EVIDENCE AND PRACTICE CHANGING TREATMENTS IN HEAD AND NECK TUMORS

Anna Merlotti

S.C. di Radioterapia

A.S.O. S.Croce e Carle Cuneo

Conflitti di interesse: nessuno

- Rinofaringe

1. IMRT sola vs IMRT-CHT per stadio II
2. Elective upper nodal irradiation

- Head and neck weekly cisplatin

- Orofaringe

1. Dose-escalated CRT vs control in high risk OPC (CompARE ph III trial)

- Rinofaringe

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1. Dose-escalated CRT vs control in high risk OPC (CompARE ph III trial)

Presented at ASCO meeting 2022

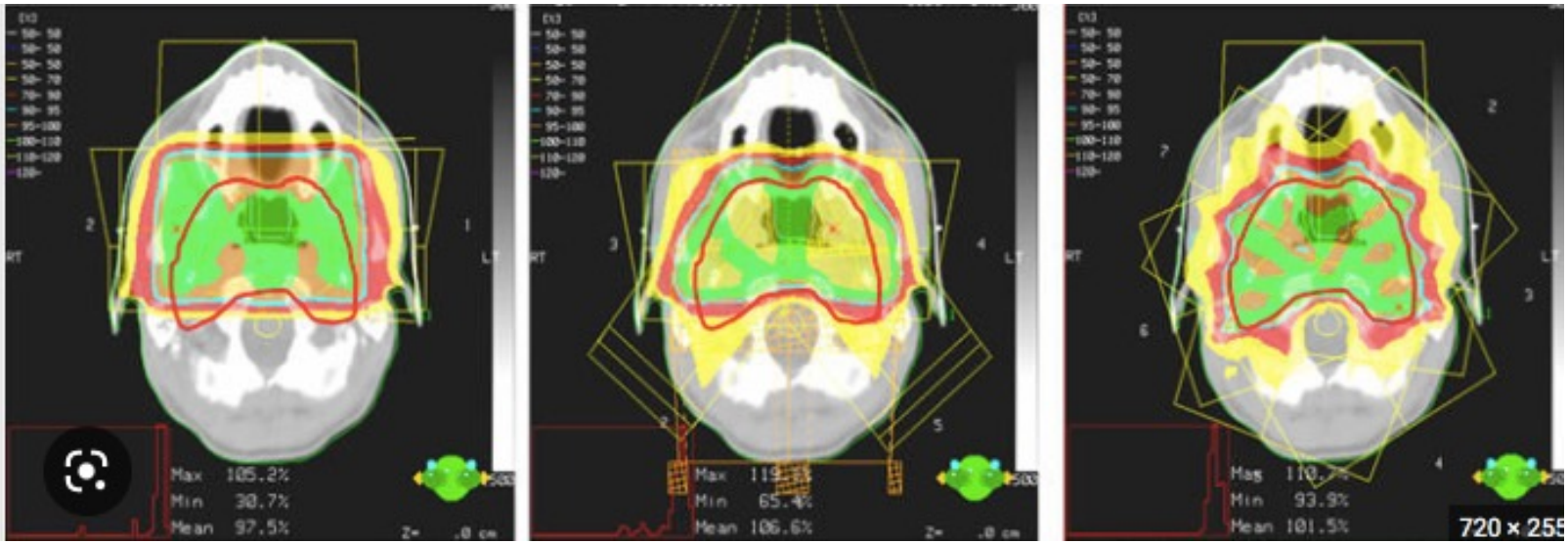
JAMA | Original Investigation

Effect of Radiotherapy Alone vs Radiotherapy With Concurrent Chemoradiotherapy on Survival Without Disease Relapse in Patients With Low-risk Nasopharyngeal Carcinoma
A Randomized Clinical Trial

Ling-Long Tang, MD; Rui Guo, MD; Ning Zhang, MD; Bin Deng, MD; Lei Chen, MD; Zhi-Bin Cheng, MD; Jing Huang, MD; Wei-Han Hu, MD; Shao Hui Huang, MD; Wei-Jun Luo, MD; Jin-Hui Liang, MD; Yu-Ming Zheng, MD; Fan Zhang, MD; Yan-Ping Mao, MD; Wen-Fei Li, MD; Guan-Qun Zhou, MD; Xu Liu, MD; Yu-Pei Chen, MD; Cheng Xu, MD; Li Lin, MD; Qing Liu, MD, PhD; Xiao-Jing Du, MD; Yuan Zhang, MD; Ying Sun, PhD; Jun Ma, MD

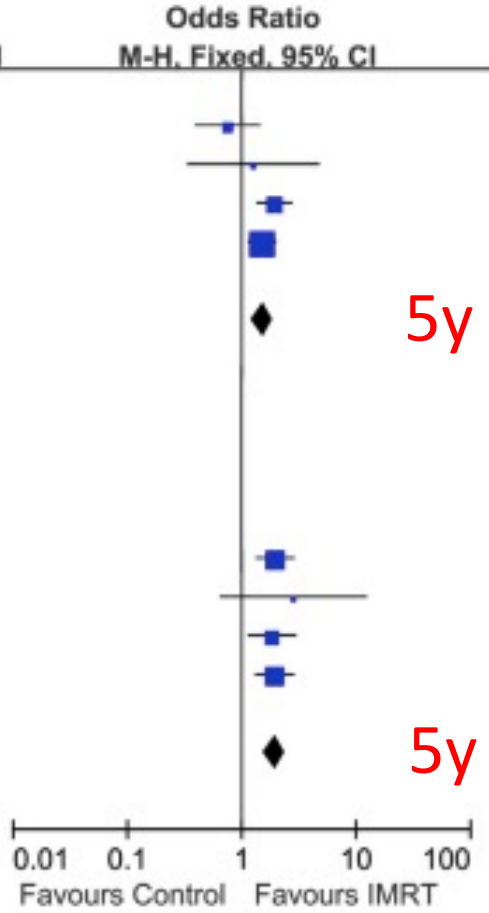
Presupposto:

Concurrent chemoradiotherapy has been the standard treatment for stage II NPC based on data using 2D-RT. There is limited evidence for the role of chemotherapy with use of IMRT.



Oral Oncology 51 (2015) 1041–1046

Study or Subgroup	IMRT Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
(A) 5-year OS						
Fang et al. 2008	82	110	74	93	14.2%	0.75 [0.39, 1.46]
Moretto et al. 2014	21	26	20	26	2.7%	1.26 [0.33, 4.79]
Peng et al. 2012	244	306	208	310	29.1%	1.93 [1.34, 2.78]
Zhou et al. 2013	421	506	573	747	54.0%	1.50 [1.13, 2.01]
Total (95% CI)		**948**		**1176**	**100.0%**	**1.51 [1.23, 1.87]**
Total events	768		875			
Heterogeneity: Chi² = 6.06, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
(B) 5-year LC						
Lai et al. 2011	475	512	663	764	37.2%	1.96 [1.32, 2.90]
Moretto et al. 2014	23	26	19	26	2.1%	2.82 [0.64, 12.44]
Peng et al. 2012	277	306	260	310	23.7%	1.84 [1.13, 2.99]
Zhou et al. 2013	469	506	648	747	37.0%	1.94 [1.30, 2.88]
Total (95% CI)		**1350**		**1847**	**100.0%**	**1.94 [1.53, 2.46]**
Total events	1244		1590			
Heterogeneity: Chi² = 0.30, df = 3 (P = 0.96); I² = 0%						
Test for overall effect: Z = 5.42 (P < 0.00001)						



5y OS

5y LC

Fig. 2. Forest plot of the comparison between IMRT and 2D-RT/3D-CRT for 5-year OS and LC.

Journal of Cancer 2017, Vol. 8 287

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2017; 8(2): 287-297. doi: 10.7150/jca.17317

Research Paper

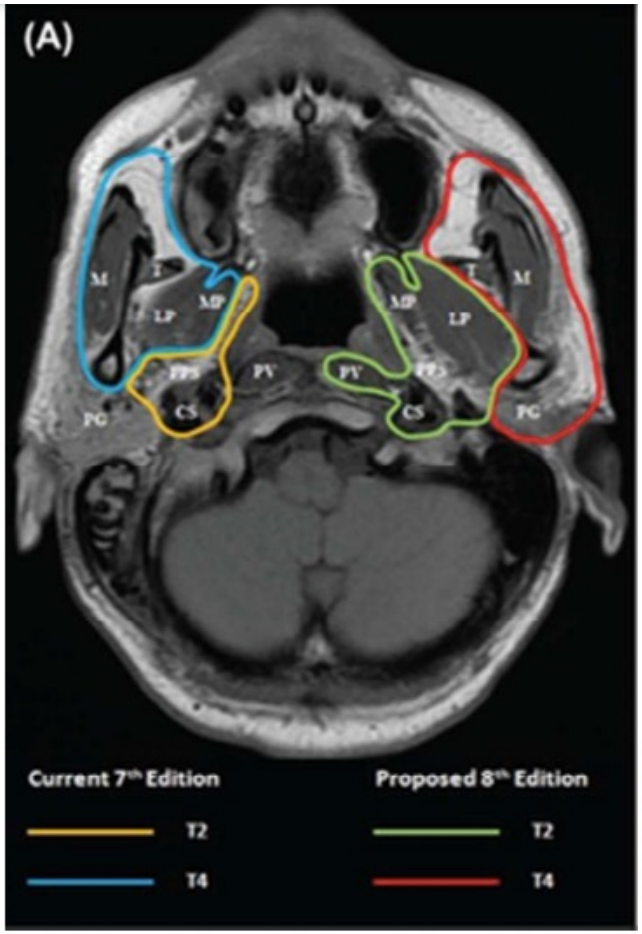
Chemoradiotherapy Versus Radiotherapy Alone in Stage II Nasopharyngeal Carcinoma: A Systemic Review and Meta-analysis of 2138 Patients

Cheng Xu[1*], Li-He Zhang[1*], Yu-Pei Chen[1*], Xu Liu[1], Guan-Qun Zhou[1], Ai-Hua Lin[2], Ying Sun[1], Jun Ma[1]✉

In the treatment of patients with stage II NPC (TNM V, VI, VII, Chinese 1992 staging system), CRT was better than 2D-RT alone with significant benefit in LRRFS.

IMRT alone could achieve equivalent OS, LRRFS and DMFS compared to CRT with fewer grade 3-4 acute toxicities.

The 7th AJCC	**The 8th AJCC**[‡]	**The Chinese 1992 staging system**
T1: Nasopharynx, oropharynx or nasal cavity	T1. Nasopharynx, oropharynx, nasal fossa	T1: Nasopharynx
T2: Parapharyngeal extension	T2. Parapharyngeal extension, prevertebral, medial and lateral pterygoid muscles	T2: Oropharynx, nasal cavity, parapharyneal extension, medial and lateral pterygoid muscles
T3: Bony structures and/or paranasal sinuses	T3. Bony structure (skull base, cervical vertebra), paranasal sinuses	T3: Bony structures, paranasal sinuses
T4: Intracranial extension and/or cranial nerves, hypopharynx, orbit, or infratemporal fossa/masticatory space	T4. Intracranial extension, cranial nerve, hypopharynx, orbit, involvement beyond the lateral surface of lateral pterygoid muscle, parotid gland)	T4: Intracranial extension and/or cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticatory space excluding medial and lateral pterygoid muscles



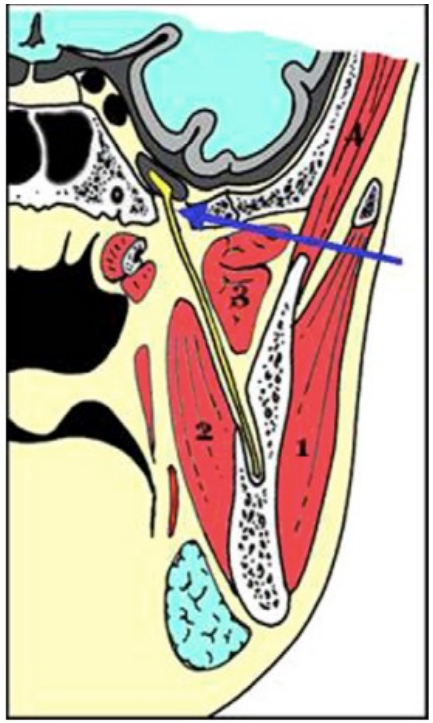
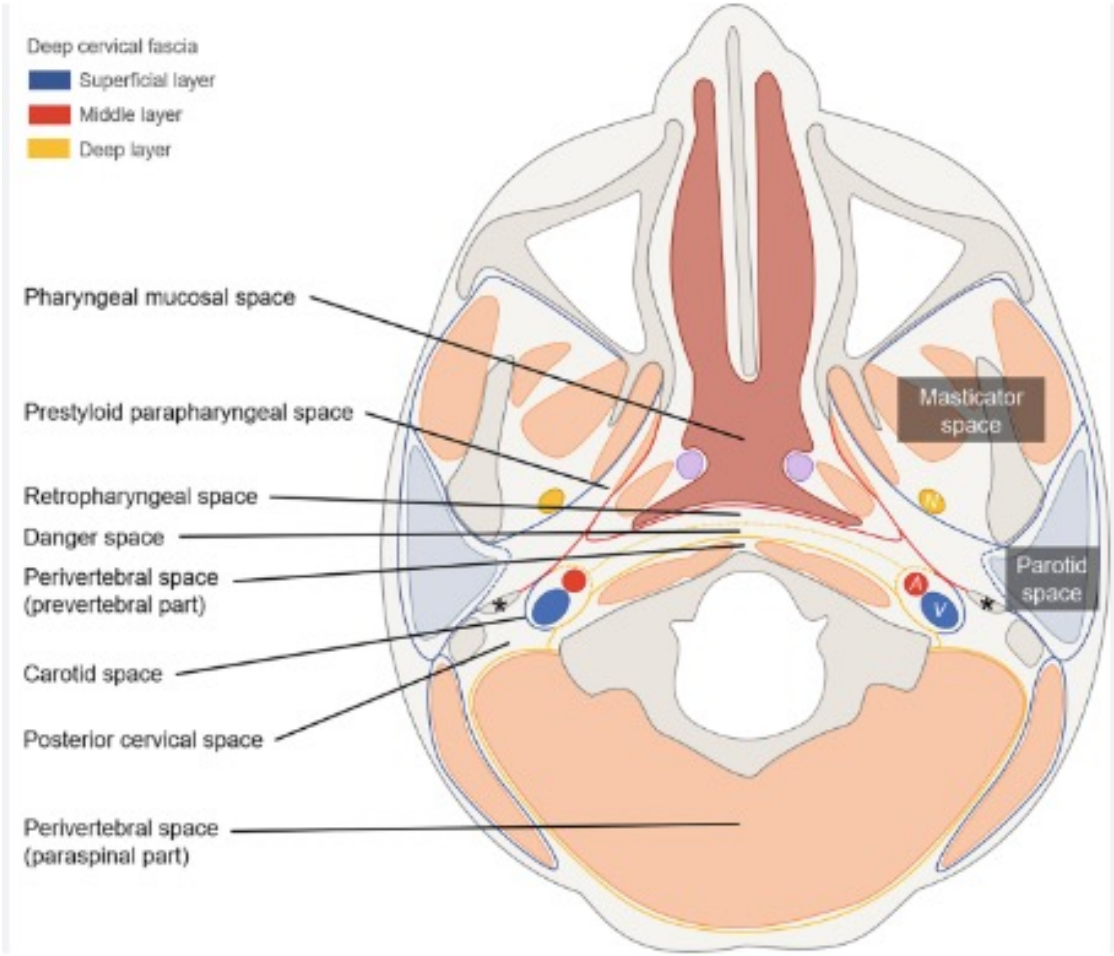


Figure 3 Graphic representation (coronal view) of structures of the left masticator space: (1) masseter muscle; (2) medial pterygoid muscle; (3) lateral pterygoid muscle; (4) temporalis muscle; and oval foramen (blue arrow), the passageway for the third branch of the trigeminal nerve (V3).

FIGURE 2. Differences in defining criteria between Current 7th Edition to the Proposed 8th Edition regarding (A) changing the extent of soft tissue involvement as T2 and T4 criteria. Abbreviation: CS= carotid space, LP= lateral pterygoid muscle, M= masseter muscle, MP= medial pterygoid muscle, PG= parotid gland, PPS= parapharyngeal space, PV= prevertebral muscle, T= temporalis muscle, (B) replacing supraclavicular fossa (blue) by lower neck i.e. below caudal border of cricoid cartilage (red) as N3 criteria.
18x13mm (600 x 600 DPI)



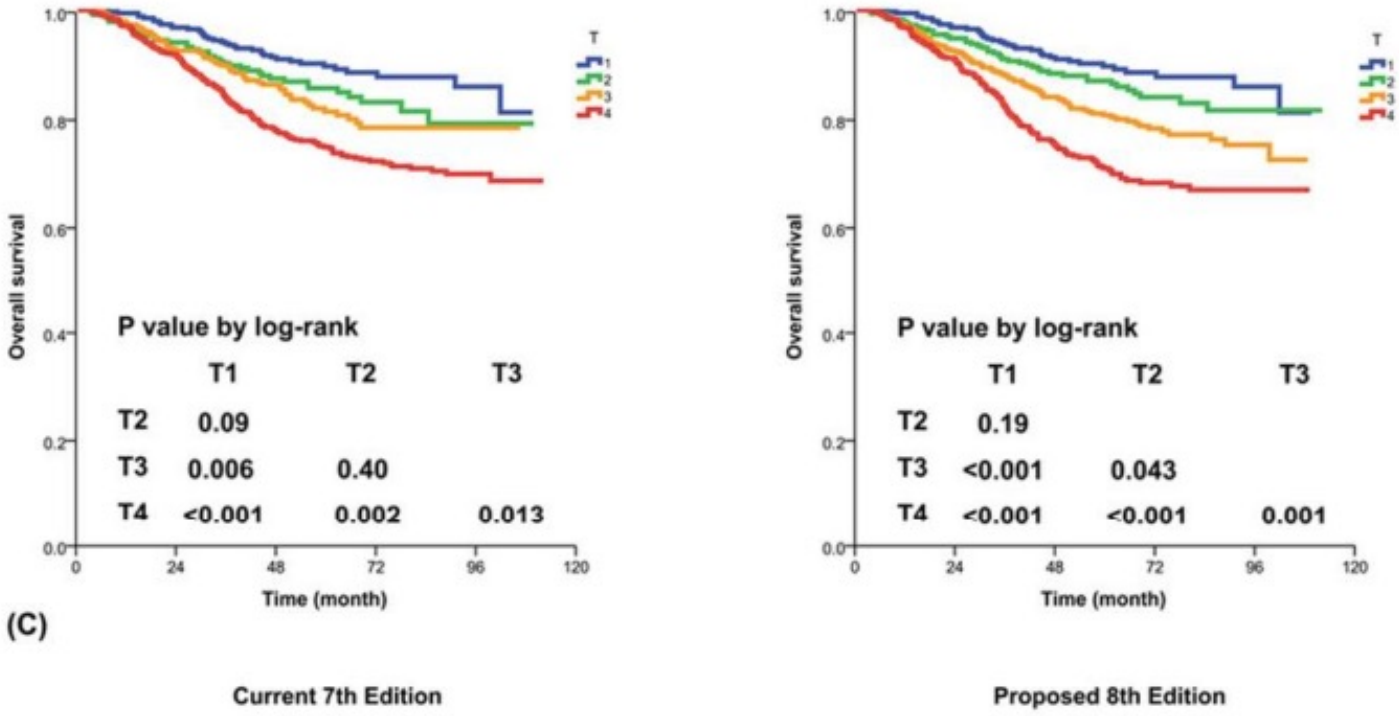
Masticator space primarily consists of the muscles of mastication. Anatomically, the superficial layer of the deep cervical fascia splits to enclose the muscles of mastication to enclose this space. These muscles are the medial and lateral pterygoid, masseter, and temporalis.

> Cancer. 2016 Feb 15;122(4):546-58. doi: 10.1002/cncr.29795. Epub 2015 Nov 20.

e degli Studi Practice Changing 2022

Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy

Jian Ji Pan [1] [2], Wai Tong Ng [3], Jing Feng Zong [1] [2], Lucy L K Chan [3], Brian O'Sullivan [4],



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

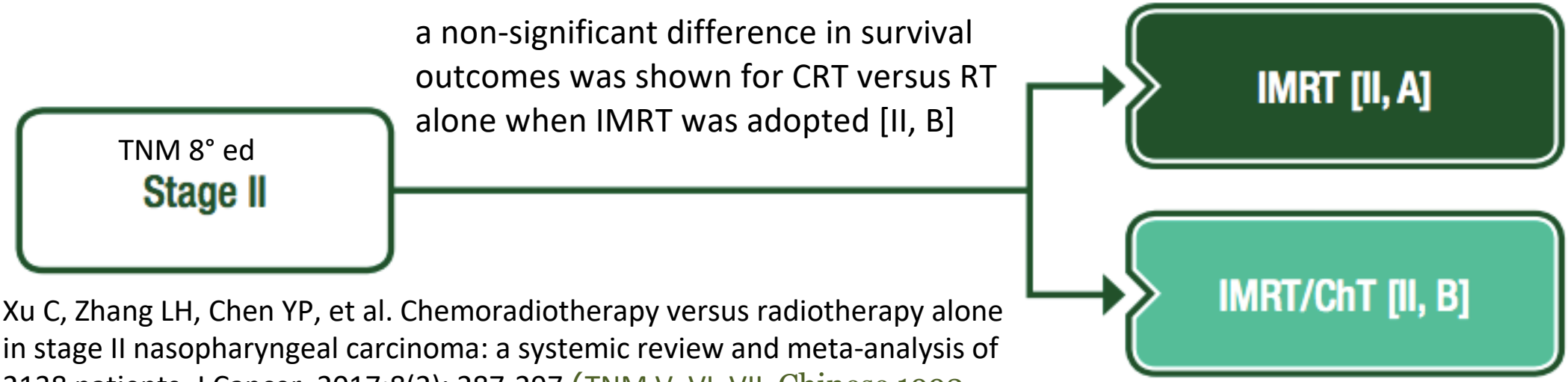
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Epub Dic 2020

Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

a non-significant difference in survival outcomes was shown for CRT versus RT alone when IMRT was adopted [II, B]



Xu C, Zhang LH, Chen YP, et al. Chemoradiotherapy versus radiotherapy alone in stage II nasopharyngeal carcinoma: a systemic review and meta-analysis of 2138 patients. J Cancer. 2017;8(2): 287-297 (TNM V, VI, VII, Chinese 1992 staging system)

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DOI: 10.1002/cac2.12218

CANCER COMMUNICATIONS

GUIDELINES AND CONSENSUS

2021

The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma

Ling-Long Tang[1] | Yu-Pei Chen[1] | Chuan-Ben Chen[2] | Ming-Yuan Chen[3] |

These guidelines use the 8th edition of the AJCC TNM staging system

T2N0	Radiotherapy alone [101] (evidence 2B)	Concurrent chemoradiotherapy [102, 103] (with poor prognostic factors, such as large tumor volume or high EBV DNA copy number) (evidence 2A)	
T1-2N1	Concurrent chemoradiother-apy [102, 103] (evidence 2A)	Radiotherapy alone [101] (evidence 2A)	

HIGH

ASCO special articles

Chemotherapy in Combination With Radiotherapy for Definitive-Intent Treatment of Stage II-IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline

J Clin Oncol 39:840-859. © 2021

Yu-Pei Chen, MD[1]; Nofisat Ismaila, MD[2]; Melvin L. K. Chua, MD PhD[3]; A. Dimitrios Colevas, MD[4]; Robert Haddad, MD[5]; Shao Hui Huang, MD, MRT(T)[6]; Joseph T. S. Wee, MD[3]; Alexander C. Whitley, MD[7]; Jun-Lin Yi, MD[8]; Sue S. Yom, MD[9]; Anthony T. C. Chan, MD[10]; Chao-Su Hu, MD[11]; Jin-Yi Lang, MD[12]; Quynh-Thu Le, MD[4]; Anne W. M. Lee, MD[13]; Nancy Lee, MD[14]; Jin-Ching Lin, MD[15]; Brigette Ma, MD[10]; Thomas J. Morgan, MR[16]; Jatin Shah, MD[14]; Ying Sun, MD[1]; and Jun Ma, MD[1]

T2N0 (AJCC 8th)= CHT is not routinely recommended, (except with adverse features, such as bulky tumor volumes or high EBV DNA copy number) (Type: evidence based; harms outweigh benefits; Evidence quality: intermediate; Strength of recommendation: moderate).
T1-2N1 (AJCC 8th) = CRT may be offered, particularly for T2 N1 patients (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

JAMA | Original Investigation

Presented at ASCO meeting 2022

Effect of Radiotherapy Alone vs Radiotherapy With Concurrent Chemoradiotherapy on Survival Without Disease Relapse in Patients With Low-risk Nasopharyngeal Carcinoma
A Randomized Clinical Trial

Ling-Long Tang, MD; Rui Guo, MD; Ning Zhang, MD; Bin Deng, MD; Lei Chen, MD; Zhi-Bin Cheng, MD; Jing Huang, MD; Wei-Han Hu, MD; Shao Hui Huang, MD; Wei-Jun Luo, MD; Jin-Hui Liang, MD; Yu-Ming Zheng, MD; Fan Zhang, MD; Yan-Ping Mao, MD; Wen-Fei Li, MD; Guan-Qun Zhou, MD; Xu Liu, MD; Yu-Pei Chen, MD; Cheng Xu, MD; Li Lin, MD; Qing Liu, MD, PhD; Xiao-Jing Du, MD; Yuan Zhang, MD; Ying Sun, PhD; Jun Ma, MD

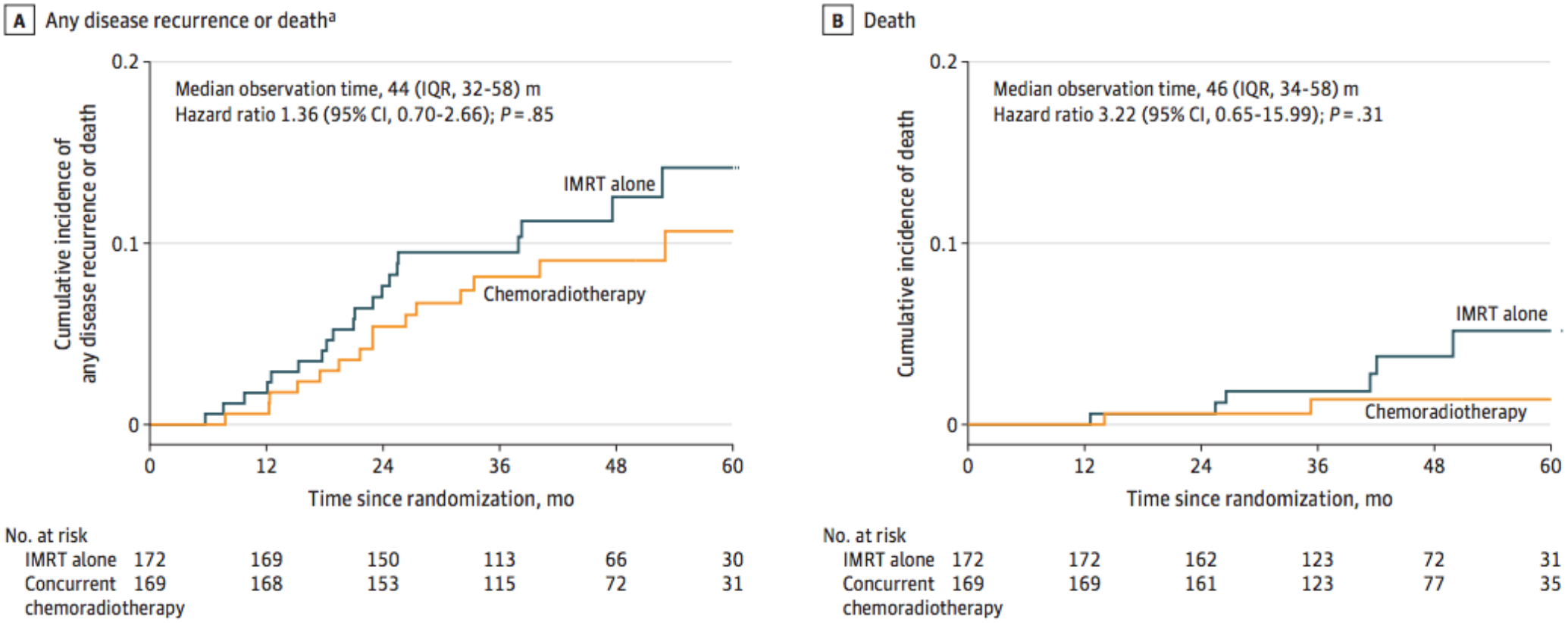
Multicenter phase 3, non-inferiority clinical trial was conducted at 5 Chinese hospitals, including 341 adult patients with low-risk NPC, defined as stage II/T3N0M0 without adverse features (no low neck N, all N < 3 cm, no ENE, < 4000 copies/ml EBV DNA)

This trial used 7th edition TNM!

- 18F-FDGPET–CT examination was carried out following local practices
- cisplatin was administered concurrently with radiotherapy at 100mg/m2 every 3 weeks for 3 cycles. All patients underwent IMRT
- The recommended prescribed dose was 68 to 70 Gy at 2.0 to 2.2 Gy per fraction administered (once per day, 5 fractions every week)
- The primary end point was 3-year failure-free survival
- The secondary end points was OS, LRRFS, DMFS, safety, and health-related QOL.
- 341 pts, 97.5% were EBV+
- Median f-up 46 months

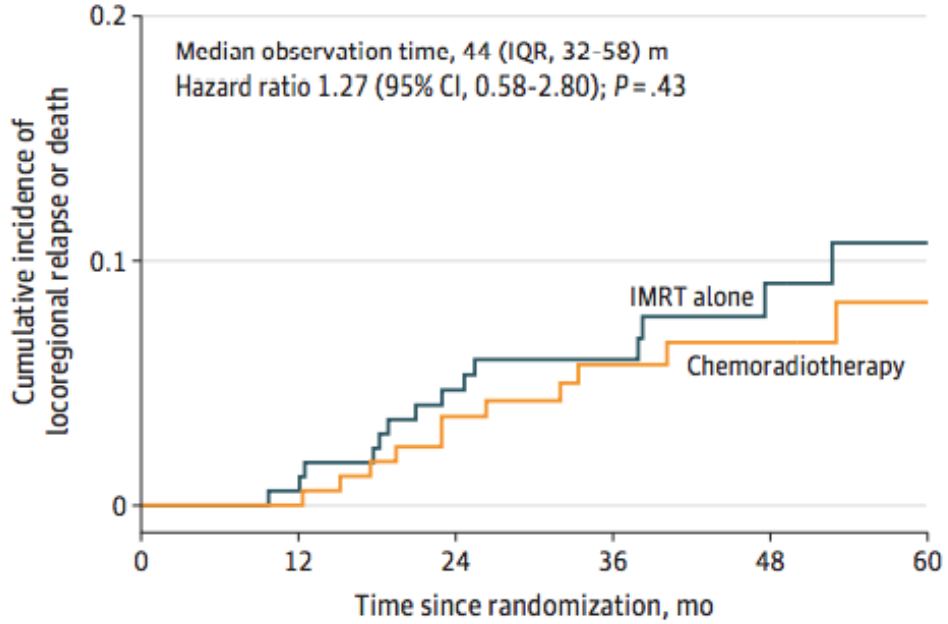
Compliance in the IMRT-alone group: 95.9%

Compliance in the CRT group: 60.4% received 3 cycles of concurrent cisplatin, 36.7% received 2 cycles, and 3.0% received 1 cycle



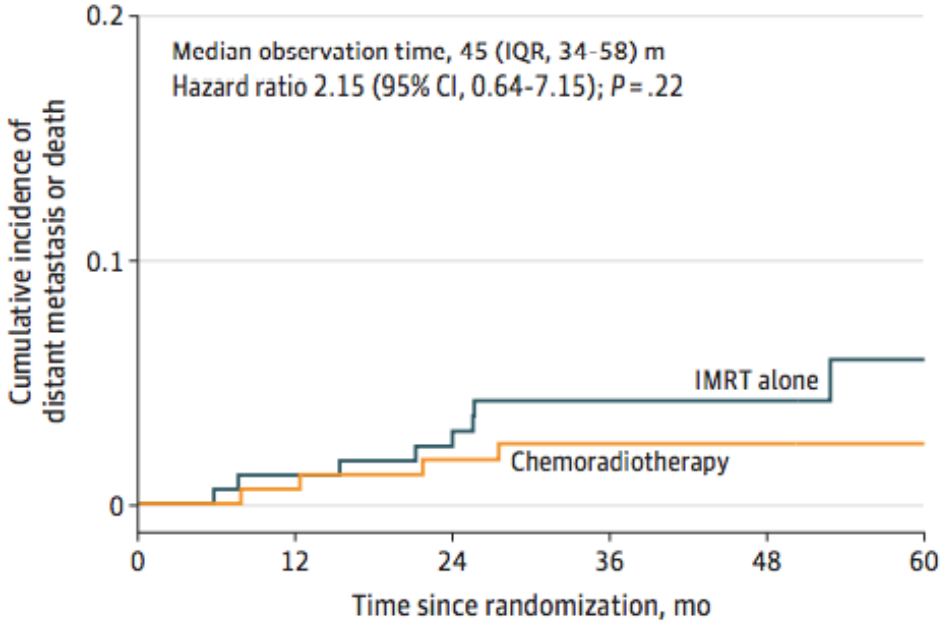
The primary outcome 3y FFS in the IMRT-alone vs CRT groups was 90.5% vs 91.9% (difference, −1.4%, which met the non-inferiority criterion)

C Locoregional relapse or death



No. at risk						
IMRT alone	172	171	154	116	67	30
Concurrent chemoradiotherapy	169	169	155	116	73	32

D Distant metastasis or death



No. at risk						
IMRT alone	172	170	157	119	70	31
Concurrent chemoradiotherapy	169	168	159	122	76	34

HIGHLIGHT

ce Changing 2022

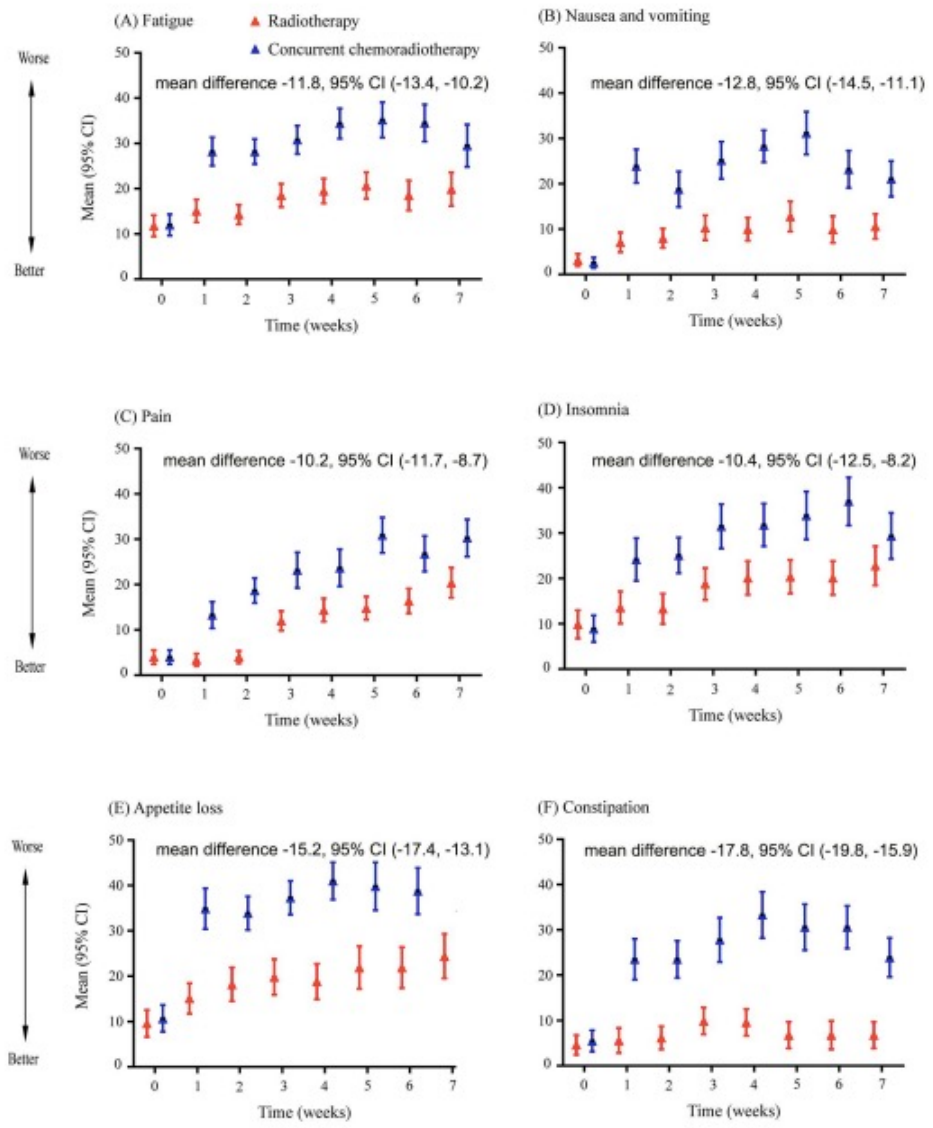
Worse

QOL

Better

187

Figure S5. The results of QOL assessments evolved over time



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IMRT

IMRT+CHT

significantly lower incidence of grade 3 or 4 hematological toxicities and nonhematological toxicities in the IMRT-alone group

ACUTE TOX

Event[a]	Group, No. (%)[b]			
	IMRT alone (n = 165)		Concurrent chemoradiotherapy (n = 169)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Nonhematologic				
Mucositis	116 (70)	16 (10)	113 (67)	32 (19)
Dry mouth	33 (20)	0	50 (30)	0
Dermatitis	31 (19)	0	54 (32)	0
Weight loss	28 (17)	1 (1)	94 (56)	8 (5)
Anorexia	22 (13)	8 (5)	28 (17)	49 (29)
Vomiting	14 (8)	2 (1)	48 (28)	25 (15)
Nausea	14 (8)	1(1)	57 (34)	22 (13)
Dysphagia	5 (3)	1 (1)	22 (13)	3 (2)
Fever	0	0	0	1 (1)

LATE TOX

Event[a]	Group, No. (%)[b]			
	IMRT alone (n = 165)		Concurrent chemoradiotherapy (n = 169)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Late toxicities				
Dry mouth	90 (55)	0	96 (57)	1 (1)
Auditory/hearing	66 (40)	1 (1)	80 (47)	1 (1)
Skin/neck tissue damage	35 (21)	1 (1)	50 (30)	0
Hypothyroidism	31 (19)	4 (2)	60 (36)	1 (1)
Peripheral neuropathy	6 (4)	0	17 (10)	0
Temporal lobe injury	6 (4)	0	6 (4)	0
Trismus	3 (2)	0	3 (2)	0
Bone necrosis	1 (1)	0	0	0

CAUTION !

- Epstein-Barr virus DNA cutoff of greater than 4000 copies/mL was an exclusion criterion. This cutoff may not be applicable to all other centers without international harmonization of Epstein-Barr virus DNA assays.
- This trial used 7th edition TNM. Rare occasions (<5%) in which the 7th edition T4 with adjacent soft tissue extension would be reclassified as T2 in the 8th edition. Caution is needed to apply the trial's findings to such cases.

T2N0	Radiotherapy alone [101] (evidence 2B)	Concurrent chemoradiotherapy [102, 103] (with poor prognostic factors, such as large tumor volume or high EBV DNA copy number) (evidence 2A)
T1-2N1	Concurrent chemoradiotherapy [102, 103] (evidence 2A)	Radiotherapy alone [101] (evidence 2A)

Evidence 1A

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CANCER COMMUNICATIONS

GUIDELINES AND CONSENSUS

The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma

Ling-Long Tang[1] | Yu-Pei Chen[1] | Chuan-Ben Chen[2] | Ming-Yuan Chen[3] |

Staging group[d]		
T2N0	28 (16)	21 (12)
T3N0	43 (25)	44 (26)
T1N1	36 (21)	33 (20)
T2N1	65 (38)	71 (42)

Elective upper-neck versus whole-neck irradiation of the uninvolved neck in patients with nasopharyngeal carcinoma: an open-label, non-inferiority, multicentre, randomised phase 3 trial

Lancet Oncol 2022; 23: 479–90

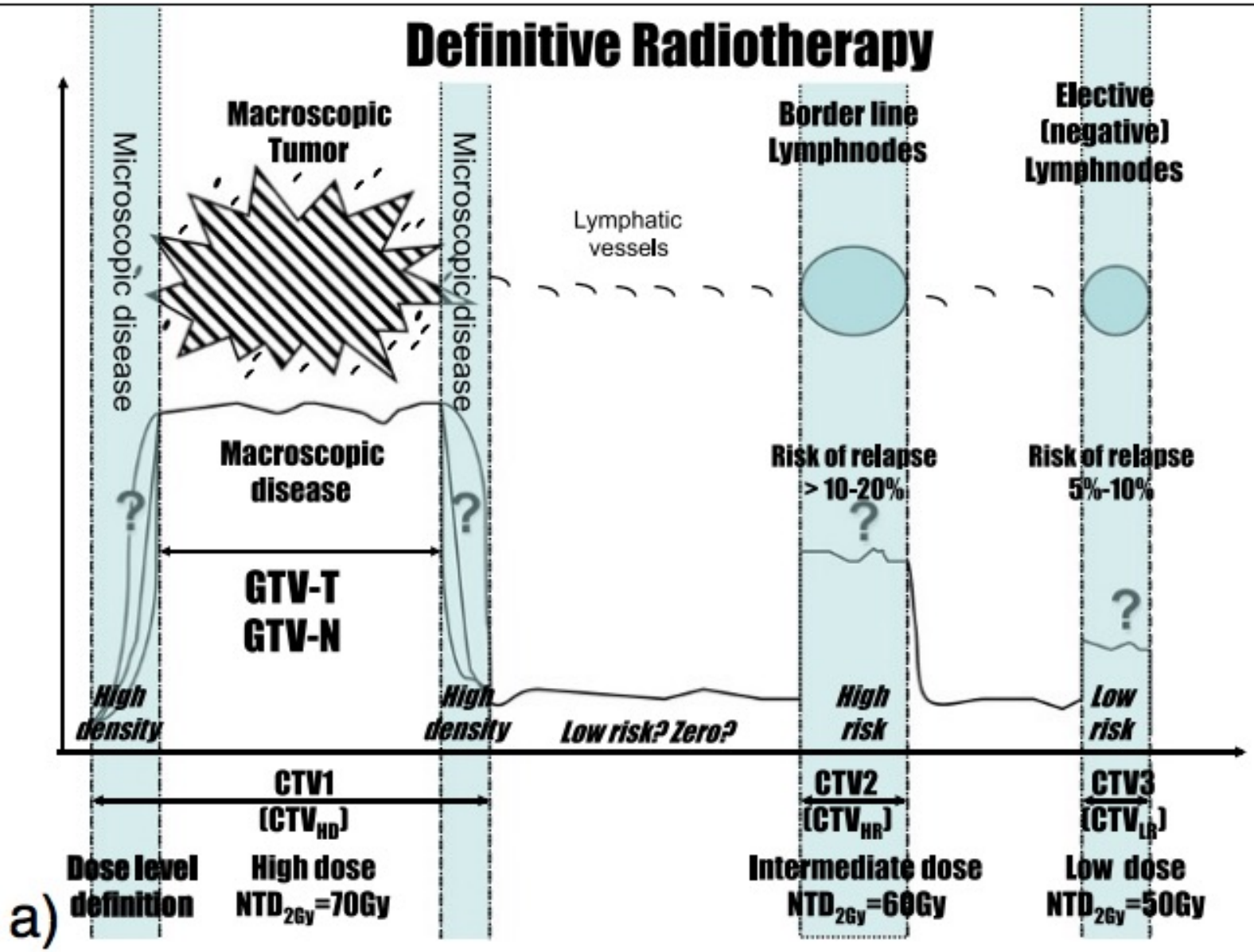
Ling-Long Tang†, Cheng-Long Huang*, Ning Zhang*, Wei Jiang*, Yi-Shan Wu*, Shao Hui Huang, Yan-Ping Mao, Qing Liu, Ji-Bin Li, Shao-Qiang Liang, Guan-Jie Qin, Wei-Han Hu, Ying Sun, Fang-Yun Xie, Lei Chen†, Guan-Qun Zhou†, Jun Ma†*

to assess whether elective upper-neck irradiation (UNI) of the uninvolved neck (including patients with both N0 and N1 disease) was non-inferior to standard whole-neck irradiation (WNI) in 446 non keratinizing NP pts

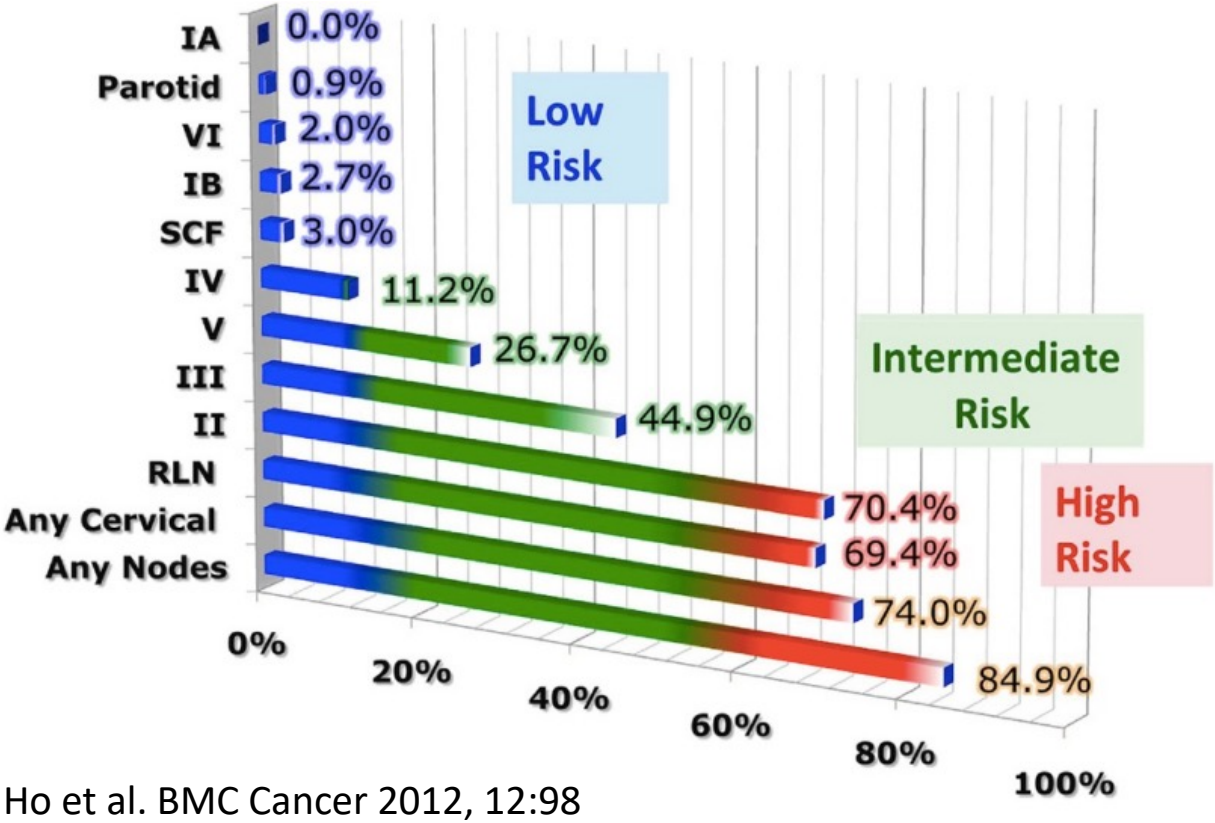
Median follow up of 53 months

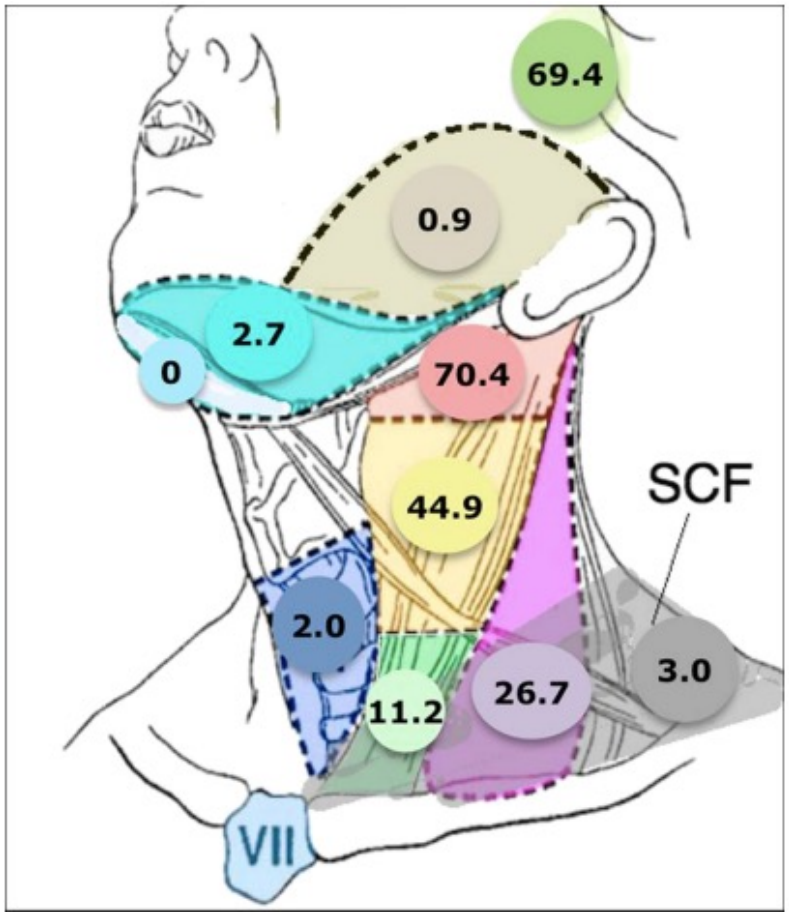
Only one other randomised clinical trial (Cancer. 2013 Sep 1;119(17):3170-6) comparing upper-neck irradiation versus standard whole-neck irradiation in N0 NPC, showed a similar proportion of regional control and survival between the two treatment groups.

BUT: single institution
2/3 2D RT
No QoL data
Only N0 pts (rare presentation)


Definitive Radiotherapy
Macroscopic Tumor
Microscopic disease
Microscopic disease
Lymphatic vessels
Border line Lymphnodes
Elective (negative) Lymphnodes
Macroscopic disease
GTV-T
GTV-N
Risk of relapse > 10-20%
Risk of relapse 5%-10%
High density
High density
Low risk? Zero?
High risk
Low risk
CTV1 (CTV$_{HD}$)
CTV2 (CTV$_{HR}$)
CTV3 (CTV$_{LR}$)
Dose level definition
High dose NTD$_{2Gy}$=70Gy
Intermediate dose NTD$_{2Gy}$=60Gy
Low dose NTD$_{2Gy}$=50Gy
a)

Lymphatic spread in cervical nodal chain from NPC primary follows an orderly fashion. There is a very low risk of 0.5% in skip nodal metastasis





Ho et al. BMC Cancer 2012, 12:98

RT to all levels of cervical lymph nodes from IB to V, including the supraclavicular might represent over-treatment using the current diagnostic and therapeutic technology.

A meta-analysis by Huang and colleagues (Radiat Oncol 2018;13:141) showed the feasibility of ipsilateral lower neck sparing RT for unilateral or bilateral neck node-negative NPC patients.

Neck nodes are probably an important source for the production of an immune response to the primary tumor

Elective upper-neck versus whole-neck irradiation of the uninvolved neck in patients with nasopharyngeal carcinoma: an open-label, non-inferiority, multicentre, randomised phase 3 trial

Lancet Oncol 2022; 23: 479–90

Ling-Long Tang†, Cheng-Long Huang*, Ning Zhang*, Wei Jiang*, Yi-Shan Wu*, Shao Hui Huang, Yan-Ping Mao, Qing Liu, Ji-Bin Li, Shao-Qiang Liang, Guan-Jie Qin, Wei-Han Hu, Ying Sun, Fang-Yun Xie, Lei Chen†, Guan-Qun Zhou†, Jun Ma†*

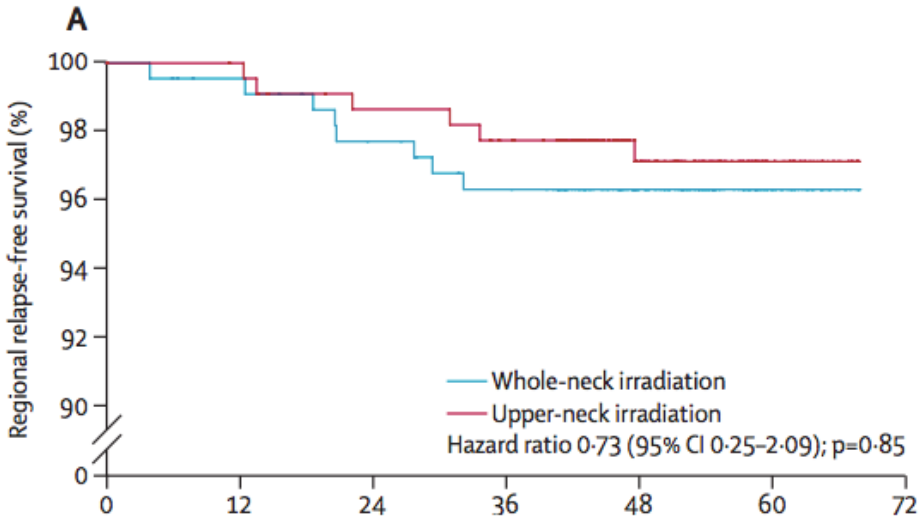
to assess whether elective upper-neck irradiation (UNI) of the uninvolved neck (including patients with both N0 and N1 disease) was non-inferior to standard whole-neck irradiation (WNI) in 446 non keratinizing NP pts

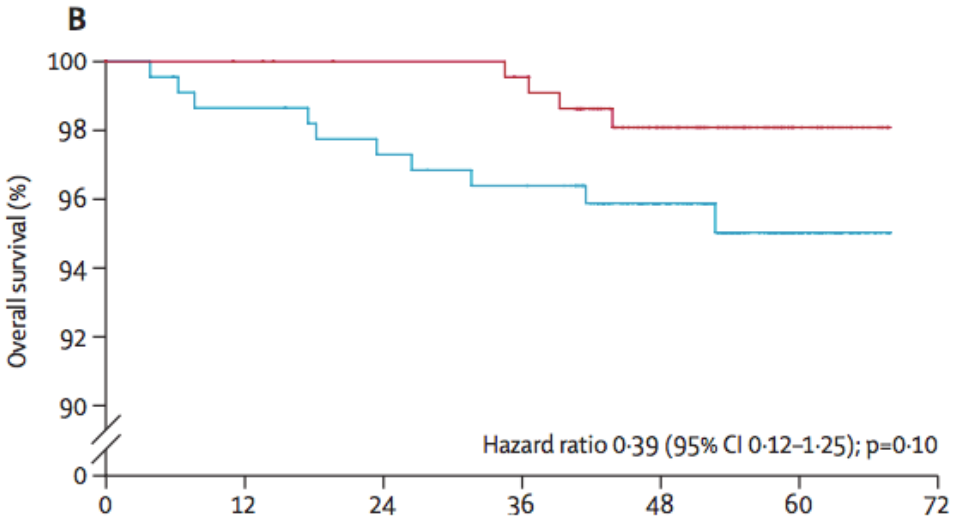
Median follow up of 53 months,

3-year RRFS = in both arms.

Acute toxicities = in both groups

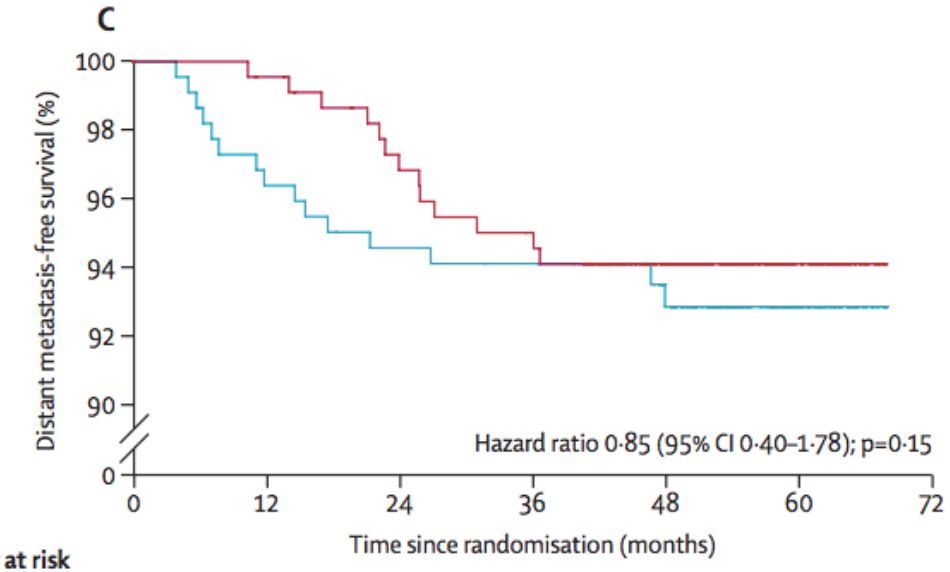
Late toxicities < in UNI (less hypothyroidism, dysphagia, skin toxicities and soft tissue damage).

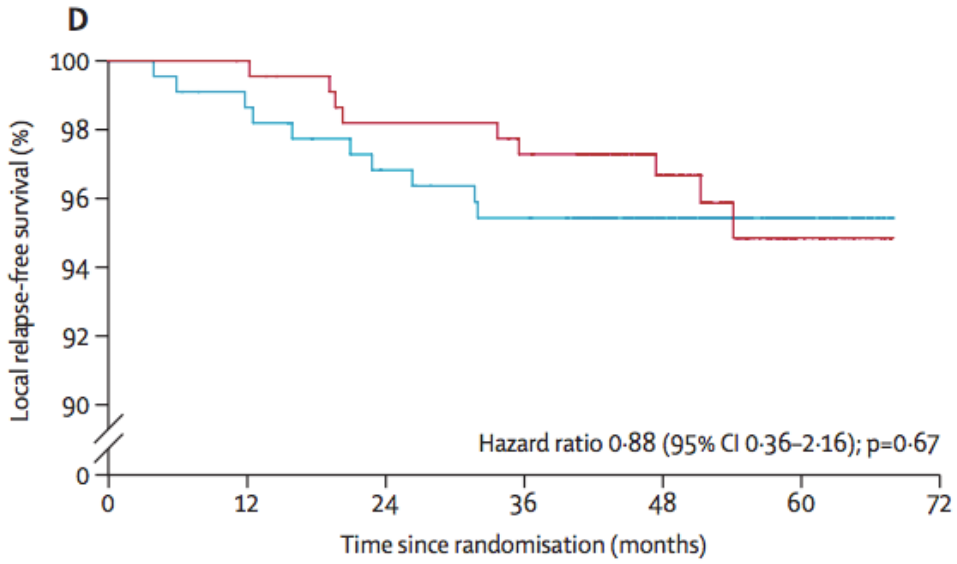




Number at risk (number censored)							
Whole-neck irradiation	222 (0)	218 (3)	211 (3)	204 (4)	143 (61)	43 (100)	0 (43)
Upper-neck irradiation	224 (0)	223 (1)	217 (3)	213 (2)	150 (62)	47 (103)	0 (47)

	222 (0)	218 (1)	214 (1)	210 (2)	146 (63)	45 (100)	0 (45)
	224 (0)	223 (1)	220 (3)	218 (1)	151 (64)	47 (104)	0 (47)

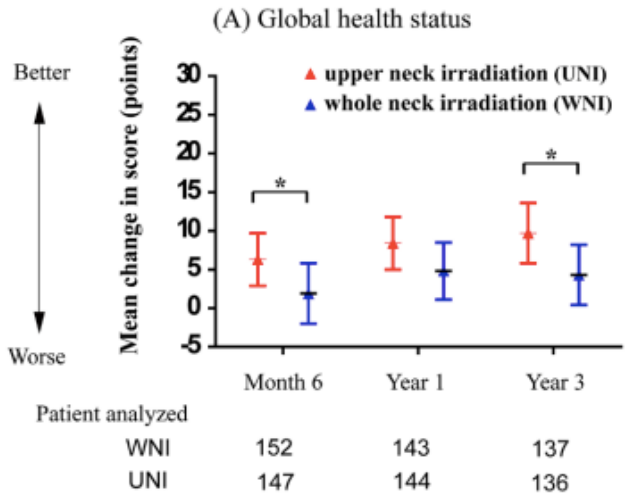


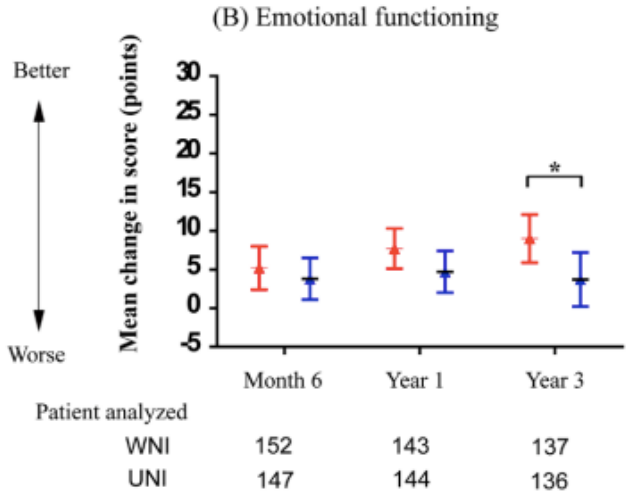


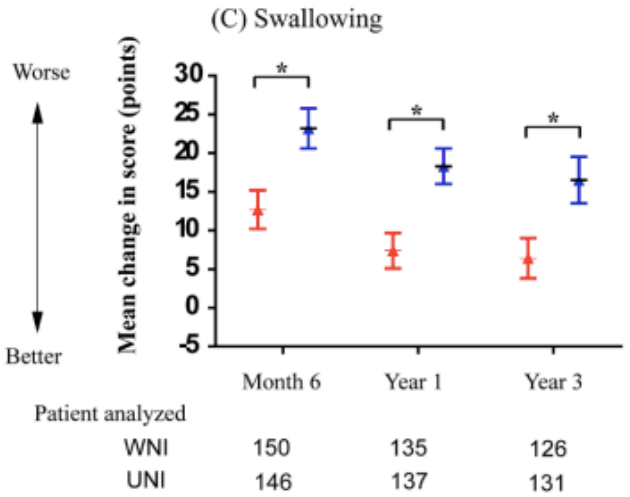
Number at risk (number censored)							
Whole-neck irradiation	222 (0)	213 (1)	207 (2)	204 (2)	141 (61)	44 (97)	0 (44)
Upper-neck irradiation	224 (0)	222 (1)	214 (3)	208 (1)	145 (61)	47 (98)	0 (47)

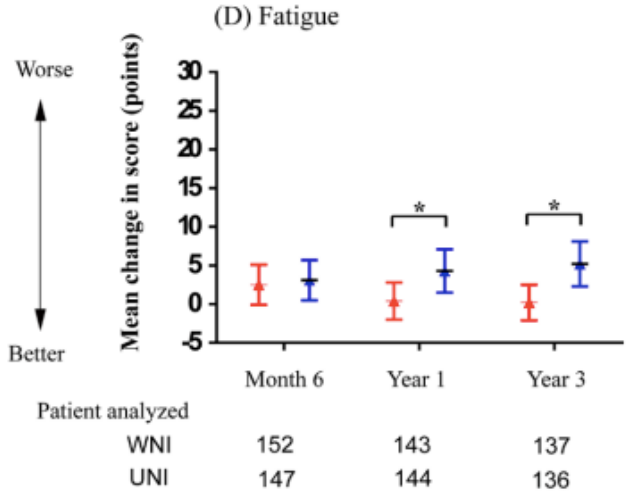
Whole-neck irradiation	222 (0)	217 (2)	210 (3)	204 (3)	142 (62)	43 (99)	0 (43)
Upper-neck irradiation	224 (0)	223 (1)	216 (3)	212 (2)	148 (63)	44 (102)	0 (44)

*: statistically significant (p<0·05) difference.



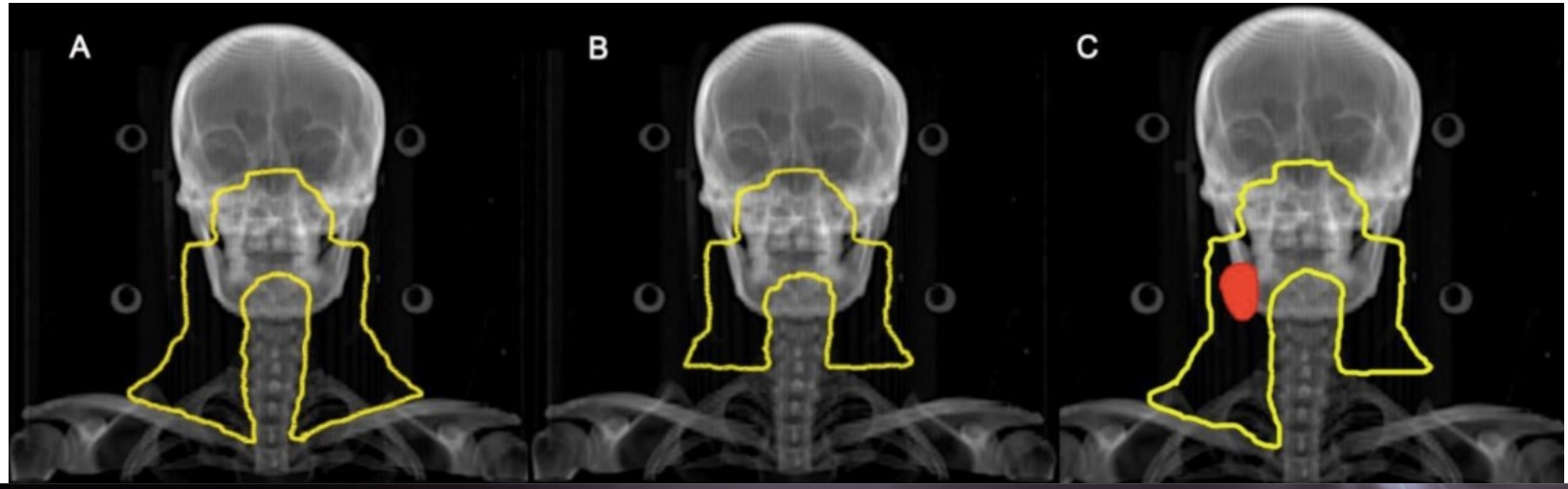






Is this high-level evidence, supporting UNI (upper neck irradiation) as a valid option to be considered in future treatment guidelines for NPC patients with N0–N1 stage disease, feasible in the case of IMPT delivery? De Felice F et al. J Clin Med 2022;11:3297

Spared unilateral lower neck would also receive a scattered dose (mean dose of 22 Gy in Tang trial)



A phase II study of Lower-Neck **S**paring **P**rot**O**n Therapy in **NA**sopharyngeal Carcinoma **P**atients with **U**ninvolved **N**ec**K** (SPONAPUNK)

To estimate the 2-year RFS rate with IMPT de-escalated volumes strategy (UNI) in a cohort of patients with T1-T3 N0 NPC treated at CNAO compared to historical data from non-endemic area.

Ester.orlandi@cnao.it

National Center for Oncological Hadrontherapy (CNAO)

- Rinofaringe

1. IMRT sola vs IMRT-CHT per stadio II
2. Elective upper nodal irradiation

- Head and neck weekly cisplatin

- Orofaringe

1. Dose-escalated CRT vs control in high risk OPC (CompARE ph III trial)

HIGH

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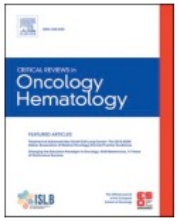

Survival and toxicity of weekly cisplatin chemoradiotherapy versus three-weekly cisplatin chemoradiotherapy for head and neck cancer: A systematic review and meta-analysis endorsed by the Italian Association of Radiotherapy and Clinical Oncology (AIRO)

Francesca De Felice [a,*,1], Liliana Belgioia [b,1], Daniela Alterio [c], Pierluigi Bonomo [d], Marta Maddalo [e], Fabiola Paiar [f], Nerina Denaro [g], Renzo Corvò [b], Anna Merlotti [h], Paolo Bossi [i], Giovanni L. Pappagallo [j], Rolando M. D' Angelillo [k], Stefano M. Magrini [e,2], Stefano Arcangeli [l,2]

Weekly cisplatin is not associated with better clinical outcomes compared to three-weekly cisplatin. Three-weekly cisplatin chemoradiotherapy should be considered the standard approach in the management of locally advanced head and neck cancer. Methodologically robust RCTs designs are needed to improve the quality of evidence. Differences on long-term toxicity and cost-effectiveness remain to be tested.

Quesito 3: ***Nei pazienti con tumore testa e collo operati candidati a trattamento chemioradioterapico concomitante postoperatorio e fit per cisplatino concomitante, è indicata una schedula settimanale rispetto a quella trisettimanale?***

Qualità globale delle prove	Raccomandazione clinica	Forza della raccomandazione
Moderata	Nei pazienti con carcinoma a cellule squamose del distretto testa-collo localmente avanzato candidabile a trattamento chemioradioterapico concomitante come trattamento curativo e fit per utilizzo di cisplatino concomitante alla radioterapia, la schedula settimanale di cisplatino non dovrebbe essere presa in considerazione come alternativa alla schedula trisettimanale, tranne nel setting postoperatorio dove non dovrebbero essere prese in considerazione schedule settimanali con dosaggio di 30 mg/mq o inferiori (73).	**Condizionata a sfavore**

original repor

Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial

J Clin Oncol 40:1980-1990. © 2022 b

Presentato ad ASCO 2020

Naomi Kiyota, MD, PhD[1]; Makoto Tahara, MD, PhD[2]; Junki Mizusawa, ME[3]; Takeshi Kodaira, MD[4]; Hirofumi Fujii, MD[5];

28 institutions in Japan

261 postoperative high-risk patients.

Median follow-up was 2.2 years

noninferiority margin of HR of 1.32.

The primary end point of the phase II part was the proportion of treatment completion among all eligible patients. The primary end point of the phase III part was OS, and secondary end points were relapse-free survival (RFS), local relapse-free survival, nutrition support–free survival, nonhospitalized treatment period during the permissible treatment period, and adverse events (AEs).

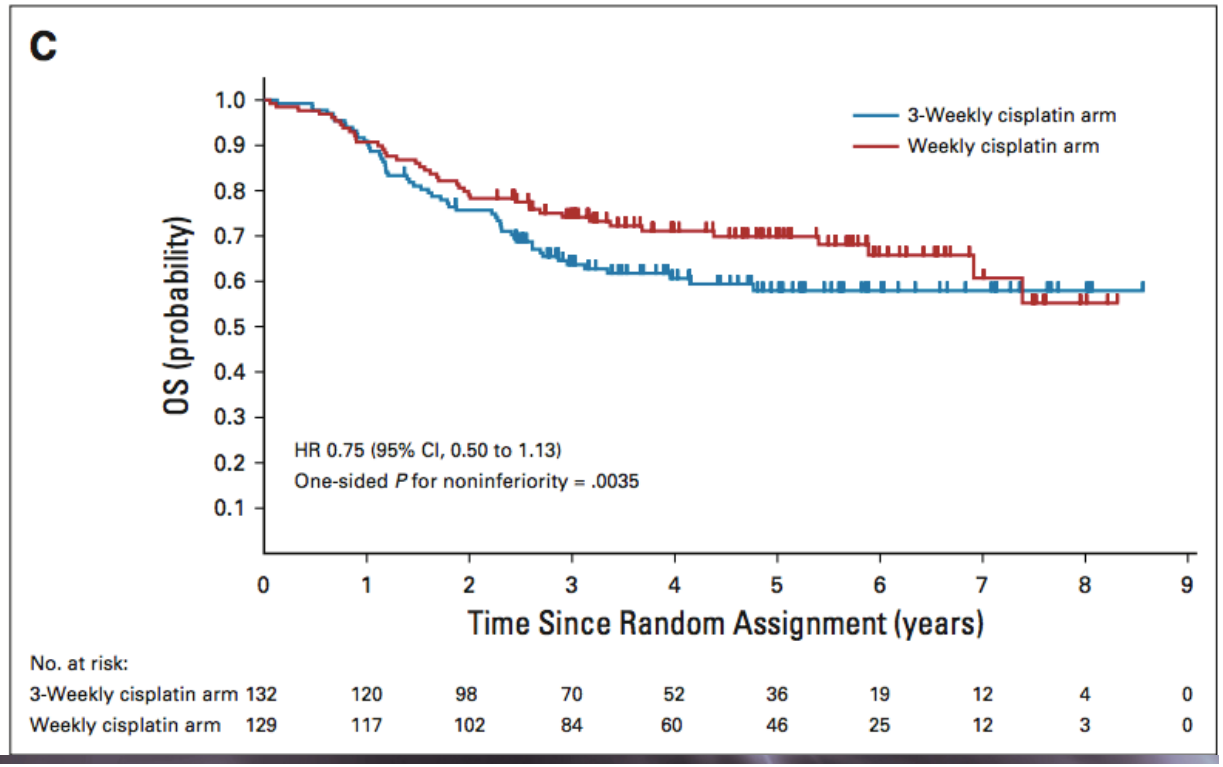

TABLE 3. Acute Adverse Events in ≥ 15% of Patients

	3-Weekly Cisplatin (n = 129), No. (%)		Weekly Cisplatin (n = 122), No. (%)	
Adverse Event	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Hematologic				
Anemia	129 (100)	18 (14)	122 (100)	16 (13)
Leukocytopenia	123 (95)	71 (55)	114 (93)	75 (62)
Neutropenia	118 (92)	63 (49)	106 (87)	43 (35)
Thrombocytopenia	85 (66)	3 (2)	102 (84)	4 (3)
Creatinine increased	51 (40)	0 (0)	36 (30)	0 (0)
Fatigue	50 (39)	5 (4)	41 (34)	1 (1)
Hypokalemia	46 (36)	7 (5)	25 (21)	3 (3)
Tinnitus	32 (25)	0 (0)	6 (5)	0 (0)
Hypermagnesemia[a]	26 (20)	3 (2)	10 (8)	1 (1)
Diarrhea				
Infection				
Fever				
Alopecia				
Vomiting	22 (17)	1 (1)	16 (13)	0 (0)
Hearing disturbance	22 (17)	5 (4)	9 (7)	2 (2)

only around 60% of patients completed 3 CDDP
In practice, this would allow for a possible 32% decrease in risk of death in chemoradiotherapy with weekly cisplatin

Meeting Abstract | 2022 ASCO Annual Meeting I

HEAD AND NECK CANCER

An open-label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (ConCERT trial).

Atul Sharma, Manish Kumar, Suman Bhasker, Alok Thakar, Raja Pramanik, Ahitagni Biswas, ...

Randomized trial from India, looking at q3 week high dose cisplatin (T), compared to a weekly schedule with 40 milligrams per meter squared (W).
Primary endpoint: 2year LRC.
Both postoperative and definitive patients.
70% of the patients in each arm treated with 2D RT on cobalt machine.
278 pts

Cumulative 2 year LRC rates were 52.6% in T and 47.4% in W (log-rank p=0.426; HR 0.86 [95%CI: 0.60-1.23]) by parametric survival estimates with an absolute difference of 5.2% (95%CI= -7.7, 18.2) within pre defined margin of 10%.
overall survival for the high dose arm median was 30 months, 25.5 months in the 40 milligrams per meter squared arm. PFS 21.3 versus 20.8.

But… small study not adequately powered (56% patients got T, compared to 60.9% W, below the statistics)

- Rinofaringe

1. IMRT sola vs IMRT-CHT per stadio II
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- Orofaringe

1. Dose-escalated CRT vs control in high risk OPC (CompARE ph III trial)

ICHNO 20
ECHNO 22

Results from CompARE phase III RCT: Dose Escalated Chemoradiation vs control in oropharyngeal cancer

Arm 1 versus arm 3 (2:1 randomisation)

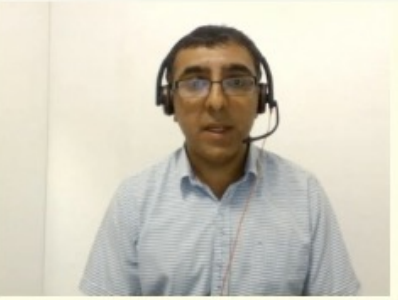
CompARE Trial

Arm 1: 70Gy in 35 fractions with cisplatin over 7 weeks +
Cisplatin 100mg/m2 3 weekly or 40mg/m2 weekly
(Elective dose 56Gy in 35 fractions)

Arm 3: 64Gy in 25 fractions with cisplatin over 5 weeks +
Cisplatin 100mg/m2 week 1 and week 5 or 40mg/m2 weekly
(Elective dose 50Gy in 25 fractions)

Centralised radiotherapy quality assurance programme

RTTQA
Radiotherapy Trials Quality Assurance



Paul SANGHERA

Primary outcome OS, interim outcome EFS.
72 control arm events are required to perform the first interim analysis.
Secondary outcome toxicity (CTCAEv4.0), QoL, swallowing using MDADI and gastrostomy dependence.
Analysis was by intention to treat.

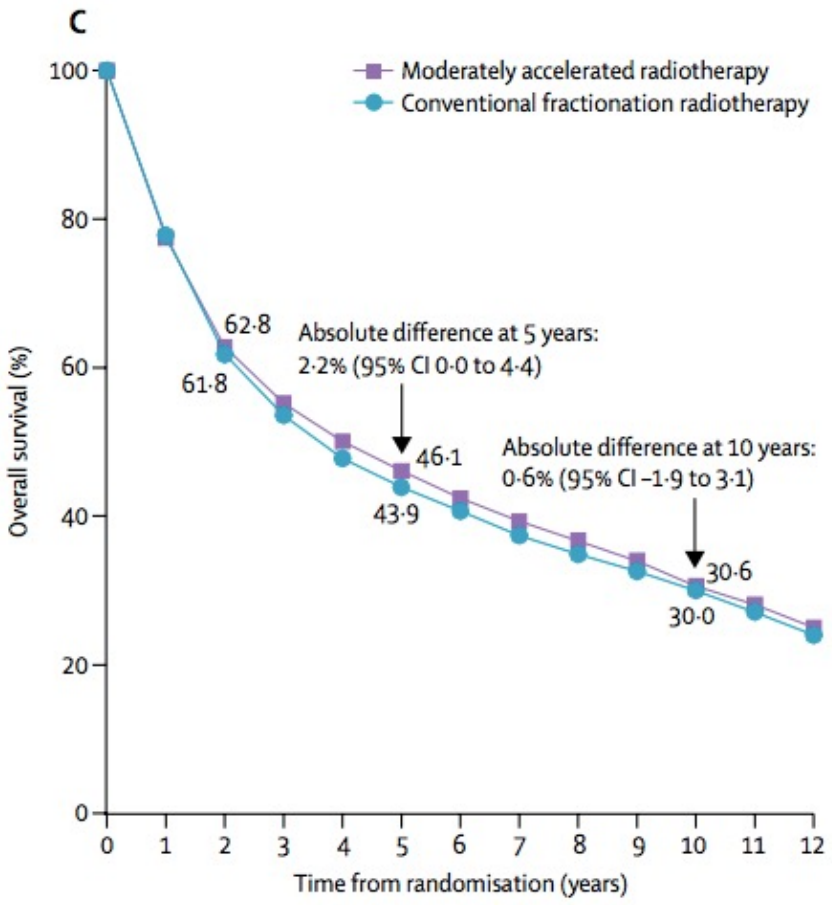
Risk	Characteristics	3-year OS
Low	HPV+, Non-Smoker HPV+, Smoker N0-2a	93% (95% CI, 88.3-97.7)
Intermediate	HPV+, Smoker, N2b-3 HPV-, Non-Smoker T2-3	71% (95% CI, 60.7-80.8)
High	HPV-, Non-Smoker, T4 HPV-, Smoker	46% (95% CI, 34.7-57.7)

- 257 patients (172 in Arm 1 and 85 in Arm 3)
- well balanced between the arms (80% intermediate risk 20% high risk).
- 97% patients received radiotherapy as planned for each arm.
- Median follow up 36.7 months (95% CI. 27.6, 37.5).
- 3y EFS rate was 72% (95%CI 64-78%) in arm 1 and 68% (95% CI 56-78%) in arm 3, (p=0.98). Adjusted hazard ratio for arm 3 versus 1 was 1.00 (95/% CI 0.62, 1.62).
- Rates of gastrostomy tube use at 2 years were 5% and 9% in arms 1 and 3 respectively (p=0.35).
- Due to SAE Arm 3 has been stopped causing evaluation of OS underpowered
- Group of patients who benefit the most from hypofractionation has to be defined as well as the role of p16 status

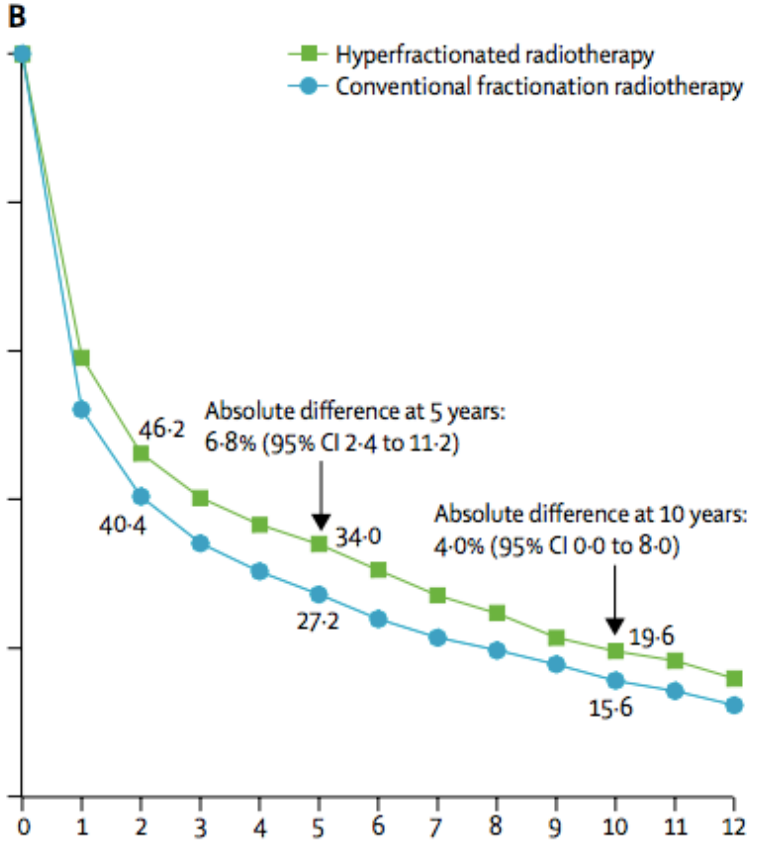
MARCH

- 33 trials, 11 423 patients. Follow-up 7.9-10 y. Per lo più orofaringe e laringe; 5221 (74%) pazienti di stadio III-IV della malattia.
- significant benefit on overall survival for hyperfractionated group: absolute differences at 5 years of 8·1% (3·4 to 12·8) and at 10 years of 3·9% (–0·6 to 8·4).
- Altered fractionation radiotherapy absolute difference at 5 years of 3·1% (95% CI 1·3–4·9) and at 10 years of 1·2% (–0·8 to 3·2).

Lucas B. Et al. MARCH Collaborative Group (MARCH): an updated meta-analysis. Lancet Oncol. 2017 Sep;18(9):1221-1237



	Years 0–2	Years 2–5	Years 5–10	Years 10+
Moderately accelerated radiotherapy (deaths/person-years)	1497/6347	610/5816	343/4291	152/1412
Conventional fractionation radiotherapy (deaths/person-years)	1525/6292	650/5528	309/4005	153/1334



	Years 0–2	Years 2–5	Years 5–10	Years 10+
Hyperfractionated radiotherapy (deaths/person-years)	449/1122	106/985	94/861	46/366
Conventional fractionation radiotherapy (deaths/person-years)	507/980	106/773	71/628	34/272

CompARE is a phase III randomised controlled trial using an adaptive, multi-arm multi-stage design to evaluate alternative regimes for escalating treatment of intermediate and high risk oropharyngeal cancer (OPC).

People will be put into 1 of 4 treatment groups:

- cisplatin and radiotherapy (chemoradiotherapy)
- docetaxel, cisplatin and 5-fluorouracil chemotherapy followed by chemoradiotherapy. **Please note this group is now closed**
- high dose radiotherapy and cisplatin. **Please note this group is now closed**
- surgery followed by chemoradiotherapy **Please note this group is now closed**
- durvalumab and chemoradiotherapy followed by durvalumab