

Editorial

Nasopharyngeal carcinoma – Improving cure with technology and clinical trials

**KEYWORDS**

Nasopharyngeal carcinoma;
Intensity modulated radiotherapy;
Concurrent chemoradiotherapy;
Neoadjuvant chemotherapy;
Nasopharyngectomy

Nasopharyngeal carcinoma is a unique cancer in the head and neck region. It has a very distinct geographic variation of incidence with more than ten times difference in incidence in high risk population compared with low-risk population. No other head and neck cancer has this large worldwide variation of incidence. It remained commonest cancer in young male adults below the age of 50 in southern China. The relative inaccessible anatomy and radiosensitivity has made radiotherapy the primary treatment in all stages of the cancer. The endemic form of the cancer is almost invariably associated with the Epstein Barr virus (EBV), making the EBV viral markers the first clinically applicable tumor marker in head and neck cancer. A large scale population study had demonstrated the feasibility to use EBV DNA titer to perform population screening for NPC in at risk population with survival benefits.¹

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Advances in radiotherapy

The cure rate of NPC has markedly improved in the last 50 years. With modern combined modality treatment, stage III disease can expect a 5-year survival of >70% and stage IV disease can expect a 5 year survival over 50%.² This is mainly due to the improvement in radiotherapy technique and additional use of chemotherapy. Conventional two dimension radiotherapy used since the 1960's were unable to deliver high dose to tumors close to critical structures without damaging the critical structures due to radiation overdose. The late toxicities of conventional two-dimensional radiotherapy were also quite high. As many patients were young, survivors had significant long term deterioration of quality of life for many years.³ The introduction of intensity modulated radiotherapy (IMRT) had drastically changed the treatment of NPC. IMRT not just reduces the radiation toxicities to normal structures by spreading the radiation from 2 parallel beams to multiple beams of lower dosage, but also improves the contouring of radiation to the tumor and delivers adequate radiation dose to the tumor. With improved imaging and IMRT, tumor extension to oropharynx and nasal cavities can now be adequately treated and this is reflected in the 7th edition of UICC/AJCC cancer staging by downstaging oropharyngeal and nasal cavities extension from T2 to T1 disease. By sparing more adjacent organs from high dose radiation, IMRT also improves quality of life of the survivors, especially in regards to xerostomia,⁴ trismus and swallowing.⁵

IMRT relies on good radiation planning and high accuracy in delivering the intended radiation dosimetry to structures. As treatment continues, the size of the tumor and shape of the patient's body may change. In order to account for these changes, a strategy of re-planning during the course of the radiotherapy treatment has been proposed.⁶ The strategy is called adaptive radiotherapy. Adaptive radiotherapy can then compensate for the shift in the target tumor and critical structures as radiation treatment progress. This, unfortunately, would translate to

extra manpower resource to re-plan the radiation treatment. Adaptive radiotherapy would probably be unnecessary in patients with small tumors and minimal weight loss during treatment. More clinical trials are required to define the patient subgroup that would benefit from adaptive radiotherapy and the most cost effective strategy to implement adaptive radiotherapy.

Another technological advancement is the use of heavy ions like proton for delivery of radiation. Theoretically intensity modulated proton therapy (IMPT) would be able to deliver a higher radiation dosage to the tumor volume while at the same time reducing the radiation dosage to organs at risk.⁷ This would be useful in advanced cancers where the tumor is close to the critical structure and also in re-irradiation setting where normal tissue already had significant exposure to prior radiation.⁸ An even newer radiation technique using heavy particles is the use of carbon ions for radiation. Initial reports showed even better toxicity sparing to critical structures than proton therapy for treatment recurrent nasopharyngeal carcinoma.^{9,10} These new technological advances would need larger scale clinical trials to define the role in management of nasopharyngeal carcinoma.

Advances in chemotherapy

The NPC 0099 trial has firmly established the value of adding chemotherapy to radiotherapy when treating nasopharyngeal carcinoma.¹¹ With IMRT and concurrent cisplatin chemotherapy, local-regional failure of NPC after treatment is now less than 15%.¹² The most common form for failure, however, is distant metastasis. It would be logical to add additional chemotherapy to reduce the incidence of distant metastasis more. However, clinical trial has not shown the benefit of additional adjuvant chemotherapy in patients already received high dose chemotherapy during the radiation treatment.¹³ Moreover, there is increased toxicities with additional high dose adjuvant chemotherapy to this group of patients. A new multi-center clinical trial from China published earlier this year, however, showed the benefit of neoadjuvant chemotherapy for advanced stage (stage III – IVb) NPC. The trial consisted of 480 patients randomly assigned to standard cisplatin based concurrent chemoradiation versus neoadjuvant chemotherapy with gemcitabine and cisplatin followed by standard chemoradiotherapy. The 3-year recurrence free survival improved from 76.5% to 85.3% when additional neoadjuvant chemotherapy was administered. Over 96% of the patient can complete all 3 courses of neoadjuvant chemotherapy.¹⁴

New target therapies and immunotherapies are coming out of research pipeline. However, when applied to NPC, most of the trials are still exploring the role of these novel therapies on metastatic diseases that failed conventional salvage treatment.¹⁵ However, these novel therapeutics, especially the immune checkpoint mediators may improve the efficacy of radiotherapy in the primary treatment setting. Also, as the mechanism of these novel therapeutics is different from chemotherapy and radiotherapy, the toxicity profile will be different. Addition of these novel

therapeutics in the primary treatment setting may be more tolerable than higher dose of chemotherapy or radiotherapy. Still, large scale clinical trials will be needed to investigate the exact role of these novel therapeutics in the treatment of NPC.

Advances in surgery

Due to the anatomical location of the nasopharynx and the radiosensitivity of endemic NPC, surgery has not been considered any role in primary treatment of NPC. For recurrent disease, because of the morbidities of additional radiation, surgery in the form of nasopharyngectomy, had been gaining attention for treating locally recurrent diseases. Before the 1980's, surgery on the nasopharynx for resection of malignant tumors had rarely been attempted. In the two decades of 1980–1990's, a variety of surgical approaches to the nasopharynx were described and larger surgical cohorts had shown survival benefits of salvage surgery for recurrent NPC.¹⁶ The disadvantages of all the traditional open approaches to nasopharynx are the morbidities related to transgressing a large amount of normal tissue in the head and neck area in order to expose the nasopharynx and perform the resection. This would lead to cosmetic and functional problems including facial scars, trismus and swallowing dysfunction. With advancement of technologies, minimally invasive surgery to the paranasal sinuses and anterior skull base can now be performed. Advancements in endoscopes, video systems and surgical tools, endoscopic surgery to the nasopharynx can now achieve comparable success in salvaging small locally recurrent NPC as with traditional open surgery, with much less morbidities. Endoscopic resection of rT1-2 recurrent NPC can achieve 3-year local control of 80%. Unfortunately, clinical trial comparing a surgical salvage versus non-surgical treatment would be very difficult to implement, partially to due to ethical issues and patients' preferences. We would still need to rely on high quality cohort studies and case-controlled studies to define the role of surgery versus other modalities of treatment in various scenarios of NPC.¹⁷

Conclusions

In the last 50 years, with the collaboration of scientists, medical physicists, engineers, radiation oncologists, medical oncologists and surgeon, there were significant improvement in all aspect of care in NPC patients. Not just survival has dramatically improved, complications from treatment have reduced and early detection screening programs can now be implemented in at risk population groups. While technologies would develop new and better machines and drugs, clinical trials are essential to define the exact benefit groups for these new and often expensive treatment modalities. Yet, the outlook is bright.

Conflict of interest

There is no conflicts of interest.

References

1. Kca C, Jks W, King A, et al. Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer. *N Engl J Med*. 2017;377:513–522.
2. Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys*. 2005;61:1107–1116.
3. Lee AW, Law SC, Ng SH, et al. Retrospective analysis of nasopharyngeal carcinoma treated during 1976–1985: late complications following megavoltage irradiation. *Br J Radiol*. 1992;65:918–928.
4. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys*. 2006;66:981–991.
5. Fang FM, Tsai WL, Lee TF, Liao KC, Chen HC, Hsu HC. Multivariate analysis of quality of life outcome for nasopharyngeal carcinoma patients after treatment. *Radiother Oncol*. 2010;97:263–269.
6. Zhao L, Wan Q, Zhou Y, Deng X, Xie C, Wu S. The role of replanning in fractionated intensity modulated radiotherapy for nasopharyngeal carcinoma. *Radiother Oncol*. 2011;98:23–27.
7. Lewis GD, Holliday EB, Kocak-Uzel E, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. *Head Neck*. 2016;38(Suppl 1):E1886–E1895.
8. Dionisi F, Croci S, Giacomelli I, et al. Clinical results of proton therapy reirradiation for recurrent nasopharyngeal carcinoma. *Acta Oncol*. 2019;58:1238–1245.
9. Hu J, Bao C, Gao J, et al. Salvage treatment using carbon ion radiation in patients with locoregionally recurrent nasopharyngeal carcinoma: initial results. *Cancer*. 2018;124:2427–2437.
10. Wang L, Hu J, Liu X, Wang W, Kong L, Lu JJ. Intensity-modulated carbon-ion radiation therapy versus intensity-modulated photon-based radiation therapy in locally recurrent nasopharyngeal carcinoma: a dosimetric comparison. *Cancer Manag Res*. 2019;11:7767–7777.
11. 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;16:1310–1317.
12. Ng WT, Lee MC, Hung WM, et al. Clinical outcomes and patterns of failure after intensity-modulated radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2011;79:420–428.
13. Lee AW, Ngan RK, Tung SY, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer*. 2015;121:1328–1338.
14. Zhang Y, Chen L, Hu GQ, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N Engl J Med*. 2019;381:1124–1135.
15. Hsu C, Lee SH, Ejadi S, et al. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1-positive nasopharyngeal carcinoma: results of the KEYNOTE-028 study. *J Clin Oncol*. 2017;35:4050–4056.
16. Ng WT, Ecy W, Akw C, et al. Patterns of care and treatment outcomes for local recurrence of NPC after definite IMRT-A study by the HKNPCSG. *Head Neck*. 2019;41:3661–3669.
17. You R, Zou X, Hua YJ, et al. Salvage endoscopic nasopharyngectomy is superior to intensity-modulated radiation therapy for local recurrence of selected T1-T3 nasopharyngeal carcinoma – a case-matched comparison. *Radiother Oncol*. 2015;115:399–406.

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