Editorial

Re-irradiation for recurrent NPC—is the treatment merited at all?

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With advances in radiotherapy (RT) technique and chemotherapy strategies, the survival of patients with nasopharyngeal carcinoma (NPC) has improved substantially in the past few decades, with most intensity-modulated radiation therapy (IMRT) series achieving up to 90% loco-regional control (1). The most common site of recurrence remains to be distant. Local recurrence of NPC, albeit uncommon, is extremely debilitating and difficult to manage. Salvage surgery and re-RT are the only curative treatment options available. Randomized study to compare surgery and re-RT is deemed difficult due to the rarity of the condition and the heterogeneity of this heavily pre-treated population. Treatment choice is, therefore, mainly based on each physician's discretion, availability of expertise and patient's choice.

Undoubtedly, a proportion of locally relapsed NPC cases could achieve long-term survival with salvage treatment. Re-RT is widely practised in many centres, especially for locally advanced disease, i.e., rT3–4. However, the therapeutic window of re-RT is extremely narrow and long-term toxicities are almost unavoidable. Is it sensible to offer re-RT to all? How much risk is imposed to our patients? Based on the available evidence, we may conclude some basic principles to guide our decision making.

Avoid re-RT if surgery is possible

This is to avoid cumulative morbidities from two RT courses. In a recent meta-analysis evaluating long-term outcomes after re-RT for relapsed NPC (2), the 5-year local failure-free survival (FFS) and distant FFS were up to 72% and 85% respectively. However, the overall survival rate (OS) was merely 41%, with a striking rate of 33% grade 5 toxicity. Mucosal necrosis and massive hemorrhage were by far the most common causes of death (2,3), followed by feeding difficulties and radiation encephalopathy. Such high treatment mortality rate is far from acceptable. If a new drug is shown to cause 33% mortality due to treatment-induced toxicities, would it be approved by any regulatory body? With advances in surgical technique, tumors that were considered inoperable in the past, have now become salvageable (4). In general, all rT1–2 and selected minimal rT3 cases are all surgical candidates, depending on the local expertise.

Select your patient wisely

If surgery is not possible and re-RT is considered, we need to balance the potential risks and benefits of re-RT. Delineation of factors that could predict patients' treatment outcome is of great value.

In a prognostic model proposed by Li *et al.* (5), several factors have been identified as predictive on the OS in patients with local recurrent NPC. The prognostic index (PI) was constructed based on the weighting of 5 significant risk factors, which included the age, gross tumour volume (GTV) of recurrence, presence of prior RT-induced grade 3 or above toxicities, T-staging at recurrence (T3–4) and the dose of repeat IMRT (EQD2 of ≥68 Gy). With a fixed PI score cutoff of 252, it consistently predicted OS and grade 5 toxicities in two other cohorts of patients. It may represent a convenient, yet robust model to guide patient selection for re-RT.

Yu *et al.* have also looked into the risk factors of lethal

Table 1 Factors affecting the outcomes of recurrent NPC

Prognostic factor	Li (5)	Leong (2)	Tian (7)
Age, years	[age]		[age >50]
Performance status			[KPS ≤70]
Time to recur		≥36 months	
rT category	[rT3–4]	rT1–2	[rT3–4]
rGTV	[rGTV]		[>30 cc]
rN+		Low nodal burden	[rN+]
2nd course RT dose	[≥68 Gy]	≥70 Gy*	
Prior RT complications	[grade 3 complications]		[present]
Addition of chemotherapy		Yes*	

[ ], negative prognostic factor; *, not associated with better outcomes. GTV, gross tumor volume; KPS, Karnofsky performance status; RT, radiotherapy.

nasopharyngeal necrosis in patients with recurrent NPC receiving re-RT (6). They have identified that a larger recurrent tumour volume, a higher accumulated dose to the GTV, presence of necrosis before re-RT, and female sex as factors that could confer a higher risk. *Table 1* summarizes some other factors affecting outcomes of relapsed NPC that were identified in various studies (2,5,7).

These studies allow better understanding on limitations of re-RT. One might argue that this may not be entirely applicable to our local practice in Hong Kong. Patients with early (rT1–2) disease would receive salvage surgery anyway, while re-RT is often reserved for those with unresectable (rT3–4) disease. Also, not all prior-RT induced toxicities should be considered equal. Some toxicities such as hormonal insufficiencies and unilateral hearing loss could be amenable to medications or modifications by hearing aids. With the potential reversibility, such factors might not impede us from offering re-RT. The factors that truely matter are, therefore, the age, GTV volume, other pre-existing grade 3 toxicities (especially necrosis) and the intended second course RT dose.

Never prescribe over 68–70 Gy for second course RT

High re-RT dose above 68–70 Gy has been consistently shown to be associated with poor treatment outcomes (2,5). The local control benefit from dose escalation could be easily offset by detrimental effect of excessive late toxicities. In treatment planning, neurological structures, e.g., brainstem, spinal cord, optic chiasm etc., are generally considered to be the most important organs at risk (OARs) to be avoided. Other structures such as carotid vessels and the nasopharyngeal mucosa itself are often ignored. Late complications of these structures, i.e., mucosal necrosis and carotid blowout have been frequently reported. Based on the pattern of complications, it appears that these structures have a very steep dose gradient of complication after a cumulative dose ≥115–120 Gy. D0.1cc <47.6 Gy to carotid artery in the setting of SBRT has been reported as a potential constraint (8). On the other hand, adequate tumour coverage (GTV D95) is an important determinant for local control (9). Even if we aim for dose escalation, the dose coverage of target volume will not be satisfactory, especially for rT3–4, due to close proximity to neurologic OARs (9). In our centre, we recommend 64.8 Gy in 54 fractions twice daily over 5.5 weeks (EQD2 =60 Gy), and never exceed 68 Gy (10). Hyperfractionation schemes are preferred as they are more biologically friendly with OARs.

Use the most conformal technique

IMRT is now considered to be the standard of care and has replaced 3D conformal techniques in management of both primary and relapsed NPC. Particle beam can further improve dosimetry and widen the therapeutic window. Promising results of carbon ion RT were demonstrated (11). However, availability of particle beam RT remains the major obstacle.

Integration with systemic treatment—an unanswered question?

Although concurrent chemotherapy and targeted therapies with re-RT are commonly used, there is no concrete evidence to support their role. Induction chemotherapy is commonly utilized to downsize the tumour when the disease extent is beyond salvage with upfront re-RT. We recently conducted a phase 2 study to evaluate the efficacy of induction docetaxel, cisplatin, and fluorouracil (TPF) followed by weekly docetaxel and cetuximab in concurrence with IMRT in rT3–4/N0–1 NPC patients (12). Treatment outcomes were better than historical data but poor tolerability of induction TPF and the high rate of temporal lobe necrosis has limited its applicability outside clinical trials. With limitations in the re-RT dose (<68 Gy), systemic treatment may have a synergistic role in potentiating the killing of tumour cells.

Palliative chemotherapy alone may not be a bad alternative

Although surgery or re-RT is the only chance to cure, the survival outcomes of palliative chemotherapy may not be worse than 'curative' treatment. A case-matched, retrospective study showed equivalent OS for patients received re-RT and chemotherapy alone (13). As expected, more RT-induced mortalities were observed in the re-RT group and more deaths due to local recurrence were observed in the chemotherapy alone group. Chemotherapy alone is associated with less toxicities and may, therefore, translate into better quality of life (QoL). Further evaluation of this approach is warranted.

Future direction

Further research is definitely needed. However, large scale prospective, randomized study is difficult to conduct and we may need to rely on retrospective data to guide our future direction.

It is crucial to have a better understanding of nasopharyngeal mucosal/carotid artery RT tolerance as these structures are always within the target volume and the high dose region. Nasopharyngeal mucosal and carotid tolerance would limit our maximum total prescribed dose to the target.

Maintaining reasonable QoL is undoubtedly one of the key aspects in management of relapsed NPC. To our patients, QoL maybe even more important than survival. When the difference in efficacies of different treatment modalities is only modest, we may want to focus on improving QoL of patients instead. However, QoL studies are extremely difficult to conduct. After undergoing salvage treatment, some of the patients are likely to be affected by the significant morbidities, e.g., impaired cognitive function, hearing and vision, to a degree that they might not even be able to complete the QoL questionnaire.

In recent years, radiogenomics, which refers to the study of genetic variation associated with response to RT, has become a hot topic. Currently, the field is still in the stage of pre-clinical development and is making progress towards clinical application. In the future, genetic based-risk models may be able to stratify patients to more tailored RT protocols.

There are currently two ongoing studies in Hong Kong. A population based, retrospective outcome study of relapsed NPC after primary IMRT is going to shed light on the current pattern of care in Hong Kong. Another study on the novel approach of immunotherapy concurrent with re-RT will be initiated later this year. We hope such studies could provide us with more information on this topic of interest, to facilitate our continual improvement in the care of patients with local recurrent NPC.

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References

1. Au KH, Ngan RKC, Ng AWY, et al. Treatment outcomes of nasopharyngeal carcinoma in modern era after intensity modulated radiotherapy (IMRT) in Hong Kong: A report of 3328 patients (HKNPCSG 1301 study). Oral Oncol 2018;77:16-21.
2. Leong YH, Soon YY, Lee KM, et al. Long-term outcomes after reirradiation in nasopharyngeal carcinoma with intensity-modulated radiotherapy: A meta-analysis. Head Neck 2018;40:622-31.
3. Tian YM, Huang WZ, Yuan X, et al. The challenge in treating locally recurrent T3-4 nasopharyngeal carcinoma: the survival benefit and severe late toxicities of re-irradiation with intensity-modulated radiotherapy. Oncotarget 2017;8:43450-7.
4. Chan JY, Wong ST, Chan RC, et al. Extracranial/intracranial vascular bypass and craniofacial resection: New hope for patients with locally advanced recurrent nasopharyngeal carcinoma. Head Neck 2016;38 Suppl 1:E1404-12.
5. Li YQ, Tian YM, Tan SH, et al. Prognostic model for stratification of radioresistant nasopharynx carcinoma to curative salvage radiotherapy. J Clin Oncol 2018;36:891-9.
6. Yu YH, Xia WX, Shi JL, et al. A model to predict the risk of lethal nasopharyngeal necrosis after re-irradiation with intensity-modulated radiotherapy in nasopharyngeal carcinoma patients. Chin J Cancer 2016;35:59.
7. Tian YM, Tian YH, Zeng L, et al. Prognostic model for survival of local recurrent nasopharyngeal carcinoma with intensity-modulated radiotherapy. Br J Cancer 2014;110:297-303.
8. Gebhardt BJ, Vargo JA, Ling D, et al. Carotid Dosimetry and the Risk of Carotid Blowout Syndrome After Reirradiation With Head and Neck Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys 2018;101:195-200.
9. Chan OS, Sze HC, Lee MC, et al. Reirradiation with intensity-modulated radiotherapy for locally recurrent T3 to T4 nasopharyngeal carcinoma. Head Neck 2017;39:533-40.
10. Ng WT, Ngan R, Chan O, et al. Chapter 26. Management of Nasopharyngeal Carcinoma. In: Bernier J, editor. Head and Neck Cancer: Multimodality Management. 2nd Eds. 2016, Springer-Verlag.
11. 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;124:2427-37.
12. Ng WT, Ngan RKC, Kwong DLW, et al. Prospective, Multicenter, Phase 2 Trial of Induction Chemotherapy Followed by Bio-Chemoradiotherapy for Locally Advanced Recurrent Nasopharyngeal Carcinoma. Int J Radiat Oncol Biol Phys 2018;100:630-8.
13. Liu LT, Chen QY, Tang LQ, et al. With or without reirradiation in advanced local recurrent nasopharyngeal carcinoma: a case-control study. BMC Cancer 2016;16:774.

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