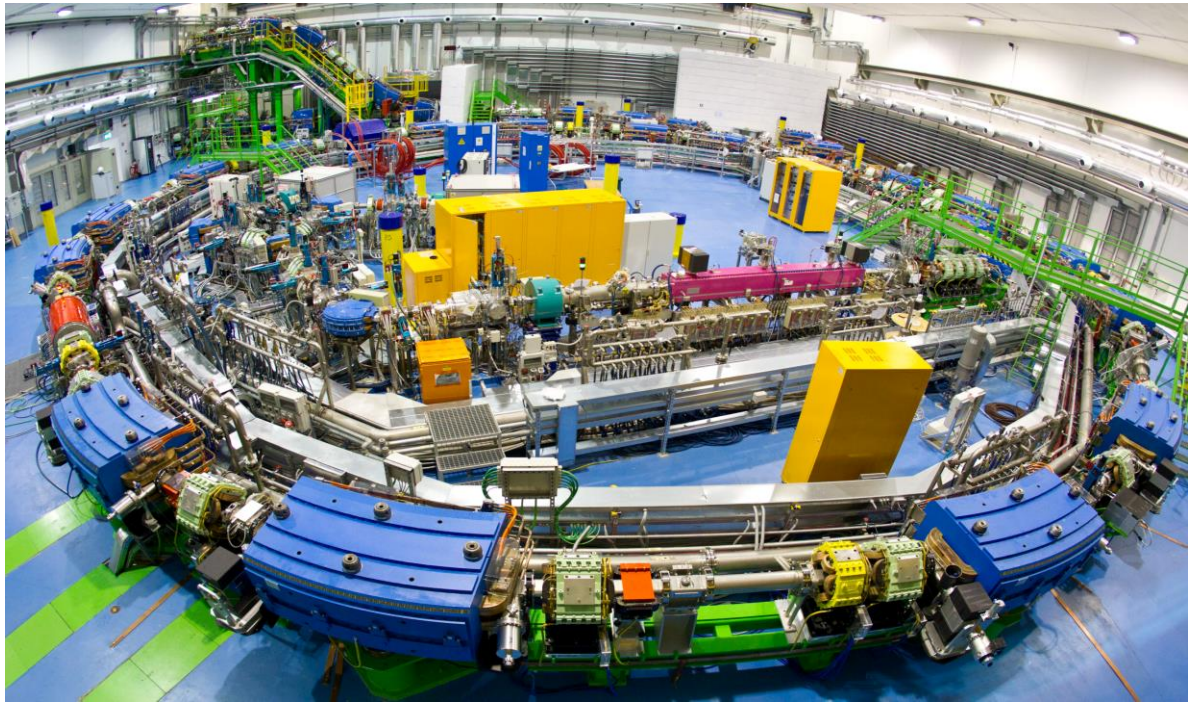
Il Centro Nazionale di Adroterapia-CNAO

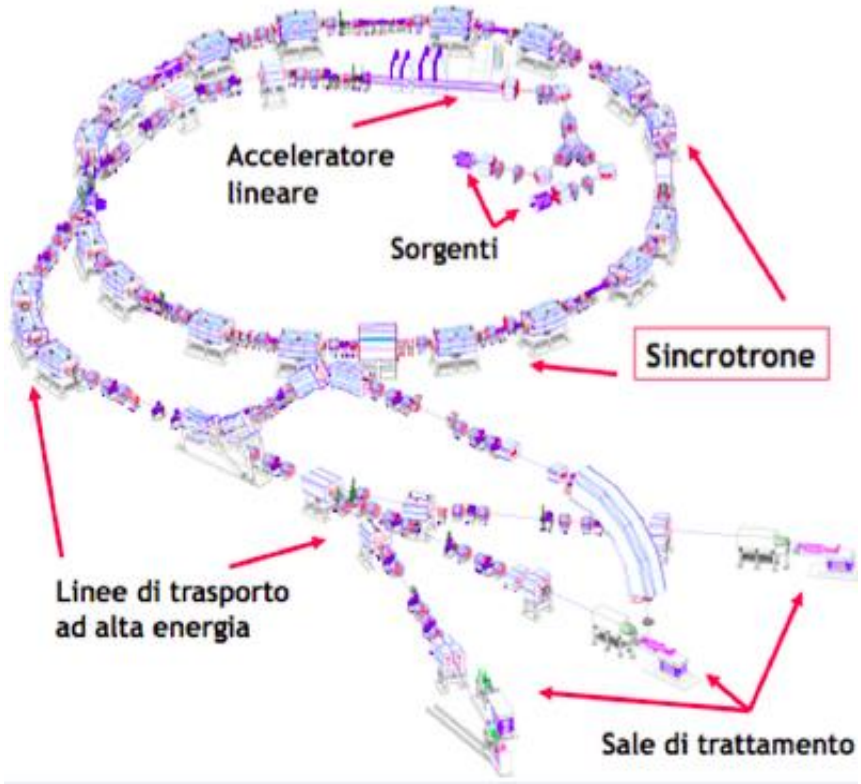
E. Orlandi

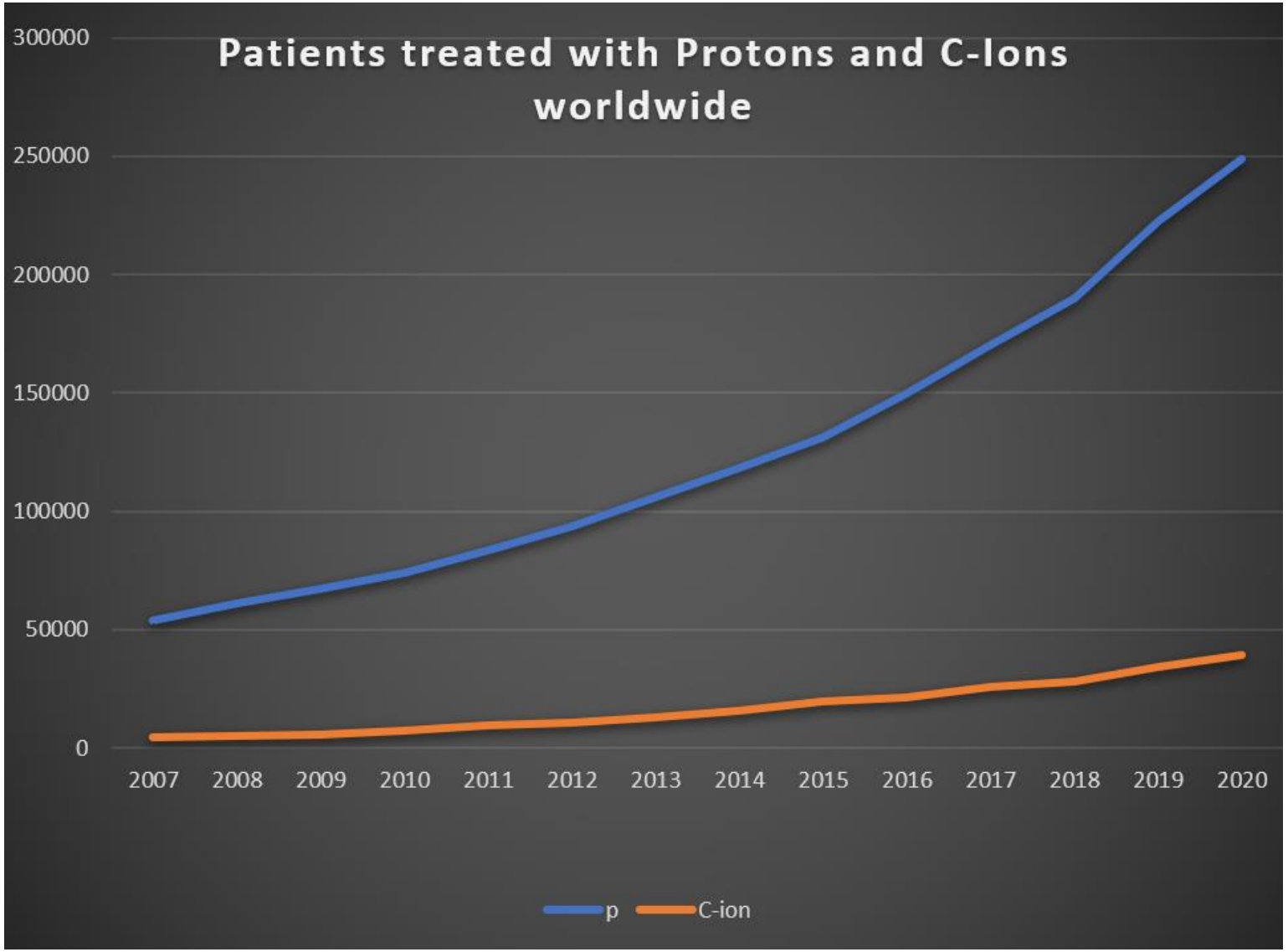
CNAO in Pavia

dual center

Protons/Carbon Ions



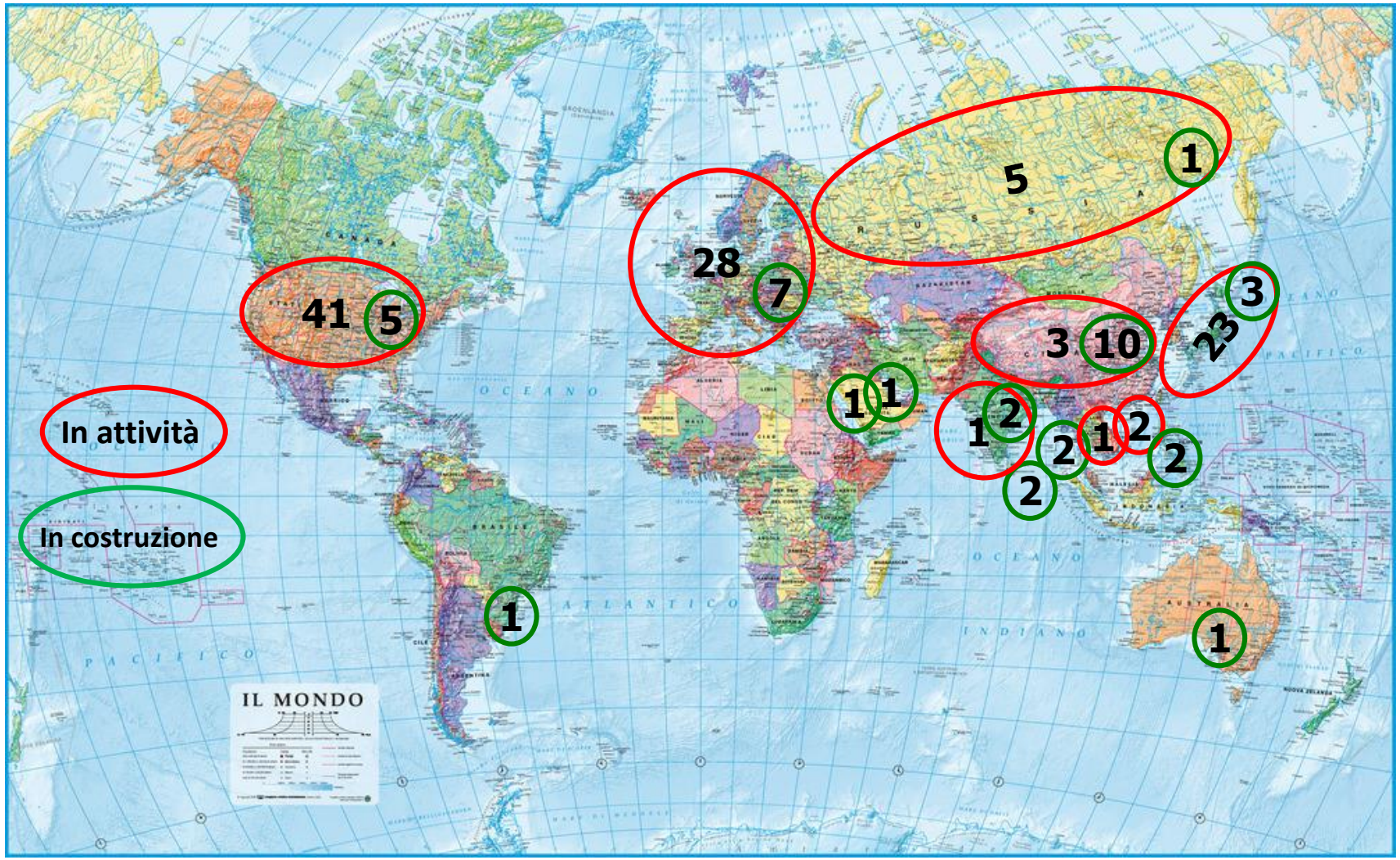




PTCOG Website, Ottobre 2021

Centri di Adroterapia nel mondo

104* Centri in attività
38 in costruzione (5 con CIRT)**
28 in planning



PTCOG Website, Ottobre 2021

Centri con Ioni Carbonio

Mayo, Jacksonville

PARALLEL OPPOSED EDITORIAL

We are ready for clinical implementation of Carbon Ion Radiotherapy in the United States

J Appl Clin Med Phys 2020; 21:12:6–9

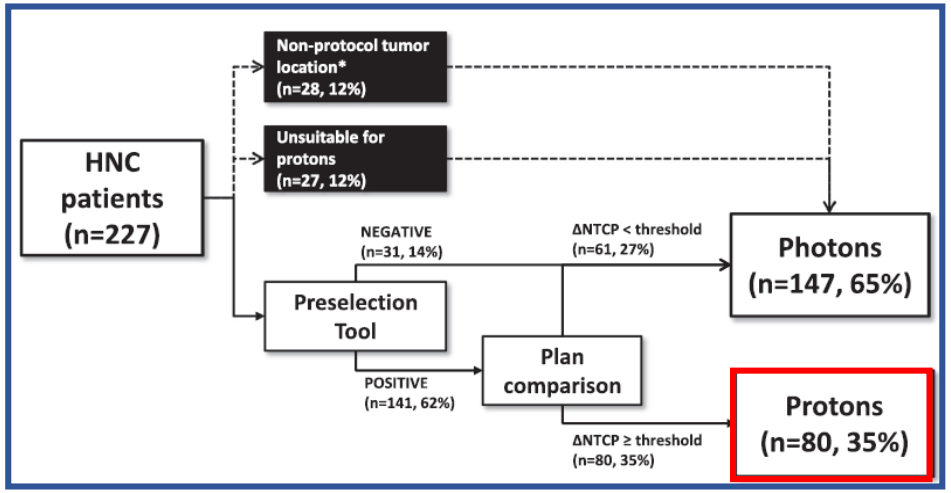
PTCOG website, Ottobre 2021

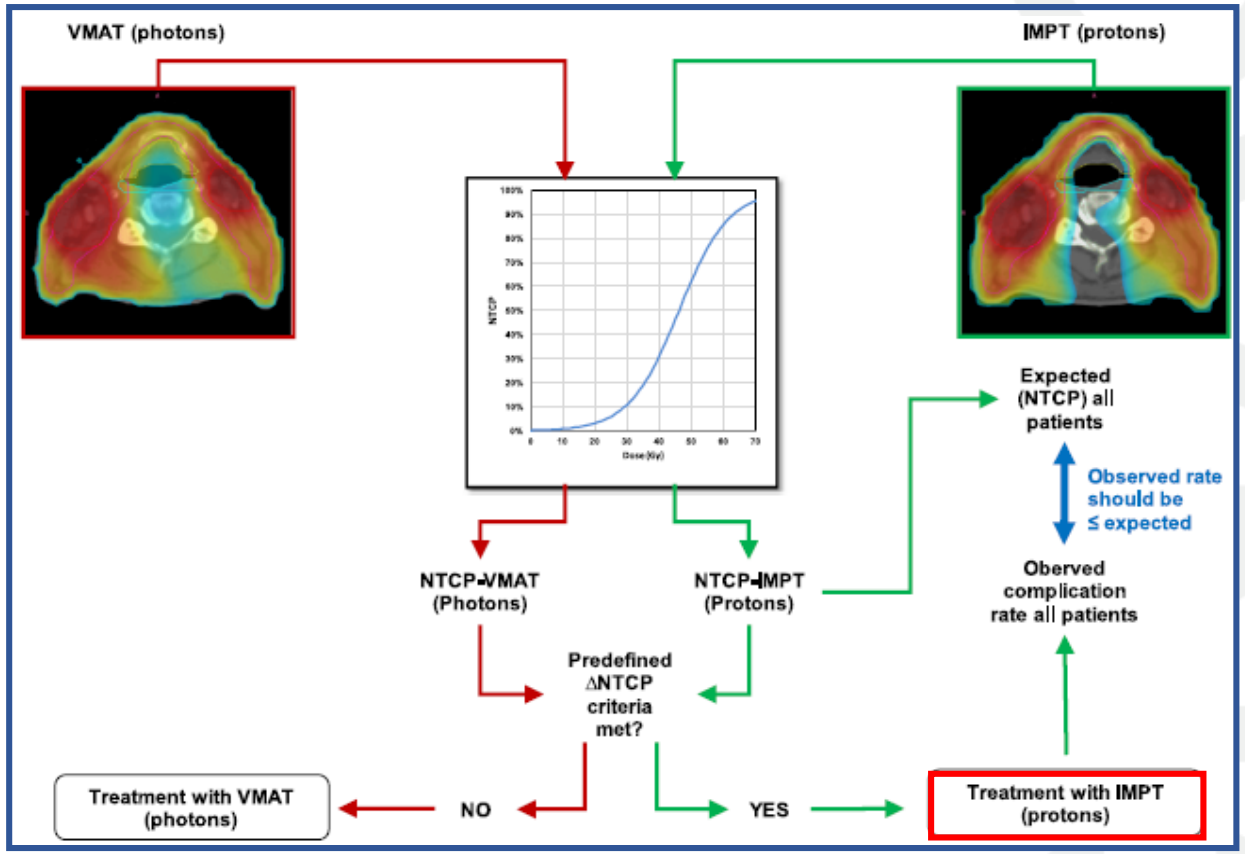
Il modello olandese

Standard indication
Skull base or spinal chordoma and chondrosarcoma
Other intracranial, spinal, and paraspinal tumors, including meningioma
Pediatric tumors, including bone tumors, soft-tissue sarcoma, low-grade glioma, meningioma, medulloblastoma, ependymoma, and neuroblastoma
Potential indications (cases for which protons may be specifically utilized to improve local control)
Re-irradiation (malignant brain tumors, head and neck cancer)
Paranasal sinus tumors, nasopharyngeal carcinoma, prostate, NSCLC, retroperitoneal sarcoma
Model based indication (cases where proton will be utilized to reduce side effect)
Re-irradiation (meningioma, head and neck cancer)
Head and neck cancers, prostate
Reduction of secondary cancer
Breast cancer
Lymphoma
Testis

Base cranica, spinali, pediatrici, re-irradiazioni, H&N, prostata, polmone, mammella, linfomi, testicolo

National Protocol for Model-Based Selection for Proton Therapy in Head and Neck Cancer





Lagendijk JA et Al. Sem Radiat Oncol 2018; Tambas M et AL. Radiother Oncol 2020; Lagendijk JA et Al. Int J Particle Ther 2021

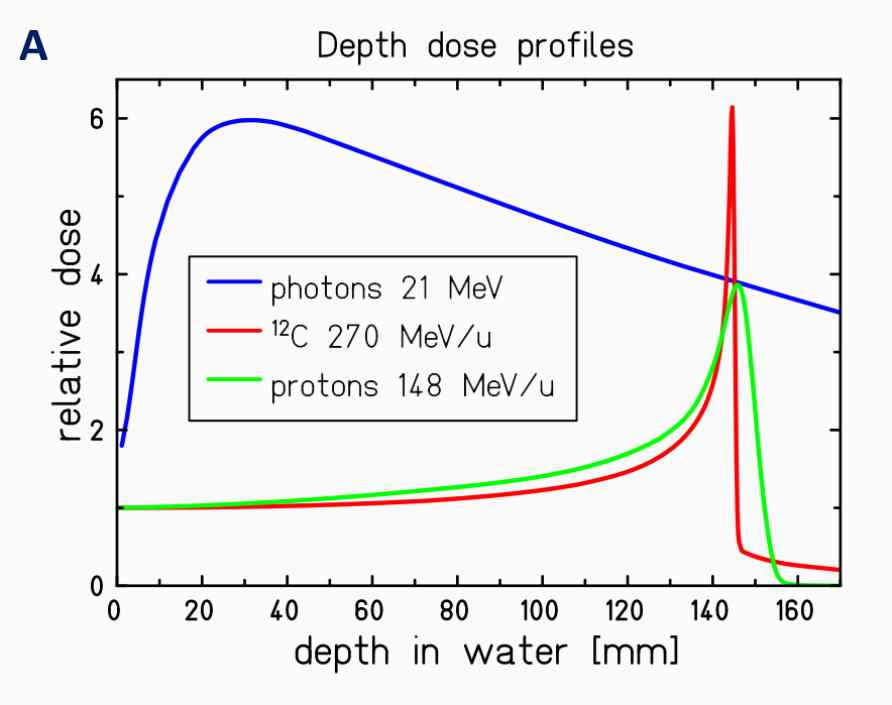
In Italia

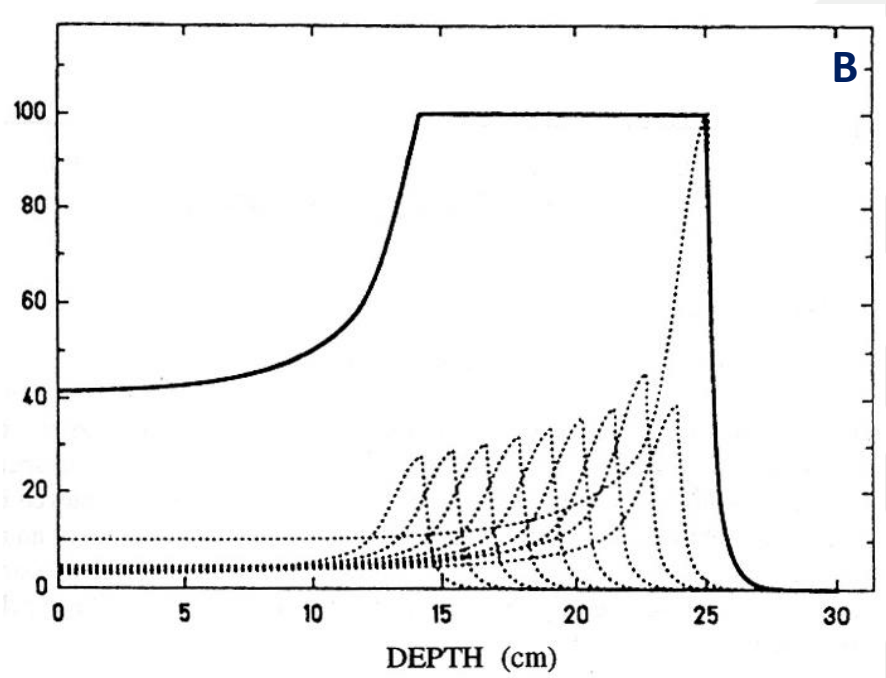
Patologie attualmente trattabili al CNAO nell'ambito del Sistema Sanitario Nazionale, inserite nei LEA (marzo 2017):

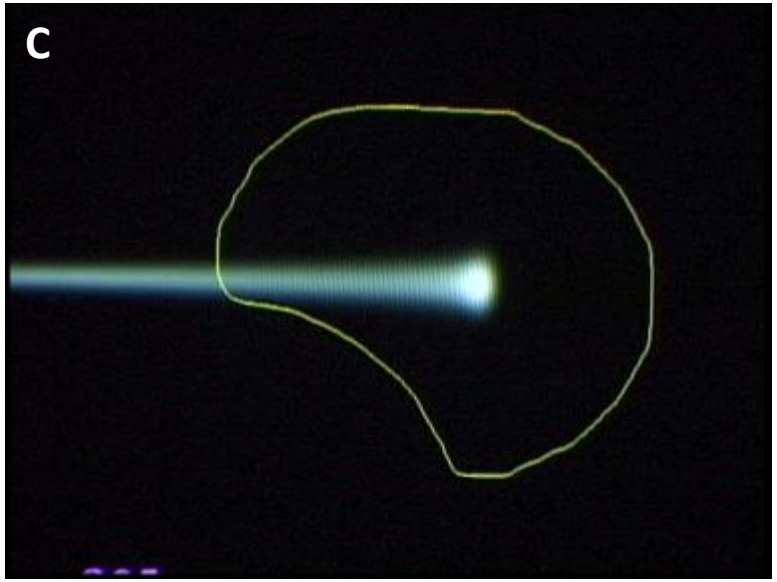
- Tumori orbitali e periorbitali, incluso il melanoma oculare
- Tumori del tronco encefalico e del midollo spinale
- Meningiomi intracranici in sedi critiche
- Carcinomi adenoideo-cistici delle ghiandole salivari
- Cordomi e condrosarcomi della base del cranio e rachide
- Tumori solidi pediatrici
- Tumori in pazienti affetti da sindromi genetiche
- Sarcomi delle parti molli
- Sarcomi ossei
- Ritrattamenti di tumori in sedi già irradiate

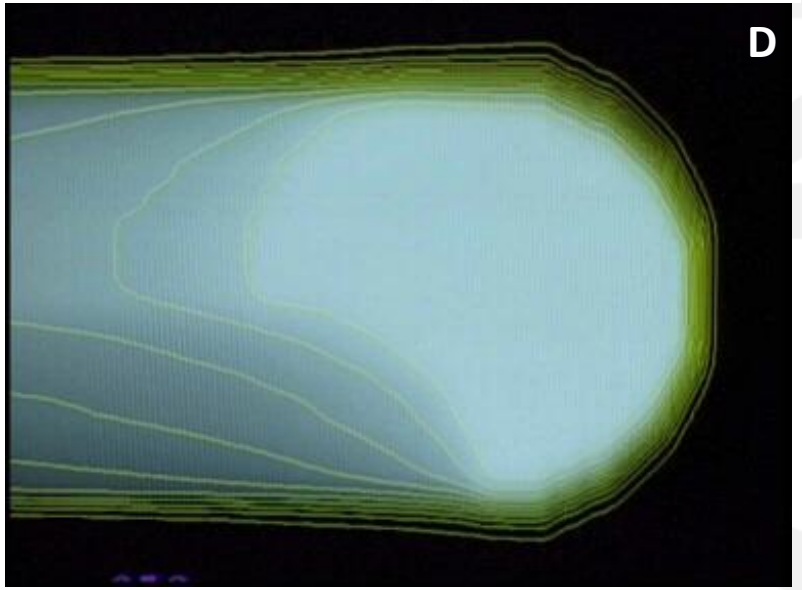
- *…confronto dosimetrico /TCP/NTCP…..*

Physical proprieties









Changed Particles: Phisics & Radiobiology

X-Ray/Protons

High-energy
Low dose
Low-LET
Fractionation sparing
RBE ~1
OER ~3

Carbon Ions

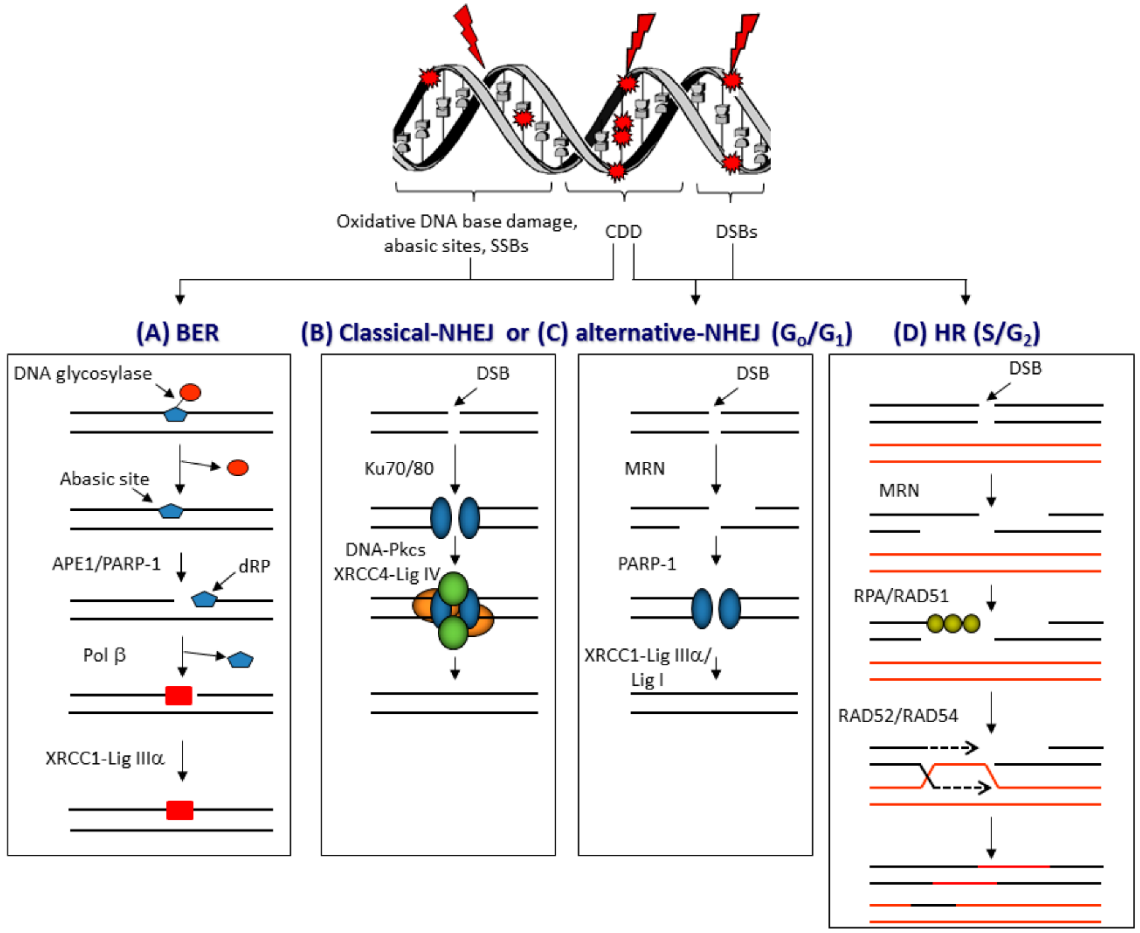
Low-energy
High dose
High-LET
Little fractionation effect
RBE > 1
OER < 3

- PT RBE : 1.1-7
- CIRT RBE :2.3-4

Durante M, Br J Cancer. 2019

Protons: Radiobiology

- Different lesions are induced along the radiation track



Most frequent:

- DNA base damage
- sites of base loss (abasic sites)
- DNA single-strand breaks (SSBs)

Less frequent (but the most lethal) at the distal edge of the SOBP

- double-strand breaks (DSBs)
- complex DNA damage (CDD) containing two or more DNA lesions in close proximity (within 1–2 helical turns of the DNA)

Down-regulation by PT of genes involved in motility which are upregulated by X-Ray

- ↓angiogenesis
- ↓ metastasis

Eccles et al. Mutat. Res. 2011
Lomax et al Clin. Oncol. R. Coll. Radiol. 2013
Vitti et al Cancers 2018

Carbon Ions: Radiobiology

- Difference in terms of molecular radiobiology

  - ✓ down-regulation by C-ions of genes involved in motility which are upregulated by X-Ray
    - ↓angiogenesis
    - ↓ metastasis

- High LET is efficient to induce cell death of resistant cells (i.e. cancer stem-like or p53 mutant cells)

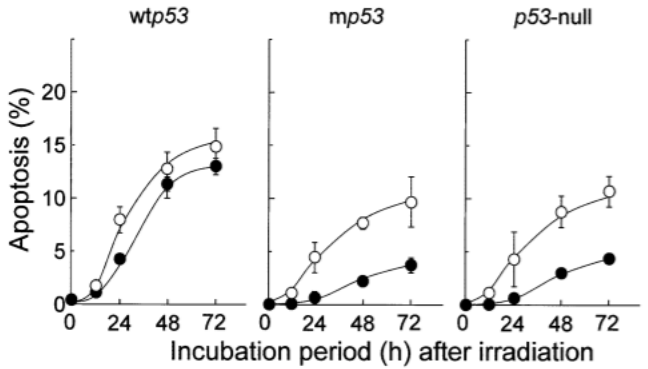


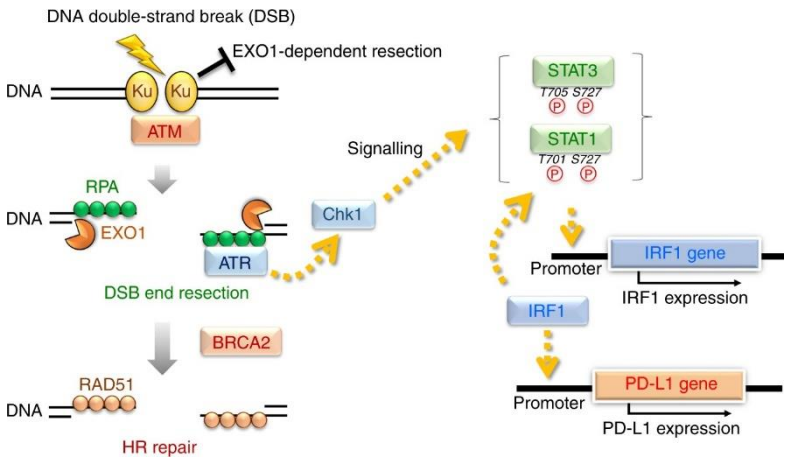
Fig. 3. Time-dependency of radiation-induced apoptosis. Apoptosis induced by X-rays (●) and 70 KeV/μm carbon beams (○) at isosurvival dose (D_{30}) was analyzed by Hoechst 33342 staining in H1299/wt*p53* (clone No. 1), H1299/m*p53* (clone No. 3), and H1299 (clone No. 5) cells. Error bars indicate standard deviations.

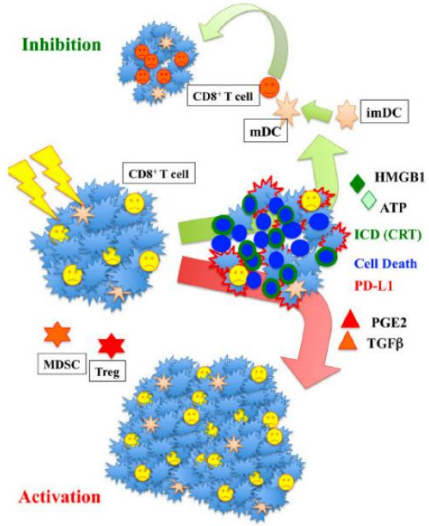
Masahiro et al Journal of Radiation Research 2018
Takahashi A et al. Int J Radiat Oncol Biol Phys. 2004

Carbon Ions: Radiobiology

- Difference in terms of molecular radiobiology

  - ✓ Clustered DNA lesions trigger different DNA damage repair signals strongly related to the immune response
    - Upregulation of PD-L1
    - Leading to cell death through different pathways (apoptosis, necrosis, mitotic catastrophe or senescence) → release of small molecules such as ATP, calreticulin, and HMGB1 that can trigger the immune response

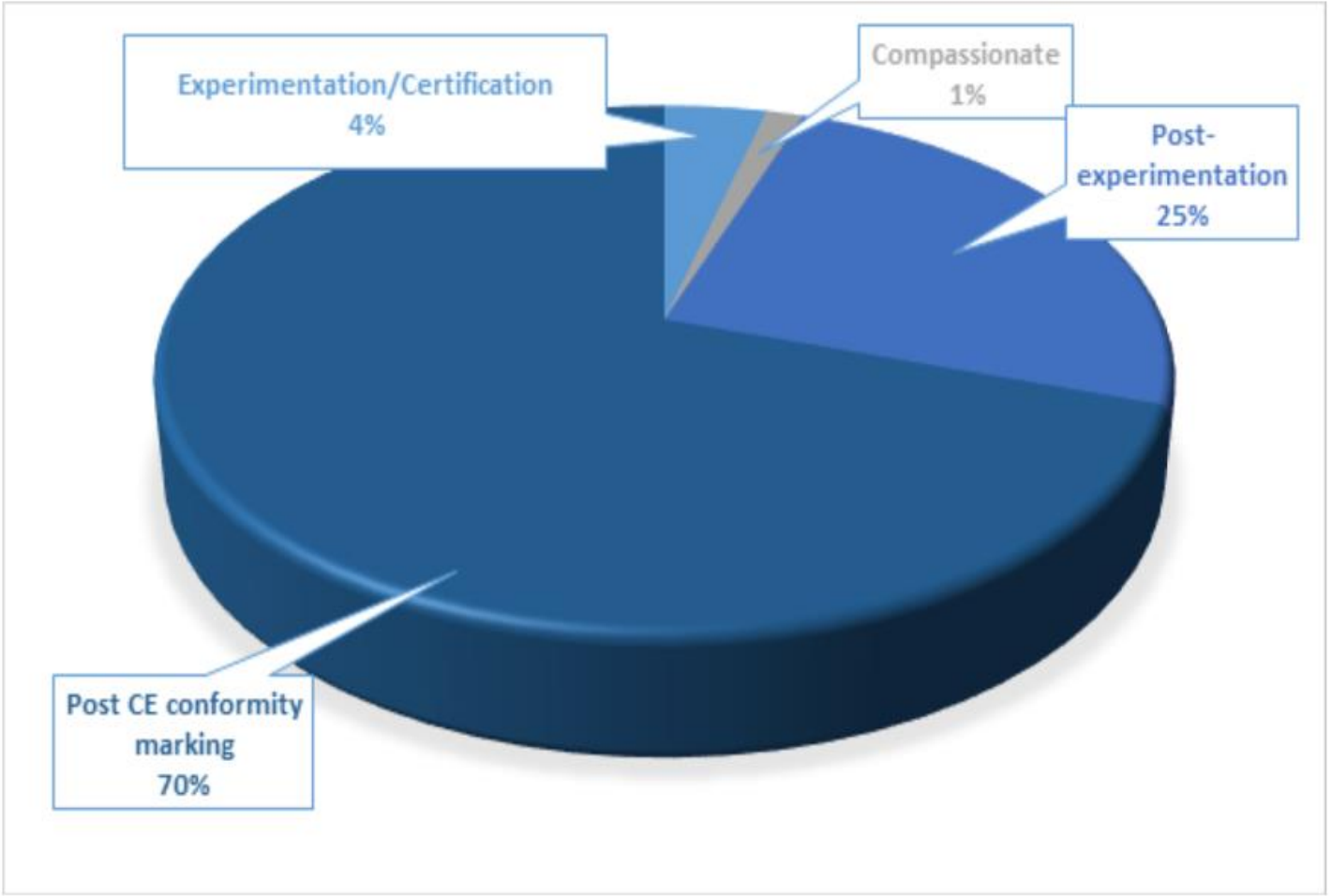




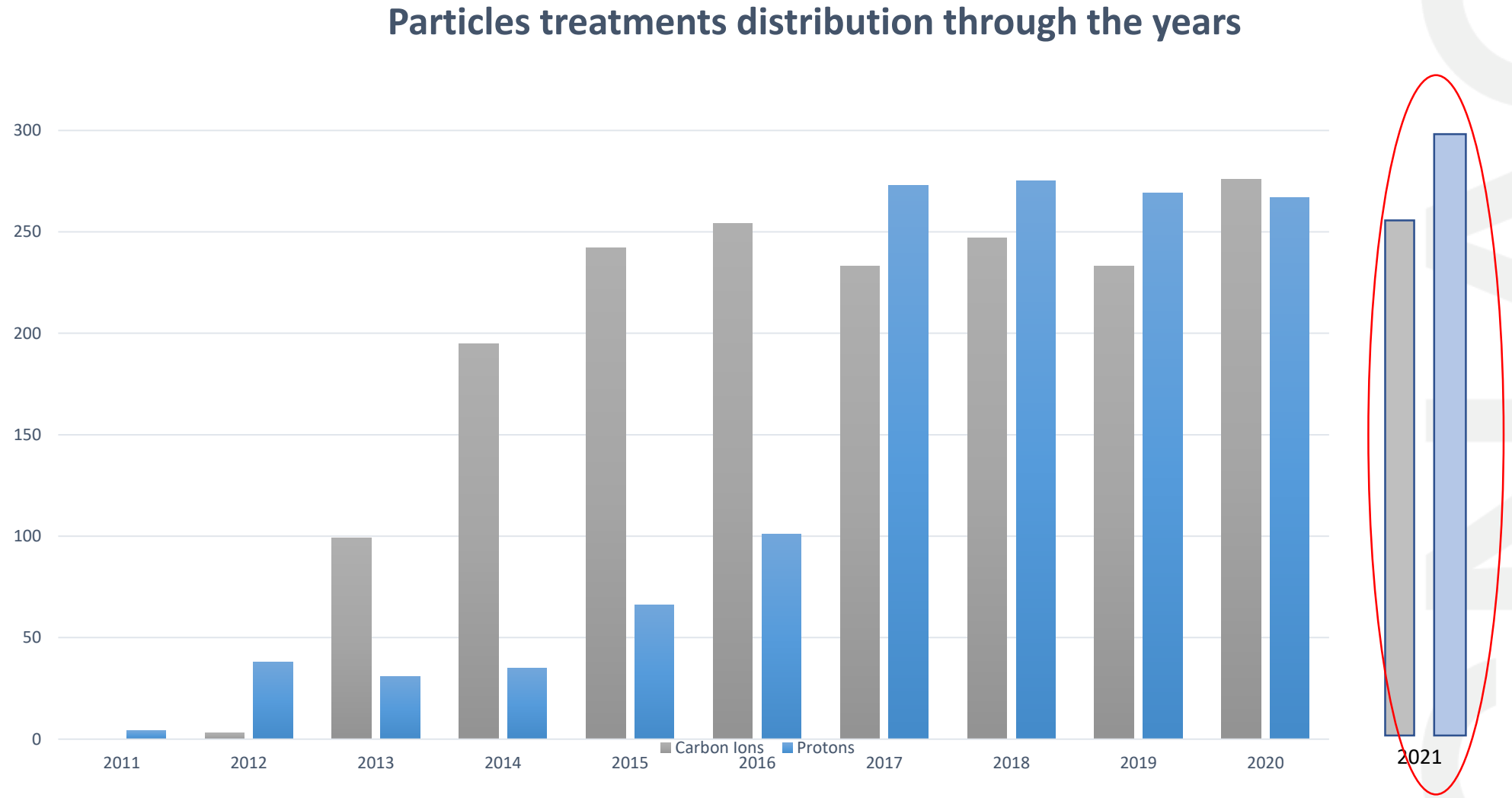
Durante M et al Int J Radiat Oncol Biol Phys. 2020
Sato et al. Nat Commun. 2017

Clinical activity in CNAO: a handful of numbers

Particella	N.
Protoni	1673
Ioni Carbonio	1991
Ioni C./Protoni	26
Totale	3690



Clinical activity in CNAO: a handful of numbers



Since 2011 , 3690 pts treated

Network

CNAO e RAdioterapie Lombarde

CNAORAL – NET

*Il progetto, che prende il nome di "CNAORAL-NET", è promosso da **CNAO**, Centro Nazionale di Adroterapia Oncologica in collaborazione con **AIRO Lombardia** (Associazione Italiana Radioterapia e Oncologia clinica) e **CODRAL** (Collegio dei Direttori delle Radioterapie Lombarde)*

Pavia, 10 giugno 2021 – Una piattaforma online dedicata ai radioterapisti che operano negli ospedali della Lombardia che consente di condividere informazioni sui casi clinici e di potersi confrontare, attraverso un sistema di video-consulto, con i medici esperti in adroterapia, forma avanzata di radioterapia indicata per i tumori non operabili o resistenti ai raggi X: è stata creata dal **CNAO**, Centro Nazionale di Adroterapia Oncologica in collaborazione con **AIRO Lombardia** (Associazione Italiana Radioterapia e Oncologia clinica) e **CODRAL** (Collegio dei Direttori delle Radioterapie Lombarde).

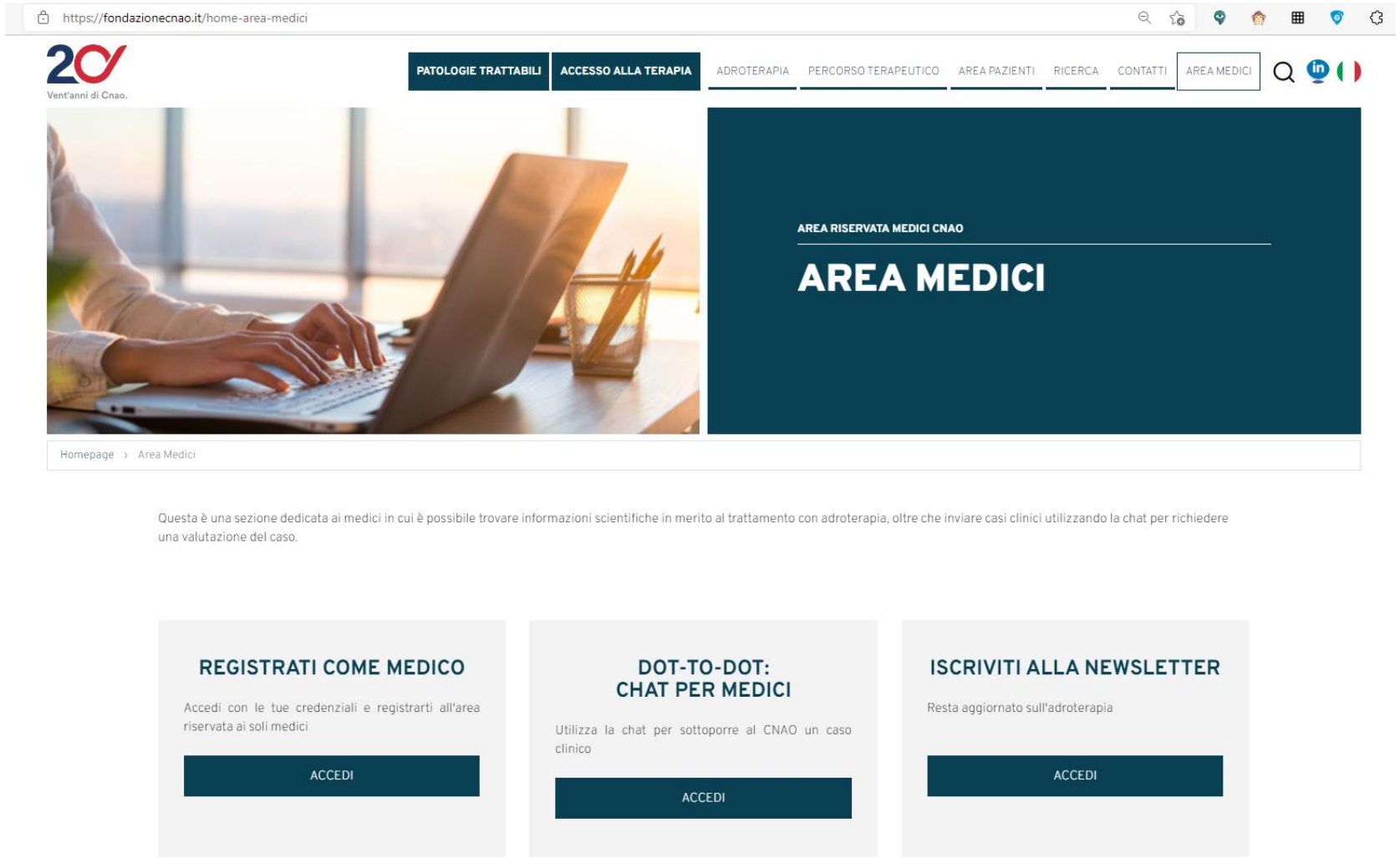
La piattaforma, che prende il nome di "Network CNAO e RAdioterapie Lombarde – CNAORAL-NET", ha l'obiettivo di agevolare il confronto tra i radioterapisti e di **favorire l'accesso dei pazienti oncologici alle terapie più avanzate** e più indicate.

Attraverso la piattaforma telematica CNAORAL-NET, che è già attiva ed è disponibile su https://fondazionecnao.it/home-area-medici, i radioterapisti oncologi che operano in Lombardia, potranno valutare, per esempio, insieme ai radioterapisti oncologi di CNAO quando è opportuno inserire nei percorsi di cura l'adroterapia, tecnica radioterapica disponibile in 5 Paesi al mondo (Italia, Germania, Austria, Cina, Giappone) e coperta dal **Servizio Sanitario Nazionale** che prevede l'utilizzo di protoni e ioni carbonio, particelle pesanti in grado di colpire con forza radiobiologica e precisione i tumori difficili da trattare. Ogni anno sono oltre **174.000 i pazienti oncologici trattati in Italia con radioterapia**. Di questi, 32.000 sono trattati nei 35 centri radioterapici presenti in Lombardia, dove operano 340 radioterapisti oncologi.

Ester Orlandi, direttore del Dipartimento clinico del CNAO, osserva: *"Il confronto costante tra oncologi radioterapisti è essenziale per individuare per ogni paziente il percorso di cura più indicato che tenga conto delle evidenze scientifiche e delle possibilità tecnologiche della radioterapia. L'obiettivo finale è una radioterapia personalizzata e di precisione".*

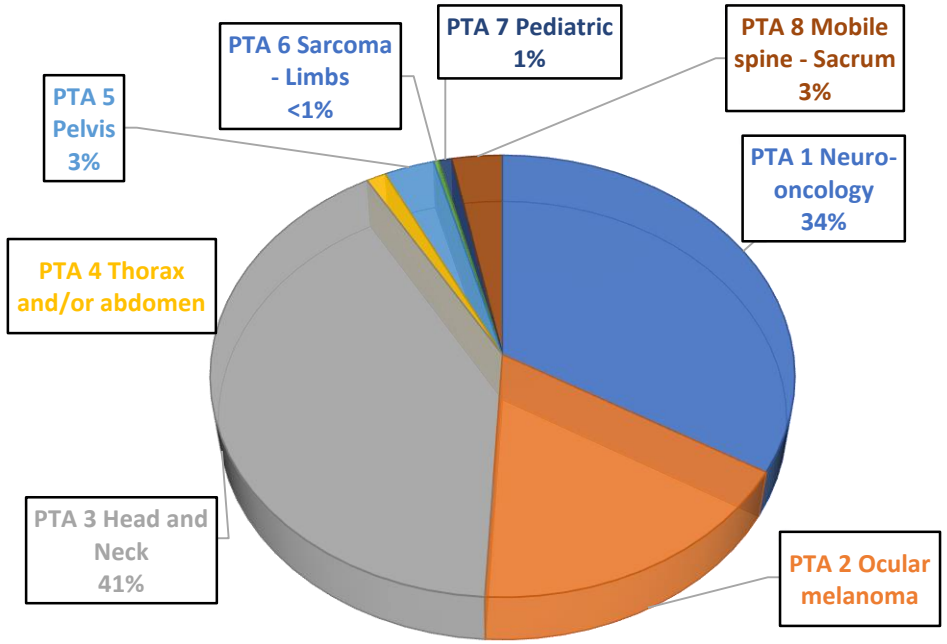
Sandro Tonoli, presidente di AIRO Lombardia: *"Il progetto CNAORAL-NET permette la presentazione da parte dell'oncologo radioterapista di casi, individuati dai gruppi multidisciplinari operanti nei vari centri lombardi e candidati a radioterapia, che potrebbero avere un beneficio clinico dall'utilizzo della adroterapia per le caratteristiche cliniche (sede, radiosensibilità, istologia, rapporto con organi critici). Questa possibilità offre l'appropriato accesso a un ulteriore strumento terapeutico, che si affianca a quelli già disponibili e utilizzati quotidianamente nei centri radioterapici, nel trattamento dei tumori del distretto capo-collo".*

Mauro Filippo Palazzi, presidente del CODRAL: *"Questo progetto consentirà fra l'altro di semplificare ed ottimizzare il percorso dei tanti pazienti potenzialmente candidati ad un trattamento radioterapico complesso: lunghe ricerche e viaggi anche impegnativi di pazienti e familiari potranno essere sostituiti da un confronto diretto fra gli specialisti curanti locali e gli specialisti di CNAO, per una migliore gestione complessiva delle persone ammalate e un migliore utilizzo di questa preziosa risorsa terapeutica".*

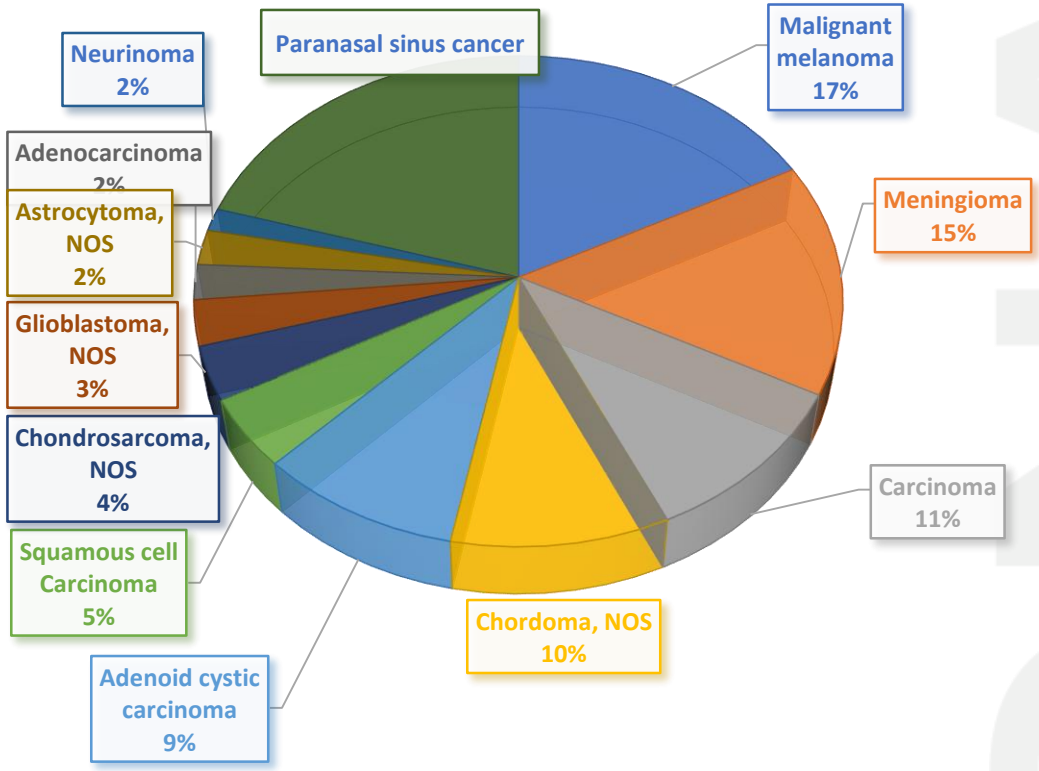

https://fondazionecnao.it/home-area-medici
Vent'anni di Cnao.
PATOLOGIE TRATTABILI
ACCESSO ALLA TERAPIA
ADROTERAPIA
PERCORSO TERAPEUTICO
AREA PAZIENTI
RICERCA
CONTATTI
AREA MEDICI
AREA RISERVATA MEDICI CNAO
AREA MEDICI
Homepage › Area Medici
Questa è una sezione dedicata ai medici in cui è possibile trovare informazioni scientifiche in merito al trattamento con adroterapia, oltre che inviare casi clinici utilizzando la chat per richiedere una valutazione del caso.
REGISTRATI COME MEDICO
Accedi con le tue credenziali e registrarti all'area riservata ai soli medici
ACCEDI
DOT-TO-DOT: CHAT PER MEDICI
Utilizza la chat per sottoporre al CNAO un caso clinico
ACCEDI
ISCRIVITI ALLA NEWSLETTER
Resta aggiornato sull'adroterapia
ACCEDI

PBT treatments

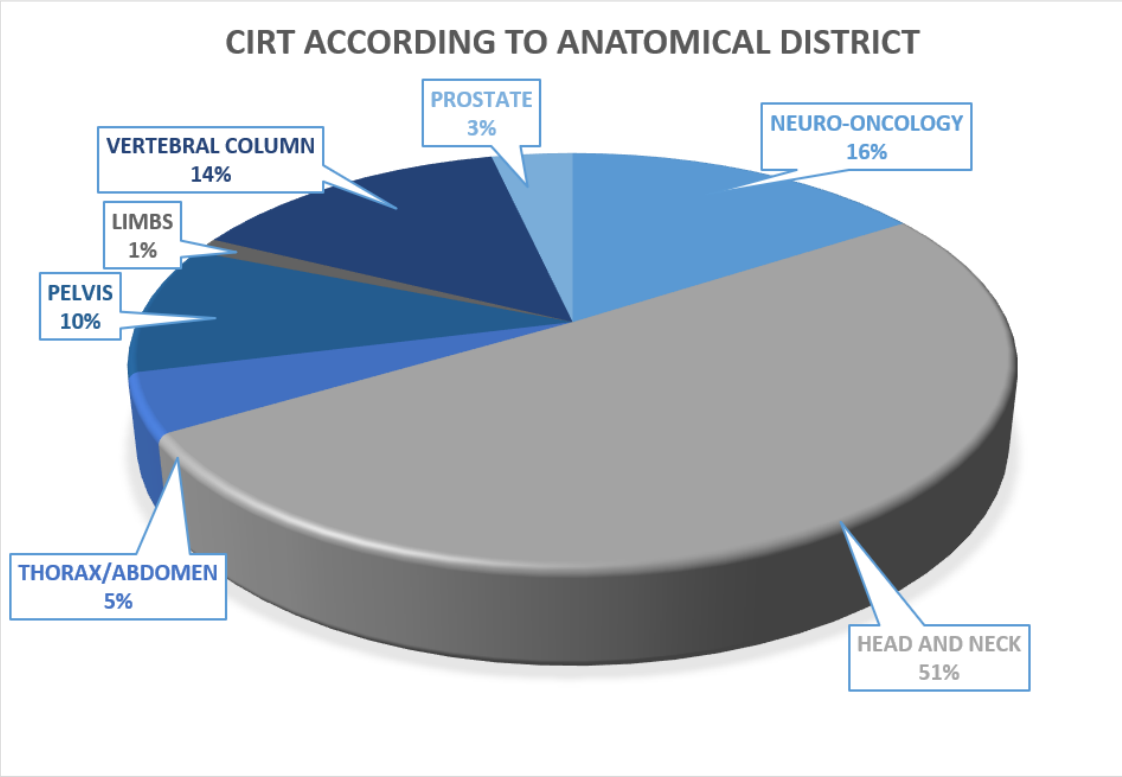
PBT according to anatomical district

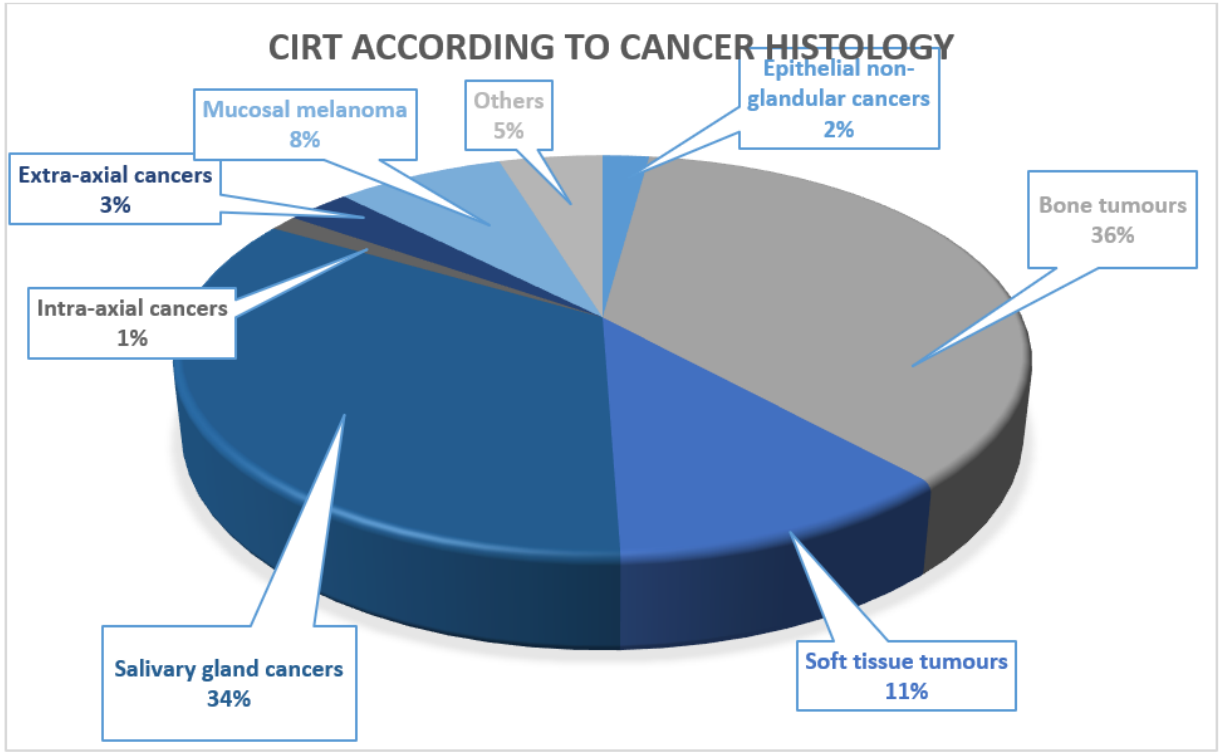


PBT according to tumor histology

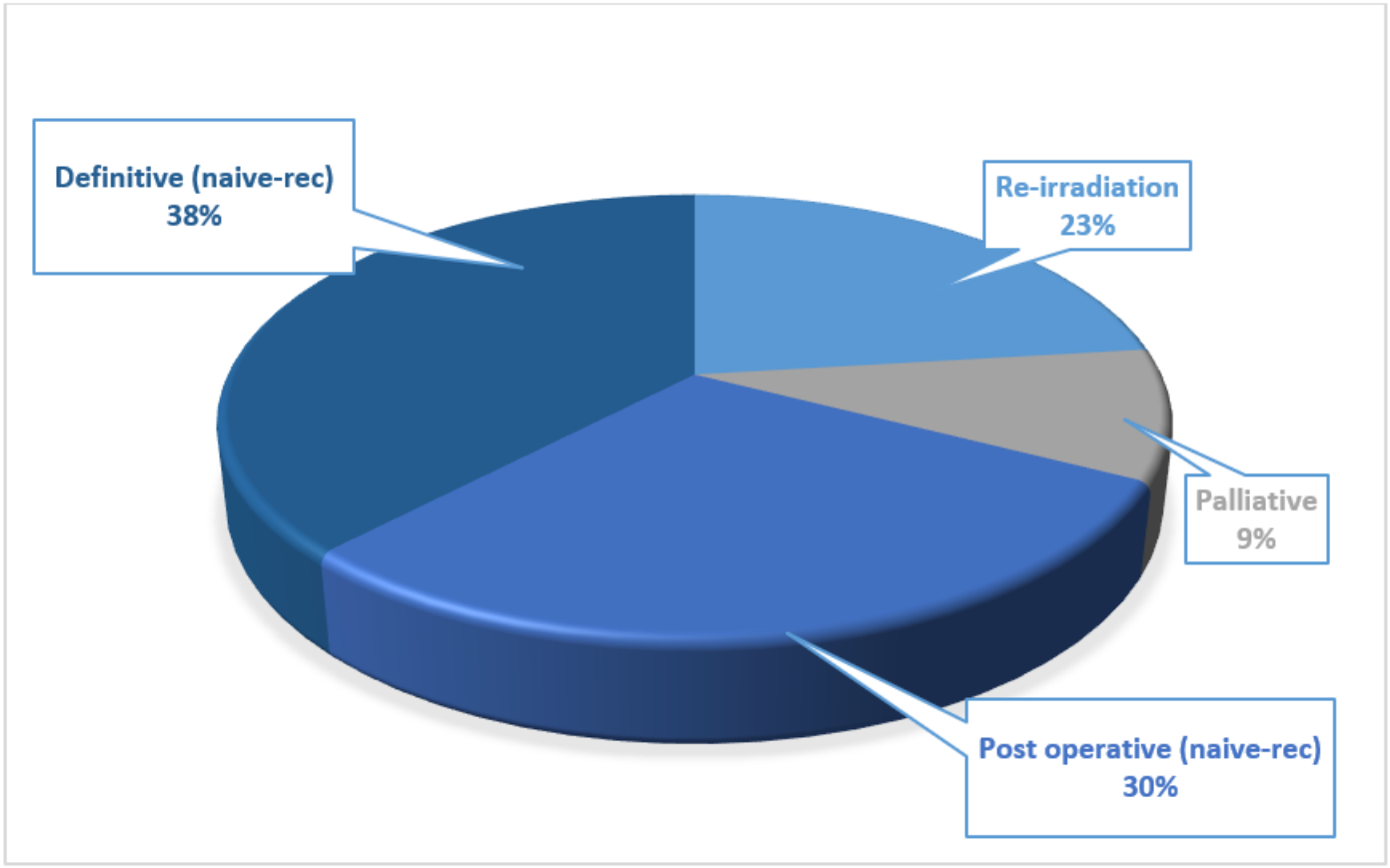


CIRT treatments





Setting of CIRT/PT treatments



27% concurrent CT(with PT)

Adenoid cystic (ACC) carcinoma of the head and neck treatment @ CNAO

Patient Characteristics

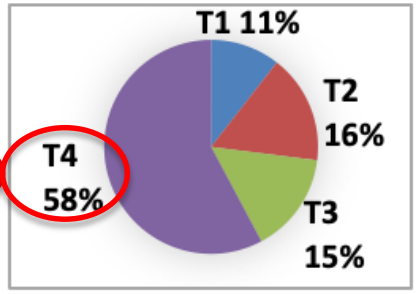
- January 2013 and January 2020
- 237 patients F: 128; M: 109
- Median age: 54 years (range: 20 – 88)
- Median KPS: 100 (range: 70-100)

Tumour site

Minor salivary gland	n=146 pts (62%)
➢ Paranasal Sinus, Nasal Cavity, Skull Base	74(51%)
➢ Oro -NPC	31(21%)
➢ Oral cavity	38(26%)
➢ Ear canal	3(2%)
Major salivary gland	n= 91 pts (38%)
➢ Parotid	55(60%)
➢ Submandibolar	35(38%)
➢ Sublingual	1(1%)

Stage

T1	25
T2	39
T3	36
T4	137
N0	213
N1	15
N2	8
N3	1
M1	17



GTV (mL)

mean:	51,7
median:	40
min:	0,11
max:	250,86

Disease status

- Primary diagnosis: 212 pts (89%)
- Local recurrence: 25 pts (11%)

Unpublished data

Treatment Characteristics

- Settings:
  - Definitive RT: 72/237 pts (30%)
  - Postoperative RT: 165/237 pts (70%)

Histological report: → ***Residual disease on post-op MRI:***

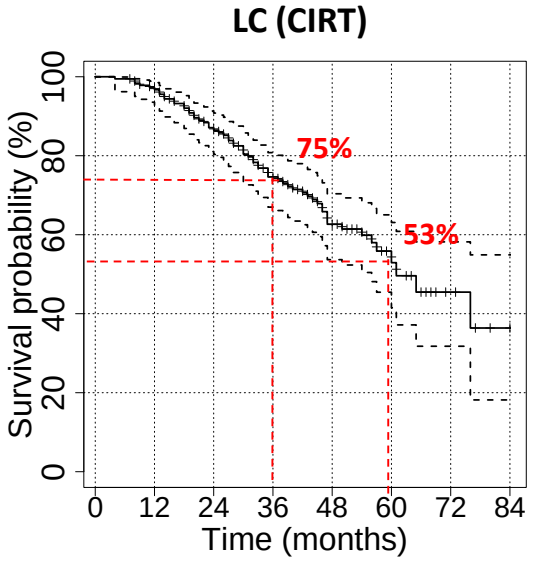
- R0: 10 pts (6%) → 0/10 pts
- R1: 118 pts (72%) → 61/118 pts
- R2: 37 pts (22%) → 37/37 pts

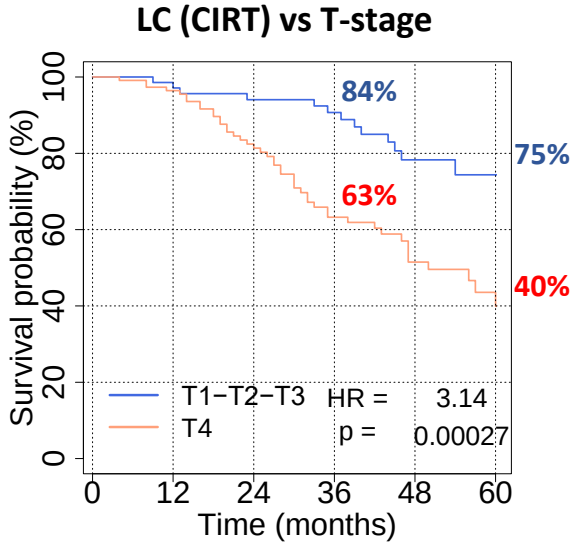
→ 42% R2

- Beam quality and fractionations:
  - CIRT 68.8 Gy[RBE] in 16 fr, 4.3 Gy[RBE]/fr: 155 pts (65%)
  - CIRT 65.6 Gy[RBE] in 16 fr, 4.1 Gy[RBE]/fr: 29 pts (12%)
  - PT 59.92-72 Gy[RBE] in 28-35 fr: 53 pts (22%)

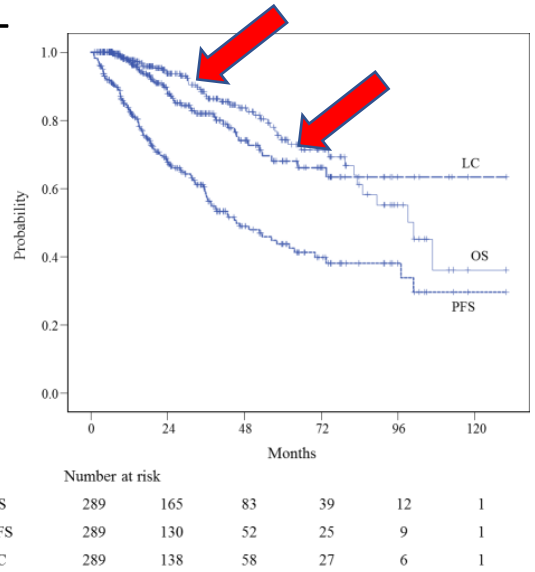
Unpublished data

Outcome





- **CIRT (n=184)**
- Median FUP: 45 months (range 7-90)



Number at risk

OS	289	165	83	39	12	1
PFS	289	130	52	25	9	1
LC	289	138	58	27	6	1

289 ACC pts (CIRT)
Sulaiman et al, 2018

- prognostic factors (MVA):

GTV, T stage, tumor site, number of Surgeries, marginal status

Unpublished data

Toxicity of CIRT for ACC of the head and neck @ CNAO

Toxicity

CIRT (n=184)	ACUTE	LATE
G0	1 (1%)	21 (11%)
G1	48 (26%)	43 (23%)
G2	94 (51%)	88 (48%)
G3	41 (22%)	28 (15%)
G4	/	3 (2%)
G5	/	1 (1%)

- G3 acute toxicity:
  - Mucositis: 37 patients
  - Erytema: 4 patients
  - Hearing impairment: 2 patients
  - Bleeding, protective tracheotomy: 1 patient
- G3 late toxicity:
  - RN (bone/sof tissue): 13 patients
  - Visual impairment: 5 patients
  - Hearing impairment: 6 patients
  - Neurophaty: 4 patients
  - Brain RN: 1 patient
  - Mucositis: 1 patient
- G4 late toxicity:
  - Epidural abscess: 1 patient
  - RN soft tissue, vascular toxicity:1 patient
  - RN soft tissue: 1 patient
- G5 late toxicity:
  - RN soft tissue, vascular toxicity: 1 patient

[289 ACC pts (CIRT)]

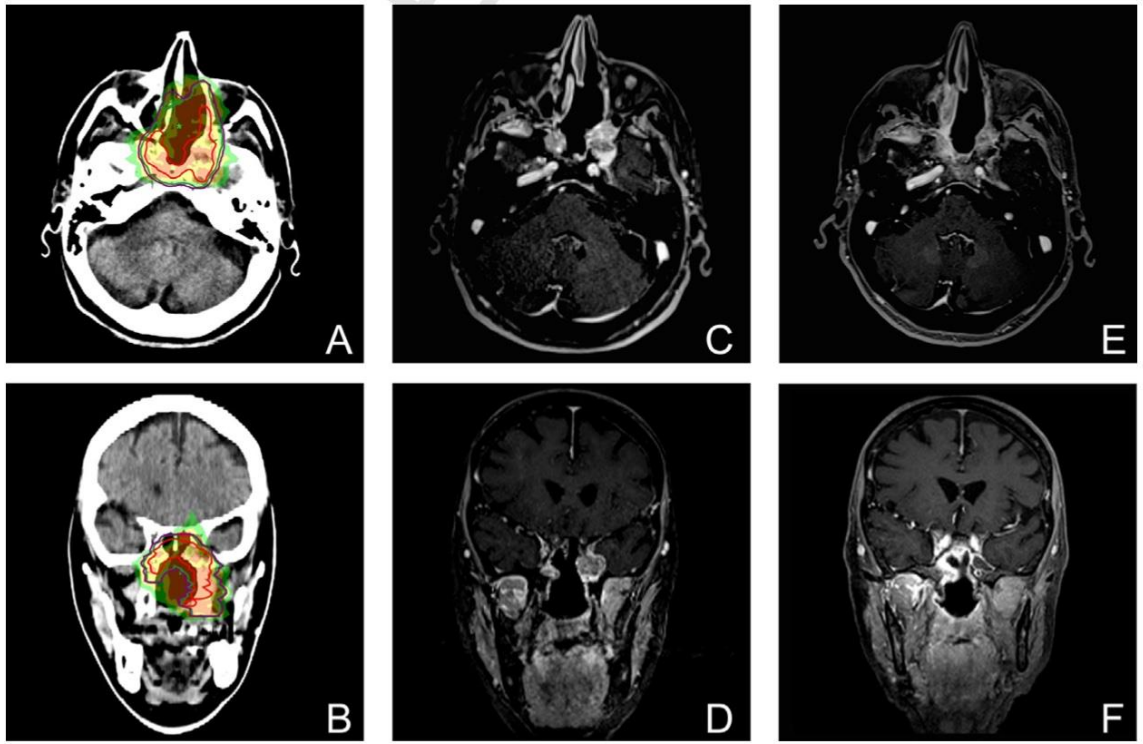
Table 5 Toxicity events

Type of toxicity	Grade 3	Grade 4	Grade 5
Acute events			
Mucositis	84	0	0
Dermatitis	11	0	0
Late events			
Osteonecrosis of the jaw bone	16	0	0
Visual impairment	6	9	0
Optic neuropathy	0	1	0
Cataract	5	0	0
Glaucoma	1	2	0
Retinopathy	0	5	0
Retinal vein occlusion	0	1	0
Brain injury	5	1	0
Hemorrhage	2	2	2
Mucositis	2	1	0
Others	1	1	0

Sulaiman et al . , Int J Radiation Oncol Biol Phys 2018

CIRT reirradiation for recurrent salivary gland tumors @ CNAO

Patients and treatment characteristics	N (%)
Sex	
Male	27 (53)
Female	24 (47)
Prior surgery	
None	1 (2)
One	10 (19.6)
Two	23 (45.1)
Three	10 (19.6)
Four	7 (11.7)
Histology	
Adenoid cystic carcinoma	38 (74.5)
Mucoepidermoid carcinoma	6 (11.8)
Myoepithelial carcinoma	3 (5.8)
Carcinoma ex pleomorphic adenoma	2 (3.9)
Mucinous adenocarcinoma	1 (2)
Ductal adenocarcinoma	1 (2)
Site of retreatment	
Parotid	17 (33.3)
Nasal cavity	5 (9.8)
Nasopharynx	3 (5.9)
Mandible	2 (3.9)
Maxillary sinus	5 (9.8)
Hard palate	3 (5.9)
Ethmoid	3 (5.9)
Para-pharyngeal space	3 (5.9)
Oropharynx	1 (2)
Lacrimal gland	2 (3.9)
Soft palate	1 (2)
Tongue	1 (2)
Retromolar trigone	1 (2)
Pterygopalatine fossa	4 (7.8)
Reirradiation stage	
rcT2	1 (2)
rcT3	5 (9.8)
rcT4a	26 (51)
rcT4b	19 (37.2)
rcN0	46 (90.2)
rcN1	4 (7.8)
rcN2b	1 (2)
M0	45 (88.2)
M1	6 (11.8)
Prior RT courses	
One	46 (90.1)
Two	5 (9.9)
CIRT fractionation scheme	
3.0 Gy [RBE]/fr × 15 fr	1 (2)
3.0 Gy [RBE]/fr × 16 fr	3 (5.8)
3.0 Gy [RBE]/fr × 18 fr	10 (19.6)
3.0 Gy [RBE]/fr × 19 fr	1 (2)
3.0 Gy [RBE]/fr × 20 fr	15 (29.4)
3.0 Gy [RBE]/fr × 22 fr	2 (3.9)
3.75 Gy [RBE]/fr × 16 fr	1 (2)
4.0 Gy [RBE]/fr × 14 fr	1 (2)
4.0 Gy [RBE]/fr × 15 fr	6 (11.7)
4.0 Gy [RBE]/fr × 16 fr	1 (2)
4.3 Gy [RBE]/fr × 16 fr	9 (17.6)
5.0 Gy [RBE]/fr × 12 fr	1 (2)



Vischioni, Radiother Oncol, 2020

CIRT reirradiation for recurrent salivary gland tumors @ CNAO

2y PFS 52%, 3y PFS 43,5%
2y OS 63%, 3y OS 54,5%

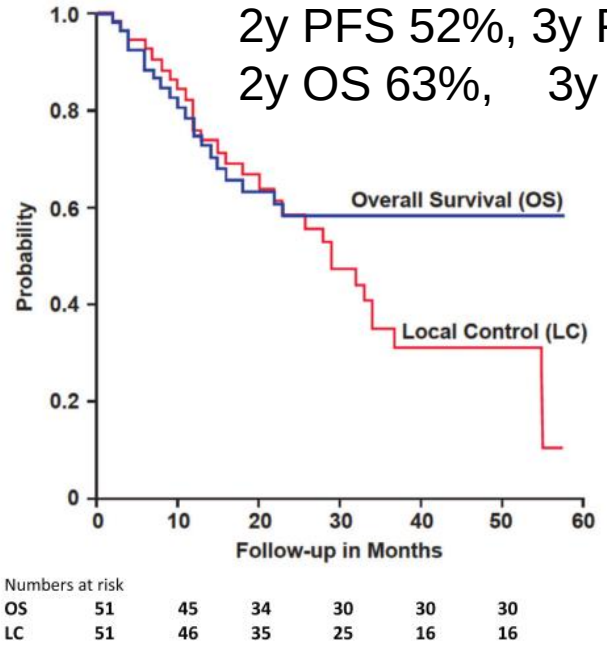


Fig. 2. Local control (LC) and overall survival (OS) following reirradiation with CIRT in a series of inoperable recurrent salivary gland tumors treated at CNAO.

Table 3
Multivariate analyses for prognostic value of major patients and treatment characteristics.

Model covariates		OS	PFS	LC
Gross tumor volume	HR	4.831	5.597	6.683
(<62 cc vs ≥62 cc)	(95% CI)	1.645–14.187	2.027–15.455	2.144–20.834
	P-value	0.004	0.0009	0.001
Nodal disease	HR	0.288	0.445	0.390
(N0 vs N+)	(95% CI)	0.031–2.690	0.110–1.793	0.088–1.741
	P-value	0.27	0.25	0.22
Re-radiation interval	HR	0.836	0.954	0.998
	(95% CI)	0.709–0.987	0.831–1.095	0.863–1.153
	P-value	0.03	0.50	0.98
Sex	HR	4.325	1.808	1.457
	(95% CI)	1.250–14.959	0.799–4.091	0.622–3.412
	P-value	0.02	0.16	0.39
M1 disease before CIRT	HR	0.156	0.740	0.863
	(95% CI)	0.018–1.361	0.245–2.238	0.282–2.640
	P-value	0.09	0.59	0.80
Age	HR	1.387	1.146	1.196
(<60 years vs ≥62 years)	(95% CI)	0.441–4.363	0.499–2.633	0.511–2.799
	P-value	0.58	0.75	0.68
CIRT radiation dose	HR	0.986	0.956	0.943
	(95% CI)	0.909–1.069	0.898–1.017	0.882–1.008
	P-value	0.73	0.16	0.09

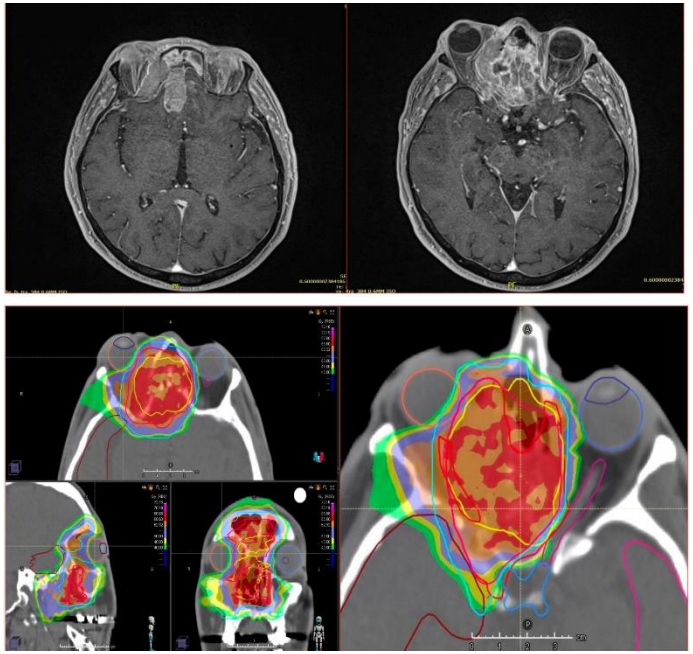
Author	Particle	No patients (Histology)	Median FU	Outcomes	G3+ toxicities
Jensen et al. 2015	Carbon ions	52 (salivary glands)	14 months	1y LC 70%, 2y LC 47% 1y OS 81%, 2y OS 63%	No acute Late **G3 = 5,8%** **G4 = 3,8%** ica blow-out
Hayashi et al. 2019	Carbon ions	48 (miscellaneous)	27,8 months	2y LC 40,5% 2y PFS 29,4% 2y OS 59,6%	Late ≥ G3 in 37.5% 1 pt G5
Gao et al. 2019	Carbon ions	141 (miscellaneous)	14,7 months	1y LPFS 84,9% 1y OS 95,9%	≥ G3 in 7,1% (4 late G5 events)
CNAO	Carbon ions	52 (salivary glands)	23 months	2y PFS 52%, 3y PFS 43,5% 2y OS 63%, 3y OS 54,5%	Acute G3 = 3,9% Late G3 = 17,5% No G4

Vischioni et al, 2020

CIRT for locally advanced head and neck malignant mucosal melanoma @ CNAO

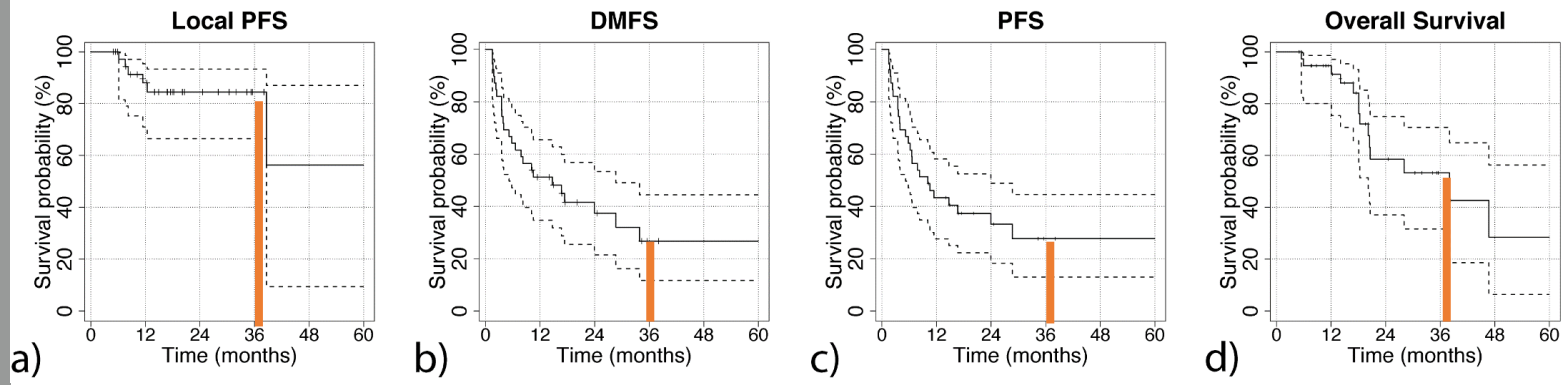
- 40 pts, median age70 years (range 39-87)
- Tumor (T) site: nasal cavity/paranasal sinuses/other in 77.5%/12.5%/10%
- T status: naïve/recurrent in 77,5%/22,5% of pts
- T stage: T3/T4 in 17(42,5%)/23(57,5%) pts
- 28 (70%) pts after surgery, 12 (30%) with exclusive CIRT

- CIRT total dose: 65.6 Gy(RBE) or 68.8 Gy(RBE) (16 fractions, 4 fractions/week)
- 18 pts (44%) received immunotherapy after CIRT
- Median follow-up (FU) time was 18 mo (range 5-81 mo)



Unpublished data

CIRT for locally advanced head and neck malignant mucosal melanoma @ CNAO

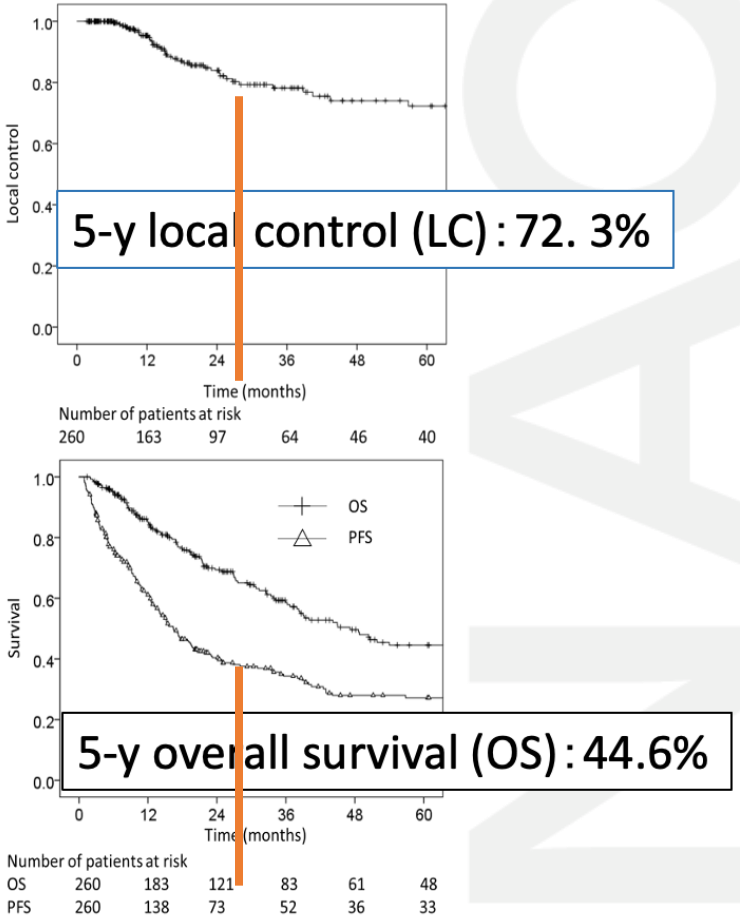


3 ys LPFS 84.5%

3ys DMFS 26.7%

3 ys PFS 27.6%

3 ys OS 53.3%



Koto M, et al. Int J Radiat Oncol Biol Phys. (2017)

	T3	T4	Immuno alone
Imm. no	10 (100%)	11 (19.2%)	21 (57.1%)
Imm. si	7 (71.4%)	**11 (72.7%)**	18 (72.2%)
T stage alone	17 (88.2%)	22 (46.5%)	39 (64.1%)

NO immunotherapy after CIRT: T3 and T4 stages maintain significant differences in 3y-OS (100% vs 19.2%)
Immunotherapy after CIRT: T3 and T4 stages reached similar OS rates (71.4% vs 72.7%).

Unpublished data

MUTATIONAL STATUS

Mutational status:
BRAF/NRAS/c-KIT wild type: 23 (57,5%)
BRAF mutated: 1 (2,5%)
NRAS mutated: 3 (7,5%)
c-KIT mutated: 1 (2,5%)
Unknown: 12 (30%)

Subanalysis on 28 pts carrying the mutational status information

Mut.	T status Recurrent	Complete Resp @ 1FU	Local PD	Dist PD	OS	T4	Immuno (yes)	4.3 Gy	GTV vol	Average FU time
No	17.4%	30.4%	91.3%	44.8%	74%	60.9%	56.5%	56.5%	35 cc	22.6 mos
Yes	60%	0%	60%	20%	80%	60%	40%	60%	44.5 cc	13.6 mos

Patients with BRAF/NRAS/cKIT wild-type status showed a trend towards a better LPFS versus patients with BRAF/NRAS/cKIT mutations (HR=4.0 and p=0.13).

Unpublished data

Skull base chordoma @ CNAO

- November 2011- December 2018
- CIRT: 65 pts (unfavourable)
- PT:70 pts
- CIRT dose: 70.4 Gy[RBE]/ 4.4Gy[RBE] FS
- PT dose 74 Gy[RBE]/ 2 Gy[RBE] FS

Table 1 Patients' characteristics

	Total *n* (%) 135 Patients	CIRT Cohort *n* (%) 65 Patients	PT Cohort *n* (%) 70 Patients	*P*-value
KPS				0.8493
≤80	22 (16)	11 (17)	11 (16)	
90–100	113 (84)	54 (83)	59 (84)	
Sex				0.374
Male	82 (61)	42 (65)	40 (57)	
Female	53 (39)	23 (35)	30 (43)	
Age, y, median (range)	57 (13–81)	58 (13–81)	53 (17–81)	0.1388
Treatment				0.019
Primary	107 (79)	46 (71)	61 (87)	
Recurrent	28 (21)	19 (29)	9 (13)	
Aim of the treatment				0.146
Postoperative	130 (96)	61 (94)	69 (99)	
Exclusive	5 (4)	4 (6)	1 (1)	
Resection status				<0.0001
Complete	19 (14)	0 (0)	19 (27)	
Incomplete	115 (85)	64 (98)	51 (73)	
Only biopsy	1 (1)	1 (2)	0 (0)	
Surgical technique				0.130
Endoscopic endonasal	112 (83)	55 (84)	57 (82)	
Other approach (transcranial)	13 (10)	5 (8)	8 (11)	
Not known	10 (7)	5 (8)	5 (7)	
Surgery (*n*)				0.285
1	77 (57)	34 (52)	43 (61)	
>1	58 (43)	31 (48)	27 (39)	
Brainstem abutment and/or compression				0.671
Y	31 (23)	14 (22)	17 (25)	
N	103 (77)	51 (78)	52 (75)	
Not evaluated *	1	0 (0)	1	
Optic pathway abutment and/or compression				0.579
Y	11 (8)	58 (89)	64 (94)	
N	123 (92)	7 (11)	4 (6)	
Not evaluated *	1	0 (0)	1	
Visual defect				0.016
Y	24 (18)	17 (26)	7 (10)	
N	110 (81)	48 (74)	62 (89)	
Not evaluated	1 (1)	0 (0)	1 (1)	
Diplopia				0.5945
Y	55 (41)	28 (43)	27 (33)	
N	80 (59)	37 (57)	47 (67)	
Hearing impairment				0.5221
Y	62 (46)	28 (43)	34 (49)	
N	73 (54)	37 (57)	36 (51)	
Pituitary dysfunction				0.303
N	112 (82.9)	51 (78.4)	61 (87.1)	
Y (1 hormonal deficit)	10 (7.4)	7 (10.8)	3 (4.3)	
Y (>1 hormonal deficits)	13 (9.6)	7 (10.8)	6 (8.6)	
Cranial nerve deficit				0.014
Y	58 (43)	35 (54)	23 (33)	
N	77 (57)	30 (46)	47 (67)	
GTV, cm^3, median (range)	7 (0–99.3)	13 (0.4–87.4)	3.5 (0–99.3)	0.0001
Dose, median (range)	–	70.4 (70.4-70.4)	74 (72–74)	–

Abbreviations: *Only CT imaging, CIRT: carbon ion radiotherapy, PT: proton therapy, Y: yes, N: no, GTV: gross target volume, KPS: Karnofsky performance status.

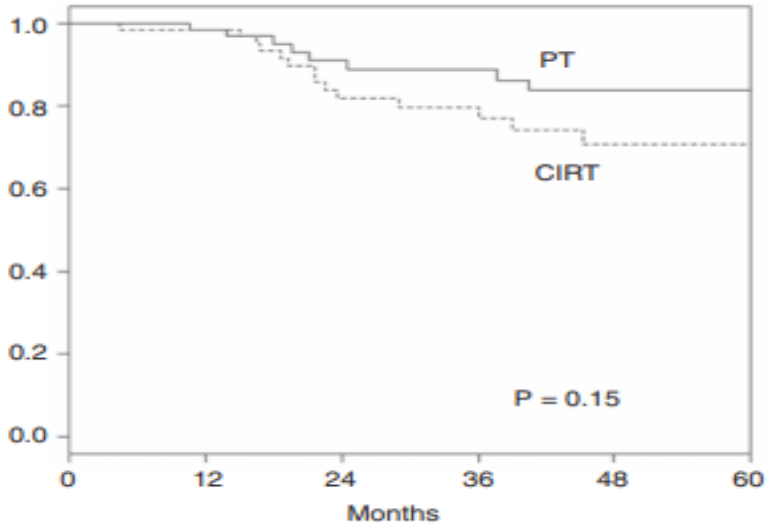
Iannalfi A, Neuro-Oncology 2020

Outcome data on chordoma treatment @ CNAO

LOCAL CONTROL

Protons : 3 ys 89% ; 5 yrs 84 %

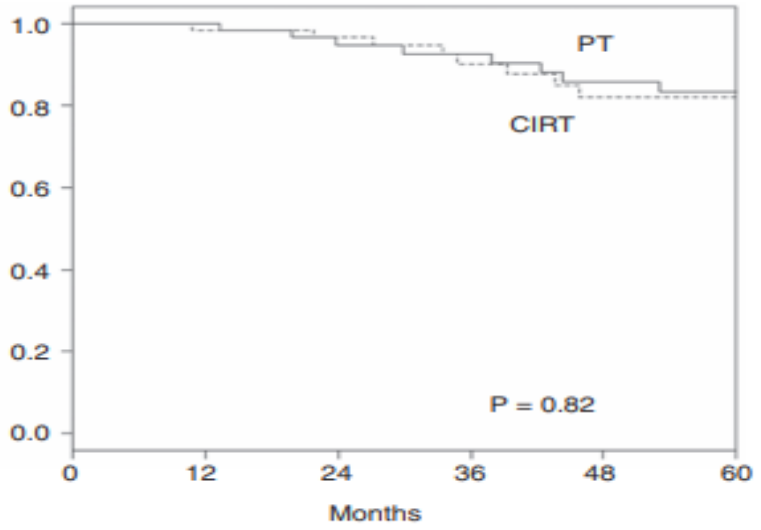
Carbon ions: 3 ys 77 % ; 5 yrs 71 %



OVERALL SURVIVAL

Protons : 3 ys 89% ; 5 yrs 84 %

Carbon ions: 3 ys 90 % ; 5 yrs 82 %



Toxicity

Table 3 Late toxicity profile for the entire cohort of patients (PT + CIRT)

		Patients	%
High grade late toxicity	No	119	88
	Yes	16	12
	G3	13	10
	G4	3	2
CTCAE high grade late toxicity	No	119	88
	Ear	8	6
	G3	7	1
	G4	1	3
	Endocrine	1	2
	G3	1	
	G4	0	
	Eye	4	
	G3	2	
	G4	2	
	Nervous system disorders	3	
	G3	3	
	G4	0	

Abbreviations: PT: proton therapy, CIRT: carbon ion radiotherapy, CTCAE: Common Terminology Criteria for Adverse Events, G: grading.

Iannalfi et al, 2020

Prognostic factors for LC : gross tumor volume (GTV),

optic pathways, and/or brainstem compression and dose coverage

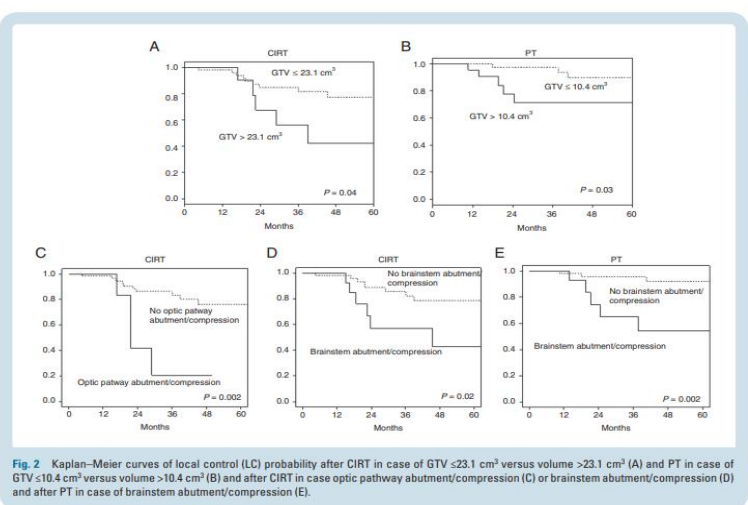


Fig. 2 Kaplan–Meier curves of local control (LC) probability after CIRT in case of GTV ≤23.1 cm³ versus volume >23.1 cm³ (A) and PT in case of GTV ≤10.4 cm³ versus volume >10.4 cm³ (B) and after CIRT in case optic pathway abutment/compression (C) or brainstem abutment/compression (D) and after PT in case of brainstem abutment/compression (E).

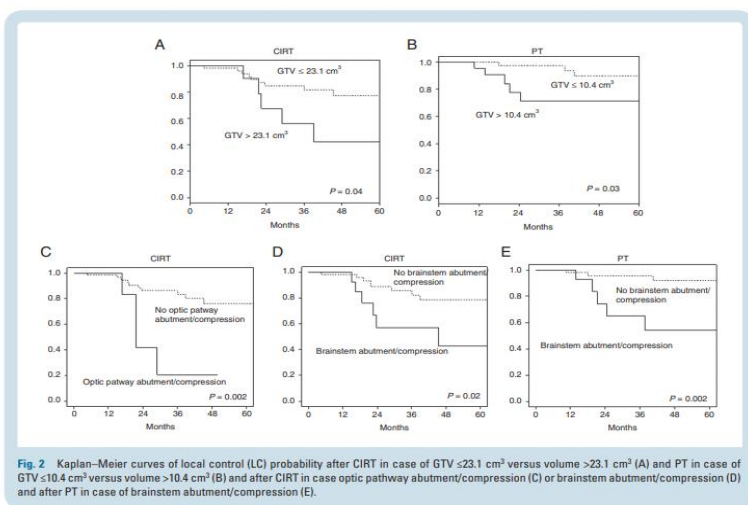
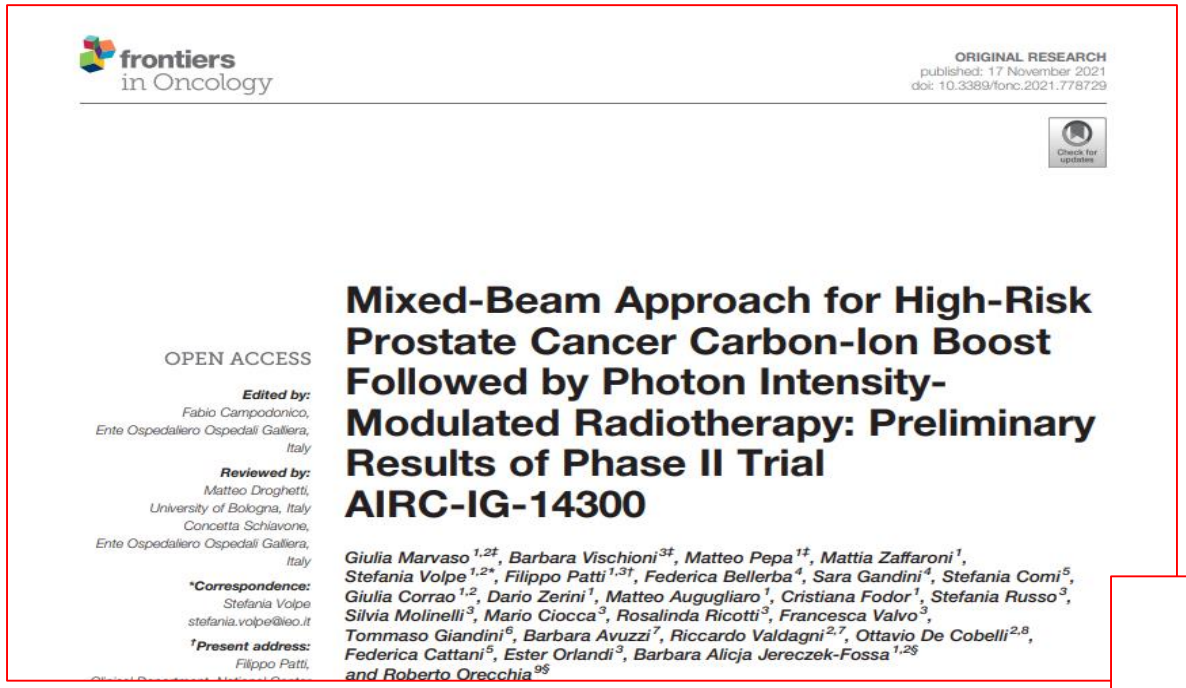


Fig. 2 Kaplan–Meier curves of local control (LC) probability after CIRT in case of GTV ≤23.1 cm³ versus volume >23.1 cm³ (A) and PT in case of GTV ≤10.4 cm³ versus volume >10.4 cm³ (B) and after CIRT in case optic pathway abutment/compression (C) or brainstem abutment/compression (D) and after PT in case of brainstem abutment/compression (E).

Table 4 Published series of skull base chordomas treated with particle radiotherapy

Study (Istitution)	Radiation Type	RT Dose (GyRBE)	Patients (number)	Follow-up Months (median)	GTV	LC (%)	OS (%)
Hug, 1999; LLMUC[4]	Ph + P	TD 71.9 median (66.6–79.2, range) Dfp: 1.8	33	32.2	9%: 0 to ≤15 mL 12%: >15 to ≤25 mL 79%: >25 mL	3-y: 67 5-y: 59	3-y: 87 5-y: 79
Munzenrider, 1999; HCL-MGH[10]	Ph + P	TD: 66–83 range Dpf: 1.8–1.92	169	41	NR	5-y: 73 10-y: 54	5-y: 80 10-y: 54
Noel, 2005; CPO[30]	Ph + P	TD: 67 median (60–71, range) Dpf: 1,8-2	100 (1993–2002)	31	23 cm³ (median)	4-y: 53	4-y: 90
Mizoe, 2009 (NIRS)[31]	C	TD: 48–60.8 range Dpf: 3–3.8	33	53 (mean)	NR	5-y: 85 10-y: 64	5-y: 88 10-y: 67
Uhl, 2014 (GSI)[9]	C	TD: 60 median (54–70, range) Dpf: 3	155	38	NR	3-y: 82 5-y: 72 10-y: 54	3-y: 95 5-y: 85 10-y: 75
Weber, 2016 (PSI)[11]	P	TD: 72.5 mean Dpf: 1,8-2	151	50 (mean)	35.4 cm³ (mean)	5-y: 7,8 7-y: 70.9	7-y: 72.9
Fung, 2018 (CPO)[12]	Ph + P	TD 68.4–73.8 range Dpf: 1.8	106 (2006–2012)	61	25 cm³ (mean)	4-y: 78.3 5-y: 75.1	4-y: 90.2 5-y: 88.3
Present study, CNAO	P or C	P:TD: 74 median (72–74, range) Dpf: 1,8-2 C: TD: 70,4 Dpf: 4,4	135 70 P 65 C	44	7 cm³ (median) P: 3.5 cm³ (median) C: 12.9 cm³ (median)	P: 3-y: 89 5-y: 84 C: 3-y: 77 5-y: 71	P: 3-y: 93 5-y: 83 C: 3-y: 90 5-y: 82

Iannalfi et al, 2020



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Mixed-Beam Approach for High-Risk Prostate Cancer Carbon-Ion Boost Followed by Photon Intensity-Modulated Radiotherapy: Preliminary Results of Phase II Trial AIRC-IG-14300

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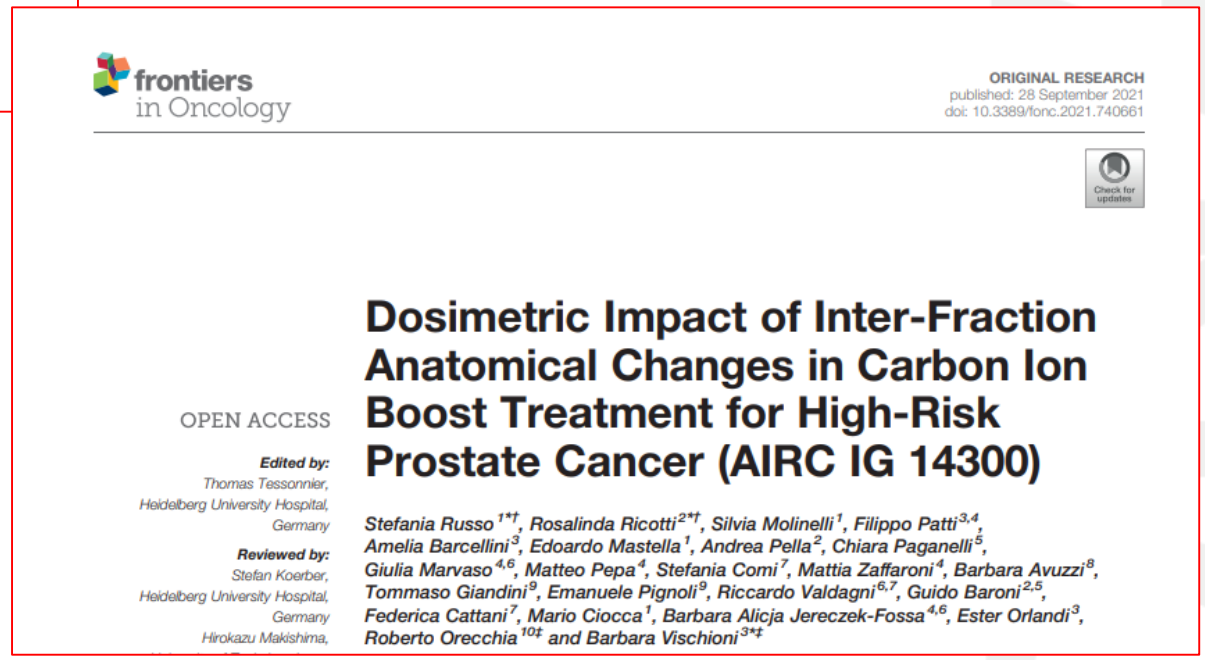

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Dosimetric Impact of Inter-Fraction Anatomical Changes in Carbon Ion Boost Treatment for High-Risk Prostate Cancer (AIRC IG 14300)

Stefania Russo[1*†], Rosalinda Ricotti[2*†], Silvia Molinelli[1], Filippo Patti[3,4], Amelia Barcellini[3], Edoardo Mastella[1], Andrea Pella[2], Chiara Paganelli[5], Giulia Marvaso[4,6], Matteo Pepa[4], Stefania Comi[7], Mattia Zaffaroni[4], Barbara Avuzzi[8], Tommaso Giandini[9], Emanuele Pignoli[9], Riccardo Valdagni[6,7], Guido Baroni[2,5], Federica Cattani[7], Mario Ciocca[1], Barbara Alicja Jereczek-Fossa[4,6], Ester Orlandi[3], Roberto Orecchia[10‡] and Barbara Vischioni[3*‡]

NTCP model based strategy for NPC

AIM

To investigate a method to estimate the proportion of NPC patients which may benefit from PT

MATERIALS AND METHODS

- Retrospective comparative bi-institutional study on a cohort of 50 non metastatic NPC patients treated between 2016 and 2019 with curative VMAT with or without chemotherapy at Fondazione IRCCS Istituto Nazionale dei Tumori.
- IMPT plan was optimized for each patient

In silico planning comparison (with rotational gantry)

We applied the NTCP model-based selection

To identify a comprehensive toxicity score (CTS)

Submitted

MATERIALS AND METHODS

- 7 of 16 NTCP models identified based on clinical relevance
- ΔNTCPx-p between VMAT and IMPT
- Stratified for tumor staging
- Thresholds estabilished based on the National Indication Protocol for Particle Therapy (NIPP):

  10% for G ≥ 2

  5% for G≥ 3

  ^15 % for xerostomia and mucositis (G3) for the relatively lower detrimental impact on the QOL

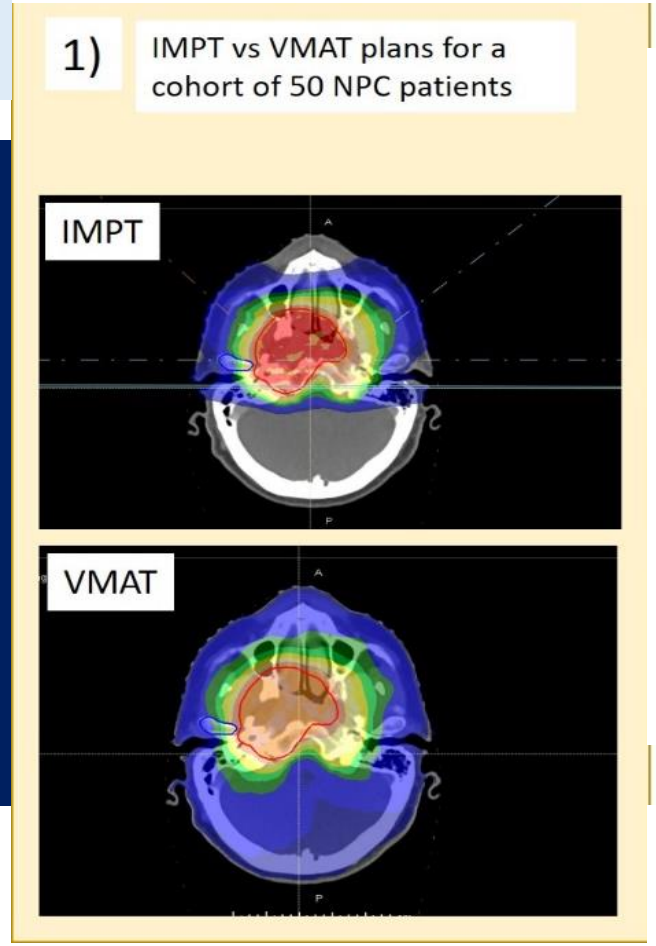
  ^35% for the composite threshold (assuming an ideal concomitant 5% variation for each of the 7 models)

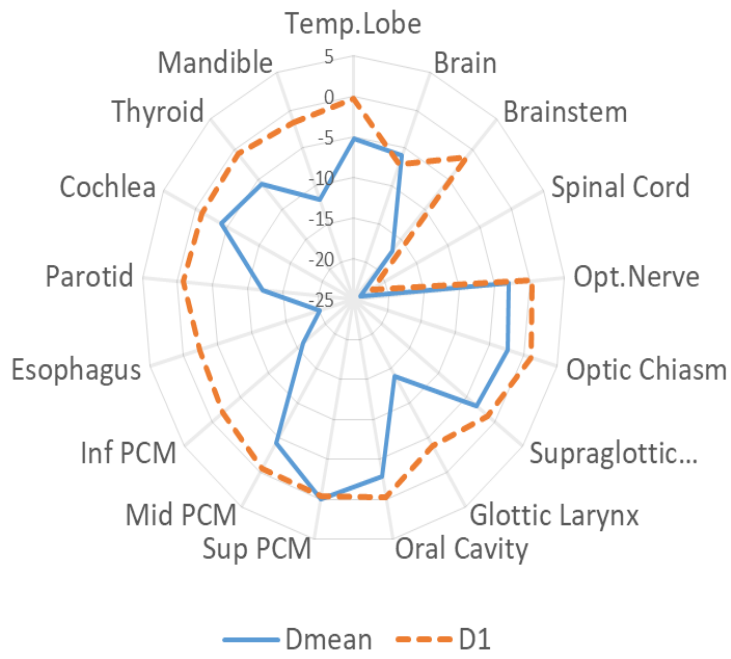
NTCP Model		NTCP filter thresholds
ORGAN	Endpoint (time post-RT)	
Brain	Necrosis > grade II (2 yrs)	10%
Optic Pathways	Radiation Induced Ocular Toxicity (RION) (>3 mths)	5%
Optic Pathways	Grade IV Visual Acuity Loss (>3 mths)	5%
Oral Cavity	Mucositis (8 wks)	15%
Superior PCM	Grade II-IV dysphagia (6 mths)	5%
Parotid	Moderate to severe xerostomia (6 mths)	15%
TMJ	Trismus (>3 mths)	10%

RESULTS

In silico dosimetric planning comparison (with gantry)

- ✓ PTV_{HD} $D_{99\%}$ and $D_{1\%}$ showed no significant difference
- ✓ no significant difference in HI values
- ✓ CI was lower for IMPT plans
- ✓ IMPT improved OARs sparing in the low-to-middle dose region for OARs close to the target while D_1 for OARs located few centimeters far from the PTV
- ✓ IMPT allowed a reduction of 45% of the integral dose



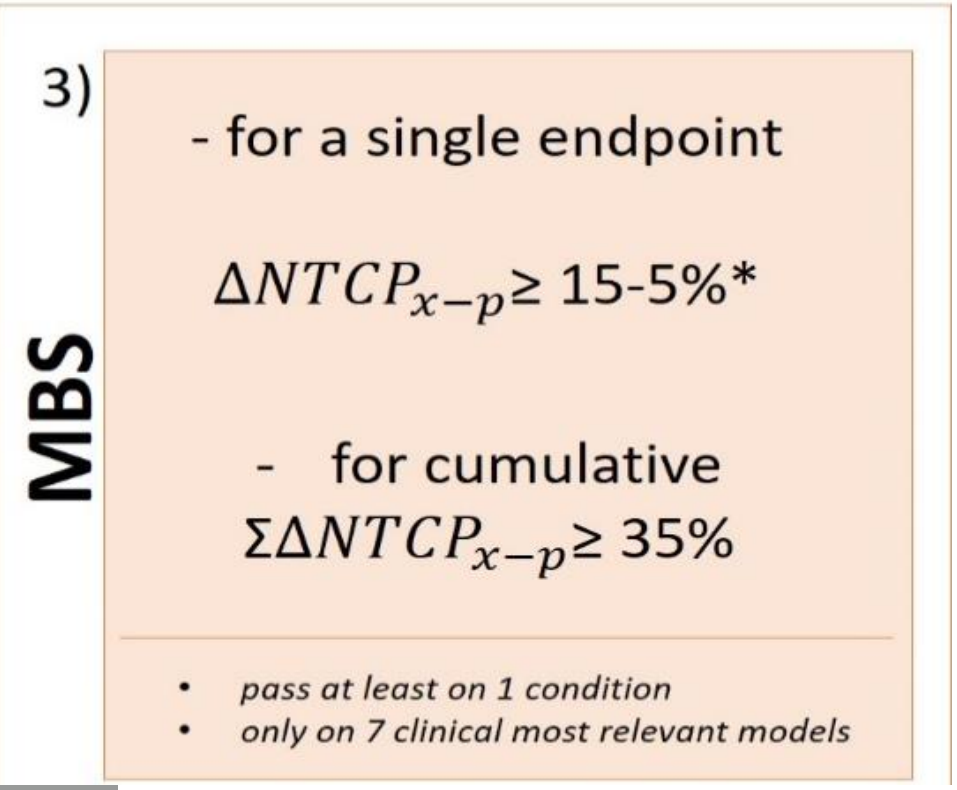


Role of IMRT/VMAT-Based Dose and Volume Parameters in Predicting 5-Year Local Control and Survival in Nasopharyngeal Cancer Patients

Nicola Alessandro Iacovelli[1†], Alessandro Cicchetti[2†], Anna Cavallo[3], Salvatore Alfieri[4], Laura Locati[4], Eliana Ivaldi[1], Rossana Ingargiola[1], Domenico A. Romanello[1], Paolo Bossi[4], Stefano Cavalieri[4], Chiara Tenconi[3], Silvia Meroni[3], Giuseppina Calareso[5], Marco Guzzo[6], Cesare Piazza[6], Lisa Licitra[4,7], Emanuele Pignoli[3], Fallai Carlo[1] and Ester Orlandi[1,8]*

RESULTS

NTCP model-based selection



40% of the analyzed patients resulted eligible for proton therapy, with a greater advantage for T3-T4 patients.

submitted

NTCP model based patient selection approach for proton therapy in sinonasal cancer patients with orbital invasion

- **Patient cohort: 22 SNUC**

- **Rationale: VMAT photon RT vs IMPT in silico study based on NTCP and DVHs statistics**
- Both are advanced and up to date RT techniques
- All plans were optimised in CNAO with Raystation TPS
- Selected clinical endpoints were analyzed in terms of validated NTCP models and DVHs. Following OARs were investigated :

List of analyzed OARs
Optic chiasm
Optical Nerves
Eyes
Lacrimal Glands
Lens
Anterior chambers
Retinas
Brain
Temporal Lobes
Frontal Lobe
Spinal Cord
Cochleas

→ Visual apparatus

→ SNC

→ others

2 selection criteria for assigning a case to protons or photon were proposed

submitted

First criterion (NTCP models based)

Enpoints were classified as severe or intermediate

if, for at least three of all investigated side-effects, i_a) ΔNTCP exceeded a threshold of 20% for intermediate toxicities or i_b) 3% for a single severe toxicities

Patient is assigned to protons

Endpoint	NTCP model	OAR
Blindness 5 years post-RT Burman et al. 1991 (Severe)	$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} exp\left(\frac{-u^2}{2}\right)du,$ $t = \frac{gEUD - TD_{50}}{m * TD_{50}}$	Optic Chiasm Left/Right Optical Nerve
Brain necrosis 5 years post-RT Bender et al. 2012 (Severe)	$NTCP = \left(1 + \left(\frac{D_{50}}{EQD_2}\right)^{4\gamma}\right)^{-1}$	Brainstem and Brain-CTV
Ocular Toxicity grade ≥ 2 Acute Batth et al. 2013 (Intermediate)	$NTCP = \left(1 + e^{-\beta_0 - \beta_1 * D_{max}}\right)^{-1}$	Left/Right Lacrimal gland
Temporal Lobe injury 5 years post-RT Kong et al. 2016 (Severe)	$NTCP = \left(1 + e^{-\beta_0 - \beta_1 * D_{max}}\right)^{-1}$	Left/Right/Frontal Lobes
Tinnitus 1-2 years post-RT Lee et al. 2015 (Intermediate)	$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} exp\left(\frac{-u^2}{2}\right)du,$ $t = \frac{gEUD - TD_{50}}{m * TD_{50}}$	Left/Right Cochlea
Cataract requiring intervention 5 years post-RT Burman et al. 1991 (Intermediate)	$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} exp\left(\frac{-u^2}{2}\right)du,$ $t = \frac{gEUD - TD_{50}}{m * TD_{50}}$	Left/Right Len
Dry Eye Syndrome Bahandare et al (Severe)	$NTCP = \frac{e^{\left(4\gamma\left(\frac{D}{D_{50}}-1\right)\right)}}{1 + e^{\left(4\gamma\left(\frac{D}{D_{50}}-1\right)\right)}}$	Left/Right Lacrimal gland
G2 necrosys Nyiazi et al 2020 (Intermediate)	$NTCP = \left(1 + \frac{39.5^{\ 10}}{gEUD}\right)^{-1}$	Brain-CTV

Second criterion (mixed, NTCP and DVH based)

$$TS = w_1 \sum_{j=0}^{4} \Delta NTCP^{severe}{}_j + w_2 \sum_{k=0}^{4} \Delta NTCP^{intermediate}{}_k + w_3 \sum_{r=0}^{m} \Delta DVH \quad _r$$

if an arbitrary mixed ΔNTCP/ΔDVHs parameter called total score (TS) is higher than a threshold of 250

Patient is assigned to protons

$W_{1,2 \text{ and } 3}$ are the weights given to the three factors.
ΔDVH is equal to +1 if a certain DVH parameter (r) is < 20% for proton plans , equal to -1 if it is <20%, 0 otherwise.

If criterion 1 or 2 is fulfilled than patient is assigned to protons

Over 22 patients, 17 would benefit from protons (77,3%)

Interventional clinical studies (Promoter/PI: CNAO)

Title	Study phase	Setting	First endpoint	State	N. of patients enrolled
CNAO 35/2017C: PIOPPO Preoperative chemotherapy and carbon ions therapy for treatment of borderline resectable pancreatic adenocarcinoma: a prospective, phase II, multicentre, single-arm study	II	Multicentric	PFS	Recruiting	12
CNAO 37-2019: 4D-MRI CIRT MRI-guidance for organ motion management in carbon ion treatments of abdominal tumours	II	Monocentric	organ motion quantification (MRI)	Recruiting	8
CNAO 40 2020C: Carbon ion radiation therapy in the treatment of mucous melanomas of the female lower genital tract (CYCLE)	II	Monocentric	PFS	Recruiting	3
CNAO 41 2020C: Phase II clinical study on the re-irradiation of lateral pelvic recurrences of gynecological malignancies (CYCLOPS)	II	Monocentric	LC	Recruiting	2

- Protect trial
- EUROCAN
- CNAO OSS 25 2021 — CNAO Registry Trial (Regal)
- CNAO OSS 30 2021 — E²-RADIatE: EORTC-ESTRO RADiotherapy InfrAstrucTure for Europe, EORTC protocol 1811

Thank you very much for your attention ….
and
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