Review Article

Treatment strategy for *de novo* metastatic nasopharyngeal carcinoma: a literature review

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Background and Objective: Nasopharyngeal carcinoma (NPC) with *de novo* distant metastasis (M1) is classified as stage IVB in the 8th edition of the staging system jointly adopted by the American Joint Committee on Cancer and the International Union against Cancer Control. Patients with M1 disease generally have a relatively short life expectancy. This review discusses the personalized and intensified treatment strategies for de novo metastatic NPC.

Methods: A literature search was conducted on PubMed to identify peer-reviewed publications on subdivisions of M1 disease and treatment of *de novo* metastatic NPC. Clinicaltrials.gov and Chinese Clinical Trial Register were searched to identify ongoing clinical trials evaluating systemic or local therapy of previously untreated metastatic NPC.

Key Content and Findings: M1 encompasses a diverse group of diseases. Several important factors, including tumor burden, EBV-DNA levels, location of involvement, the number of metastasis, and treatment strategies, influence the prognosis of NPC patients. Researchers have attempted to define M1 subcategorization to reflect the underlying risk profile and tailor personalized treatment. Recent advancements have brought new hope for this otherwise incurable condition. In the era of immunotherapy, checkpoint inhibitors have become the first-line systemic treatment for metastatic NPC in JUPITER-02, CAPTAIN-1st, and RATIONALE-309. Additionally, the value of radical locoregional radiation therapy and ablative treatment to distant metastatic sites should not be overlooked in patients with *de novo* metastatic diseases. Locoregional radiation with concurrent chemotherapy, maintenance chemotherapy, and radical local treatment to metastatic sites are emerging as potential treatment options.

Conclusions: Given the diversity of metastatic NPC, a multimodality approach incorporating chemotherapy, immunotherapy, locoregional radiation and ablative treatment to metastatic sites has been shown to improve overall control. Further research is needed to determine the efficacy and optimal duration of maintenance therapy.

Keywords: Metastatic nasopharyngeal carcinoma; radiation therapy; chemotherapy; immunotherapy

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Introduction

Nasopharyngeal carcinoma (NPC) arises from the epithelial lining of the nasopharynx. According to GLOBOCAN 2020, there were 133,354 new cases and 80,008 cancer deaths globally (1). Although NPC only accounts for 0.7% of all new cancer cases diagnosed globally, it has a skewed geographic distribution, with more than 70% of new cases diagnosed in East and Southeast Asia (2). Historically, approximately 4–6% of patients present with de novo metastasis at diagnosis (3,4). With more sensitive radiological examinations, such as [18F] fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT), 12.9–14.8% of patients were found to have de novo metastatic NPC (5,6).

With contemporary state-of-art treatment, the majority of NPC patients could achieve good outcomes. However, patients with metastatic (M1) disease have a significantly worse prognosis than those without distant metastases at presentation. The 5-year disease-specific survival rate for patients with M1 disease was estimated to be 20%, while the 5-year survival rate for those without metastases was greater than 70% (4). Chemotherapy using gemcitabine and cisplatin (GP) combination was the standard of care in the first line setting before the era of immunotherapy (7). Emerging evidence supports the role of immunotherapy and locoregional radiotherapy in patients with de novo metastatic nasopharyngeal (8-11). However, metastatic NPC is a complex and heterogeneous disease. The prognosis of patients with metastatic NPC differs considerably.

In this article, we discuss the current literature and clinical trials on the risk stratification and treatment of metastatic NPC, focusing on intensifying systemic therapy with immunotherapy and radiotherapy. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-32/rc).

Methods

A literature review was conducted to identify studies on the subcategorization and treatment of newly diagnosed metastatic NPC. PubMed, Clinicaltrials.gov and the Chinese Clinical Trial Register (ChiCTR) were searched separately using combinations of keywords. The PubMed search included the terms “nasopharyngeal carcinoma”, “metastatic nasopharyngeal carcinoma”, “metastasis”, “subdivision”, “locoregional radiotherapy” and “local treatment”. The Clinicaltrials.gov and ChiCTR searches used the terms “metastatic NPC”, “radiotherapy”, and “interventional study”. Trials that did not include patients with previously untreated *de novo* metastatic NPC were excluded in the analysis. *Table 1* provides a summary of the search strategy.

Recommendations on management of *de novo* metastatic NPC by national and international guidelines

There are variations in the recommendation by different major guidelines. The Chinese Society of Clinical Oncology (CSCO) recommends GP with or without camrelizumab or toripalimab (evidence 1A) and local radiotherapy (evidence 1A) as first-line treatment for recurrent and metastatic NPC (12). The National Comprehensive Cancer Network (NCCN) guideline recommends induction chemotherapy followed by radiotherapy (RT) with or without chemotherapy or systemic therapy for oligometastatic disease (13). GP chemotherapy is the preferred first-line regime for patients with widely disseminated disease and good performance status. NCCN recently added GP plus a programmed cell death 1 (PD-1) inhibitor (pembrolizumab or nivolumab) as an “other recommended regimen” for the first-line treatment of recurrent and metastatic NPC, even though no phase 3 data supported the use of these two immune-checkpoint inhibitors (13). Definitive locoregional RT (LRRT) can be considered following a good response to systemic therapy. The European Society of Medical Oncology (ESMO) guideline recommends chemotherapy followed by radiation to the primary tumor and involved lymph nodes for newly diagnosed metastatic disease (14). Consideration should be given to adding immunotherapy to systemic chemotherapy and using it as maintenance therapy as first-line therapy (15).

Controversy about the subcategorization of M1 disease

Many studies have attempted to subcategorize metastatic NPC (*Table 2*). The prognoses of patients with metastatic NPC depend upon disease burden, locations of involvement, and timing of metastasis. Patients with oligometastatic disease had significantly better clinical outcomes than patients with widely disseminated NPC (28). The Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) level, a surrogate marker of the tumor load, also plays an important

Table 1 Search strategy summary for literature included in the review

Items	Specification
Date of search	10 March 2023
Databases and other sources searched	PubMed, ClinicalTrials.gov, Chinese Clinical Trial Register
Search terms used	Search: "nasopharyngeal carcinoma" AND "metastasis" AND "subdivision", Filters: Filters: Full text, from 2000–2023
	Search: "metastatic nasopharyngeal carcinoma", Filters: Clinical Trial, Randomized Controlled Trial, from 2000–2023
	Search: "metastatic nasopharyngeal carcinoma" AND "metastasis" AND "locoregional radiotherapy" OR "local treatment", Filters: Full text, from 2000–2023
	Keywords: "metastatic nasopharyngeal carcinoma", "radiotherapy", "interventional study"
Timeframe	January 2000 to March 2023
Inclusion and exclusion criteria	Prospective and retrospective trials on subcategorization of metastatic NPC and treatment of newly diagnosed metastatic NPC were included. Studies involving only pretreated patients were excluded. Articles in languages other than English were excluded
Selection process	The authors conducted literature search and reviewed the selected literature
Any additional considerations	Articles were also identified by examining references of pertinent publications and prior knowledge of key studies

role in predicting the prognosis of patients with distant metastasis (29). Elevated levels of plasma EBV-DNA, along with certain clinical parameters such as the number of metastatic lesions, have been found to predict poor prognosis in patients (21-23,25-27). On the other hand, faster clearance rates of plasma EBV-DNA are associated with better treatment response and patient outcomes (30). However, it should be noted that a significant proportion (12% to 29%) of confirmed NPC cases have undetectable EBV-DNA (31), and there is no universal cutoff value for patient segregation based on plasma EBV-DNA levels. As a result, incorporating plasma EBV-DNA levels into the TNM staging system poses a challenge. Furthermore, patients with lung metastasis alone generally have a more favorable prognosis compared to those with metastasis in other organs, as evidenced by the Hong Kong NPC Study Group study, showing a median overall survival (OS) of 3.9 years for patients with metastases to lung versus ≤1.9 years to other sites, respectively (32). A similar observation was recently reported by Chee *et al.*, patients with lung metastases only had the best prognosis with an OS of 51.1 months. In contrast, those with liver or abdominal metastases had the worst clinical outcomes, with an OS of 15.4 and 8.8 months, respectively (28). Regarding the timing of M1 disease, patients with synchronous metastases at presentation had better OS than those with metachronous metastases (33). In summary, most studies proposed an M1 subcategorization system based on the number of metastatic lesions and sites, liver involvement, and EBV-DNA as key prognosticators. Given the variety of definitions proposed, no standard classification is concluded. Nevertheless, it highlighted the importance of characterizing M1 patients according to the underlying risk profile and providing individualized treatment strategies.

The evolution of 1st line systemic therapy for *de novo* metastatic NPC

NPC is a chemo-sensitive tumor; however, head-to-head trials in patients with metastatic NPC were lacking in the past, and most chemotherapy regimens were based on phase 2 trials. The most frequently used regimen was cisplatin plus continuous intravenous infusion of fluorouracil (PF), with an overall response rate (ORR) of 76% (34). Other active agents included taxane, gemcitabine, capecitabine, vinorelbine, and some older drugs, such as bleomycin, epirubicin, and cyclophosphamide (35-40).

The preferred first-line chemotherapy regimen recommended by NCCN guideline, was based on a phase III randomized controlled trial demonstrated that GP was superior to the traditional regimen of PF in 2016 (7). Patients who received GP had longer progression-free

Table 2 Summary of proposed M1 subcategorizations

Author	Year	Proposed subdivision	No. patients	Survival outcome
Shen *et al.* (16)	2015	M1a: single extra-liver metastasis M1b: single liver metastasis or multiple extra-liver metastases M1c: multiple liver metastases	505	Median OS: M1a: 46 months M1b: 25.1 months M1c: 18.3 months 3-year OS rates: M1a: 62.1%; M1b: 36.1%; M1c: 17.9%; P=0.001
Jiang *et al.* (17)	2016	The classifier uses three clinical parameters and seven hematological markers to classify M1a and M1b	347	2-year OS rates: M1a: 71.4%; M1b: 18.8%, P<0.001
Shen *et al.* (18)	2016	M1a: a solitary lesion confined in a single organ or site M1b: multiple lesions confined in a single organ or site M1c: multiple metastatic sites	1,172	M1b *vs*. M1a: HR (95% CI): 2.28 (1.71, 3.05) M1c *vs.* M1a: HR (95% CI): 3.65 (2.75, 4.85)
Tian *et al.* (19)	2016	M1a: single-organ metastases or oligometastases M1b: multi-organ metastases or ≥6 lesions	263	5-year OS rates: M1a: 38.7%; M1b: 7.0%, P<0.01
Zou *et al.* (20)	2017	M1a: oligometastases with no hepatic metastasis M1b: multiple lesions with no hepatic metastasis M1c: presence of liver lesions	Training: 462 Internal validation: 272 External validation: 243	3-year OS rates: M1a: 54.5% to 72.8% M1b: 34.3% to 41.6% M1c: 22.6.0% to 23.6% P<0.001
Sun *et al.* (21)	2019	Low risk: ≤3 lesions with undetectable EBV DNA after PCT Intermediate risk: >3 lesions and undetectable EBV DNA after PCT; or ≤3 lesions and detectable EBV DNA after PCT High risk: >3 lesions and detectable EBV DNA after PCT	226	3-year OS rates: Low risk: 80% Intermediate risk: 54.9% High risk: 37.8% 5-year OS rates: Low risk: 66.7% Intermediate risk: 41.3% High risk: 11.6%
Zheng *et al.* (22)	2020	M1a: oligometastases with low EBV DNA M1b: multiple metastatic lesions with low EBV DNA M1c: high EBV DNA without liver involvement M1d: high EBV DNA with liver involvement	Training: 613 Internal validation: 204	3-year OS rates: M1a: 49.9%; M1b: 33.4% M1c: 22.6%; M1d: 6.7% P<0.001
Yang *et al.* (23)	2021	Low risk: single organ involvement with ≤5 lesions and EBV DNA ≤25,000 copies/mL Intermediate risk: single organ involvement with ≤5 lesions and EBV DNA >25,000 copies/mL High risk: >5 lesions or multi-organ involvement or both	498	OS differences with or without LRRT Low-risk subgroup: P=0.039 Intermediate-risk subgroup: P=0.010 High-risk subgroup: P=0.076

Table 2 (*continued*)

Table 2 (*continued*)

Author	Year	Proposed subdivision	No. patients	Survival outcome
Chan *et al.* (24)	2022	M1a: no co-existing liver-bone metastases M1b: co-existing liver-bone metastases	Training: 120 Validation: 63	Median OS in training cohort: M1a: 39.5 months M1b: 23.7 months, P=0.004 Median OS in validation cohort: M1a: 47.7 months M1b: 16.0 months, P=0.008
Chan *et al.* (25)	2022	Set 1: M1a: no co-existing liver-bone metastases M1b: co-existing liver-bone metastases Set 2: M1a: EBV DNA ≤2,500 copies/mL M1b: EBV DNA >2,500 copies/mL	69	Median OS in set 1: M1a: 28.1 months M1b: 19.2 months, P=0.023 Median OS in set 2: M1a: 44.2 months M1b: 19.7 months, P<0.001
Qiu *et al.* (26)	2022	M1a: low risk, low PPS and absence of hepatic involvement M1b: intermediate risk, low PPS and presence of hepatic involvement, high PPS and low EBV DNA M1c: high risk, high PPS with high EBV DNA	586	3-year OS rates: PCT + LRRT *vs.* PCT M1a: 77% *vs.* 55%, P=0.00033 M1b: 50% *vs.* 48%, P=0.103 M1c: 20% *vs.* 22%, P=0.224
Yao *et al.* (27)	2023	Low risk: ≤4 lesions in organs other than the liver Intermediate risk: ≤4 lesions involving the liver or >4 lesions with EBV-DNA <62,000 copies/mL High risk: >4 lesions with EBV-DNA >62,000 copies/mL	Training: 264; validation: 298	3-year OS rates: Low risk: 80.4% Intermediate risk: 42.0% High risk: 20.4% P<0.05

OS, overall survival; HR, hazard ratio; LRRT, locoregional radiotherapy; EBV-DNA, Epstein–Barr virus DNA; PCT, palliative chemotherapy; PPS, PET-CT parameter score.

survival (PFS) and OS than those who received PF. After a median follow-up time of over 60 months, the median OS was 22.1 months with GP versus 18.6 months with PF. The 5-year OS rate in the GP arm was more than double that of the PF arm (19.2% *vs.* 7.8%) (41). Two recent randomized phase III trials (JUPITER-02 and CAPTAIN-1st) further demonstrated an improvement in PFS when anti-PD-1 immune checkpoint inhibitors (toripalimab or camrelizumab) were added to first-line treatment with GP, followed by maintenance immunotherapy (8,9). Key results are summarized in *Table 3*. Adding toripalimab or camrelizumab to GP as the first-line therapy for metastatic NPC reduced the risk of cancer progression or death by nearly half, as evidenced by hazard ratios (HRs) of 0.52 and 0.54, respectively. Pending full publication of RATIONALE-309, tislelizumab is the third PD-1 inhibitor to show PFS benefit when combined with GP (42). This study also provided evidence on optimal treatment-sequencing. PFS after next-line treatment (PFS2) was not reached at the time of data cutoff for tislelizumab plus chemotherapy versus 13.9 months for placebo plus chemotherapy with a 62% reduction in risk of disease progression on first subsequent therapy or death (10). Although the OS data from these three phase 3 trials are not yet mature, the PFS, as a surrogate for survival, provided an early indication of survival benefit. We recommend adding a PD-1 inhibitor to chemotherapy every 3 weeks for up to six cycles, followed by maintenance therapy with a PD-1 inhibitor as first-line treatment for eligible patients with *de novo* metastatic NPC. Several phase 3 clinical trials are ongoing evaluating the efficacy and safety of other anti-PD1 and anti-CTLA4 monoclonal antibodies (*Table 4*).

Table 3 Key randomized phase III trials evaluating 1st line systemic therapy for metastatic nasopharyngeal carcinoma

Trial	Year	Regime	No. patients	Survival outcome
GEM20110714 (7,41)	2016, 2021	Gemcitabine + cisplatin *vs.* fluorouracil + cisplatin	362	Median PFS: 7.0 *vs.* 5.6 months
				HR (95% CI), 0.55 (0.44–0.68), P<0.0001
				Median OS: 22.1 *vs.* 18.6 months
				1-year OS rate: 79.9% *vs.* 71.8%
				3-year OS rate: 31.0% *vs.* 20.4%
				5-year OS rate: 19.2% *vs.* 7.8%
JUPITER-02 (8)	2021	Toripalimab + gemcitabine + cisplatin *vs.* Gemcitabine + cisplatin	289	Median PFS: 11.7 *vs.* 8.0 months
				HR(95% CI), 0.52 (0.36–0.74), P=0.0003
CAPTAIN-1st (9)	2021	Camrelizumab + gemcitabine + cisplatin *vs.* gemcitabine + cisplatin	263	Median PFS: 9.7 *vs.* 6.9 months
				HR (95% CI), 0.54 (0.39–0.76), P=0.0002
RATIONALE-309 (10,42)	2021	Tislelizumab + gemcitabine + cisplatin *vs.* gemcitabine + cisplatin	263	Median PFS: 9.6 *vs.* 7.4 months, P<0.0001
				HR (95% CI), 0.50 (0.37–0.68)
				Median PFS2 and OS are not reached
				PFS2: HR (95% CI), 0.38 (0.25–0.58)
				OS: HR (95% CI), 0.60 (0.35–1.01)

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.

Value of adding "radical" locoregional RT to chemotherapy

The natural course of patients with metastatic NPC is commonly perceived as governed by distant disease, and the primary treatment has been palliative systemic therapy. Increasing evidence suggests that LRRT contributes to improved clinical outcomes in patients who responded well to chemotherapy. To date, one phase III randomized controlled trial has evaluated the efficacy and safety of adding LRRT to backbone chemotherapy in *de novo* metastatic NPC (11). Patients eligible for LRRT were those who achieved partial response (PR) or complete response (CR) after 3 cycles of PF. Additional LRRT reduced the risk of progression by 64% and the risk of death by 58% at 2 years. The majority of patients (69.8%) included in this study had more than 3 metastatic lesions. In addition to the anticipated decrease in locoregional relapses, the rate of distant metastatic recurrences was reduced following LRRT (54.0% *vs.* 68.3%). The study delivered "radical" doses of 70 Gy to the primary tumor and the retropharyngeal lymph nodes, and 60–66 Gy to the cervical lymph nodes. 16.4% of patients had a CR on completion of radiotherapy. Notably, no survival benefit was observed in patients who are not chemo-sensitive, including those who progressed between 3–6 cycles despite initial response.

Several retrospective trials have reached similar conclusions (*Table 5*). In addition, it was demonstrated that patients who received a dose greater than 65 Gy had better survival outcomes compared to those who received less than 65 Gy (43). No survival benefit was seen with an RT dose of less than 50 Gy (45). Patients with a single organ metastasis are anticipated to survive longer than those with multiple organ metastases. Yet, patients with multiple metastases also benefited from the addition of LRRT. In contrast, those with liver involvement, regardless of metastatic lesions, did not have a substantial improvement in OS with additional LRRT (20). Consistent with previous findings, the absence of liver involvement and oligometastases were strong predictors of survival (48). Regarding treatment sequencing, concurrent chemoradiation or induction chemotherapy followed by RT offered significant survival advantages over chemotherapy alone (HR 0.629 and 0.573, respectively) (45). RT followed by adjuvant chemotherapy had no survival advantage over chemotherapy alone (45). The patients who underwent LRRT plus systemic chemotherapy exhibited

Table 4 Ongoing phase III trials evaluating 1st line systemic therapy for de novo metastatic nasopharyngeal carcinoma

Trial	Enrollment	Treatment
NCT05294172	291	KL-A167 Injection + cisplatin + gemcitabine *vs.* cisplatin + gemcitabine
NCT04974398	298	Penpulimab (AK105) + cisplatin + gemcitabine *vs.* cisplatin + gemcitabine
NCT04458909	316	Nivolumab + cisplatin or carboplatin + gemcitabine *vs.* cisplatin or carboplatin + gemcitabine
NCT05576272	460	QL1706 + gemcitabine + cisplatin *vs.* camrelizumab + gemcitabine + cisplatin
NCT04890522	622	5-Fluorouracil + toripalimab (JS001) + cisplatin *vs.* gemcitabine + toripalimab (JS001) + cisplatin
NCT03924986	256	Tislelizumab + cisplatin + gemcitabine *vs.* cisplatin + gemcitabine
NCT02633176	120	Cetuximab + cisplatin + docetaxel *vs.* cisplatin + docetaxel
NCT05854849	244	Gemcitabine + Camrelizumab + apatinib *vs.* gemcitabine + camrelizumab + cisplatin
NCT03581786	289	Toripalimab + cisplatin + gemcitabine *vs.* cisplatin + gemcitabine

the highest survival rate compared to those who underwent LRRT or systemic therapy alone (44). The 5-year survival rate improved by about 17% with induction chemotherapy following concurrent chemoradiation compared to induction chemotherapy following RT alone (48). The 5-year OS rate improved by nearly 20% in patients receiving 4–6 cycles compared to those receiving only 1–3 cycles of chemotherapy (48). However, chemotherapy over 6 cycles did not prolong survival (44). Therefore, we recommend the use of 4–6 cycles of induction systemic therapy followed by LRRT with a "radical" dose of 66–70 Gy, preferably with concurrent chemotherapy if patients' tolerance allowed, in those who responded well to induction chemotherapy (undetectable EBV DNA or CR/PR) or those with oligometastases.

Value of local treatment to metastatic sites

The number of metastases reflects the biological progression of the tumor. Curative treatments have been successfully contemplated in patients with metastatic disease that is not widespread (49). Emerging evidence has supported the value of local treatment, usually by ablative methods, to metastatic sites in oligometastatic diseases, such as non-small cell lung cancer and colon cancer (50,51). A randomized open-label phase 2 study assessed the value of stereotactic ablative radiotherapy (SABR) in patients with a controlled primary tumor and oligometastases (52). Median overall survival time was longer with SABR (41 *vs.* 28 months; P=0.090). The 5-year OS rate reached 42.3% in the SABR group versus 17.7% in the control group (P=0.006). The 5-year PFS rate remained not reached in the SABR arm after a median follow-up of 51 months (53). This study had a high proportion of breast, colorectal, lung, and prostate cancers. Nevertheless, this work heralds the advent of a new therapy paradigm that could shift the clinical goal from control to cure in patients with metastatic disease.

To date, there is limited but promising evidence supporting the use of local treatment for metastatic sites for NPC. *Table 6* summarizes the retrospective trials evaluating the local treatment of metastatic lesions. In those with less than 5 pulmonary lesions, radiofrequency ablation (RFA) and surgical resection doubled the median OS compared to no local treatment (56). The addition of RT to chemotherapy increased the local control rate of distant metastases by 34.2%, while surgery plus chemotherapy increased it by 42.6% (54). Although liver metastases generally have a poor prognosis, local treatment of liver lesions following radical treatment of the primary tumor increased median OS from 16.5 to 48.1 months (55). Moreover, combined RFA and chemotherapy reduced the risk of death and progression in NPC patients with oligometastasis in the liver by 47% and 40%, respectively (58). In another report, 7 out of 15 patients who underwent partial hepatectomy achieved long-term survival over 3 years (57). Furthermore, survival benefits were not limited to patients with oligometastases, as patients with greater than 5 metastases or greater than 2 metastatic sites might still benefit from high-dose RT (60).

Regarding the optimal radiation dose in treating distant metastases, patients treated with an equivalent dose at 2 Gy (EQD2) of ≥60 Gy had longer OS compared to those with EQD2 <60 Gy (59,60). A fractionated dose of ≤2 Gy increased the bone relapse-free survival rate (88.5% *vs.* 81.3%, P=0.026). For patients with sclerotic bone metastases, radical irradiation substantially reduced

Table 5 Retrospective studies evaluating survival benefits by adding locoregional RT/CRT to chemotherapy

Author	Duration	Treatment	No. patients	Survival outcome
Lin *et al.* (43)	1995–2002	Chemotherapy + local regional RT + local treatment to metastatic lesions	105	Median OS: 25 months 2-year OS rate: 50% 5-year OS rate: 17%
Chen *et al.* (44)	2001–2009	Chemotherapy + local regional RT *vs.* local regional RT alone	408	Median OS: 34 *vs.* 17.7 months, P<0.001
Rusthoven *et al.* (45)	2004–2013	Chemotherapy + local regional RT *vs.* chemotherapy alone	718	Median OS: 21.4 *vs.* 15.5 months 5-year OS rate: 28% *vs.* 10% HR (95% CI), 0.68 (0.55–0.84), P<0.001
Verma *et al.* (46)	–	Chemotherapy + local regional RT *vs.* chemotherapy alone	555	Median OS: 25.8 *vs.* 13.7 months, P<0.001
Zou *et al.* (20)	2000–2010	Chemotherapy + local regional RT *vs.* chemotherapy alone	Training: 462 Internal validation: 272 External validation: 243	M1b: HR (95% CI), 0.61 (0.33–0.78), P=0.005 M1c: HR (95% CI), 1.81 (0.82–4.03), P=0.144
Du *et al.* (47)	2008–2018	Chemotherapy + local regional RT	118	5-year PFS: 34.2% 5-year OS: 44% 5-year DMFS: 41.1% 5-year LRFS: 82.6%
Zheng *et al.* (48)	2000–2017	Chemotherapy + CCRT *vs.* chemotherapy + RT	746	5-year OS rate: 55.7% *vs.* 39.0%, P=0.034 Median DPFS: 29.4 *vs.* 18.7 months, P=0.052

RT, radiation therapy; CRT, chemoradiation; OS, overall survival; HR, hazard ratio; CI, confidence interval; PFS, progression free survival; DMFS, distant metastasis-free survival; LRFS, local, regional recurrence free survival; CCRT, concurrent chemoradiation; DPFS, distant progression-free survival.

the incidence of in-situ relapse, but not for those with osteolytic lesions or soft tissue involvement (59). Given the emerging role of ablative treatment, especially SBRT, in oligometastatic disease in other cancers, there are many ongoing trials studying the combination of systemic therapy and local ablative treatment in metastatic NPC (*Table 7*).

As M1 disease can present in a variety of ways, there is currently no available research regarding the optimal timing of local treatment for distant metastases. Our typical strategy is to offer "upfront" ablative treatment either before or after 1–2 cycles of induction to patients with small oligometastasis, particularly solitary lesions in the liver or lung. This approach helps to prevent difficulties in locating completely regressed lesions after intensive induction therapy. For patients with larger distant lesions (e.g., >5 cm), a "deferred" approach is preferred to allow for downsizing of lesions through induction therapy. In this scenario, regular radiological examinations are necessary.

Other treatment strategies

A retrospective study of 64 patients with *de novo* metastatic NPC who underwent LRRT showed that capecitabine maintenance therapy improved OS for patients with baseline EBV DNA ≤30,000 copies/mL (62). A phase 3 randomized clinical trial recently evaluated this maintenance strategy and found an impressive survival benefit in the capecitabine arm, with a PFS of 35.9 months (63). However, before adopting capecitabine maintenance as the new standard of care, several considerations were suggested (64). First, the trial used paclitaxel, cisplatin, and capecitabine (TPC) as induction chemotherapy, which is not a commonly used first-line regimen. Second, the median PFS in this trial was considerably longer than earlier data reported on capecitabine (65) and immune checkpoint inhibitors (8-10), and it is uncertain whether this difference is due to TPC sensitization. Furthermore, the optimal

Table 6 Studies evaluating local treatment to metastases in addition to systemic chemotherapy

Author	Year	Study	Treatment	No.	Survival outcome
Ma *et al.* (54)	1994–2008	Retrospective	Local RT to lung metastases ± chemotherapy *vs.* operation ± chemotherapy *vs.* chemotherapy alone	105	Local control rate: 53.8% in chemotherapy cohort 88.0% in RT cohort 96.4% in operation cohort, P<0.01
Pan *et al.* (55)	2000–2008	Retrospective	RFA of liver metastases *vs.* no RFA	376	Median OS: 48.1 *vs.* 16.5. months, P=0.016
Pan *et al.* (56)	2000–2009	Retrospective	RFA to lung metastases *vs.* no RFA	480	Median OS: 77.1 *vs.* 32.4 months, P=0.009
Huang *et al.* (57)	1993–2010	Retrospective	Partial hepatectomy *vs.* TACE	30	Median OS: 45.2 *vs.* 14.1 months 1-year OS: 85.7% *vs.* 53.3% 3-year OS: 64.2% *vs.* 26.6% 5-year OS: 40.2% *vs.* 20%, P=0.039 Median PFS: 21.2 *vs.* 4.2 months 1-year PFS: 70% *vs.* 27% 3-year PFS: 53% *vs.* 7% 5-year PFS: 18% *vs.* 0%, P=0.007
Li *et al.* (58)	2003–2011	Retrospective	RFA of liver metastases + chemotherapy *vs.* chemotherapy alone	328	OS: HR (95% CI), 0.53 (0.30–0.93), P=0.025 PFS: HR (95% CI), 0.60 (0.36–0.97), P=0.037
Li *et al.* (59)	2002–2018	Retrospective	Palliative *vs.* radical RT to metastatic bone	300	OS: HR (95% CI), 2.60 (1.40–4.82), P=0.003 PFS: HR (95% CI), 1.57 (1.10–2.24), P=0.013 *In-situ* bone RFS: HR (95% CI), 3.46 (1.57–7.66), P=0.002
Liao *et al.* (60)	2010–2017	Retrospective	Chemotherapy + local treatment to metastatic lesions *vs.* chemotherapy alone	147	Entire cohort: Median OS: 71.7 *vs.* 16.2 months 3-year OS rate: 55.4% *vs.* 25.9%, P<0.001 PSM cohort: Median OS: 55.6 *vs.* 17.6 months 3-year OS rate: 50.6% *vs.* 32.55, P=0.011
Lin *et al.* (61)	2007–2017	Retrospective	Chemotherapy + LRRT + local RT *vs.* chemotherapy + LRRT	131	Median OS: 83 *vs.* 45 months Median PFS: 60 *vs.* 36.5 months, P>0.05

RT, radiation therapy; RFA, radiofrequency ablation; TACE, transcatheter hepatic artery chemoembolization; HR, hazard ratio; CI, confidence interval; LRRT, loc-regional radiation therapy; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; RFS, relapse-free survival; PSM, propensity score matching.

Table 7 Ongoing trials

Trial	Phase	Enrollment	Treatment
NCT05417139	II	43	Sintilimab + GP + LRRT
NCT05385926	II	34	Toripalimab + GP + RT
NCT04351282	II	43	Chemotherapy ± immunotherapy + LRRT + SBRT for oligometastatic lesions
NCT05520814	II	50	Immunotherapy + RT for metastatic lesions
NCT05431764	II	38	Camrelizumab + LRRT + SBRT for all oligometastatic lesions
NCT03129412	II	64	Chemotherapy + LRRT + local treatments for oligometastatic lesions
NCT04517214	II	126	Toripalimab + GP + LRRT + maintenance toripalimab and capecitabine
NCT05652192	II	37	Tislelizumab + chemotherapy + LRRT+ SBRT for metastatic lesions
NCT04398056	II	22	Toripalimab + chemotherapy + LRRT
NCT04421469	II	39	Triprilimab + nedaplatin f + local treatment of metastatic lesions
ChiCTR2100046735	II	118	Carrelizumab + GP + LRRT
ChiCTR2100045190	II	32	GP + anlotinib + toripalimab + SBRT

GP, gemcitabine plus cisplatin; LRRT, locoregional radiotherapy; RT, radiotherapy; SBRT, stereotactic body radiation therapy.

dose of oral capecitabine needs to be explored, and as the number of first-line therapeutic options increases, treatment sequencing may become crucial. Mature OS data is needed to compare maintenance use of capecitabine with drug holiday and later rechallenge of chemotherapy. Further research is also warranted to assess the value of adding capecitabine to PD-1 inhibitor maintenance, especially when patients were initially treated with GP and a PD-1 inhibitor.

Recommendation on treatment strategy for *de novo* metastatic NPC

Treatment for *de novo* metastatic NPC should be individualized. *Figure 1* depicts a summary of treatment recommendations. For patients with oligometastases, upfront ablative treatment of metastatic sites should be considered before systemic treatment, whenever possible. Chemotherapy and immunotherapy, followed by radical locoregional RT with concurrent cisplatin are recommended. For patients with widespread metastases, systemic therapy with chemotherapy and immunotherapy should be offered in eligible patients as first-line treatment. High dose locoregional RT with concurrent chemotherapy and local ablative treatment to distant metastases are recommended in those who achieve completed or PR after systemic treatment. Aggressive treatment with radiotherapy is not recommended in those who respond poorly to first-line systemic therapy. Maintenance therapy with checkpoint inhibitor or capecitabine may be considered for both groups.

Strengths and limitations

In this review, the risk stratification of metastatic NPC is examined, and a summary of research on systemic and local therapies, including radical locoregional radiotherapy to primary cancers and cervical nodes, as well as aggressive local ablative therapy to metastatic sites is presented. It highlights the importance of risk stratification for metastatic NPC and recommends an intensified treatment strategy for metastatic NPC. A key limitation is that most studies evaluating the role of radical locoregional radiotherapy and local ablative treatments were retrospective in nature. In addition, the present review does not provide a systematic evaluation of the quality of the included studies due to lack of high-quality prospective studies on the local treatment of metastatic NPC.

Conclusions

The natural history of metastatic NPC is highly variable, with several crucial factors impacting the prognosis, including tumor burden, EBV-DNA levels, location

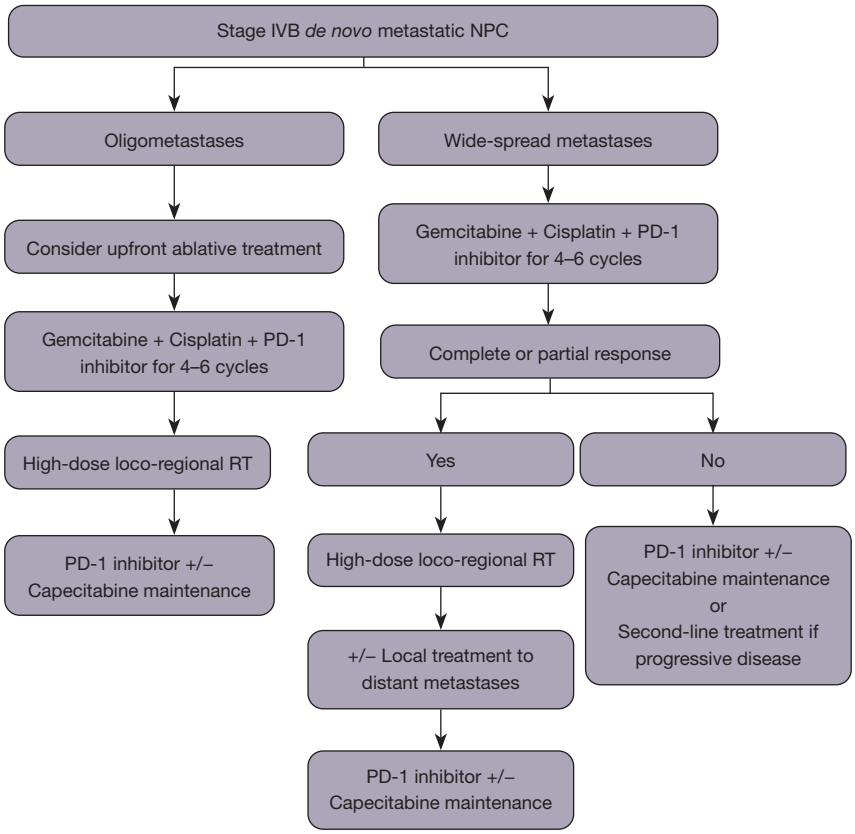

Figure 1 Summary of recommendations on treatment strategy for *de novo* metastatic NPC. NPC, nasopharyngeal carcinoma; PD-1, programmed cell death 1; RT, radiotherapy.

of involvement, timing of metastasis, and treatment strategies. Therefore, treatment for *de novo* metastatic NPC should be individualized. Intensifying systemic treatment with immunotherapy has been shown to improve overall control. Additionally, locoregional radiation therapy to the primary tumor and regional nodes can offer a survival benefit for good responders to systemic treatment. In cases of oligometastases, aggressive treatment through ablative means to distant sites should be explored whenever possible. Further studies on maintenance therapy using PD-1 inhibitor and/or capecitabine, and determination of optimal duration, are warranted.

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Footnote

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