

RESEARCH HIGHLIGHT

Surgery as an alternative to radiotherapy in early-stage nasopharyngeal carcinoma: innovation at the expense of uncertainty

Luo Huang^{1,2} | Melvin L.K. Chua^{1,3,4} ¹Division of Radiation Oncology, National Cancer Centre Singapore, Singapore 169610²Division of Radiation Oncology, Chongqing University Cancer Hospital and Institute, Chongqing 400030, P. R. China³Division of Medical Sciences, National Cancer Centre Singapore, Singapore 169610⁴Oncology Academic Clinical Programme, Duke-National University of Singapore Medical School, Singapore 169857**Correspondence**

Dr Melvin L. K. Chua, Division of Radiation Oncology, National Cancer Centre Singapore, 11 Hospital Crescent, 169610, Singapore.

Email: melvin.chua.l.k@singhealth.com.sg

KEY WORDS: Early stage, nasopharyngeal carcinoma, resection, surgery, toxicities

Radiotherapy (RT) has an unassailable track record as the backbone of treatment in nasopharyngeal carcinoma (NPC). Several reasons explain its dominance. Likewise to human papilloma virus-associated oropharyngeal squamous cell carcinoma, Epstein-Barr virus (EBV)-associated NPC is exquisitely sensitive to RT. Thus, huge leaps with technological advances in RT delivery over the past decades have led to substantial improvements in tumor control, while reducing debilitating late RT-induced complications [1, 2]. Innovations in this space continue to drive the enhancement of the therapeutic ratio of RT, with the goal of enhancing the quality of life (QoL) among long-term survivors [3]. Therefore, there has not been any compelling reason to disrupt this time-honored convention of employing RT as the standard of care in NPC.

Currently, intensity-modulated RT (IMRT) is the standard RT modality for NPC and other head and neck cancers. High-quality level 1 evidence confirms its superiority to historical 2- and 3-dimensional techniques, particularly for the reduction of severe late RT adverse events such as xerostomia, hearing impairment, brain necrosis, and cranial nerve palsies [4].

However, patients continue to suffer from a high incidence of severe acute toxicities to RT. Interestingly, in a prospective observational study of reduced volume and dose IMRT in 103 NPC patients, all of whom had early-stage NPC (T1-2 and N0-1), the study investigators still observed grade 2 or worse acute xerostomia, mucositis, and dermatitis in about 40%-50% of patients [5]. Such data highlights the perennial limitations of RT and emphasizes the need for close supportive care to assist patients through the acute phase of RT. Additionally, apart from affecting the tolerability of RT, acute toxicities such as severe mucositis and xerostomia could harbor long-term consequences on QoL among the survivors [4]. These non-minuscule issues support the relentless pursuit of innovative strategies to de-intensify treatment, especially in patients with early-stage, curable NPC. In this regard, advances in RT modalities such as proton beam therapy and FLASH-RT (delivery of ultra-high dose rate of > 40 Gy/s) are being investigated as potential means to mitigate RT toxicities [6, 7].

To address this clinical unmet need, Chen and colleagues [8] presented the preliminary results of their prospective single-arm observational study on the outcomes following

Abbreviations: ¹⁸F-FDG-PET, ¹⁸F-fluorodeoxyglucose positron emission tomography; EBV, Epstein-Barr virus; ENPG, endoscopic nasopharyngectomy; IMRT, intensity-modulated RT; MRI, magnetic resonance imaging; NPC, nasopharyngeal carcinoma; QoL, quality of life; RT, radiotherapy.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. *Cancer Communications* published by John Wiley & Sons Australia, Ltd. on behalf of Sun Yat-sen University Cancer Center

endoscopic nasopharyngectomy (ENPG) in a cohort of T1 NPC patients. The underlying rationale of this study was simple and intuitive: to explore the possibility of “replacing” IMRT with ENPG in early-stage NPC patients, so as to avoid potential acute and late toxicities due to RT, without compromising the excellent survival outcomes of these individuals. Patient selection was stringent, as judged by the enrolment criteria: (1) biopsy-confirmed T1 NPC and tumor size of ≤ 1.5 cm as defined by magnetic resonance imaging (MRI); (2) no evidence of retropharyngeal and cervical lymph node metastasis (note that all patients were staged by MRI and/or ^{18}F -fluorodeoxyglucose positron emission tomography [^{18}F -FDG-PET]); and (3) ≥ 0.5 cm margin from the internal carotid artery for feasibility of ENPG. Briefly, the surgical procedure involved complete excision of the NP mucosa, with the surgical anatomical boundaries defined as such: the mucoperiosteum was dissected superiorly to posteriorly from the floor of sphenoid sinus to the clivus; the anterior margin was defined by the posterior nasal cavity; and the bilateral eustachian cartilage from the pharyngeal recess under the mucous membrane and foramen lacerum and the soft palate constitute the lateral and inferior margins, respectively. Finally, the nasal septum and floor mucosa were transposed to cover the surgical defect.

Using this surgical technique, the median duration of ENPG was 92.5 min (range: 60-135 min), and the median quantity of blood loss was 20 mL (range: 10-100 mL). Recovery was quick, with flap re-epithelization occurring within 2-4 weeks post-ENPG. No severe ENPG-related complications or death was observed; information on hospital stay duration was not reported. Crucially, the authors did not observe any tumor recurrence and all patients remained alive at the time of analysis. Notably, while the reported median follow-up was 59.0 months, it must be cautioned that only half of the study cohort was monitored for longer than 5 years, and in fact, three patients had follow-up duration of less than 2 years (this can be inferred from the reported numbers at risk indicated in the Kaplan-Meier survival curves). Although the authors included an IMRT-treated cohort for comparison, one would be circumspect about such an analysis given the feasibility of “perfect matching” of clinical and tumor characteristics. Expectedly, none of the patients experienced acute and delayed toxicities of xerostomia and neuropathies, and all patients reported minimal deterioration in QoL post-ENPG. Finally, the authors presented a preliminary cost-effective analysis in favor of ENPG over IMRT in the treatment of these low-risk NPC patients.

These are certainly impressive results. However, they have to be weighed against several caveats. Foremost, as with any surgical technique, there is an acute learning phase that will affect procedural quality, and this metric certainly corresponded to tumor control and toxicity outcomes [9, 10]. Therefore, while excellent results were achieved by the team

at Sun Yat-sen University Cancer Centre (Guangzhou, Guangdong, China), it remains to be seen if similar quality can be attainable by lower volume centers [11]. Next, it must be emphasized that the present study cohort has been carefully selected. In addition to recruiting only small T1 tumors, patients were meticulously screened for occult retropharyngeal and cervical nodal metastases using both MRI and PET imaging, given the omission of nodal dissection/RT. Future prospective studies will inform us if high-resolution imaging alone is sufficient for the screening of suitability for ENPG or if additional biomarkers like EBV DNA are needed. Third, it is notable that ENPG in this study entailed the removal of the entire NP mucosa. This extent of resection contradicts the principle of target contouring in head and neck cancer, which ascribes to the 5+5 mm rule for the definition of high-risk and low-risk subclinical disease [12]. Fourth and most importantly, the authors had not actually outlined a detailed protocol in the instance when adjuvant/salvage treatment is required for margin-positive disease or local/nodal recurrence. These unresolved issues require consensus among the NPC expert community, ideally prior to the design and conduct of larger-scale clinical trials of ENPG in T1-2 NPC patients.

To conclude, Liu and colleagues ought to be applauded for challenging the status quo in the treatment of NPC. Evidently, patients still suffer from RT-induced toxicities despite the phenomenal success of IMRT, and ENPG represents a disruptive innovation in this space. It is unlikely that these impressive results of zero recurrence will be replicated in future trials with larger cohorts, and thus begs the pertinent question of the measurable impact of disease relapse on a patient's QoL. Ultimately, how does the primary physician decide on the appropriate treatment recommendation for such a highly curable disease? The truth probably lies somewhere in the individual patient's tolerance for the cost of treatment toxicities versus the uncertainty of tumor recurrence. Meanwhile, it remains our responsibility to continue pushing the frontiers of innovation in the treatment of NPC.

ACKNOWLEDGMENTS

The authors thank members of the Soo's and Chua's lab for their critical comments.

AUTHORS' CONTRIBUTIONS

Study conception: Melvin L.K. Chua.

Collection and assembly of data: Melvin L.K. Chua, Luo Huang.

Administrative and funding support: Melvin L.K. Chua.

Manuscript writing and approval of the final manuscript: All authors.

FUNDING

MC is supported by the National Medical Research Council Singapore Clinician-Scientist Award - #NMRC/CSA/0027/

2018 and the Duke-NUS Oncology Academic Program Proton Research Program.

AVAILABILITY OF DATA AND MATERIALS

Not applicable

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

COMPETING INTERESTS

The author declares no competing interests; Melvin L.K. Chua reports grants and personal fees from Ferring Singapore, personal fees from Janssen, personal fees from Astellas, personal fees from Merck, personal fees from Illumina, personal fees and non-financial support from Varian, non-financial support from PVMed Inc., non-financial support from Medlever Inc, non-financial support from Decipher Biosciences, outside the submitted work.

ORCID

Melvin L.K. Chua  <https://orcid.org/0000-0002-1648-1473>

REFERENCES

1. Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. *Lancet*. 2016;387(10022):1012–24. [https://doi.org/10.1016/S0140-6736\(15\)00055-0](https://doi.org/10.1016/S0140-6736(15)00055-0).
2. 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>.
3. Liu LT, Chua MLK, Tao Y, Tang LQ, Mai HQ. Optimal sequencing of chemotherapy with chemoradiotherapy based on TNM stage classification and EBV DNA in locoregionally advanced nasopharyngeal carcinoma. *Cancer Commun (Lond)*. 2019;39(1):64. <https://doi.org/10.1186/s40880-019-0398-0>.
4. Chen L, Zhang Y, Lai SZ, Li WF, Hu WH, Sun R et al. 10-Year Results of Therapeutic Ratio by Intensity-Modulated Radiotherapy Versus Two-Dimensional Radiotherapy in Patients with Nasopharyngeal Carcinoma. *Oncologist*. 2019;24(1):e38–e45. <https://doi.org/10.1634/theoncologist.2017-0577>.
5. Miao J, Di M, Cao Y, Wang L, Xiao W, Zhu M, et al. Long-term results of phase II trial of reduced modified clinical target volume in low-risk nasopharyngeal carcinoma treated with intensity modulated radiotherapy. *Annals of Oncology*. 2020;30(Supplement 9), November 2019, Page ix99. doi:<https://doi.org/10.1093/annonc/mdz428.004>.
6. de Kruijff RM. FLASH radiotherapy: ultra-high dose rates to spare healthy tissue. *Int J Radiat Biol*. 2019;1–5. <https://doi.org/10.1080/09553002.2020.1704912>.
7. Li YQ, Tan JSH, Wee JTS, Chua MLK. Adaptive radiotherapy for head and neck cancers: Fact or fallacy to improve therapeutic ratio? *Cancer Radiother*. 2018;22(3):287–95. <https://doi.org/10.1016/j.canrad.2018.01.003>.
8. Liu YP, Lv X, Zou X, Hua YJ, You R, Yang Q et al. Minimally invasive surgery alone compared with intensity-modulated radiotherapy for primary stage I nasopharyngeal carcinoma. *Cancer Commun (Lond)*. 2019;39(1):75. <https://doi.org/10.1186/s40880-019-0415-3>.
9. Holsinger FC, Ferris RL. Transoral endoscopic head and neck surgery and its role within the multidisciplinary treatment paradigm of oropharynx cancer: robotics, lasers, and clinical trials. *J Clin Oncol*. 2015;33(29):3285–92. <https://doi.org/10.1200/JCO.2015.62.3157>.
10. Howard J, Masterson L, Dwivedi RC, Riffat F, Benson R, Jefferies S et al. Minimally invasive surgery versus radiotherapy/chemoradiotherapy for small-volume primary oropharyngeal carcinoma. *Cochrane Database Syst Rev*. 2016;12:CD010963. <https://doi.org/10.1002/14651858.CD010963.pub2>.
11. Wuthrick EJ, Zhang Q, Machtay M, Rosenthal DI, Nguyen-Tan PF, Fortin A et al. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. *J Clin Oncol*. 2015;33(2):156–64. <https://doi.org/10.1200/JCO.2014.56.5218>.
12. Lee AW, Ng WT, Pan JJ, Poh SS, Ahn YC, AlHussain H et al. International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. *Radiother Oncol*. 2018;126(1):25–36. <https://doi.org/10.1016/j.radonc.2017.10.032>.

How to cite this article: Huang L, Chua ML. Surgery as an alternative to radiotherapy in early-stage nasopharyngeal carcinoma-innovation at the expense of uncertainty. *Cancer Communications*. 2020;40:119–121. <https://doi.org/10.1002/cac2.12015>