Supplementary Online Content

You R, Y-P Liu; P-Y Huang, et al. Efficacy and safety of locoregional radiotherapy with chemotherapy vs chemotherapy alone in de novo metastatic nasopharyngeal carcinoma: a multicenter randomized phase 3 clinical trial. *JAMA Oncol*. Published online July 23, 2020. doi:10.1001/jamaoncol.2020.1808

This supplementary material has been provided by the authors to give readers additional information about their work.

Chemotherapy dose modification

To prevent the nephrotoxic effects of cisplatin, we provided 4-day hydration before and during cisplatin administration (D0-D3) along with furosemide (D1) and mannitol (D1-D2). We used antiemetic drugs such as the 5-HT_3-receptor antagonist dexamethasone to prevent chemotherapy-induced nausea and vomiting.

We applied the following recommendations for treatment interruption and dose reduction: the cisplatin dose was decreased to 80 mg/m^2 if the absolute neutrophil count was 1000-1500 cells per μL, platelet count was 50000-75000 per μL, or creatinine clearance was 40-50 mL/min; the cisplatin dose was decreased to 60 mg/m^2 if the absolute neutrophil count was less than 1000 cells per μL or the platelet count was less than 50000 per μL; the 5-fluorouracil dose was decreased to 4 g/m^2 in cases of grade 3 mucositis or diarrhea; and the 5-fluorouracil dose was decreased to 3 g/m^2 in cases of grade 4 mucositis or diarrhea.

Chemotherapy was stopped if the creatinine clearance rate fell below 40 mL/min and/or the bilirubin level was more than 2 times the upper limit of the normal value.

Intensity-modulated radiation therapy (IMRT) planning protocol in this trial

All patients were immobilized in the supine position, using a thermoplastic mask that covered the head, neck, and shoulder regions. Both non-enhanced CT (for dose calculation) and contrast-enhanced CT (for target delineation) images were obtained from the vertex to 2cm below the stemoclavicular joint at 3 mm slice thickness.

Target volumes were defined in accordance with the International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62. The primary nasopharyngeal gross tumor volume (including retropharyngeal nodes; GTVnx) and corresponding cervical lymph node volumes (GTVnd) were determined with magnetic resonance imaging/computerized tomography (MRI/CT) imaging, as well as ^{18}F-fluorodeoxygenase-position emission tomography-CT (^{18}F-FDG-PET-CT) imaging, clinical examination and endoscopic findings before chemotherapy. The high-risk clinical tumor volume (CTV1) was defined by the pre-chemotherapy GTVnx with a 0.5-1.0 cm margin (0.2-0.3 cm posterior margin). The low-risk clinical target volume (CTV2) was defined as CTV1 plus a 0.5-1.0 cm margin (0.2-0.3 cm posterior margin) to encompass the clivus, sphenoid sinus, foramen lacerum, ovale and spinosum, parapharyngeal space, pterygoid fossa, posterior nasal cavity, pterygopalatine fossa, retropharyngeal nodal regions, the involved and at-risk cervical nodal levels, including levels II to Vb, and the supraclavicular fossa. Level Ib was electively irradiated if: 1) level Ib lymph nodes (LNs) were involved, 2) presence of extracapsular extension or size of ≥3 cm nodes at level IIa, and 3) involvement of the soft or hard palate, oral cavity, or ipsilateral nasal cavity. PTV1 and PTV2 were created by adding a circumferential 0.5 cm margin (0.3 cm posterior margin) to CTV1 and CTV2 to compensate for uncertainties in treatment set-up and internal organ motion. A 0.3 cm margin was added to the critical organs (e.g., brainstem and spinal cord) to form the planning organ at risk volume (PRV).

The prescribed doses were 70 Gy to the pre-chemotherapy GTVnx, 60-66 Gy to

the pre-chemotherapy GTVnd (60 Gy and 66 Gy for complete and partial response to six cycles of PF, respectively), 56-66 Gy to PTV1, and 50-60 Gy to PTV2 in 33 fractions, five times per week. The normal tissue dose constraints are listed in Table below. All plans were generated by a team of dosimetrists using a wide-field simultaneous integrated boost technique. In general, when critical normal tissues (e.g. brain stem and spinal cord) were adjacent to the high-dose target volumes, the target volume coverage is compromised to not exceed the dose constraints. All radiotherapy plans underwent quality assurance by independent peer review at each recruiting site. Time to commencement of radiotherapy from the end of chemotherapy cycle was set at 21 days.

Normal tissue dose constrains used for plan optimization.

Structure	**Dose constraints**
Spinal cord	Dmax* ≤45 Gy
Spinal cord_PRV	D1† ≤54 Gy
Brain stem	Dmax ≤54 Gy
Brain stem_PRV	D1 ≤60 Gy
Optic nerves	Dmax ≤54 Gy
Optic nerves_PRV	D1 ≤60 Gy
Optic chiasm	Dmax ≤54 Gy
Optic chiasm_PRV	D1 ≤60 Gy
Temporal lobe	Dmax ≤60 Gy

Temporal lobe_PRV	D1 ≤65 Gy
Lens	Dmean‡ <8Gy
Pituitary	Dmax ≤60 Gy
Eyes	Dmean <35 Gy
Mandible	Dmax ≤70 Gy
Temporomandibular joint	Dmax ≤70 Gy
Parotid	Dmean <26 Gy
Parotid	V30¶ <50%
Cochlea	Dmean <50 Gy
Larynx	Dmean <45 Gy

PRV=planning organ-at-risk volume.

*Maximum point dose to the target volume.

†Dose received by 1% of the target volume.

‡ Mean dose to the target volume.

¶At least 50% of the gland received <30 Gy (was achieved in at least gland)

Figure S1. Median relative dose intensity of cisplatin and 5-fluorouracil in each cycle.

cisplatin (A); 5-fluorouracil (B)

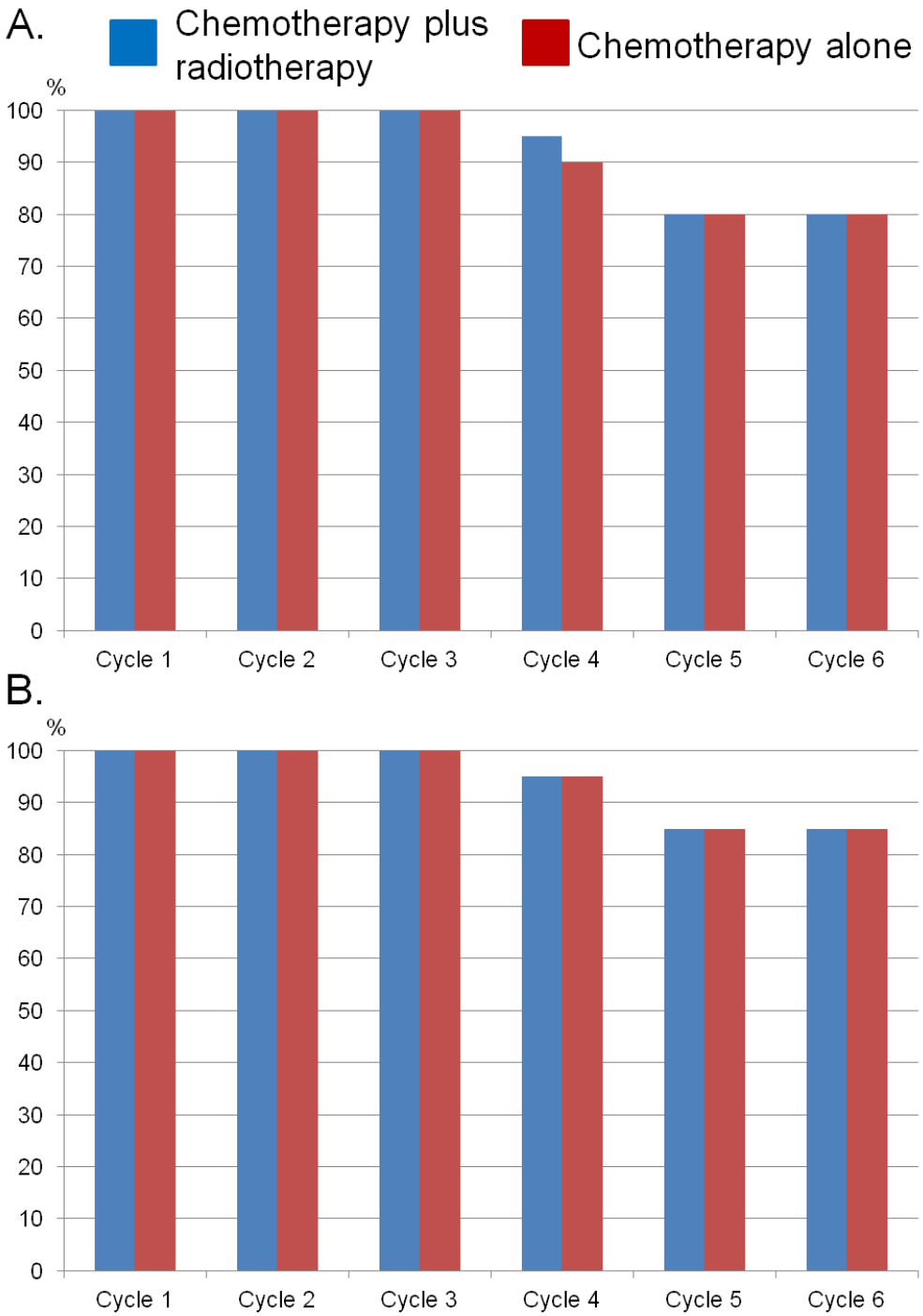
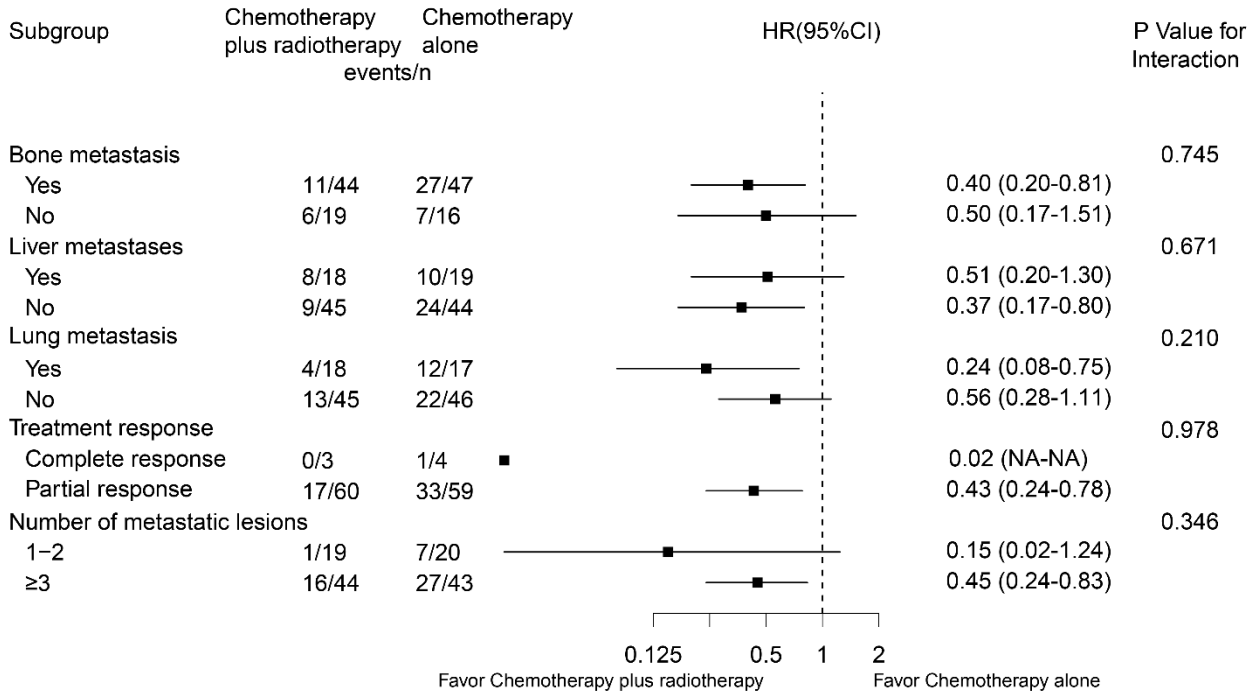


Figure S2. Treatment effect on overall survival within subgroups .



HR*, hazard ratio, which were calculated using the Cox proportional hazards model. CI, confidence interval. NR, not reached.

Table S1. Chemotherapy and local treatment in primary metastasized malignancies.

Study	Cancer type	Study design	Selection critera	Treatment arms	Total number	Survival outcome
Michisch et al (2001)[6]	Renal cell cancer	Multicenter, prospective	All M1 patients	Interferon alone *vs* Interferon+Nephrectomy	84	OS: 7 mo vs 17 mo (HR 0.54, 95%CI, 0.31-0.94; p = 0.03)
Robert et al (2001)[7]	Renal cell cancer	Multicenter, Prospective	All M1 patients	Interferon Alone *vs* Interferon+Nephrectomy	241	OS: 8.1 mo vs 11.1 mo (p=0.012)
Gomez et al (2016)[8]	Non-Small Cell Lung cancer	Multicenter, Prospective	Oligo M1 patients	Maintenance Therapy *vs* Local consolidative therapy	48	PFS: 3.9 mo vs 11.9 mo (HR 0.35, 90%CI, 0.18-0.66 p=0.005)
Thomas et al (2016)[9]	Urothelial Carcinoma of the Bladder	National Cancer Date Base, Retrospective	All M1 patients	Low Intensity Local Teatment *vs* High Intensity Local Treatment	3747	OS: 10.0 mo vs 14.9 mo (HR 0.56, 95%CI, 0.48-0.65, p<0.001)
David et al (2018)[10]	All cancer	Multicenter, Prospective	Oligo M1 patients	Palliate Treatment Alone *vs* Palliate Treatment+SABR	99	OS: 28 mo vs 41 mo (HR 0.57, 95%CI, 0.30-1.10 p=0.09)
Christopher et al (2018)[11]	Prostate cancer	Multicenter, Prospective	All M1 patients	ADT alone *vs* ADT+radiotherapy	2061	OS: 41.6 mo vs 42.5 mo (HR 0.92, 95%CI, 0.80-1.06, p=0.27)

OS, overall survival; PFS, progression-free survival; mo, months; HR, hazard ratio, which were calculated using the Cox proportional hazards model; ADT, androgen deprivation therapy; SABR, stereotactic ablative radiotherapy.

Table S2. Chemotherapy plus local radiotherapy in metastatic NPC.

Study	Study design	Selection critria	Treatment arms	Total number	Survival outcome
Rusthoven et al (2017)[12]	Multi-center registry, Retrospective	All M1 patients	Chemo Alone *vs* Chemo+RT	718	OS: 15.5 mo vs 21.4 mo (Multivariate HR 0.61, 95%CI, 0.51-0.74, p<0.001)
Chen et al (2017)[13]	Multi-center, Retrospective	All M1 patients	Chemo Alone *vs* Chemo + RT (70 Gy)	846	OS: Multivariate HR 0.37, 95%CI, 0.29-0.47, p<0.001
Lin H et al (2013)[14]	Single center, Retrospective	All M1 patients	Chemo Alone *vs* Chemo + RT (68-72 Gy)	226	OS: 16 mo vs 36 mo (HR 0.34, P<0.001)
Chen et al (2013)[15]	Single center , Retrospective	All M1 patients	Chemo Alone *vs* Chemo+RT	345	OS: 26 mo vs 48 mo (HR 0.4, 95%CI, 0.3-0.5, p<0.001)

OS, overall survival; PFS, progression-free survival; mo, months; HR, hazard ratio, which were calculated using the Cox proportional hazards model; chemo, chemotherapy; RT, radiotherapy.

Table S3. Distribution of patients by site of enrollment.

City	Institution	Investigators	Number of randomized patients
Guangzhou	Sun Yat-sen University Cancer Center	Ming-Yuan Chen	122
Guangzhou	Guangdong General Hospital	Hong-Dan Zhang	2
Guangzhou	The First Affiliated Hospital, Sun Yat-sen University	Bi-Xiu Wen	2

Table S4. Members of the Independent Data Monitoring Committee (IDMC).

Position	Name	Job Title	Specialty
Chairman	Yi-Min Liu	Department of Radiotherapy Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University/Professor	Radiotherapy Oncology
Member	Wen Chen	School of Public Health, Sun Yat-sen University/Professor	Health Statistics
Member	Gang Li	Department of Otorhinolaryngology, Southern Medical University Nanfang Hospital/Professor	Otorhinolaryngology
Member	Yi Pan	Department of Radiotherapy Oncology, Guangdong Provincial People's Hospital/Professor	Radiotherapy Oncology
Member	Jing-Qi Chen	The Ethics Committee and Department of Medical Oncology of the Second Affiliated Hospital of Guangzhou Medical University Chairman/Professor	Oncology

Table S5. Members of the ethics committee of SYSUCC

Position	Name	Job Title	Specialty
Chairman	Wang-Qing Peng	Secretary of the Committee for Discipline Inspection	Public Administration
Vice Chairman	Li-Wu Fu	Director of Experimental Research/Professor	Tumor Pharmacology
Member	Zhi-Yong Zhong	Member of the Residents Committee	Public Administration
Member	Wei-wei Cao	Vice Director of the Central Office/Research Associate	Public Administration
Member	Yang Zhang	Department of Medical Oncology/Physician	Clinical Medicine
Member	Hui-Ying Qin	Director of the Nursing Department/Chief Nurse	Nursing
Member	Li Xu	Hepatopancreatobiliary Surgery Department/Professor	Surgical Oncology
Member	Xin-Xi Zhou	Science and Education Division/Associate Researcher	Oncology
Member	Meng-Bin Liu	Director of Guangdong San Huan Hui Hua Law Office/Director, Lawyer	Law
Member	Qiu-Yan Chen	Department of Nasopharyngeal Carcinoma/Professor	Radiotherapy Oncology
Alternate Member	Hong Yang	Department of Thoracic Surgery/Associate Professor	Surgical Oncology
Alternate Member	Yong-Hong Li	Department of Urological Surgery/Associate Professor	Surgical Oncology
Alternate Member	Yun-Peng Yang	Department of Medical Oncology/Associate Professor	Medical Oncology
Alternate Member	Ling-Long Tang	Department of Radiotherapy Oncology/Associate Professor	Radiotherapy Oncology

Alternate Member	Yan-Xia Shi	Department of Medical Oncology/Professor	Medical Oncology
Alternate Member	Yuan-Hong Gao	Department of Radiotherapy Oncology/Associate Professor	Radiotherapy Oncology

Table S6. Treatment exposure in the intention-to-treat population.

	Chemotherapy plus radiotherapy (N = 63)	**Chemotherapy alone (N = 63)**
Cycles received†		
4	1 (1.6%)	0 (0.0%)
5	0 (0.0%)	3 (4.8%)
6	62 (98.4%)	60 (95.2%)
Total	63 (100.0%)	63 (100.0%)
Cumulative dose intensity for cisplatin, mg/m2		
Median	560	540
IQR	520–600	500–600
Cumulative dose intensity for 5-fluorouracil, mg/m2		
Median	5500	5600
IQR	5000–6000	5000–6000
Patients who received definitive IMRT, no. (%)	61 (96.8%)	1 (1.6%)
Patient who completed definitive IMRT, no. (%)	59 (96.7%)	1 (100.0%)
Median (IQR) dose of IMRT (Gy)	70 (70 - 70)	------*
Median (IQR) dose per fraction (Gy)	2.19 (2.12-2.33)	------*
Median (IQR) duration of IMRT (days)	42 (40-49)	------*

Data are n(%) unless otherwise specified. ---† All patients received 3 cycles before randomization. *There was only one patient who received IMRT in the chemotherapy alone group.

Table S7. Disease recurrence distribution in the two treatment groups.

	Chemotherapy plus radiotherapy N = 63	Chemotherapy alone N = 63
First site of disease recurrence	37 (58.7%)	56 (88.9%)
Distant alone	27 (42.9%)	12 (19.0%)
Local alone	1 (1.6%)	1 (1.6%)
Regional alone	2 (3.2%)	6 (9.5%)
Local+regional	0	6 (9.5%)
Distant+local	1 (1.6%)	5 (7.9%)
Distant+regional	2 (3.2%)	12 (19.0%)
Distant+local+regional	4 (6.3%)	14 (22.2%)
Distant metastatic recurence	34 (54.0%)	43 (68.3%)
Bone	13 (20.6%)	15 (23.8%)
Lung	8 (12.7%)	11 (17.5%)
Liver	8 (12.7%)	11 (17.5%)
Other	1 (1.6%)	0 (0.0%)
Multiple	4 (6.3%)	6 (9.5%)

Data are n(%) unless otherwise specified.

Table S8. Summary of subsequent therapies.

	Chemotherapy plus radiotherapy N = 63	Chemotherapy alone N = 63
Subsequent chemotherapy		
None	27 (42.9%)	22 (34.9%)
Gemcitabine plus cisplatin/carboplatin	25 (39.7%)	24 (38.1%)
Docetaxel plus cisplatin/carboplatin	10 (15.9%)	10 (15.9%)
Others	1 (1.6%)	7 (11.1%)
Time to subsequent chemotherapy, months		
Median	11.8	7.7
IQR	9.2 to 17.9	5.7 to 12.8
Locoregional radiotherapy	0 (0.0%)	4 (6.3%)
Palliative treatment to the metastatic sites (%)		
Bone	10 (15.9%)	9 (14.3%)
Lung	1 (1.6%)	0 (0.0%)
Liver	0 (0.0%)	1 (1.6%)
Other sites	1 (1.6%)	1 (1.6%)

Data are n (%) unless otherwise specified. Other regimens included cisplatin plus fluorouracil and docetaxel, gemcitabine plus navelbine, gemcitabine plus docetaxel, and others.