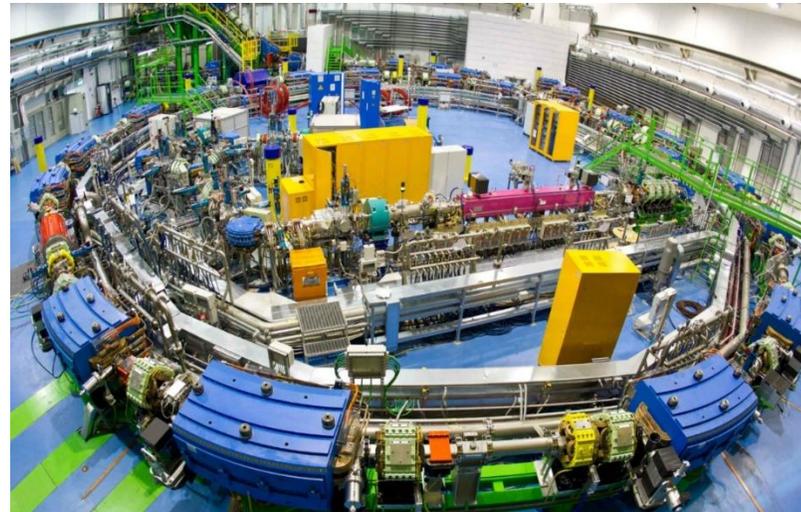




Opening Seminar of HITRIplus - CNAO

Clinical aspects- the use of carbon ions for the treatment of complex tumors: CNAO experience

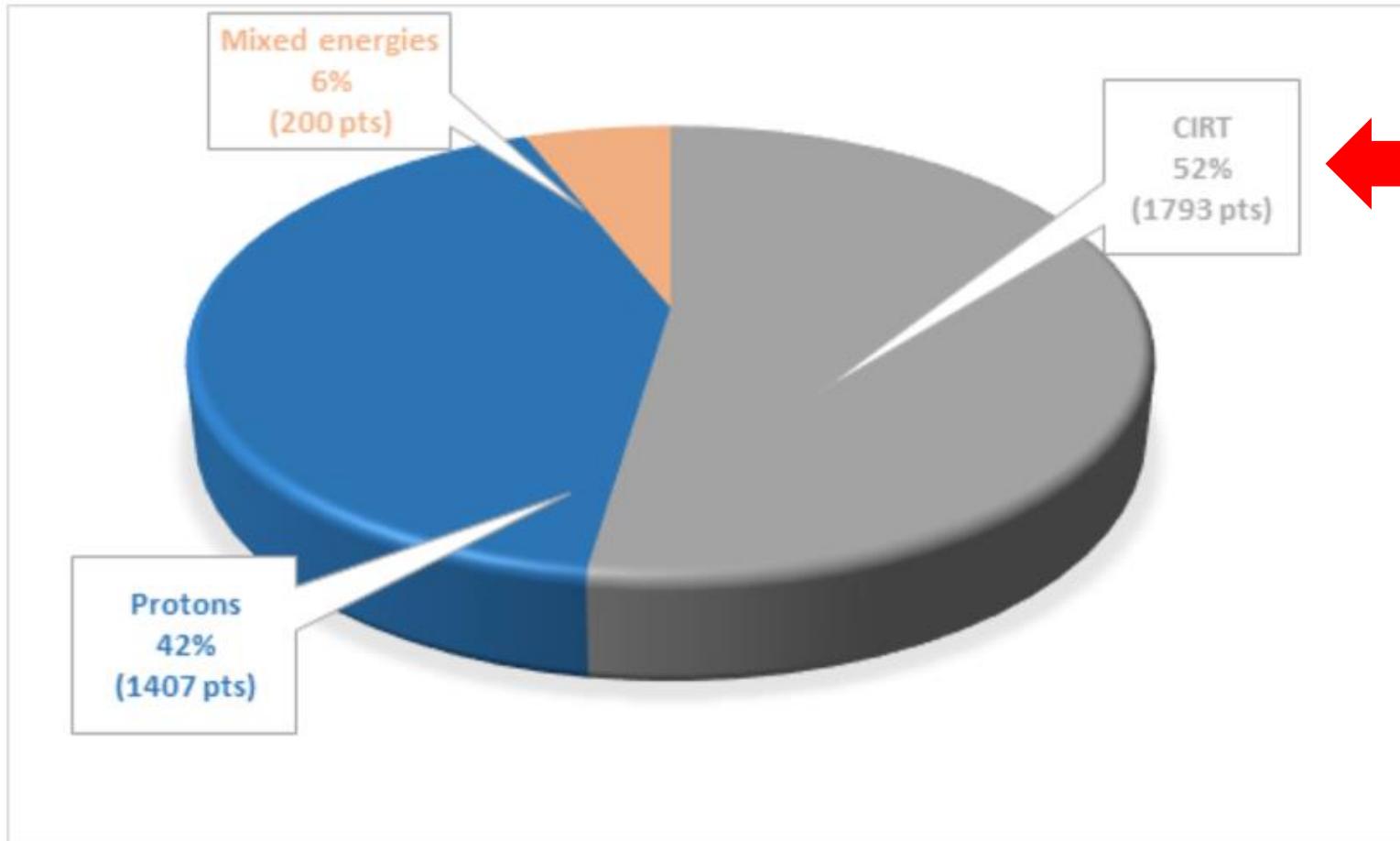
Ester Orlandi

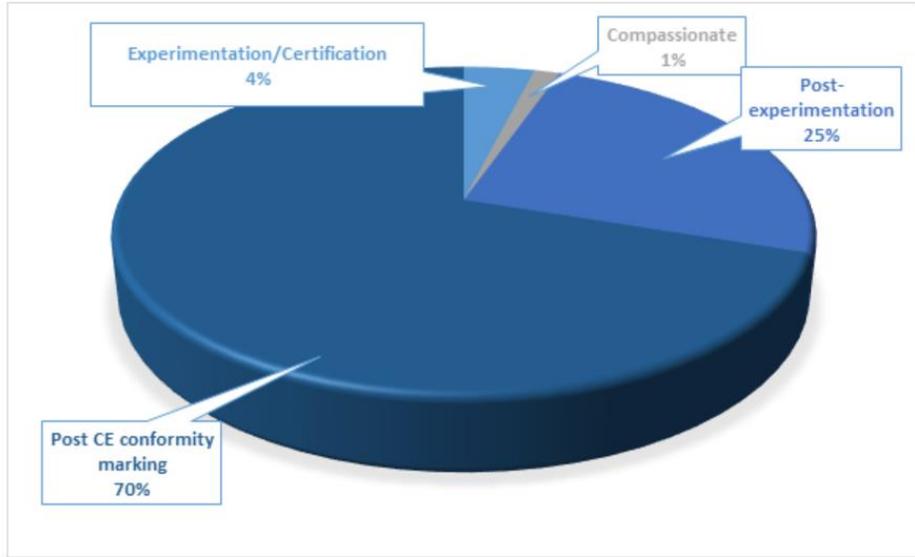


21 Jun 2021

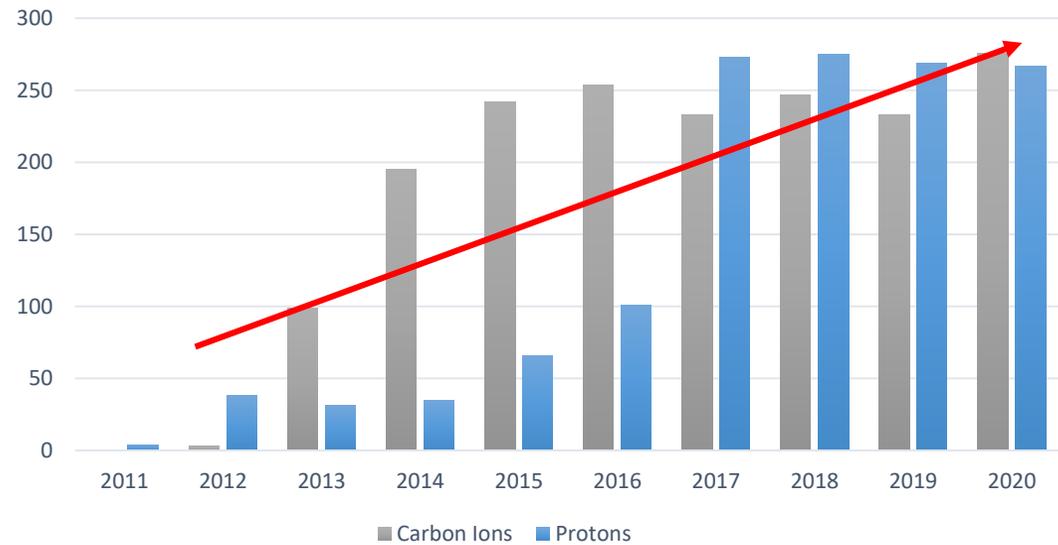


Clinical activity in CNAO: a handful of numbers

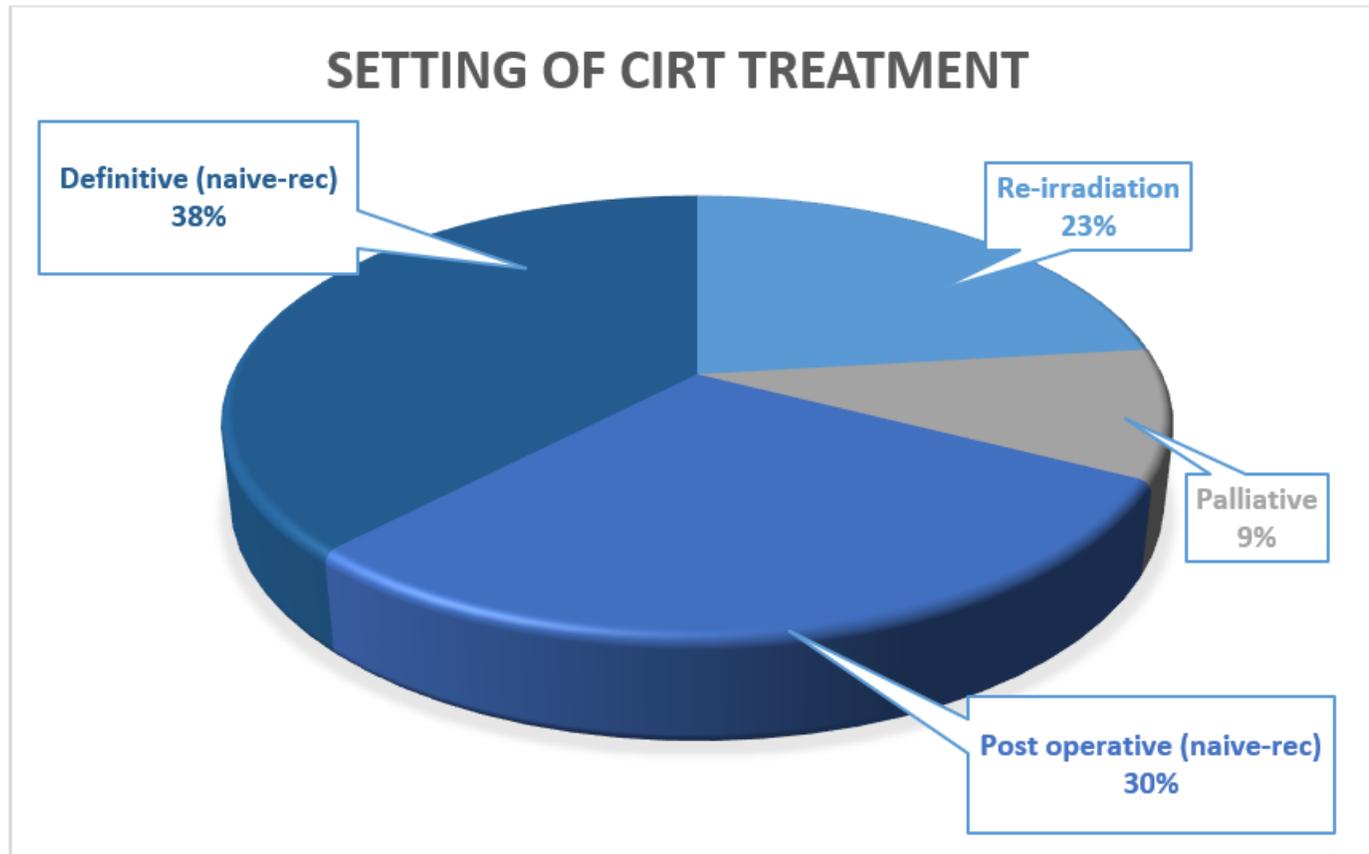




Particles treatments distribution through the years

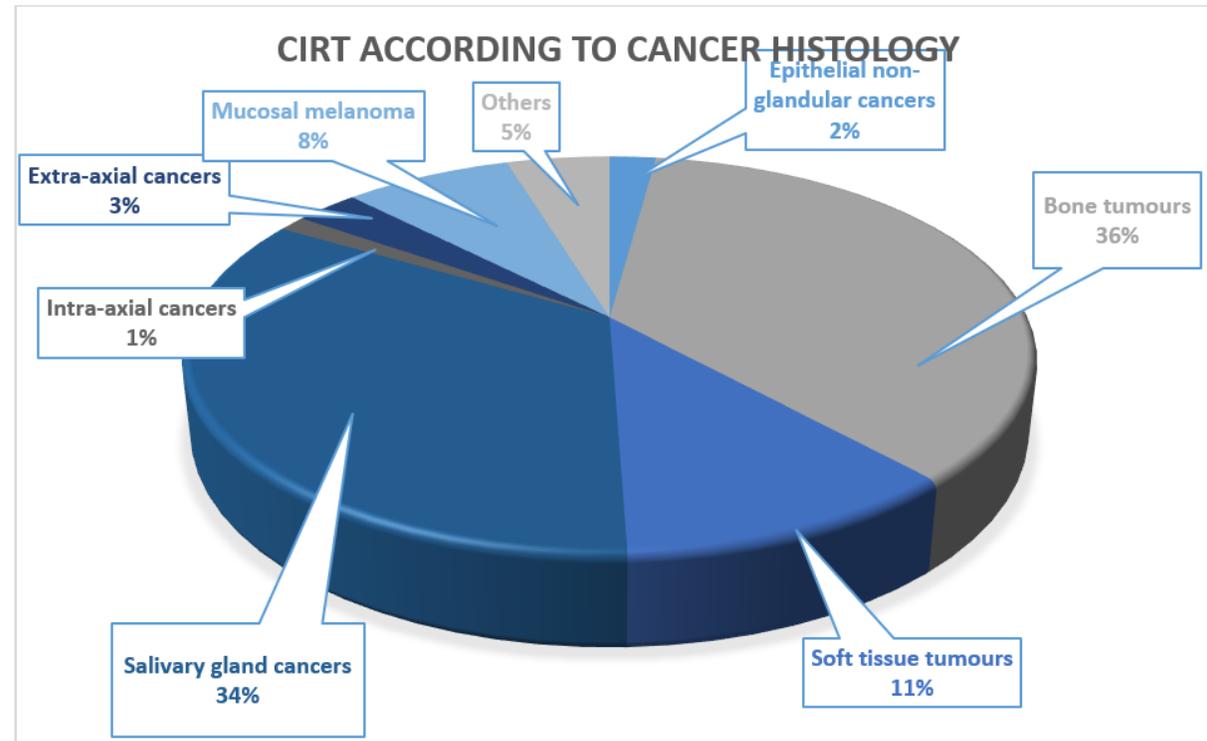
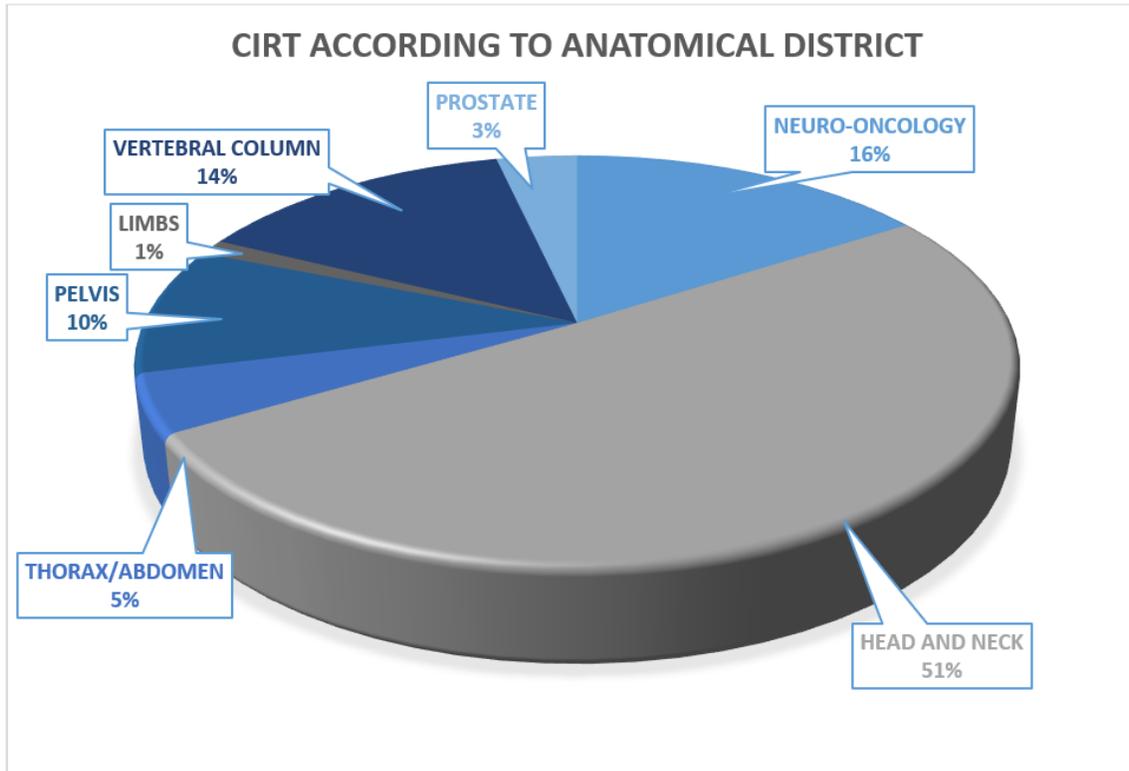


CIRT treatments

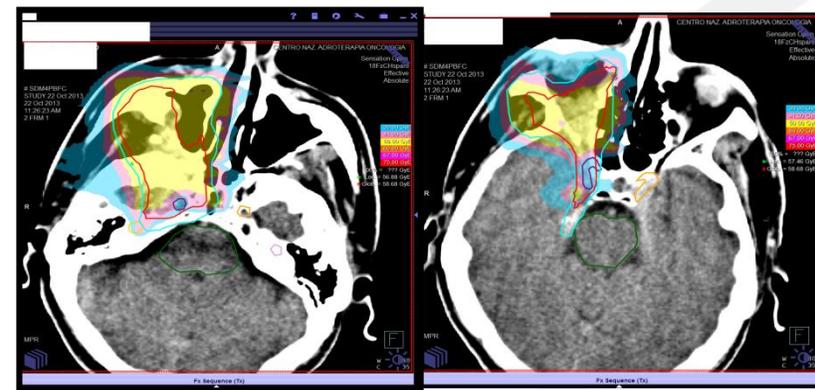
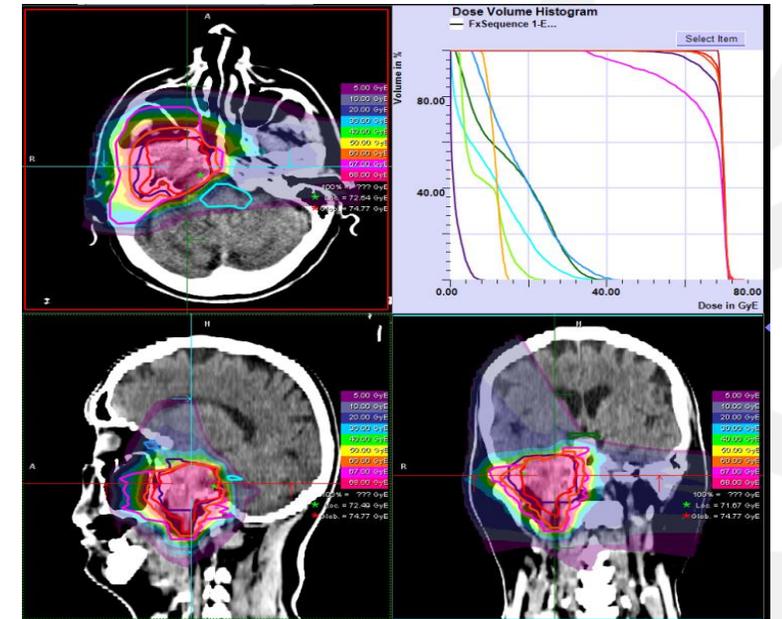
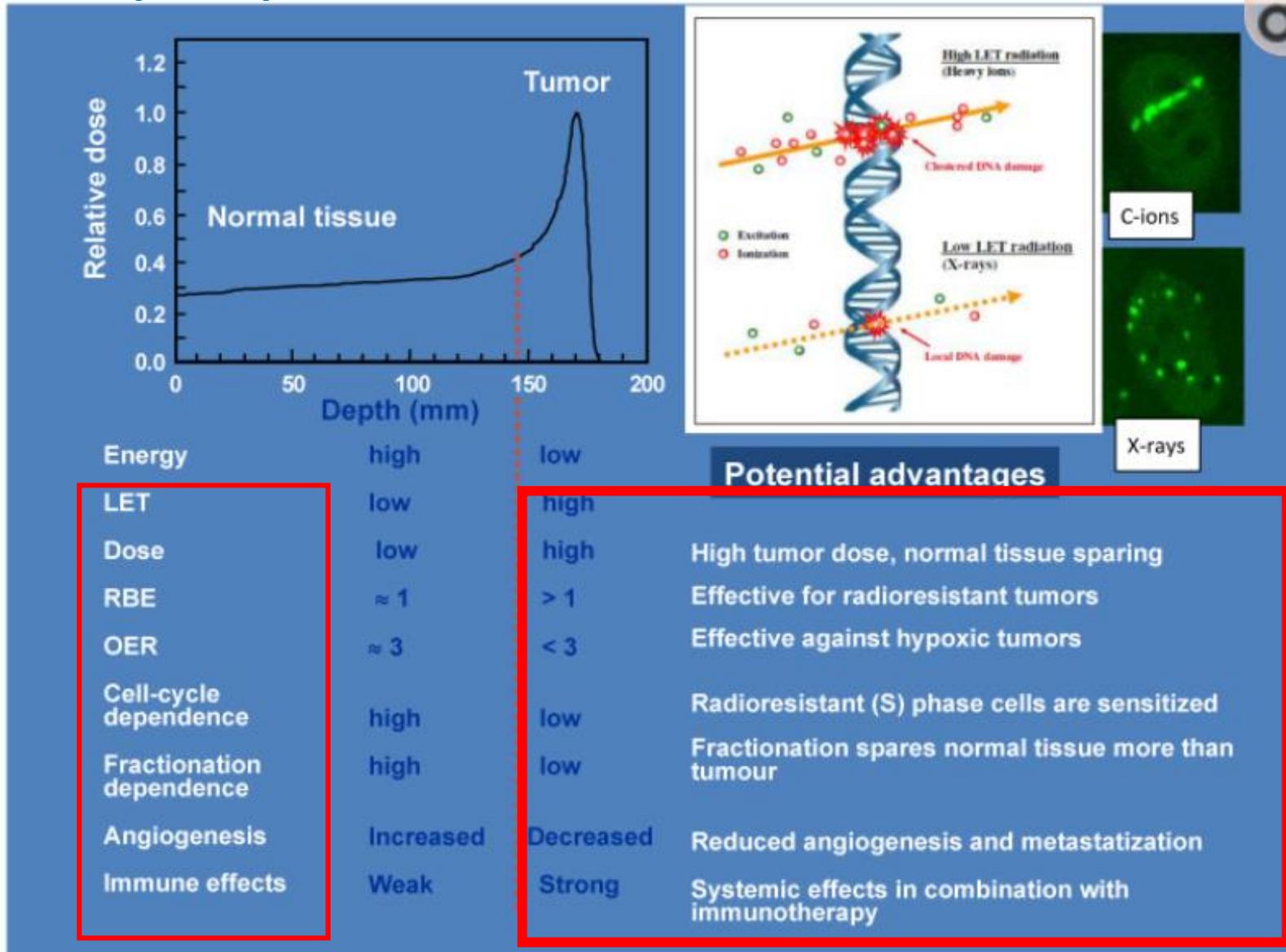


11% of pts received systemic therapy before and/or after CIRT

CIRT treatments



Selection Criteria for CIRT (Rare)/Radioresistant/recurrent tumors



Adenoid cystic carcinoma (ACC) of the Head and neck

March 2013- June 2020

■ Main pts characteristics

- 255 pts: 117 M; 138 F
- Median age: 56 years (range: 20-89)
- **Naive pts: 70%**; Recurrent after S (no previous RT) pts: 30%
- Site: paranasal sinus/NP 44%; parotid 21.6%; submandibular: 15.5%
- **Stage: T4:58.8% (T4 unresectable 32%); T3:19.6%**
- Positive node(s): 10.3%; Oligometastatic stage: 9.3%
- microPNI: 96.4%; macroPNI: 25.7%

■ Radiotherapy treatment:

➤ Settings:

- ✓ **definitive RT: 82/255 (32.1%)**
- ✓ **postoperative RT: 173/255 (67.9%):**
 - R0: 18.1%
 - R1 : 34.9% (36% multiple)
 - **R2: 47%**

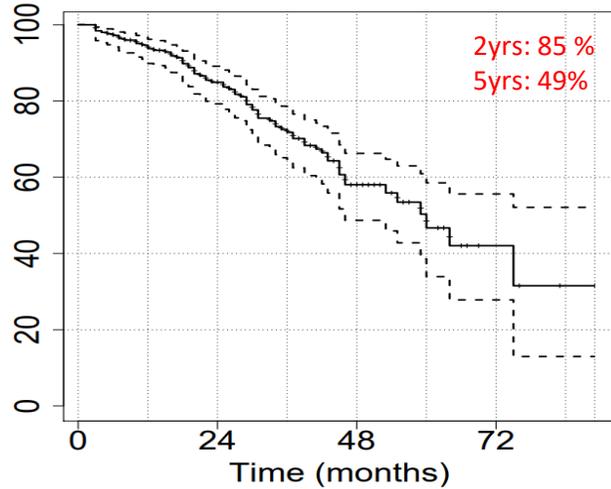
➤ Beam quality and fractionations:

- ✓ **CIRT: 4.3 Gy[RBE] FS/16fs/ 68.8Gy[RBE] : 65%**
- ✓ **CIRT: 4.1 Gy[RBE]FS/16 frs/ 65.6Gy [RBE]: 13%**
- ✓ **protons: 2 Gy[RBE]FS/27-37 frs/54-74Gy [RBE]: (22%)**
- ✓ **SEQ strategy**

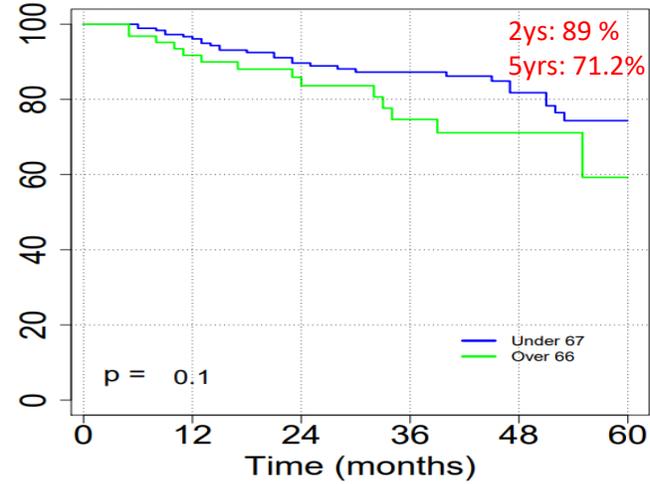
Outcome results

MedianFU: 33 months (range: 3-89 months)

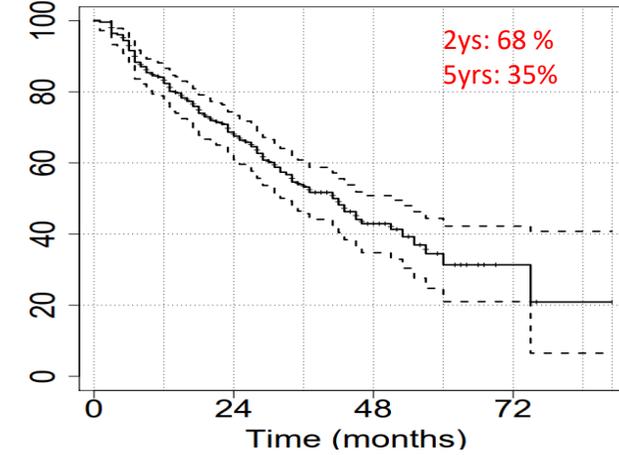
LC



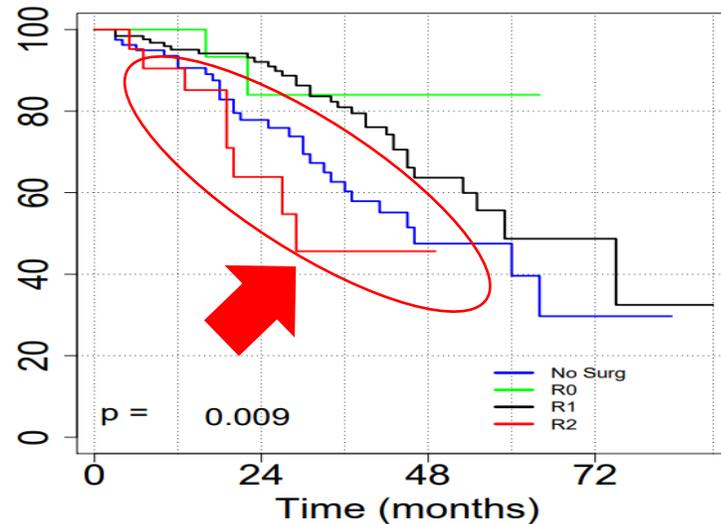
OS



PFS



LC



R1: 2/5yrs: 90%/44%
R2: 2/5yrs: 63%
Unresectable: 2/5yrs: 78%/42%



Toxicity

CIRT 4.3	ACUTE	LATE
G0	1%	12%
G1	21%	22%
G2	53%	47%
G3	25%	16%
G4	/	2%
G5	/	1%

- G3 acute toxicity:
 - mucositis: 38 patients (23%)
 - erythema: 3 patients (2%)
- G5 late toxicity: vascular toxicity: 1 patient
- G4 late toxicity:
 - epidural abscess: 1 patient
 - radionecrosis: 1 patient
- **G3 late toxicity:**
 - **osteoradionecrosis: 8 patients (5%)**
 - **soft tissue necrosis: 4 patients (2%)**
 - **neuropathy: 4 patients (2%)**

- G3 grade acute toxicity: erythema: 1 patient
- **G3 grade late toxicity: decrease of vision: 1 patient**

CIRT 4.1	ACUTE	LATE
G0	/	10%
G1	41%	47%
G2	56%	40%
G3	3%	3%

PT	ACUTE	LATE
G0	/	7%
G1	3%	35%
G2	81%	53%
G3	16%	5%

- G3 grade acute toxicity (16%):
 - mucositis: 4 patients (7%)
 - erythema: 4 patients (7%)
- **G3 grade late toxicity (5%):**
 - **hearing loss: 2 patients (4%)**
 - **necrosis of the surgical flap: 1 patient**

Unpublished data

Mucosal Melanoma of the Head and neck

June 2013- June 2020

■ Main pts characteristics

- 40 pts; F 62,5%, M 37,5%
- Median age: 70 years (range 39 – 87)
- Naive pts: 77%; Recurrent (no previous RT) : 23%
- Site: Nasal cavity: 77,5%; Paranasal sinuses: 12,5%
- Stage: T3:42.5%; T4: 57.5%
- Adjuvant immunotherapy:46%

■ Radiotherapy treatment:

➤ Settings:

- ✓ definitive RT: 30%
- ✓ postoperative RT: 70%
- ✓ Macroscopic disease before CIRT: 80%

➤ GTV volume:

- ✓ All pts: 27 cc (range 0 – 276)
- ✓ unresectable+R2 cases: 137 cc (range 5 – 276)
- ✓ Preop mean GTV volume: 52 cc (range 5 – 141)

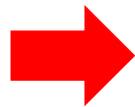
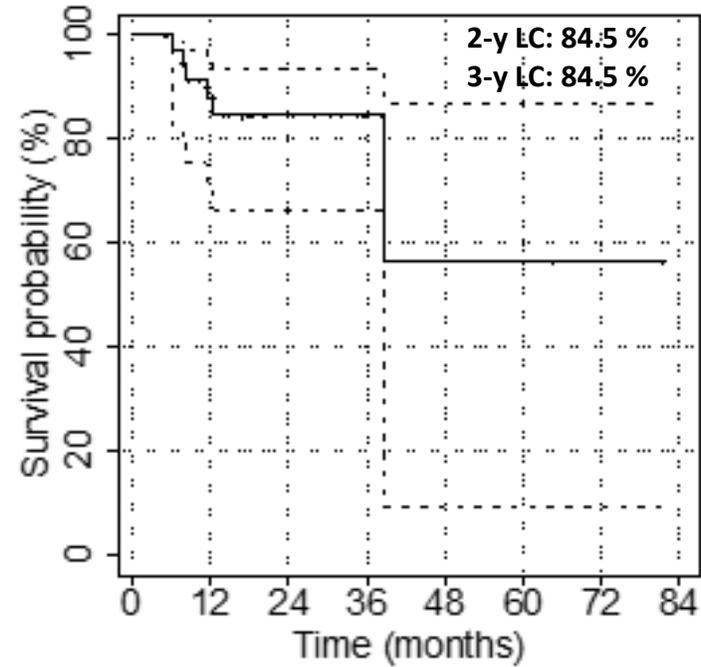
➤ CIRT fractionations:

- ✓ 4.3 Gy[RBE] FS/16frs/ 68.8Gy[RBE] : 45%
- ✓ 4.1 Gy[RBE]FS/16 frs/ 65.6 Gy [RBE]: 55%
- ✓ SEQ strategy

Clinical results

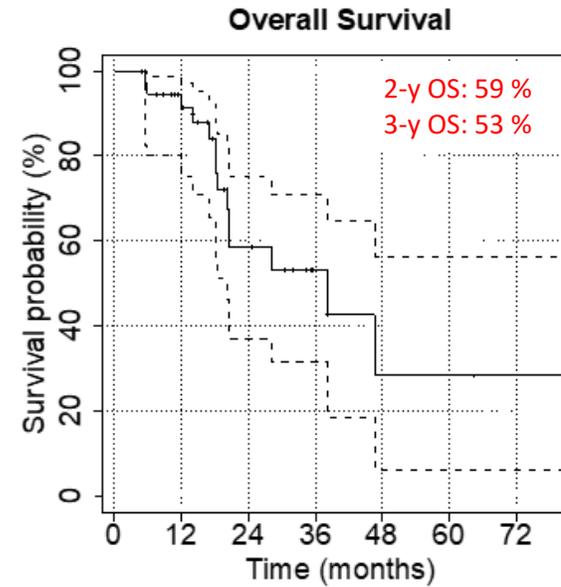
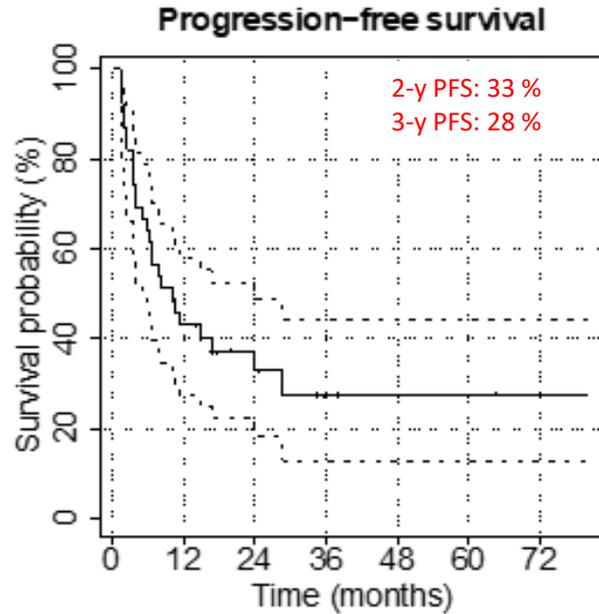
MedianFU: 18.8 months (range: 3-89 months)

Local control



Better LC:

- No surgery or only one surgery before CIRT (p=0.004)
- Naive T status vs recurrent (p=0.004)



Better PFS:

- Naive T status vs recurrent (p=0.03)
- Complete Best radiological response (CR vs non-complete) (p=0.004)
- T3 stage vs T4 (p=0.01)

Better OS:

- T3 stage vs T4 (p=0.01)
- Age (as continuous variable)

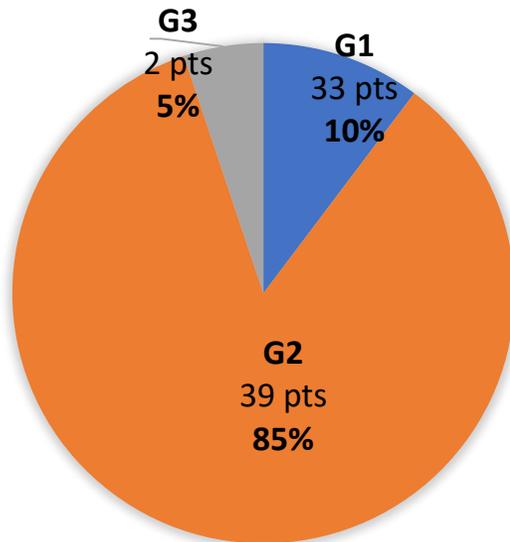


Toxicity

Acute max toxicity (during/end of CIRT):

G3 events:
1 eritema
1 mucositis

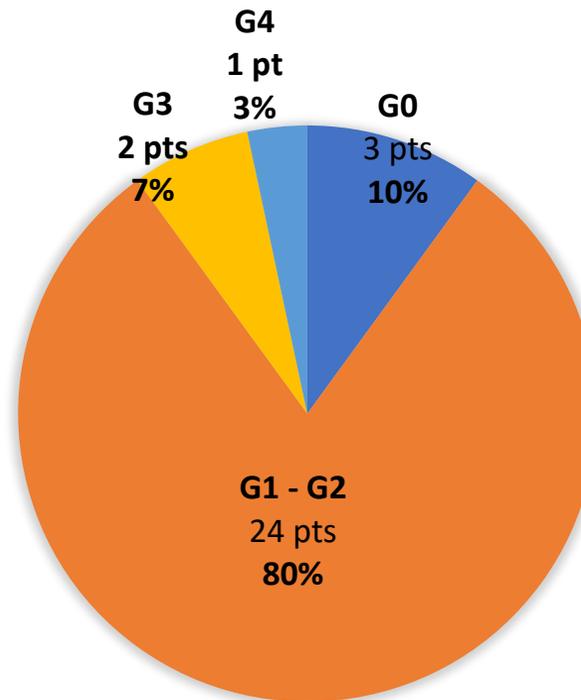
No > G3
acute tox
@ 3 months



Late max toxicity > 3 months (evaluabile for 30/40 pts)

G3 events:
1 unilateral hearing impairment
1 unilateral visual impairment

G4 events:
1 unilateral visual loss

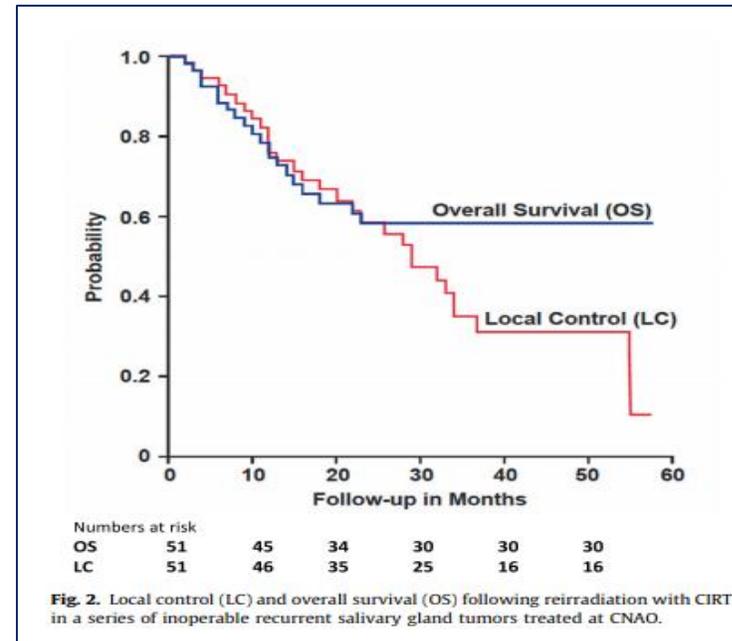


Re-irradiation of SGCs

Table 1
Major patients and radiotherapy characteristics.

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)

- November-2013-September2016
- 51 pts
- Median CIRT dose 60 Gy[RBE]/ 3Gy[RBE] FS
- Median follow-up: 18 months



Toxicity

Table 4
Acute and late toxicity at last follow up.

	ACUTE TOXICITY N (%)	LATE TOXICITY N (%)
G0	11 (21.5)	14 (27.5)
G1	19 (37.3)	9 (18)
G2	19 (37.3)	19 (37)
G3	2 (3.9)	9 (17.5)

Skull base chordoma

- 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)	-

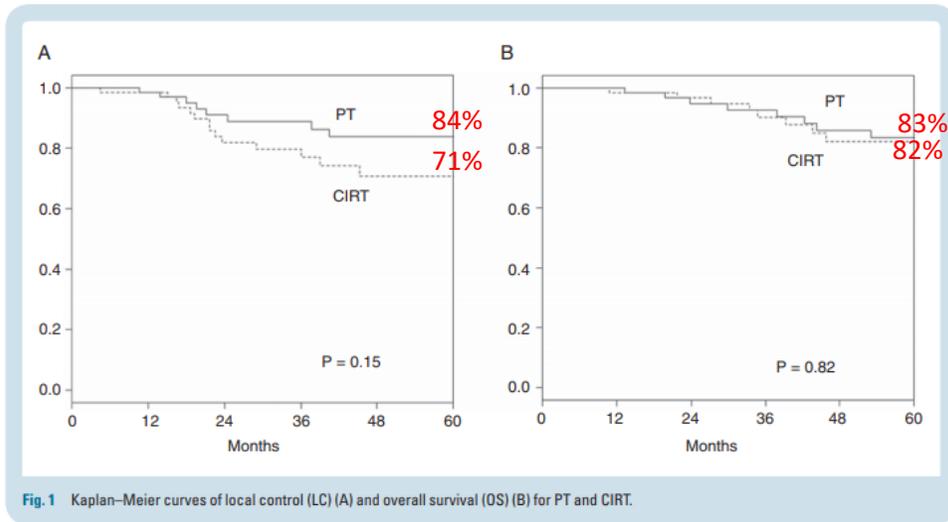
Abbreviations: *Only CT imaging, CIRT: carbon ion radiotherapy, PT: proton therapy, Y: yes, N: no, GTV: gross target volume, KPS: Karnofsky performance status.

Clinical results

MedianFU: 44 months (range: 6-87 months)

Local control

Overall survival



Late 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.

Axial and pelvic bone tissue sarcoma

- January 2013 to September 2018
- Median follow-up :(range=4-61 months)

Table II. *Patients characteristics.*

Patients=54	N (range or %)
M:F	32:22
Age	50 (19-79)
Histologic subtypes	
Osteosarcoma	13 (24%)
Solitary fibrous tumor	3 (6%)
Chondrosarcoma	21 (39%)
Other	17 (31%)
Grading	
G1	11 (20%)
G2	12 (22%)
G3	23 (43%)
Gx	8 (15%)
Disease presentation	
<i>De novo</i>	41 (76%)
Recurrent	13 (24%)
Tumor site	
Pelvis	27 (50%)
Cervical spine	8 (15%)
Thoracic spine + Chest wall	13 (24%)
Lumbar spine	6 (11%)
Surgery	
Unresectable	37 (68%)
Subtotal resection	17 (32%)
Chemotherapy Pre-RT	22 (40%)
Median total dose	73.6 Gy RBE (70.4-76.8)
Median daily dose	4.6 Gy RBE (4.4-4.8)
Median GTV	268.51 cc (72-3199.74)
Median PTV	1177.93cc (178-6596.99)



Late tox: G3 neuropathy in 2 cases (4%)

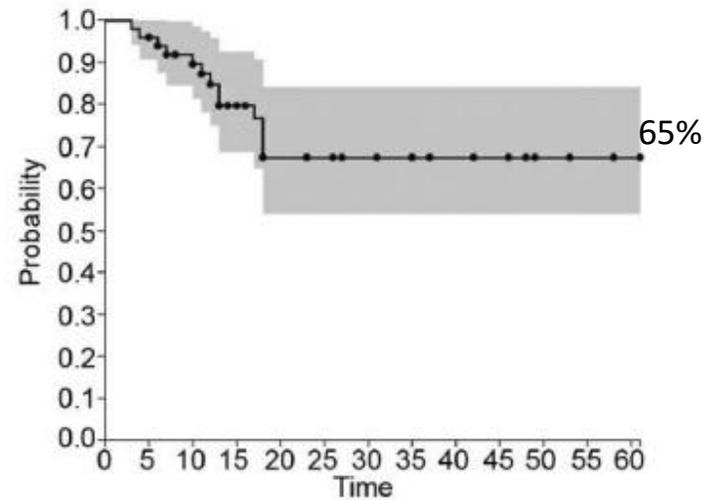


Figure 1. *Kaplan-Meier curve for local control (LC) of the study population.*

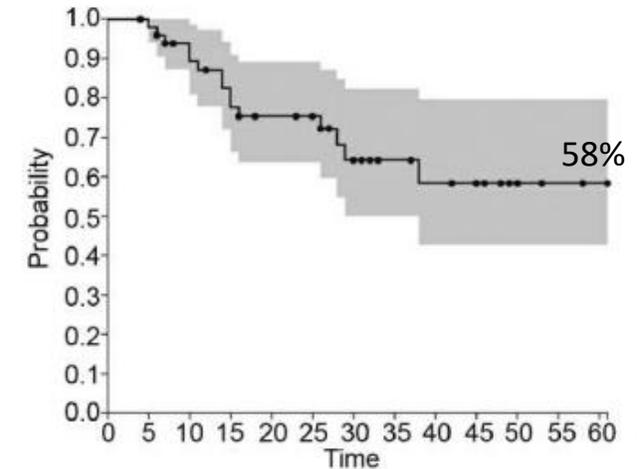
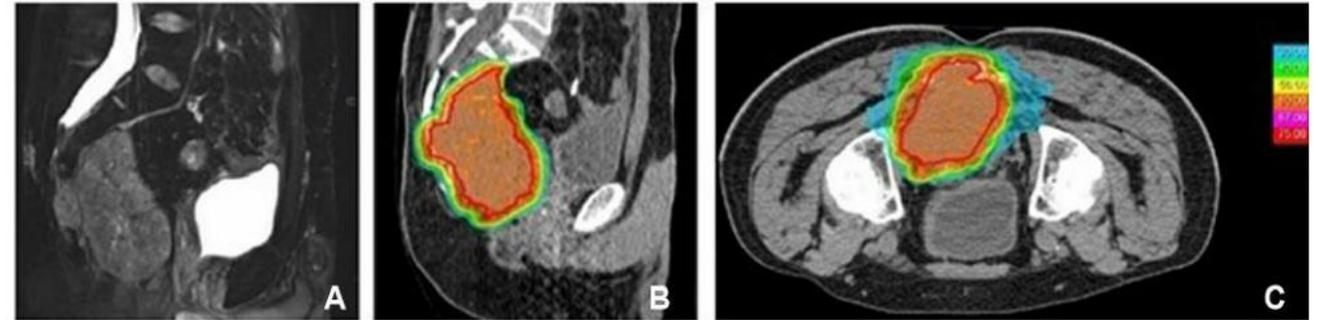


Figure 3. *Kaplan-Meier curve for overall survival (OS) of the study population.*

Re-irradiation for unresectable pelvic rectal recurrence

	Value
Number	14
Gender (number)	
Male	12
Female	2
Age, years	
Median (range)	58.5 (34-78)
Dose of prior EBRT (at time of first diagnosis)	
Median (range)	45 Gy (45-76*)
Dose of prior BT boost (at time of first diagnosis)	
Total dose (1 patient)	20 Gy
Dose of prior Re-irradiation	
Total dose (1 patient)	30 Gy
Interval between EBRT and CIRT, months	
Median (range)	65 (14 - 139)
Relapse site	
Pre-sacral	10
Perineal	1
Perianal	1
Pre-coccygeal	2
GTV volume, ml	
Median (range)	154.63 (7.21-359.94)
PTV volume, ml	
Median (range)	306.7 (53.55-742.64)
Total dose of CIRT	
Median (range)	60 Gy RBE (35-76.8)
Dose for fraction (CIRT)	
Median (range)	3 Gy RBE (3-4.8)
Number of fraction (CIRT)	
Median (range)	16 (15-20)



1-year LC 78%

2-year LC 52%

Close to the bowel in 6 pts

1-year OS 100%

2-year OS 76.2%

No G \geq 3 acute/late reaction or pelvic infections were observed;
a sacral asymptomatic insufficiency fracture was observed (12 months)

Spacer implantation via open surgery : 4 patients!

AMENDED!

STUDY PROTOCOL

Open Access



Preoperative chemotherapy and carbon ions therapy for treatment of resectable and borderline resectable pancreatic adenocarcinoma: a prospective, phase II, multicentre, single-arm study

Primary endpoint
PFS

Secondary Endpoints
OS

Radical resectability rate (R0 resection)
Treatment toxicity (acute, intermediate, late)
Intra and perioperative toxicity

**Neoadjuvant
CT**

FOLFIRINOX m
3 cycles

**Neoadjuvant
CIRT**

38.4 Gy [RBE]
4.8 Gy[RBE]/8
fractions

SURGERY

**Adjuvant
Chemotherapy**

FOLFIRINOXm
(up to 9 cycles)
If KI <70 or unfit
Gemcitabine (up to 6
months)

Restaging

**Thank you very much for your attention
and
..... thank's a lot to all my clinical staff**

RTTs & Nurses:

S. Tampellini

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