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Current management of stage IV nasopharyngeal carcinoma without distant metastasis☆

Wai Tong Ng[a,*], June Corry[b], Johannes A. Langendijk[c], Anne W.M. Lee[d,e], Antti Mäkitie[f,g,h], William M. Mendenhall[i], Alessandra Rinaldo[j], Juan P. Rodrigo[k,l], Nabil F. Saba[m], Robert Smee[n], Primož Strojan[o], Carlos Suárez[p,k], Jan B. Vermorken[q], Alfio Ferlito[r]

[a] Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong
[b] Department Radiation Oncology, GenesisCare St Vincent's Hospital, Melbourne, Australia
[c] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[d] Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[e] Clinical Oncology Center, The University of Hong Kong-Shenzhen Hospital, Shenzhen, People's Republic of China
[f] Department of Otorhinolaryngology – Head and Neck Surgery, HUS Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[g] Research Program in Systems Oncology, Faculty of Medicine, University of Helsinki, Finland
[h] Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
[i] Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, United States
[j] University of Udine School of Medicine, Udine, Italy
[k] Instituto Universitario de Oncología del Principado de Asturias, University of Oviedo, Oviedo, Spain
[l] Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
[m] Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia
[n] Department of Radiation Oncology, The Prince of Wales Cancer Centre, Sydney, NSW, Australia
[o] Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia
[p] Instituto de Investigación Sanitaria del Principado de Asturias and CIBERONC, ISCIII, Oviedo, Spain
[q] Department of Medical Oncology, Antwerp University Hospital, Belgium
[r] International Head and Neck Scientific Group, Padua, Italy

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ABSTRACT

Up to one in four patients with nasopharyngeal carcinoma present with non-metastatic stage IV disease (i.e. T4 or N3). Distinct failure patterns exist, despite the routine adoption of contemporary treatment modalities such as intensity modulated radiotherapy and systemic chemotherapy. Concurrent chemoradiotherapy (CCRT) followed by adjuvant chemotherapy or induction chemotherapy followed by CCRT are commonly employed in this setting, with the latter emerging as the preferred option. Additionally, emerging radiation technologies like proton therapy has become available offering new opportunities for prevention of radiation-induced side effects. This article reviews not only the current treatment strategies, but also discusses novel ways to tackle this challenging disease with respect to the patterns of failure.

Introduction

Stage IV nasopharyngeal carcinoma (NPC) without distant metastasis is defined as clinically T4 or N3 disease in the American Joint Committee on Cancer (AJCC) and the International Union against Cancer Control (UICC) 8th edition [1]. This is either a locally infiltrative tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle (T4), or unilateral or bilateral metastasis in cervical lymph node(s) larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage (i.e. level IV and VB in the consensus nomenclature for neck dissection [2]) (N3). Fig. 1 shows examples of relevant radiological images. An important consideration in nodal staging is the correct measurement of the greatest nodal dimension. Confluent and/or contiguous nodes should be measured in the radiological plane with the maximal dimension [3], rather than a measurement on the axial plane only.

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* Corresponding author at: Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong.

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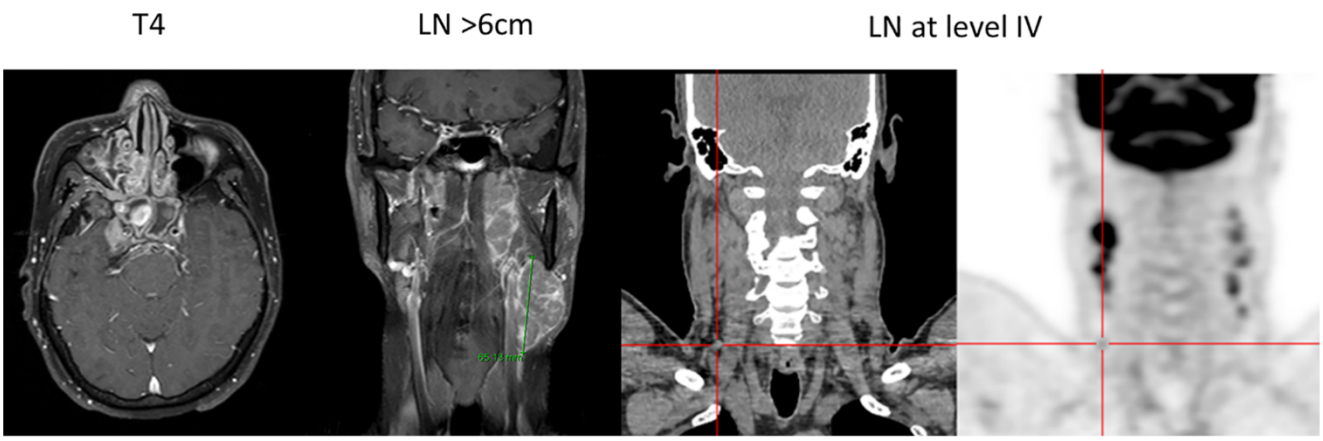

Fig. 1. Illustrations of stage IV nasopharyngeal carcinoma without distant metastasis, Abbreviation: LN – lymph node.

In the AJCC/UICC 8th edition, three major changes have been made from the 7th edition [4,5]. The first is the definition of the infratemporal fossa. The original idea was to use the term "masticator space" as a synonym for this region. However, the boundaries of masticator space described in most anatomy textbooks include both the medial and lateral pterygoid muscles, which is not a correct descriptor of the infratemporal fossa. Furthermore, the prognosis associated with involvement of these two muscles is, in comparison, much more favorable (hence staged as T2 in the current edition) [6]. The 8th edition also avoids the ambiguity of the term "supraclavicular fossa" (SCF) that was defined by three clinical landmarks [5]: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder. No corresponding radiological landmarks exist to support this interpretation [7]. Lymph node involvement in the lower neck was found to be a significant prognosticator and replacing "SCF" with "lower neck" not only maintains the hazard distinction between N categories, but also provides consistent radiological landmarks with the ease of reproducibility. Lastly, there is merging of T4 (previously IVA) and N3 (previously IVB) under stage IVA.

As most clinical studies have been reported based on the AJCC/UICC 7th edition [5], unless otherwise stated, the terms stage IVA and IVB will be used in the subsequent text to describe stage IV NPC without distant metastasis.

Patterns of failure

The Hong Kong NPC Study Group evaluated treatment outcomes of 3328 patients with NPC treated with intensity modulated radiotherapy (IMRT) from 2001 to 2010 [8]. In this large multi-institution cohort, stage IVA and IVB disease represented 27% of patients at presentation. The corresponding 5-year overall survival (OS) was approximately 65% after IMRT, concurrent chemoradiotherapy (CCRT) and adjunctive chemotherapy, compared with 81% for stage III disease.

Although T4 and N3 are both classified under stage IVA in the AJCC/UICC 8th edition [1], they have distinct clinical behavior and failure patterns. Three types of advanced disease have been described [9]: 1) predominantly advanced local disease with limited nodal spread (i.e. ascending type or Type A); 2) extensive nodal disease with small primary tumor (i.e. descending type or Type D); and 3) less commonly both local and regional advanced disease (i.e. Type AD).

Patients with T4 disease carry higher risk of local failure, with 5-year local failure-free survival of 76%, compared with over 90% for T1-3 [8]. They are also at high risk of distant failure, with 5-year distant failure-free survival of 73%. Local failure likely results of both bulky local disease and inadequate target dose coverage of radiation; while the rich vascular network around the skull base increases the potential for distant metastasis.

On the other hand, patients with N3 disease are at highest risk of distant failure – the 5-year distant failure-free survival is approximately 66% [8]. This may be due to the existence of microscopic distant deposits already present at the time of diagnosis. A similar differential failure pattern was reported by Huang et al. [10], in a cohort of 3107 patients with non-metastatic stage IV disease. It is noteworthy that baseline plasma Epstein-Barr virus (EBV) DNA at disease presentation tends to be higher in patients with N3 compared with T4 disease [10], and PET scan is recommended for metastatic work up [11]. Furthermore, in the study reported by Yao et al. on Type A and D diseases [9], it was found that the hazard of death following disease recurrence was higher in Type D compared with A.

International guideline recommendations for the treatment of IVA/IVB disease

The National Comprehensive Cancer Network guidelines (version 3.2019) recommends CCRT with adjuvant chemotherapy (AC) (2A recommendation) or induction chemotherapy (IC) followed by CCRT (2A recommendation), while CCRT alone was listed as category 2B [12].

The latest European Society of Medical Oncology guidelines [13], albeit dated back to 2012, suggests CCRT with or without AC (I, A) for advanced stage IVA and IVB disease. For patients with tumors in close proximity to important anatomical structures (e.g. tumor abutting the optic chiasm), suggesting inadequate tumor coverage with appropriate radiation therapy (RT) dose, IC followed by CCRT is recommended (II, B).

Concomitant chemoradiotherapy with adjuvant chemotherapy as standard of care

The Intergroup-0099 Study, that randomized stage III-IVB patients (AJCC 4th edition) to RT alone vs. CCRT and AC, was the landmark study that established the current standard of care [14]. Patients in the experimental arm were given cisplatin 100 mg/m^2 on days 1, 22 and 43 concurrent with conventional-fractionated RT followed by cisplatin 80 mg/m^2 on day 1 and 5-fluorouracil (5FU) 1000 mg/m^2/day on days 1 to 4 every 4 weeks for three courses in the post-RT period. This study was practice-changing as the preliminary results showed that the addition of chemotherapy resulted in significant improvement in both the 3-year progression free survival (PFS) (69% vs. 24%; $p < 0.001$) and 3-year OS (78% vs. 47%; $p = 0.005$). Although this study was criticized for the poor outcomes in the RT-alone arm, subsequent confirmatory randomized trials in endemic regions have consistently demonstrated improvement in PFS, albeit with modest absolute benefit of 9–13% [15–22]. Furthermore, due to the poor compliance with AC after CCRT (46–76% completion rate), the contribution of the adjuvant phase has been questioned. Recently, Chen et al. reported the updated results of a randomized study that compared CCRT with or without AC in 508 stage

III-IVB (except T3-4 N0) patients [23]. Completion rates of chemotherapy during the CCRT phase (45% in CCRT plus AC vs. 41% in CCRT) and AC phase (63% in CCRT plus AC) were low and there was no significant improvement in any survival end point (OS and failure-free survival (FFS)) in the AC arm. However, insufficient sample size was a major caveat of this study, suggesting that meta-analysis is required to provide a more definite conclusion [24].

Meta-analysis of the role of chemotherapy in NPC (MAC-NPC) using individual patient data was reported in 2006 [25]. The overall result from 1753 patients in eight trials showed an absolute survival benefit of 6% at 5 years and an absolute event-free survival benefit of 10% at 5 years with the addition of chemotherapy. Patients who received CCRT + AC or CCRT alone were grouped together as a concomitant group to be compared with RT alone. Significant interaction between the timing of chemotherapy and OS was observed ($p = 0.03$), with the most benefit deriving from the use of CCRT. Similar results were found in another meta-analysis, including 2450 patients with NPC, showing an overall survival benefit of 4% after 5 years, while the largest effect was found for CCRT with an overall survival benefit of 20% after 5 years [26].

The first update of MAC-NPC was reported in 2015 [27]. In this update, 4806 patients from 19 trials published before 2010 were included and separate analyses were performed for the benefit of CCRT plus AC. Ninety-six percent of the patients had non-keratinizing or undifferentiated carcinoma, which were the most common histological types in endemic regions and were almost always EBV-related. After a median follow-up of 7.7 years, the study confirmed a small, but significant benefit in OS by adding chemotherapy, which echoed the initial results from 2006: the absolute gain for OS was 6% at 5-years and 8% at 10-years. The benefit of the addition of chemotherapy was consistent for all the analyzed endpoints (all $p < 0.0001$): PFS (hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.69–0.81), locoregional control (HR 0.73, 95% CI 0.64–0.83), distant control (HR 0.67, 95% CI 0.59–0.75), and cancer mortality (HR 0.76, 95% CI 0.69–0.84). With regard to the timing of chemotherapy, the HR for the use of CCRT + AC was most favorable (HR 0.65, 95% CI 0.56–0.76) compared with CCRT alone (HR 0.80, 95% CI 0.70–0.93), IC alone (HR 0.96, 95% CI 0.80–1.16) and AC alone (HR 0.87, 95% CI 0.68–1.12).

Furthermore, the individual patient data network meta-analysis by the MAC-NPC provided additional supportive evidence on the role and timing of chemotherapy [24]. Compared with RT alone, CCRT + AC, CCRT alone and IC + CCRT attained the highest probability of benefit in OS with HR of 0.65 (95% CI 0.56–0.75), 0.77 (95% CI 0.64–0.92), and 0.81 (95% CI 0.63–1.04), respectively. However, increased chemotherapy was clearly associated with higher risk of acute toxicities.

Emerging role of induction chemotherapy followed by concomitant chemoradiotherapy

Due to significant residual toxicities from CCRT, compliance with AC is generally poor and the dose intensity of chemotherapy is usually compromised. Switching AC to IC may improve treatment outcome by early eradication of micrometastasis, especially for patients with advanced nodal disease. Furthermore, IC has the potential to downsize tumors with significant intracranial extension (i.e. T4 disease) and facilitate subsequent RT delivery by increasing the likelihood that all viable tumor cells will be included in the high-dose irradiation field.

In NPC, induction chemotherapy has been extensively tested, since the early 1990s, with varying degree of success [28]. Excellent disease control rate and acceptable toxicities were reported. In contrast to AC after CCRT, the majority of these case series reported relatively good compliance with IC. Updated results from MAC-NPC confirmed that IC significantly improved distant-failure free rate (HR 0.62, 95% CI 0.48–0.79), although this did not translate into a significant reduction of cancer deaths (HR 0.89, 95% CI 0.73–1.09) [27].

The NPC-0501 study directly compared IC followed by CCRT with CCRT followed by AC [29]. A total of 803 patients were recruited in this 6-arm trial to explore the therapeutic benefit of changing the chemotherapy sequence, fractionation of RT (5 vs. 6 fractions/week) and substitution of 5FU with capecitabine plus cisplatin as the induction regimen. A significantly higher proportion of patients in the induction group completed all scheduled non-concurrent cycles of chemotherapy than those in the adjuvant group (88% vs. 64%, $p < 0.01$). However, a lower proportion of patients in the induction group received greater than or equal to two concurrent cycles (90% vs. 95%, $p = 0.09$). Preliminary results showed that changing the timing of chemotherapy alone did not achieve a significant improvement in PFS. However, a better outcome was achieved by changing both the timing and regimen of chemotherapy. Induction cisplatin and capecitabine produced better PFS compared to adjuvant cisplatin and 5FU (81% vs. 75% at 3 years; $p = 0.045$). Reduction in hazard of progression (HR 0.54 [0.36–0.80]) and death (HR 0.42 [0.25–0.70]) reached significance when adjusted for other significant factors and fractionation. In addition, induction cisplatin and capecitabine resulted in less toxicity (neutropenia and electrolyte disturbance). Final results on 5-year treatment outcomes will be published in 2020.

On the other hand, multiple randomized trials comparing IC plus CCRT with CCRT alone have been reported, and the results are summarized in Table 1 [30–37]. Most of these trials employed a combination of chemotherapy including cisplatin, 5FU, anthracycline, taxane or gemcitabine as the induction regimen. The early trials on IC plus CCRT vs. CCRT alone demonstrated conflicting results [30–32]. However, five recent trials showed more encouraging results [33–36,38]. Discrepancies in treatment outcomes among these trials are likely due to differences in patient selection, type of induction chemotherapy regimen and the dose intensity of individual chemotherapeutic agents. Docetaxel based IC appears to provide more consistent benefit when compared with gemcitabine-based IC [30,32,33,35,36]. However, there are concerns related to the acute toxicity of IC, especially with the combination of docetaxel, cisplatin and 5FU (TPF), which could impact on the ability to deliver the subsequent standard CCRT. In the study reported by Sun et al. [39], the starting dose of TPF was only 80% of the conventional regimen and recruited patients had to be younger than 65 years. In a recently reported randomized study by Jin et al. comparing TPF vs. PF as IC, followed by CCRT [40], tolerance in the TPF-arm was poor with significantly more treatment delays and dose modifications than in the PF arm (33.3% vs. 18.1%, $P = 0.004$). This interim study also found that TPF was not significantly superior to PF in terms of PFS (84.5% vs. 77.9%, $p = 0.380$) and OS (91.1% vs. 91.1%, $p = 0.821$) after a minimum of 2-years follow-up.

Recently, several meta-analyses of published data also support the survival improvement with IC plus CCRT, albeit with higher treatment toxicity [41–44]. In the meta-analysis reported by Zhang et al. [41], a total of 8036 patients from 28 randomized clinical trials were included. The additional of IC to RT or CCRT was associated with an improvement in OS (HR 0.84, 95% CI 0.74 – 0.95), locoregional recurrence-free survival (LRFS; HR 0.74, CI 0.64 – 0.85) and distant metastasis-free survival (DMFS) (HR 0.67, CI 0.59 – 0.78). Similarly, in the study reported by Chen et al. [45] on individual patient data pooled analysis of four randomized trials comparing IC plus CCRT versus CCRT alone, the outcomes were in favor of IC plus CCRT: both in terms of OS (HR 0.75, 95% CI 0.57–0.99) and distant failure (HR 0.68, 95% CI 0.51–0.90).

Clearly, IC before CCRT is now replacing CCRT as the standard of care in locoregionally advanced NPC, in particular, T4 or N3 disease. Future studies of IC should not only focus on selecting patient groups that will derive most benefit from IC, but also on the treatment scheme, dose intensity as well as subsequent compliance with CCRT.

The second update of MAC NPC is currently in progress and results are expected in 2020. Apart from addressing the effects of treatment sequence across different stages, a planned subgroup analysis will also be conducted on taxane and non-taxane IC followed by CCRT. The results may shed further light on the optimal treatment, especially for patients who present with stage IV disease without distant metastasis.

Table 1
Randomized phase II-III trials evaluating induction-concurrent chemoradiotherapy (CCRT) versus CCRT alone.

Author	No	IVA – IVB (%)	Induction chemotherapy regimen	Median follow up (year)	Endpoint (year)	Progression free survival	Overall survival
Hui et al. [30]	65	41.5	Docetaxel 75 mg/m^2 D1 Cisplatin 75 mg/m^2 D1 Q 3 weeks × 3	4.3	3	88.2% vs. 59.5% HR = 0.49, p = 0.12	94.1% vs. 67.7% HR = 0.24, p = 0.012
Fountzilas et al. [31]	141	41.1	Cisplatin 75 mg/m^2 D1 Epirubicin 75 mg/m^2 D1 Paclitaxel 175 mg/m^2 D1 Q 3 weeks × 3	4.6	3	64.5% vs. 63.5% HR – NR, p = 0.708	66.6% vs. 71.8% NR – NR, p = 0.652
Tan et al. [32]	172	40.1	Gemcitabine 1000 mg/m^2 D1, D8 Carboplatin AUC × 2.5 D1, D8 Paclitaxel 70 mg/m^2 D1, D8 Q 3 weeks × 3	3.3	3	74.9% vs. 67.4% HR = 0.77, p = 0.362*	94.3% vs. 92.3% HR = 1.05, p = 0.494
Frikha et al. [33]	83	NR	Docetaxel 75 mg/m^2 D1 Cisplatin 75 mg/m^2 D1 5FU 750 mg/m^2 D1-D5 Q 3 weeks × 3	3.6	3	73.9% vs. 57.2% HR = 0.44, p = 0.042	86.3% vs. 68.9% HR = 0.40, p = 0.05
Hong et al. [34]	479	100	Mitomycin 8 mg/m^2 D1 Epirubicin 60 mg/m^2 D1 Cisplatin 60 mg/m^2 D1 5FU 450 mg/m^2 D8 Leucovorin 30 mg/m^2 D8 Q 3 weeks × 3	6.0	5	61% vs. 50% HR = 0.739, p = 0.026*	72% vs. 68% HR = 0.923, p = 0.624
Yang et al. [37]	476	47.3	Cisplatin 80 mg/m^2 D1 5FU 800 mg/m^2 D1-D5 Q 3 weeks × 2	6.9	5	73.4% vs. 63.1% HR = 0.66, p = 0.007*	80.8% vs. 76.8% HR = 0.69, p = 0.040
Zhang et al. [35]	480	51.8	Gemcitabine 1000 mg/m^2 D1, D8 Cisplatin 80 mg/m^2 D1 Q 3 weeks × 3	3.6	3	85.3% vs. 76.5% HR = 0.51, p = 0.001#	94.6% vs. 90.3% HR = 0.43, p - NR
Li et al. [36]	480	45.4	Docetaxel 60 mg/m^2 D1 Cisplatin 60 mg/m^2 D1 5FU 600 mg/m^2 D1-D5 Q 3 weeks × 3	6.0	5	77.4% vs. 66.4% HR = 0.67, p = 0.019‡	85.6% vs. 77.7% HR = 0.65, p = 0.042

Abbreviation: 5FU – 5-fluorouracil, AUC – area under the concentration-time-curve, HR – hazard ratio, NR – not reported.
* Disease-free survival.
\# Recurrence-free survival.
‡ Failure-free survival.

Other potential treatment strategies

Precision radiotherapy

Precision RT is characterized by high conformity of the radiation dose to target volumes and steep dose gradients on their margins to spare surrounding normal organs. This is particularly important for T4 disease due to the very close proximity of tumor to important organs at risk (OARs). At present, intensity modulated radiotherapy (IMRT) is considered standard of care, and results in lower rates of acute and late xerostomia as compared to more conventional techniques like 2D and 3D-conformal radiotherapy [46,47]. Moreover, higher rates of local-recurrence free survival have been reported [48].

Changes in body contour and the variations in size, shape and location of target volumes as well as OARs during the course of RT are well-recognized and can lead to suboptimal target dose coverage or excessive dose to the OARs [49–52]. The concept of adaptive RT emerged to optimize planned dose delivery by incorporating interval evaluation of the body contour, target volumes and OARs. Adaptive re-planning has shown to improve loco-regional control for patients with T3-4 tumors [53–55] and to reduce late toxicities for patients with advanced nodal (N2-3) diseases [53] in retrospective series.

In a non-randomized study of 110 patients with T4 NPC treated with IMRT [55], 47 patients received re-planning during the RT course according to physician's discretion. The 5-year local recurrence-free survival rates were 98% and 84% for the patients that received and did not receive RT re-planning, respectively. Another prospective study of 129 NPC patients demonstrated improvement in loco-regional control and quality of life (mainly in the subdomains of saliva related issues) by IMRT re-planning. However, it is worth mentioning that 43 recruited patients actually declined re-planning in this study and the results should be interpreted with caution [56]. Further prospective studies are warranted to confirm the optimal timing and benefit of such an adaptive approach.

Proton beam and carbon ion therapy are particularly relevant for the treatment of T4 disease due to the inherent physical characteristics that allow delivery of a high dose radiation to the tumor and maximal sparing of surrounding normal tissues [57]. Treatment planning studies confirmed improved tumor coverage and conformation and significant reduction of the mean dose to several organs at risk (OARs) over photon-based IMRT [58,59]. However, proton therapy is currently limited in availability and the related clinical studies in NPC are scarce. A phase II trial of proton therapy with chemotherapy reported in abstract form has reported excellent loco-regional control and functional outcomes in 23 patients with stage III to IVB NPC [60]. The disease-free survival and OS at 2 years were 90% and 100%, respectively. There was no ≥ grade 3 xerostomia and the stimulated and unstimulated flow rates were > 25% of baseline in 70% of patients at 12 months. However, less impressive results were reported by Beddok et al. in seventeen stage III to IVA NPC patients where proton was used as a boost after photon radiotherapy [61]. The 5-year locoregional failure free survival and OS were 86% and 74%, respectively.

Loosening of dose constraints

International guideline on dose prioritization and acceptance criteria in RT planning has been published [62]. Maximal acceptance criteria (MAC) were suggested for neurological OARs relevant to NPC RT. Specifically, the recommended acceptable dose to the temporal lobe (D0.03 cc) is < 72 Gy (priority 2 structure), and that for the optic nerve (D0.03 cc) is < 60 Gy (priority 3 structure).

A controversial strategy is to adopt more aggressive RT target coverage by exceeding constraints to selected neurological OARs while accepting a higher risk of complications. In a study by Ng et al. [63], dosimetric inadequacy was reported to be one of the major causes for treatment failure. Under-dosing (< 66.5 Gy) to primary GTV (3.4 cm^3) was found to be highly detrimental to local control. Less stringent dose constraints of a maximum accepted dose of 66 Gy to the optic nerve and 75 Gy to the temporal lobe, with patient consent, were suggested to improve tumor coverage.

A recent retrospective study evaluating the outcomes and late toxicities in 200 patients with T3-4 NPC, treated with IMRT and loosening of dose constraints for selected critical structures was reported by Gou et al. [64]. The maximum median dose to left and right temporal lobe was 76.5 Gy and 73.7 Gy respectively. Seventeen out of 166 evaluable patients developed a temporal lobe injury (TLI), while the 5-year LRFS was 90%. Long-term follow-up is crucial to assess the impact, severity and cognitive impairment of such TLI.

Integration of systemic therapy

Various novel systemic treatment agents in combination with RT have been tested. Strategies include intensification of chemotherapy, maintenance and metronomic chemotherapy, and development of targeted therapy and immunotherapy agents. Table 2 summarizes important ongoing trials, and those that have completed accrual but are pending published results.

Intensification of systemic treatment

While it is logical to attempt to enhance systemic control by delivering more intensive systemic treatment, there is always the need to consider treatment toxicity. The aim is to maximize treatment efficacy while maintaining treatment compliance. The optimal dose of chemotherapy agents needs to be considered in view of this balance. An example of this is the study reported by Sun et al. [39], where the starting dose of TPF was 80% of the recommended dosage [65]. Similarly, the preferred cisplatin regimen (low-dose weekly regimen vs. standard high-dose 3-weekly regimen) in CCRT remains undefined and only one randomized phase II study has been reported suggesting similar efficacy [66].

Newer generation platinum compounds have emerged, including nedaplatin (second generation) and lobaplatin (third generation) [67–69]. Nedaplatin and lobaplatin are potentially less nephrotoxic than cisplatin, while lobaplatin may also overcome cisplatin resistance. The role of these agents in induction and concomitant chemotherapy for NPC is under active clinical investigation (see Table 2). Preliminary findings from a randomized phase 3 study of nedaplatin-based versus cisplatin-based CCRT in stage II-IVB disease demonstrated similar treatment efficacy, but significantly fewer acute gastrointestinal and late auditory toxicities [69].

Other chemotherapy agents such as newer-generation taxanes and capecitabine have also been studied. A phase II trial by Ke et al. [70] evaluated the use of induction nab-paclitaxel combined with cisplatin followed by CCRT in 36 stage III-IVB patients. The study reported an encouraging clinical response rate (97%), while nab-paclitaxel reduced the risks of solvent-related toxicities and peripheral neuropathy. The role of capecitabine was explored in the NPC-0501 study [29], where induction cisplatin and capecitabine had the potential advantages of lower marrow toxicity and electrolyte disturbances.

Maintenance and Metronomic chemotherapy

In view of the overall poor treatment compliance reported with the use of intravenous AC, studies have explored the role of maintenance and metronomic chemotherapy with various oral agents.

Two studies have reported on the use of maintenance TS-1 (combination tegafur/gimeracil/oteracil). In a retrospective study on 44 patients with N3 NPC [71], patients received CCRT with high dose 3-weekly cisplatin followed by 4 cycles of TS-1, on days 1–28, given 6 weeks apart (i.e. maintenance chemotherapy duration of approximately 6 months). In this study, the 3-year OS and DMFS rates were 86% and 84%, respectively. Another recent retrospective study reported by Zong et al. [72] explored the use of maintenance TS-1 administered on days 1–14, every 4 weeks for 12 cycles (i.e. total 1 year) or 24 cycles (i.e. total 2 years) after CCRT. The reported OS for the 21 patients who received maintenance TS-1 was 95%, compared with 76% for the 109 patients who did not ($p < 0.05$); the DMFS was 91% and 70% ($p = 0.04$) respectively. Maintenance TS-1 was generally well tolerated in both studies.

Metronomic chemotherapy refers to the administration of low doses of cytotoxic drugs (usually 10–30% of the maximal tolerated dose) for an extended period without prolonged drug-free intervals. Benefits of such a treatment strategy may include delay in the emergence of drug resistance and better tolerability compared with the traditional intermittent intravenous AC. Uracil-Tegafur (UFT), TS-1 and capecitabine are potentially effective agents. Mechanisms of action include direct cytotoxic effects on tumor cells, inhibition of tumor angiogenesis, modulation of the host immune system, and effects on progenitors and neighboring stromal cells.

Two retrospective studies on the use of metronomic chemotherapy have been reported in Taiwan. Twu et al. investigated the role of UFT in 85 patients with detectable plasma EBV DNA after the completion of definitive RT [73]. Of the 85 patients, 33 were administered continuous UFT for one year, with or without preceding intravenous chemotherapy mitomycin-C, epirubicin and cisplatin. The remaining 52 patients did not receive metronomic therapy. The 5-year OS was significantly better (72%) for patients who received metronomic chemotherapy compared with those who did not (29%). This is largely attributed to the effect of prolonged chemotherapy in the reduction of distant metastasis. Similar observations were reported by Chen et al. [74], who evaluated the impact of UFT for 1 year in a group of stage IV patients without distant metastasis and found an improvement of OS from 58% to 92%. Ongoing trials are underway to further examine this treatment strategy (see Table 2).

Targeted therapy

Epidermal growth factor receptor (EGFR) has been shown to be overexpressed in 85% of NPC tumor biopsy material, and is associated with a poorer prognosis [75]. In-vitro studies of cetuximab have demonstrated both single-agent activity in NPC cell lines, as well as enhancement of the anti-tumor effects of cisplatin and paclitaxel [76]. Moreover, cetuximab demonstrated clinical activity in heavily pretreated patients when combined with carboplatin [77]. Similar to other head and neck squamous cell carcinoma, anti-EGFR agents have been investigated as a substitute for chemotherapy to reduce toxicity [78], or as an adjunct to intensify current treatment regimens in patients with high-risk disease [79].

Several single-arm studies have investigated the effectiveness and toxicity of integrating cetuximab with CCRT [80–83]. All of these studies have reported encouraging results with a tolerable toxicity profile. However, prospective randomized data comparing cetuximab-CCRT and CCRT are lacking. An observational study conducted in China retrospectively compared outcomes of patients treated with CCRT plus cetuximab to CCRT alone [84]. The addition of cetuximab was associated with improved DMFS (94.1% vs. 87.3%, $p = 0.044$) but not OS. This improvement was more pronounced among patients with advanced N category (87.9% vs. 66.2%, $p = 0.045$), which in turn translated into a borderline improvement of OS (90.7% vs. 79.7%, $p = 0.073$). Further investigation in patients with advanced N status is warranted.

Nimotuzumab, a novel humanized anti-EGFR monoclonal antibody, has also been investigated in China. Several clinical studies have been

Table 2
Ongoing trials that include T4 or N3 disease.

Trial	No. patients	Treatment
Cytotoxic chemotherapy		
Induction chemotherapy: addition to concomitant chemotherapy		
NCT02460887	236	RT + concomitant cisplatin vs.
		Induction gemcitabine + cisplatin, then RT alone
NCT02512315	144	RT + concomitant cisplatin vs.
		Induction docetaxel + cisplatin, then RT + concomitant cisplatin
NCT02786641	235	3 arms but one outside randomization (nomogram-predicted low risk group)
		RT + concomitant cisplatin vs.
		Induction docetaxel + cisplatin + capecitabine, then RT + concomitant cisplatin
Induction chemotherapy: comparison of different chemotherapy		
NCT01479504	NA	Induction nedaplatin + docetaxel, then RT + concomitant nedaplatin vs.
		Induction cisplatin + docetaxel, then RT + concomitant cisplatin
NCT01536223	400	Induction docetaxel + cisplatin + 5 FU, then RT + concomitant cisplatin vs.
		Induction 5 FU + cisplatin, then RT + concomitant cisplatin
ChiCTR-TRC-13003285	492	Induction lobaplatin + 5 FU, then RT + concomitant lobaplatin vs.
		Induction cisplatin + 5 FU, then RT + concomitant cisplatin
NCT03503136	632	Induction docetaxel + cisplatin + 5 FU, then RT + concomitant cisplatin vs.
		Induction docetaxel + nedaplatin + 5 FU, then RT + concomitant nedaplatin vs.
		Induction docetaxel + cisplatin + capecitabine, then RT + concomitant cisplatin vs.
		Induction docetaxel + nedaplatin + capecitabine, then RT + concomitant nedaplatin
NCT02940925	220	Induction paclitaxel + cisplatin + capecitabine, then RT + concomitant cisplatin vs.
		Induction 5 FU + cisplatin, then RT + concomitant cisplatin
NCT03840421	468	Induction gemcitabine + cisplatin, then RT + concomitant cisplatin vs.
		Induction 5 FU + cisplatin, then RT + concomitant cisplatin
NCT02500940	54	Induction cisplatin + 5 FU Q3week vs.
		Induction alternative weekly cisplatin + 5 FU / Leucovorin
Induction chemotherapy +/- concomitant chemotherapy		
NCT01854203	300	Induction gemcitabine + cisplatin, then RT + concomitant cisplatin vs.
		Induction gemcitabine + cisplatin, then RT alone
NCT02434614	440	Induction docetaxel + cisplatin + 5 FU, then RT + concomitant cisplatin vs.
		Induction docetaxel + cisplatin + 5 FU, then RT alone
Concomitant chemotherapy		
NCT01817023	590	RT vs.
		RT + concomitant cisplatin
NCT03047265	164	RT + concomitant cisplatin (3 cycles) vs.
		RT + concomitant cisplatin + paclitaxel (2 cycles)
Adjuvant chemotherapy		
NCT02363400	147	Detectable EBV DNA post-treatment:
		RT (± induction and/or concurrent chemo) vs.
		RT (± induction and/or concurrent chemo + adjuvant mitomycin, epirubicin, cisplatin and tegafur
NCT02135042	758	No detectable EBV DNA post-treatment:
		RT + concomitant cisplatin vs.
		RT + concomitant cisplatin, then adjuvant cisplatin + 5 FU
		Detectable EBV DNA post-treatment:
		RT + concomitant cisplatin, then adjuvant cisplatin + 5 FU vs.
		RT + concomitant cisplatin, then adjuvant gemcitabine + paclitaxel
NCT02143388	180	Adjuvant capecitabine vs.
		Observation
NCT02958111	406	Adjuvant capecitabine vs.
		Observation
NCT02973386	278	Adjuvant capecitabine vs.
		Observation
NCT03904225	220	Adjuvant tegafur-gimeracil-oteracil vs.
		Observation
Induction chemotherapy vs. *adjuvant chemotherapy with concomitant chemotherapy in both arms*		
NCT03306121	322	Induction paclitaxel (liposome) + cisplatin + 5 FU, then RT + concomitant cisplatin vs.
		RT + concomitant cisplatin, then adjuvant cisplatin + 5 FU
NCT01797900	130	Induction paclitaxel + cisplatin, then RT + concomitant cisplatin vs.
		RT + concomitant cisplatin, then adjuvant paclitaxel + cisplatin
Adjuvant chemotherapy vs. *concomitant chemotherapy with induction chemotherapy in both arms*		
NCT03366415	420	Induction gemcitabine + cisplatin, then RT, followed by adjuvant gemcitabine + cisplatin vs.
		Induction gemcitabine + cisplatin, then RT + concomitant cisplatin
Concomitant chemotherapy +/- induction chemotherapy + adjuvant chemotherapy		
NCT02621970	534	Induction docetaxel + cisplatin, then RT + concomitant cisplatin + capecitabine, followed by adjuvant capecitabine vs.
		RT + concomitant cisplatin
Anti-EGFR agent		
NCT01074021	480	RT + concomitant cisplatin + placebo vs.
		RT + concomitant cisplatin + nimotuzumab
NCT02012062	320	Induction docetaxel + cisplatin + 5 FU, then RT + concomitant cisplatin vs.
		Induction docetaxel + cisplatin + 5 FU, then RT + concomitant nimotuzumab
NCT01614938	46	Induction docetaxel + cisplatin, then RT + concomitant cisplatin vs.
		Induction docetaxel + cisplatin, then RT + concomitant cetuximab

(*continued on next page*)

Table 2 (*continued*)

Trial	No. patients	Treatment
Anti-angiogenic agent		
NCT02874651	103	Detectable EBV DNA post-treatment: Adjuvant apatinib vs. placebo
NCT02237924	120	RT + concomitant cisplatin (2–3 cycles) vs. RT + concomitant Endostar (2 cycles) , then adjuvant Endostar
NCT02907710	300	RT + concomitant cisplatin (2–3 cycles) vs. RT + concomitant Endostar (3 cycles) , then adjuvant Endostar
Immunotherapy		
NCT03427827	400	After chemoradiotherapy: Adjuvant camrelizumab vs. observation
NCT03700476	420	Induction sintilimab + gemcitabine + cisplatin, then RT + concomitant cisplatin + sintilimab, followed by adjuvant sintilimab vs. Induction gemcitabine + cisplatin, then RT + concomitant cisplatin
NCT02421640	116	RT + concomitant cisplatin followed by adjuvant tumor infiltrating lymphocytes vs. RT + concomitant cisplatin

Abbreviations: 5FU – 5-fluorouracil, NA – not available, RT – radiotherapy.

published to date [85–88]. In the phase III trial reported by Kong et al. in abstract form, 155 patients received 3 cycles of induction TPF, and were then randomized to receive either CCRT with cisplatin or RT concurrent with nimotuzumab [89]. After a median follow-up of 24 months, nimotuzumab produced similar rates of PFS and OS compared with cisplatin. Gastrointestinal and hematological toxicities were significantly lower and the treatment completion rate was significantly higher in the nimotuzumab arm (97% vs. 40%, $p < 0.001$). Full publication is still pending, and long-term results are needed to confirm these observations.

Finally, in a propensity scores adjusted study, anti-EGFR agents (cetuximab or nimotuzumab) in combination with CCRT were compared with IC plus CCRT. While comparable efficacy was noted, more severe hematological toxicity and diarrhea were observed in patients treated with IC plus CCRT. However, it should be noted that more than 80% of patients in this study had stage III disease and its efficacy in more advanced disease setting was less clear [79].

Apart from EGFR, overexpression of vascular endothelial growth factor (VEGF) was also found in more than two-third of patients with NPC. This was associated with higher rates of nodal failure and inferior OS [90]. A phase II trial evaluated the efficacy and safety of adding bevacizumab, an anti-VEGF antibody, to both the concurrent and adjuvant phases of the Intergroup 0099 regimen [91]. Compliance with bevacizumab was excellent – nearly 70% of patients completed all 3 cycles of cisplatin and no grade 3 or 4 toxicity was reported. However, the 2-year PFS was only 74.7%.

Endostar is a novel recombinant human endostatin, which is an endogenous inhibitor of angiogenesis. Endostar inhibits tumor growth primarily through direct inhibition of VEGF, vascular endothelial growth factor receptor-2 and platelet-derived growth factor receptor [92]. In pre-clinical studies, it has been shown to create a “vascular normalization window” to alleviate tumor hypoxia and enhance the inhibitory effects of RT in xenografted human NPC models. While this drug was tested in the metastatic and recurrent NPC setting with promising results [93,94], no significant advantages were observed in the first-line curative treatment of locally advanced disease [95], although its side effects were relatively mild [96].

Immunotherapy

Recent breakthroughs in the study of immune-checkpoint inhibitors have rekindled our interest in immuno-oncology in the management of NPC [97]. It is well known that NPC is an inflamed tumor with a dense lymphocytic infiltration [98]. Preclinical studies have also confirmed the high expression of programmed death-ligand 1 (PD-L1) of up to 50–80% in nasopharyngeal tumor specimens [99–101]. Promising activities have been demonstrated by immune check-point inhibitors including nivolumab [102], pembrolizumab [103] and camrelizumab [104] in patients with PD-L1 positive metastatic NPC. However, it is noteworthy that some tumors may express type II latency EBV proteins which are weakly immunogenic, leading to evasion of host immune surveillance [105].

It is now well recognized that RT to the tumor has the potential of converting cancer cells into an in situ vaccine by releasing relevant epitopes and neo-antigens, which in turn induces cell death signals that enable cross priming of activated tumor-specific T cells. This immune activation not only contributes to the elimination of the primary irradiated tumor, but may also help to destroy systemic metastasis outside the radiation portal (the abscopal effect). The optimal combination of immune-checkpoint inhibitors and RT is currently under intensive study and determining how immunotherapy and RT interact may be a next crucial step in the management of locally advanced NPC [97].

Similarly, the presence of EBV-associated tumor antigens in NPC serves as an important target. Cellular based immunotherapy has been tested for several decades with clear evidence of an enhanced EBV-specific antitumor response. Multiple phase I/II studies have been published, mainly in the setting of refractory disease [106–108]. However, this treatment response may be less relevant in the post-primary treatment setting as the residual tumor burden is minimal (or absent) and the immunosuppressive environment is less intense compared with that of refractory disease. Ongoing clinical studies are underway in China [109]. However, the high costs and the complexity of treatment are expected to limit its application.

Therapeutic vaccination is another treatment strategy under active clinical research. Both dendritic cell vaccine [110] and vaccine comprising a recombinant vaccinia virus [111,112] to target EBV-related tumor antigens have been evaluated, showing a promising T-cell response. A study conducted at The Chinese University of Hong Kong (NCT01094405) has completed accrual, and results are awaited.

Biomarker driven treatment strategy

While T4 and N3 are known to be adverse prognostic factors, post-treatment plasma EBV DNA titer is also found to be very useful in predicting treatment outcome and OS [113]. One major limitation is that quantitative PCR assays in different clinical laboratories can yield large variability in plasma EBV DNA copy numbers, which makes comparison of these studies difficult. Efforts should be made to standardize and homogenize the detection methodology across laboratories [114]. Standardization of assays would enable stratification of patients into multicenter clinical trials.

Currently, there is lack of evidence to guide the optimal way to

incorporate plasma EBV DNA into treatment protocols. Several trials attempted to use post-treatment plasma EBV DNA for tailoring of adjuvant treatment. The Hong Kong NPC Study group 0502 study randomized 218 patients with detectable EBV DNA at 6 weeks after CCRT to AC or observation. Preliminary results failed to demonstrate any improvement in treatment outcomes with the use of AC [113]. The NRG-HN001 trial segregated patients into two risk groups based on plasma EBV DNA at 1 week after CCRT. Those with undetectable EBV DNA were randomized to AC using PF or observation, to address whether AC can be safely omitted in this low-risk group. Those with detectable EBV DNA were randomized to AC using standard PF or paclitaxel-gemcitabine (PaG) to test whether PaG is more potent for this high-risk group. Similar treatment strategy was employed in the NCT02363400 and NCT02874651 trials (see Table 2 for ongoing studies).

Conclusion

Stage IV non-metastatic NPC is a distinct clinical entity, for which treatment outcomes remain unsatisfactory despite contemporary treatment techniques. Prognosis of these patients is significantly worse when compared with stage III disease and novel treatment strategies are required to tackle this problem. There is increasing clinical evidence to support the use of IC followed by CCRT as the standard of care for non-metastatic stage IV disease.

T4 and N3 disease produce distinct failure patterns and future treatment approaches should be tailored to address the dominant risk of failure. Precision RT may widen therapeutic window to improve local control for T4 disease, while for N3 disease, intensification of systemic treatment and integration of novel therapeutic agents may be necessary to enhance systemic control. The role of maintenance and metronomic chemotherapy requires further active research, particularly for patients with persistent detectable EBV DNA after definitive CCRT [73]. Most importantly, design of future clinical trials shall stratify patients according to their individual risks of failure in order to derive optimal personalized strategy. One example is to tailor treatment according to kinetics of EBV DNA clearance [115]. Finally, close surveillance for aggressive treatment of oligo-recurrences is also recommended [116].

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JA Langendijk: Departmental research collaboration with RaySearch, IBA, Siemens, Mirada and Elekta. Member of the International Advisory Board of IBA, honorarium paid to UMCG Research BV. Nabil F. Saba: Consulting for Merck, Aduro, Rakuten, Pfizer, CUE, Blupoint

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