ESMO GUIDELINES:
REAL WORLD CASES

NASOPHARYNGEAL CARCINOMA
(ESMO-EURACAN)

Jean-Pascal Machiels

Institut Roi Albert II, Cliniques universitaires Saint-Luc, UCLouvain
Brussels

ESMO WEBINAR SERIES

Programme

30 July 2024

10 min	**Welcome and introduction** Jean-Pascal Machiels
10 min	**Case Presentation** Myrto Moutafi
20 min	**Presentation of the ESMO Clinical Practice Guideline for Critical Analysis of the Case** Paolo Bossi
10 min	**Considerations Related to Guideline Implementation in Everyday Clinical Practice and Discussion** Alberto Jacobo Cunquero Tomás
10 min	**Live Q&A and Discussion** All speakers

Jean-Pascal Machiels
Chair
Institut Roi Albert II, Cliniques universitaires Saint-Luc, UCLouvain Brussels

Myrto Moutafi
Speaker
Attikon University Hospital, Athens

Paolo Bossi
Speaker
Università degli Studi di Brescia

Alberto Jacobo Cunquero Tomás
Speaker
Medical Oncology Department, General University Hospital of Valencia

EPIDEMIOLOGY

- Nasopharyngeal carcinoma (NPC) is a disease with unique epidemiological features.
- The global age-standardised incidence rates varied from 2.1 to 0.4 per 100 000 in Asia and Europe.
- In low incidence areas, the incidence of NPC increases with age with a bimodal peak: the first in adolescents and young adults and the second after 65 years of age.
- In endemic areas, the incidence increases after 30 years of age, peaks at 40-59 years and decreases thereafter.
- The male female incidence ratio is 2.75
- Prognosis seems to be better in endemic areas

Ferlay J, et al. International Agency for Research on Cancer 2018; Bossi P, et al. ESMO Guidelines. Ann Oncol 2021.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Table 1. WHO classification of nasopharyngeal carcinomas

	ICD-O code
Non-keratinising squamous cell carcinoma	8072/3
Keratinising squamous cell carcinoma	8071/3
Basaloid squamous cell carcinoma	8083/3

ICD-O, International Classification of Diseases for Oncology; WHO, World Health Organization.

- ✓ Definitive diagnosis is made by endoscopic-guided biopsy of the primary nasopharyngeal tumour
- ✓ Non-keratinising cancer (differentiated and undifferentiated) comprises the vast majority of cases and is linked to EBV infection.
- ✓ Keratinising cancer is more frequent in nonendemic than endemic areas
- ✓ EBV is identified by ISH by the presence of EBV-encoded RNAs in NPC tissue

Bossi P, et al. ESMO Guidelines. Ann Oncol 2021.

DIAGNOSIS WORK-UP

- ✓ Medical history, physical examination with cranial nerve examination, CBC, serum biochemistry (including liver and renal function tests and LDH)
- ✓ Nasopharyngoscopy
- ✓ MRI is the most accurate way of defining local and nodal tumour
- ✓ FDG-PET for detecting distant metastases
- ✓ Baseline audiometric testing, dental examination, nutritional status evaluation and ophthalmological and endocrine evaluation

Bossi P, et al. ESMO Guidelines. Ann Oncol 2021.

TNM 8TH EDITION

T categories

T1 Nasopharynx, oropharynx, nasal cavity

T2 Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles

T3 Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses

T4 Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle

N Categories

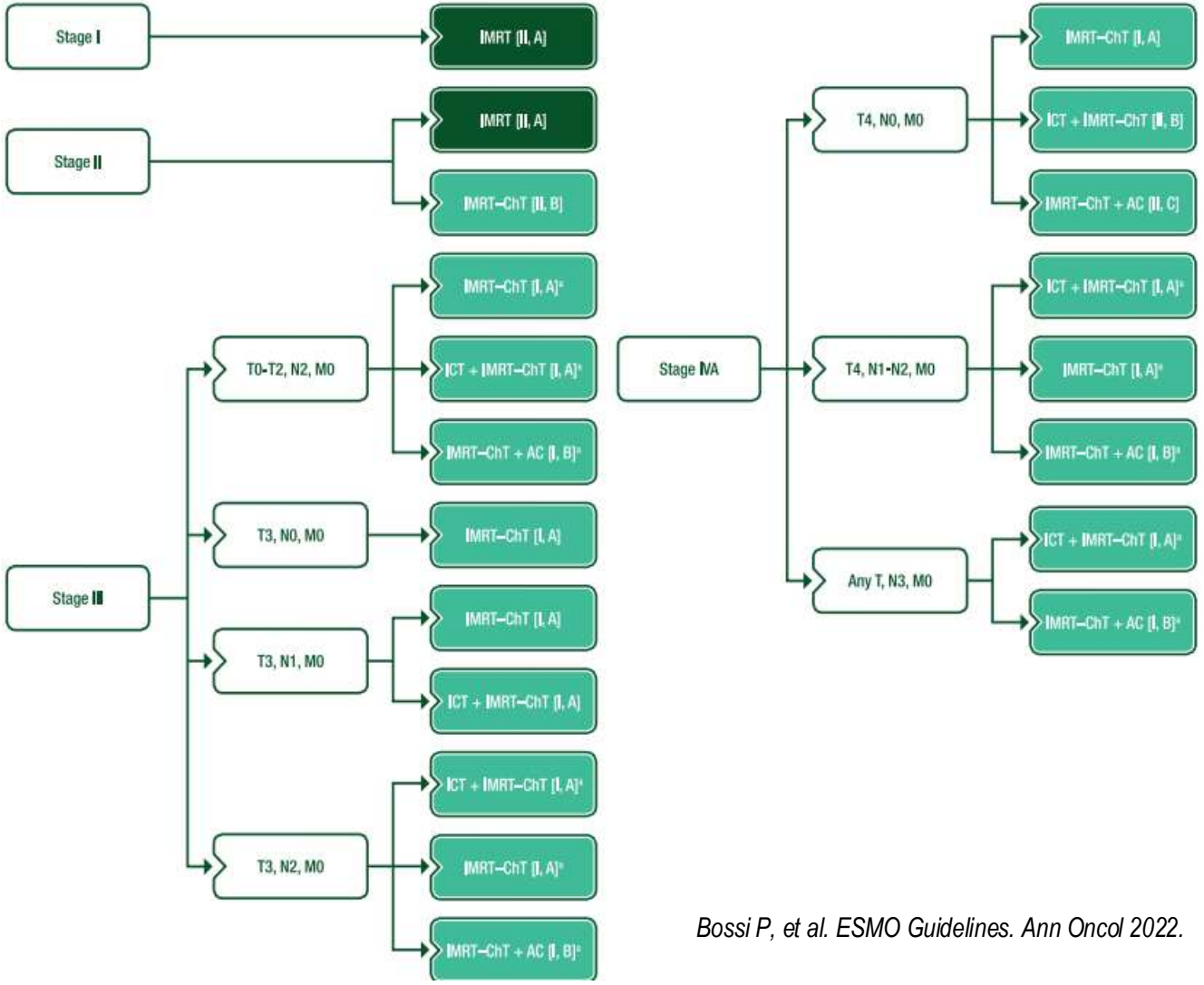
N1 Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less ,above the caudal border of cricoid cartilage

N2 Bilateral metastasis in cervical lymph node(s), 6 cm or less above the caudal border of cricoid cartilage

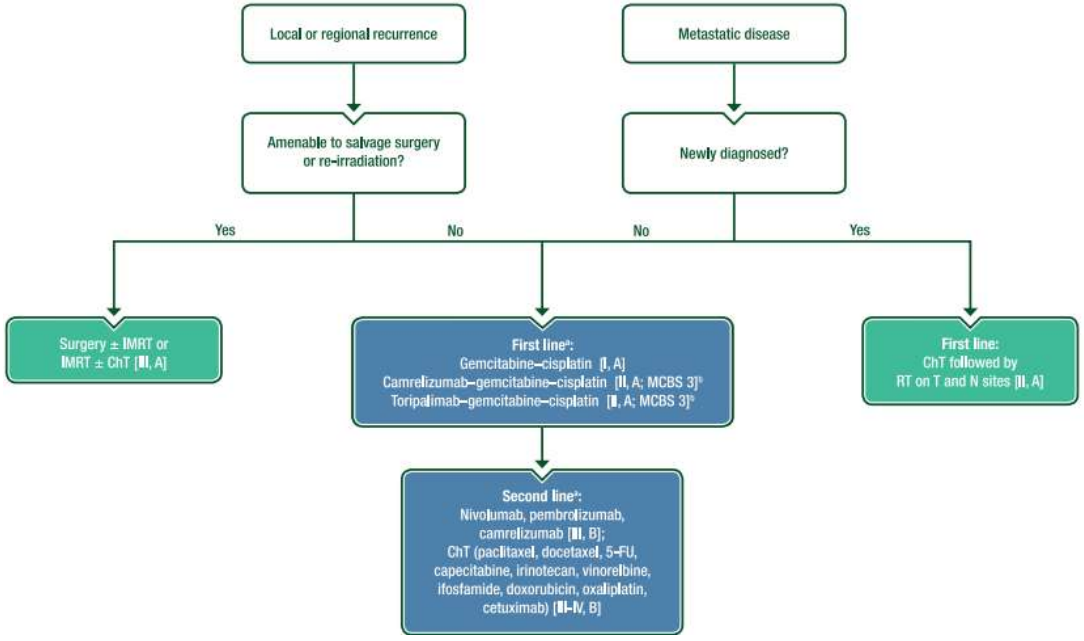
N3 Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage

TREATMENT GUIDELINES

Stage I and IVA



Recurrent/metastatic



Bossi P, et al. ESMO Guidelines. Ann Oncol 2022.

ESMO GUIDELINES:
REAL WORLD CASES

NASOPHARYNGEAL CARCINOMA

Case Presentation

Myrto Moutafi

MD, MSc, PhD (c)

Attikon University Hospital, Athens, GR

ESMO WEBINAR SERIES

NASOPHARYNGEAL CARCINOMA

Case Presentation

PATIENT INFO

Medical History

Male 54 yo (10/2018), PS=0

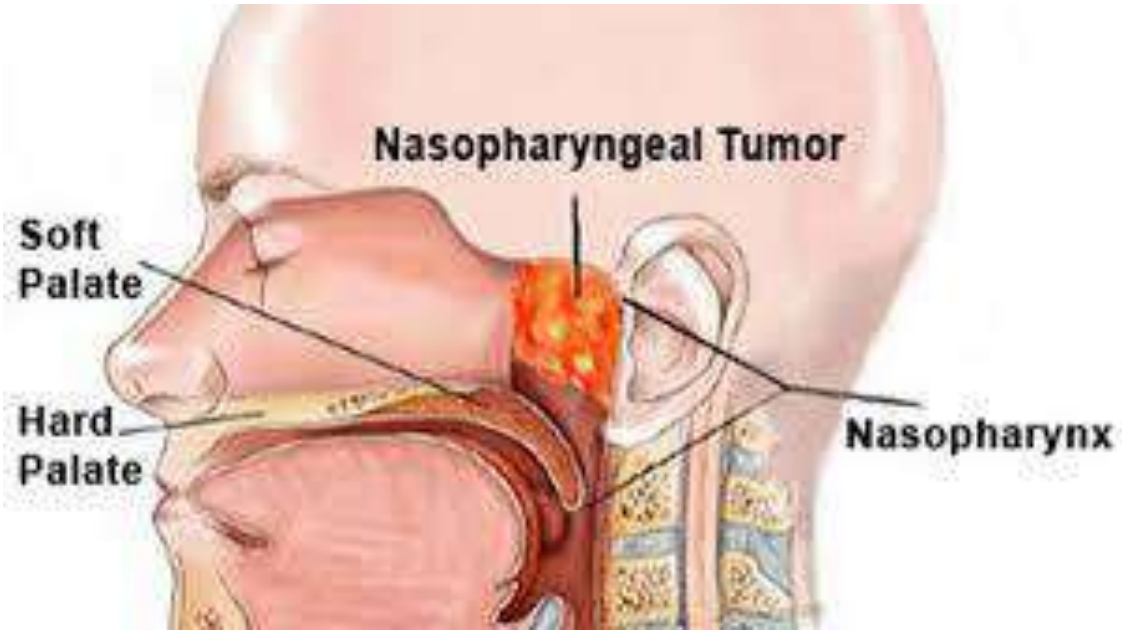
ROS: stuffy nose (bloked on L side), headache 5 mo

Meds: no Rx, All: NKDA. FH: none

PMH: no. No surgeries

SH: former (stop 10y ago) / no eoth.

ENT visit -> biopsy



CASE PRESENTATION

Initial Workup

10/2018 Nasopharyngeal Mass Biopsy:

- Keratinizing squamous cell carcinoma (WHO type I)

10/2018

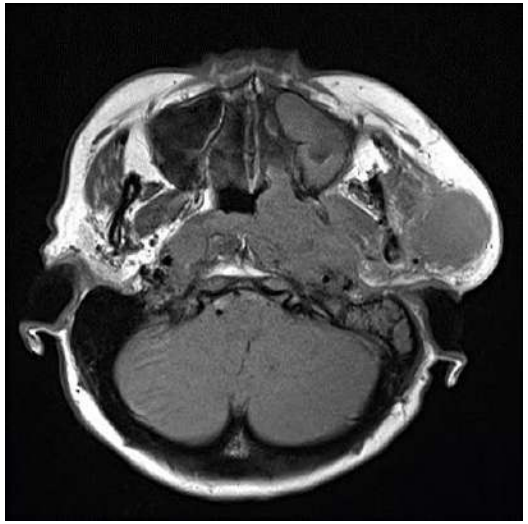
PET-CT scan : lung nodules, liver metastatic lesions (VIII, VII, VI), splenic metastatic lesion 0.9cm, T4 and lumbar vertebrae bone metastasis

MRI: Soft tissue fullness in the region of the LEFT nasopharynx (3.2x3.3x3.1cm) with extension to parapharyngeal space

• Several enlarged LNs in the both sides of the neck at levels II and III

– Diagnosis: Nasopharyngeal Squamous Cell Carcinoma,

Stage IVB (de novo metastatic)



CASE PRESENTATION

Management -1st Line Treatment

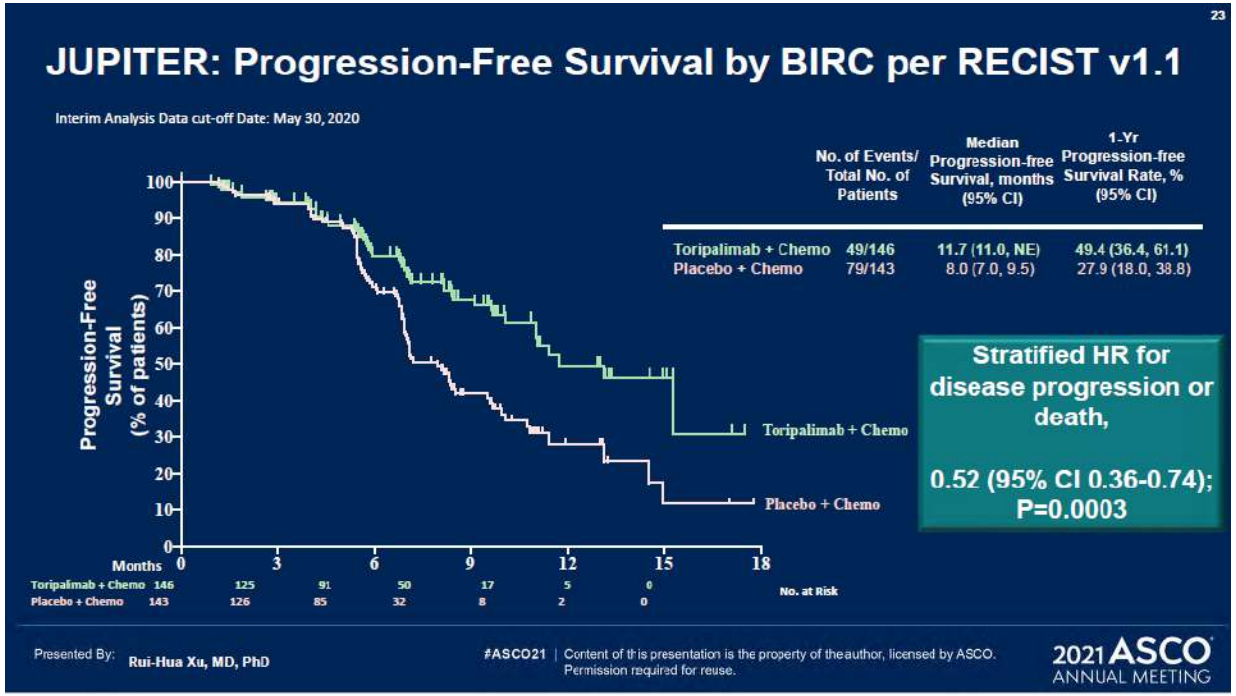
23/10/2018 1st line Treatment:

- Cisplatin + Gemcitabine +Nivolumab x 4 cycles
- Denosumab

19/12/2018 : Best response after 3 cycles:

Local and liver PR .

- PD-L1 IHC 22C3 pharmaDx Kit : CPS 50-60



CASE PRESENTATION

Management -1st Line Treatment

24/05/2019

- Pt started replacement with thyroid hormone and endocrinology consultation (incidence rates for hypothyroidism due to nivolumab is 7% vs 3.9% due to pembrolizumab)

15/09/2019

- Pt presented with diabetic ketoacidosis in ER; -> required insulin therapy at diagnosis and remained insulin-dependent for diabetic control

Acute onset of type 1 diabetes mellitus (DM) -> insulin-dependent for diabetic control

- Treatment with ICIs has been associated with acute onset of type 1 diabetes mellitus in approximately 0.2 to 0.9 percent of cases
- In contrast to other immune-related adverse events, treatment with glucocorticoids or other immunosuppressive agents is not effective in these patients, due to the almost complete destruction of the pancreatic beta cells by immunotherapy

CASE PRESENTATION

Management – 2nd Line Treatment

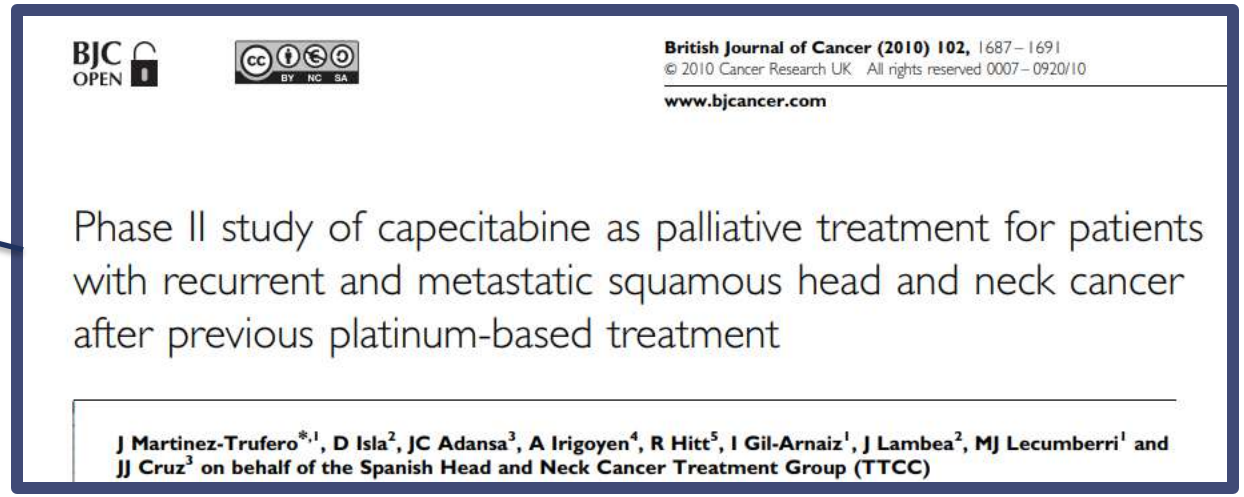
July 2019 : local PD, increase in number and size of regional and non-regional lymph nodes, liver nodules and lung nodules

- DFI: 10 months

30/08/2019 2nd line Treatment:

• Capecitabine

16/11/2020 : Best response after 3 cycles: SD



BJC OPEN

British Journal of Cancer (2010) 102, 1687 – 1691

www.bjcancer.com

Phase II study of capecitabine as palliative treatment for patients with recurrent and metastatic squamous head and neck cancer after previous platinum-based treatment

J Martinez-Trufero*,[1], D Isla[2], JC Adansa[3], A Irigoyen[4], R Hitt[5], I Gil-Arnaiz[1], J Lambea[2], MJ Lecumberri[1] and JJ Cruz[3] on behalf of the Spanish Head and Neck Cancer Treatment Group (TTCC)

February 2021: PD (hoarseness – ENT consultation : r/o airway obstruction, MRI : extension to oropharyngeal space, CTT :SD, CTA: increase in size and number of liver and splenic lesion

- DFI: 18 months

CASE PRESENTATION

Management -3rd Line Treatment

05/03/2021 3rd line Treatment:

- Carboplatin / Gemcitabine / Nivolumab

STOP Denosumab

12/05/2021 : Best response after 3 cycles: PR (lung and splenic PR) / PS=0

August 2021: local, bone PD (PS=2)

DFI: 6 months

CASE PRESENTATION

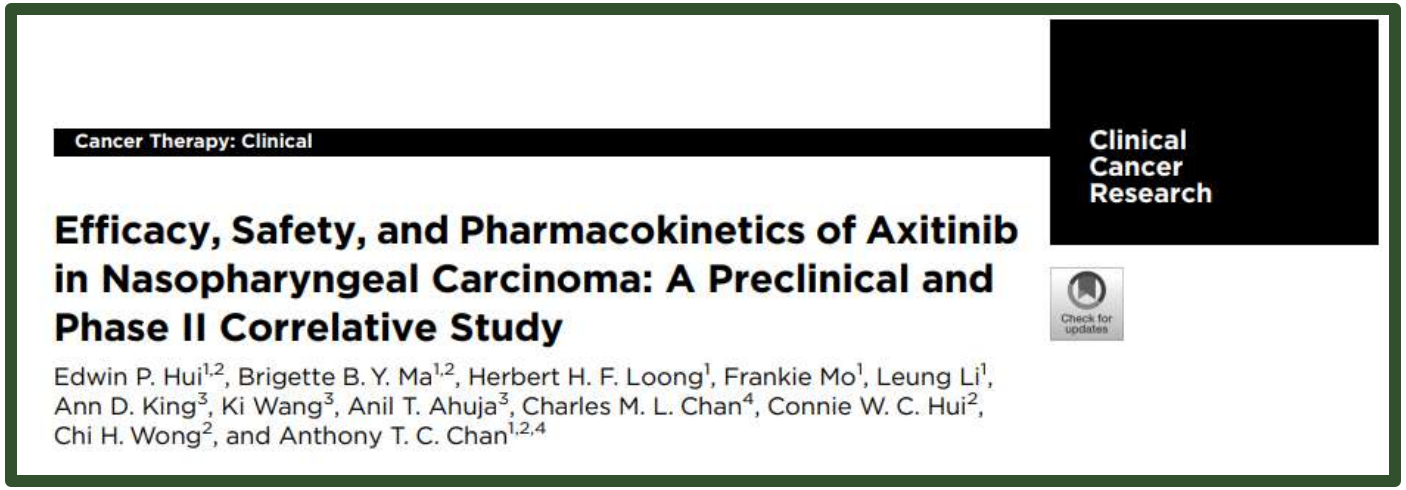
Management -4th Line Treatment

10/08/2021 5th line Treatment:

- Axitinib monotherapy

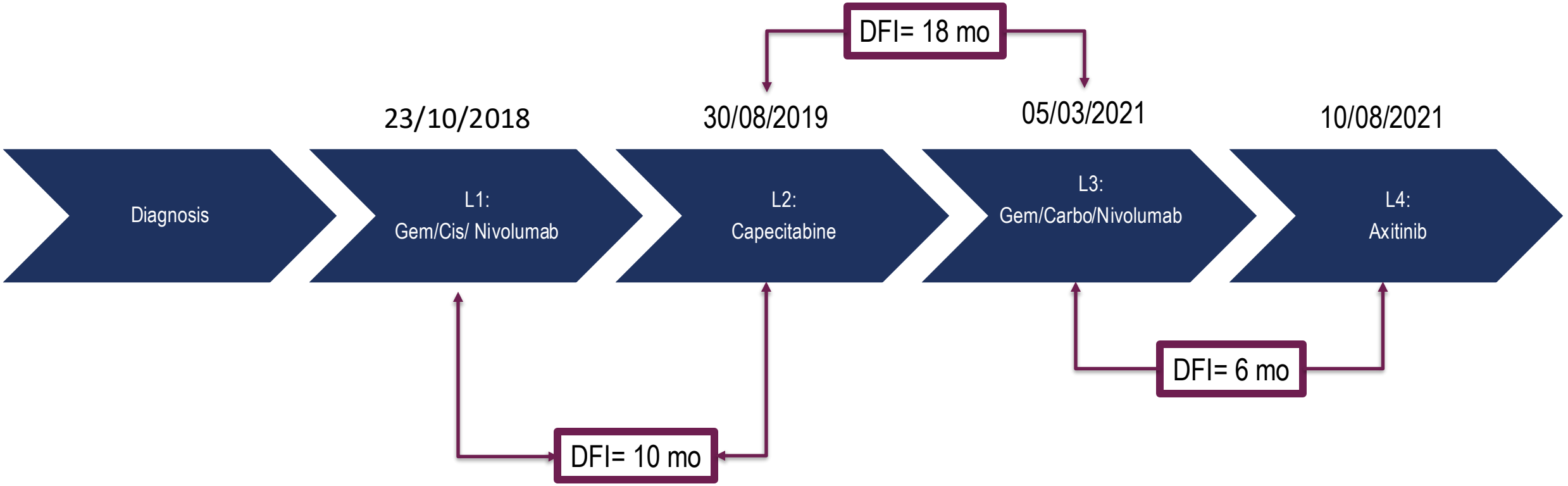
November 2021: DOD

DFI: 3 months



CASE PRESENTATION

Timeline



QUESTIONS

- Role of concurrent chemo-IMRT -> could improve survival in De Novo metastatic NPC following response to 1st line induction chemo ?
- High PDL1 association with response ? Other biomarkers?
- EBV DNA for disease response monitoring?

ESMO GUIDELINES: REAL WORLD CASES

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

ESMO WEBINAR SERIES

ESMO GUIDELINES:
REAL WORLD CASES

CRITICAL ANALYSIS OF THE CASE AND PRESENTATION OF THE CPG ESMO GUIDELINES

Nasopharyngeal Cancer

Paolo Bossi
Humanitas University
Milan, Italy

ESMO WEBINAR SERIES

WHAT ABOUT THE CASE?

Insights and discussion

DE NOVO METASTATIC KERATINIZING WHO TYPE I NPC

10/2018 Nasopharyngeal Mass Biopsy:

- Keratinizing squamous cell carcinoma (WHO type I)

10/2018

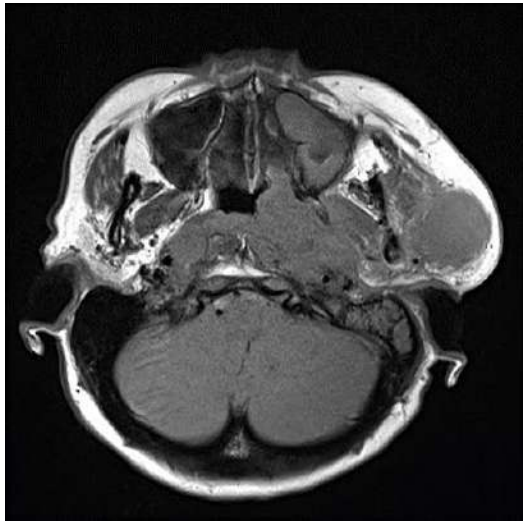
PET-CT scan : lung nodules, liver metastatic lesions (VIII, VII, VI), splenic metastatic lesion 0.9cm, T4 and lumbar vertebrae bone metastasis

MRI: Soft tissue fullness in the region of the LEFT nasopharynx (3.2x3.3x3.1cm) with extension to parapharyngeal space

• Several enlarged LNs in the both sides of the neck at levels II and III

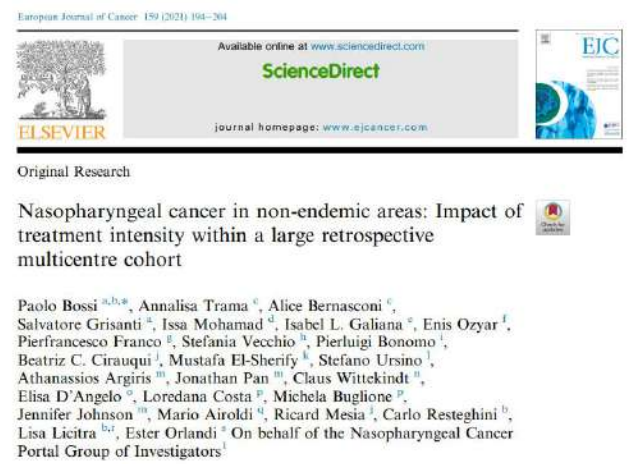
– Diagnosis: Nasopharyngeal Squamous Cell Carcinoma,

Stage IVB (de novo metastatic)



WHO TYPE I NPC

What we know about this histotype?


European Journal of Cancer 159 (2021) 194–204

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC

Original Research

Nasopharyngeal cancer in non-endemic areas: Impact of treatment intensity within a large retrospective multicentre cohort

Paolo Bossi [a,b,*], Annalisa Trama [c], Alice Bernasconi [c], Salvatore Grisanti [a], Issa Mohamad [d], Isabel L. Galiana [e], Enis Ozyar [f], Pierfrancesco Franco [g], Stefania Vecchio [h], Pierluigi Bonomo [i], Beatriz C. Cirauqui [j], Mustafa El-Sherify [k], Stefano Ursino [l], Athanassios Argiris [m], Jonathan Pan [m], Claus Wittekindt [n], Elisa D'Angelo [o], Loredana Costa [p], Michela Buglione [p], Jennifer Johnson [m], Mario Airoldi [q], Ricard Mesia [j], Carlo Resteghini [b], Lisa Licitra [b,r], Ester Orlandi [a] On behalf of the Nasopharyngeal Cancer Portal Group of Investigators[1]

Table 1
Clinical characteristics and treatment strategies of patients included in the study overall and by EBER status.

	Overall N = 1230	EBER + N = 511	EBER- N = 114	Comparison EBER+ and EBER-
Age, years				p-value = 0.5064
mean (SD)	49.9 (14.8)	48.8 (15.0)	49.9 (15.4)	
Age (%)				p-value = 0.787
<65 (%)	1012 (82%)	425 (83%)	96 (84%)	
≥65 (%)	218 (18%)	86 (17%)	18 (16%)	
Sex (%)				p-value = 0.105
Male	885 (72%)	375 (73%)	75 (66%)	
Female	345 (28%)	136 (27%)	39 (34%)	
Histology (%)				p-value<0.001
Keratinising	146 (12%)	38 (7%)	25 (22%)	
Non-keratinising	1051 (86%)	464 (91%)	80 (70%)	
Basaloid	18 (1%)	6 (1%)	8 (7%)	

Bossi P et al., Eur J Cancer 2021

WHAT WE KNOW ABOUT KERATINIZING NPC

- **The presence of EBV is rare, what about HPV?**

  → It is difficult to ascertain the real prevalence of HPVpos NPC, as testing HPV might be considered particularly for EBV negative cancer patients

- **Difficult to draw conclusions about clinical behaviour and type of treatments**

  → HPV-positive NPC and EBV-positive NPC seem to be **mutually exclusive diseases**.
  Patients who have **HPV-positive NPC** have greater local symptom burden and larger primary tumors but have **similar outcomes** compared with patients who have EBV-positive NPC or HPV-positive OPC

  Treatment choices are derived from clinical trials conducted in eastern Asia (endemic countries)

Verma V et al, Head and Neck 2017
Huang SY et al, Cancer 2022

METASTATIZED NPC: NEWS FROM TREATMENT APPROACH?

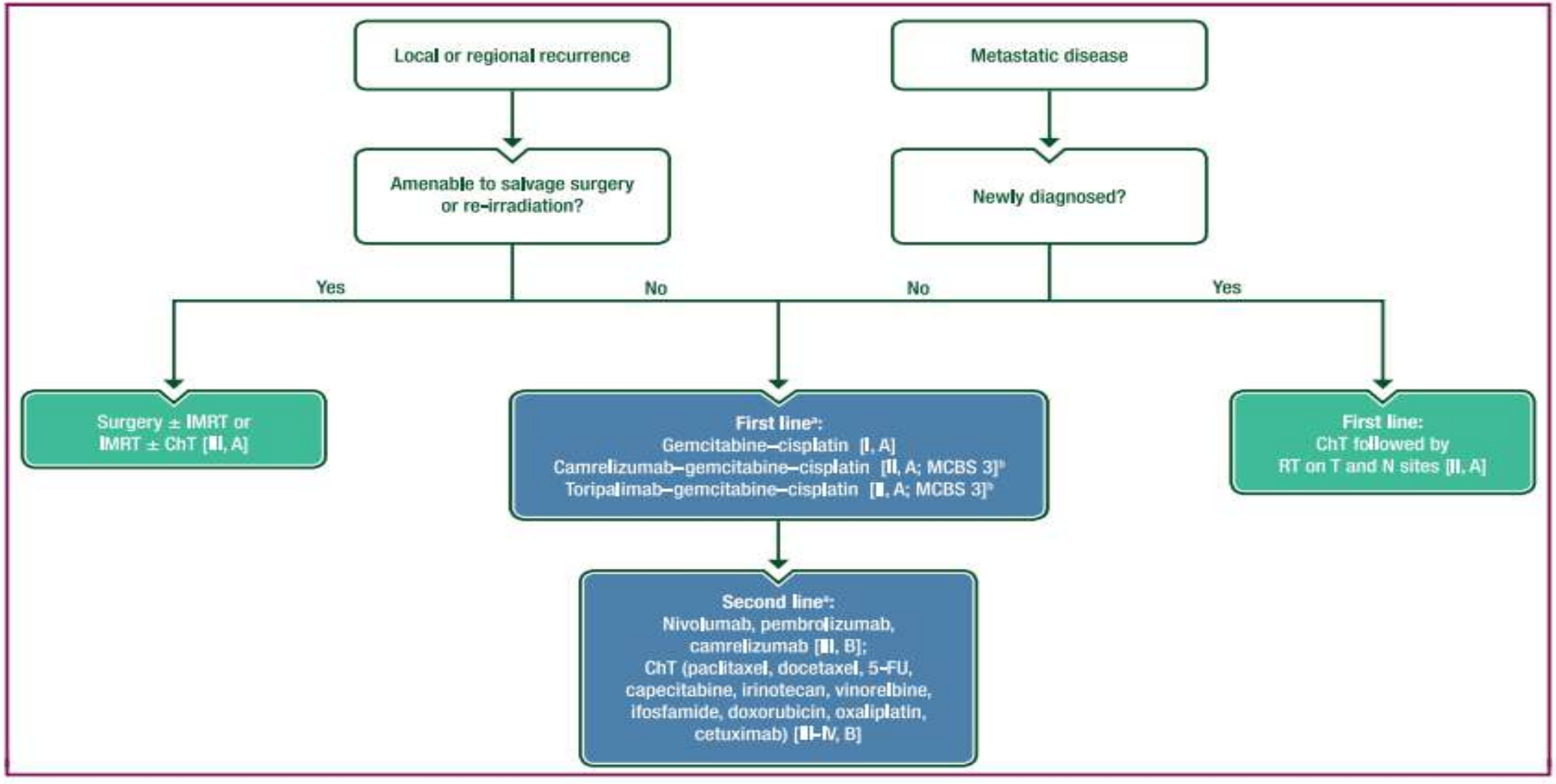


Figure 2. Treatment algorithm for recurrent and/or metastatic NPC.

Recurrent/metastatic NPC: chemo-immunotherapy

Anti-PD1 + cisplatin + gemcitabine

	ref	ORR	mPFS	mOS	Dose intensity
Camrelizumab + CT*	1	87.3%	9.7 mos	NR	>4 cycles: 80% 6 cycles: 69%
Toripalimab + CT*	2	77.4%	11.7 mos	NR	Median n. cycles: 6
Tislelizumab + CT*	3,4	69.5%	9.6 mos	17.2 m vs 10.6	Not presented for CT
Comparator arms (CT*)	1,2,3	55.3-80.6%	6.9-8 mos		>4 cycles[2]: 78% 6 cycles[2]: 66%

1. Yang Y, Lancet Oncol 2021; 2. Mai HQ, Nat Med 2021; 3. Yang Y, Abs 1210, ESMO 2021; 4. Xu Lancet Oncology 2023

Licitra L, ESMO 2023 presentation

Contents lists available at ScienceDirect
Oral Oncology
journal homepage: www.elsevier.com/locate/oraloncology

WHAT WE KNOW ABOUT DE NOVO METASTATIZING NPC?

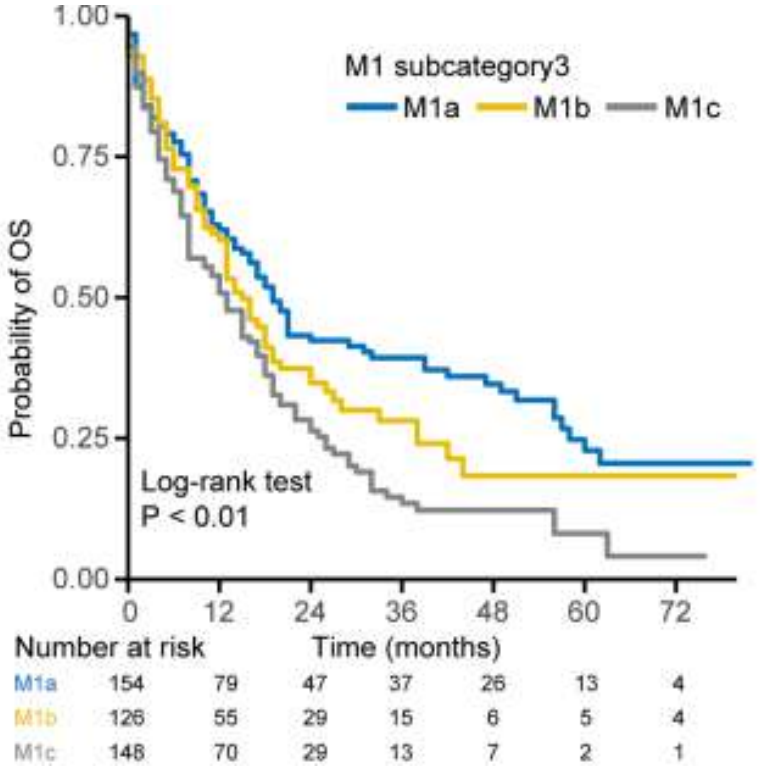
Metastatic characteristics associated with survival of synchronous metastatic nasopharyngeal carcinoma in non-epidemic areas

Mei Lin[a,b,c,1], Qi Yang[a,b,c,1], Rui You[a,b,c], Xiong Zou[a,b,c], Chong-yang Duan[d],

- **Prognosis of de novo metastatic NPC may be refined through a more granular classification**

The Authors established a new M1 subdivision system based on metastatic characteristics:

M1a, without bone and liver involvement; **M1b**, single bone or liver involvement;
M1c, multiple metastatic locations including bone and/or liver



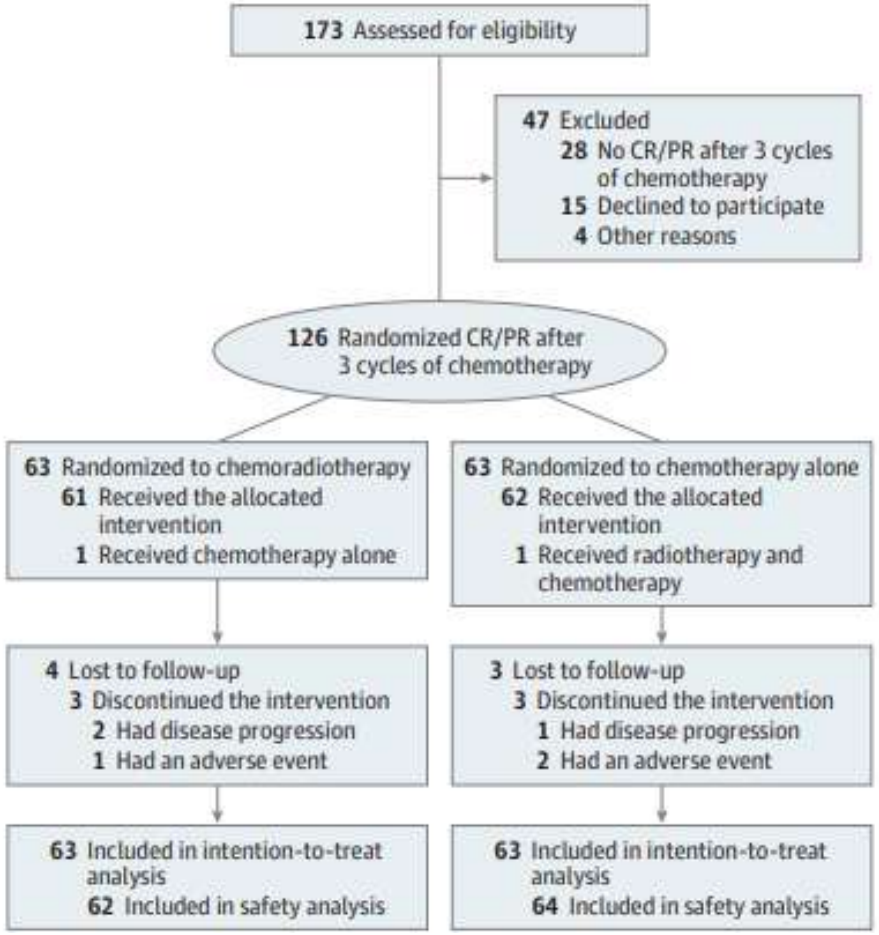
May the use of immunotherapy have changed the disease outcome?

Lin M et al. Oral Oncol 2022

WHAT WE KNOW ABOUT DE NOVO METASTATIZING NPC?

- **De novo metastatizing NPC pts benefit from the locoregional treatment of primary/nodes!**

Multicenter, randomized Ph 3 clinical trial investigating the efficacy of locoregional radiotherapy to the primary T + regional N in pt with mNPC who demonstrated an initial complete or partial response to palliative PF chemotherapy



You R, JAMA Oncol 2020

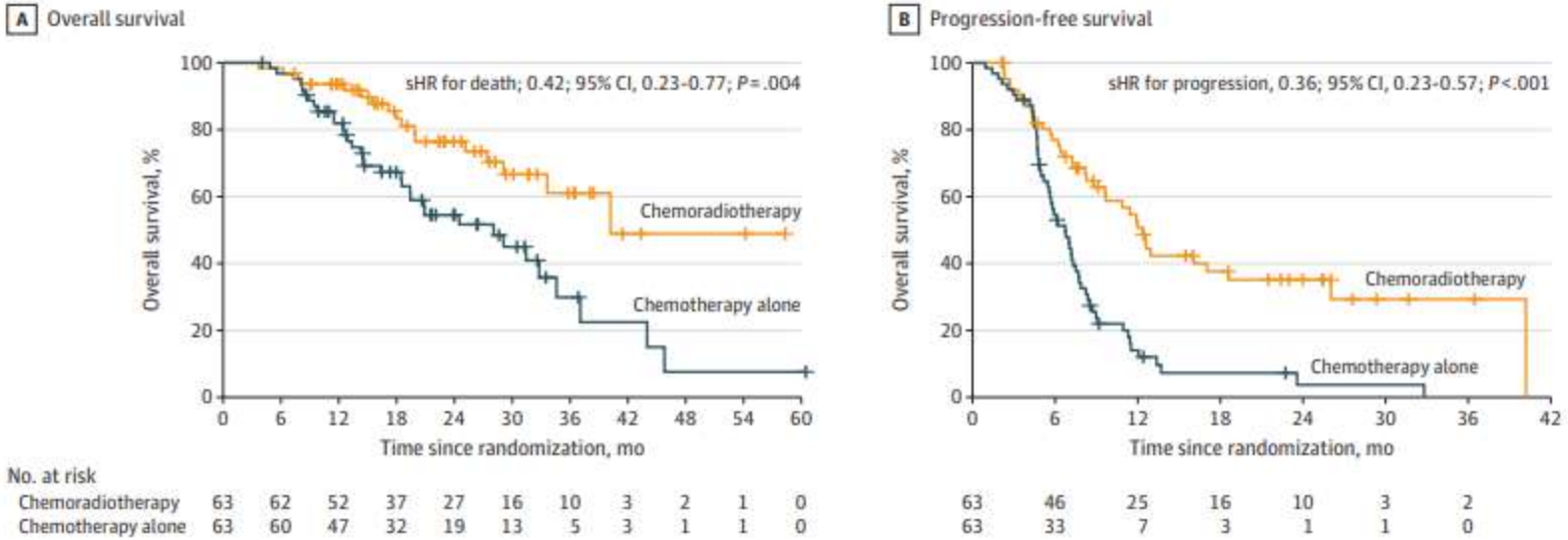
WHAT WE KNOW ABOUT DE NOVO METASTATIZING NPC?

- **De novo metastatizing NPC pts benefit from the locoregional treatment of primary/nodes!**

Reduction of locoregional relapses and fewer distant metastatic recurrences (54.0% vs 68.3%).

The importance of treating T and N!

Figure 2. Overall Survival and Progression-free Survival in the Intention-to-Treat Population



What the role of locoregional Tx in pts with SD/PD?

Will the administration of IO in 1st line change the results?

You R, JAMA Oncol 2020

METASTATIZED NPC: NEWS FROM TREATMENT APPROACH?

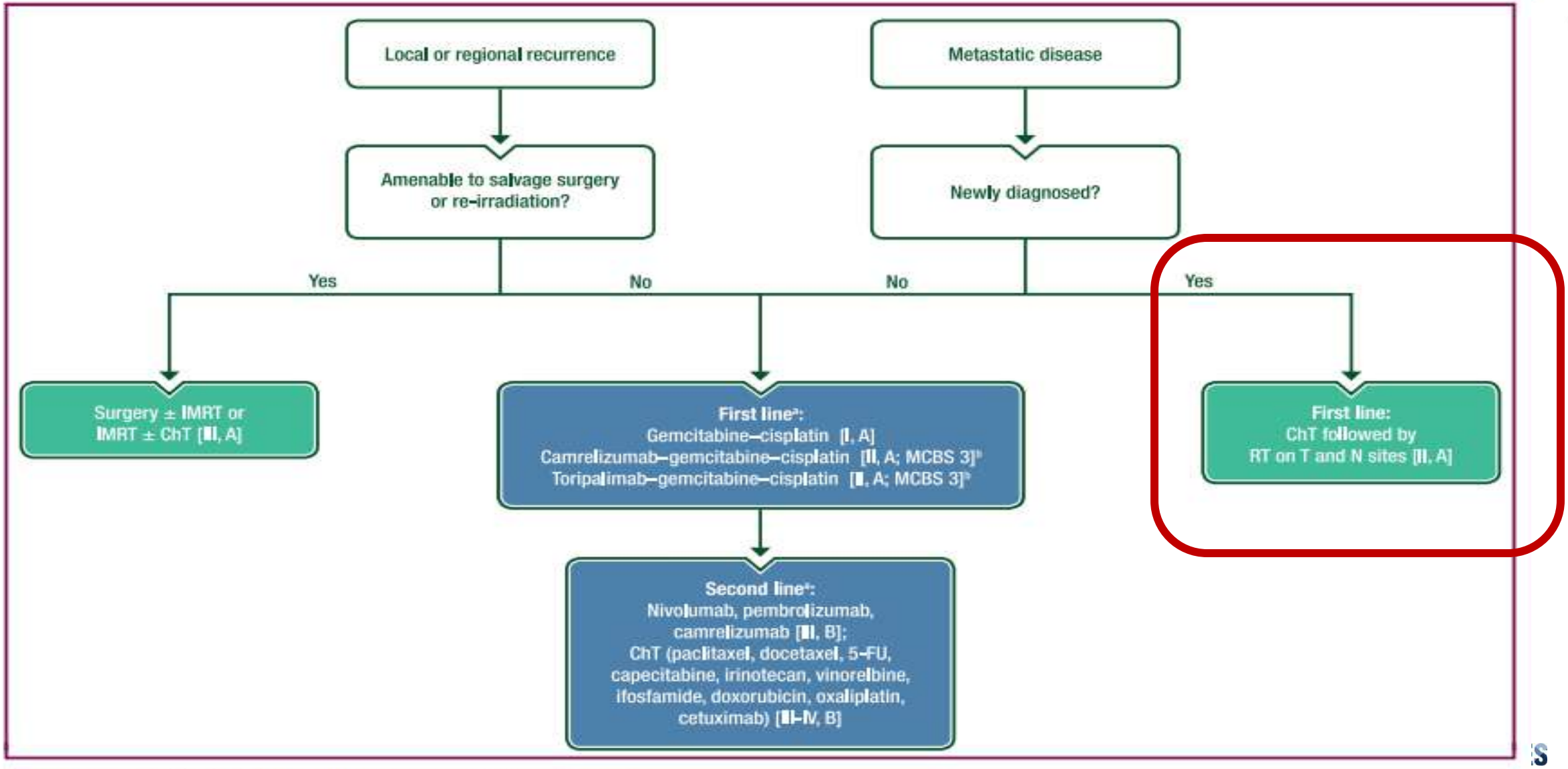


Figure 2. Treatment algorithm for recurrent and/or metastatic NPC.

BRIEF UPDATE FROM THE ESMO CPG ON NPC

- **Diagnostic work-up: emphasis on PET, EBV DNA and QoL**

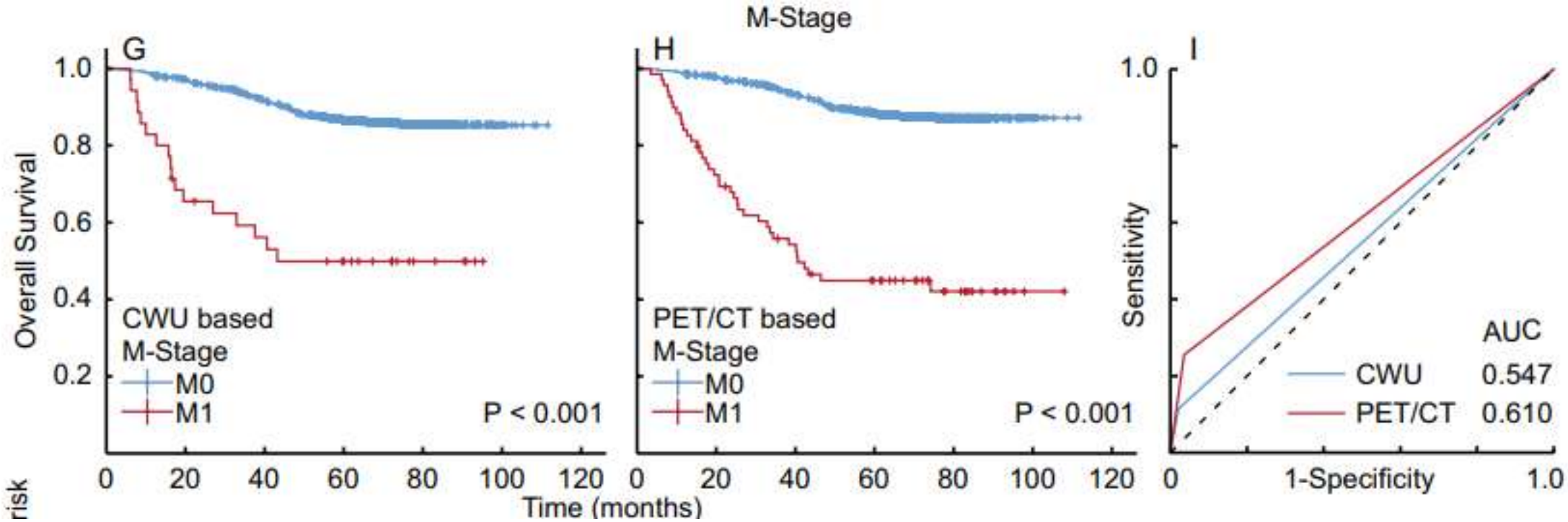
Table 2. Diagnostic work-up

1. Medical history and physical examination
2. CBC, serum biochemistry
3. Nasopharyngoscopy
4. Tumour biopsy (EBER by ISH [III, B])
5. CT scan or MRI of the nasopharynx and base of the skull and neck (to the clavicle) (MRI preferred [III, B])
6. ^{18}F-FDG-PET/CT imaging [III, B]
7. Baseline audiometric testing, dental examination, nutritional status evaluation, ophthalmological and endocrine evaluation
8. Plasma EBV DNA [III, B]
9. QoL assessment (e.g. EORTC QLQ-C30) [III, B]

BRIEF UPDATE FROM THE ESMO CPG ON NPC

- **PET in NPC staging:**

The MRI is superior to [18F]FDG PET/CT in T stage, and [18F]FDG PET/CT is superior to CWU in N/M stage.



Xie HJ et al. Eur Radiol 2023

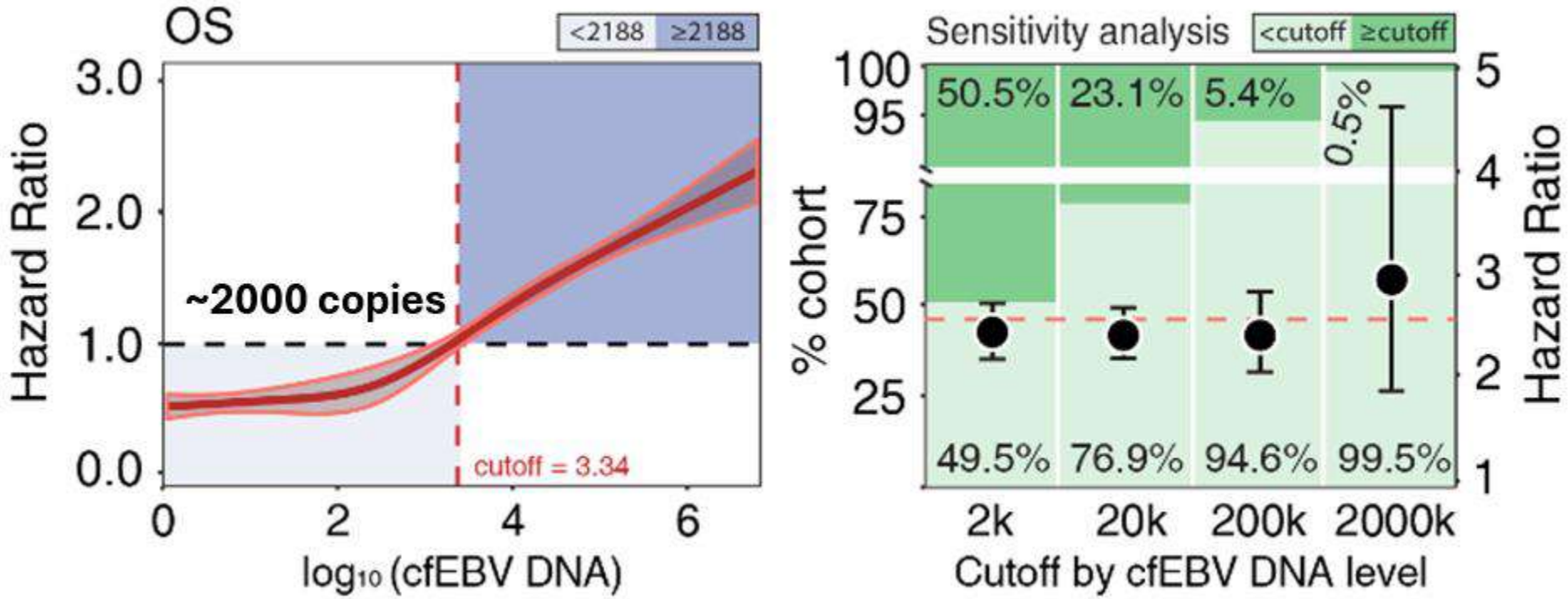
BRIEF UPDATE FROM THE ESMO CPG ON NPC

Development of a risk classification system combining TN-categories and circulating EBV DNA for non-metastatic NPC in 10,149 endemic cases

Fo-Ping Chen, Li Lin, Jin-Hui Liang, Sze Huey Tan, Enya H.W. Ong, Ying-Shan Luo

➢ **The importance of circulating EBV DNA at baseline**

EBV DNA definition of the cutoff is important

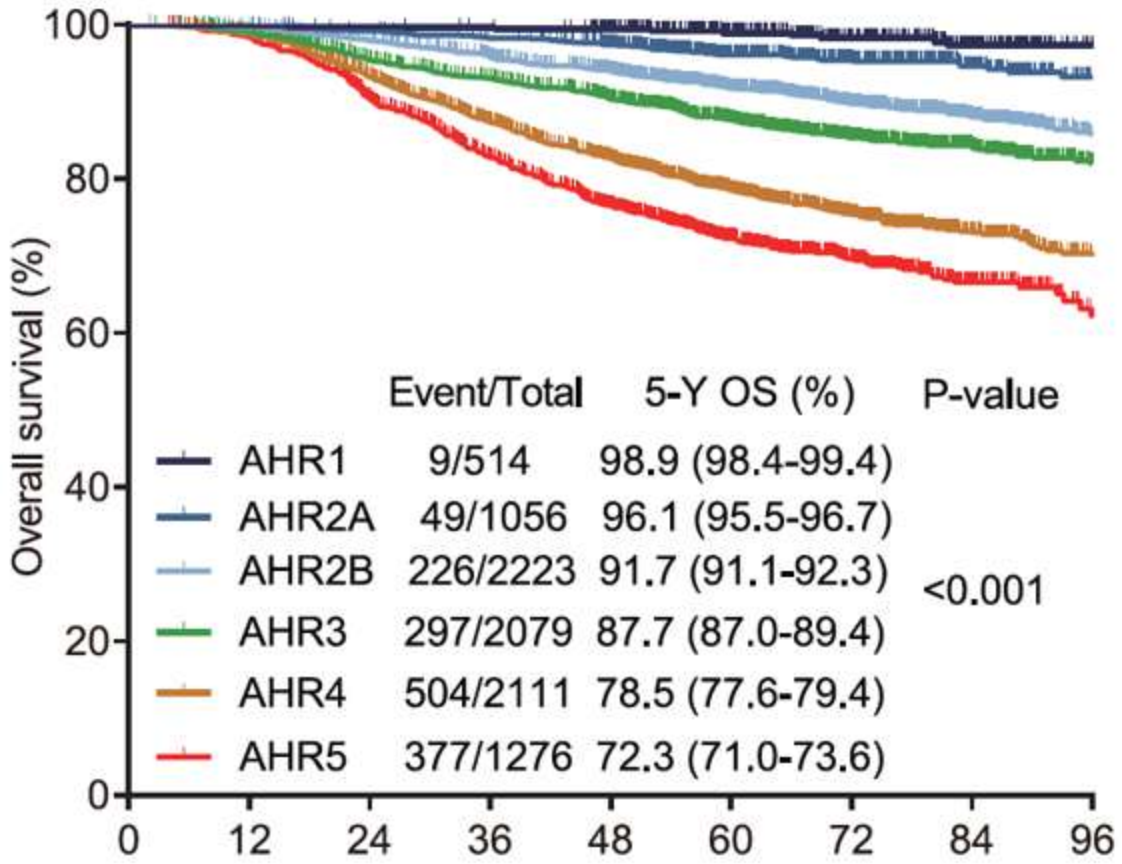


Chen FP et al, Ther Adv Med Oncol 2021

BRIEF UPDATE FROM THE ESMO CPG ON NPC

- **Integration of EBV DNA value with TNM: refining the TNM staging?**

AHR	EBV DNA <2000copies/mL				EBV DNA ≥2000copies/mL			
	N0	N1	N2	N3	N0	N1	N2	N3
T1	AHR1	AHR2A	AHR2B	AHR4	AHR1	AHR2B	AHR3	AHR5
T2	AHR2A	AHR2B	AHR2B	AHR4	AHR2B	AHR3	AHR3	AHR5
T3	AHR2A	AHR2B	AHR3	AHR4	AHR2B	AHR3	AHR4	AHR5
T4	AHR3	AHR4	AHR4	AHR4	AHR4	AHR4	AHR5	AHR5



BRIEF UPDATE FROM THE ESMO CPG ON NPC

- **Possible application of circulating EBV DNA at baseline**

  - Deintensification of low-risk NPC:
    reducing the amount of radiosensitizing CDDP? IMRT vs IMRT + cddp?

  - Refining the indications for induction chemotherapy

  - Use as dynamic biomarker for response-adapted treatment

BRIEF UPDATE FROM THE ESMO CPG ON NPC

- **The underestimated importance of QoL assessment**

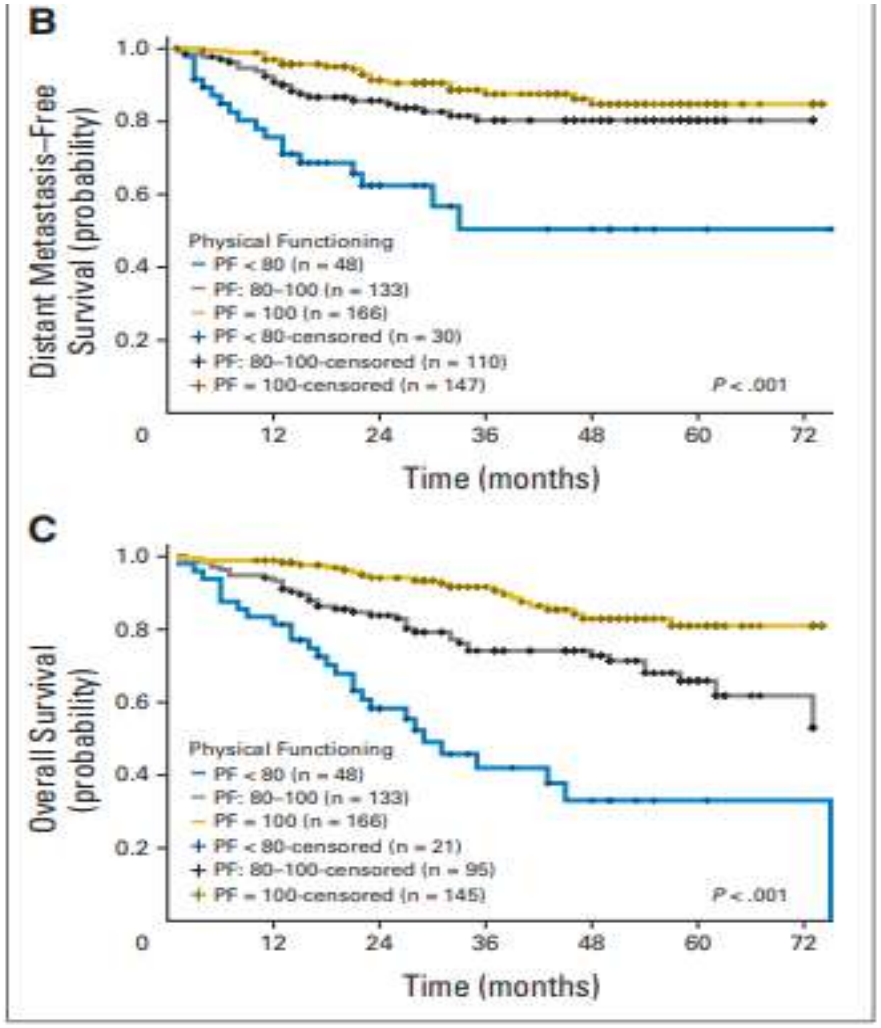
VOLUME 28 · NUMBER 28 · OCTOBER 1 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pretreatment Quality of Life As a Predictor of Distant Metastasis and Survival for Patients With Nasopharyngeal Carcinoma

Fu-Min Fang, Wen-Ling Tsai, Chih-Yen Chien, Hui-Chun Chen, Hsuan-Chih Hsu, Tai-Lin Huang, Tsair-Fwu Lee, Hsuan-Ying Huang, and Chien-Hung Lee

Table 3. Multivariate Analysis of Clinical Variables and Physical Functioning to Predict DMFS and OS

Model	DMFS			OS		
	P	HR	95% CI	*P*	HR	95% CI
Age, 10-year increment	.13	1.17	0.95 to 1.40	< .001	1.37	1.18 to 1.57
KPS, ≤ 80 *v* > 80	.04	0.38	0.14 to 0.95	.02	0.38	0.17 to 0.85
AJCC stage, III-IV *v* I-II	.001	3.38	1.60 to 7.12	.001	2.93	1.53 to 5.61
T stage, T3-4 *v* T1-T2	.98	1.00	0.57 to 1.79	.19	1.40	0.85 to 2.29
Age, 10-year increment	.49	1.08	0.85 to 1.31	.004	1.29	1.09 to 1.49
KPS, ≤ 80 *v* > 80	.72	0.82	0.27 to 2.45	.65	0.812	0.32 to 2.02
AJCC stage, III-IV *v* I-II	.004	2.99	1.41 to 6.33	.005	2.53	1.32 to 4.87
T stage, T3-4 *v* T1-T2	.99	1.00	0.56 to 1.79	.15	1.44	0.88 to 2.36
Physical functioning, 10 points	.001	0.78	0.64 to 0.91	< .001	0.77	0.66 to 0.88

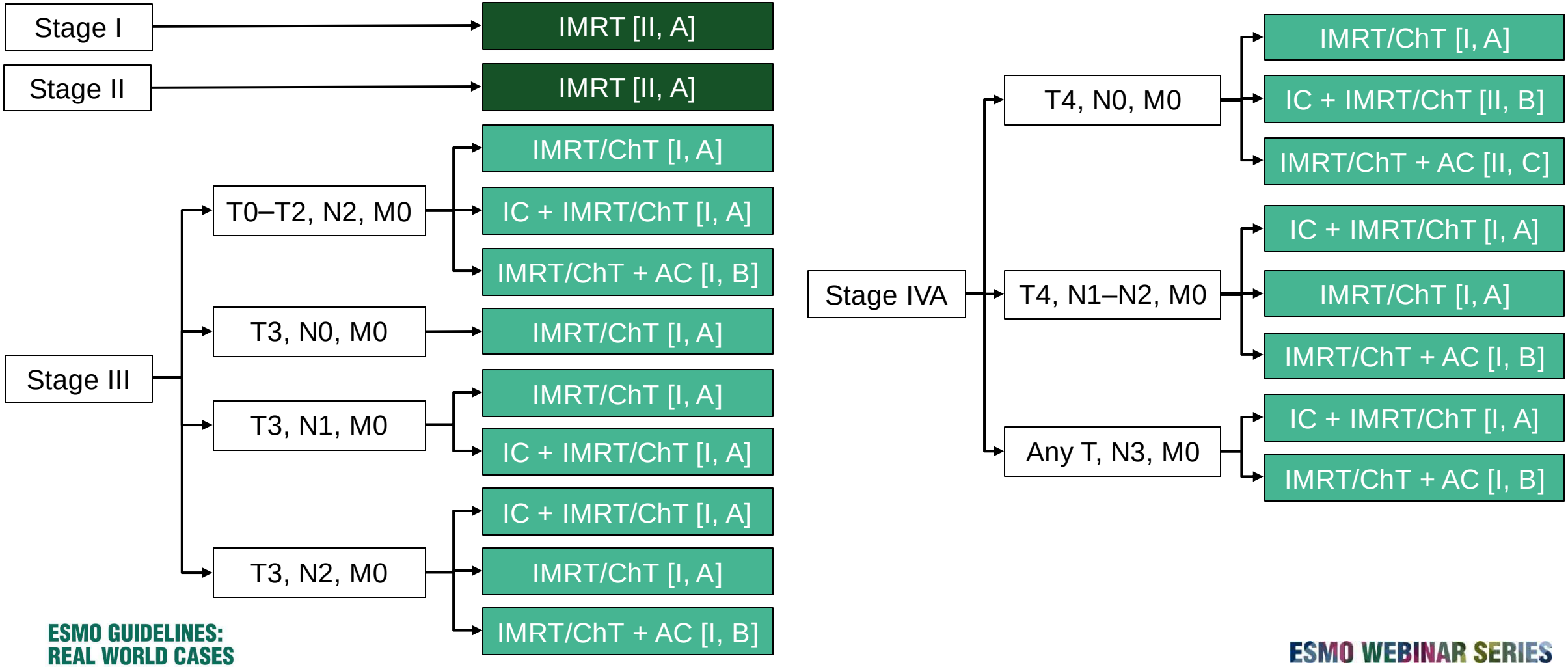


Feng FM, J Clin Oncol 2010

ESMO GUIDELINES: REAL WORLD CASES

ESMO CPG

Brief overview on the treatment – stage by stage



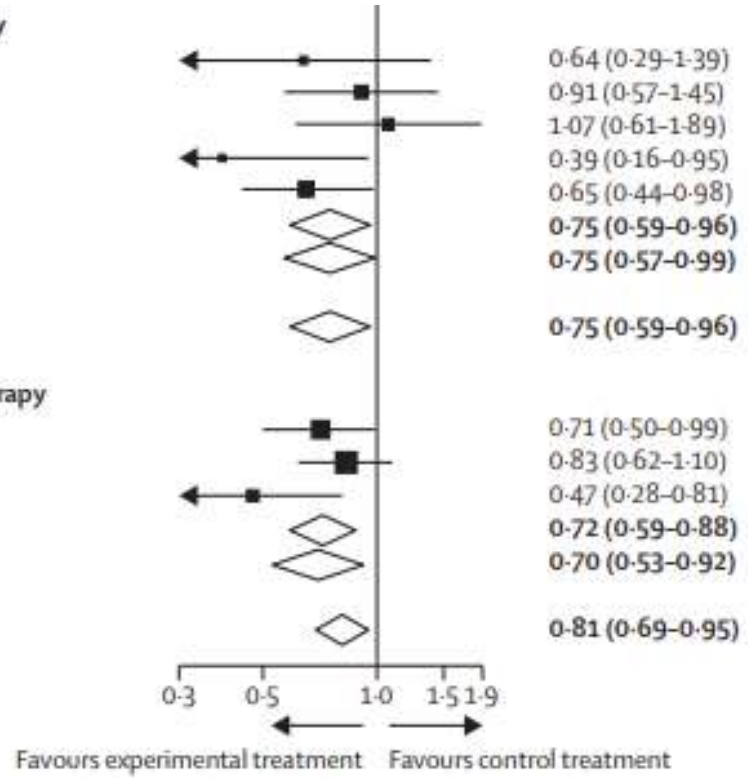
BRIEF UPDATE FROM THE ESMO CPG ON NPC

- **The unnevereding story: the role of induction chemotherapy**

Role of chemotherapy in patients with nasopharynx carcinoma treated with radiotherapy (MAC-NPC): an updated individual patient data network meta-analysis

Claire Petit, Anne Lee, Jun Ma, Benjamin Lacas, Wai Tong Ng, Anthony T C Chan, Ruey-Long Hong, Ming-Yuan Chen, Lei Chen, Wen-Fei Li,

Induction chemotherapy with taxanes followed by chemoradiotherapy vs chemoradiotherapy		
NPC008[56]	12/34	14/31
HeCOG 1303[57]	34/72	38/72
NCC 0901[9]	25/86	23/86
GORTEC 2006-02[10]	6/42	14/41
Guangzhou 2011[12]	38/241	56/239
Fixed effect model meta-analysis	**115/475**	**145/469**
Random effect model meta-analysis		
I^2=18%, p=0·30		
Network meta-analysis		
Induction chemotherapy without taxanes followed by chemoradiotherapy vs chemoradiotherapy		
Guangzhou 2008[13]	55/238	78/238
TCOG1303[11]	87/239	99/240
Guangzhou 2013[14]	18/242	36/238
Fixed effect model meta-analysis	**160/719**	**213/716**
Random effect model meta-analysis		
I^2=39%, p=0·19		
Network meta-analysis		



Petit C et al, Lancet Oncol 2023

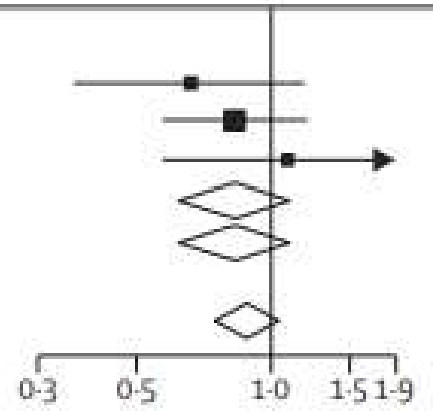
BRIEF UPDATE FROM THE ESMO CPG ON NPC

Role of chemotherapy in patients with nasopharynx carcinoma treated with radiotherapy (MAC-NPC): an updated individual patient data network meta-analysis

Claire Petit, Anne Lee, Jun Ma, Benjamin Lacas, Wai Tong Ng, Anthony T C Chan, Ruey-Long Hong, Ming-Yuan Chen, Lei Chen, Wen-Fei Li,

- **What about the role of adjuvant chemotherapy?**

	Experimental group	Control group	Hazard ratio (95% CI)
	Number of events/number of patients	Number of events/number of patients	
Chemoradiotherapy followed by adjuvant chemotherapy vs chemoradiotherapy			
QMH-95Adj+[35,36]	19/57	25/56	0·66 (0·36–1·19)
Guangzhou 2006[42]	49/251	58/257	0·83 (0·57–1·21)
NPC 0502[34]	18/52	18/52	1·09 (0·57–2·10)
Fixed effect model meta-analysis	**86/360**	**101/365**	**0·83 (0·62–1·10)**
Random effect model meta-analysis			**0·83 (0·62–1·10)**
I^2=0%, p=0·53			
Network meta-analysis			**0·88 (0·75–1·04)**



Petit C et al, Lancet Oncol 2023

BRIEF UPDATE FROM THE ESMO CPG ON NPC

- **Induction chemotherapy or adjuvant chemotherapy? That is the question**

"By combining the two modalities of induction chemotherapy, based on the similar results of induction chemotherapy with or without taxanes followed by chemoradiotherapy in respective trials, additional sensitivity analyses showed that induction chemotherapy followed by chemoradiotherapy ranked first for all endpoints except locoregional progression"

BRIEF UPDATE FROM THE ESMO CPG ON NPC

- **Personalized medicine**

Table 5. Personalised medicine synopsis

Biomarker	Methodology	Use	LoE, GoR
Plasma EBV DNA	PCR	Prognostic before curative treatment	III, B (IV, B[a])
		Prognostic role of clearance during ICT and CRT	IV, B
		Prognostic 1-4 weeks after RT	II, B
		Early diagnosis of recurrence during follow-up	V, B
		Prognostic in recurrent and/or metastatic disease	III, B

ESMO CPG

The **follow up after treatment**: how should it be organized?

Imaging	Three months after IMRT, then every 6 months till the 3rd year (for T3 and T4 disease): • MRI or PET [II, B] • MRI [V, B]
Nasal examination	Endoscopic assessment every 3 months in the 1st year, every 6 months in the 2nd and 3rd years and annually thereafter for the first 5 years [V, B]
Plasma EBV DNA	One to four weeks after IMRT [II, B] then every year [V, B]
Thyroid and pituitary assessment	Hormonal function assessment every year [V, B]

ESMO GUIDELINES: REAL WORLD CASES

Paolo Bossi

paolo.bossi@hunimed.eu

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

ESMO WEBINAR SERIES

ESMO GUIDELINES:
REAL WORLD CASES

NASOPHARYNGEAL CARCINOMA

Considerations related to Guideline implementation in everyday clinical practice

Alberto Jacobo Cunquero Tomás

Consorcio Hospital General Universitario, Valencia (Spain)

Member of the ESMO Practising Oncologist Working Group (POWG)

ESMO WEBINAR SERIES

The ESMO POWG serves to identify the practice needs of oncologists who are hospital and office-based by developing educational services, practice tools and quality indicators that will facilitate the implementation of best practice at the point of care.

The POWG members are relevant stakeholders to the ESMO Guidelines Webinars as experts who are consulting and implementing the guidelines in their daily practices

For more information about the ESMO POWG visit **esmo.org**

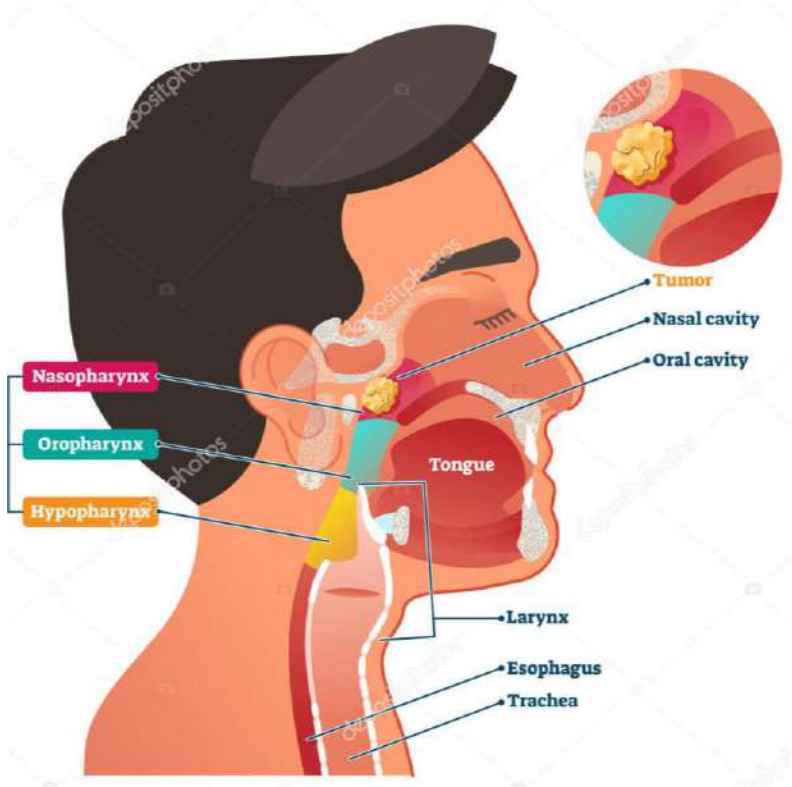
ESMO > About ESMO > Organisational Structure > Educational Committee

ESMO PRACTISING ONCOLOGISTS WORKING GROUP

Don't miss:

- The «ESMO Checklists» on OncologyPRO

NPC PATIENT JOURNEY



"Pre-Treatment"

Treatment

"Post- Treatment"

Bossi P et al, Ann Oncol, 2021

PRE-TREATMENT

Studying

Table 2. Diagnostic work-up

1. Medical history and physical examination
2. CBC, serum biochemistry
3. Nasopharyngoscopy
4. Tumour biopsy (EBER by ISH [III, B])
5. CT scan or MRI of the nasopharynx and base of the skull and neck (to the clavicle) (MRI preferred [III, B])
6. ^{18}F-FDG-PET/CT imaging [III, B]
7. Baseline audiometric testing, dental examination, nutritional status evaluation, ophthalmological and endocrine evaluation
8. Plasma EBV DNA [III, B]
9. QoL assessment (e.g. EORTC QLQ-C30) [III, B]

WHO – IARC. Global Cancer Observatory. Available at: https://gco.iarc.fr/en ; Chattopadhyay NR et al, Drug Discov & Ther, 2017; Trama A et al, ESMO Asia Congress 2022; Botta L et al, Front Oncol 2023

PRE-TREATMENT

The environment

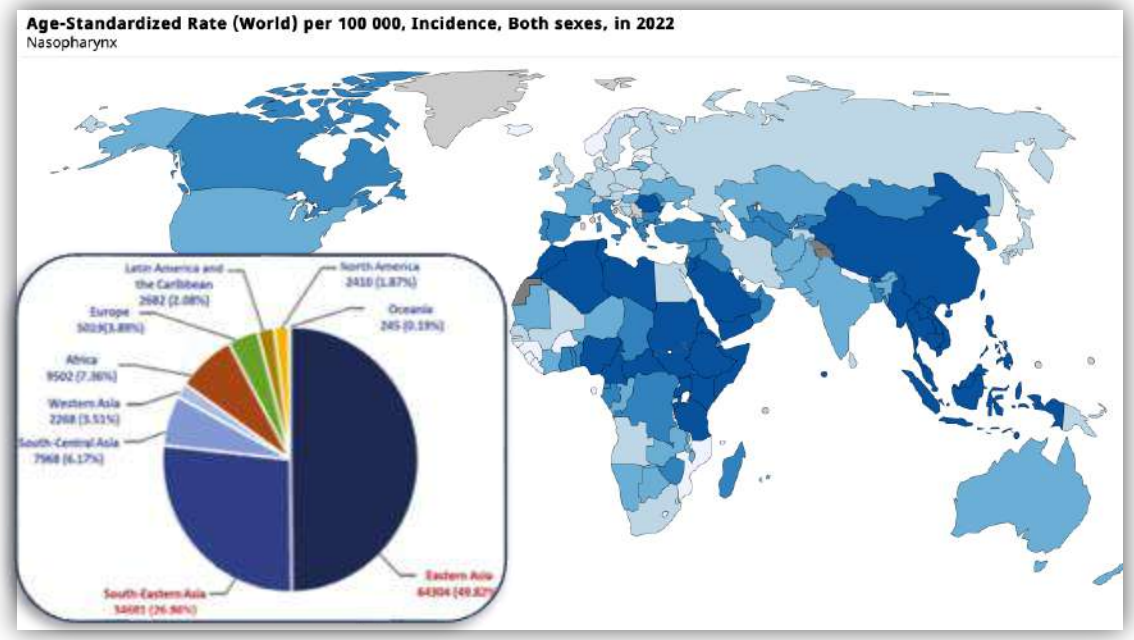
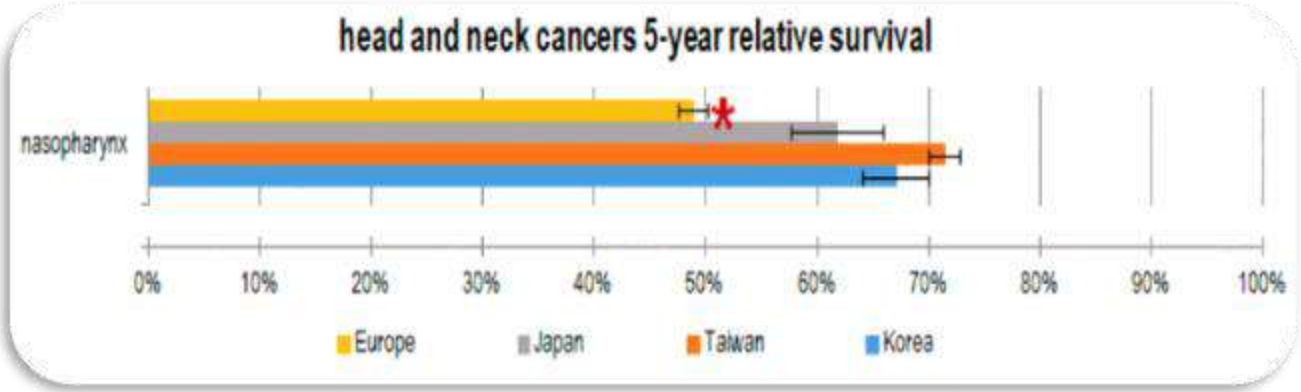


Table 1. A global perspective of NPC distributions in respect to the incidence pattern

Occurrence of NPC in respect to ethnic and geographical distribution		Factors responsible for NPC		
Geographical Distribution	Specific populations	Genetic Factors	Virus	Diet/Environment/lifestyle
Asian Continent	East and south Asian population/Arabian population	+	+	+
	Chinese population	+	+	+
	Naga Population in North East India	+	+	+
	Turkish Population	-	-	+
	Thailand population	+	-	-
Arctic continent	Arctic Eskimos/Inuit population	+	+	+
African Continent	North African population	+	+	+
	Population of Tunisia	+	-	+
	Population of Kenya	-	-	+
Australian Continent	Papua New Guinea	-	+	-
North-American Continent	Greenland	-	-	+
European Continent	Spanish population	-	+	-

+, incidence of a particular factor; –, no incidence of a particular factor.



Screening

Diagnosis

Prognosis

Treatment

ESMO WEBINAR SERIES

PRE-TREATMENT

The patient - Ethnicity / Gender

Five-year relative survival rates for different racial groups, stratified by stage at diagnosis and histologic type.

	Non-Hispanic white (n=4013)	Hispanic white (n=535)	Black (n=937)	Asian (n=3381)	Other (n=148)	P-value
Stage at diagnosis						
Localized	61.6 (55.9–66.7)	74.5 (53.1–87.2)	62.6 (46.8–75.0)	83.5 (77.8–87.8)	81.0 (18.5–97.4)	<0.001
Regional	50.6 (48.0–53.2)	51.6 (44.1–58.6)	46.5 (41.0–51.8)	64.0 (61.5–66.4)	43.9 (30.7–56.3)	<0.001
Distant	22.4 (18.6–26.5)	30.3 (17.8–43.7)	30.3 (21.7–39.4)	34.1 (28.6–39.6)	15.8 (4.9– 32.2)	<0.001
Histologic type						
Keratinizing squamous cell carcinoma	39.3 (36.9–41.7)	43.4 (34.8–51.7)	34.8 (29.3–40.3)	57.1 (53.5–60.6)	32.7 (15.4–51.3)	<0.001
Differentiated non-keratinizing carcinoma	57.8 (51.4–63.7)	55.3 (39.1–68.8)	58.9 (46.8–69.2)	64.0 (59.2–68.4)	45.2 (23.7–64.5)	0.002
Undifferentiated non-keratinizing carcinoma	65.9 (61.2–70.1)	62.8 (51.2–72.4)	65.6 (57.1–72.8)	71.5 (68.1–74.6)	47.8 (27.4–65.7)	<0.001
Others	49.5 (45.9–53.0)	57.8 (48.8–65.8)	52.3 (44.9–59.1)	62.2 (58.5–65.6)	44.3 (28.5–59.0)	<0.001

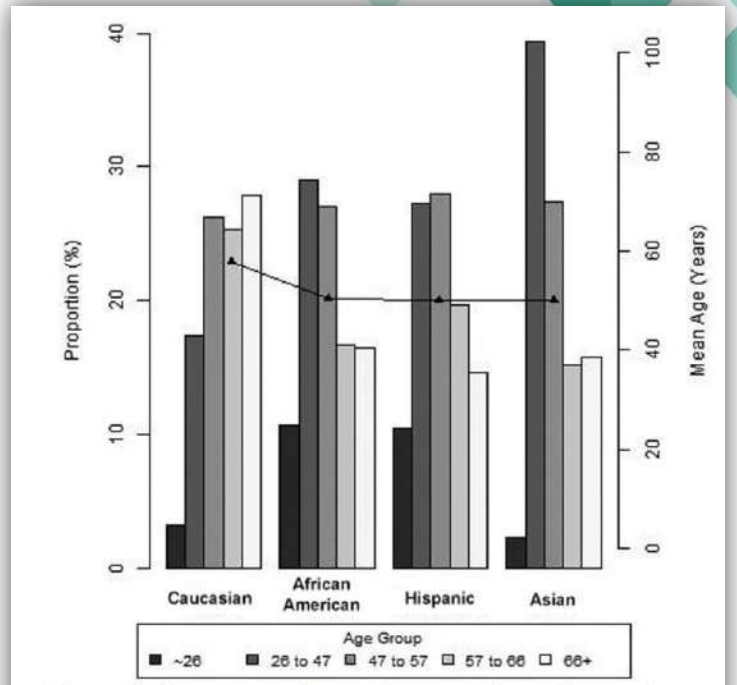


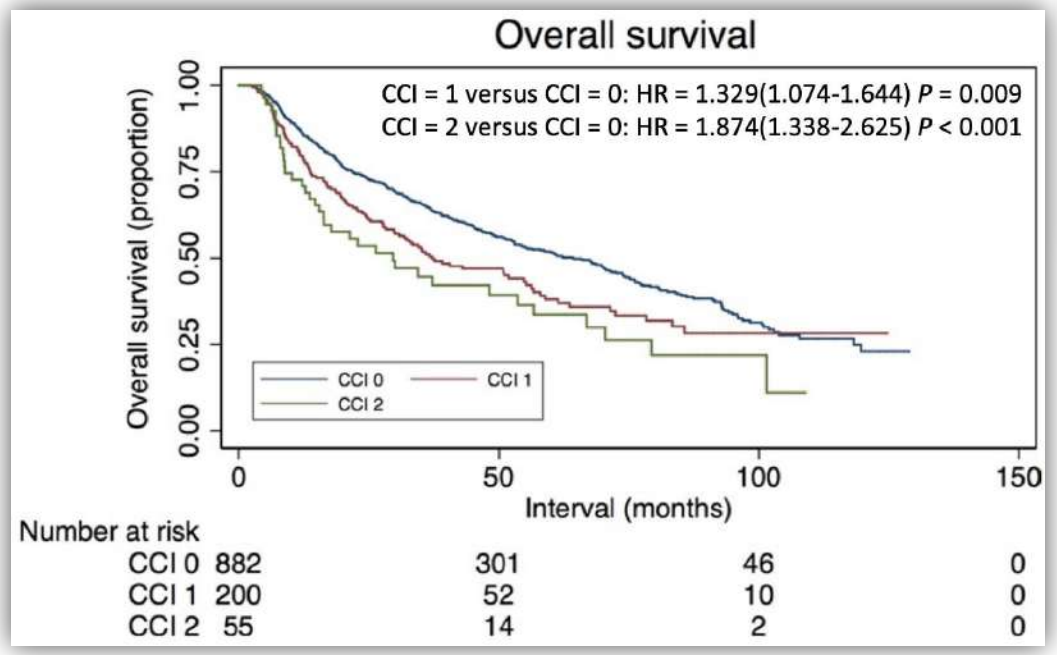
Figure 2. Distribution of age at diagnosis of nasopharyngeal tumors according to World Health Organization classification for Caucasian, African American, Hispanic, and Asian patients.

Gender modulates PK and PD

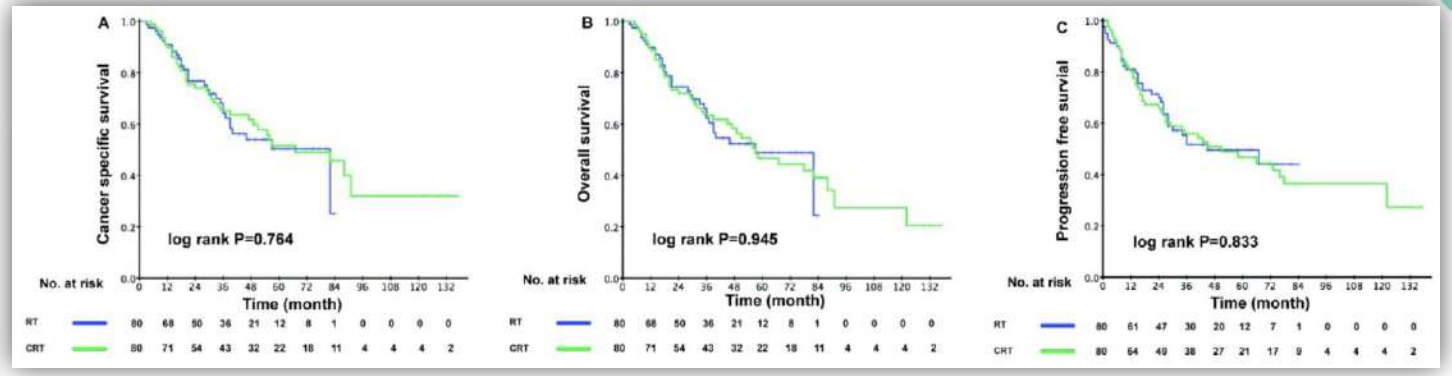
- Women are more susceptible to the toxicity of different types of drugs
- Problably more impact in Chemotherapy drugs, were doce-intensity is more important

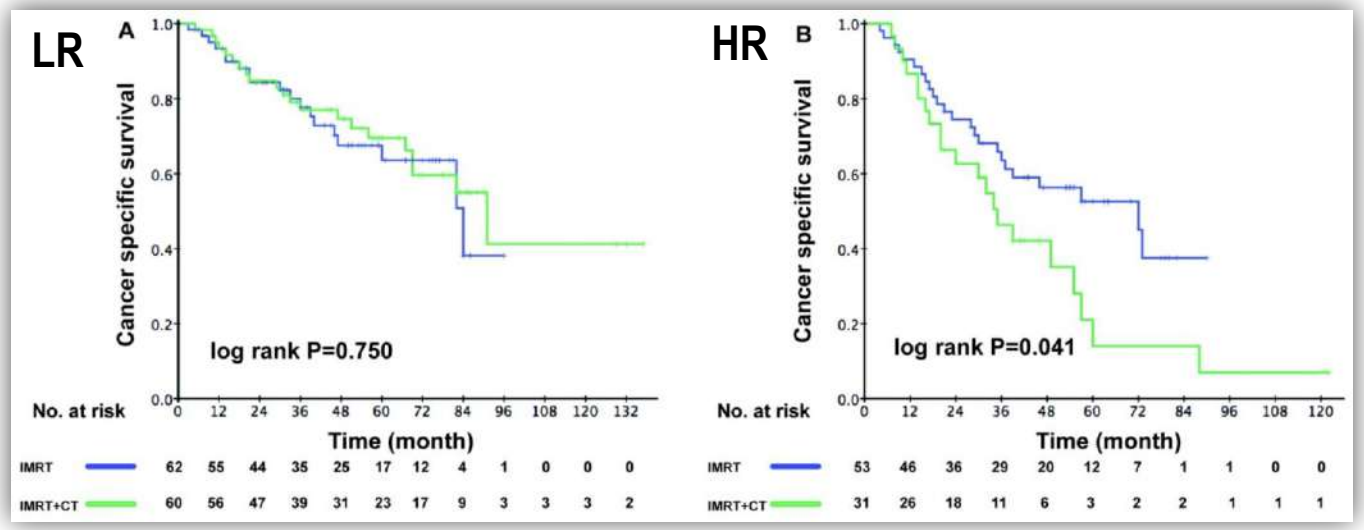
PRE-TREATMENT

The patient - Age



RT vs ChRT





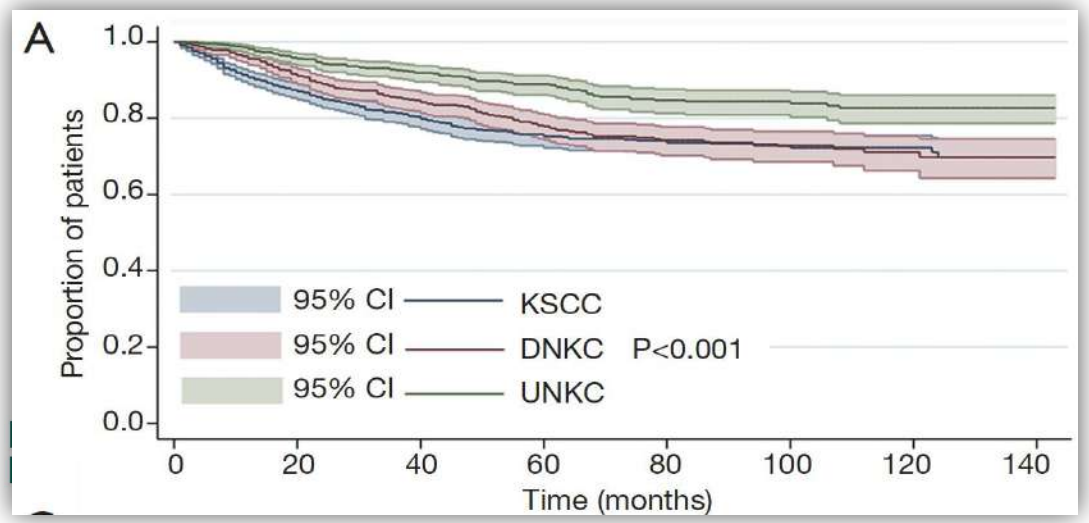
PRE-TREATMENT

The disease – Histology / Stage

Table 1. Nasopharyngeal cancer histology and clinicopathological features.

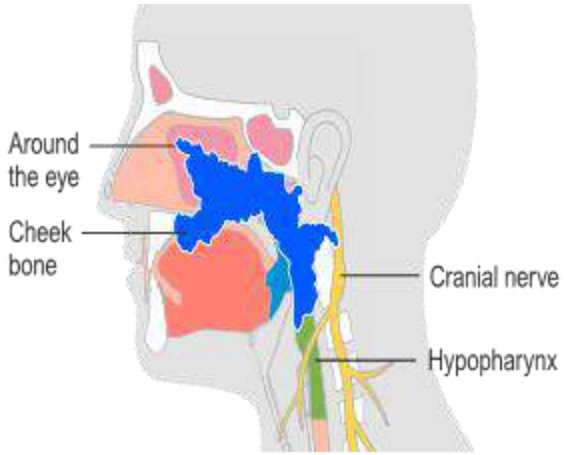
	WHO I	WHO II	WHO III
Differentiation status	well differentiated	moderately to poorly differentiated	undifferentiated
Histological category in WHO classification	keratinizing	nonkeratinizing-differentiated	nonkeratinizing-undifferentiated
TIL infiltration	fair to moderate	heavy	
EBERs in tumor	(−) or faint	(+)	
EBV antibodies	not elevated	elevated	
Chemoradiosensitivity	moderate	good	
Metastatic property	low to moderate	high	
Epidemiology	20% in non-endemic area; <5% in endemic areas	80% in non-endemic areas; >95% in endemic areas	

EBERs; EBV-encoded small RNAs, TIL; tumor-infiltrating lymphocytes, WHO; World Health Organization.



	Endemic areas	Non-endemic areas
Stage I-II	24%	25%
Stage III-IV	76%	75%

Stage	5yr OS
I	93.2%
II	86.6%
III	80.5%
IVA	65.1%
IVB	63.2%

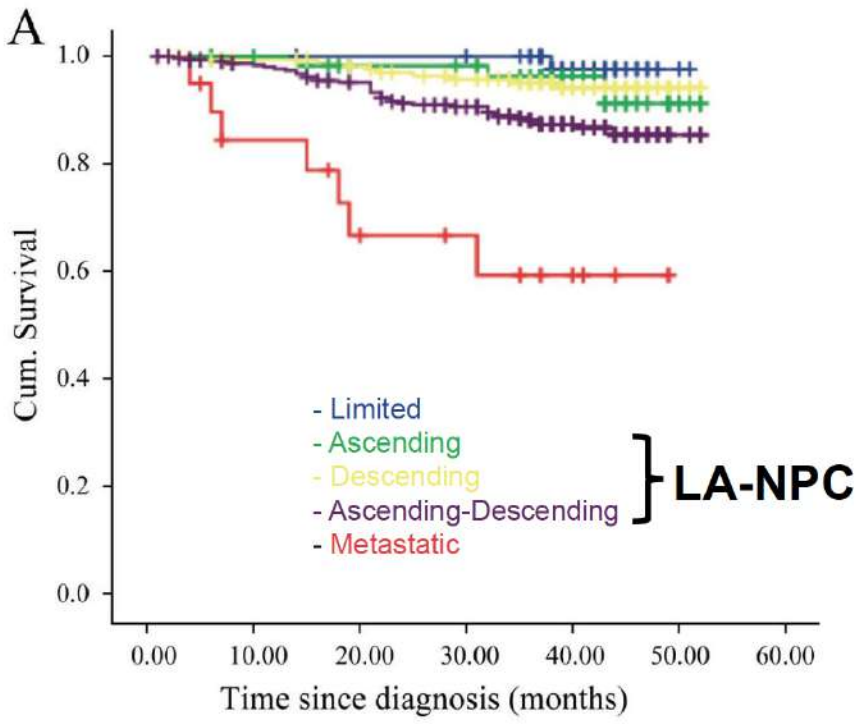


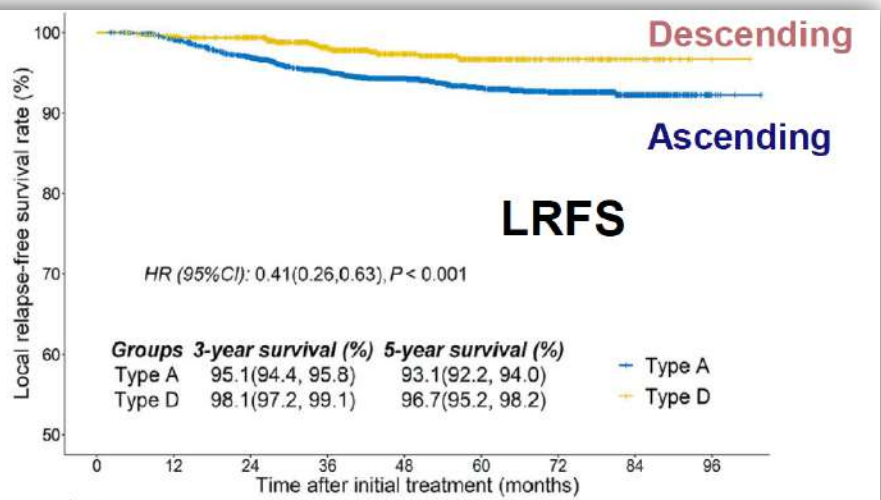
Toxicities

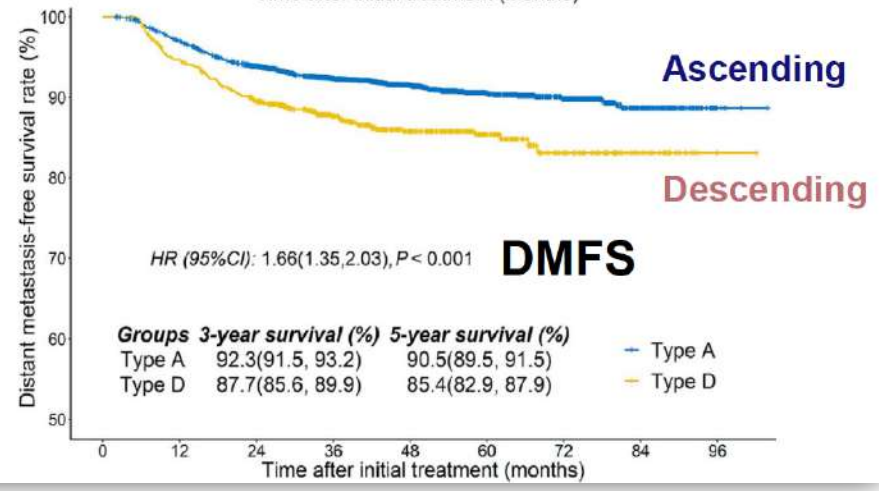
PRE-TREATMENT

The disease - Phenotype

Phenotypic classification was able to predict prognosis independent of TNM and exhibit different patterns of relapse.







Bossi P et al, Ann Oncol, 2021

PRE-TREATMENT

Planning

Table 2. Diagnostic work-up

1. Medical history and physical examination
2. CBC, serum biochemistry
3. Nasopharyngoscopy
4. Tumour biopsy (EBER by ISH [III, B])
5. CT scan or MRI of the nasopharynx and base of the skull and neck (to the clavicle) (MRI preferred [III, B])
6. ^{18}F-FDG-PET/CT imaging [III, B]
7. Baseline audiometric testing, dental examination, nutritional status evaluation, ophthalmological and endocrine evaluation
8. Plasma EBV DNA [III, B]
9. QoL assessment (e.g. EORTC QLQ-C30) [III, B]

PRE-TREATMENT

Multidisciplinary Tumour Board

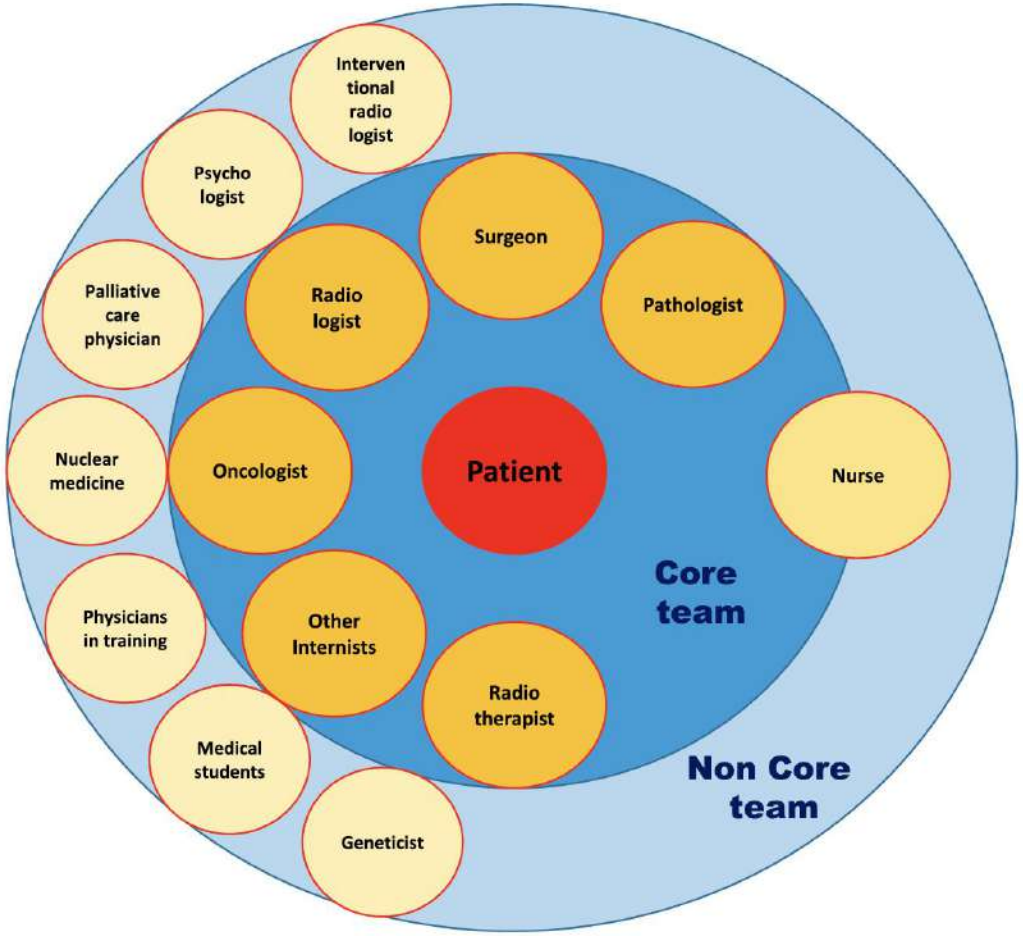


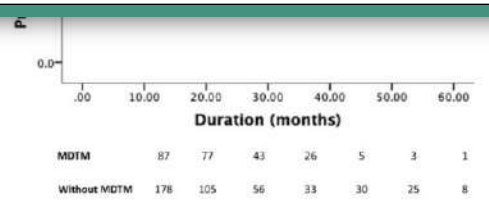
Table 2. Clinical responses of patients with NPC according to multidisciplinary team meeting (MDTM).

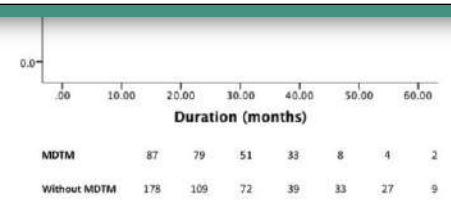
CONDITIONS	WITH MDMT (N=87)	WITHOUT MDTM (N=178)	*P*-VALUE*
Clinical response			
CR	29 (33.3)	20 (11.2)	

Comparison of acute toxicity between experimental group and routine group ($N = 104$).

Nutritional intervention

Acute toxicity	Experimental group ($n = 52$), Mean ± SD		Routine group ($n = 52$), Mean ± SD	
	During CRT	After CRT	During CRT	After CRT
Neutropenia	1.02 ± 0.37^{b}	1.30 ± 0.55^{ac}	1.05 ± 0.34	1.77 ± 0.63^{a}
Cutireaction	1.01 ± 0.44^{b}	1.78 ± 0.52^{ac}	1.03 ± 0.42	2.62 ± 0.68^{a}
Mucosa reaction	1.14 ± 0.51^{b}	1.77 ± 0.60^{ac}	1.18 ± 0.52	2.68 ± 0.71^{a}
Swallowing function	1.33 ± 0.66^{b}	1.98 ± 0.79^{ac}	1.35 ± 0.68	2.74 ± 0.89^{a}
Xerostomia	1.06 ± 0.42^{b}	1.38 ± 0.55^{ac}	1.09 ± 0.45	2.01 ± 0.67^{a}
Nausea and vomiting	1.08 ± 0.47^{b}	1.39 ± 0.60^{a}	1.12 ± 0.50	1.87 ± 0.77^{a}

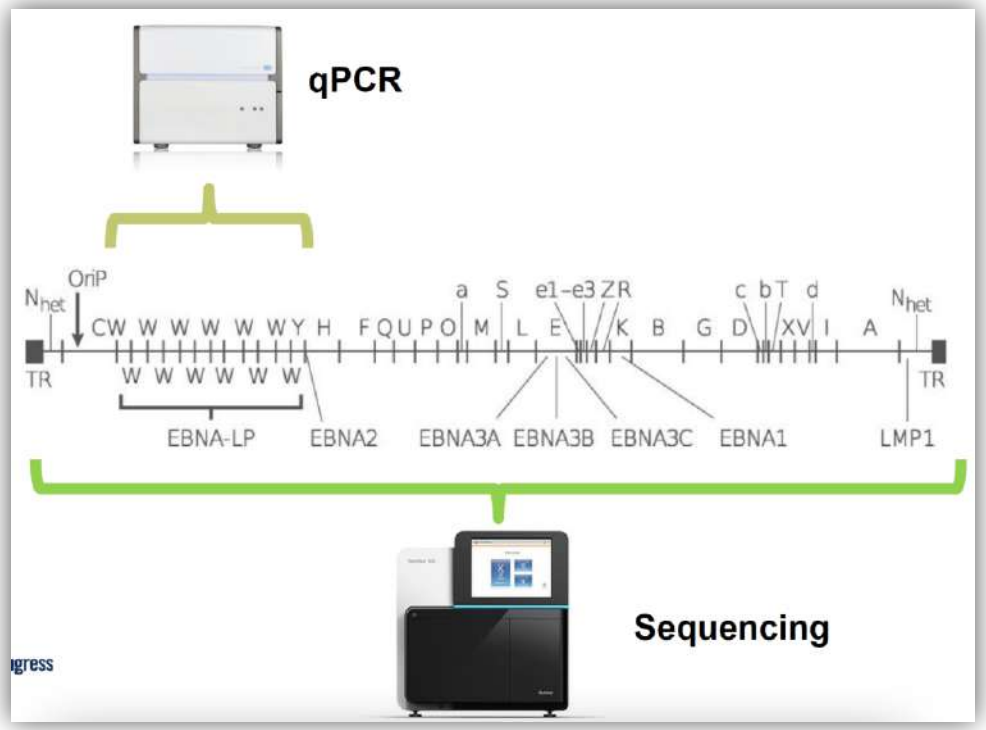




PRE-TREATMENT

Biomarkers - EBV

Endemic areas	Non-endemic areas
Causative factor – Non keratinising	Limited studies available
Prognostic role well stablished	Pre-treatment load correlated with DFS and OS (worst if positive)
Different pre-treatment cut-off proposed (mostly 4000 copies/ml)	No baseline cut-off available related to DFS and OS



	Sensitivity	Specificity	PPV
PCR, single time-point	97.1%	94.8%	3.1%
PCR, two time-point	97.1%	98.6%	11.0%
NGS, count + size	97.1%	99.3%	19.6%

TREATMENT

LA-NPC - Optimal strategy

Standard Meta-Analysis

Network Meta-Analysis

IC-Tax-CRT (1) 5y-AB: 5.9%			0.75 [0.57-0.99]				
0.93 [0.70-1.25]	IC-NoTax-CRT (2) 5y-AB: 4.5%	0.84 [0.56-1.24]	0.70 [0.53-0.92]	0.93 [0.77-1.12]			
0.85 [0.64-1.15]	0.92 [0.77-1.09]	CRT-AC (3) 5y-AB: 2.8%	0.83 [0.62-1.10]		0.87 [0.55-1.38]	0.63 [0.34-1.15]	0.68 [0.59-0.79]
0.75 [0.59-0.96]	0.81 [0.69-0.95]	0.88 [0.75-1.04]	CRT (4) 5y-AB: ref			0.94 [0.54-1.65]	0.65 [0.44-0.96]
0.75 [0.55-1.02]	0.80 [0.69-0.94]	0.88 [0.72-1.06]	0.99 [0.82-1.21]	IC-RT (5) 5y-AB: -0.1%			0.97 [0.78-1.20]
0.65 [0.40-1.06]	0.70 [0.46-1.07]	0.77 [0.52-1.13]	0.87 [0.57-1.32]	0.87 [0.57-1.34]	IC-RT-AC (6) 5y-AB: -3.4%		1.30 [0.62-2.73]
0.62 [0.41-0.93]	0.66 [0.48-0.93]	0.72 [0.53-0.99]	0.82 [0.59-1.13]	0.83 [0.59-1.16]	0.95 [0.58-1.55]	RT-AC (7) 5y-AB: -4.8%	0.99 [0.72-1.36]
0.60 [0.45-0.80]	0.64 [0.54-0.76]	0.70 [0.62-0.80]	0.80 [0.68-0.93]	0.80 [0.67-0.95]	0.92 [0.61-1.37]	0.97 [0.72-1.30]	RT (8) 5y-AB: -5.7%

- Age?
- ECOG?
- Genetic factors?
- Ethnicity?
- Disease load?
- Biomarkers / EBV?
- Chemo regimen?

Are data extrapolable to all environments?

Bossi P et al, ESMO Congress 2019

SURVIVAL AND PROGNOSTIC FACTORS OF NASOPHARYNGEAL CANCER PATIENTS IN NON-ENDEMIC COUNTRIES: A LARGE MULTICENTRIC DATABASE ANALYSIS

P. Bossi, S. Grisanti, I. Mohamad, I. Linares Galiana, E. Ozyar, P. Franco, S. Vecchio, L. Livi, B. Cirauqui Cirauqui, M. El-Sherify, S. Ursino, A. Argiris, J. Pan, C. Wittekindt, E. D'Angelo, M. Buglione, M. Airoldi, R. Mesia Nin, L. Licitra, E. Orlandi

ON BEHALF OF ALL THE NPC PORTAL GROUP OF INVESTIGATOR

TREATMENT

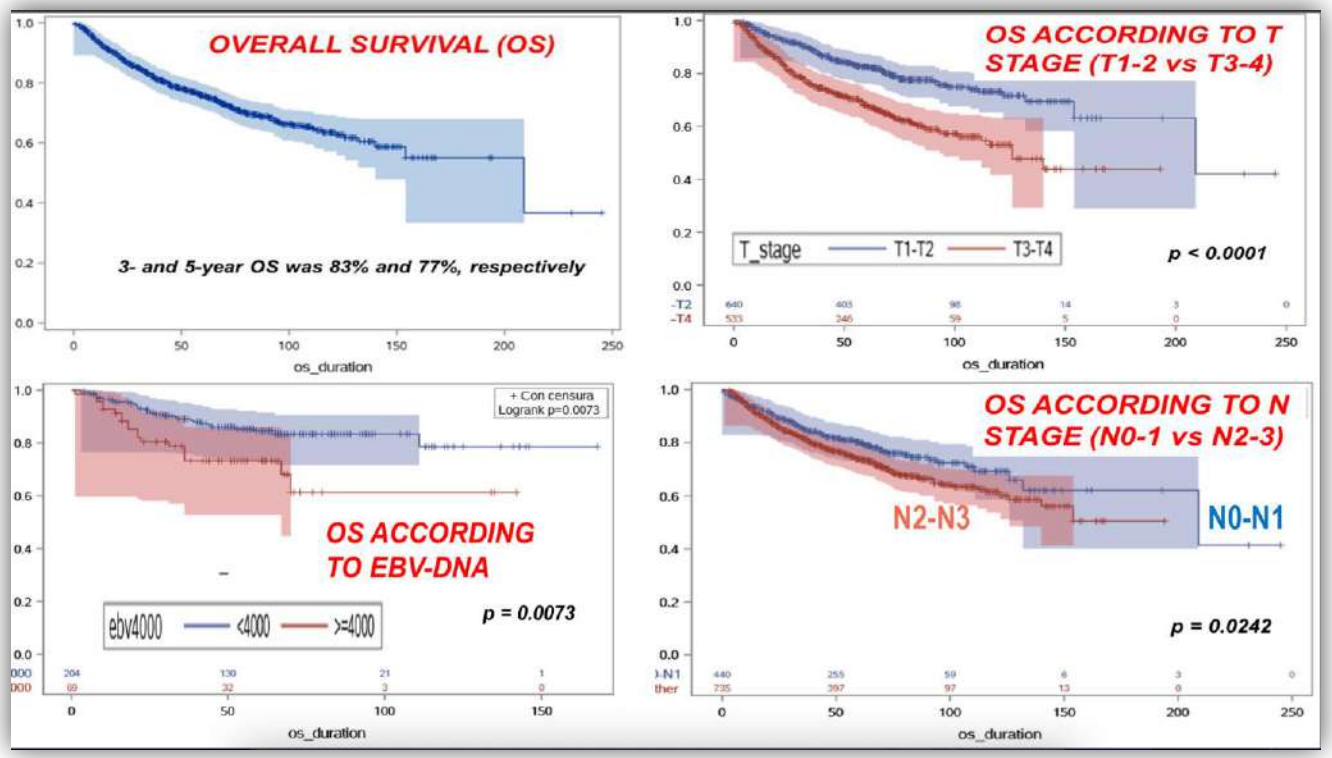
LA-NPC - Optimal strategy

Histotype	%
Non-keratinizing (EBV-related)	86
Keratinizing	13
Basaloid	1

EBV-DNA in plasma	%
Negative-not assessed	77
Positive	23

N=1220

Type of treatment	Type of chemo/RT	%
Induction CT (45%)	TPF *	52
	PF **	26
	Other	23
CRT (83%)	Cisplatin	85
	Carboplatin	6
	Cisplatin --> carboplatin	2
	cetuximab	1
Adjuvant CT (11%)	TPF *	2
	PF **	74
	Other	3
Type of RT	IMRT	81
	3DRT	19

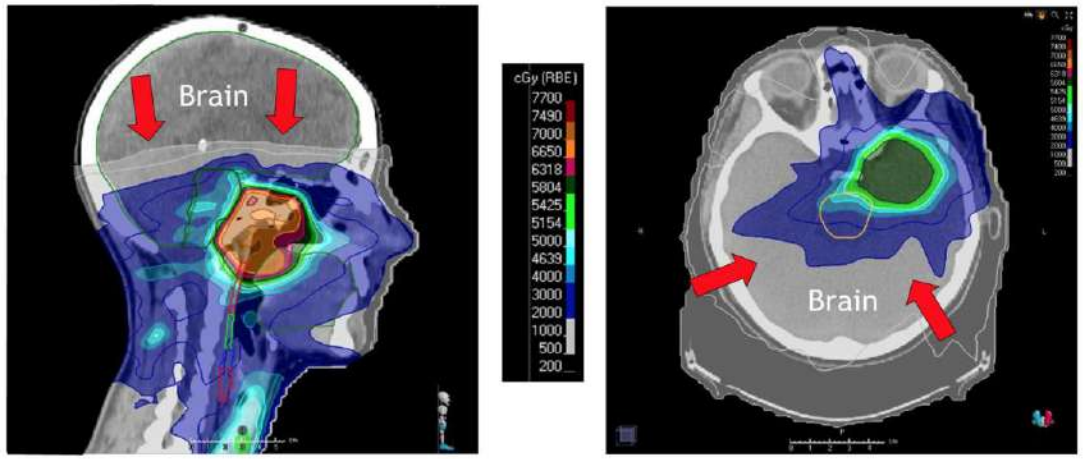


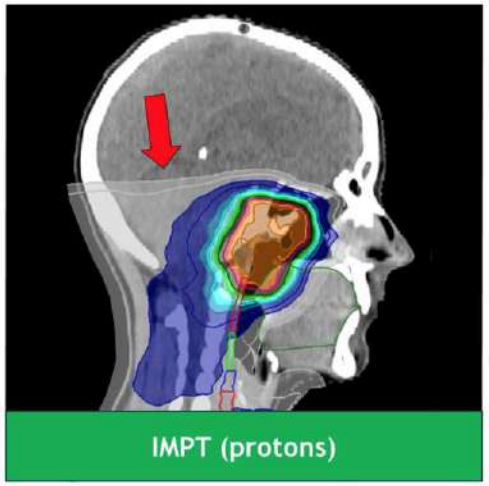
Prognostic factors and outcomes in Europe are comparable to those in high-risk / endemic areas

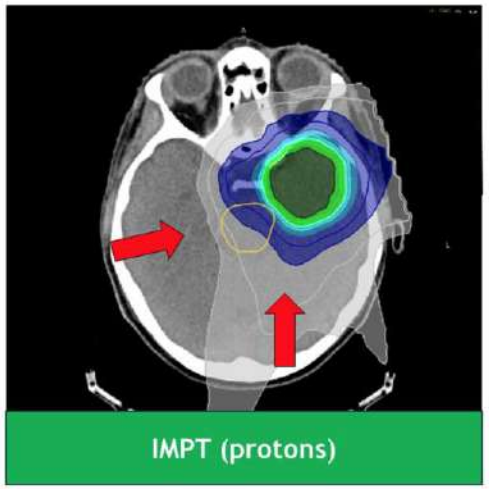
TREATMENT

LA-NPC – IMRT vs IMPT

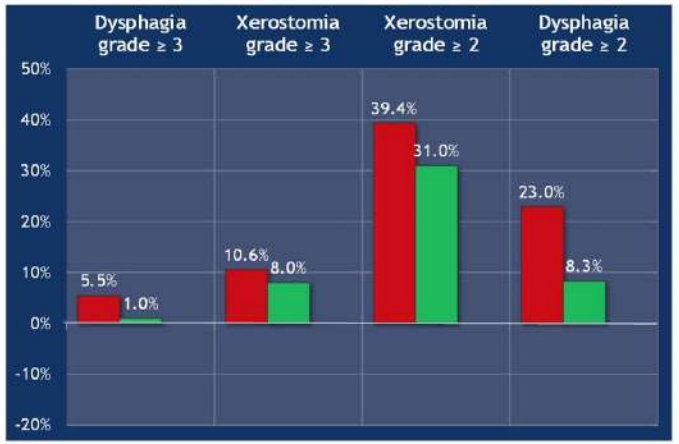
VMAT (Photons)

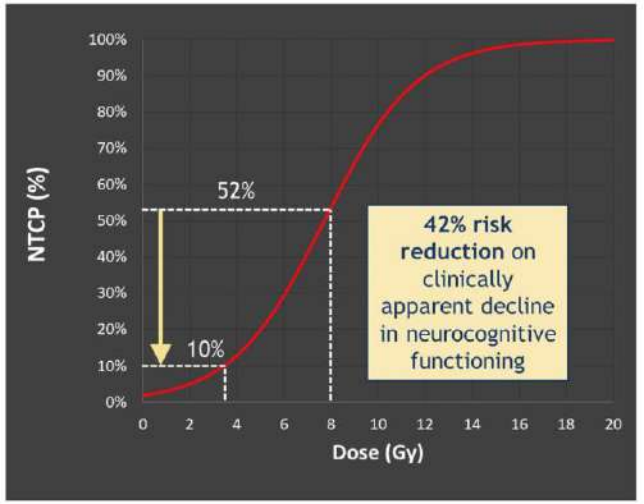






NTCP-profiles VMAT and IMPT



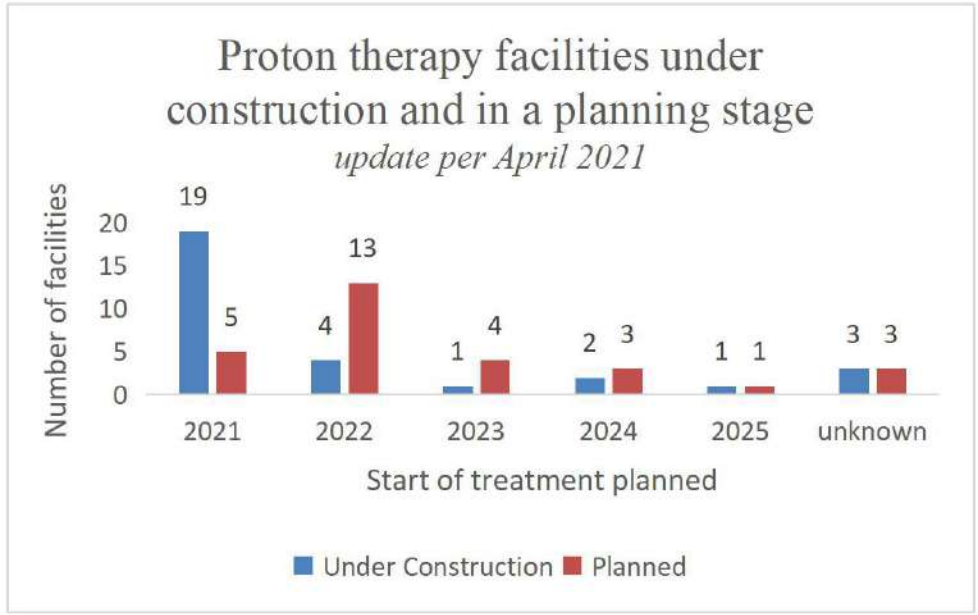


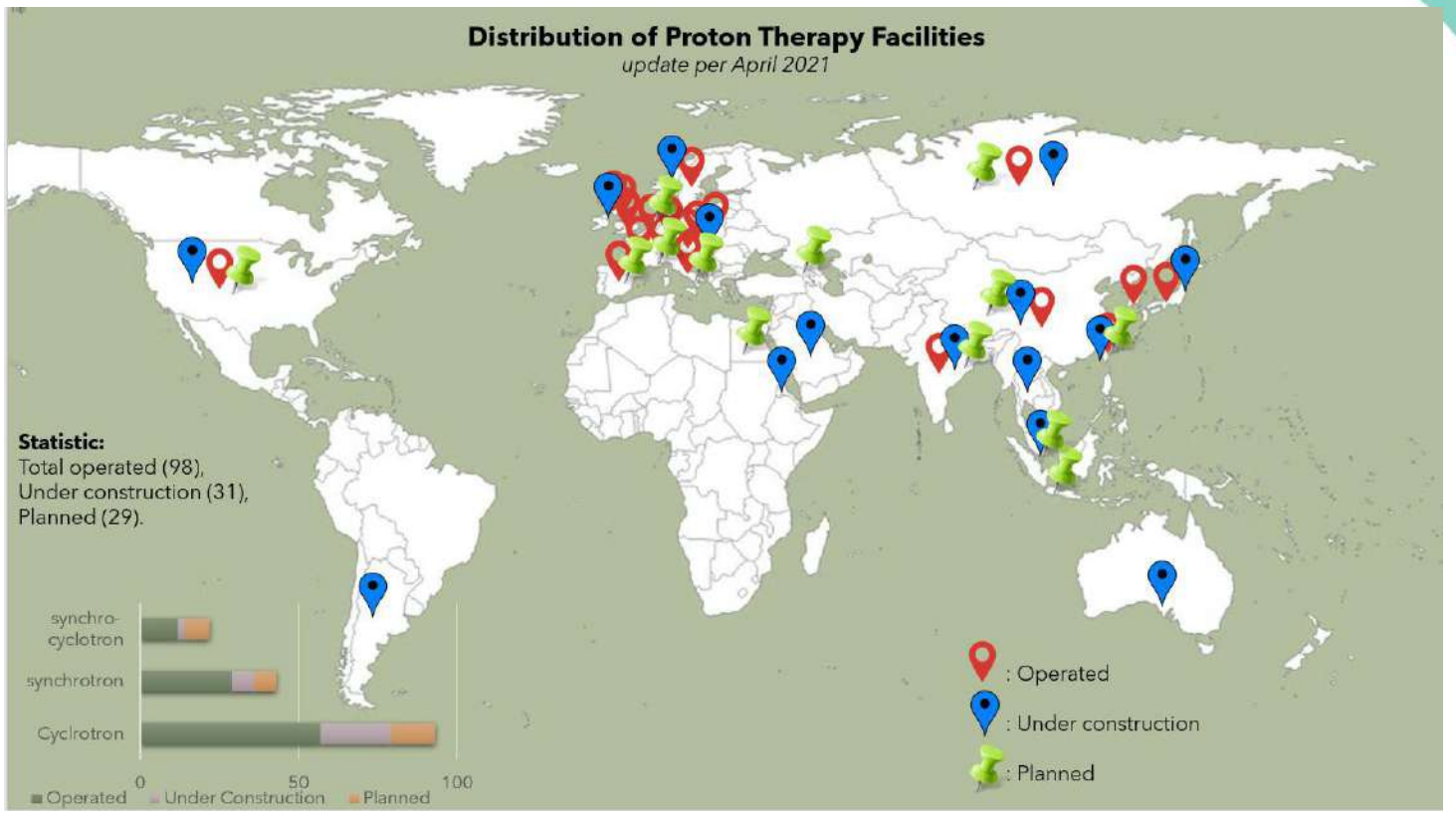
Patient-rated symptoms (EORTC QLQ-H&N35)

PROMS	PHOTONS									PROTONS								
	T0	W1	W2	W3	W4	W5	W6	W7	W12	T0	W1	W2	W3	W4	W5	W6	W7	W12
Pain killer use	70	54	46	63	76	73	80	84	77	60	31	36	38	29	43	43	43	17
Nutritional supplements	24	33	29	37	53	71	63	61	63	10	38	36	38	29	57	57	71	50
Dry mouth	26	28	26	39	49	54	65	70	64	27	33	21	33	38	43	57	62	60
Weight loss	17	31	44	50	68	62	62	45	37	40	8	18	13	0	29	14	14	17
Sticky saliva	22	18	26	39	49	54	65	70	57	20	21	21	33	38	43	57	62	39
Tube feeding use	3	5	19	32	41	59	69	77	66	20	8	9	0	14	29	29	43	17
Problems with senses	9	17	23	30	46	54	53	58	34	8	9	14	13	14	21	24	29	17
Problems with swallowing	12	9	14	29	37	45	49	56	39	3	2	11	16	18	17	23	23	13
Head and neck pain	21	14	15	33	34	39	44	51	35	19	10	20	20	24	23	31	23	18
Feeling ill	18	18	30	25	23	41	41	47	31	30	15	27	21	24	19	19	10	17
Cough	19	18	18	23	29	36	46	40	34	20	13	15	21	29	24	19	10	0
Social eating	7	10	17	24	36	42	42	45	33	3	1	10	9	12	15	14	26	10
Problems with opening mouth	13	15	16	27	29	33	34	41	31	17	10	15	8	14	14	19	19	33
Problems with speech	10	13	12	13	19	28	32	37	28	4	8	4	7	8	3	5	8	7
Weight gain	8	10	17	21	24	12	19	20	38	20	23	18	13	0	14	0	0	0
Problems with teeth	19	14	7	16	21	17	18	17	16	20	8	15	8	5	0	0	0	17
Problems with social contact	2	5	2	5	8	13	13	18	15	2	2	5	2	2	2	4	11	10
TOTAL TOXICITY SCORE	18	18	21	30	38	43	47	49	41	19	14	17	17	17	23	24	27	20

TREATMENT

LA-NPC – IMRT vs IMPT



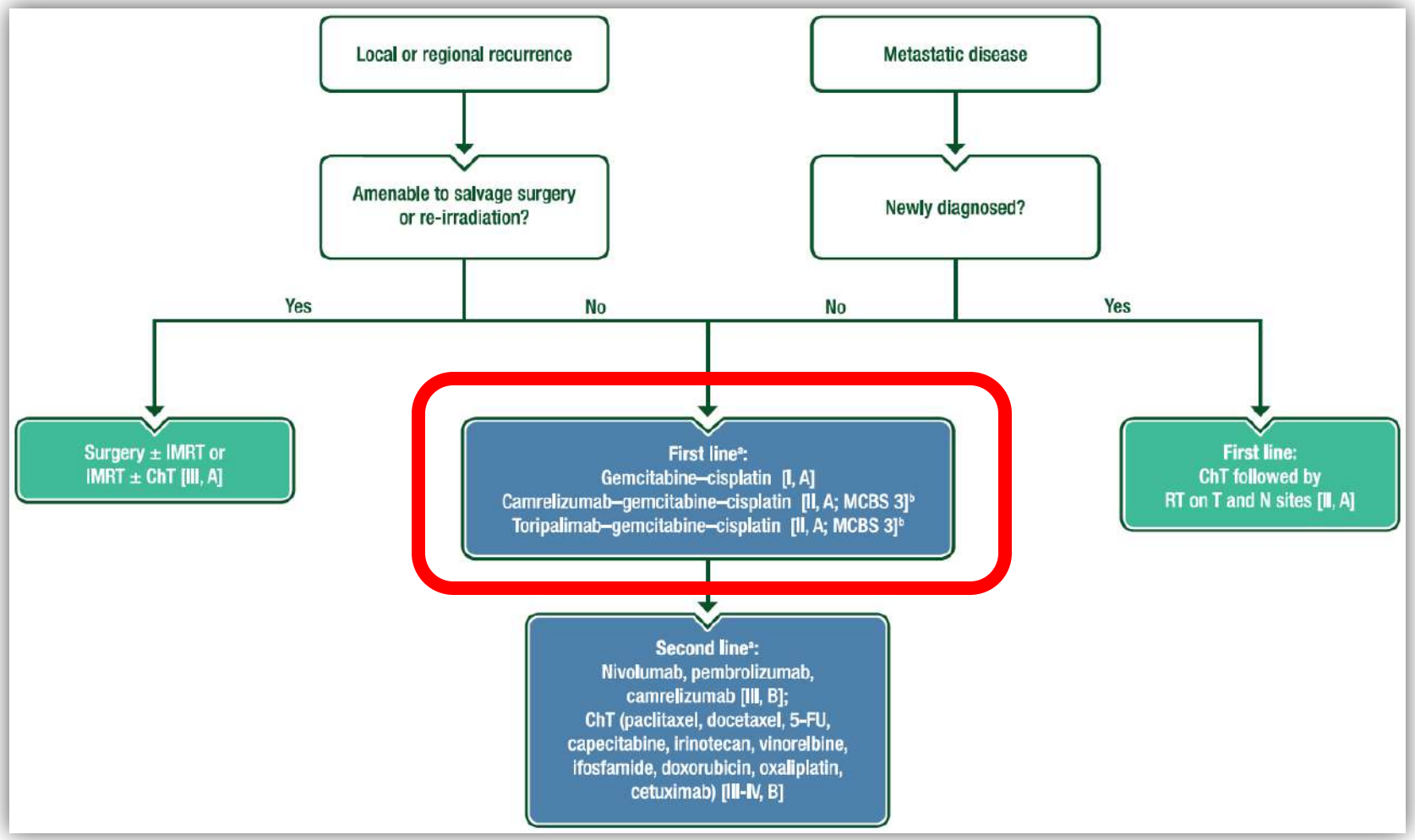


Accesible technology?
How to select candidates?

Bossi P et al, Ann Oncol, 2023

TREATMENT

mNPC - Optimal strategy



TREATMENT

mNPC – 1st line

Table 1. ESMO-MCBS table for therapies/indications in nasopharyngeal carcinoma

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[a]
Camrelizumab—gemcitabine—cisplatin[b]	First-line treatment of recurrent or metastatic nasopharyngeal carcinoma	CAPTAIN-1st [4] Phase III NCT03707509	Placebo—gemcitabine—cisplatin PFS: 6.9 months (prespecified interim analysis)	PFS gain: 3.9 months	PFS HR: 0.51 (0.37-0.69)	QoL not a prespecified endpoint 4% versus 1% treatment-related deaths ($P = 0.21$)	3 (Form 2b)
Toripalimab—gemcitabine—cisplatin[c]	First-line treatment of recurrent or metastatic nasopharyngeal carcinoma	Toripalimab injection combined with ChT versus placebo combined with ChT for recurrent or metastatic nasopharyngeal cancer[5] Phase III NCT03581786	Placebo—gemcitabine—cisplatin PFS: 8.0 months (prespecified interim analysis)	PFS gain: 3.7 months	PFS HR: 0.52 (0.36-0.74)	QoL data pending	3 (Form 2b)

None approved by EMA

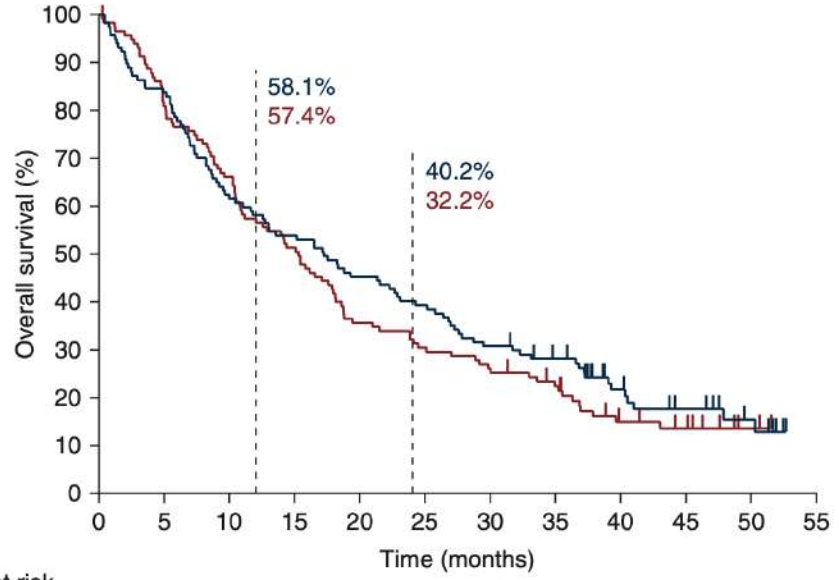
Data from endemic areas

Are anti-PD1 equivalent?

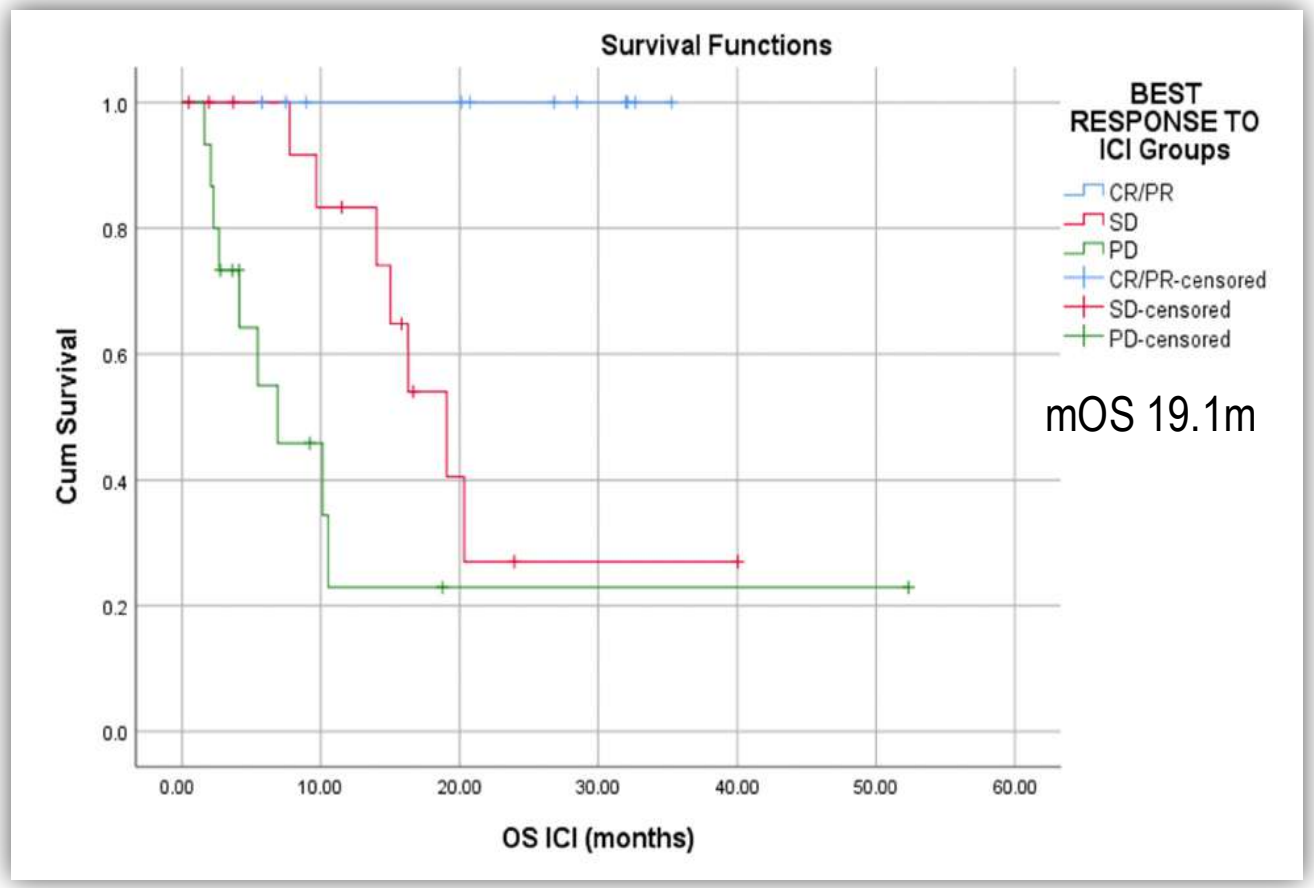
TREATMENT

mNPC – Refractory disease

	Events, *n* (%)	Median OS, months (95% CI)	HR (95% CI)[a]	*P* value[b]
Pembrolizumab	95 (81.2)	17.2 (11.7-22.9)	0.90 (0.67-1.19)	0.2262
Chemotherapy	97 (83.6)	15.3 (10.9-18.1)		



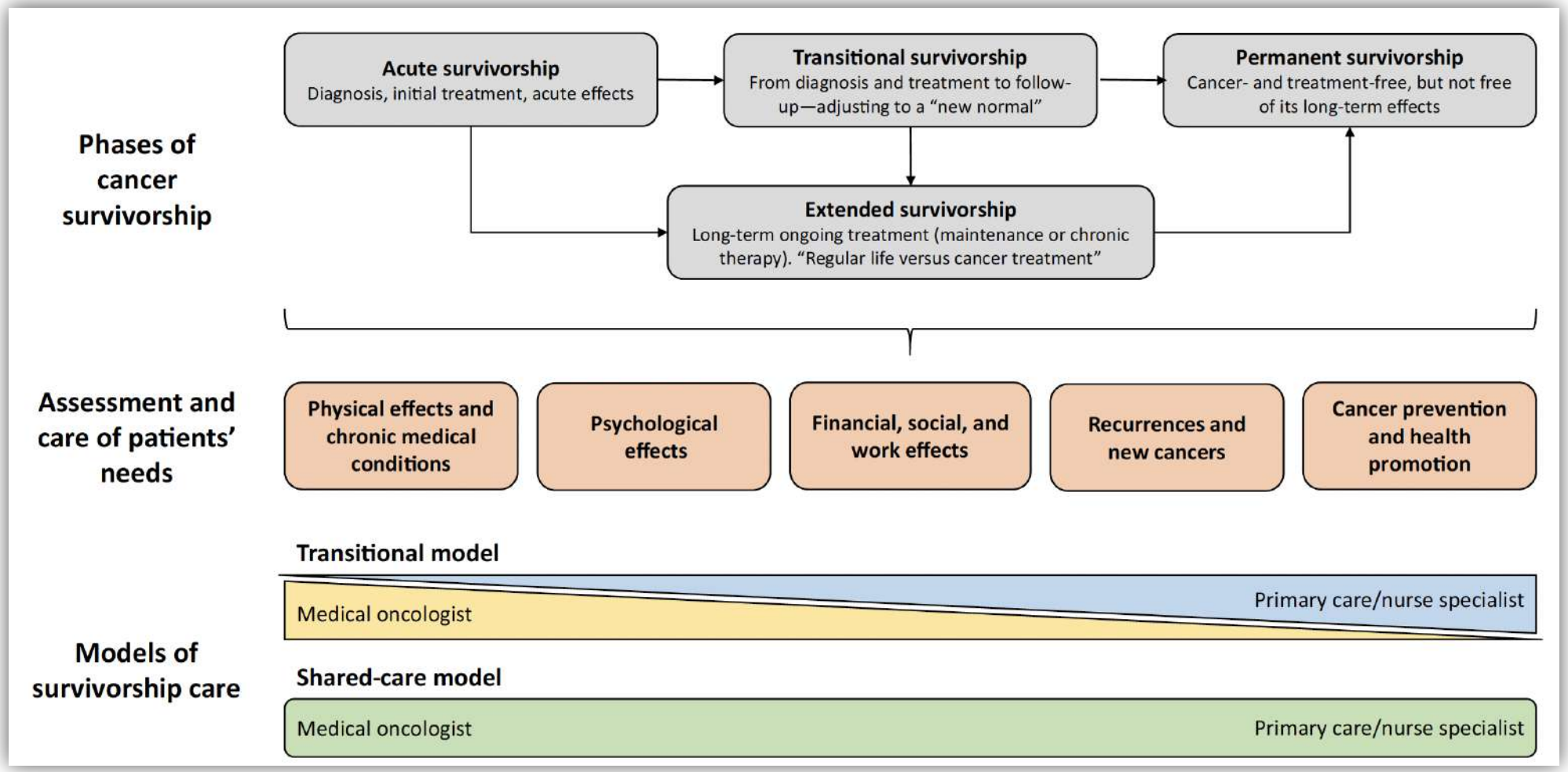
No. at risk											
Pembrolizumab	117	98	72	63	53	46	36	30	17	11	6	0
Chemotherapy	116	93	76	59	41	35	30	23	12	9	2	0



DCR: 59% vs 61.9%

POST-TREATMENT

Survivorship



POST-TREATMENT

Late Toxicities - Survivorship

Attention should be paid to the recognition of late treatment-related toxicities, mainly consisting of xerostomia, trismus, hearing impairment, TLN, cognitive impairment, cranial nerve injuries and second primary tumours possibly related to RT. The employment of IMRT instead of 2D-RT has substantially reduced these late events with the exception of TLN; significant factors affecting the risk of TLN include T stage, the addition of ChT and the maximal RT dose to the temporal lobe.[97]

Long-term survivors after IMRT may experience a decline in cognitive function and in NPC-specific domains of QoL.[98]

Radiotherapy **Chemotherapy**

Bossi P et al, Ann Oncol, 2021; Siala W et al,J Radiother, 2014

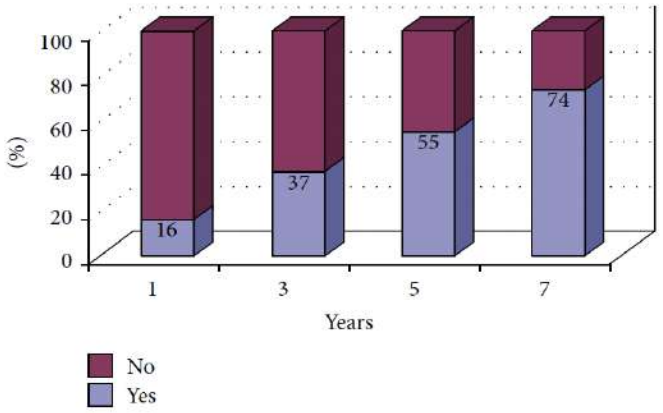


FIGURE 3: Incidence of dental toxicity after radiotherapy.

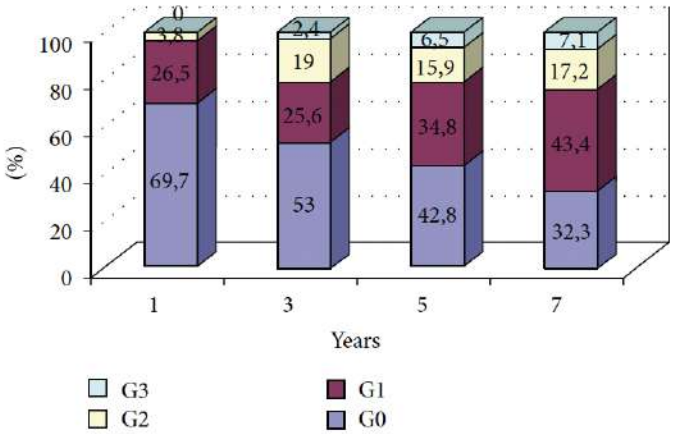


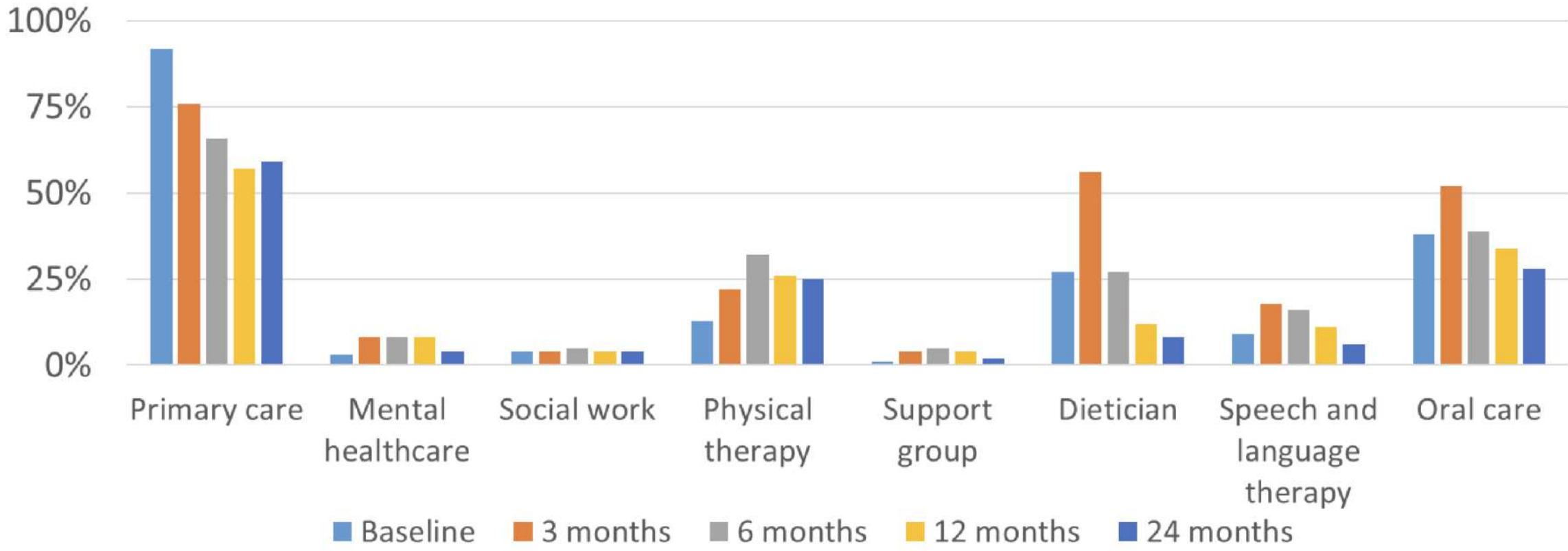
FIGURE 2: Incidence of neck fibrosis at 1, 3, 5, and 7 years.

	Percentage (%)	Mean time to occurrence (months)
Temporal necrosis	3.8	85
Frontal necrosis	0.8	46.5
Brain stem necrosis	2.1	54
Temporal atrophy	2.1	86
Frontal atrophy	0.4	72
Myelitis	0.4	17
Optic nerve atrophy	0.8	20
Demyelinization of the white matter	0.4	84

Van Beek et al, Current Oncoil, 2022

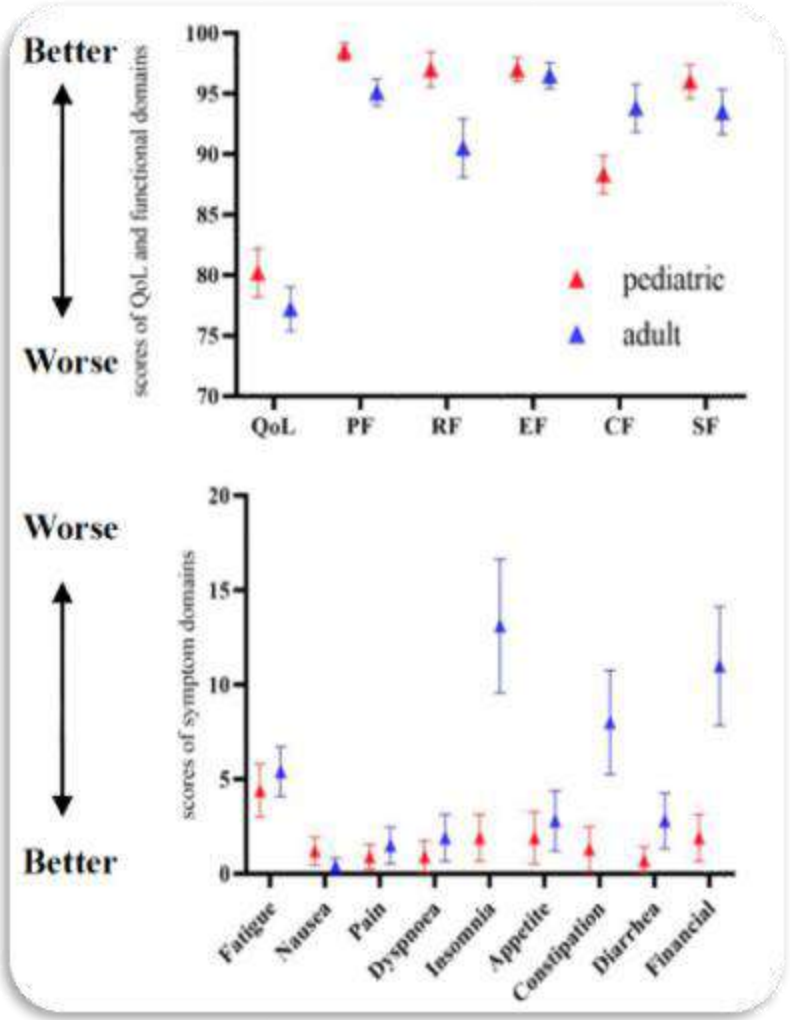
POST-TREATMENT

Late Toxicities - Survivorship



POST-TREATMENT

Late Toxicities - Survivorship



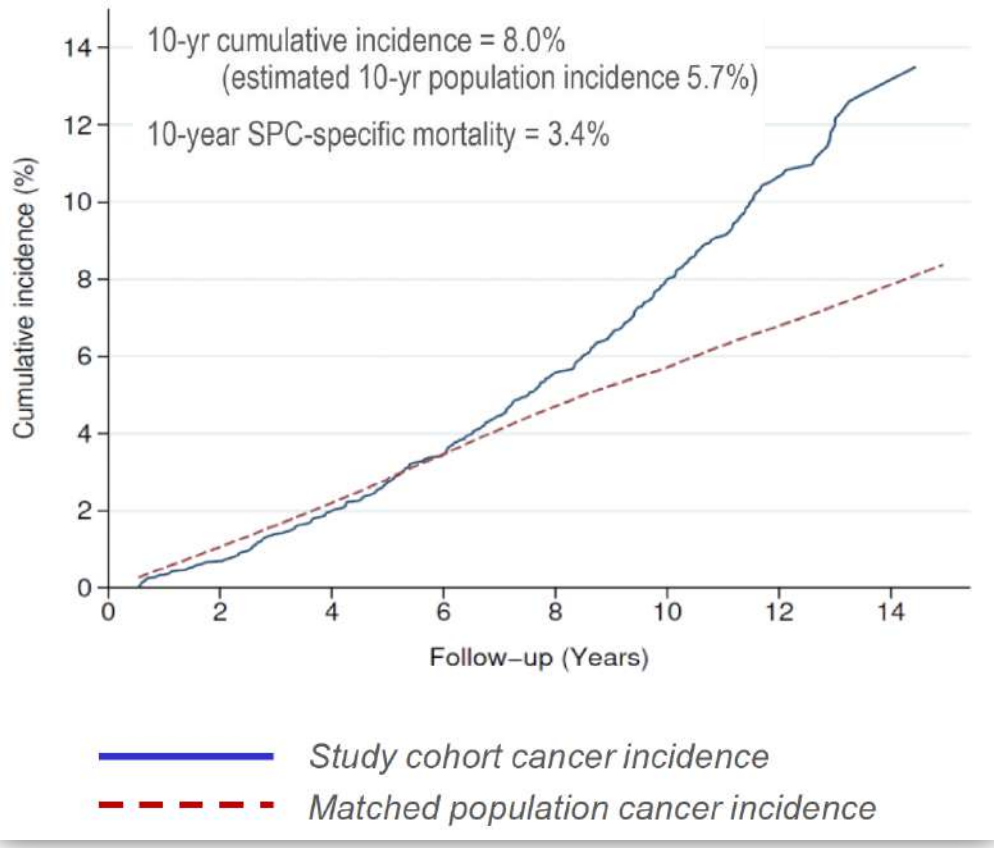
Quality of Life

	Adult(N=155)	P
Global health status/QoL	77.2 (11.5)	0.027*
Functional Scale/Items		
Physical functioning (PF)	95.1 (7.0)	<0.001*
Role functioning (RF)	90.5 (15.2)	<0.001*
Emotional functioning (EF)	96.5 (6.8)	0.511
Cognitive functioning (CF)	93.8 (12.6)	<0.001*
Social functioning (SF)	93.5 (11.8)	0.038*
Symptom Scale/Items		
Fatigue	5.4 (8.3)	0.301
Nausea and vomiting	0.4 (2.7)	0.083
Pain	1.5 (6.1)	0.278
Dyspnoea	1.9 (7.8)	0.158
Insomnia	13.1 (22.3)	<0.001*
Appetite loss	2.8 (10.0)	0.420
Constipation	8.0 (17.4)	<0.001*
Diarrhea	2.8 (9.3)	0.010*
Financial difficulties	11.0 (19.8)	<0.001*

Chow J et al, ESMO Congress 2020

POST-TREATMENT

Late Toxicities - Survivorship



Secondary neoplasms

Cancer Site	Number of SPC	SIR (95% C.I.)	AER (95% C.I.) per 10,000 PYR
All sites	290	**1.9 (1.7 – 2.2)**	**52.1 (36.8 – 67.3)**
Soft tissue and bone sarcoma	25	**15.2 (9.3 – 21.2)**	**8.5 (4.8 – 12.2)**
Leukemia and myeloma	6	2.4 (0.5 – 4.4)	1.3 (-0.8 – 3.4)
Lymphoma	3	0.6 (0.1 – 1.8)	-0.7 (-2.7 – 1.3)
Head and neck			
Oral cavity	51	**26.3 (19.1 – 33.6)**	**17.9 (12.7 – 23.1)**
Non-melanoma skin	11	**3.6 (1.5 – 5.7)**	**3.1 (0.2 – 5.6)**
Oropharynx	9	**11.4 (4.0 – 18.9)**	**3.0 (0.8 – 5.2)**
Lung	51	**1.8 (1.3 – 2.3)**	**8.4 (2.1 – 14.8)**

Post-IMRT NPC survivors had **90% higher** risk of SPC than demographic-matched general population

Almost all excess cancer risk occurred in previously irradiated organs.

Re-irradiation is an independent predictor for subsequent second primary cancers

Second primary cancers **impair longevity** of NPC survivors

ISSUES TO THINK ABOUT

- Is NPC one unique disease? How can this change its management?
- How can we, in a practical way, incorporate all the patient's information in one tailored treatment plan?
- Can EBV be used reliably in the screening, diagnosis, therapy and follow-up of our NPC patients?
- Will european patients benefit some day from anti-PD1 ICIs in 1st line R/M NPC?
- With such morbility secondary mostly to local treatments, how can we tailor treatments to be better tolerated by our patients, wthout loosing efficacy?

ESMO GUIDELINES: REAL WORLD CASES

Alberto Cunquero

cunquero_alb@gva.es

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

ESMO WEBINAR SERIES