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REVIEW ARTICLE

Recurrent nasopharyngeal carcinoma: a clinical dilemma and challenge

Tao Xu MD,[*†] *J. Tang MD,*[‡] *M. Gu MD,*[§a] *L. Liu MD,*[‖] *W. Wei MD,*[*] *and H. Yang MD PhD*[†a]

ABSTRACT

Recurrent nasopharyngeal carcinoma, which represents a small proportion of head-and-neck cancers, has a unique set of patho-clinical characteristics. The management of recurrent nasopharyngeal carcinoma remains a challenging clinical problem. Traditional treatments offer limited local control and survival benefits; more seriously, they frequently induce severe late complications. Recently, novel treatment techniques and strategies—including precision radiotherapy, endoscopic surgery or transoral robotic resection, third-generation chemotherapy regimens, and targeted therapies and immunotherapy—have provided new hope for patients with recurrent nasopharyngeal carcinoma. Some of these patients can potentially be cured with modern treatments. However, a lack of adequate evidence makes it difficult for clinicians to apply these powerful techniques and strategies. Individualized management guidelines, full evaluation of quality of life in these patients, and a further understanding of the mechanisms underlying recurrence are future directions for research into recurrent nasopharyngeal carcinoma.

KEY WORDS

Nasopharyngeal carcinoma, recurrence, surgery, radiotherapy, chemotherapy, biotherapy

1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is more common in northern Africa, Alaska, Southeast Asia, and southern China, especially Guangdong province[1]. Radiotherapy with or without chemotherapy is the mainstream treatment for primary NPC (pNPC).

Outcomes in patients with pNPC have improved mainly because of advances in radiotherapy and comprehensive chemotherapy strategies: 5-year survival increased to 70% in the 1990s from 50% in the 1980s, and it currently averages about 80%[2,3]. However, 15%–58% of NPC patients will experience recurrent disease and must undergo re-treatment[4–6].

Clinicians treat NPC according to U.S. National Comprehensive Cancer Network guidelines. However, those guidelines are not specific to the management of recurrent NPC (rNPC)[7], which still represents a clinical dilemma because of an incomplete understanding of the mechanism of action of advanced treatments and a lack of adequate medical evidence for the effectiveness of such treatments in rNPC. Traditionally, then, rNPC is treated in a manner similar to that used in palliation of metastatic disease. The mainstream salvage treatments for rNPC include radiotherapy, surgery, and palliative chemotherapy. A proportion of rNPC cases can achieve long-term survival, indicating that highly individualized treatment may cure some rNPC patients[8–10].

The clinical situation of rNPC patients is complicated. These patients always have local or regional failure (and sometimes both), with or without distant metastasis. Recurrent tumours extensively damage surrounding tissue, especially in patients with paranasopharyngeal spread or skull-base involvement. In rNPC patients, physical status and immune system are generally poor because of prior treatment for the primary disease[11]. Outcomes of conventional salvage surgery or two-dimensional (2D) radiotherapy are unsatisfactory: the average 5-year overall survival (OS) rate after re-treatment is 20%. In the era of conventional radiotherapy, rates of recurrence after primary treatment ranged from 15% to 58%[4–6,12]. Late toxicities such as temporal lobe necrosis, cranial nerve damage, nasopharyngeal infections, and a high risk of hemorrhage can seriously affect quality of life (QOL) in rNPC patients[6,8,12].

In recent years, modern anticancer techniques and strategies have provided opportunities to improve local control and survival in rNPC. Precision radiotherapy techniques—including three-dimensional conformal radiotherapy (3D CRT), intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery

(SRS), and fractionated stereotactic radiotherapy (FSRT)—constitute one such development. Novel surgical approaches such as endoscopic surgery and transoral robotic resection have recently been reported and are associated with minimal morbidity.

The role of chemotherapy, based mainly on cisplatin, is still not clear. Third-generation chemotherapy drugs such as paclitaxel, docetaxel, and gemcitabine have shown encouraging results in locoregionally advanced PNPC and other head-and-neck cancers—especially docetaxel-based regimes[13–15]. Some trials have also tested the efficacy of these drugs in RNPC. Novel therapies targeting the epidermal growth factor receptor (EGFR) and autologous cytotoxic T lymphocytes targeting the Epstein–Barr virus (EBV) have the potential to produce optimal outcomes with minimal toxicity.

In the present review, we analyze the existing problems, focus on key questions (including evaluation and early diagnosis of RNPC patients, and individualized treatment), and critically assess future directions for the management of RNPC.

2. PATHO-CLINICAL CHARACTERISTICS

Recurrent NPC is defined as tumour relapse after achievement of complete remission with radical radiotherapy[16]. Recurrent NPC can further be subdivided into local and regional recurrence[17]. Local-alone and regional-alone failures respectively account for 70% and 25% of RNPC cases[18], and 8%–28% of patients experience synchronous locoregional failure[19]. However, some authors include both persistent and recurrent disease in their definition of RNPC. "Persistent disease" is defined as the presence of residual tumour at the primary site after primary treatment; it has a better outcome than does recurrent disease[8].

The most common manifestations of RNPC are bloody nasal discharge and headache. In a study by Li *et al.*[20], those symptoms were present in 37.9% and 31.1% respectively of 351 patients. The skull base (54.4%), the prestyloid space (43.3%), and the carotid sheath area (31.3%) are high-risk sites for recurrence[20]. Interestingly, RNPC presents a sex distinction: the male:female ratio for RNPC is between 4:1 and 6:1 compared with 2:1 or 3:1 for PNPC[1,6,9].

The median interval between initial treatment and recurrence ranges from 1 month to 10 years. According to data from the Sun Yat-sen University Cancer Center (Guangzhou, PR China), most patients experience recurrence within 3 years of initial treatment: 5.9% within 6 months, 23.7% within less than 1 year, 48.7% within less than 2 years, 16.9% after 5 years, and 3.3% after 10 years[4]. A study from Hong Kong by Lee *et al.* reported that 52% of patients developed RNPC within 2 years, and 39%, within 2–5 years[8]. Those data suggest that close follow-up after primary treatment might help to detect RNPC as soon as possible.

In PNPC patients with undifferentiated carcinoma (which accounts for 90% of cases in endemic regions), the disease is generally sensitive to radiation and chemotherapy[1]. Radiotherapy with or without chemotherapy is therefore the first choice of treatment. However, the situation is different for RNPC. Experience in treating recurrent head-and-neck cancer demonstrates that recurrent tumours might be more radioresistant than the primary tumours[21]. Radiation can induce tissue fibrosis and microvasculature damage, and alter the tumour microenvironment. In addition, recurrent tumours contain radioresistant stem cells and demonstrate hypoxia, presenting significant obstacles to treatment. Interestingly, epithelial cells in recurrent tumours tend to transform from non-keratinizing to keratinizing and from an undifferentiated to a differentiated type. Luo *et al.*[22] compared pathologic tumour characteristics in 240 local RNPC patients and in 2370 PNPC patients and found that keratinizing carcinomas (10.0% vs. 2.3%) and a differentiated type (18.7% vs. 8.7%) were more common in RNPC than PNPC.

3. EARLY DETECTION AND ACCURATE DIAGNOSIS

Conventional follow-up after primary treatment includes physical examinations, endoscopic nasopharyngeal examinations, and computed tomography (CT) imaging or magnetic resonance imaging (MRI).

Confirmation by biopsy is the "gold standard" for a diagnosis of RNPC; however, samples are obtained only from a small proportion of RNPC patients because of the technical difficulty in obtaining biopsies from sites of recurrence close to critical organs. Flexible endoscopy is widely used to confirm mucosal RNPC; however, contact endoscopy provides a better view[23]. Recently, Wang *et al.* reported that narrow-band imaging endoscopy could improve the detection rate (sensitivity, 97.1%; specificity, 93.3%; accuracy, 94.9%)[24]. However, endoscopy can overlook some submucosal and deep-seated RNPC lesions; CT or MRI are required in that situation. Ng *et al.*[25] found that MRI could detect up to 27.8% of RNPC cases that were not detected on endoscopy. Compared with CT, MRI can provide a better contrast between soft tissue and tumour tissue, and it is superior for differentiating recurrent disease from radiation-induced tissue changes. Routine MRI follow-up might therefore detect RNPC at an early stage.

Another sensitive radiologic tool—positron-emission tomography combined with CT (PET/CT) using the tracer fluorine-18 fluorodeoxyglucose (FDG)—can provide more information about biologic function than MRI or CT alone can. In a meta-analysis of 21 high-quality articles, Liu *et al.*[26] compared the accuracy of CT, MRI, and FDG-PET/CT for diagnosing local residual disease and RNPC, reporting that FDG-PET/CT had a higher sensitivity and specificity (95%,

90%) than either CT (76%, 59%) or MRI (78%, 76%). However, increased FDG uptake is easily confused with an inflammatory reaction and may produce false-positive results. Comoretto *et al.*[27] reported that MRI could detect rNPC more accurately (92.1%) than FDG-PET/CT (85.7%). Ng *et al.*[28] compared the sensitivity, specificity, and diagnostic capability of 3 T whole-body MRI with FDG-PET/CT in 179 suspected cases of rNPC. The authors found no difference between the techniques and recommended the combined use of MRI and FDG-PET/CT.

In the pathogenesis of NPC, EBV plays a significant role. Cell-free EBV DNA can easily be detected by quantitative polymerase chain reaction and has been used as a biomarker for screening, monitoring, and predicting NPC. Lin *et al.*[29] showed that patients with a high pre-treatment plasma EBV DNA concentration had a higher risk of relapse. Patients with an undetectable concentration of EBV DNA 1 week after radiotherapy had better rates of relapse-free survival and OS. In a cohort of 245 NPC patients studied by Wang *et al.,* 14.7% of patients with an abnormal plasma EBV DNA copy number after treatment developed recurrence, further localized by subsequent detection of lesions using PET[30]. However, EBV DNA was not detected in more than one third of rNPC patients in a study by Wei *et al.*[31], indicating that the value of EBV DNA for detecting rNPC needs to be evaluated further.

Evaluation of EBV genomic DNA, latent membrane protein 1, or Epstein–Barr nuclear antigen 1 have also been used for the early detection of rNPC. Hao *et al.*[32] monitored tumour recurrence in 84 cases of NPC by analysis of *LMP1* (now called *PSMB10*) and *EBNA1* gene expression in nasopharyngeal swabs. Of the 12 patients who were positive for both *LMP1* (*PSMB10*) and *EBNA1,* 11 developed local recurrence (sensitivity, 91.7%; specificity, 98.6%). This method is convenient and simpler than blood tests; however, one limitation of the technique is that nasopharyngeal swabs may not be able to detect some deep-seated rNPCs.

4. PURPOSE OF RE-TREATMENT: CURABLE OR PALLIATIVE?

Once disease is diagnosed, prompt administration of anticancer therapy is essential. In a cohort of 200 patients with isolated rNPC, patients who received radiotherapy or surgery (or both) experienced better survival than did patients who received chemotherapy and supportive treatment[33]. However, because of the technical difficulties of surgery or radiotherapy and the lack of effective chemotherapeutic agents, rNPC was previously viewed mainly as an incurable disease, with patients receiving palliative treatment. With the development of comprehensive evaluation and treatment strategies, it is now potentially possible to cure selected rNPC patients. Treatment decisions should consider the patient's physical status and age, and the efficacy and toxicity of the selected treatment.

Better definition of prognostic factors may guide the provision of individualized treatment and lead to a higher chance of local salvage. As summarized in Figure 1, the T stage and histologic type of the recurrent tumour, the patient's age, the interval between initial treatment and recurrence, and factors influencing treatment are important prognostic factors in rNPC. Of the foregoing factors, T stage of the recurrent tumour is the most important[5,6,18,33–35]. In a prospective study by Lee *et al.*[18], the 5-year local control and OS rates for rT3 were distinctly lower than those for rT1 (11% and 4% vs. 35% and 27% respectively).

The volume of the recurrent tumour is another independent prognostic factor. In a cohort of 239 patients treated with IMRT, Han *et al.*[36] reported that 5-year survival rates were poorer in patients with a tumour volume exceeding 38 cm^3 than in patients with a tumour volume of 38 cm^3 or less (30.1% vs. 55.9%, $p < 0.001$). Most studies have found that a short interval to recurrence is associated with poorer outcomes; variations in the time to recurrence[8,9,36] suggest that different underlying biologic mechanisms may regulate recurrence. World Health Organization histologic type also determines outcome in rNPC patients. Hwang *et al.*[9] found that locoregional progression-free survival (PFS, $p < 0.035$) and actuarial survival ($p < 0.0001$) were both better for patients with World Health Organization type III disease than with World Health Organization type I or II disease.

Application of aggressive treatments can translate into improved outcomes. Han *et al.*[36] reported that fractional doses above 2.30 Gy can improve local control and OS. In a multivariate analysis, Vlantis *et al.*[37] demonstrated that recurrent regional disease and positive surgical margins were independent prognostic factors. Chua *et al.*[38] established a prognostic scoring system based on age, recurrent or persistent disease, recurrent tumour stage, tumour volume, and previous salvage treatment that could be used to guide the selection of individualized treatment.

The half-life of the plasma EBV DNA clearance rate has also been reported to be a prognostic marker[30].

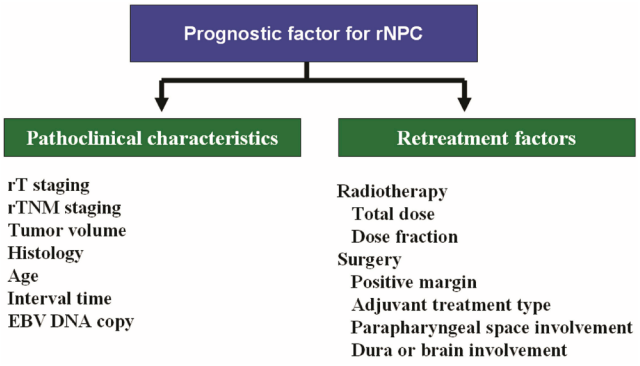

FIGURE 1 Prognostic factors for recurrent nasopharyngeal carcinoma (rNPC). EBV = Epstein–Barr virus.

An *et al.*[39] showed that the plasma EBV DNA concentration could predict prognosis in recurrent or metastatic NPC after palliative chemotherapy. Although patients with early T-stage tumours, a long latency to recurrence, and younger age might potentially be curable, most cases of rNPC are diagnosed at an advanced stage, and the optimal treatment decisions for those patients remain challenging.

5. IS IMRT A SUPERIOR TECHNIQUE COMPARED WITH OTHER RADIOTHERAPY TECHNIQUES?

Previous retrospective studies were based mainly on conventional radiotherapy; typically spanned long periods of imaging, diagnosis, and treatment; and often used heterogeneous criteria. In addition, conventional 2D radiation can induce severe damage such as bone necrosis, temporal lobe necrosis, cranial neuropathies, and trismus. The introduction of new radiotherapy techniques to minimize the risk of complications is therefore an encouraging development.

Brachytherapy is commonly applied by intracavitary insertion, especially for early-stage non-bulky tumours; however, with the advent of precision radiotherapy, the value of brachytherapy in NPC has declined. Compared with conventional 2D techniques and 3D CRT, IMRT can provide superior dose coverage to the tumour and better sparing of surrounding tissues, potentially improving local control and long-term survival and, more importantly, enhancing QOL for these patients[40,41]. Hisung *et al.*[42] reported that, compared with 5-field 3D CRT, 5- to 7-field IMRT distinctly reduced radiation in the brain stem by about 16%. In rNPC patients, IMRT might often be an ideal choice when the spinal cord or brain stem have reached their tolerance limits after primary radiotherapy. Compared with non-IMRT techniques, IMRT leads to better local control and OS rates in head-and-neck cancer. A series of IMRT studies have been reported in rNPC, with satisfactory preliminary results[36,43–45]. Table I summarizes those studies. Limiting the recurrent gross target volume with tight margins may help to avoid re-radiation damage to normal tissue. Recurrent gross target volume contouring in rNPC has been reported in a relatively consistent manner and is usually defined by MRI and physical examinations. A FDG PET/CT might provide more valuable information for radiotherapy planning.

Clinical target volumes are similar at various institutions; the most recommended clinical target volume was a 0.2–1.5 cm expansion of the gross target volume[36,43–46]. In 239 rNPC patients treated with IMRT, Han *et al.*[36] recently reported 5-year rates of local relapse-free survival, disease-free survival, and OS as 85.8%, 45.4%, and 44.9% respectively. Among the 7.9% of patients who experienced grade 3 acute toxicities, mucositis and otitis media were the most common. In the study by Qiu *et al.*[45], 70 rNPC patients treated with IMRT (median dose: 70 Gy; range: 50–77.4 Gy) achieved 2-year locoregional control and OS rates of 66% and 67.4% respectively. Cranial nerve palsy was a common toxicity (24.3%), and late toxicities have not been determined.

Even when using IMRT at a high dose, difficulties and the risk of radiation damage are still present in stage rT4, in which the tumour is surrounded by critical organs[50]. However, there might be ways to solve those problems. First, the development of more advanced techniques or a combination of different precision techniques is one future direction. Kung *et al.*[51] reported that the newly developed intensity-modulated stereotactic radiotherapy technique could provide a better dosimetric distribution than circular arc, static conformal beam, or dynamic conformal arc radiotherapy, especially with respect to sparing vital organs at risk. In addition, the use of particle-beam radiation instead of photon radiation might maximize clinical benefit by combining physical and biologic advantages. Taheri–Kadkhoda *et al.*[52] reported that 3-field proton IMRT provided a better dose distribution than 9-field photon IMRT. In the study by Feehan *et al.*[53], 11 cases of rT3–4 rNPC were treated with heavy charged particles, achieving 5-year local control and OS rates of 45% and 31% respectively. Lastly, hyperfractionation may theoretically help to reduce late toxicities in rNPC patients treated with IMRT. The Radiation Therapy Oncology Group 96-10 study[54] treated 86 patients with recurrent head-and-neck squamous cell cancer. Radiotherapy was delivered twice daily (1.5 Gy per fraction; total dose: 60 Gy) and combined with a concurrent 5-fluorouracil (5FU) bolus and hydroxyurea. The 2-year OS rate was 15.2%; however, 23.4% of patients developed grade 3 or 4 late toxicities.

6. WHAT IS THE OPTIMAL DOSE AND FRACTIONATION WHEN DELIVERING RADIOTHERAPY?

The presence of radioresistant tumour cells in rNPC may require a higher dose of radiation. On one hand, a dose–response relationship has been confirmed in most tumours; on the other, high doses might sacrifice normal tissues to radiation. The optimal dose for re-irradiation in rNPC has still not been established, and based on retrospective evidence, a total dose of 60 Gy or more (2 Gy per fraction) is widely accepted by most radiation oncologists[6,8,34,55]. Leung *et al.*[56] showed that a total equivalent dose of 60 Gy or more resulted in better local control, and total equivalent dose remained a significant prognostic factor in multivariate analyses. Lee *et al.*[3] studied the relationship between late complications and the biologically effective dose (BED). Assuming an α/β ratio of 3 Gy and estimating that a BED-σ (summated BED) of 143 Gy would induce 20% more toxicity than a BED-1 (primary course) of 111 Gy, they found that

TABLE I Treatment outcomes and complications of precise radiotherapy in patients with recurrent nasopharyngeal carcinoma

Reference	*Pts (n)*	*Relapse period*	*T3–4 (%)*	*Re-treatment modalities*	*Target*	*Margins (cm)*	*Dose (Gy)*		*Local control (%)*	*Survival (%)*	*Complications*
							Total	*Single*			
Chua *et al.,* 2005[44]	31	2001–2004	74	IMRT	GTV	+0.2–1	Median: 54 Range: 50–60	Not reported	56 at 1 year	63 at 1 year	Cranial nerve palsies: 10% Ototoxicity: 10% Brain necrosis: 7%
Zheng *et al.,* 2005[46]	86	1997–2003	51	3D CRT	GTV	+0.5–1	Median: 68 Range: 66–72	2	LFFS: 71 at 5 years	40 at 5 years	Cranial nerve palsies and trismus: 50% ≥ grade 3
Li *et al.,* 2006[47]	36	1999–2002	33	EBRT plus 3D CRT boost	GTV	+0.5	54 plus 16/20/24 in 4–6 fractions (groups I, II, III)	4	I: 37 at 3 years II: 28 at 3 years III: 72 at 3 years	I: 72, 3 years II: 59, 3 years III: 82 at 3 years	One hemorrhage in group III
Chua *et al.,* 2009[48]	43	1994–2005 at QMH	30	43 SRS	GTV	+0.2–0.3	Median:12.5 Range: 8–18	—	51 at 3 years	51 at 3 years	Brain necrosis: 16% SRS vs. 12% SRM
	43	1999–2005 at SYSUCC		43 SRM			Median: 48 in 4–6 fractions Range: 20–49		83 at 3 years (p=0.003)	83 at 3 years	Hemorrhage: 5% SRS vs. 2% SRM
Seo *et al.,* 2009[49]	35	2002–2008	43	FSRT with CyberKnife[a]	GTV	+0.2	Median: 33 in 3–5 fractions	Median: 11 Range: 7.5–12	LFFS: 79 at 5 years	60 at 5 years	Grade 4 or 5 late toxicity: 16%
Han *et al.,* 2011[36]	239	2001–2008	75	IMRT	GTV	+1–1.5	Median: 70.04 Range: 61.73–77.54	2.31 Range: 1.98–2.91	LFFS: 85.8 at 5 years	44.9 at 5 years	Hemorrhage: 47/132
Roeder *et al.,* 2011[50]	17	None reported	36	14 IMRT 3 FSRT	GTV	+0.5	Median: 66 Range: 50–72	Range: 1.8–2	69 at 2 years	37 at 3 years	Grade 3 late toxicity: 29%
Qiu *et al.,* 2012[45]	70	2003–2009	57	IMRT	GTV	+0.8–1	Median:70 Range: 50–77.4	1.8–2	65.8 at 2 years	67.4 at 2 years	Cranial nerve palsies: 24.3% Trismus: 17.1% Deafness: 17.1%

[a] Accuray, Madison, WI, U.S.A.

Pts = patients; IMRT = intensity-modulated radiation therapy; GTV = gross tumour volume; LFFS = local relapse-free survival; FSRT = fractionated stereotactic radiotherapy; 3D CRT = three-dimensional conformal radiotherapy; QMH = Queen Mary Hospital; SRS = stereotactic radiotherapy, single fraction; SYSUCC = Sun Yat-sen University Cancer Center; SRM = stereotactic radiotherapy, multiple fractions.

late reactive toxicities partially recovered after 2 years or more. However, severe acute and late toxicities can be induced by high total doses or fractions, and the optimal total dose and fractionation schedule remain a puzzle for both pNPC and rNPC in the precision radiotherapy era. Zheng *et al.*[46] treated 86 rNPC cases with 3D CRT, using a median total dose of 68 Gy (66–72 Gy) and achieved 5-year local control and OS rates of 71% and 40% respectively; however, 50% of patients developed grade 3 or greater cranial neuropathy and trismus. Li *et al.*[47] conducted a prospective randomized trial to compare three levels of dose escalation delivered as boost with 3D CRT (16 Gy, 20 Gy, or 24 Gy) after 54 Gy of conventional radiotherapy, but recurrence-free survival was not significantly improved in the 78 Gy (54 Gy + 24 Gy) group. Han *et al.*[36] re-treated 239 rNPC cases with IMRT at mean total dose of 70.04 Gy (61.73–77.54 Gy), fractionated at 2.32 Gy. Fractionation doses above 2.3 Gy ($p = 0.011$) and a GTV less than 38 cm^3 ($p < 0.001$) were good prognostic factors for OS, but the incidence of nasopharyngeal necrosis and severe inflammation was 40.6% (97 of 239 patients).

Stereotactic radiotherapy is another method that may improve local tumour control by virtue of its precise and sharp dose gradient, but this technique has limited ability to treat large recurrent lesions. Considering the late toxicities of SRS, FSRT is now increasingly used. Wu *et al.*[57] treated 56 rNPC patients with FSRT, delivering 48 Gy in 6 fractions; 63% of the patients achieved a complete response, and the 3-year PFS was 42.9%. Using FSRT, Leung *et al.*[58] found that a total equivalent dose of 50 Gy or more improved local control. A study by Chua *et al.*[48] compared single-fraction (SRS) and multiple-fraction (SRM) stereotactic radiotherapy in a matched-pair design. Compared with SRS, SRM led to better local control in NPC ($p = 0.003$), but OS was not significantly different ($p = 0.31$). Seo *et al.* treated rNPC using a CyberKnife (Accuray, Madison, WI, U.S.A.) to deliver FSRT at a median dose of 33 Gy in 3–5 fractions. The 5-year local relapse-free survival, disease progression-free survival, and OS rates were 79%, 74%, and 60% respectively. Neurologic toxicities were not obvious; however, some patients suffered fatal hemorrhages. When using IMRT or stereotactic radiotherapy, excessive doses and large fractioned doses should therefore be avoided, especially in patients with recurrent large-volume tumours[36,49,57].

7. NEW SURGICAL APPROACHES

A small proportion of recurrent tumours are localized to the cavity of the nasopharynx where salvage surgery is a suitable treatment, especially for rT1–2 and some rT3 tumours. Various techniques have been described[59–69], which can be divided into two main approaches: classical open nasopharyngectomy and endoscopic surgery. As summarized in Table II, classical open nasopharyngectomy can be subdivided into transpalatal, transcervical, transmaxillary, and maxillary disassembly approaches. The appropriate surgical approach depends on the size, location, and extent of the recurrent tumour. The 5-year OS rate for open-access surgery ranges from 30% to 55%[59–62]. Nasopharyngectomy complications are associated with each approach; complications occur in up to 50% of patients and include palatal fistula, trismus, otitis media with effusion, wound infection, skull base osteomyelitis, and rupture of the internal carotid artery. Postoperative radiotherapy after nasopharyngectomy is required in rNPC patients with close or positive surgical margins.

Endoscopic nasopharyngectomy is a minimally invasive and safe method. For recurrent disease, it is commonly chosen when the tumour is located in the central roof of the nasopharynx or has minimal lateral invasion. Chen *et al.*[64] treated 37 rT1–2 patients with endoscopic nasopharyngectomy. The primary results were encouraging, with 2-year OS, local relapse-free survival, and PFS rates of 84.2%, 86.3%, and 82.6% respectively. No severe complications were observed after surgery, but 22% of patients developed secretory otitis media, and long-term follow-up is required. Endoscopic surgery is limited by exposure of tumour and margin status, and it should be carried out by experienced operators. Also, strict selection criteria should be established, limiting this surgery to rT1–2 tumours or recurrent tumours a suitable distance from the internal carotid artery and skull base. In addition, Chen *et al.*[65] used a mucoperiosteum floor flap and posterior pedicle nasal septum technique to resurface nasopharyngeal defects, which also effectively reduced postoperative headache. Transoral robotic resection, first introduced by Wei and Ho[66], is another method to minimize surgical complications. Yin Tsang *et al.*[67] recently reported that transoral robotic surgery combined with transnasal endoscopic surgery could improve the resection of rNPC.

8. THE ROLE OF CHEMOTHERAPY

The efficacy of chemotherapy for rNPC, either as a sole treatment or combined with radiotherapy, is still extremely unclear. In the retrospective analysis by Chang *et al.*[6] of 186 rNPC patients treated with radiotherapy, 82 of whom also received chemotherapy, chemotherapy did not significantly improve OS.

Chemotherapy alone is always used for palliative treatment; however, cisplatin-based doublets or triplets produce a better response. Although cisplatin plus 5FU is a widely accepted regimen, a series of phase II trials have treated recurrent and metastatic NPC using third-generation chemotherapy drugs such as docetaxel and gemcitabine. Most of the published studies aimed to treat coexisting recurrent and metastatic NPC with palliative intent, and median survival ranged from 9 months to 13

TABLE II Treatment outcomes and surgical complications in patients with recurrent nasopharyngeal carcinoma

Reference	*Patients (n)*	*T stage (%)*	*Salvage approach*	*Local control (%)*	*Survival (%)*	*Complications*
King *et al.,* 2000[59]	31	rT1: 65	Transpalatal, maxillary swing, or transmandibular	LRFS: 85.8 at 5 years	44.9 at 5 years	Hemorrhage: 47/132
Fee *et al.,* 2002[60]	37	rT1: 59	Transpalatal, transmaxillary, or transcervical	67 at 5 years	DFS: 60 at 5 years	Total: 54%, 1 died from carotid artery injury
Hao *et al.,* 2008[61]	53	rT1–2: 66	Endoscopic approach, facial translocation, craniofacial resection	53.6 at 5 years	48.7 at 5 years	Not reported
Chen *et al.,* 2009[65]	37	rT1–2: 100	Endoscopic resection	86 at 2 years	84 at 2 years	Not reported
Wei *et al.,* 2011[62]	37 Persistent 209 Recurrent		Maxillary swing	LRFS: 74 at 5 years	DFS: 56 at 5 years	Not reported

DFS = disease-free survival; LRFS = local relapse-free survival.

months[70–75], as summarized in Table III. Recently, Ji *et al.*[82] reported a prospective multicentre phase II trial in 47 patients (29 with rNPC) who received 6 weekly cycles of docetaxel and cisplatin; median PFS and OS were 9.6 months and 28.5 months. However, the lack of randomized trials with strict inclusion criteria has made it hard to confirm optimal chemotherapy regimens for rNPC.

Concurrent chemoradiotherapy plus adjuvant chemotherapy is recommended as a standard strategy for locoregionally advanced pNPC, based on evidence from the Intergroup 0099 phase III study[84]. However, whether patients with rNPC can benefit from adjuvant chemotherapy remains controversial. Wong *et al.*[76] retrospectively analyzed 42 cases of rNPC and showed that, compared with palliative cisplatin–5FU, concurrent chemoradiotherapy followed by adjuvant cisplatin–5FU led to better local control (58% vs. 38%); however, no significant differences in OS were observed. Nakamura *et al.*[79] treated 36 rNPC cases with chemoradiotherapy. The radiotherapy was delivered mostly using a dynamic rotational arc technique (median dose: 37.9 Gy), and most of the patients received concurrent nedaplatin or cisplatin plus 5FU over 2 cycles. The 3-year PFS was 25.0%, and the 3-year OS was 58.3%. Central nervous system damage occurred in 8% of patients (median follow-up: 40.0 months). In the series of rNPC patients reported by Poon *et al.*[77], concurrent cisplatin or cisplatin–5FU led to 5-year PFS and OS rates of 15% and 26% respectively. The incidence of grades 3 and 4 late toxicities, including temporal lobe necrosis, cranial neuropathy and endocrine abnormalities, was significant.

Recently, induction chemotherapy followed by current chemoradiotherapy has been shown to represent a promising strategy in head-and-neck cancer. Better control of micrometastases and a reduction in the tumour burden for subsequent treatment are its merits. Docetaxel-based induction chemotherapy has shown encouraging preliminary results in two phase III trials (TAX 323, TAX 324) for head-and-neck cancer and in a phase II trial in locoregionally advanced pNPC[13–15]. Extensive tumour masses are common in rNPC, and induction chemotherapy can be used to shrink the mass to permit better target contouring for radiotherapy and to provide a chance of cure in response to salvage treatment. Chua *et al.*[78] reported 20 cases of rNPC treated with 3 cycles of gemcitabine–cisplatin induction chemotherapy followed by IMRT, in which 75% of the patients achieved complete response after chemotherapy. However, 60% of the patients developed grade 3 or 4 hematologic toxicities. The 1-year locoregional PFS and OS rates were 63% and 80% respectively.

9. THE STATUS OF TARGETED THERAPY AND BIOTHERAPY

In recent years, investigations of NPC biology have focused on therapies targeting EGFR or vascular endothelial growth factor (VEGF) and on EBV-targeted immunotherapy—techniques that are providing another important and hopeful strategy for rNPC. High rates of EGFR expression (ranging from 73% to 89%)[85,86] and VEGF expression (67%)[87,88] have been proven to occur in NPC. Anti-EGFR or anti-VEGF agents can inhibit a

TABLE III The role of chemotherapy in patients with recurrent nasopharyngeal carcinoma

Reference	*Pts (n)*	*Re-treatment modalities*	*Chemotherapy regimen*	*Progression-free survival (%)*	*Survival (%)*	*Complications*
Studies in recurrent nasopharyngeal carcinoma						
Wong *et al.*, 2002[76]	42	Group 1: Chemotherapy plus adjuvant chemotherapy	Cisplatin plus 5-fluorouacil	58 at 2 years	OS: 55 at 2 years	Emesis: 70% Neutropenia: 55%
		Group 2: Palliative chemotherapy	Cisplatin plus 5-fluorouacil	38 at 2 years (p=0.0381)	38 at 2 years (p=0.4938)	Emesis: 68% Neutropenia: 68%
Altundag *et al.*, 2004[70]	21	Palliative chemotherapy	Ifosfamide plus doxorubicin	Not reported	Median TTP: 7.0 months (range: 2–32 months)	Neutropenic fever: 28.5
Poon *et al.*, 2004[77]	35	Chemoradiotherapy	77% Received at least 2 cycles of cisplatin chemotherapy	Not reported	PFS: 15 at 5 years OS: 26 at 5 years	Temporal lobe necrosis: 3% Cranial nerve palsy: 6% Endocrine abnormalities: 14%
Chua *et al.*, 2005[78]	20	Induction chemotherapy plus IMRT	Gemcitabine plus cisplatin	rT2–3: 100 at 1 year rT4: 52	rT2–3: 83 at 1 year rT4: 91	Temporal lobe necrosis: 18% Hearing: 6%
Nakamura *et al.*, 2008[79]	36	Chemoradiotherapy	Cisplatin or nedaplatin or carboplatin plus 5-fluorouacil	25.0 at 3 years	OS: 58.3 at 3 years PFS: 25.0 at 3 years	Temporal lobe necrosis: 8.3% Hearing: 5.5%
Studies in recurrent or metastatic nasopharyngeal carcinoma						
Chua *et al.*, 2000[73]	18	Palliative chemotherapy	Ifosfamide, 5-fluorouracil, and leucovorin	Median TTP: 6.5 months	51 at 1 year	Grade 3 emesis: 5.5%
Ma *et al.*, 2002[71]	32 GEM: 18 GC: 14	Palliative chemotherapy	GEM alone or with cisplatin (GC)	Not reported	OS at 1 year: 48 (GEM), 69 (GC)	Reversible reactivation of hepatitis (n=1); Grade 3 cisplatin-related sensory neuropathy (n=1) Cardiovascular events (n=3)
McCarthy *et al.*, 2002[74]	9	Palliative chemotherapy	Gemcitabine plus cisplatin	8.4 Months	76 at 1 year	Grade 3–4 neutropenia: 100%
Ngan *et al.*, 2002[72]	44	Palliative chemotherapy	Gemcitabine plus cisplatin	>1 Year: 36	OS>1 year: 62	Mainly hematologic toxicity
Chua *et al.*, 2003[75]	17	Palliative chemotherapy	Capecitabine	4.9 Months	7.6 Months	Hand–foot syndrome: 58.8%
Chua *et al.*, 2008[80]	49	Palliative chemotherapy	Capecitabine	5 Months	14 Months	Grade 3 hand–foot syndrome: 25%

TABLE III Continued

Reference	*Pts (n)*	*Re-treatment modalities*	*Chemotherapy regimen*	*Progression-free survival (%)*	*Survival (%)*	*Complications*
Studies in recurrent or metastatic nasopharyngeal carcinoma						
Wang *et al.*,, 2008[81]	75	Palliative chemotherapy	Gemcitabine plus cisplatin	5.6 Months	9.0 Months	Grades 3 and 4: "uncommon"
Ji *et al.*,, 2012[82]	29	Palliative chemotherapy	Weekly docetaxel and cisplatin	Median: 9.6 months Range: 5.7–13.5 months	28.5 Months	Grade 3 stomatitis (1.2%); Neutropenia, anemia, infection, and diarrhea (0.8%)
Yau *et al.*,, 2012[83]	15	Palliative chemotherapy	Pemetrexed plus cisplatin	Median TTP: 30 weeks	Not reported	Grade 3 toxicities: neutropenia, 27%; anemia, 20%

Pts = patients; OS = overall survival; IMRT = intensity-modulated radiotherapy; PFS = progression-free survival; TTP = time to progression; GEM = gemcitabine; GC = gemcitabine plus cisplatin.

series of malignant signalling pathways that regulate tumour cell proliferation, angiogenesis, apoptosis, invasion, and metastasis. More importantly, these agents may produce an enhanced effect in combination with radiotherapy[89,90]. Cetuximab, a monoclonal antibody against EGFR, showed encouraging results in combination with radiotherapy for advanced head-and-neck cancer in a study by Bonner *et al.*[91] and also in combination with chemotherapy for recurrent and metastatic head-and-neck cancer[92]. Chua *et al.*[93] conducted a phase II trial using carboplatin and cetuximab for recurrent and metastatic NPC; 11.7% of the patients achieved a partial response, and median time to progression and survival time were 3 and 6 months respectively.

The receptor tyrosine kinase inhibitors gefitinib and erlotinib were evaluated in rNPC[94–96], but the objective responses were not satisfactory. In a phase II study by Lim *et al.*[97] of pazopanib—a small-molecule inhibitor of VEGF, platelet-derived growth factor, and C-kit tyrosine kinases—in recurrent or metastatic NPC, 6.1% patients achieved a partial response, and 48.5% experienced stable disease, with 1-year PFS and OS rates of 13% and 44.4% respectively. Elser *et al.*[98] treated recurrent or metastatic squamous cell carcinoma of the head and neck ($n = 20$) or NPC ($n = 7$) with sorafenib, an inhibitor of serine and threonine kinases such as C-Raf and B-Raf, VEGF, and platelet-derived growth factor. Ten patients achieved disease stabilization, and the median time to progression and survival time were 1.8 months and 4.2 months respectively.

Nasopharyngeal carcinoma is an EBV-associated malignancy. The EBV-specific antigens LMP1 and LMP2 can activate a series of signalling pathways, including the phosphoinositol-3-kinase, mitogen-activated protein, and nuclear factor κB pathways. Activation of those pathways is closely associated with tumour progression. Autologous cytotoxic T lymphocyte immunotherapy has recently been reported as a cellular therapy to target EBV and might potentially prolong survival in advanced NPC. Chua *et al.*[99] reported the first use of the adoptive transfer of autologous EBV-specific cytotoxic T cells in 4 cases of advanced NPC. The serum EBV DNA copy number declined, but no tumour shrinkage occurred. Straathof *et al.*[100] used autologous cytotoxic T lymphocyte immunotherapy to treat 4 NPC patients at high risk of relapse and 6 patients with relapsed or refractory disease and reported that 4 patients obtained a clinical benefit and that 1 experienced stable disease. The serum EBV DNA copy number was significantly reduced in 6 patients—but more importantly, the treatment was demonstrated to be safe.

10. LATE TOXICITIES AND QOL

Late complications depend on the site of recurrence, the tumour volume, local treatment techniques, the radiotherapy fractionation schedule, and whether concurrent chemoradiotherapy was administered (in addition to a number of other factors). Lee *et al.*[18] retrospectively analyzed 654 rNPC patients who received re-irradiation by a 2D technique and found that the total incidence of late complications reached 25.7%. Temporal lobe necrosis, cranial neuropathy, and bone necrosis were very common. Leung *et al.*[56] found that a high risk of central nervous system complications was closely associated with advanced rT stage.

Increasing evidence is showing that precision radiotherapy techniques can improve dose distribution, spare vital organs, and minimize neurologic complications. Chang *et al.*[6] observed no temporal lobe necrosis in rNPC patients treated with 3D CRT, but 14% of patients who received 2D radiotherapy showed such necrosis. In the IMRT study by Chua *et al.*[44],

hearing impairment and cranial neuropathy respectively accounted for 60% and 29% of the neurologic complications; 12% of patients experienced grade 3 temporal lobe necrosis. Hua *et al.*[35] observed that severe late toxicities after IMRT were more frequent in advanced rNPC (39.0%) than in early-stage disease. Furthermore, as indicated by MRI, 21.9% of those patients (33 of 151) developed radiation-induced brain injury within a median follow-up of 40.0 months. Even so, a high total dose or high single dose of IMRT is closely associated with another serious issue: massive hemorrhage, which is linked to coexisting inflammation in the nasopharynx, and which can be fatal. In the primary study by Han *et al.*[36], IMRT was delivered with a mean dose to the GTV of 70.04 Gy (range: 61.73–77.54 Gy) and with a mean dose per fraction of 2.31 Gy (range: 1.98–2.91 Gy). Of 239 patients, 97 experienced severe nasopharyngeal necrosis or inflammation. Endoscopy-guided debridement and systemic anti-inflammatory treatments might be helpful in reducing the risk of fatal massive hemorrhages[101].

Although satisfactory long-term survival rates have been achieved in NPC, QOL is increasingly emphasized. A number of instruments have been proposed to accurately measure QOL in these patients. Widely accepted QOL questionnaires include the European Organization for the Research and Treatment of Cancer (EORTC) head-and-neck QOL questionnaire, the EORTC Core QOL questionnaire, and the Functional Assessment of Cancer Therapy questionnaire[102]. Fang *et al.*[103] used the EORTC Core and head-and-neck QOL questionnaires to compare QOL after 4 different radiotherapy techniques and found that conformal techniques (3D CRT and IMRT) were associated with better QOL scores in terms of pain, appetite loss, senses, speech, social eating, and other factors.

However, reports of QOL assessment are rare in rNPC. Recently, Chan *et al.*[104] used the EORTC Core and head-and-neck QOL questionnaires to assess QOL in 185 rNPC patients who underwent curative resection using a maxillary swing approach or palliative resection. Palatal fistula, trismus, and osteoradionecrosis were negative factors affecting QOL in 80% of the patients. Future clinical research in rNPC patients should include QOL assessments.

11. CONCLUSIONS AND FUTURE DIRECTIONS

Recurrent NPC represents a small proportion of recurrent head-and-neck cancers and has unique pathoclinical characteristics. Local control and OS have improved with modern treatment techniques and strategies. Highly individualized guidelines for the management of rNPC urgently need to be established. To detect rNPC as soon as possible, close follow-up after primary treatment should be emphasized. In Figure 2, we suggest a treatment approach to rNPC based on current evidence.

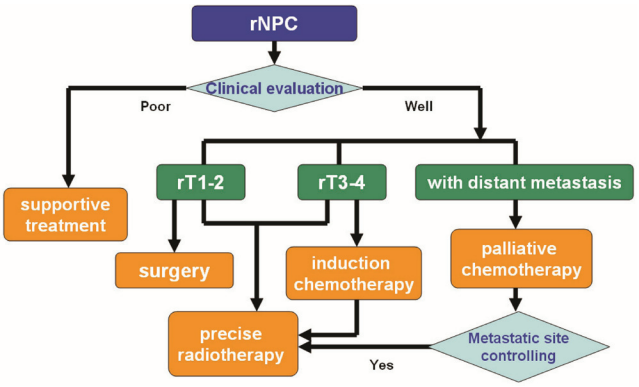

FIGURE 2 Treatment suggestion for recurrent nasopharyngeal carcinoma (rNPC).

For early-stage rNPC, endoscopic nasopharyngectomy and robotic surgery may represent useful methods with minimal associated toxicity. The advent of IMRT might help to improve tumour control and translate into prolonged survival and increased QOL for rNPC patients. Although precision radiotherapy techniques and novel surgical techniques might improve local control, the management of rNPC is still extremely challenging. The key issues of suitable patient selection and provision of individualized treatment to improve QOL should form the basis of future research. We believe that a series of well-designed randomized controlled clinical trials can provide powerful evidence to address those issues. Furthermore, uncovering the precise molecular mechanisms underlying radioresistance in rNPC may help to further a fuller understanding of the disease and better treatments.

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13. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to report.

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Correspondence to: Mofa Gu, Department of Radiation Oncology, Cancer Center, Sun Yat-Sen University, or Huiling Yang, Department of Pathophysiology, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou 510060, Guangdong Province, PR China.
E-mail: asian.you@hotmail.com, hlyangsums@hotmail.com

* Department of Radiation Oncology, First People's Hospital of Foshan Affiliated to Sun Yat-Sen University, Foshan, PR China.
† Department of Pathophysiology, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, PR China.
‡ Department of Otolaryngology, First People's Hospital of Foshan Affiliated to Sun Yat-Sen University, Foshan, PR China.
§ Department of Radiation Oncology, Cancer Center, Sun Yat-Sen University; Guangzhou, PR China.
‖ Department of Radiology, Cancer Center, Sun Yat-Sen University, Guangzhou, PR China.