Role of Primary and Metastasis Directed Radiotherapy in Metastatic Nasopharyngeal Cancer

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ABSTRACT

Background: Role of primary and metastasis directed radiotherapy established for several cancer sites. While it is not yet clarified in metastatic nasopharyngeal cancer (mNPC).

Material and method: A research of relevant studies published in the literature through Pubmed between 2000 and 2020 in English language. The following key words used; metastatic nasopharyngeal cancer, role of radiotherapy in metastatic nasopharyngeal cancer, metastasis directed radiotherapy, primary treatment in metastatic nasopharyngeal cancer.

Results: Fifteen retrospective studies, one meta-analysis and one randomized controlled trial (RCT) found. All retrospective studies showed a significant overall survival (OS) benefit of primary radiotherapy in addition to induction chemotherapy. This confirmed by RCT and the meta-analysis. Number of metastasis, response to chemotherapy and EBV DNA level could be part of a prognostic scoring system to indicate primary treatment.

Conclusion: primary and metastasis directed radiotherapy has a role in metastatic nasopharyngeal cancer. Further RCT are necessary to establish this indication.

Keywords: *Local Treatment, Metastatic, Nasopharyngeal Carcinoma, Radiotherapy, Metastasis Directed Radiation Therapy*

Introduction

Nasopharyngeal carcinoma, represent 0·7% of worldwide cancers diagnosed in 2018. Its geographical distribution is heterogeneous; more than 70% of new cases are in east and Southeast Asia (Bray *et al*., 2018). Thirty to 60% of patients with locally advanced disease will develop distant metastasis within five years of diagnosis, while 5 to 8% present with distant metastasis at diagnosis (Khanfir *et al*., 2007). Metastatic cancer is a heterogeneous entity, with different prognosis and treatment outcome. All the efforts developed to identify a subgroup of patients who will beneficiate

from radical management combining systemic and local treatments. The role of primary and metastasis directed radiotherapy in metastatic nasopharyngeal cancer (mNPC) treatment is not yet established. This document will try to clarify this issue and answer several questions: i Is there a role for primary treatment in metastatic nasopharyngeal cancer? ii Shall we select candidates for primary radiotherapy in metastatic nasopharyngeal cancer population? iii Is there a role for metastasis directed therapy in metastatic nasopharyngeal cancer?

Methodology

A PubMed research of relevant studies published in the literature between 2000 and 2020, English language. The following key words used; metastatic nasopharyngeal cancer, role of radiotherapy in metastatic nasopharyngeal cancer, metastasis directed radiotherapy, local treatment in metastatic nasopharyngeal cancer. Fifteen retrospective studies, one meta-analysis and one randomized controlled trial (RCT) found. These studies stratified according to study type and year of publication. Data extracted about studied population, Pre-radiation treatment, nasopharynx radiation treatment, metastasis directed treatment, follow up time and results about OS and independent prognostic factors influencing OS.

Rational of Primary Treatment in Metastatic Cancer

Several theories were the basis of the studies focusing on the role of local treatment in metastatic cancers. For some authors, the primary tumor is the predominant source of metastasis through circulating tumor cells. Removing the primary tumor will eliminate the primary source of the dissemination of metastatic cells and will allow an improved response to systemic treatment (Kaplan *et al*., 2006). For others, the primary site is a sanctuary site harboring resistant and lethal clones responsible of progression and metastases (Powell *et al*., 2002; Tzelpi *et al*., 2011).

Other concepts raised and discussed. “Tumor self-seeding” process in which circulating tumor cells can colonize the primary tumor, resulting a tumor growth and the production of metastatic progenies. [6]. The “premetastatic niche” concept is based on persistence of some molecular features within the primary after systemic treatments, which will promote the growing and invasion of tumor cells in a favorable microenvironment. This concept supported by Tzelepi *et al*., they reviewed prostatectomy specimens one year after treatment with docetaxel and anti-androgen treatment and found three major pathways possibly involved in progression (Tzelpi *et al*., 2011).

Benefit of primary treatment in metastatic cancer is well established in some indications such as ovarian cancer and renal cell carcinoma (Bookman *et al*., 2016; Flanigan *et al*. 2004). While it is still

controversial for other cancer sites (Badwe *et al*., 2015). For metastatic prostate cancer role of primary treatment proved to be beneficial in some selected cases (Parker *et al*., 2018). In metastatic nasopharyngeal cancer, a survival benefit is expected. However, the mechanism remains unknown. One theory explains this benefit by the fact that treating the primary will reduce death by uncontrolled local disease and its impact on the critical organs around it. The other theories joined the self-seeding theory. Treatment of the primary or metastatic foci will reduce number of circulating tumor cells, and remove tumor-promoting factors and immunosuppressive cytokines (Hu *et al*., 2017).

Is There a Role for Primary Treatment in Metastatic Nasopharyngeal Cancer?

The first information about feasibility benefit and selection of cases came from case series studies (Table 1). These studies showed a promising rate of overall survival with primary radiotherapy in addition to systemic treatment. Lin and colleagues analyzed data of 105 mNPC cases, majority of them (85%) had single organ metastasis. Ninety two percent of patients received induction chemotherapy followed by nasopharyngeal and neck irradiation, with a well tolerable treatment. The 2 and 5-year overall survival rates were 50% and 17%, respectively. Overall survival was independently correlated to radiation dose to the primary region (> 65 Gy), and number of organs with metastases (single vs. multiple) (Lin *et al*., 2012). Comparable results about benefit of local radiation to the primary in case of limited number of metastasis (single or less than 5) showed by other studies (Yin *et al*., 2017; Hu *et al*., 2015; Tian *et al*., 2016; Zeng *et al*., 2014). Moreover, Shuang and his colleagues designed a study concerning 39 oligo-metastatic mNPC (no more than five metastatic lesions and no more than two metastatic organs). Association of chemotherapy and radiotherapy showed more than 50% of 5 years OS and progression free survival (PFS). Survival was significantly better if less than 3 metastatic lesions (Shuang *et al*., 2019). These initial studies confirmed feasibility and safety of combining radiation to chemotherapy for mNPC, with promising results.

To demonstrate benefit of combined treatment, several authors did retrospective case-control studies (Chen *et al*., 2013; Rusthoven *et al*., 2017; Verma *et al*., 2017; Sun *et al*., 2019; Huang *et al*., 2020; Liao *et al*., 2020; Sun *et al*. 2020; Li *et al*., 2021). Patients in these different studies received induction multi-agents cisplatin-based chemotherapy (various number of cycles), alone or followed by loco-regional radiotherapy (with or without concomitant chemotherapy). Chen *et al*. studied 408 patients with mNPC, most of them (70.1%) had single metastatic site. Chemotherapy alone given to 345 patients, while radiotherapy associated to chemotherapy to 214. A median of 6 cycles Cisplatin-based induction chemotherapy recommended for all patients. Median radiation dose of 70-72 Gy at the primary site using conventional or Intensity modulated radiation therapy (IMRT). Median follow-up time was 19.2

months, survival was significantly better in the group undergoing combined treatment in comparison to chemotherapy alone. Both locoregional radiotherapy and systemic chemotherapy were significant independent prognostic factors of overall survival (Chen *et al*., 2013). The largest retrospective study by Huang *et al*. about 821 patients, 43.7% were oligometastatic and 56.3% with multiple metastasis. 39.0% patients received systemic chemotherapy alone, while 56.8% underwent systemic chemotherapy-combined to locoregional radiotherapy. Patients received initially a median of 6 cycles of platinum-based chemotherapy. Radiotherapy dose of 68 Gy over 30 fractions and 6 weeks. With a median follow-up time of 22.40 months, chemotherapy-sequential locoregional radiotherapy to the nasopharyngeal primary tumor site were associated with a significantly increased 3-year overall survival rate (Huang *et al*., 2020). Li *et al* studied 460 de-novo mNPC. Combined treatment delivered to 244 patients, 77.5% had single metastatic site vs 22.5% with multiple sites. Chemotherapy without radiotherapy to 216, from whom 52.8% with single metastatic site vs 47.2% with multiple. Treatment plan included baseline cisplatin-based chemotherapy followed by radiotherapy for the combined treatment population. Radiation to the primary 66 to 72 Gy over 30 to 33 fractions. This study had the longest median follow-up time of 64.1 months. Overall survival was significantly longest in the chemotherapy-radiotherapy group Sun *et al*., 2020). Similar results showed in other retrospective studies (Table 1). The unique multicenter Phase 3 Randomized Clinical Trial conducted by You *et al*. about 126 Patients with mNPC with complete or partial response following 3 cycles of cisplatin and fluorouracil chemotherapy. These patients equally randomized to chemotherapy plus radiotherapy or chemotherapy alone. Among them 39 had 1-2 metastatic lesions and 87 equal or more than 3 lesions. The chemotherapy regimens were fluorouracil continuous intravenous infusion and intravenous cisplatin administered every 3 weeks for 6 cycles. Prescribed doses of IMRT were 70 Gy to primary gross volume including retro pharyngeal nodes, 60 to 66 Gy to gross cervical lymph nodes, 56 to 66 Gy to PTV high risk clinical volume, and 50 to 60 Gy to PTV low-risk clinical target volume, over 33 fractions. Time to start radiotherapy from the end of last chemotherapy cycle was at 21 days. The primary endpoint of the study was overall survival (OS). The secondary endpoint was progression-free survival (PFS) and safety. Median follow-up duration was 26.7 months. Chemotherapy plus radiotherapy improved OS comparing to chemotherapy alone, with a statistically significant difference. Progression-free survival also improved in the chemotherapy plus radiotherapy group compared with the chemotherapy-alone group. No significant differences in acute hematological or gastrointestinal toxic effects observed between the treatment arms. The frequency of acute grade 3 or higher dermatitis, mucositis, and xerostomia was 8.1%, 33.9%, and 6.5% respectively in the chemotherapy plus radiotherapy group. The frequency of late severe grade 3 or higher hearing loss and trismus was 5.2% and 3.4%, respectively, in the chemotherapy plus radiotherapy group (You *et al*., 2020). Recently a meta-analysis of 15 retrospective studies and one randomized controlled trial,

published by Wang and colleagues. The population consisted of 3402 mNPC patients, 1387 chemotherapy alone and 2015 chemotherapy plus loco-regional radiotherapy. Although the presence of some limitations, the superiority in favor of combined treatment was statistically significant without being affected by the heterogeneity of different studies (Wang and Shen, 2021).

Shall We Select Candidates for Primary Radiotherapy in Metastatic Nasopharyngeal Cancer Population?

Role of radiotherapy with chemotherapy in non-metastatic nasopharyngeal cancer established as standard of care (Blanchard *et al*., 2015; Wang *et al*. 2020). However, its possible side effects well-known as well [30]. Offering this treatment to patients without clear benefit, means giving them side effects and deterioration of quality of life only. In the other hand, we have known from the previous studies that a subgroup of metastatic cases will get benefit in term of survival. Since there is no strong evidence about the indication of primary radiotherapy in mNPC, several questions raised in our daily practice about which patient can beneficiate from this treatment i. shall we irradiate oligometastatic cases only? ii. Is the indication of radiotherapy depend on metastasis response to chemotherapy? iii. Is there other biologic factors for selection?

Most of the retrospective studies showed heterogeneity in patient inclusion criteria, especially regarding the number of metastatic lesions or sites. Some authors differentiated their population as single versus multiple metastatic sites or organs. It is important to note the absence of clear definition of the term oligometastatic diseases. In some studies it reflected single metastatic lesion (Hu *et al*. 2015; Tian *et al*., 2016; Chen *et al*., 2013; Sun *et al*., 2019; Huang *et al*., 2020; Li *et al*., 2021), in others single metastatic organ without clear precision about number of lesions (Lin *et al*., 2012; Yin *et al*., 2017; Huang *et al*., 2020; Li *et al*., 2021). In some other studies, there was no definition of the metastatic burden (Hu *et al*., 2017; Rusthvoen *et al*., 2017; Verma *et al*., 2017; Sun *et al*., 2020). However, Shuang *et al*. in their retrospective study focused on 39 newly diagnosed oligo-metastatic nasopharyngeal carcinoma. oligo-metastatic disease defined as no more than five metastatic lesions and no more than two metastatic organs (Shuang *et al*., 2019). Tian *et al*, stratified their studied population according to the number of metastatic sites (single lesion, 2–5 lesions and > 6 lesions). In their conclusion about the benefit of local treatment, they divided the population in two groups: single-organ metastases and 1 to 5 lesions, versus multiple-organ metastases or ≥6 lesions (Tian *et al*., 2016). Toumi and his colleague in a retrospective study about 112 metastatic nasopharyngeal cancer patients, found a better survival for the oligometastatic patients, the one who received primary and metastasis directed irradiation (Toumi *et al*., 2020).

In the randomized controlled study of You *et al*, the authors did not include number of metastatic

sites in their inclusion criteria and not reflected in the results (You *et al*., 2020). Finally, in the meta-analysis of Wang and Shen, could not define the best candidates for primary treatment due to the wide heterogeneity of baseline patient characteristics (Wang and Shen, 2021). It is important to mention that different multivariate analysis of these studies, showed single versus multiple metastatic sites as independent factor for overall survival, with other factors. In controversy, Rusthoven *et al*. showed that the benefits of radiotherapy remained consistent for single versus multi-organ metastases and anatomic sites of metastatic involvement (Rusthoven *et al*., 2017).

About response to chemotherapy, most of the studies reported in their subgroup analysis a significant improvement of survival by radiotherapy of the primary tumor in patients who achieved complete remission (CR), partial remission (PR) or stable disease (SD) of metastatic lesions after chemotherapy. It represented significant independent prognostic factors for overall survival in multivariate analysis (Zeng *et al*., 2014; Chen *et al*., 2013; Sun *et al*., 2020; Li *et al*., 2021). Based on these data You and his colleagues took complete or partial response following 3 cycles of cisplatin and fluorouracil chemotherapy, as one of the inclusion criteria in their randomized controlled study (You *et al*., 2020). In another hand, Rusthoven *et al* showed benefit for primary radiotherapy independently from response to chemotherapy (Rusthoven *et al*., 2017).

About the biologic factors, LDH level and EBV DNA level reported as independent prognostic factors in several publications (Hu *et al*., 2015; Zeng *et al*., 2014; Sun *et al*., 2019; Huang *et al*., 2020; Li *et al*., 2021).

Metastatic site did not appear as independent factor for survival after local radiation therapy in several studies. However, liver metastasis reported in some studies as worse prognostic factor for survival (Tian *et al*., 2016; Zeng *et al*., 2014; Huang *et al*., 2020; Li *et al*., 2021).

Sun *et al*. divided patients in two groups. Low-risk group defined as patients with undetectable EBV DNA level and satisfactory tumor response post-chemotherapy (CR/PR), and high-risk group defined as patients with detectable EBV DNA level or/and unsatisfactory tumor response post-chemotherapy (SD/PD). They found a statistically significant benefit for loco-regional radiotherapy comparing to no radiotherapy, for low-risk group only. For high-risk group no significant difference with or without radiation (Sun *et al*., 2019).

Khanfir and her colleagues did a retrospective study about 95 metastatic patients, in aim to identify prognostic factors. In the univariate analysis worse prognostic factors were: poor performans status (PS) (≥ 1), multiple metastatic sites, multiple bone metastasis, previous chemotherapy, visceral or

node metastasis and non-irradiated metastasis. While in the multivariable analysis, poor PS, multiple metastatic sites, and prior chemotherapy were independently significant poor prognostic factors (Khanfir *et al*., 2007).

To summarize, number of metastasis, response to chemotherapy (CR/PR/SD) and EBV DNA level could be part of a prognostic scoring system to indicate primary treatment.

Is There a Role for Metastasis Directed Therapy in Metastatic Nasopharyngeal Cancer?

Metastasis directed treatment reported in eight retrospective studies (Table 1) and offered to 20-30% of the studied population only. It consisted of radiation therapy, surgery, hyperthermia, percutaneous alcohol injection, radiofrequency ablation (RFA) or interventional embolization. There were no details about metastasis directed radiotherapy, as these studies focused essentially on primary radiotherapy treatment. The reported dose varies from 30 to 66 Gy in 10 to 33 fractions (Tian *et al*., 2016; Zeng *et al*., 2014; Liao *et al*., 2020). There were controversies about its role in improving overall survival. Taking in consideration the recent trials about role of metastasis directed radiotherapy using stereotactic radiation therapy, in the context of oligometastatic cancer (Palma *et al*., 2019), it is judiciable to adopt this concept for oligo-metastatic nasopharyngeal cancer. Further randomized studies are necessary.

Conclusion

The optimal treatment for patients with mNPC remains controversial. Primary and metastasis directed radiotherapy plays a role in improving overall survival of metastatic nasopharyngeal cancer patients. Selection of candidates to this treatment is important. Further randomized trials are necessary to establish a new standard of care in favor of combined systemic and primary treatment. Based on the above-mentioned studies, it is recommended to offer local treatment (primary and metastasis) to patients with good performance, having oligometastatic disease, responding to induction chemotherapy. Regarding patients with high burden disease consider primary radiotherapy in case of complete response to chemotherapy and primary with metastasis directed radiation in case of partial response to systemic treatment.

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Table 1: List of studies about local RT in metastatic nasopharyngeal cancer (mNPC)

Reference Study type	Population	Pre-RT treatment	Nasopharynx RT Treatment	Metastasis directed treatment	Follow up	Results
Lin et al., 2012 Retrospective study *Case Series*	105 mNPC Single organ (85%) Multiple organs (15%)	PF regimen 0 cycle for 9% 1-3 cycles for 81% 4-6 cycles for 11%	conventional 2D RT Median dose of 70 Gy (>65Gy in 68%; <65 Gy in 32%)	radiation therapy, surgery, and/or hyperthermia Percutaneous alcohol injection 47 RT for metastatic sites	22 months (range: 2 to 142 months)	Median survival 25 months. 2 and 5-year OS, 50% and 17% RT dose > 65 Gy to the primary region, and number of organs with Mets (single vs. multiple) independent factors for OS.
Zeng et al., 2014 retrospective study *Case Series*	234 patients 94 CHT 140 CHT+RT Single 22% Multiple 78%	cisplatinum-based CHT. Median 5 cycles	117 patients received a radiation dose >66 Gy and 23 patients <66 Gy. Median dose 70 Gy.	39 RT to bone lesion, 10 radiofrequency ablation (RFA) and 3 interventional embolization of liver lesions, and 3 surgery of lung lesions.	median 22 months (range, 2-125).	2-year, 3-year OS 51.3% and 34.1%, RT of the primary independent significant factor for OS. Significant improved OS by RT of the primary tumor if CR/PR or SD of metastatic lesions after CHT. Significant independent prognostic factors of OS: KPS, liver metastasis, levels of LDH, and multiple Mets. Treatment modality, response to CHT and number CHT cycles.
Hu et al., 2015 Retrospective study *Case Series*	41 mNPC patients: Single 12 (29.3%) Multiple 29 (70.7%)	Median 4 cycles of CHT (range 2–8). PF regimen TP regimen: TPF or DPF regimen	IMRT : Total dose 70–76 Gy concomitant: 14 Cisplatin, 1 Cetuximab, 4 Nimotuzumab	RT and/or surgery for single metastasis cases	median 25 months (range 5–108 months).	Median survival 31.2 months 2 years, 3 years OS: 67.4% and 41.1% Number of metastatic sites (single vs. multiple) and serum LDH level were found to be significant predictors for OS.
Tian et al., 2016 Retrospective study *Case Series*	263 patients with mNPC 103 CHT alone 160 CHT+ RT Single lesion 19.4% 2–5 lesions 37.3% >6 lesions 43.3%	All the patients received cisplatin based CHT,	80.0% of the patients conventional techniques and 20.0% underwent IMRT or 3D conformal RT. Median dose 70 Gy.	45 patients RT to the bone lesions (30–60 Gy/10–30 fractions), 16 received radiofrequency ablation or surgery for liver lesions, and 3 surgery for lung lesions	-	median OS 25 months 5-year OS rate for single-organ Mets and 1 to 5 lesions, was 38.7% compared to 7.0% for multiple-organ Mets or ≥6 lesions. Poor OS if KPS _70, liver Mets, multiple-organ Mets , _6 lesions, no RT to the primary tumor, and <4 CHT cycles. Local therapy for Mets was not significantly associated with OS.
Yin et al., 2017 Retrospective study *Case Series*	32 patients Single 29 (91%) Multiple 3 (9%)	CHT: cisplatin and 5-fluoruouracil Neoadjuvant 78% of patients Adjuvant 38%	RT dose higher than 66 Gy.	31% of patients RT, surgery, or percutaneous alcohol injection	The median follow-up 20 months (range 9–59 months)	The 2-year OS 75.2%, 3-year OS 50.1%. 2-year OS was 67.5% for single- vs 0% for multiple-organ metastasis
Shuang et al., 2018 Retrospective study *Case Series*	39 oligo-mNPC: no more than 5 metastatic lesions and no more than 2 metastatic organs	22 patients: TP or TPF 17 patients: PF or GP	The total dose ≥ 66 Gy 31 patients: Concurrent CHT using platinum	Local treatments to distant Mets delivered to 16 patients	median follow-up of 38 months	3 and 5-year OS 70%, and 57.9%, 3 and 5-year PFS 59%, and 50.9%, Higher survival if no more than three metastasis lesions, more than four cycles CHT

Chen et al., 2013 retrospective *Case-Control Study*	408 patients with mNPC CHT (*n*=345) CHT+RT (*n*=214) Single metastatic sites 70.1% Multiple metastatic sites 29.9% Single metastatic lesions 17.2% Multiple metastatic lesions 82.8%	cisplatin based CHT to all patients Median of 6 cycles.	Median dose of 70-72 Gy	-	median follow-up 19.2 months (range, 0.7–134.1 months)	RT and CHT were significant independent prognostic factors of OS. Nodes classification, CHT, RT, and CR to treatment are independent prognostic factors. 60% reduction in the risk of death with RT
Hu et al., 2017 Retrospective study *Case-Control Study*	679 cases with metastatic NPC 448 patients (66.0%) RT+CHT 231 patients (34.0%) CHT	-	-	-	median follow-up 13 months	OS significantly improved with RT ($p < 0.001$) Cancer-specific survival better with RT ($p < 0.001$).
Rusthoven et al., 2017 Retrospective study *Case-Control Study*	718 cases mNPC 39% CHT-alone 61% CHT + RT	-	Median RT dose 66 Gy IMRT technique for most of patients	-	median follow-up of 4.4 years	median OS 21.4 vs 15.5 months 5-year OS 28% vs 10%; $p < 0.001$); in favor of RT The benefits of RT consistent for single vs multi-organ Mets and anatomic sites of Mets.
Verma et al., 2017 Data base study *Case-Control Study*	555 Patients mNPC 296 (53%) CHT alone 259 (47%) CHT + Rt	-	doses ≥66 Gy to gross disease	-		3 years OS 21% versus 41% 5-year OS 10% versus 34% Median OS of 13.7 and 25.8 months RT was an independent predictor of higher OS (P<.001).
Sun et al., 2019 Retrospective cohort study *Case-Control Study*	502 patients with de novo mNPC 315 patients RT + CHT 187 patients CHT 374 patients (74.5%) had one metastatic site 128 patients (25.5%) more than one metastatic site	PF, GP, TP, TPF regimens Median number of cycles was five	The median radiation dose: 70Gy the primary tumor, 66Gy metastatic lymph node-positive 168 patients received cisplatin based concurrent CHT	-	median follow-up 26.3 months (range, 2–126 months)	Low-risk group (patients with undetectable EBV DNA level and CR/PR to CHT): the 3-year OS 80.4% with RT and 45.3% without RT ($P < 0.001$). High-risk group (patients with detectable EBV DNA level or/and SD/PD post CHT), the 3-year OS with and without RT 40.2% vs. 31.0%, $P = 0.111$.
Huang et al., 2020 retrospective study *Case-Control Study*	821 patients Oligometastatic 359 (43.7%) Multiple metastasis 462 (56.3%) 320 (39.0%) patients CHT alone 466 (56.8%) CHT + RT 35 (4.3%) received RT alone	PF, TP, GP and TPF regimens median number of cycles 6 Monoclonal antibody with epidermal growth factor receptor with CHT in 64 patients	68 Gy/30 fractions/6 weeks	RT, surgery, radiofrequency ablation, or interventional embolization provided to 158 (19.2%) patients.	median follow-up 22.40 months (range, 3.53-113.10 months)	Better OS with CHT+RT ($P < .001$). Significant Better PFS and OS: female patients, ECOG PS score ≤1, S-LDH ≤ 245 IU/L, EBVDNA ≤ 1 × 103copy/mL, N 0-1, oligometastatic, single metastatic organs, absence of liver and distant lymph node metastasis, CR/PR to first line CHT, triplet regimen as a first-line CHT, and local therapy for metastatic lesions

						Metastasis directed RT significantly improved OS and PFS
Liao et al., 2020 retrospective study *Case-Control Study*	150 synchronous mNPC M1a (a single site with a single lesion) M1b (a single site with multiple lesions) M1c (multiple sites with multiple lesions) 117 patients CHT + RT 43 patients CHT	Cisplatin-based CHT: TPF, TP and GP Median number of cycles 4	all patients received IMRT Total dose of 66–74 Gy,	38 cases local RT alone (equivalent 50 Gy), one surgery, and one transarterial chemoembolization	median follow-up was 23.7 months (Range, 1.0 to 107.9 months)	The median OS was 53.2, 25.8, and 18.9 months for M1a, M1b, and M1c, CHT + RT significantly improved OS compared to CHT (p = 0.002). Metastasis directed RT did not improve OS for CHT + RT patients (p = 0.374).
Sun et al., 2020 retrospective study *Case-Control Study*	502 mNPC 308 patients (61.4%) RT + CHT 194 patients (39.6%) CHT	All patients received cisplatin-based combination CHT: PF or GP or TP or TPF	A total dose of 66-70 Gy 168 patients: concomitant cisplatin	-	median follow-up 26.6 months (range, 1–127 months)	3-year OS rate 63.7% with RT vs. 31.8% without RT, P < 0.001) Concurrent CHT did not improve survival (P = 0.141).
Li et al., 2020 retrospective study *Case-Control Study*	460 mNPC CHT+RT: n = 244 CHT: n = 216 Single (S) metastatic site 65.9% Multiple (M) metastatic sites 34.1% CHT+RT: 77.5%S vs 22.5%M CT: 52.8%S vs 47.2%M	The CHT regimens: PF, TP, GP and TPF	The prescribed radiation doses: 66 to 72 Gy in 30 to 33 fractions	-	median follow-up time of 64.1 months	median OS: 60.9 months CHT+RT versus 20.9 months CHT (P < .001) Independent prognostic factors: serum lactate dehydrogenase level, number of metastatic sites, presence of liver metastasis, post treatment EBV DNA level, and response of Mets to CHT
You et al., 2020 Multicenter Phase 3 Randomized Clinical Trial	126 Patients mNPC, CR/PR following 3 cycles of cisplatin and fluorouracil. CHT + RT (n = 63) CHT alone (n = 63) 1-2 metastatic lesions: n=39 ≥ 3 metastatic lesions: n=87	The CHT regimens: PF every 3 weeks for 6 cycles.	IMRT: total dose 70 Gy in 33 fractions Time to RT from the end of CHT 21 days.	None	Median follow-up duration 26.7 (17.2-33.5) months.	CHT + RT improved OS comparing to CHT alone (P = .004). PFS improved in the CHT + RT group compared with the CHT-alone

mNPC: metastatic nasopharyngeal cancer, CHT: Chemotherapy, RT: Radiotherapy, OS: overall survival, CR: complete response, PR: partial response, SD: stable disease, PF: platinum and 5-fluoruouracil, TP: paclitaxel plus platinum, TPF: paclitaxel plus platinum and 5-fluorouracil, SPF: docetaxel plus platinum and 5-fluorouracil, GP: platinum plus gemcitabine, IMRT: intensity modulated radiation therapy, KPS: Karnofsky performance status, PFS: progression-free survival, ECOG PS: Eastern Cooperative Oncology Group performance status, PFS: progression free survival