Long-term survival after reduced-dose radiotherapy in pediatric nasopharyngeal carcinoma

Looi Wen Shen[1], Ah Moy Tan[2], Shui Yen Soh[2], YOKE LIM SOONG[1], and Wong Ru Xin[1]

[1]National Cancer Centre Singapore Division of Radiation Oncology
[2]KK Women's and Children's Hospital

September 28, 2023

Long-term survival after reduced-dose radiotherapy in pediatric nasopharyngeal carcinoma

Wen Shen Looi, MBBS, FRCR, FAMS[1], Ah Moy Tan, MBBS[2], Shui Yen Soh, MBBS[2], Yoke Lim Soong, MBBS[1], Ru Xin Wong, MBBS[1]

[1]Division of Radiation Oncology

National Cancer Centre Singapore

[2]Haematology/Oncology Service

KK Women's and Children's Hospital

Corresponding author:

Wen Shen Looi

Division of Radiation Oncology

National Cancer Centre Singapore

Email address: looiwenshen@gmail.com

Phone number: +65 97340834

Fax number: +65 6234854

Text Word Count: 695 words (excludes title page, Conflicts of Interest, Acknowledgments, References, Tables, Figures, and Legends).

Number of figures: 2.

Keywords : adolescent; children; nasopharyngeal carcinoma; radiotherapy; rare diseases; case report

Abbreviations key:

Abbreviation	Full phrase
MRI	Magnetic resonance imaging
FDG	18F-fluorodeoxyglucose
PET/CT	Positron emission tomography with computed tomography
PCR	Polymerase chain reaction
EBV	Ebstein-Barr Virus
DNA	Deoxyribonucleic acid

Abbreviation	Full phrase
WHO	World Health Organization
AJCC	American Joint Committee on Cancer
PD-1	Programmed cell death-1
VMAT	Volumetric-modulated arc radiotherapy
COG	Children's Oncology Group

To the editor:

Radiotherapy forms the cornerstone of the curative treatment of nasopharyngeal carcinoma. Relatively high doses of radiotherapy are used and as such, late toxicity is a concern in children and adolescents with nasopharyngeal carcinoma who are treated with radiotherapy. We report on a patient with a long disease-free survival of 5 years after treatment despite receiving a reduced dose of radiotherapy.

A 15-year-old girl presented with a 4-cm left-sided neck mass of 2 weeks' duration. Nasoendoscopic evaluation demonstrated a mass in the right nasopharynx. Magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) demonstrated a nasopharyngeal mass, which was more prominent on the right side, and conglomerate lymph nodes, more prominent on the left, involving bilateral levels II, III, IV, V, and VII, with no distant metastases (Fig. 1). Findings from a biopsy of the posterior nasal space mass and fine needle aspiration cytology of a neck node were consistent with undifferentiated carcinoma with nodal metastases. Quantitative polymerase chain reaction (PCR) for Ebstein-Barr Virus (EBV) deoxyribonucleic acid (DNA) yielded 5,395 copies. She disease was staged as T1 N3b M0, Stage IVB, nasopharyngeal undifferentiated carcinoma, World Health Organization (WHO) type 3, using the American Joint Committee on Cancer (AJCC) 7$^{\text{th}}$ Edition Staging Manual. Despite counselling, her parents and her declined standard treatment and sought alternative medicine. She also received 1 cycle of the humanized monoclonal programmed cell death-1 (PD-1) antibody pembrolizumab at an external institution.

She was lost to follow-up, but returned 10 months later with progressive neck nodal disease. Repeat investigations with MRI and FDG PET/CT demonstrated bulkier locally advanced disease without distant metastases, with the same stage of T1 N3b M0, Stage IVB. Quantitative PCR for EBV DNA yielded 175,575 copies, which was much higher than her prior result. She was treated with 3 cycles of induction chemotherapy with cisplatin/5-fluorouracil followed by concurrent cisplatin chemoradiotherapy. The original intention was to deliver a total dose of 70 Gy to gross disease using volumetric-modulated arc radiotherapy (VMAT), which is consistent with our standard practice in adult nasopharyngeal carcinoma. We had considered a reduction of radiotherapy dose based on the protocol of a Children's Oncology Group (COG) study that was ongoing at that time, but she did not meet the criteria for dose reduction.[1] After just 50 Gy was delivered, the patient refused further treatment due to dermatitis with dry desquamation, although this was within expectations due to the large volume of disease and anticipated skin dose (Fig. 2). Our patient has continued to be disease-free for 5 years since completion of reduced-dose radiotherapy. Late toxicity from radiotherapy has been mild- she has had infrequent episodes of epistaxis due to bleeding at Little's area as well as mild dryness of the skin of the neck. She has developed Graves' disease, which is a known complication of pembrolizumab.

As the severity of late toxicity after radiotherapy is strongly correlated with the dose received, reduction of dose presents an opportunity to reduce the severity of late toxicity. Retrospective studies have suggested that lower doses can be used in children compared to adults.[2,3,4] Prospective evidence has also been provided by the COG study ARAR 0331 on childhood nasopharyngeal cancer, which has demonstrated excellent outcomes with a reduction in total dose from 70.2 Gy to 61.2 Gy in patients achieving an adequate response to induction chemotherapy.[1] Our patient's long-term survival is remarkable given that she had advanced disease at presentation, a prolonged delay in starting standard treatment, and a high pre-treatment EBV DNA load, which has been inversely correlated with survival.[5] Notably, she had stopped radiotherapy treatment

prematurely and received a radiotherapy dose of just 50 Gy, which is significantly lower than the dose of 61.2 Gy used in the COG ARAR 0331 study. Although not our standard practice, our patient received 1 cycle of pembrolizumab 6 months before irradiation in an external institution, which bears mentioning as immunotherapy has demonstrated promising activity against nasopharyngeal carcinoma.[6] While we recognize that this is a case report and that the findings cannot be generalized, it is thought-provoking that the required dose of radiotherapy for disease control may be lower than expected, at least in some patients.

Acknowledgement

We would like to thank the patient and her parents. There was no grant support for this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Ethics Statement

Informed consent was obtained from the patient and parents for this publication.

References

1. Rodriguez-Galindo C, Krailo MD, Krasin MJ, et al. Treatment of Childhood Nasopharyngeal Carcinoma With Induction Chemotherapy and Concurrent Chemoradiotherapy: Results of the Children's Oncology Group ARAR0331 Study [published correction appears in J Clin Oncol. 2021 May 10;39(14):1602]. J Clin Oncol. 2019;37(35):3369-3376. doi:10.1200/JCO.19.01276
2. Jouin A, Helfre S, Bolle S, et al. Adapted strategy to tumor response in childhood nasopharyngeal carcinoma: the French experience. Auf die Tumorreaktion angepasste Behandlungsstrategie beim Nasopharynxkarzinom in der Kindheit: Erfahrungen aus Frankreich. Strahlenther Onkol. 2019;195(6):504-516. doi:10.1007/s00066-019-01461-6
3. Buehrlen M, Zwaan CM, Granzen B, et al. Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. Cancer. 2012;118(19):4892-4900. doi:10.1002/cncr.27395
4. Uezono H, Indelicato DJ, Rotondo RL, et al. Proton therapy following induction chemotherapy for pediatric and adolescent nasopharyngeal carcinoma. Pediatr Blood Cancer. 2019;66(12):e27990. doi:10.1002/pbc.27990
5. Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. J Clin Oncol. 2006;24(34):5414-5418. doi:10.1200/JCO.2006.07.7982
6. Fang W, Yang Y, Ma Y, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. Lancet Oncol. 2018;19(10):1338-1350. doi:10.1016/S1470-2045(18)30495-9

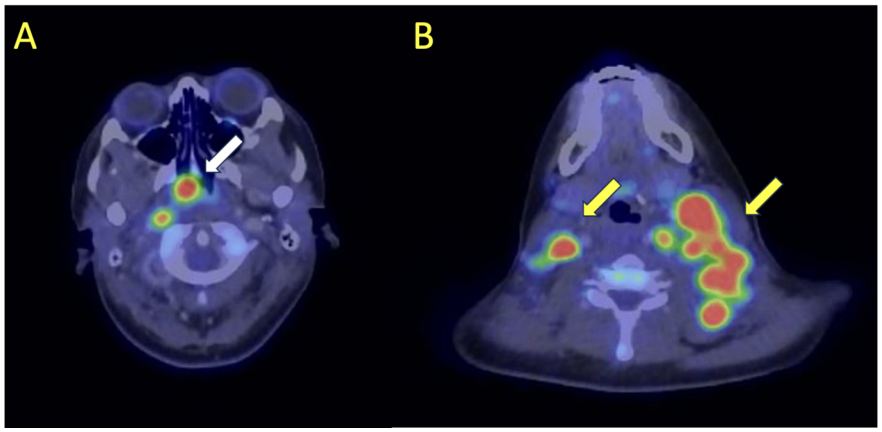

Figure 1. PET/CT imaging before induction chemotherapy demonstrating: A) Avid nasopharyngeal mass, more prominent on the right than the left side (white arrow). B) Involvement of bilateral lymph nodes (yellow arrows).

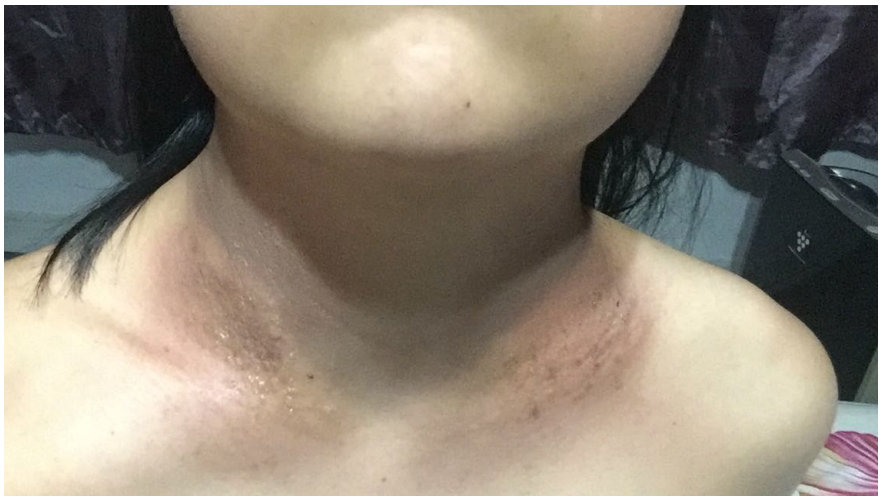

Figure 2. Acute dermatitis with dry desquamation after 50 Gy of radiotherapy, which was delivered using volumetric modulated arc radiotherapy (VMAT).