Roma 23 Aprile 2024

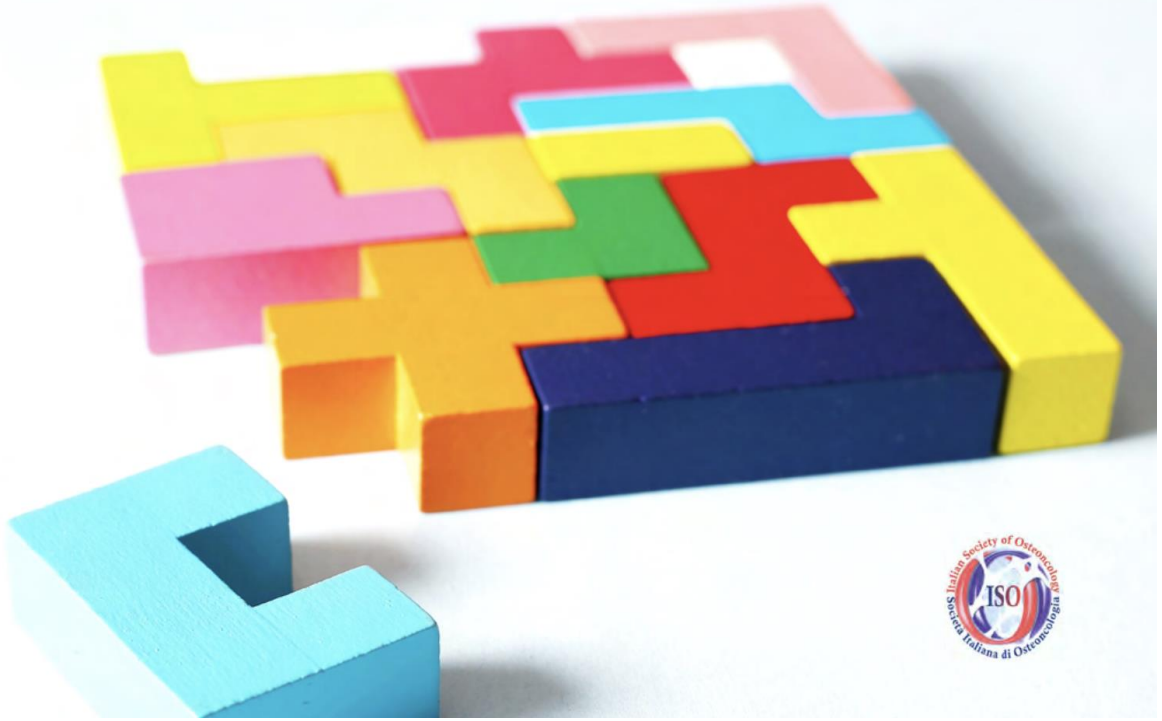
CORSO SOCIETÀ ITALIANA DI OSTEONCOLOGIA - ISO

23 APRILE 2024 ROMA ISTITUTO DI STORIA DELLA MEDICINA

QUALI STRATEGIE TERAPEUTICHE E QUALI NOVITÀ NELLA GESTIONE DELLE METASTASI OSSEE

RESPONSABILI SCIENTIFICI: **G. LANZETTA - T. IBRAHIM - D. SANTINI**

IL DOLORE DA METASTASI OSSEE UN DOLORE DIFFICILE DALLA FISIOPATOLOGIA ALLA PRATICA CLINICA: QUALI ARMI E QUALI NOVITA'?



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Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

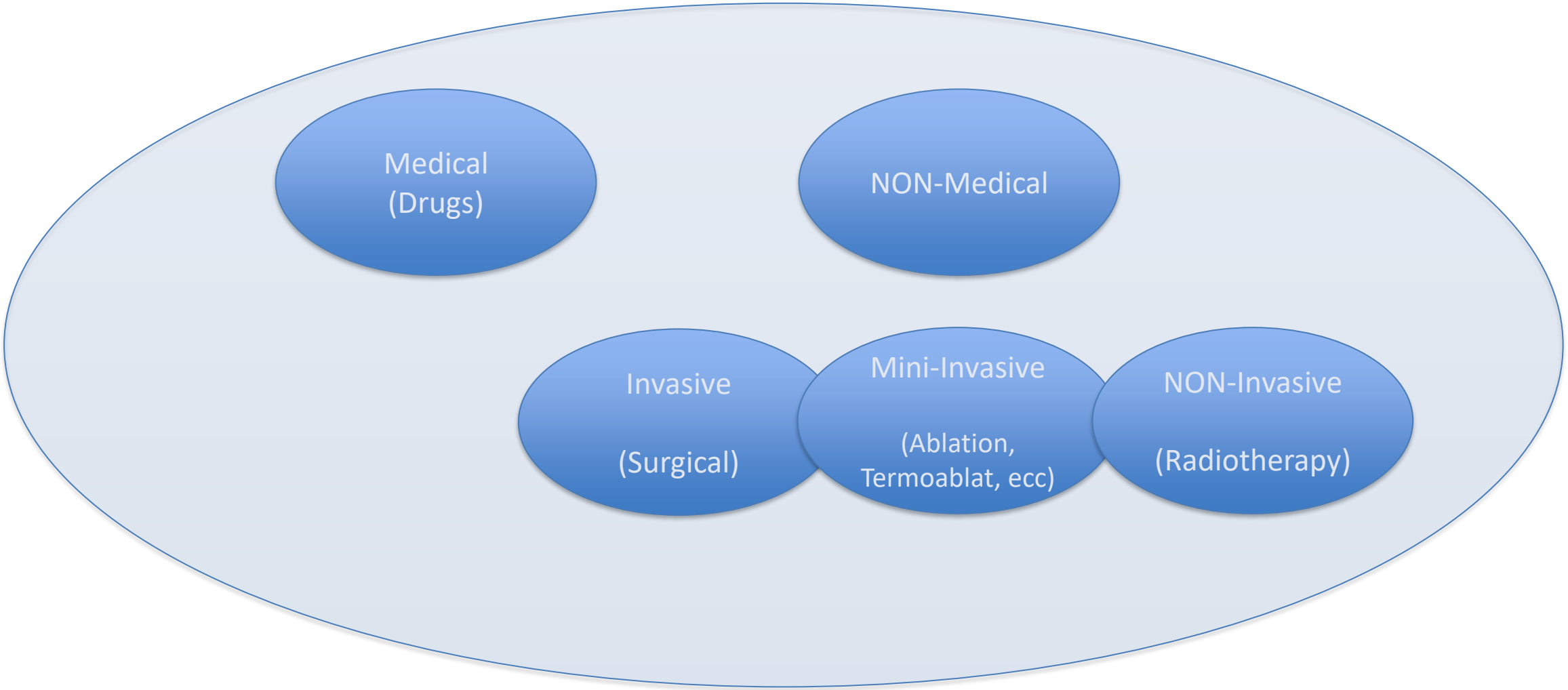
ART
Advanced Radiation Therapy

Associazione Italiana Radioterapia e Oncologia clinica

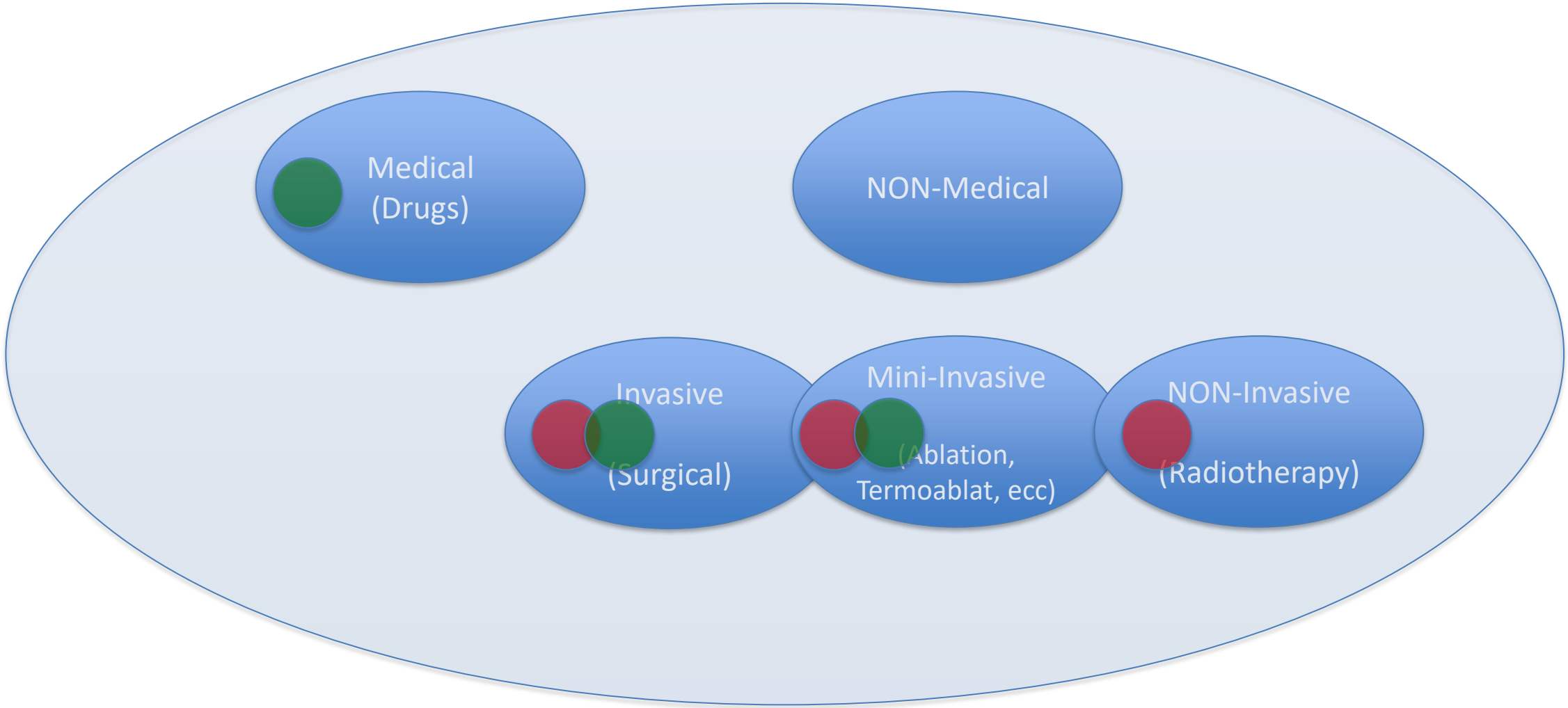
OUTLINE

- Introduction & general consideration: What is Standard? (before innovation)
- What is “Innovation” in RT for Bone Mets?
- Current widespread application of SBRT
- Final Considerations (Quick Questions on SBRT)
- Conclusions

Pain Management Therapies

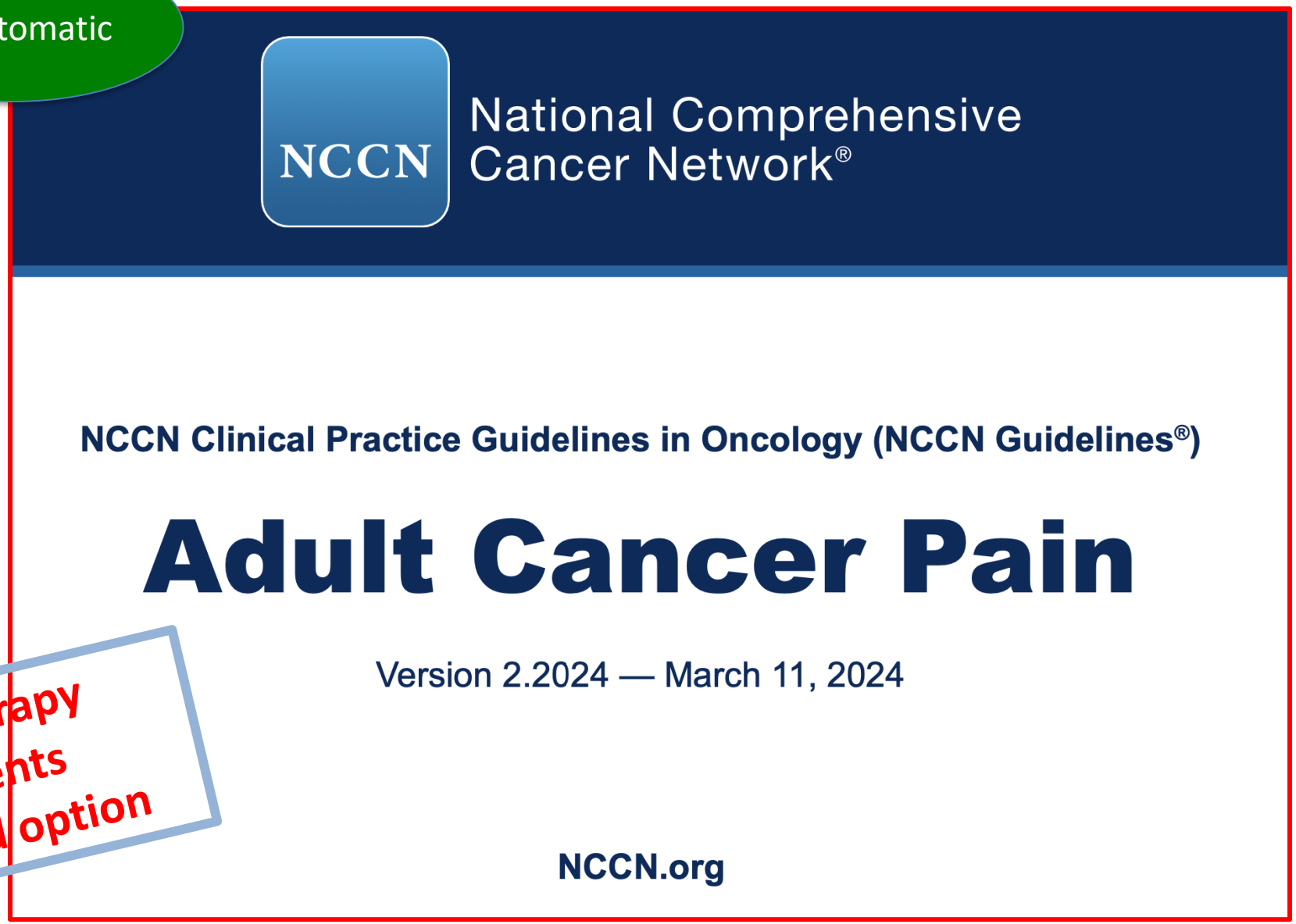


Pain Management Therapies



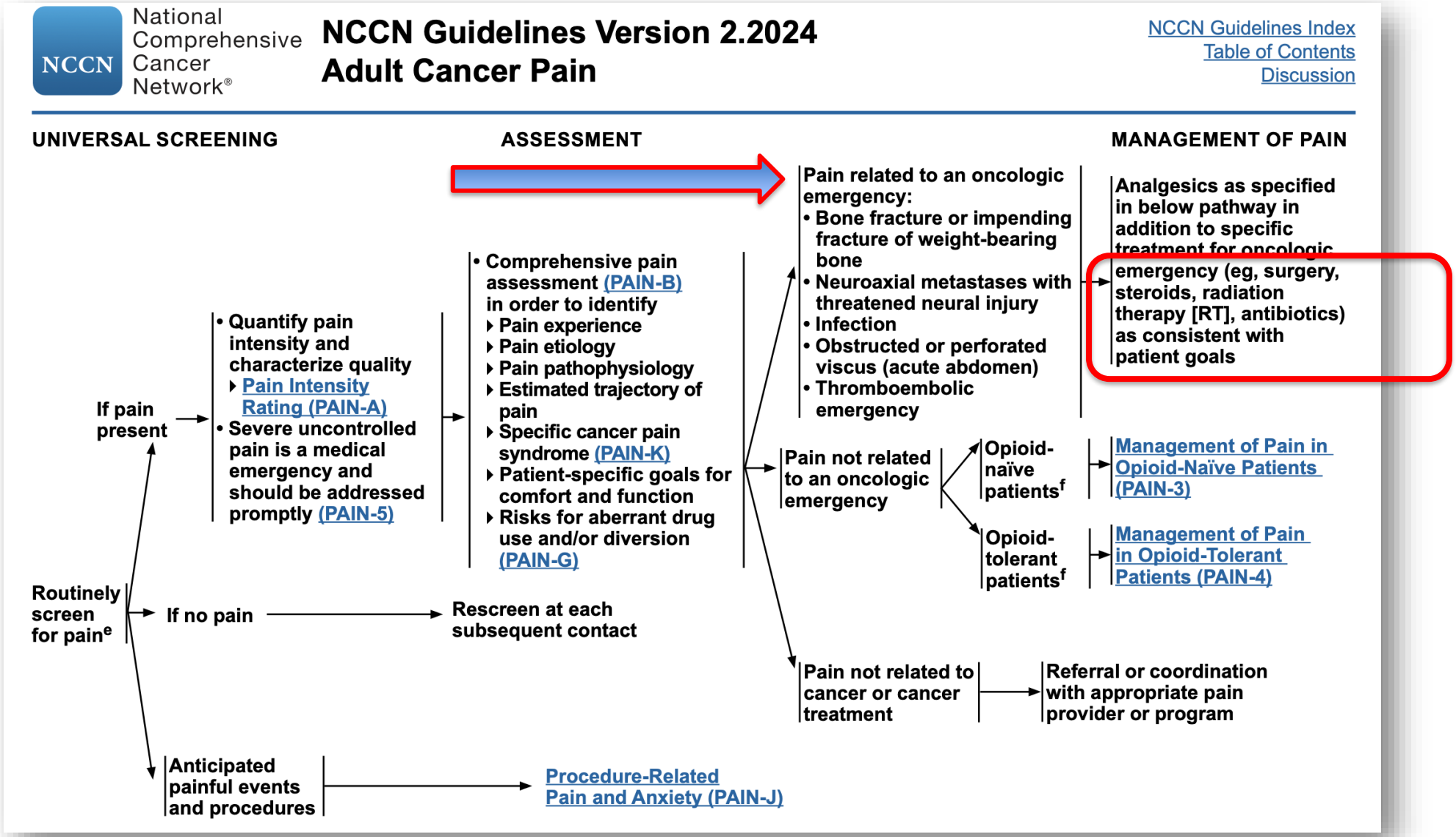
Guideline's Indication

Symptomatic



Radiotherapy represents a standard option

Guideline's Indication



Guideline's Indication

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Adult Cancer Pain

NCCN Guidelines Index
Table of Contents
Discussion

MANAGEMENT STRATEGIES FOR SPECIFIC CANCER PAIN SYNDROMES

Moderate to severe cancer pain is treated with opioids as indicated (PAIN-3 and PAIN-4); these interventions are meant to complement opioid management. Adjuvant analgesics are used depending on the pain diagnosis, comorbidities, and potential for drug interactions. Integrative interventions should also be optimized (PAIN-D).

- **Painful lesions that are likely to respond to antineoplastic therapies:**
  - **Consider trial of RT, hormones, or chemotherapy.**

- **Disease-specific pain: Refer to tumor-specific guidelines for details on palliative RT as applicable.**

- **Pain from PO mucositis:**
  - **Gabapentin PO or in liquid preparation**
  - **Local anesthetic formulations/PO care protocols**
  - **For more information on the prevention and treatment of mucositis, see**
    - **https://www.ons.org/pep/mucositis**
    - **MASCC Guidelines**
    - **ESMO Guidelines**

- **Nerve pain**
  - **Nerve compression or inflammation:**
    - **Trial of corticosteroids[a]**
    - **Optimize local disease control as appropriate; consider RT or other treatments**
  - **Neuropathic pain:**
    - **Trial of antidepressant (SNRI or TCA) (PAIN-F) and/or**
    - **Trial of anticonvulsant (PAIN-F) and/or**
    - **Consider trial of topical agent (PAIN-F)**
    - **For refractory pain, consider referral to a pain specialist and/or the use of interventional strategies (Interventional Strategies (PAIN-M)**

- **Bone pain without oncologic emergency:**
  - **NSAIDs, acetaminophen, or steroids[a]; See Non-Opioid Analgesic (Nonsteroidal Anti-Inflammatory Drugs [NSAIDs] and Acetaminophen) Prescribing (PAIN-E).**
  - **Consider bone-modifying agents (eg, bisphosphonates, denosumab[b]).**
  - **Diffuse bone pain: Consider hormonal therapy or chemotherapy, corticosteroids[a] and/or systemic administration of radioisotopes.**
  - **Local bone pain:**
    - **Consider local RT, nerve block (eg, rib pain), vertebral augmentation, or percutaneous ablation techniques.**
    - **Assess for impending fracture with plain radiographs.**
  - **Consider physical medicine evaluation. See Specialty Consultations for Improved Pain Management (PAIN-L).**
  - **Consider orthopedic consultation for stabilization, if feasible.**

Consider referral to a pain specialist or interventional therapist for interventional pain therapies including percutaneous ablation techniques for bone lesions. See Interventional Strategies (PAIN-M).

- **For severe refractory pain in the imminently dying, consider palliative sedation (NCCN Guidelines for Palliative Care).**

- **Immunotherapy-related polyarthralgias (NCCN Guidelines for Management of Immunotherapy-Related Toxicities)**

General Considerations

Associazione Italiana di Oncologia Medica

Linee guida

TERAPIA DEL DOLORE IN ONCOLOGIA

Edizione 2021

Aggiornamento ottobre 2021

In collaborazione con:

AISD

SIAARTI

SICP

SIMG

SOCIETÀ ITALIANA DI MEDICINA GENERALE E DELLE CURE PRIMARIE

3. Dolore iatrogeno in oncologia

Numerose sono le condizioni cliniche in cui una componente iatrogena può essere ipotizzata nella genesi di sindromi dolorose complesse; tra queste possono essere identificati, con intenti didattici:

- Il dolore acuto e cronico post-chirurgico;
- Il dolore acuto e cronico post-radioterapia;
- Il dolore acuto e cronico post-chemioterapia;
- Il dolore ac

adiuvante o

La radioterapia ha un buon effetto nella palliazione delle metastasi ossee dolorose, con un tasso di risposta al dolore di oltre il 60%. Tuttavia, durante o poco dopo il trattamento, in circa il 40% dei pazienti si verifica una temporanea riacutizzazione del dolore. Due studi randomizzati suggeriscono che il desametasone riduce l'incidenza di una riacutizzazione del dolore.

- Dolore da danno diretto a cute o mucose;
- Dolore da danno/irritazione a strutture nervose periferiche;
- Dolore da espansione di compartimenti ematopoietici;
- Dolore da squilibrio idro-elettrolitico o scompenso metabolico (1).

Il dolore post-chirurgico.

Il dolore post-chirurgico può essere distinto in dolore acuto (o dolore post-operatorio) e dolore cronico. Se le componenti del dolore acuto hanno un interesse minore per l'oncologo medico, in quanto di pertinenza

General Considerations

Standard RT

Overall Pain Response: 62%
Complete Pain Response: 24%

1 yy Local Control: 81%

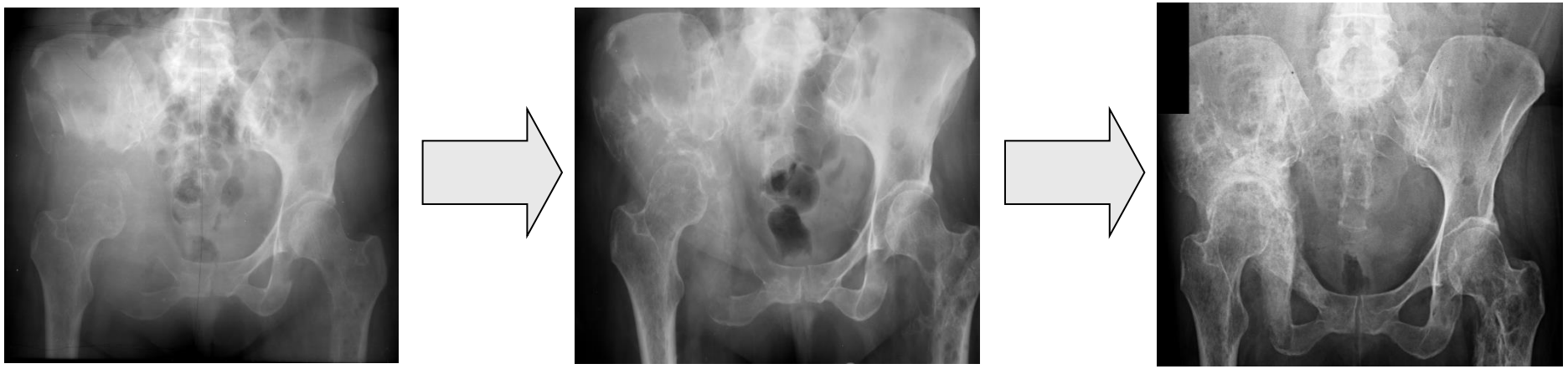
Rich et al; Radiother Oncol - 2018

Singh et al; Radiother Oncol - 2020

Palliative Radiotherapy: bone metastases

ANALGESIC ACTION
Early

STRUCTURAL ACTION
Late



Pre RT

2 months after RT

8 months after RT

Hoskin PJ, 1988

Radioterapy and Palliative Treatments: Timing

Original Article

Palliative Radiotherapy for Bone Metastases in the Last 3 Months of Life: Worthwhile or Futile?

K. Dennis, K. Wong, L. Zhang, S. Culleton, J. Nguyen, L. Holden, F. Jon, M. Tsao, C. Danjoux, E. Barnes, A. Sahgal, L. Zeng, K. Koo, E. Chow

Rapid Response Radiotherapy Program, Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

Radiotherapy represents a Palliative Care for Pain Management

"Despite limited lifespan, patients reported pain relief after palliative radiotherapy.

Patients with an estimated survival of 3 months should still be considered for palliative radiotherapy"

Pain response rates to radiotherapy for the study populations of the Edmonton Symptom Assessment System (ESAS), Brief Pain Inventory (BPI) and combined cohorts

Follow-up time point	Response	ESAS			BPI			Combined		
		n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
1 month	Responder	37	64.9	51–77	25	78.1	60–91	62	69.7	59–79
	Complete response	3	5.3	1–15	0			3	3.4	1–10
	Partial response	34	59.7	46–72	25	78.1	60–91	59	66.3	56–76
	Non-responder	20	35.1	23–49	7	21.9	9–40	27	30.3	21–41
2 months	Responder	7	53.9	25–81	5	83.3	36–99	12	63.2	38–84
	Complete response	0			0			0		
	Partial response	7	53.9	25–81	5	83.3	36–99	12	63.2	38–83
	Non-responder	6	46.2	19–75	1	16.7	0–64	7	36.8	16–62

Dennis 2011 Clin Oncol

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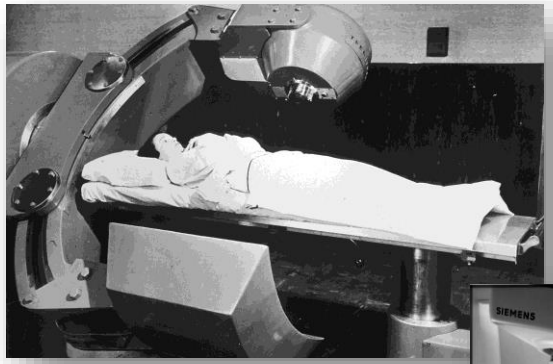
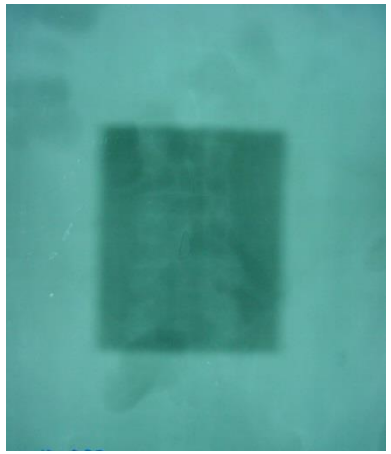
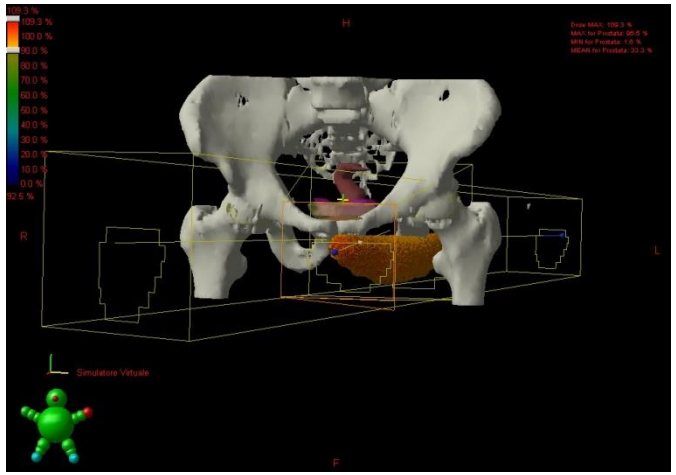
Palliative Radiotherapy: bone metastases

2DRT



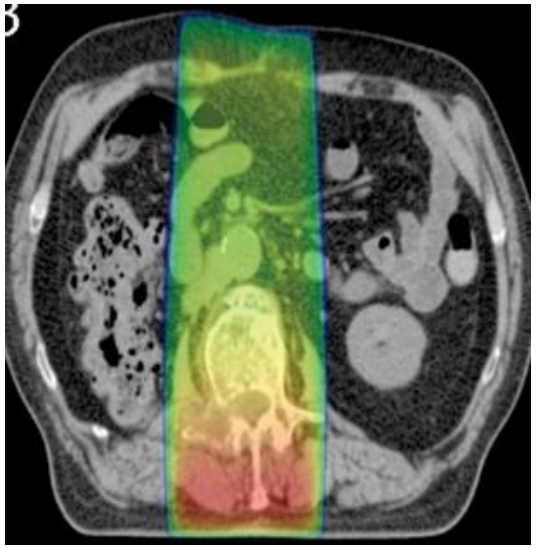


3DRT

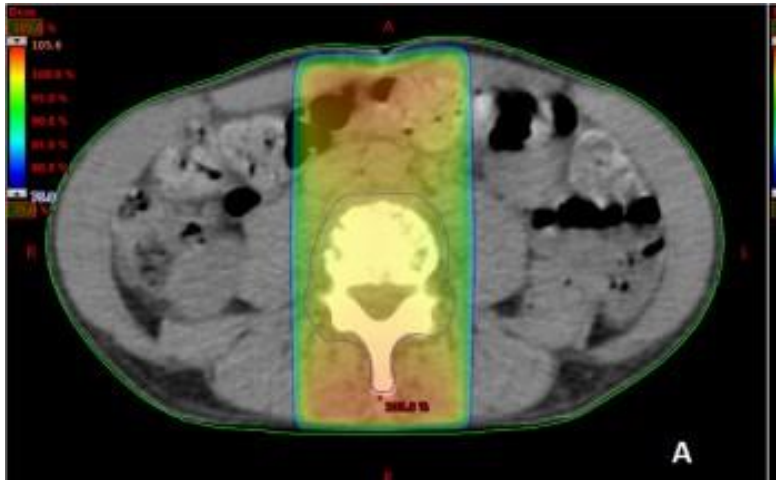


SRBT

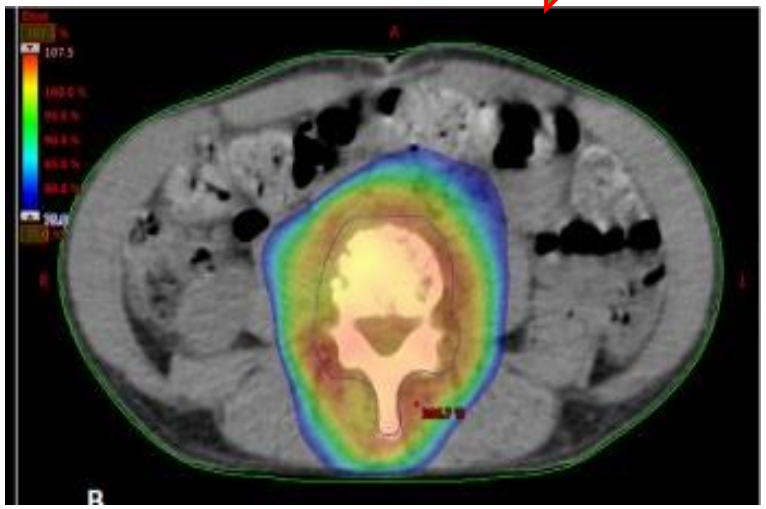
“Innovation” in RT for Bone Mets
Technical Evolution



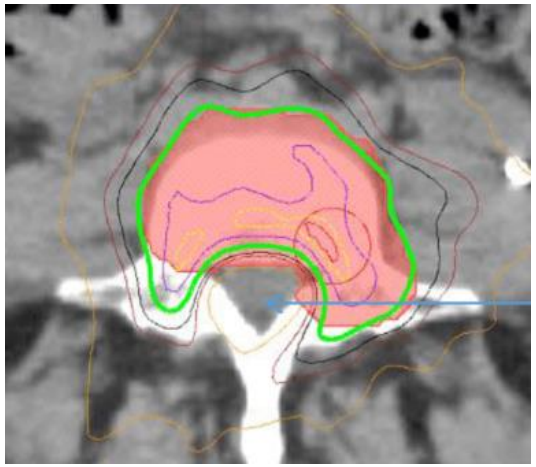
2D-RT: fascio unico posteriore



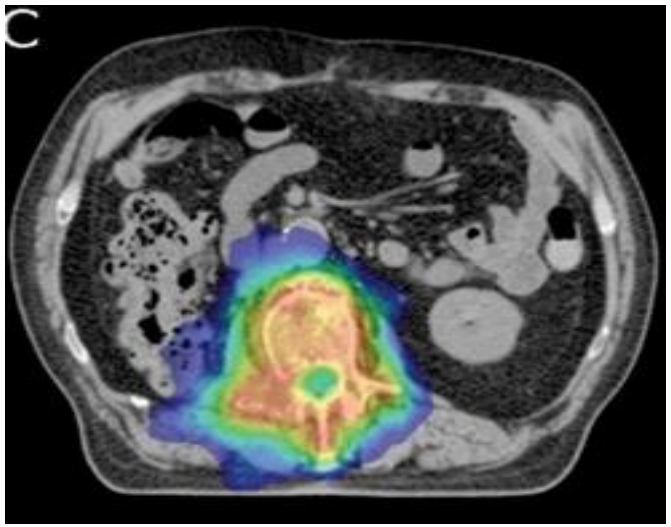
3D-CRT: due fasci contrapposti



IMRT

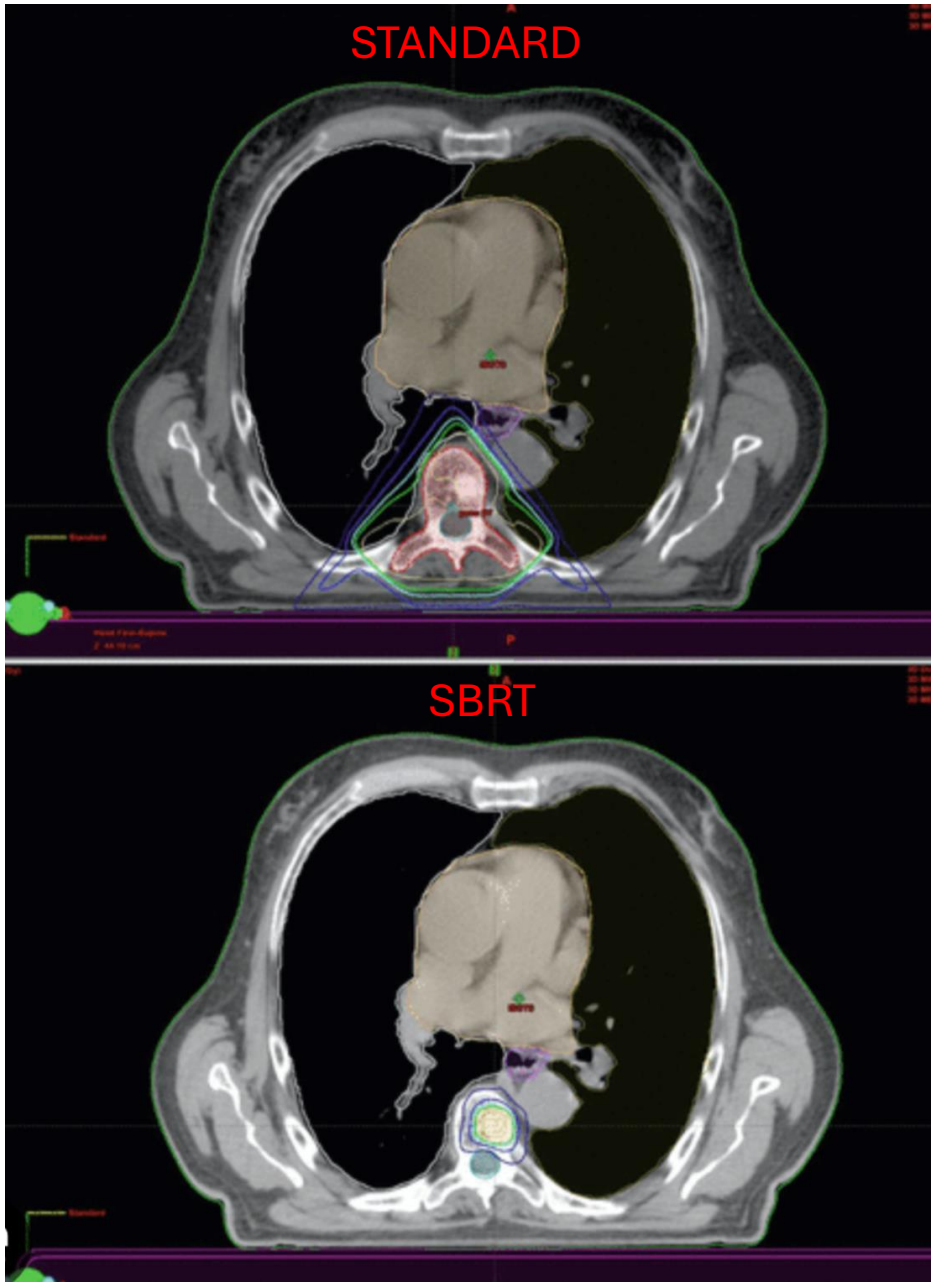


SBRT



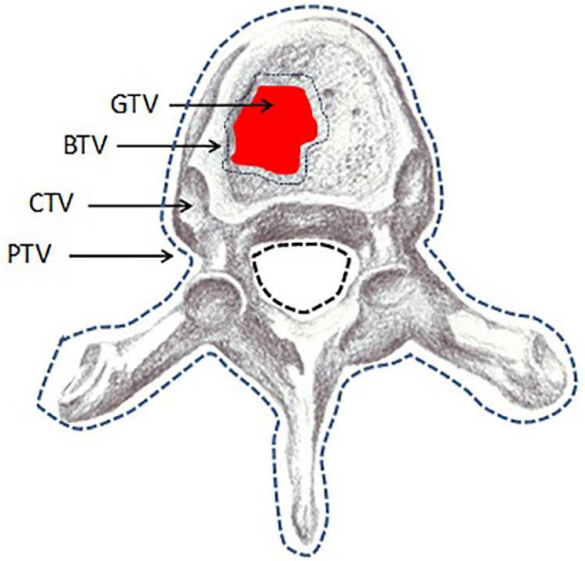
VMAT

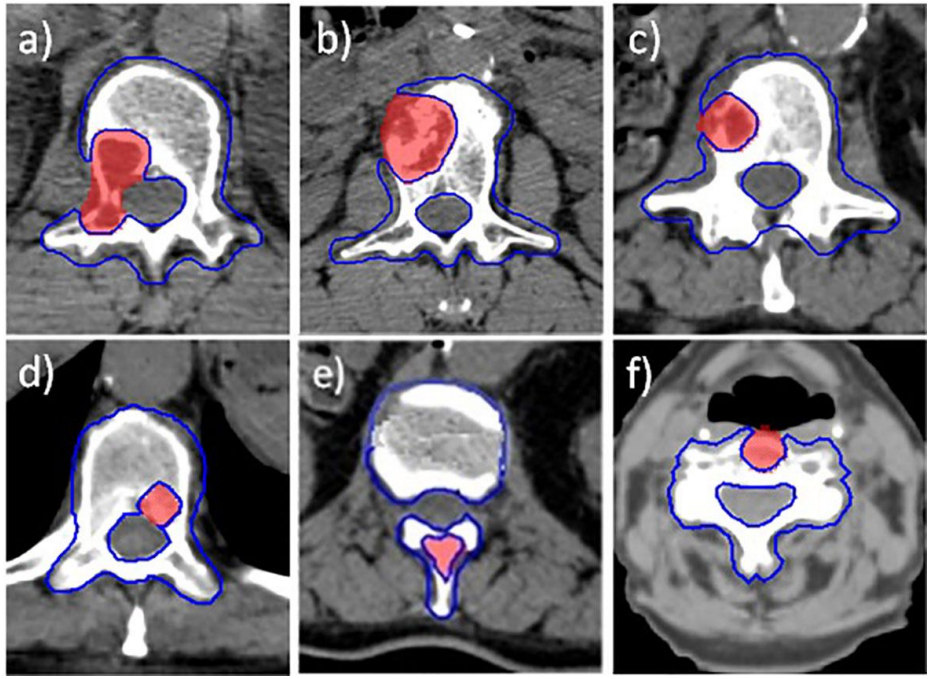
“Innovation” in RT for Bone Mets

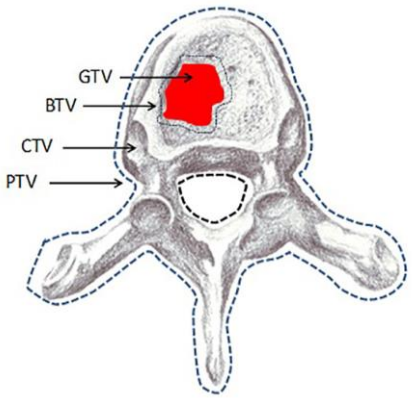


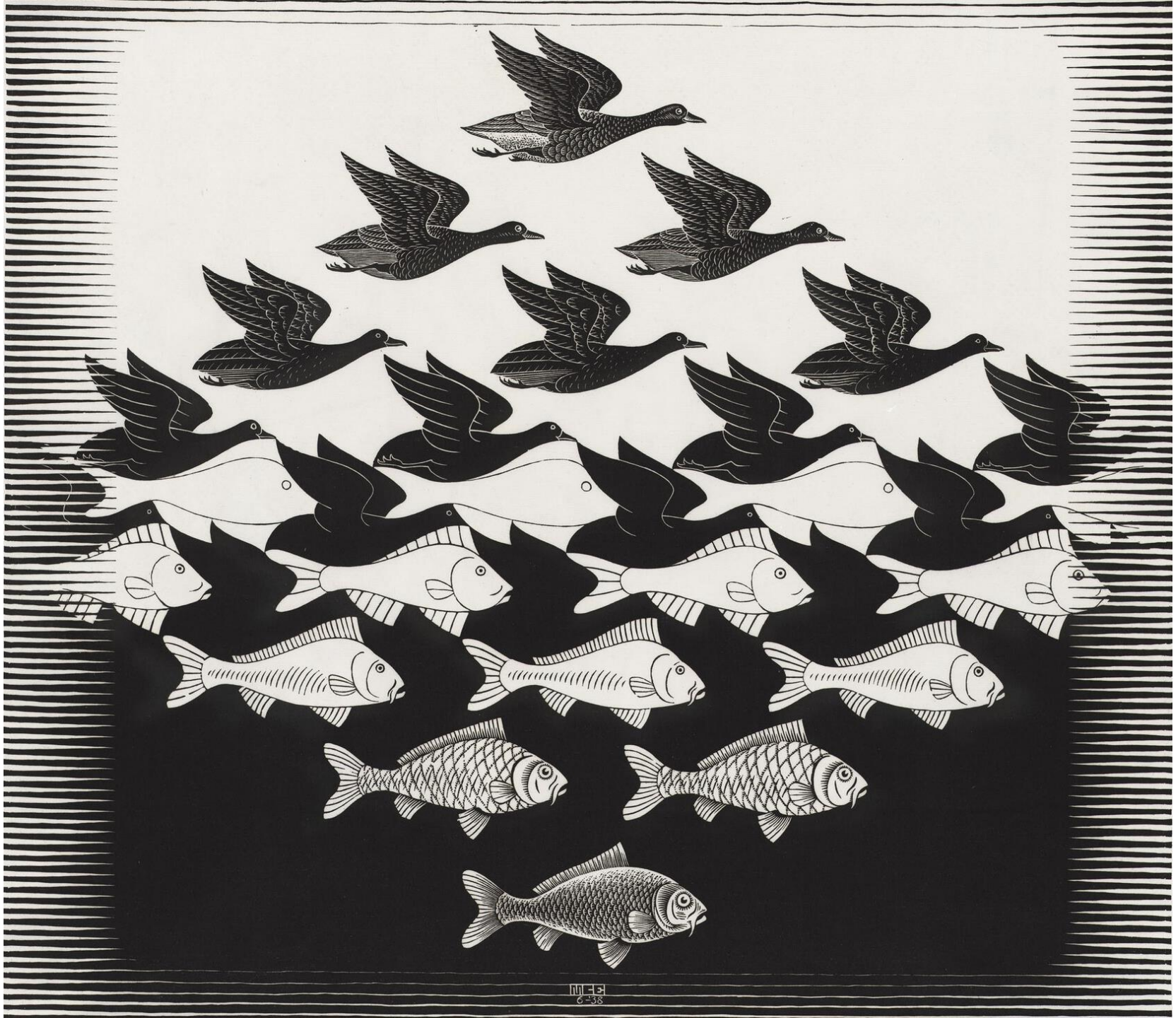
- SBRT can focus higher doses on smaller volumes
- Higher precision

- Innovative Perspective

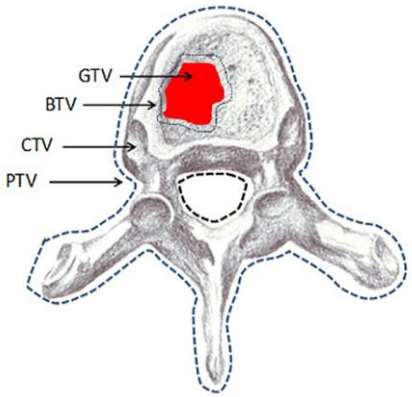


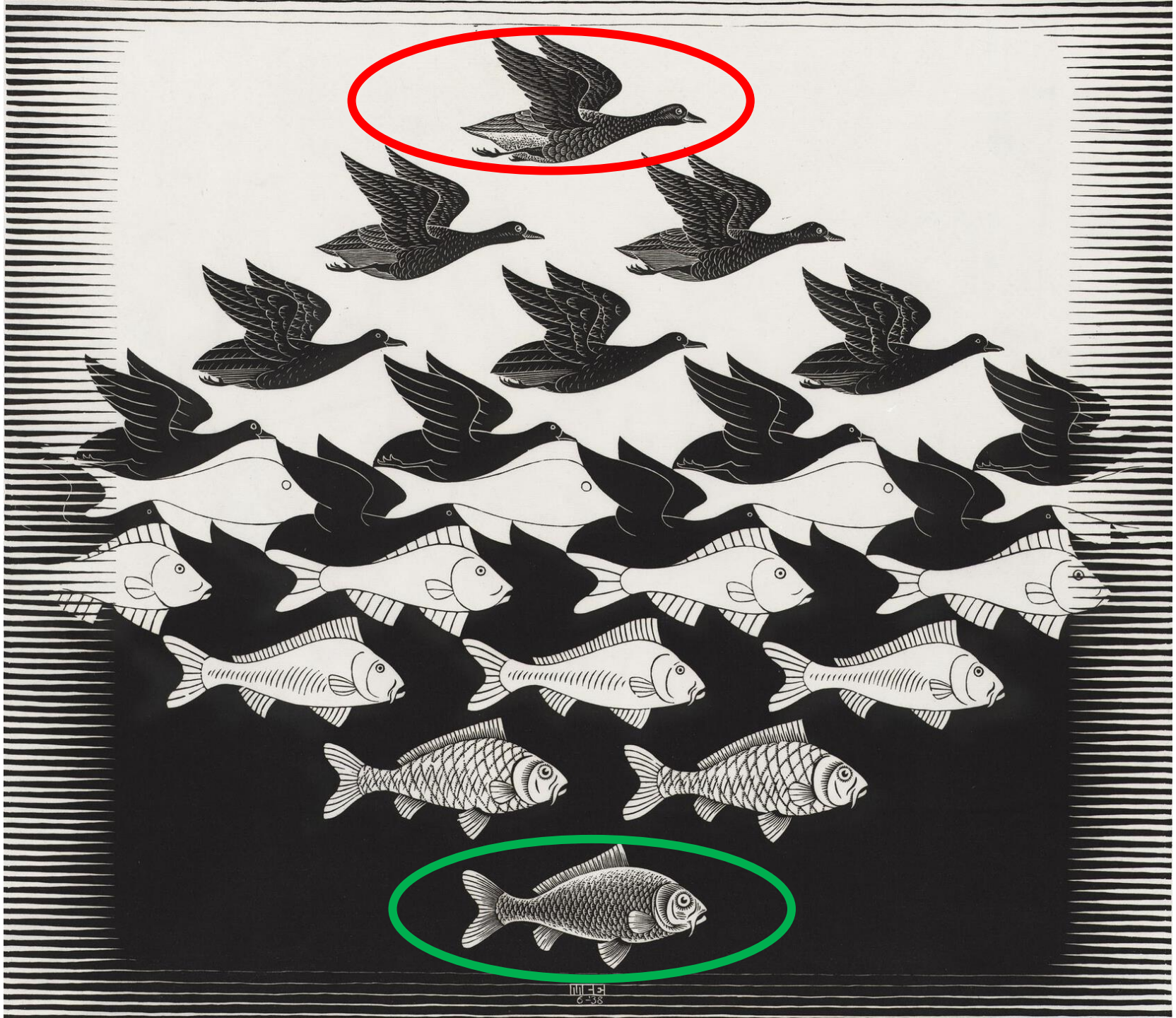


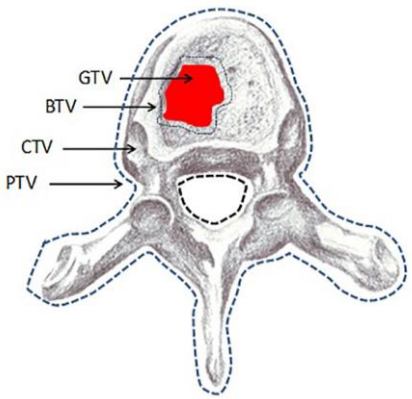




Escher Cielo e acqua 1938


GTV
BTV
CTV
PTV

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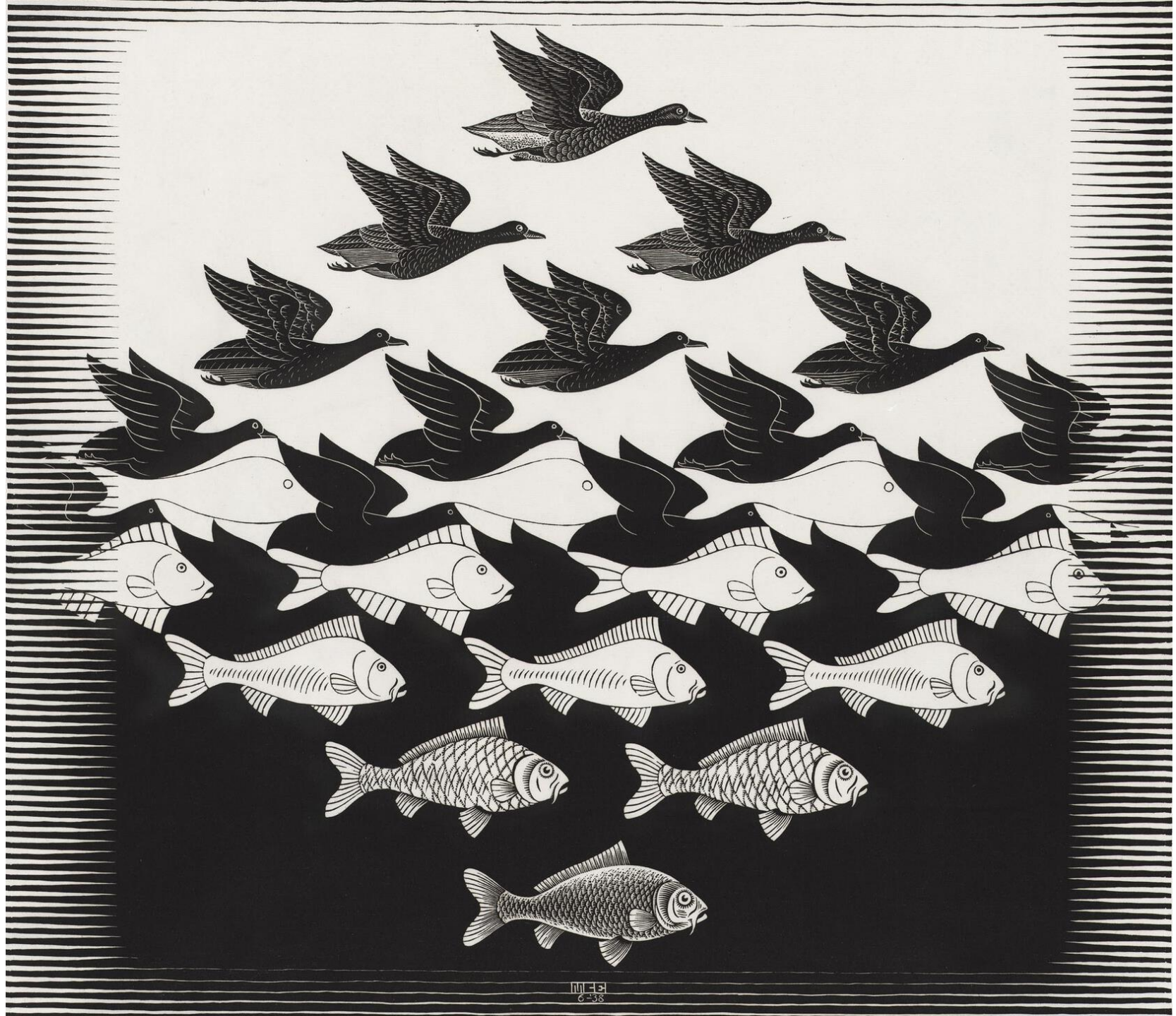

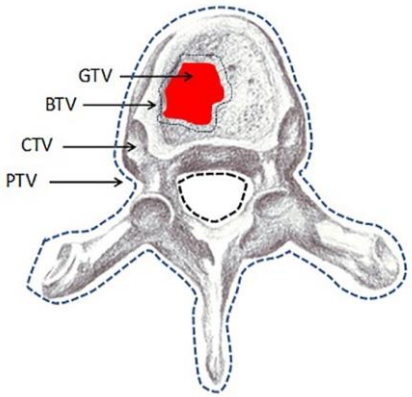
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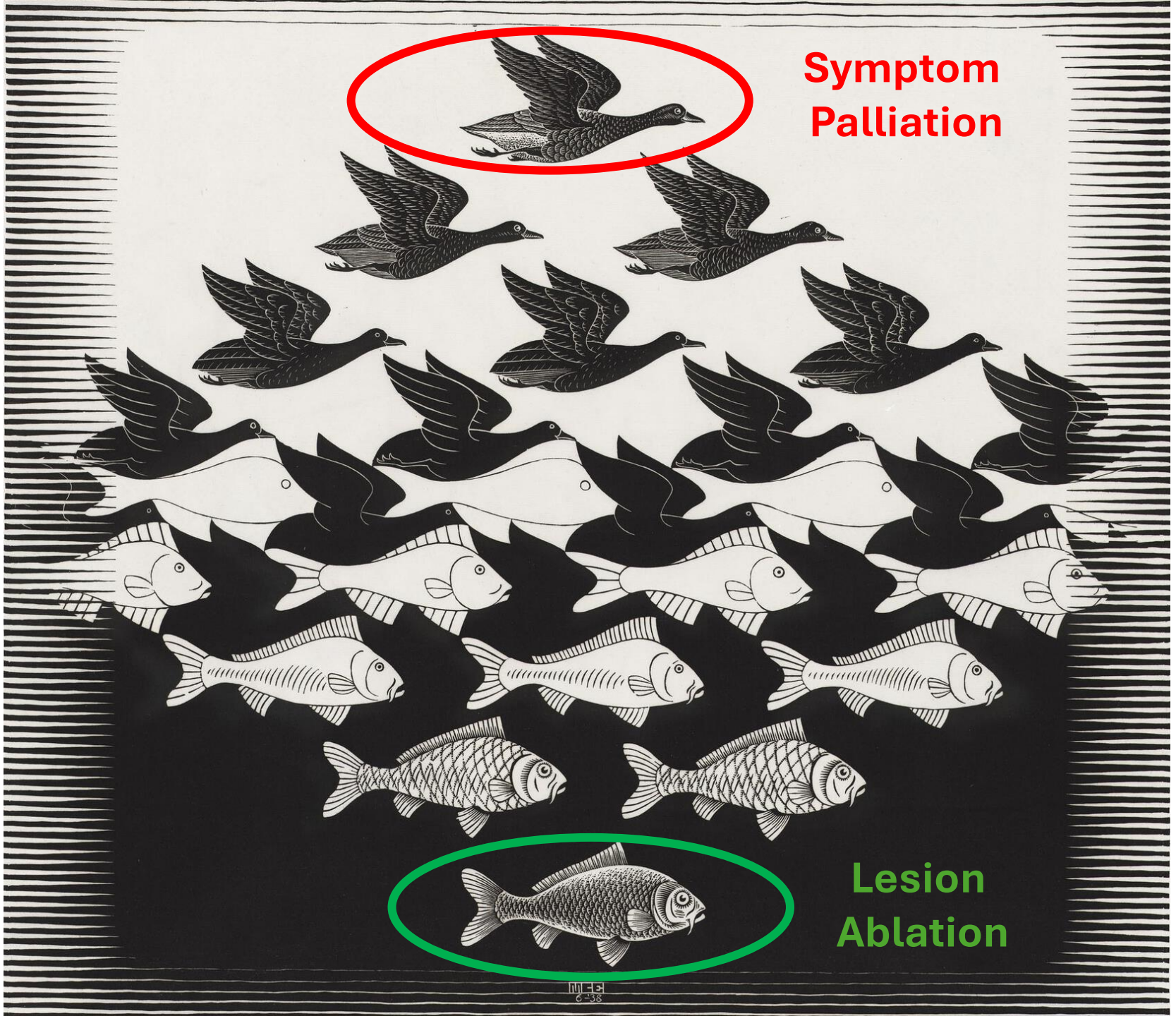
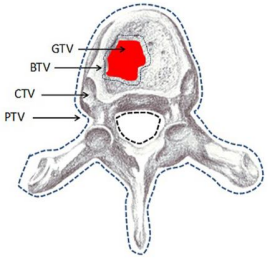

Symptom
Palliation
Lesion
Ablation

"Innovation" in RT for Bone Mets
Ablative SBRT



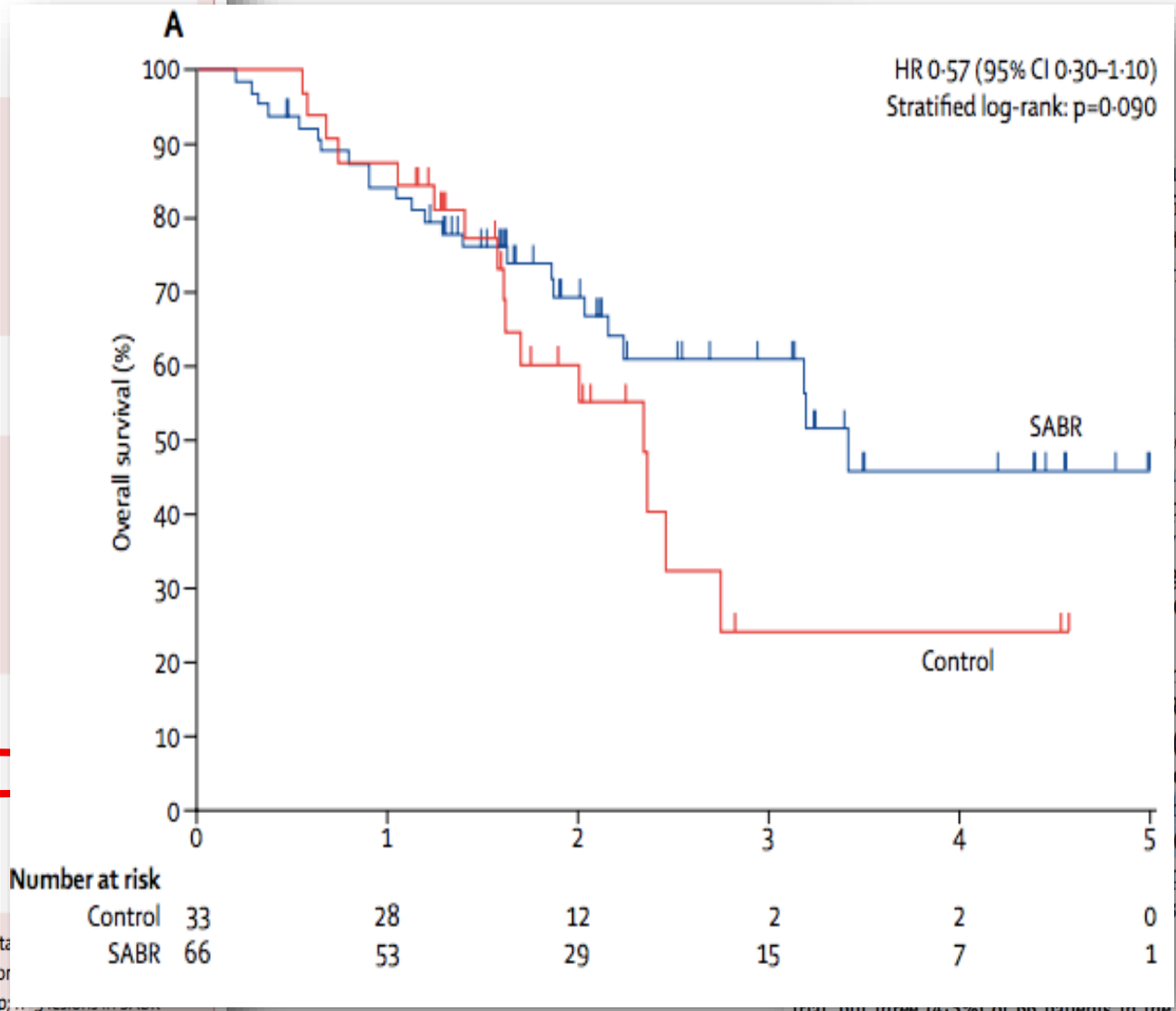
Ste
pal
(SA

David A
George
Mitchel

	Control group (n=33)	SABR group (n=66)
Age	69 (64–75)	67 (59–74)
Sex		
Men	19 (58%)	
Women	14 (42%)	
Site of original primary tumour		
Breast	5 (15%)	
Colorectal	9 (27%)	
Lung	6 (18%)	
Prostate	2 (6 %)	
Other	11 (33%)	
Time from diagnosis of primary tumour to randomisation (years)	2·3 (1·3–4·5)	
Number of metastases		
1	12 (36 %)	
2	13 (40%)	
3	6 (18%)	
4	2 (6%)	
5	0 (0%)	
Location of metastases		
Adrenal	2/64 (3%)	
Bone	20/64 (31%)	
Liver	3/64 (5%)	
Lung	34/64 (53%)	
Other*	5/64 (8%)	

Data are n (%), n/N (%), or median (IQR). SABR=stereota
radiotherapy. *Other comprises brain (n=3 lesions in cor
SABR group), lymph nodes (n=1 lesion in control group;
group), and para-renal (n=1 lesion in control group).

Table 1: Baseline characteristics



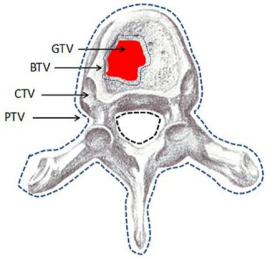
ggests that some patients with a limited number of metastases might be
rom randomised controlled trials to support this paradigm is scarce. We
tive radiotherapy (SABR) on survival, oncological outcomes, toxicity, and
imary tumour and one to five oligometastatic lesions.

2 study was done at 10 hospitals in Canada, the Netherlands, Scotland,
a controlled primary tumour and one to five metastatic lesions, Eastern
a life expectancy of at least 6 months were eligible. After stratifying by the
omly assigned patients (1:2) to receive either palliative standard of care
rd of care plus SABR to all metastatic lesions (SABR group), using a
ermuted blocks of nine. Neither patients nor physicians were masked to
as overall survival. We used a randomised phase 2 screening design with
nates a positive trial). All analyses were intention to treat. This study is
CT01446744.

n Feb 10, 2012, and Aug 30, 2016. Of 99 patients, 33 (33%) were assigned to
group. Two (3%) patients in the SABR group did not receive allocated
(6%) patients in the control group also withdrew from the trial. Median
ontrol group versus 26 months (23–37) in the SABR group. Median overall
e control group versus 41 months (26–not reached) in the SABR group
0). Adverse events of grade 2 or worse occurred in three (9%) of 33 controls
(p=0·026), an absolute increase of 20% (95% CI 5–34). Treatment-related
after SABR, compared with none in the control group.

improvement in overall survival, meeting the primary endpoint of this
trial, but three (4·5%) of 66 patients in the SABR group had treatment-related death. Phase 3 trials are needed to
conclusively show an overall survival benefit, and to determine the maximum number of metastatic lesions wherein
SABR provides a benefit.

"Innovation" in RT for Bone Mets
Palliative SBRT



Standard RT

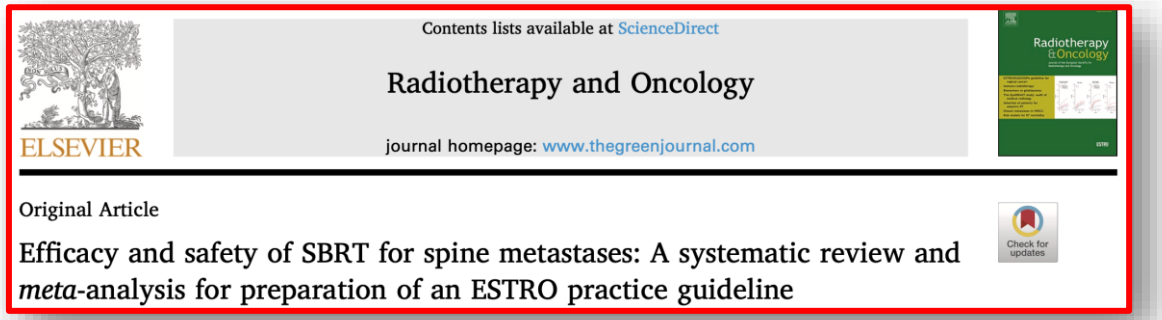
Overall Pain Response: 62%
Complete Pain Response: 24%

1 yy Local Control: 81%

SBRT

Overall Pain Response: 83%
Complete Pain Response: 36%

1 yy Local Control: 94%


Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Original Article

Efficacy and safety of SBRT for spine metastases: A systematic review and *meta*-analysis for preparation of an ESTRO practice guideline

Rich et al; Radiother Oncol - 2018

Guninski et al; Radiother Oncol - 2024

Singh et al; Radiother Oncol - 2020

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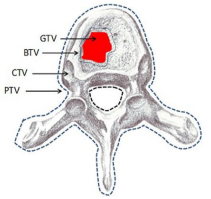
Current widespread application of SBRT

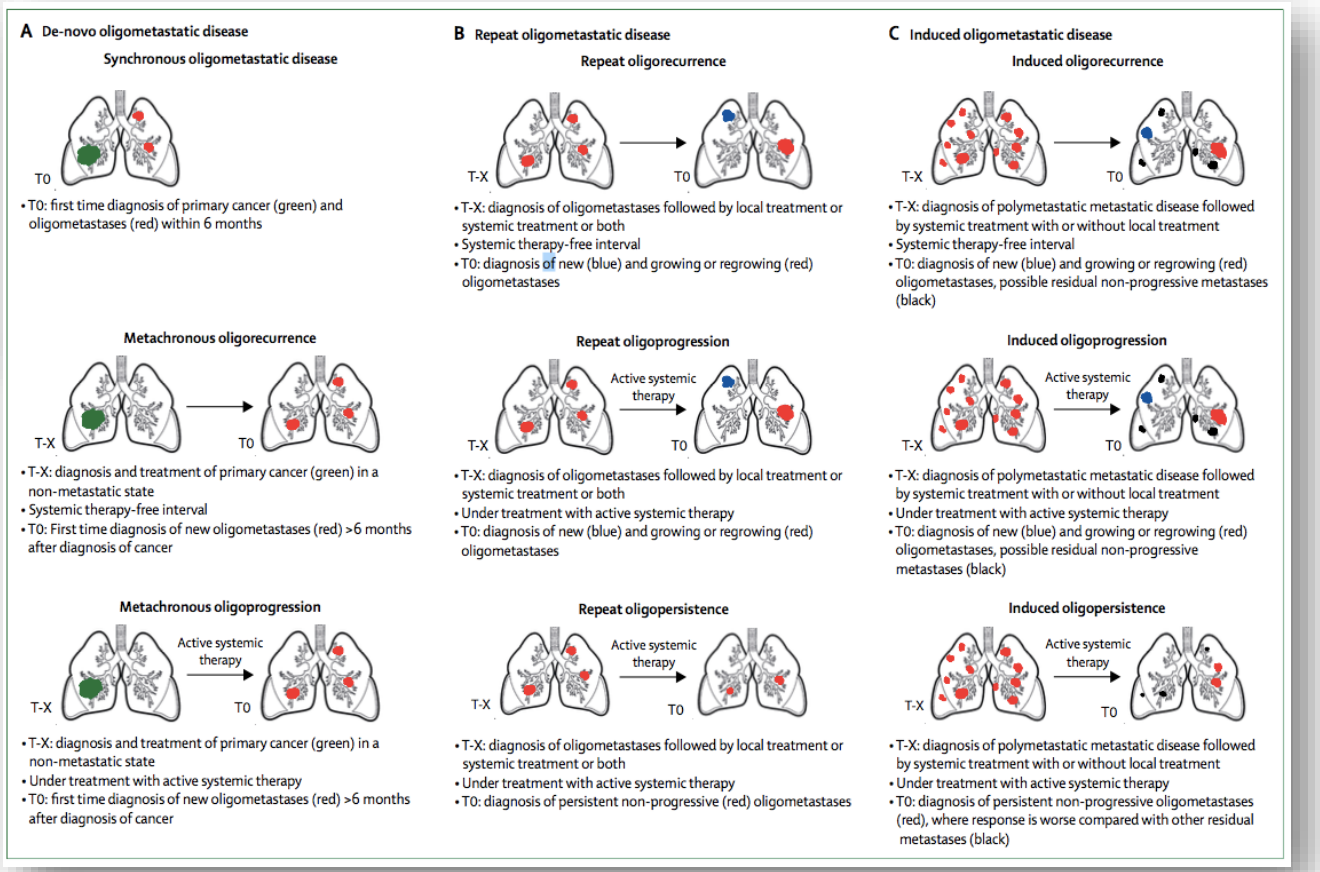
ABLATIVE



Review

Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

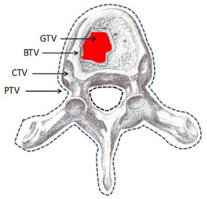
Matthias Guckenberger, Yolande Lievens, Angelique B Bouma, Laurence Collette, Andre Dekker, Nandita M deSouza, Anne-Marie C Dingemans, Beatrice Fournier, Coen Hurkmans, Frédéric E Lecouvet, Icro Meattini, Alejandra Méndez Romero, Umberto Ricardi, Nicola S Russell, Daniel H Schanne, Marta Scorsetti, Bertrand Tombal, Dirk Verellen, Christine Verfaillie, Piet Ost



Guckenberger et al; Lancet Oncol - 2020

Current widespread application of SBRT

PALLIATIVE



METASTASI OSSEE E SALUTE DELL'OSSO

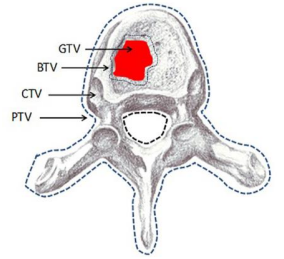
LINEE GUIDA 2021

6.8. Il paziente con metastasi ossee può beneficiare anche delle tecniche di Radiochirurgia e Radioterapia Stereotassica?

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
BASSA	Per pazienti, sintomatici, a buona prognosi con coinvolgimento del rachide, l'impiego di moderne tecnologie radioterapiche dovrebbe essere preso in considerazione preferibilmente all'interno di studi clinici, oppure per casi selezionati, applicando l'approccio riportato da Shagal et al., preferibilmente in Centri ad alto volume per SBRT IGRT.	**Positiva Debole**

AIOM; Linee Guida Metastasi Ossee e Salute Osso – 2021, 2022, 2023

Current widespread application of SBRT



Potential Limits to widespread SBRT application (particularly for Palliative Intent)

- Still not univocal evidences
- Relatively few single randomized trials evidences (efficacy by Meta-analises)
- Complexity in term of: Clinical Presentations + Hystologies + Anatomical Sites
- Focal investigation about reccommended dose

Current widespread application of SBRT

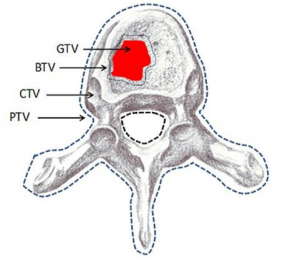
Clinical Presentations:

- Oligometastatic Asymptomatic
- Oligometastatic Symptomatic
- Multiple Metastatic (Bone ± Visceral) Symptomatic
- (Multiple Metastatic Asymptomatic)

Metastasis Presentations
(type, stability, compression, “extra-bone”, etc…):

- Spinal (cervical, C1-C2) 
- Non-Spinal (Sacral, Pelvic, Long bone) 

Current widespread application of SBRT



Stereotactic body radiotherapy for painful spinal metastases

We would like to congratulate Arjun Sahgal and colleagues[1] on the excellent trial they have presented. The relevant results and innovative approach make their work a cornerstone in current radiotherapy. However, we would like to direct the

Discussion, other randomised trials did not show significant results in term of pain relief.[2-4] The associated biological equivalent dose (appendix) might hold a key role for the interpretation of this discrepancy, but the issue remains open. In other words, why is a schedule of 12 Gy in two daily fractions (biological equivalent dose: 52·8 Gy) effective, whereas a schedule of a single 18 Gy dose (biological equivalent dose: 50·4 Gy)[3,4] or of a single 24 Gy dose

the inclusion criteria and treatment conditions of the presented trial are followed. However, we believe that it is still too early to replace conventional palliative schedules with stereotactic body radiotherapy for the investigated clinical presentation.

We declare no competing interests.

*Francesco Cellini, Stefania Manfrida, Maria Antonietta Gambacorta, Vincenzo Valentini

Author/Protocol	N° of Fractions	Total Dose	Dose per Fraction	BED10	Symptom Relief Statistical Significance
Sprave et al[2]	1	24	24	81,6	Not significant
Ryu et al /RTOG 0631[4]	1	18	18	50,4	Not significant
Pielkenrood et al/VERTICAL[3]	1	18	18	50,4	Not significant
Pielkenrood et al/VERTICAL[3]	3	30	10	60	Not significant
Pielkenrood et al/VERTICAL[3]	5	35	7	59.5	Not significant
Shagal et al[1]	**2**	**24**	**12**	**52,8**	**Significant**
Cellini et al/PREST[5]	3	30/21 (SIB GTV/vertebra)	10/7 (SIB GTV/vertebra)	60 /35,7 (SIB GTV/vertebra)	Ongoing study

(Abbreviations: N°= number; BED_{10}= Biological Equivalent Dose; SIB= Simultaneous Integrated boost

- ✓ The workflow to select the best treatment for each presentation needs to be further refined
- ✓ The biological equivalent dose (BED) associated to different schedules applied might hold a key role for the interpretation of this discrepancy
- ✓ Delineation is not yet unanimously agreed on by clinicians and could affect realword practice
- ✓ We believe that it is still too early to replace conventional palliative schedules with SBRT

Cellini, Manfrida, Gambacorta, Valentini; Lancet Oncol 2021; 22
van der Velden, van der Linden; Lancet Oncol 2021; 22
Shagal et al.; Lancet Oncol 2021; 22: 1023–33

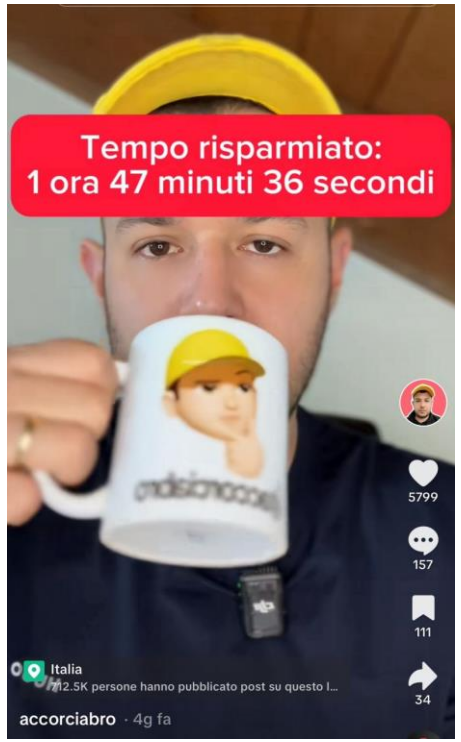
OUTLINE

- Introduction & general consideration: What is Standard? (before innovation)
- What is “Innovation” in RT for Bone Mets?
- Current widespread application of SBRT
- Final Considerations (Quick Questions on SBRT)
- Conclusions

Final Considerations (Quick Questions on SBRT)

1. Does SBRT represents the future of (RT) Management for Bone Mets (Oligo/Multiple)?
2. How Radiation Oncologist frame main presentations, for Bone Mets, aiming SBRT ?
3. What is the gold reference imaging for SBRT relatively to Bone Mets?
4. How Radiation Oncologist evaluate symtom response ?
5. What advantage can SBRT represent for Medical Oncology ?

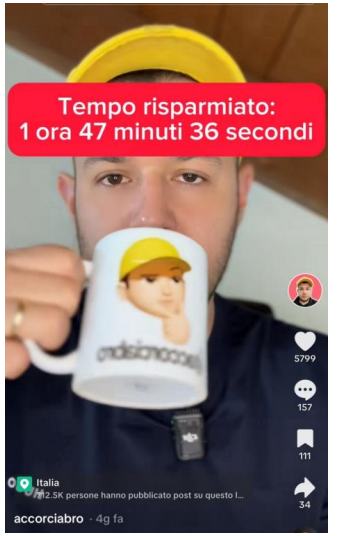
Accorciabro ‘s approach…….



Final Considerations (Quick Questions on SBRT)

1. Does SBRT represents the future of (RT) Management for Bone Mets (Oligo/Multiple)?

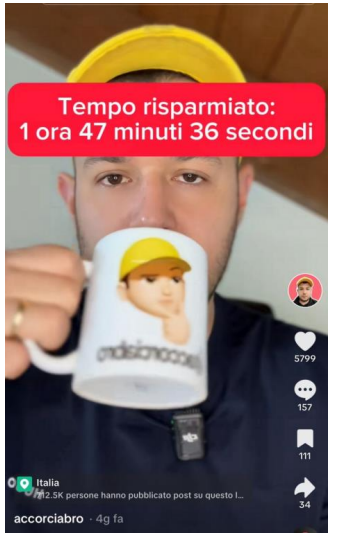
Yes, definitely



Final Considerations (Quick Questions on SBRT)

2. How Radiation Oncologist frame main presentations, for Bone Mets, aiming SBRT ?

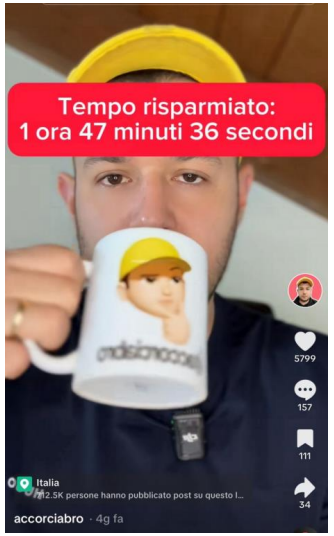
- Emergency (Spinal Cord Compression, Max 48 hour to manage patient)
- Non-Complicated versus Complicated (extracompartimental; Spinal Canal+)
- Oligometastatic versus Multiple Metastatic
- Spinal versus Non-Spinal (if ‘Spinal’: C1-2 ; Lower than L3)
- Symptomatic versus Asimptomatic



Final Considerations (Quick Questions on SBRT)

3. What is the gold reference imaging for SBRT relatively to Bone Mets?

- MRI (no contrast strictly needed)



Final Considerations (Quick Questions on SBRT)

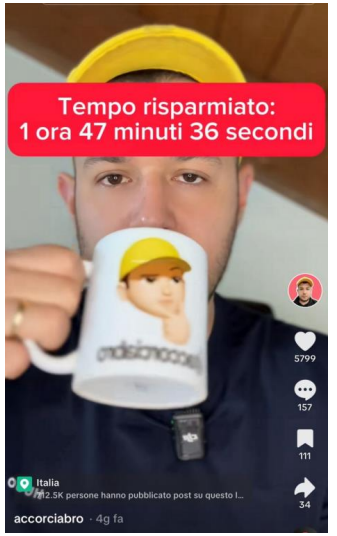
4. How Radiation Oncologist evaluate symtom response ?

- ‘Chow’s criteria, 2012’

Table 1. Response categories

Term	Definition
Complete response	A pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent [OMED])
Partial response	Pain reduction of 2 or more at the treated site on a scale of 0 to 10 scale without analgesic increase, or Analgesic reduction of 25% or more from baseline without an increase in pain.
Pain progression	Increase in pain score of 2 or more above baseline at the treated site with stable OMED, or An increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline
Indeterminate response*	Any response that is not captured by the complete response, partial response, or pain progression definitions

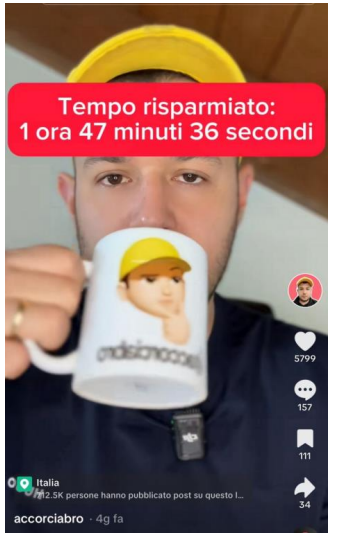
Chow et al, IJROBP; 82,5,1730; 2012



Final Considerations (Quick Questions on SBRT)

5. What advantage can SBRT represent for Medical Oncology ?

- Can be more easily embriched with systemic therapy (it is shorter, no additonal toxicity)
- Enables easier retreatment
- Theorically/Research: Abscopal Effects



Conclusions

- RT is one of the standard management option for Bone metastases
- Currently and in future: for both Symptomatic and Asymptomatic (Oligo-) Presentations
- RT is a palliative antalgic solution and can be offered beyond the “active” management
- Innovative, SBRT gains both Palliative and Ablative Effect
- Clinical Trials on SBRT aim to optimal dose finding, and delineation details