ZDRAVLJENJE BOLNIKOV Z LOKALNO NAPREDOVALIM RAKOM GLAVE IN VRATU DANES IN JUTRI

PRIMOŽ STROJAN
Onkološki inštitut Ljubljana

Ljubljana, 26.3.2021

DANES

- Lokalno/regionalno napredovali tumorji: ≈60%
- Standardno zdravljenje:
  - operacija → RT (+/- KT)
  - sočasna radiokemoterapija
  - (indukcijska KT → sočasna radiokemoterapija)

} **IMRT**
Cisplatin
TPF

TERAPEVTSKI KONCEPTI NESPREMENJENI ≈10-20 LET!

EORTC 22931
Bernier et al, N Engl J Med 2004

RTOG 9501
Cooper et al, N Engl J Med 2004

Primerjalna analiza:
Bernier & Cooper et at, Head Neck 2005

MACH-NC (meta-analiza)
Pinon et al, Lancet 2000
Pignon et al, Int J Radiat Oncol Biol Phys 2007
Pignon et al, Radiother Oncol 2009
Blanchard et al, Radiother Oncol 2011
Lacas et al, Radiother Oncol 2021

TPF vs. druge sheme
Blanchard et al, J Clin Oncol 2013 (meta-analiza)

sKRT vs. iKT→cRT
Vidal et al, Cancer 2017 (meta-analiza)

IMRT vs. 3DCRT/2DRT
Marta et al, Radiother Oncol 2014 (meta-analiza)
Pow et al, Int J Radiol Biol Phys 2006
Nutting et al, Lancet Oncol 2011 (PARSPORT)

5-letno preživetje: p16/HPV- tumorji OF, ostali ne glede status p16/HPV, <50%
p16/HPV+ tumorji OF (nizko/srednje tveganje), >60%

Chow LQM, N Engl J Med 2020

JUTRI

- Inhibitorji kontrolnih točk
- Modulacija apoptoze
- SBRT
- Protonska RT

IT: NEOADJUVANTNA/PERIOPERATIVNA

ŠTUDIJA	FAZA/N/TU	**IT→KRG**	sODG/mpODG	TX G≥3
NCT03144778 Ferrarotto et al. 2020	II/28/OF (p16+ 86%)	2xDURVA 2xDURVA+TREMELI	43% 43%29%	14%
NCT02919683 Schoenfeld et al, 2020	II/29/UV	2xNIVO 2xNIVO+1xIPILI	50%/7% 53%/20%	13% 36%
NCT02296684 Uppaluri et al 2020	II/36/HPV-	1xPEMBRO	44%/0%	0%
		IT→RT+IT		
NCT03426657 Hecht et al, 2020	II/57/UV,OF,HF,L (p16+ 25%)	1xDURVA/TREMELI+ CP/DOCE	43% (pCR 48%)	68%

✓ študije neustrezno načrtovane za statistično oceno učinkovitosti IT
✓ zmerno visok delež patoloških odgovorov po IT

? Napoved patološkega odgovora (RECIST/PET-CT)
? Vrsta (definicija) patološkega odgovora, ki sovpada s preživetjem
? Kateri pODG napoveduje dobrobit (onkološko): min, večji, popoln
? Časovno okno za oceno odgovora na IT
Pojav toksičnosti IT mesece po aplikaciji!

IT: SOČASNO Z RT (± VZDRŽEVALNA IT)

ŠTUDIJA	FAZA/N/stadij	RT+**IT**	IZID	TX G≥3
NCT02609503 Weiss et al, 2020	II/29/III-IV	3xPEMBRO→adj (3xPEMBRO)	24-PFS: 71% 24-OS: 75%	59% (limfopenija)
NCT 02952586 Cohen et al, 2020 JAVELIN HN 100	III/697/III-IV	AVELU/2T+CP/2T PLACEBO/2T+CP/3T (+/- uvodni krog & vzdrž.)	PFS: HR 1.21 p=0.92 OS: HR 1.31, p=0.94 (v korist placebo roki)	88% 82%
NCT02999087 Tao et al, 2020 GOTRC 2017-01 REACH	III/688/III-IV »safety phase«: 82	CP/3T ± AVELU/2T CMb/T ± AVELU/2T		G≥4 Eksp: 12% Stand: 15%, 10%
NCT03040999 KEYNOTE-412	III/780/III-IV	CP/3T+PEMBRO/3T PLACEBO/3T+PEMBRO/3T (+/- uvodni krog & vzdrž.)		

Načrtovane raziskave faze III:

IMvoke010 N=400: atezolizumab kot vzdrževalna TH (1 leto)
KEYNOTE-689 N=704: pembro→KRG→RT±KT+pembro
ADHERE (EORTC) N=650: KRG→durva→RT±KT+durva→durva (re-evaluacija protokola)
MK-3475-689 N=704: pembro→KRG→RT±KT+pembro
NIVOPOSTOP N=680: KRG→RT±KT+nivo
IMSTAR-HN N=276: nivo→KRG→STH+nivo±ipi

MODULACIJA APOPTOZE

Debio 1143 and high-dose cisplatin chemoradiotherapy in high-risk locoregionally advanced squamous cell carcinoma of the head and neck: a double-blind, multicentre, randomised, phase 2 study

Lancet Oncol 2020

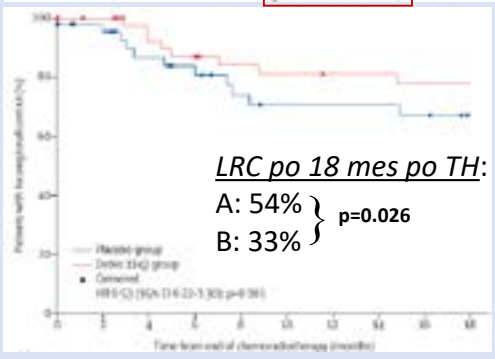
- DEBIO 1143 = oralni antagonist inhibitorjev proteinov apoptoze

Toksičnost:
G≥3 85% vs. 87%
G5: 0% vs. 4%

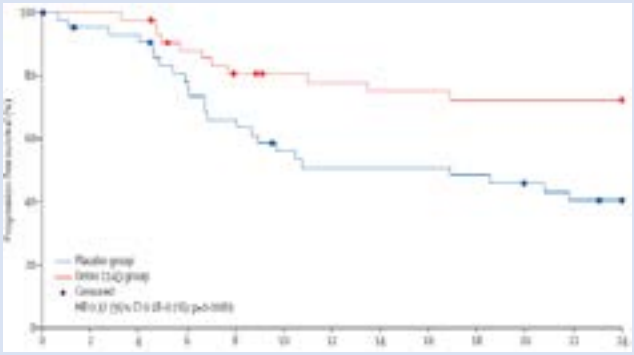
NCT02022098, faza II
N=96 (2x48), III/IV & >10py
FUP_{med} = 25 mes

- roka A: RT+CP100+DEBIO (200 mg/d 1-4/21 dni x3)
- roka B: RT+CP100+placebo

Interpretation To our knowledge, this is the first treatment regimen to achieve superior efficacy in this disease setting against a high-dose cisplatin chemoradiotherapy comparator in a randomised trial. These findings suggest that inhibition of inhibitor of apoptosis proteins is a novel and promising approach in this poor prognostic population and warrant confirmation in a phase 3 study with the aim of expanding the therapeutic options for these patients.



LRC po 18 mes po TH:
A: 54%
B: 33%
p=0.026



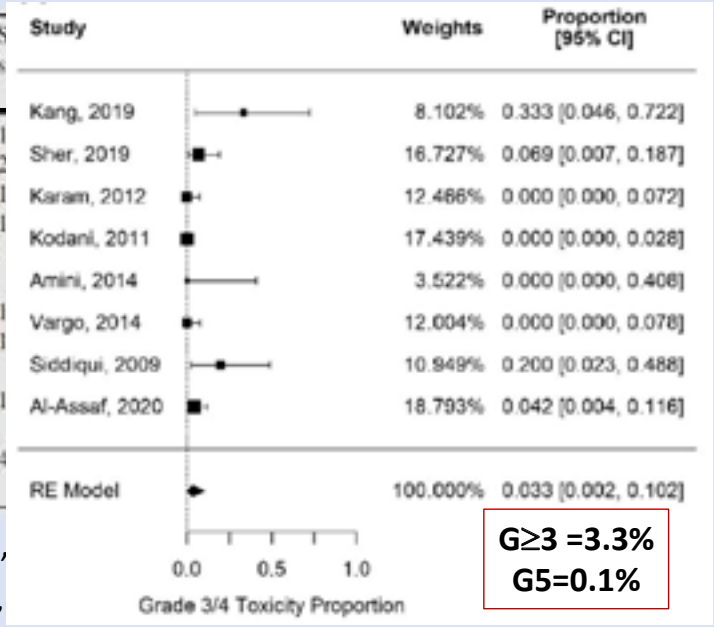
SBRT: 1°TU

Stereotactic Radiation Therapy for De Novo Head and Neck Cancers: A Systematic Review and Meta-Analysis

Nauman H. Malik, MD,[a] Michael S. Kim, MD,[b] Hanbo Chen, MD,[a] Ian Poon, MD,[a] Zain Husain, MD,[a] Antoine Eskander, MD,[c,d] Gabriel Boldt, MLIS,[e] Alexander V. Louie, MD, PhD,[a] and Irene Karam, MD[a,*]

Adv Radiat Oncol 2021

PTV (cc)	Study	Subsite	Study design	S
5.3 (3.9-10.9)	Kang[20]	Larynx	Prospective	1
–	Sher[25]	Larynx	Prospective	2
89 (13-393)	Karam[26]	Parotid	Retrospective	1
22 (0.7-78)	Kodani[27]	Mixed	Retrospective	1
15, 21, 37	Amini et al[10]	Mixed	Retrospective	
42 (15-248)	Vargo[28]	Mixed	Retrospective	1
–	Khan et al[9]	Mixed	Retrospective	1
–	Siddiqui et al[15]	Mixed	Retrospective	1
33 (2-369)	Al-Assaf[30]	Mixed	Retrospective	4



G≥3 =3.3%
G5=0.1%

Kang et al, IJROBP 2019,

Sher et al, IJROBP 2019,

There is lack of evidence of use of stereotactic radiotherapy in primary HNC and therefore cannot be recommended as standard of care. The previous studies have been small case series and a phase I trial with inherent methodological weaknesses.

SBRT: reRT

A systematic review and practical considerations of stereotactic body radiotherapy in the treatment of head and neck cancer

Br J Radiol 2020

MUHAMMAD SHAHID IQBAL, NICK WEST, NEIL RICHMOND, JOSEF KOVARIK, ISABEL GRAY, NICK WILLIS, DAVID MORGAN, GOZDE YAZICI, MUSTAFA CENGIZ, VINIDH PALERI and CHARLES KELLY

NAJVEČJA ŠTUDIJA (retro): N=291

Ling et al, Int J Radiat Oncol Biol Phys 2016 (Pittsburgh)

PTV_{med} 29 cm^3 (0,8 – 209), TD_{med} 44 Gy/#5

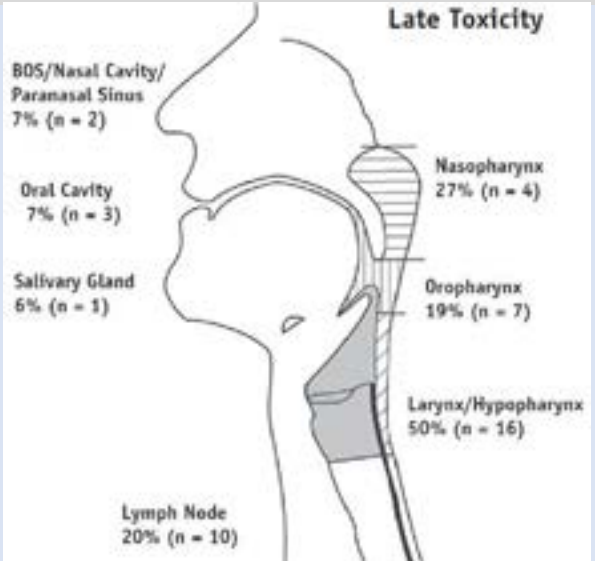
Toksičnost:

G≥3, akutna = 11,3%

kasna = 18,9% → **HF/Lx : drugo = 50% : 6-20%**

Faza I = 1
Faza II = 2
Register (prospektiven) = 1
Retrospektiva = 17

21 poročil, 1381 bolnikov



IZBOR BOLNIKOV:
- <6 mes od predhodne RT
- resekcija TU
- ni KRG: funkcionalen organ
- seznanitev s tveganjem za kasno Tx!

VOLUMEN PTV = ? (≤25 cm^3)

REŽIM: 35-40 Gy/#5 2x/T ali na 2 dni

PTV: ni CTV, izotropen rob 1,5-3 mm

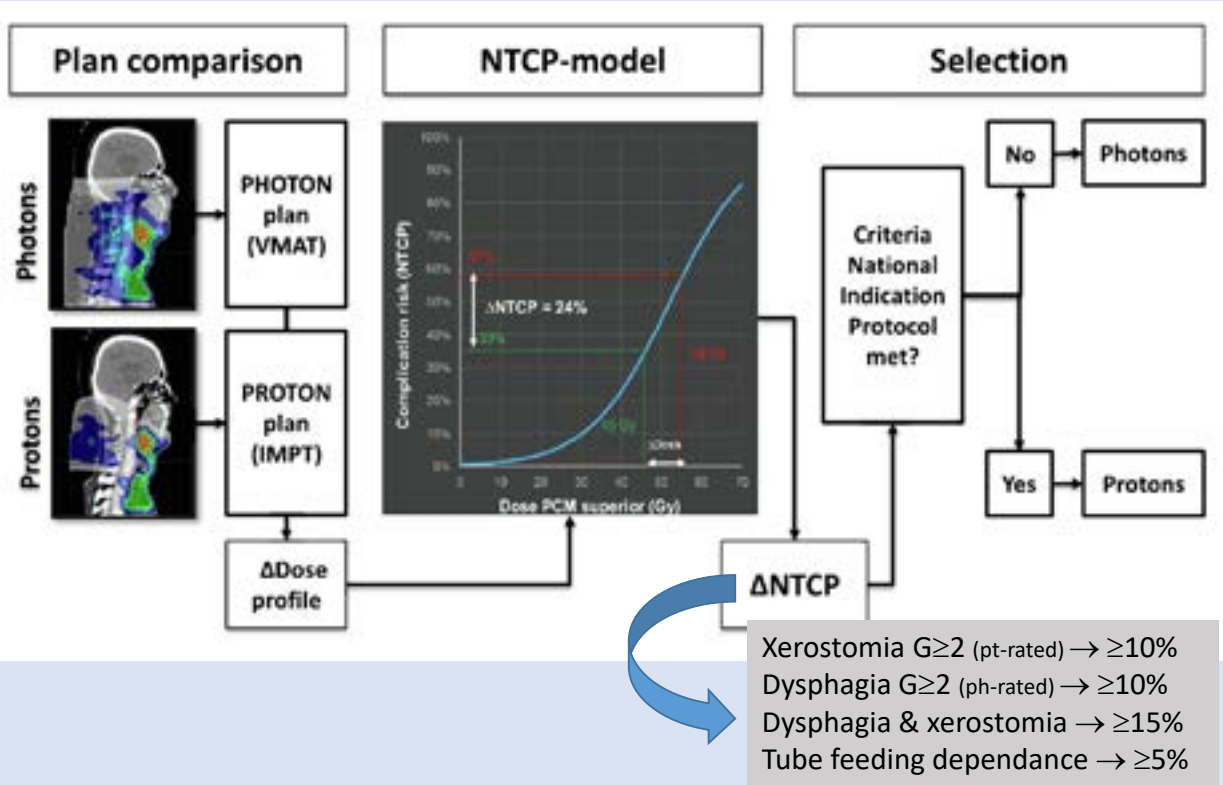
VARNA & UČINKOVITA

PROTONSKA RT

First experience with model-based selection of head and neck cancer patients for proton therapy

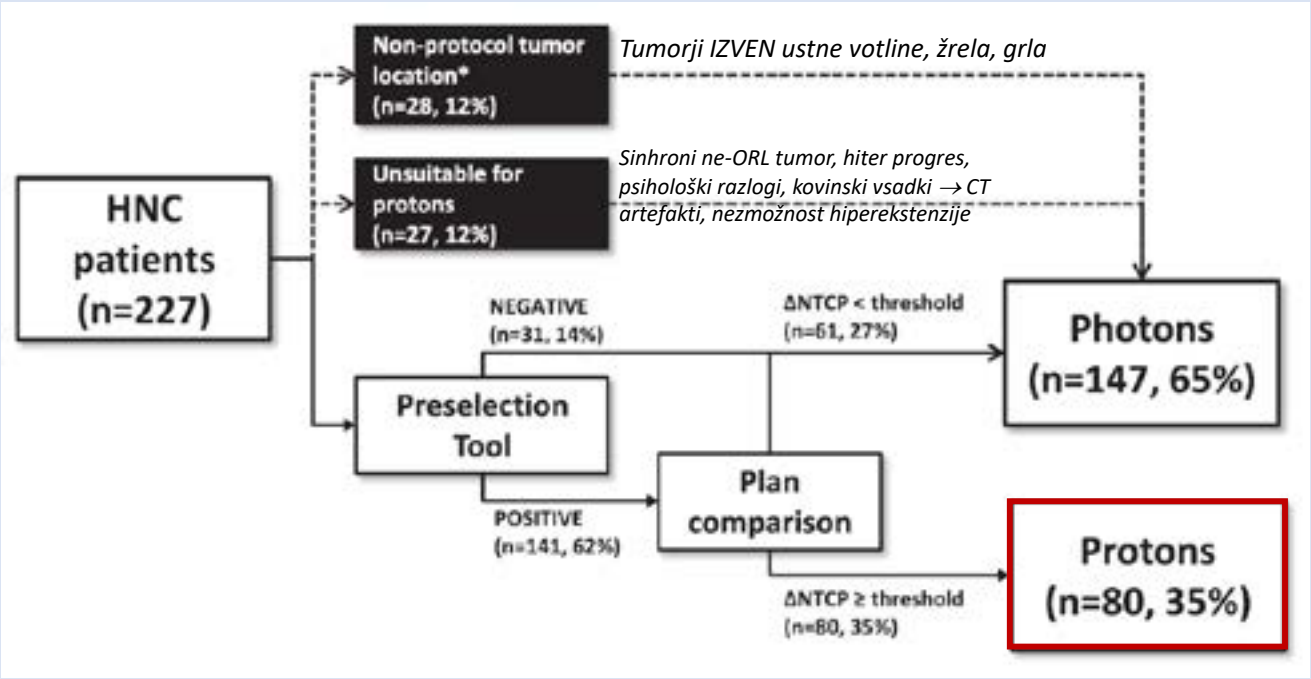
Makbule Tambas, Roel J.H.M. Steenbakkers, Hans P. van der Laan, Atje M. Wolters, Roel G.J. Kierkels, Dan Scandurra, Erik W. Korevaar, Edwin Oldehinkel, Tineke W.H. van Zon-Meijer, Stefan Both, Johanna G.M. van den Hoek, Johannes A. Langendijk

Radiother Oncol 2020



Xerostomia G≥2 (pt-rated) → ≥10%
Dysphagia G≥2 (ph-rated) → ≥10%
Dysphagia & xerostomia → ≥15%
Tube feeding dependance → ≥5%

PROTONSKA RT



Tambas et al, Radiother Oncol 2020