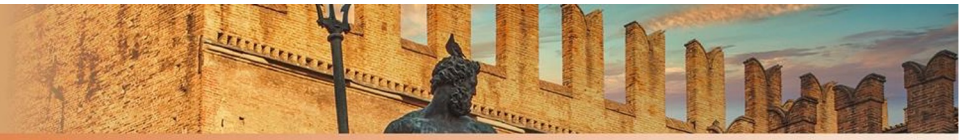

XXXII CONGRESSO NAZIONALE AIRO
XXXIII CONGRESSO NAZIONALE AIRB
XII CONGRESSO NAZIONALE AIRO GIOVANI
AIRO2022
Radioterapia di precisione per un'oncologia innovativa e sostenibile
BOLOGNA, 25-27 NOVEMBRE
PALAZZO DEI CONGRESSI
Associazione Italiana
Radioterapia e Oncologia clinica
Società Italiana di Radiobiologia

Preoperative robotic stereotactic radiotherapy in early breast cancer: phase II Rock Trial (NCT03520894)

I. Bonaparte[1,2], B. Bettazzi[1,2], N. Bertini[1,2], L. Visani[1], C. Becherini[1], E. Scoccimarro[1], V. Salvestrini[1], I. Desideri[1], V. Scotti[1], R. Doro, L. Masi, G. Francolini[1], V. Di Cataldo[1], M. Mangoni[1], M. Loi[1], L. Orzalesi[1], M. Bernini[1], J. Nori[1], S. Bianchi, I. Meattini[1], L. Livi[1]

1. Radiation Oncology Unit, Azienda Ospedaliera-Universitaria Careggi, Florence, Italy;
2. Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Florence, Florence, Italy

Associazione Italiana Radioterapia e Oncologia clinica
Società Italiana di Radiobiologia



DICHIARAZIONE

Dott.ssa Ilaria Bonaparte

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board **NIENTE DA DICHIARARE**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Altro **NIENTE DA DICHIARARE**

Background

Standard of care in women with early breast cancer (eBC)

→

Breast-Conserving Surgery (BCS)
+/-
Postoperative Radiation Therapy (RT)
+/-
Systemic Therapy

Cardoso F. et al. Ann Oncol. 2019
Meattini I et al. Lancet Oncol 2022

Rationale for preoperative radiation therapy (RT) in breast cancer

- Easier tumour site identification and better **target volume delineation**
- Tumour **downstaging** with increased rates of BCS
- To facilitate **breast reconstruction** and improve surgical cosmetic outcomes
- **No delay** to local therapy (i.e., due to wound healing after surgery)
- Increase rates of pathological **Complete Response** (pCR) and possible risk-stratify for other adjuvant therapies
- Possible **predictive biomarkers** for response after preoperative RT

We conducted a phase II, single arm, exploratory study on early BC patients undergoing preoperative robotic stereotactic radiosurgery (prRS) with CyberKnife® (NCT03520894-ROCK trial)

Primary Objective

- To assess the **incidence of acute cutaneous toxicity** of prRS followed by BCS according to the EORTC/RTOG scale

Secondary Objective

- To assess the **activity of prRS** followed by BCS
- To determine the **incidence of chronic cutaneous and extracutaneous toxicities** of prRS followed by BCS

Exploratory Objective

- To identify a correlation between **radiogenomic, immunological and biochemical biomarkers** with treatment-related response and toxicity

Material and methods

Inclusion criteria	Exclusion criteria
Women aged ≥50 years	Breast tumors with disease extension within 5 mm of the skin
New histological diagnosis of unifocal invasive breast cancer	Patients with tumors larger than 25 mm
ER positive (≥10% of tumor cells must express receptor for ER) and / or PR positive (≥10% of tumor cells must express receptor for PR)	Patients with comorbidities for collagen diseases
HER2 negative (IHC 0-1 +; for IHC 2+ patients, FISH negative)	BRCA1/2-carrier patients
Any tumor grade	Patients previously irradiated to the ipsilateral breast
Clinically and radiologically defined disease with a maximum size of 25 mm and clinically negative lymph node status	Patients previously irradiated at the level of the ipsilateral chest wall
Candidate patients for conservative treatment	Patients with DCIS including Paget's disease of the nipple

Material and methods - study design

- Expected **enrollment of 25 patients** in an interval of 12 months
- **36-month follow-up** for a total duration of 48 months from first enrollment
- **Clinical visit every 6 months** with evaluation of the efficacy and toxicity of the treatment
- Annual **mammography** and bilateral **breast ultrasound**
- **Doppler Cardiac US** and **spirometry** before prRS, at the first post-surgery check-up and at 12 months

Material and methods - study timeline

Enrollment

Fiducials Injection
Breast MRI
Planning CT

Treatment (21 Gy, single fraction with Cyberknife)

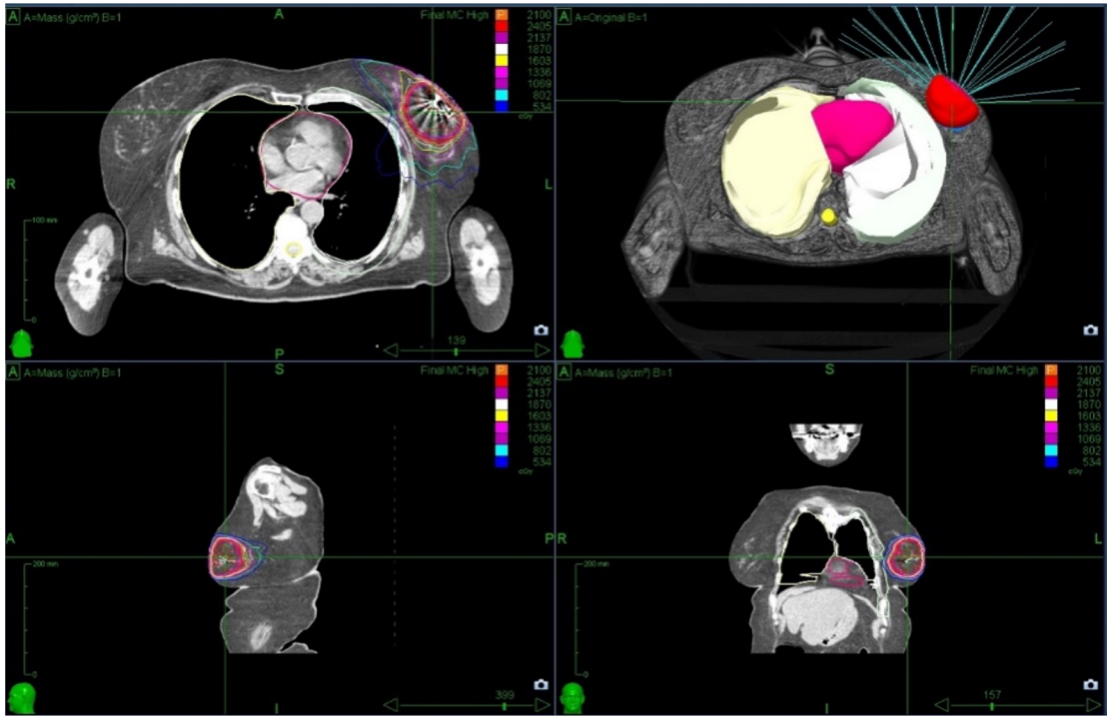
Surgery

Blood Samples:
- 1 hour before treatment
- 1 hour after treatment
- 1 week after treatment
- 24 hours before surgery
- 2-4 weeks after surgery

NGS/Real Time PCR on biopsy samples to evaluate molecular gene signatures

Material and methods

- Fiducial markers (3-5) were introduced in peri/intralesional position
- Contrast enhanced planning CT in supine position, with 1.25 mm slice thickness, was performed at least 1 week after fiducial markers positioning
- Magnetic resonance imaging (MRI) was co-registered with standard computed tomography (CT)-based planning to identify contrast enhancing tumors
- Patients received 21 Gy in single fraction with CyberKnife® followed by BCS two weeks later



Material and methods

CTV = GTV+1.5 cm

- The 5 mm from the skin surface was excluded from CTV
- An additional 3-mm margin excluding the first 5 mm of subcutaneous tissue was used to generate the planning target volume (PTV) to account for set up uncertainty

Dose constraints	
Skin	V10 ≤10 cc; V20 <1cc
Ipsilateral Breast	V10.5 ≤60% or 50%; V21 ≤35%
Contralateral Breast	≤1 Gy at any point
Heart	V3 ≤5 cc
Ipsilateral Lung	V7 ≤1000cc
Contralateral Lung	≤1 Gy at any point
Chest Wall	V10 ≤10 cc
Spinal Cord	V3 ≤1 cc

Dose constraints used for OARs derived from National Surgical Adjuvant Breast and Bowel Project/Radiation Therapy Oncology Group partial breast trial, after variations in order to consider the single fraction.

Results

From August 2018 to June 2021:

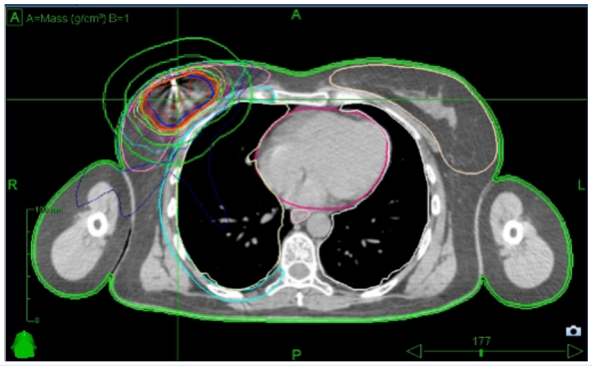
70 patients screened on mammography findings → 41 excluded due to ER negative or HER2 positive disease at biopsy, clinical positive nodal disease or skin distance ≤ 5mm

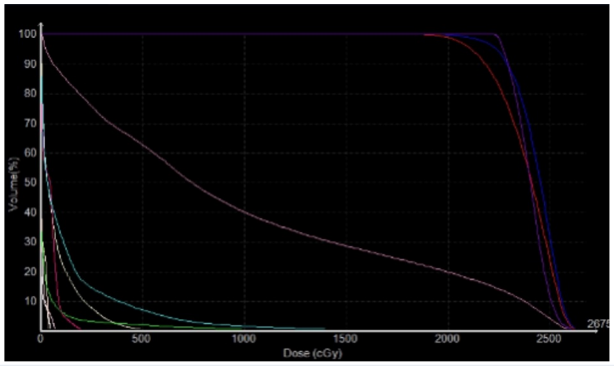
↓

29 eligible for histology → 7 excluded at the time of MRI due to multifocal disease

↓

22 patients successfully treated → All required dosimetric parameters were met in all patients, as were normal tissue constraints





Name	Dose (cGy)	Dose (%)	Volume (cm³)	Volume (%)
Cute	1380	51.6	**1.00**	0.1
Cute	**1000**	37.4	8.64	0.5
mammella dx	**1050**	39.2	219.41	38.4
mammella dx	**2100**	78.5	100.40	17.6
Right Lung	**700**	26.2	0.01	0.0
Heart	**300**	11.2	0.00	0.0
parete toracica dx	**1000**	37.4	8.60	1.5
mammella sx	**100**	3.7	0.00	0.0
ptv	**2100**	78.5	90.95	95.5
GTV	**2100**	78.5	7.37	100.0

Results

Patients' characteristics	N. of patients (Tot N=22)
Breast tumour location *Right Side* *Left Side*	 **15** 7
Involved Breast Quadrant *Upper Outer* *Upper Central* *Upper Inner* *Lower Central* *Lower Inner* *Subareolar*	 **11** 4 3 2 1 1
Tumour size (mm)	**13** (7.5-25)
Ki67<20% Ki67≥20%	19 3
ER≥20% ER<20%	22 0

Patients' characteristics	N. of patients (Tot N=22)
PgR≥20% PgR<20%	20 2
Median age (years)	68 (50-86)
ECOG performance status 0 1	 19 3
Median basal 2D-LVEF (%)	63.5 (58-71)
Median basal FEV1 (%)	1.9 (1.2 -2.72)
Median basal DLCO (%)	15.0 (6.02-21.2)

Results

The median follow-up was 18 months (range 6-29.8).

All treated patients underwent BCS + sentinel node biopsy (SNB) within 14 day (median time of 29 days from enrollment) from preoperative stereotactic radiotherapy without any procedure delay or complication, and no wound dehiscence was observed.

According to Chevallier's classification, **2** patients (9%) had a pathological complete response (pCR).

Meattini I et al. Clinical and Translational Radiation Oncology, 2022

Results - patients' outcomes

Pathological positive axillary nodes were found in 3 out of 22 patients (13.6%), and 3 out of 22 patients (13.6%) had positive surgical margins (2 patient had second surgery).

Postoperative whole breast RT was delivered, according to histopathological results, in 2 patients.

Systemic adjuvant treatment was administered in 21 patients (95.4%), with 21 and 3 patients undergoing exclusive endocrine therapy or endocrine therapy plus chemotherapy (for N+ disease), respectively.

Results - acute toxicity

- Three G1 adverse events were recorded within 7 days from prRS (one erythema, two breast pain)
- Three events were recorded between 7 and 30 days from prRS, one G2 breast edema and two G1 breast pain
- No acute toxicity greater than G2 was recorded
- No postoperative complications related to breast surgery were reported

Outcomes	G1 (N)	G2 (N)	G3 (N)	G4 (N)
Breast pain	4	0	0	0
Breast erythema	1	0	0	0
Breast edema	0	1	0	0

Results - late toxicity

- Five patients experienced G1 toxicity (one breast pain, four breast induration)
- One patient reported G2 breast induration
- No toxicity greater than G2 was observed

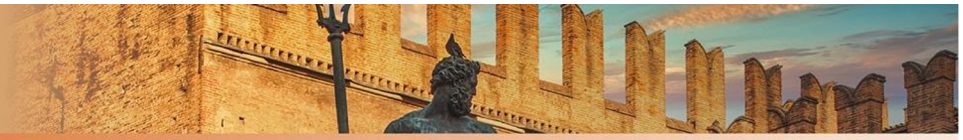
Outcomes	G1 (N)	G2 (N)	G3 (N)	G4 (N)
Breast pain	1	0	0	0
Breast induration	4	1	0	0
Breast edema	0	0	0	0

- At 12 months evaluation, spirometry and cardiac echocardiography demonstrated no cases of cardiac and/or pulmonary toxicity of any grade and no clinically meaningful changes in LVEF and DLCO

Conclusions

ROCK trial showed that a single 21 Gy dose Preoperative stereotactic radiotherapy represents a feasible technique for selected eBC patients, with a good safety profile and a promising rate of response.

This new approach in BC management is currently based on limited data but warrants further investigations.



Thanks for your attention