treated with IMRT in a non-endemic center, it should be highlighted that the majority of the investigated cohort was comprised of patients born in endemic regions. In addition, 7% of patients in this study did not receive chemopotentiation. More recently, in 2019, Zhao *et al* published 10-year results of a phase 2 prospective study where subcutaneous neck fibrosis was present in 91% patients, predominantly of a lesser grade (11). As can be seen from these data, a wide range of cumulative incidences of this late side effect span across different clinical studies, even though they were all conducted on patients from endemic regions, which brings us back to the pressing issue of inhomogeneity of study designs. It seems that the present group of non-endemic patients may be more prone to the neck fibrosis, when keeping in mind that IMRT was applied in just over one-third of patients and that all of them received one or more cycles of cisplatin.

According to the previously published studies on head and neck tumors of various subsites treated with RT, the frequency of late xerostomia ranged from 64 to 95% depending on tumor localization, RT planning technique and delivered TD, but also depending on patient-orientated factors (10,25). Several studies have strongly supported IMRT in terms of decreasing permanent xerostomia (20,26,27). In the present study, late xerostomia was recorded in almost two-thirds of patients (58.3%), with grade 2 found in 16.7% of patients. This result aligns closely with that from a study performed by Lee *et al* (8), where only 14% of patients reported grade 2 xerostomia and 35% of the patients did not develop xerostomia. In a study by Zeng *et al* (9) conducted in 2014 on NPC survivors irradiated with IMRT with or without chemotherapy, xerostomia was observed in 78.1% of patients. However, a notably higher incidence of this long-term consequence was registered in the study by McDowell *et al* (22) performed in a non-endemic RT center. Overall, 95% of the patients treated with IMRT suffered from low-grade late xerostomia according to physician-reported outcomes (22). Several reasons for this discrepancy compared with the present results could be offered, from the different study designs (cross-sectional cohort study vs. retrospective study), the longer time to event (subjects enrolled were disease-free ≥4 years after treatment), the influence of sample size and differences in adverse events reporting, to the impact of ethnicity on toxicity manifestation (majority of patients were of Asian descent). In the study by Huang *et al* (10), female survivors were observed to have a 2.6-fold higher probability of secondary xerostomia, but a significant association could not be confirmed between

patient and tumor demographics and the later development of xerostomia (10). While it is well established that the development and degree of xerostomia is largely dependent on the dose and volume of the salivary gland in the radiation field, the role of chemotherapy is less clear and literature data are somewhat contrasting. Zeng *et al* (9) concluded that chemotherapy was not a relevant factor affecting xerostomia, which agrees with studies by Miah *et al* (28) and Chao *et al* (29), where the research was performed on patients with head and neck cancer. By contrast, the study by Ou *et al* (30) demonstrated that concurrent chemotherapy significantly increased xerostomia compared to RT alone (46.4 vs. 36.3%), as well as total cisplatin dose increasing overall late toxicities. That being said, the present result is comparable with the findings from previously mentioned studies regarding the cumulative prevalence rate of xerostomia even though the patients were irradiated both with non-IMRT and IMRT planning techniques. Also, in alignment with the results by Ou *et al* (30), the present study demonstrated a statically significant impact of cisplatin chemopotentiation on late xerostomia prevalence, with a median of 5 cycles (P=0.02).

The only common significant factor for overall late sequela and the most prevalent ones (subcutaneous neck fibrosis and late xerostomia) that could be identified in the present study was the delivered TD (P=0.02, P=0.002 and P=0.02, respectively). The difference became statistically significant when the mean TDs of 67.0, 67.15 and 68.1 Gy were reached. The cumulative incidences of these three chronic toxicities were numerically notably lower in the subgroup of patients irradiated with IMRT in comparison to patients irradiated with 3D conformal RT, but the differences did not reach statistical significance, possibly due to the small sample size.

On the matter of cranial neuropathy, which presented with numbness, faint pain and cranial nerve palsy in the current patients, the record of 8.3% in this population of patients is comparable with published data. For example, in a study performed by Huang *et al* (10), in the group of patients irradiated with non-IMRT, neuropathy was found in 19.1% of cases, while notably less, only 5.0% of cases, exhibited neuropathy in the group of patients irradiated with IMRT. Also, Zeng *et al* (9) reported a frequency of 2.2% for cranial neuropathy in patients treated with CRT, and Zhao *et al* (11) reported a frequency of 6.5% in patients irradiated with the IMRT technique only. These numbers are in close alignment with the results of the present study. Notably, during the study period, no case of temporal lobe necrosis, as the most severe scenario of neuropathy, was registered in the present patient cohort.

One of the most troublesome late sequela is late dysphagia due to its potential to cause aspiration and a decrease in body mass index. Across the literature, data are scarce and heterogeneous. Huang *et al* (10) found 53.5% of cases with late dysphagia in a non-IMRT group of patients and 22% of cases in the IMRT group. By contrast, only 1.3% of this sequela was reported in the study by Ou *et al* (30). The present finding of 5.6% late dysphagia of lesser grade is closer to that of the latter study.

Secondary hypothyroidism was registered in 11.1% of cases in the present study, which is slightly higher than the rate in the study by Lee *et al* (8), where 6.6% patients developed this hormonal dysfunction.

As already mentioned, NK-NPC is a malignant disease with prominent ethnic and geographical disparities, so the vast majority of studies considered regarding this topic are conducted in the endemic population, with practically no studies performed in non-endemic regions (8-11,29,30). It is particularly relevant to contrast and compare results driven from both regions, since treatment protocol is still based on a 'one size fits all' approach, and the ultimate goal in modern oncology tends to be individualization and optimization of therapy.

Novel promising therapeutical approaches are, however, changing the landscape of NPC therapy. In the aspect of RT options, intensity-modulated proton therapy (IMPT) is proven to have dosimetry advantages over IMRT, thus facilitating the delivery of markedly reduced radiation doses to surrounding normal tissues. However, according to the study conducted by Li *et al* (31) on 77 patients with non-metastatic NPC, differences in the incidence of grade 3 or higher late toxicities between groups of patients treated with IMPT and IMRT were not significant. The median follow-up in this study was 2 years and it could be a potential factor impacting such results.

Current perspectives on immunotherapy and targeted therapy application in NK-NPC are established in recurrent and metastatic settings. There are numerous ongoing prospective clinical trials at phases II and III exploring the role of treatments in a locoregional advanced stage of NPC (clinical trial numbers: NCT06019130, NCT04833257, NCT02421640, NCT05628922 and NCT06781112). Efficacy and safety results are highly anticipated.

The present study, inevitably, has several limitations. The study included subjects treated in the Department of Radiotherapy for Solid Tumors and Hematological Malignancies, Institute for Oncology and Radiology of Serbia (Belgrade, Serbia) within a 5-year period, between January 2015 and December 2020. The study was closed in 2022, so there was a minimum 2-year period of follow-up, making it enough time for late sequelae to manifest and to be recorded, as these occur as early as 6 months after completion of RT. However, this was a shorter follow-up period for those patients treated in 2020, compared with those treated in 2015, which should be considered as a limitation of the study, as it could lead to underestimation of late toxicity occurrence in that subgroup of patients due to the long latency. It has been proposed by several studies that time-to-event analyses could address this issue (32,33). The retrospective nature of the study should be taken as a major limitation factor that could underpower the conclusions. A relatively small sample number could also be perceived as a limitation to the results. Further investigations with pooled data from another non-endemic centers would be of a tremendous importance.

In conclusion, according to the results of the present study, the majority of patients with non-endemic NK-NPC who underwent CRT will experience some form of late toxicities, but predominantly of lesser grade. The most frequent registered late toxicity is neck fibrosis, followed by xerostomia. In the constant attempt to improve treatment, aiming for remission or prolongation of a patient's lifetime, the importance of late morbidities is increasingly being recognized and should be justified by further research, especially in the challenging field of NK-NPC. The impact of ethnic differences on the

manifestation of post-treatment complications is quite undetermined, and possibly, underestimated, therefore investigations in the non-endemic population of patients are warranted.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JJR, TA and MN were responsible for study conceptualization. JJR, TA and NJK were responsible for the design of the study methodology. Data acquisition was performed by JJR, VV and NJK. Statistical analysis was performed by JJR. Data interpretation was performed by JJR, TA, MN and VV. Original draft preparation was the responsibility of JJR. TA and MN critically reviewed and edited the manuscript. Final approval was granted by TA and MN. JJR, TA and VV confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived in this study, since no experiments or novel treatments were conducted on humans. The methodology represents a standard treatment modality that does not need ethical approval. The decision to treat the patients in the manner described in the study was made by the Multidisciplinary Tumor Board of the Institute for Oncology and Radiology of Serbia (Belgrade, Serbia) according to the current treatment protocols. Written informed consent was obtained for all subjects involved in the study.

The manuscript is a part of the academic sub-specialistic thesis of JJR approved by the Faculty of Medicine, University of Belgrade (Belgrade, Serbia) on May 30, 2022 (protocol number: 04 BR:20-UON-10). The Institute for Oncology and Radiology of Serbia serves as a scientific teaching base for the Faculty of Medicine of University of Belgrade.

Patient consent for publication

Written informed consent was obtained for all subjects involved in the study. Before obtaining the consent, patients were thoroughly informed about all aspects of the planned combined treatment, its effects, possible acute and late toxicities. All subjects were fully aware that the data would be published.

Competing interests

The authors declare that they have no competing interests.

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