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NASOPHARYNGEAL CARCINOMA SPECIAL FEATURE: REVIEW ARTICLE

Does East meet West? Towards a unified vision of the management of Nasopharyngeal carcinoma

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ABSTRACT

Nasopharyngeal cancer (NPC) is notable for its wide geographic variation, with incidences as high as 30 in 100,000 in endemic regions but < 1 in 100,000 worldwide. This review aims to identify areas where there could be differences in prognosis, management or outcomes among countries with high or low incidence of NPC. The incidence has generally declined both in endemic and non-endemic regions throughout the years, which may be attributed to the decrease in exposure to risk factors such as early exposure to salted fish and smoking. Ethnicity has an impact both on incidence and prognosis, with Southeast Asians having the highest incidence but also better survival. Concurrent chemoradiotherapy, with or without adjuvant and/or induction chemotherapy, is the standard of care for locoregionally advanced disease, as reflected in clinical practice guidelines. Despite improvements in management, a proportion of patients relapse. Salvage treatment is associated with significant morbidity due to the critical location of the nasopharynx and the toxicities of initial therapy. Clinical expertise is paramount, but is easier to attain in endemic regions and high volume centers where enrollment of patients in clinical trials is more feasible. Collaboration between low and high incidence countries and between low and high volume facilities is key to improving NPC prognosis worldwide.

INTRODUCTION

Nasopharyngeal cancer (NPC) is a malignant epithelial tumor most commonly arising from the Fossa of Rossenmueller. A rare cancer globally with an incidence of approximately one per 100,000 people,[1] it is notable for its wide geographic variation, with incidences as high as 30 in 100,000 in endemic regions such as South China and Southeast Asia.[2] WHO classifies NPC into three histologic subtypes: keratinizing squamous cell, nonkeratinizing (differentiated or undifferentiated (UCNT)), and basaloid carcinoma.[3] Undifferentiated carcinoma comprises over 95% of NPC in high-incidence areas and is associated with the Epstein Barr Virus (EBV) and better survival, while squamous cell carcinoma is predominant in low-incidence regions and is associated with poorer outcomes, and may have an aetiology more akin to other head and neck (H&N) cancers.[4,5] A new classification has been proposed which divides NPC into epithelial carcioma, sarcomatoid carcinoma, mixed sarcomatoid-epithelial carcinoma, and squamous cell carcinoma, which had a better correlation with overall survival (OS).[6]

The TNM staging has recently been modified in the AJCC eighth edition.[7] There were two changes to the T classification. In the previous T4 criteria, "masticator space" and "infratemporal fossa" were used synonymously, but these have been replaced by a specific description of soft-tissue involvement, decreasing ambiguity. Adjacent muscle involvement (including medial and lateral pterygoids and prevertebral muscles) was down-staged to T2. In the N classification, the supraclavicular fossa was replaced by the caudal border of the cricoid cartilage as the border for the upper and lower neck nodes, more suited to standardly used axial cross-sectional imaging. Low neck involvement and 6 cm node size were merged into a single N3 designation. T4 and N3 disease were both designated stage IVA (formerly IVA and IVB).

With its unique distribution worldwide, the purpose of this review is to compare the management of NPC among endemic countries and those where the disease is considered rare, and to highlight differences, if any. This review aims at identifying areas where there could be differences in

prognosis, treatment or outcomes among countries at high and low incidence of NPC.

ETHNICITY AND INCIDENCE

GLOBOCAN 2012[1] details the very distinct regions of high NPC risk. The disease has a global incidence of 87,000 (0.6% of all cancers) and an age-standardized rate (ASR) of 1.7 in males and 0.7 in females, but high ASRs of 6.4 and 2.4 in males and females, respectively, in Southeast Asia. ASRs are also high in Micronesia/Polynesia (2.6 and 1.3), East Asia (2.5 and 1.0), and North Africa (2.3 and 1.0). Less developed regions likewise have higher cumulative ASRs of 2.0 and 0.8 compared to more developed regions with 0.6 and 0.2.

Incidence has however not remained constant throughout the years. For instance, in Hong Kong, a decrease from 28.5 in 1980 to 1984 to 20.2 in 1995 to 1999 in males and from 11.2 to 7.8 in females has been observed, with both incidence and mortality constantly being lower in females.[8] Worldwide, a decrease in incidence has likewise been seen in almost all high-incidence areas, some ethnic populations in the USA and some European countries from 1970 to 2007.[9]

Different ethnic populations in the same country may have vastly different incidence rates, such as in China, an endemic region, where ASR in males are as high as 26.8 in Zhongshan (Southern) and as low as 0.4 in Yangcheng County (Northeastern). In the USA, a non-endemic country, incidence rates vary widely among different ethnicities: highest in Chinese, then Southeast Asians and Pacific Islanders, and low in Black and White Americans. Migrant studies have shown that ethnicity is a strong predictor of NPC, suggesting a strong genetic predisposition in its aetiology, as well as probable cultural transmission of risk factors. For instance, in Israelis and Swedes, migrants of Asian and North African descent have increased incidence of NPC, which persisted in the second and third generations in the Israeli cohort.[10,11]

ETHNICITY AND RISK FACTORS

Several risk factors have been associated with the development of NPC. EBV is an identified factor especially for the undifferentiated subtype; however, infection alone does not define disease development as the virus infects over 90% of the general population. The eventual development of cancer is influenced by other host and environmental factors.[12] Certain human leukocyte antigen (HLA) genes have been found to confer a genetic susceptibility to NPC, such as the HLA-A2 and HLA-B46 which are associated with increased susceptibility in geographical areas of high incidence.[13,14] Hypotheses for the link between EBV and HLA are that HLA may incite the development of NPC by modulating the expression of EBV proteins, and that HLA may represent a genetic marker of predisposition to NPC. In addition, genetic polymorphisms of some metabolic enzyme genes *i.e.* CYP2E1 and GSTM1 and some DNA repair genes *i.e.* hOGG1 and XRCC1 have also been found to be associated with increased risk of NPC.[15–17]

A decreased exposure to certain risk factors, such as previous early exposure to salted fish which was commonly used in weaning infants,[18,19] is likely partly responsible for the decrease in incidence of NPC in certain regions such as Singapore and Hong Kong.[20] This is supported by the higher incidence rate of NPC in first generation Chinese migrants, with a gradual decrease among successive generations who become more integrated into non-Chinese cultures.[21]

It has been shown that cigarette smoking increases the risk of NPC, particularly the squamous or keratinizing subtype.[22] A recent decrease in smoking, for instance from 20.9% in 2005 to 16.8% in 2014 in the United States,[23] is likely contributory to the decrease in NPC cases, more importantly for the keratinizing subtype in non-endemic areas.[24]

ETHNICITY AND PROGNOSIS

Ethnicity likewise plays a role in prognosis. A study conducted in the USA investigating racial disparities in survival of NPC in 5,427 patients from the Surveillance, Epidemiology, and End Results (SEER) database showed a statistically significantly better disease-specific survival (DSS) for African-Americans ($p = 0.02$) and Asians ($p = 0.01$) relative to Caucasian patients.[25] A similar study from the SEER database corroborated that Asians had the highest incidence rates and longest survival times, consistent across all histologic types.[26] Yet another study conducted in North America corroborated that Asian ethnicity was associated with improved OS and DSS ($p < 0.05$) on multivariate analysis. In addition, testing the interaction of chemoradiotherapy and Asian versus non-Asian ethnicity yielded a hazard ratio (HR) of 3.9, suggesting that concurrent chemoradiotherapy (CCRT) conferred more benefit in non-Asian compared to Asian subjects, yet this did not translate to improved outcomes.[27] A more recent publication focused on minority groups (Blacks, Hispanics, Asians/Pacific Islanders, American Indians/Alaska Natives) who may present with different stages at diagnosis, access to healthcare and other factors which may influence outcomes. The authors found that Non-Hispanic American Indians/Alaska Natives consistently had the worst and that non-Hispanic Asians/Pacific Islanders consistently had the best survival ($p < 0.001$).[28]

In non-endemic regions, human papillomavirus (HPV) may be a contributory factor to poorer prognosis. In Michigan, HPV-positive tumors were found to be associated with smoking, older age and had a mutually-exclusive positivity with EBV, with 94% of HPV-positive status being in whites. HPV-positive tumors exhibited worse outcomes than EBV-positive tumors, with decreased OS (HR 2.98, $p = 0.01$), progression-free survival (PFS) (HR 2.55, $p = 0.02$), and local control (LC) (HR 4.01, $p = 0.03$).[29]

TREATMENT OPTIONS

CCRT has long been the standard of care in the treatment of NPC, following the impressive improvements in PFS and OS compared to radiotherapy (RT) alone in the landmark Intergroup 00–99 trial.[30] However, this study has received some criticism due to the high proportion of patients with a well-differentiated histology enrolled (only 41% had the undifferentiated subtype), such that the results might not be applicable to endemic regions with more undifferentiated subtypes. CCRT has since been studied in endemic regions, with most showing

significant improvements in outcomes. The primary endpoint of PFS was not significant in Hong Kong,[31] while OS was significant in Singapore (p = 0.0061)[32] and in endemic regions of China (p = 0.043).[33] The update of the MAC-NPC meta-analysis which included 19 trials with 4,806 patients confirmed that the addition of concomitant chemotherapy to RT significantly improves survival in patients with locoregionally advanced NPC (HR for OS 0.79, $p < 0.0001$; absolute benefit at 5 years 6.3%).[34] However, the most dramatic improvement remained to be in the Intergroup trial, arguably in part because the control group who received RT alone had considerably poorer outcomes compared to stage-equivalent patients treated in endemic areas.

Adjuvant chemotherapy (ACT), in addition to CCRT, has not consistently been shown to be beneficial in all trials; for instance, a randomized Phase III multicenter trial in China had 2-year failure-free survival rates (FFS) of 86 versus 84% in the CCRT +ACT versus CCRT group (HR 0·74, 95% CI 0·49–1·10; p = 0·13).[35] However, CCRT +ACT was found to be of highest significant benefit for OS in the MAC-NPC meta-analysis (HR 0.65, p = 0.01) and in a network meta-analysis from the same database (HR 0.65). Induction or neoadjuvant chemotherapy (NACT) was not found to be of significant benefit in the abovementioned MAC-NPC meta-analysis (HR 0.96, 0.80–1.16). Nonetheless, the value of NACT has been recently shown in a randomized Phase III multicenter trial in China, where the use of cisplatin, fluorouracil, and docetaxel (TPF) was associated with a 3-year FFS of 80 versus 72% for the CCRT alone group (HR 0·68, p = 0·034).[36] Therefore, high level evidence exists to support the use of ACT and NACT for locoregionally advanced disease.

COMPARISON OF CLINICAL PRACTICE GUIDELINES

An online search was conducted for clinical practice guidelines (CPGs) on NPC using the keywords "guidelines" and "nasopharyngeal cancer". A total of 11 were found spanning all continents, including the United Kingdom,[37] Spain,[38] the EHNS-ESMO-ESTRO guideline,[39] Malaysia,[40] Asia,[41] four from Canada,[42–45] and two from the United States.[46,47] Recommendations are summarized in Table 1.

The guidelines are generally in concordance with the exception of minor differences in certain points. No publicly available guideline recommends EBV screening for NPC. EBV testing at diagnosis is recommended by the Princess Margaret Hospital (PMH), the Asia Pacific Head and Neck Cancer Expert Panel (APHNCEP), the National Comprehensive Cancer Network (NCCN), the National Cancer Institute (NCI), by the Sociedad Española de Oncología Médica (SEOM) for the nonkeratinizing histologies, and by Malaysia in case of ambiguous histology.

For treatment, all guidelines are consistent with the recommendation of RT alone for stage I disease. There is some heterogeneity for Stage II disease, with some advocating RT alone, while others having CCRT as an option in the presence of adverse risk factors (significant nodal disease, parapharyngeal tumor extension, and high plasma EBV level (SEOM)), and others recommending CCRT outright.

For locally advanced disease, CCRT is a consensus. For stages II to IV, the recommendation of the use of ACT is likewise heterogenous. PMH advocates ACT, the UK, ESMO, and Malaysian guidelines only recommend CCRT, while the rest leave ACT as an option. The regimens for concurrent chemotherapy are either Cisplatin 100 mg/m2 every 3 weeks, or 40 mg/m^2 weekly. NACT, however, is not systematically recommended, mainly because high level evidence has only recently been published. The NCCN guidelines advocate CCRT with either NACT or ACT (category 2A), with CCRT alone classified as category 2B. It is worth noting, however, that variations in recommendations may be the result of differences in selecting evidence and interpreting data.[48]

Intensity modulated radiotherapy (IMRT) is the recommended RT technique, as it has been shown to significantly decrease treatment sequelae such as xerostomia.[49,50] Hsuing et al compared 3DCRT and IMRT plans for 14 patients and showed that the benefits of IMRT are greater if patients had at least one of five risk factors - vertical length of target >7 cm, minimal distance between target and brainstem <0.1 cm, maximal anteroposterior (AP) overlap of target and brainstem >0.6 cm, maximal AP overlap of target and spinal cord >1 cm, and vertical overlap of target and eyes > 0 cm.[51] In addition, a single center study from China has shown that IMRT improves clinical outcomes, including OS.[52]

CLINICAL OUTCOMES IN VARIOUS COUNTRIES AND CONTINENTS

A Chinese study of 720 exclusively stage I patients treated with RT alone from 1990 to 2012 showed an increase in the 5-year OS from 86.7% from the period of 1990 to 1996 to 99.3% from 2008 to 2012 ($p < 0.001$), reflecting the effectivity of IMRT as treatment techniques evolved from 2D, then 3D, then IMRT over the years.[53] In India, 143 cases of NPC treated between 2005 to 2011 had a 2-year PFS and OS of 67.2 and 79.5%, respectively, with a median follow-up of 20 months.[54] Another study from the same country with 206 patients from 1994 to 2004 showed high rates of 3-year DFS, OS and LC of 64%, 82.3%, and 71.1%, respectively.[55] In France, 5-year OS and PFS were 78.3 and 72.5%, and 82.7 and 68.2%, respectively, for patients receiving induction plus CCRT versus CCRT alone, with no significant differences between the two groups.[56] A multicenter Italian study reported OS and DFS at 5 years of 91 and 69%, respectively,[57] comparable to outcomes in endemic regions. In Canada, an epidemiologic study of patients from 1993 to 2010 showed an unchanging incidence of NPC. An average annual percent increase in the 5-year OS of 1.14% was seen, with a median 5-year OS of 62.6%.[58] Conditional survival (CS), calculated after a given duration of survival using data for only individuals who have survived to that predefined time of interest and thus may be better in assessing dynamic changes in prognosis, was calculated from the SEER registry of the US from 1973 to 2007. It was shown that adjusted 5-year OS improved significantly from 36.0% in 1973–1979, 41.7% in 1980–1989, 46.6% in 1990–1999, to 54.7% in 2000–2007 ($p < 0.01$). Interestingly, a steady improvement in CS was seen further from the time of diagnosis, which reached a plateau only at the ninth conditional year, with an OS rate of nearly 82% for long-term NPC survivors.[59]

Table 1. Comparison of Clinical Practice Guidelines

REGION	CENTER/ GROUP/ ORGANIZATION	SCREEN-ING	EBV TESTING AT DIAGNOSIS	MANAGEMENT				EBV monitoring	LOCAL SALVAGE TREATMENT
				Stage I T1 N0	Stage II T1-2 N0-1	Stage III T1-3 N0-2	Stage IVA T4N1-2 TXN3		
CANADA	PRINCESS MARGARET HOSPITAL/ CANADA[42]	NO	YES	RT alone	CCRT + ACT[a]	CCRT + ACT[a]	CCRT + ACT[a]	YES	Surgery (primary and/or neck)
	ONTARIO CANADA[44]					CCRT ± ACT[b]	CCRT ± ACT[b]		
	ALBERTA CANADA[43]	NO	NO	RT alone	CCRT ± ACT[a]	CCRT ± ACT[a]	CCRT ± ACT[a]	NO	Surgery OR re-irradiation (option of SBRT)
	SASKATCHEWAN[45]	NO	NO	RT alone	CCRT ± ACT	CCRT ± ACT	CCRT ± ACT	NO	Multidisciplinary conference
EUROPE	UNITED KINGDOM[37]	NO	NO	RT alone	RT alone or CCRT[c]	CCRT[c]	CCRT[c]	NO	Surgery (primary and/or neck (first line) OR re-irradiation OR palliative chemo
	SPAIN[38]	NO	CONSIDER (non- keratizing/ undifferentiated type)	RT alone	RT alone or CCRT[a]	CCRT[a] ± NACT or ACT	CCRT[a] ± NACT or ACT	NO	Neck dissection for persistent nodes Multidisciplinary conference for local relapse
	EHNS-ESMO-ESTRO[39]	NO	NO	RT alone	CCRT	CCRT	CCRT	NO	Surgery (primary and/or neck (first line) OR re-irradiation OR palliative chemo
ASIA	APHNCEP[41]	NO	YES	RT alone	CCRT[a] ± NACT or ACT	CCRT[a] ± NACT or ACT	CCRT[a] ± NACT or ACT	YES	Surgery OR re-irradiation
	MALAYSIA[40]	NO	EBER if ambiguous histology	RT alone	CCRT[d]	CCRT[d]	CCRT[d]	NO	Surgery OR re-irradiation
UNITED STATES	NCCN[46]	NO	May be considered	RT alone	CCRT + NACT or ACT[e]	CCRT + NACT or ACT[e]	CCRT + NACT or ACT[e]	May be considered	Surgery and/or re-irradiation ± systemic therapy
	NCI[47]	NO	YES	RT alone	CCRT ± ACT	CCRT ± ACT or Altered fractionation RT	CCRT ± ACT or Altered fractionation RT	YES	Surgery OR re-irradiation

ACT, adjuvant chemotherapy; APHNCEP, Asia Pacific Head and Neck Cancer expert panel; CCRT, concurrent chemoradiotherapy; EBER, EBV encoded early RNAs; EHNS-ESMO-ESTRO, European Head and Neck Society-European Society of Medical Oncology-European Society for Therapeutic Radiology and Oncology; NACT, neoadjuvant chemotherapy; NCCN: National Comprehensive Cancer Network;NCI, National Cancer Institute; RT, radiotherapy; SBRT, stereotactic body radiotherapy.

[a]Concurrent: Cisplatin 100 mg/m2 q3weeks, Adjuvant: Cisplatin 80 mg/m2 + 5 FU 1000 mg/m2 x three cycles. Option: Cisplatin weekly 40 mg/m2

[b]Concurrent only: Cisplatin 20 mg/m2/day and 5FU 400 mg/m2 as a 96 h continuous infusion during weeks 1 and 5 Concurrent and Adjuvant: Cisplatin 100 mg/m2 q3weeks, then Cisplatin 80 mg/m2 + 5 FU 1000 mg/m2 x three cycles

[c]Cisplatin 100 mg/m2 q3weeks, option of weekly 40 mg/m2 for older patients and/or those with significant comorbidities.

[d]Cisplatin-based

[e]Cisplatin for CCRT. Cisplatin-5FU or Carboplatin-5FU (category 2B) for ACT. Docetaxel/Cisplatin/5FU, Cisplatin/5FU, Cisplatin/Epirubicin/Paclitaxel, Docetaxel/Cisplatin (category 2B) for NACT.

Table 2. Summary of key differences between East and West

	EAST - Endemic	WEST - Non-endemic
Incidence	High[1]	Low[1]
Histology	Mostly undifferentiated[2]	Higher percentage of squamous keratinizing[2]
Ethnicity	Only endemic populations[9]	Both endemic migrant and autochthonous populations[9–11]
Preventable risk factors	EBV, salted fish[12,18]	EBV, HPV, Smoking and alcohol[12,22,29]
Genetic risk factors	Human leukocyte antigens (*i.e.* HLA-A2, HLA-B46)[13,14]	Depends on population
Radiosensitivity	More radiosensitive[4,5]	Less radiosensitive[4,5]
Outcomes	Better survival[9,61]	Worse survival[9,61]

EBV: Epstein Barr Virus; HPV: Human Papilloma Virus.

Although not easily comparable across publications, these survival outcomes seem to be similar to published studies, with 5-year OS ranging from 58 to 92% with CCRT.[60] The improvements in survival over the years likely reflect progress in treatment techniques and management such as the use of advanced imaging, which improves identification of local, regional, and metastatic disease extension. However, despite these general trends, notable epidemiologic differences exist. For instance, in non-Caucasians in the US, Asians and Pacific Islanders consistently had the best survival compared to other ethnicities ($p < 0.001$).[28] Another study found that Chinese ethnicity, versus Caucasian, is an independent and favorable prognostic factor for survival in NPC with the keratinizing histology.[61] This shows that the improved survival of Chinese patients cannot simply be explained by the increased proportion of them having the undifferentiated histology, which in turn may be due to genetic differences. In fact, a study of genetic polymorphisms showed that ERCC1 C8092A was an independent predictor of PFS in Chinese NPC patients treated with cisplatin-based chemotherapy, of 7.9 versus 9.3 months ($p = 0.047$) for the C/C phenotype versus others. Thus, further genetic and molecular studies are awaited to further elucidate differences in outcomes among different and even within the same ethnicities.[62] Table 2 summarizes the key differences of NPC between the East and the West.

SALVAGE TREATMENT FOR LOCALLY RECURRENT DISEASE

Despite improvements in patient outcomes with the improvement in radiation and chemotherapy techniques, approximately 10% of patients still experience relapse.[63] Options for salvage treatment for local recurrence (LR) include nasopharyngectomy, external beam radiotherapy, stereotactic radiosurgery, and brachytherapy, alone or in combination. Choice of treatment typically depends on the extent of recurrence, as well as availability of equipment and experience or expertise of clinicians in the aforementioned salvage therapies. Disease that relapses in less than a year is generally considered radioresistant, and should be considered for surgical resection if feasible. Recently published studies on salvage options are summarized in Table 3.

A prognostic index was recently published which dichotomized patients into low or high risk subgroups that correlated with OS after salvage IMRT, using cohorts from endemic regions China and Singapore, with Harrell's C indices of 0.71 in the training and 0.72 and 0.69 in the validation cohorts.[73] The index was composed of the variables recurrence gross tumor volume (GTV), age at recurrence, dose of re-irradiation >68 Gy, prior RT toxicity ≥Grade 3, and rT3 or rT4. The validity of this index was studied in France on 35 recurrent NPCs but the results were not statistically significant for predicting survival or toxicity, raising the question of the applicability of this nomogram for non-endemic populations.[74]

60 patients from Sun Yat Sen University in China underwent re-irradiation with full course IMRT (60 to 70 Gy) for rT1 or rT2 disease. 17 patients with bulky gross tumors or a short interval between the end of primary RT and recurrence received concurrent chemotherapy. Five-year OS was 67.2%, the volume of GTV > 20 cm and presence of significant complications were independent factors for poor survival. 66% died of radiation-induced injuries.[68] A similar study in Hongkong of 38 patients with rT3 and rT4 disease[69] reported 3-year OS, PFS, and LC of 47.2%, 17.5%, and 44.3%, respectively. Toxicities equal to or greater than Grade 3 was 73.7%, with three patients dying of massive epistaxis. Another study from China reports Grade 3–4 toxicity rates of 53%.[70] Thus, even if IMRT leads to good tumor control, treatment-related complications are a real challenge.

Long-term outcomes of 20 patients rT1 or rT2 disease treated with open nasopharyngectomy through a maxillectomy approach was reported in Singapore. The 5-year LC, DFS and OS were 70%, 48.9%, and 66.7%, respectively. 50% of patients developed tumor recurrence despite of negative surgical margins.[66] Endoscopic nasopharyngectomy (ENPG) may be more advantageous than open surgery due to less morbidities compared to the open approach. A trial of 91 patients in China who underwent ENPG resulted in 5-year OS and DFS of 38.3 and 30.2%, respectively. Severe treatment-related complications due to infection secondary to delayed wound healing included nasopharyngeal necrosis (12.1%), nasopharyngeal hemorrhage (9.9%), and temporal lobe necrosis (2.2%).[65] A preliminary report from Malaysia with 15 patients with only rT3 or rT4 disease showed 2-year OS and DFS of 66.7 and 40%, respectively.[64] However, only carefully selected patients are eligible for surgical resection. Those with extensive tumors (T3/T4) as well as post-operative patients with positive margins would likely undergo re-irradiation. A case-matched study of 144 patients in China compared ENPG with IMRT[67] concluded that IMRT was associated with

Table 3. Recent publications on salvage treatment for locally recurrent nasopharyngeal carcinoma

Author, region/ country, year	N	Salvage treatment	Secondary treatment	LC	OS	DFS	Post- treatment complications
Wong et al, Malaysia, 2017[64]	15	ENPG	pre-op brachytherapy		2-year 66.7 %	2-year 40%	No serious intraoperative complications
Liu et al, Fudan, China, 2017[65]	91	ENPG	radio ± chemotherapy		5-year 38.3%	5-year 30.2%	No serious complication
Ng et al, Singapore, 2016[66]	20	open NPG		5-year LC 70%	5-year 48.9%	5-year 66.7%	No major intraoperative complications
You et al, China, 2015[67]	144 case matched	ENPG *vs* IMRT	chemotherapy (9 ENPG, 30 IMRT)		5-year 77.1 *vs* 55.5%, p = .003		12.5 *vs* 65.3%, p < .001
Tian et al, China, 2016[68]	60	IMRT	chemotherapy	5-year LFFS 85.7%	5-year 67.2%	5-year DFFS 96.1%	65% at least one severe complication, 18 deaths
Chan, et al Hongkong, 2017[69]	38	IMRT	chemotherapy	3-year 44.3%	3-year 47.2%	3-year 17.5%	73.7% ≥ 1 Grade three toxicity, three deaths
Kong et al, Fudan, China 2018[70]	184	IMRT	chemotherapy	3-year LRFS 85.1%	3-year 46%	3-year DMFS 91.1%	53% grade III-IV toxicities
Dizman et al, Turkey,2014[71]	24	SBRT (FSRT)	chemotherapy	3-year 21%	3-year 31%	3-year 17%	one grade III temporal lobe necrosis, one death
Yan et al, China, 2017[72]	39 (A) 42 (B)	A: brachytherapy B: IMRT		36 mos 23.1 *vs* 13.7%	3-year 30.7 *vs* 32.6%		25.6 *vs* 66.7% ≥ grade III toxicity

DFFS, distant failure-free survival; DMFS: distant metastasis-free survival;ENPG, endoscopic nasopharyngectomy; FSRT, fractionated stereotactic radiotherapy; IMRT, intensity modulated radiotherapy; LC, local control; LFFS, local failure-free survival; LRFS, local recurrence-free survival; N, number of patients; OS, overall survival; PFS, progression-free survival; SBRT: stereotactic body radiotherapy.

higher medical costs (€11,847.80 versus 2371.71, p < 0.001), higher treatment-related complications and deaths (34.7% versus 5.6%, p < 0.001), and lower 5-year OS (77.1% versus 55.5%, p = 0.003).

The increasing use of stereotactic body radiotherapy may be a better option for re-irradiation. 24 patients were treated with fractionated stereotactic radiotherapy with a median dose of 30 Gy in five fractions in Turkey, with 3-year LC, PFS and OS Of 21%, 17 and 31%, respectively.[71] One patient exhibited grade III temporal lobe necrosis, and one died of grade IV mucositis with overlapping infection.

Brachytherapy is an appealing option; however, its use is limited by several factors such as operator dependence and disease which is relatively limited with no skull base or bony invasion. A recent study compared brachytherapy with IMRT and reported similar 3-year OS rates but significantly less toxicities with brachytherapy, with 25.6 versus 66.7% having at least grade 3 toxicity, and a 14% rate of complication-related death in the IMRT group.[72] Yet another promising option is the use of heavy ion therapy, which allows precise delivery of radiation to the target while sparing adjacent organs, in addition to its higher linear energy transfer (LET) and relative biological effectiveness (RBE). A Phase I/II trial has been initiated in Shanghai, China to evaluate the efficacy and safety as well as clinical outcomes of carbon ions in recurrent NPC.[75]

Recurrences are considerably more difficult to manage than primary NPC, given the great risk of cumulative toxicities with the initial and salvage treatments. As seen in the publications above, both RT and surgical options come with non-negligible morbidities. In addition, the nasopharynx has traditionally been considered difficult to access surgically. Experience and publications in non-endemic regions are very limited due to the rarity of the disease, of paramount importance in disease recurrence where negative margins impact control and survival.[76]

SYSTEMIC THERAPY FOR RECURRENT AND METASTATIC DISEASE

Chemotherapy has been the mainstay first-line treatment for metastatic NPC. Single agent and platinum doublets have been studied, mostly in Phase II retrospective trials.[77] A pivotal Phase III randomized-controlled trial using gemcitabine-cisplatin (GP) in comparison with 5FU-cisplatin (PF) as first-line treatment for recurrent or metastatic NPC has recently been published. With a median follow-up of 19.4 months, the median PFS was statistically longer in the GP regimen versus PF (7.0 versus 5.6 months, HR 0.55, p < 0.0001).[78] A meta-analysis comparing four commonly used first line regimens including PF, GP, taxanes plus platinum (TP), and triplet combination showed that the triplet combination demonstrated best short-term efficacy with a highest overall response rate (ORR) (0.74; 95% CI, 0.62–0.87), but with a 1-year OS rate lower than that of the TP regimen (0.74; 95% CI, 0.61–0.87 versus 0.79,95% CI, 0.65–0.92), which

still showed the best prognosis, making the necessity of triplet regimens uncertain.[79]

Immunotherapy has recently been found to be of potential benefit in these cases. A Phase II trial of 44 patients resulted to a 20.5% ORR and 1-year OS of 59% in multiply pretreated recurrent or metastatic NPC patients.[80] Pembrolizumab has likewise been found to have an ORR of 25.9% in 27 patients.[81] Large-scale studies are awaited to validate these results and determine the role of immunotherapy in metastatic NPC.

RADIOTHERAPY TARGET DELINEATION

Recently, an update of consensus contouring guidelines was published for H&N squamous cell cancers, with the general rule of the GTV being expanded by 5 + 5 mm to create the clinical target volumes (CTVs) of high and intermediate doses, respectively.[82] The rationale is that 10 mm accounts for tumoral microscopic spread, and this rule allows increased reproducibility of contours. However, it is notable that the nasopharynx has not been included in this guideline, and a separate one has been published for NPC.[83] With the narrow therapeutic window necessitating a precarious balance between tumor control and avoidance of toxicity to adjacent critical organs at risk (OARs), adequate target volume coverage is of paramount importance as it has been shown to impact tumor control.[84] Because of the proximity of the nasopharynx to the skull base and the skull foraminae, the risk of intracranial extension is significant, but coverage has not been easy to achieve while respecting the dose constraints of OARs, especially for extensive disease. Also, unlike in other H&N localizations, there is paucity of surgical data in terms of the depth and distance of infiltration of NPC. Therefore, contouring guidelines are generally more generous to avoid missing potential sites of tumor spread. The high risk CTV still follows the GTV + 5 mm margin. Notable is that 55% of the experts recommend the inclusion of the entire nasopharynx in the high risk volume. The intermediate risk CTV is also recommended to be a 5 mm expansion from the CTV1, however, several key structures are mandatory. Contours need to be adjusted and expanded to include the following: superiorly, the vomer and surrounding ethmoid sinus, the inferior part of the sphenoid sinus in T1 and T2 disease and the entire sinus in T3 or T4 tumors, the cavernous sinus in T3 and T4 tumors, the bilateral foramina ovale, foramina rotunda and foramina lacera in all stages; anteriorly, 5 mm of the posterior nasal cavity, 5 mm of the posterior maxillary sinus electively to ensure adequate coverage of the pterygo-maxillary fissure and pterygo-palatine fossae; laterally, 5 mm of pterygoid muscles, the entire parapharyngeal space; and posteriorly, the anterior 1/3 of the clivus if not involved and the whole clivus if with any involvement.

BIOMARKERS

The role of EBV as a diagnostic, prognostic and predictive factor in NPC has been extensively studied, notably in endemic regions. Several methods of EBV detection have been employed, including EBV immunoglobulin A/viral capsid antigen (IgA/VCA) and early antigen (IgA/EA), encoded small RNAs (EBER), and DNA. EBER *in situ* hybridization of biopsies is a useful tool in the diagnosis of NPC, especially for metastatic lymph nodes of unknown primary.[85,86] Plasma EBV DNA levels and serum levels of EBV VCA/IgA were compared in a study conducted in Guangzhou, with results suggesting that EBV DNA is more sensitive and specific in diagnosis and monitoring of NPC patients. EBV DNA levels were undetectable in patients in clinical remission, whereas VCA/IgA levels remained high. Patients with higher TNM and T stages also had significantly higher EBV DNA levels.[87] EBV VCA/IgA was likewise not significant as a prognostic biomarker in patients with undetectable pretreatment EBV DNA.[88]

In Hong Kong, a study which screened more than 20,000 individuals identified 300 patients with persistently elevated EBV DNA levels, who subsequently underwent further work-up. Of these, 34 were found to be afflicted with NPC. Compared to a matched historical cohort, cancers detected by screening were in the earlier stages, and had a significantly better PFS (HR 0.10, 95% CI 0.05–0.18).[89] Screening, however, is foreseeably only applicable to endemic regions where the incidence is significant enough to justify the procedure.

A study involving the quantification of plasma EBV DNA levels showed that undetectable levels post treatment correlated with improved relapse-free survival. Furthermore, the same study demonstrated that increased levels of EBV DNA was associated with more advanced tumor stages and patients who relapse, 6 months earlier than clinical detection.[90] Yet another study showed that the post treatment levels of EBV DNA correlated with survival rates. However, the addition of adjuvant chemotherapy with a cisplatin doublet did not improve clinical outcomes for those with high post-treatment levels.[91] A retrospective study from China compared 36 patients who underwent ENPG plus CCRT versus 26 who had CCRT alone for recurrent NPC, and showed that EBV DNA levels decreased significantly for the ENPG +CCRT group ($Z = -3.484$, $p < 0.001$), and that pre-treatment EBV DNA levels correlated with OS ($p < 0.026$) on multivariate analysis.[92]

CONCLUSION

Due to the unique geographical distribution of NPC, more studies and publications come from endemic areas secondary to more feasible patient accrual. Trials from Asia usually have large study populations, and randomization is commonplace. With this unequal patient load, expertise of clinicians becomes an important question. NPC is an especially challenging disease to manage due to its complex anatomy with proximity of tumors to dose-limiting critical structures, as well as its complicated patterns of spread and its propensity for distant metastases. In fact, a recent study showed an approximately 20% decrease in the relative risk of death for patients treated at high volume facilities (HVFs), and that there was a progressive decline in risk of death with increasing number of NPC patients treated.[93] The positive effect of being treated at HVFs is corroborated by literature on other head and neck cancers. Risk of death or progression was 90% greater for stage III and IV H&N cancers treated in low (LVF) versus high volume centers. More cases of radiotherapy protocol deviations were judged as unacceptable in LVFs (11% versus 5%; $p = 0.04$), although this alone did not account for the

disparity in 5-year OS (51.0% versus 69.1%; $p = 0.002$).[94] Another study confirmed that treatment at HVFs versus LVFs and at academic versus non-academic facilities resulted in improved survival (5-year OS 61.6% versus 55.5% and 52.3% versus 49.7%, respectively, $p < 0.001$). Similar findings were seen for post-operative patients, wherein surgical HVFs were independently associated with improved OS in patients undergoing resection and post-operative RT for H&N cancer, but this survival benefit persists only when patients remain in the same facility for RT (5-year OS 63.1% versus 49.3%, $p < 0.0001$).[95]

Therefore, it is prudent to recommend that patients be managed in centers with experience and adequate patient load, especially in non-endemic areas. Establishing regional or national referral centers where patients can be sent for management is a good option. In cannot be overemphasized that proper treatment is paramount for this complex disease, especially since options for tumor recurrence are limited and are associated with significant treatment-related morbidities. Collaboration between low and high incidence countries and between low and high volume facilities is key to improving NPC prognosis worldwide.

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