SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Ortopedico Rizzoli di Bologna
Istituto di Ricovero e Cura a Carattere Scientifico

L'Osteoncologia nel 2024

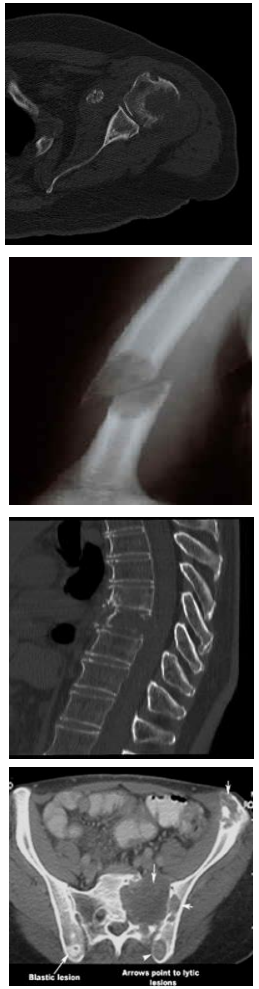
Toni Ibrahim BSc, MSc, MD, PhD

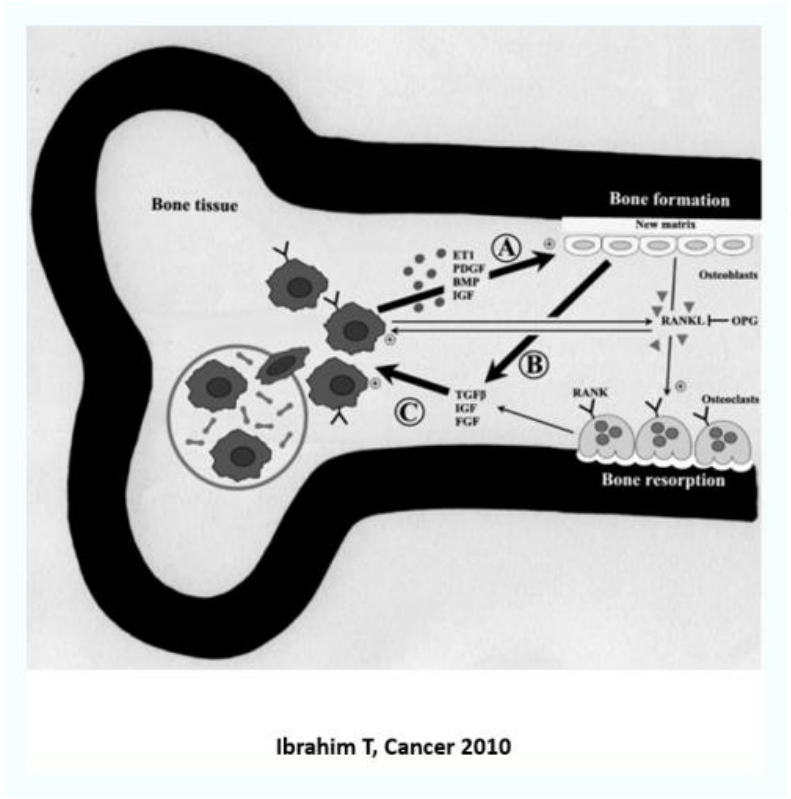
Direttore SC Osteoncologia, Sarcomi dell'Osso e dei Tessuti molli e Terapie innovative (OSOTT)
Coordinatore percorsi, Reti e Ricerca Oncologica IOR (CRRO)

IRCCS- Istituto Ortopedico Rizzoli, Bologna

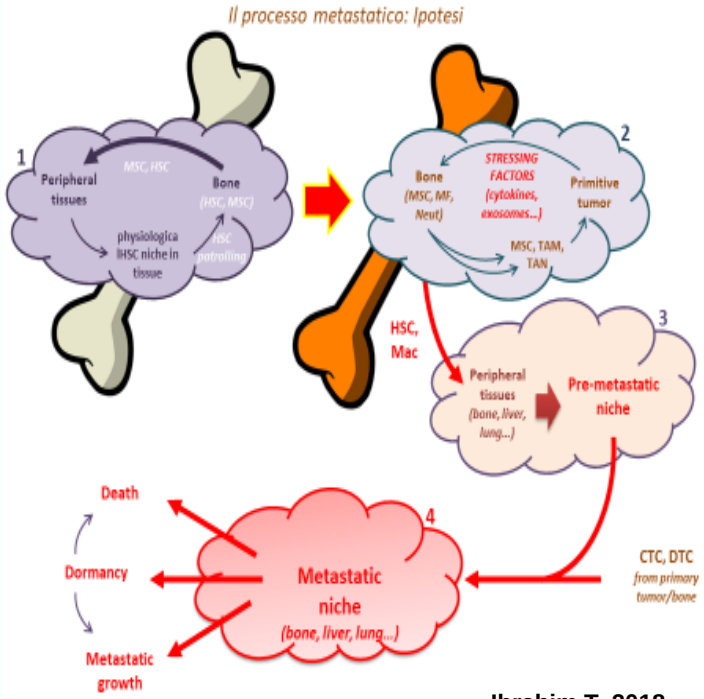
Roma, 23/04/2024

The Osteoncology





Ibrahim T, Cancer 2010



Ibrahim T, 2018

2000 — 2010 — 2024

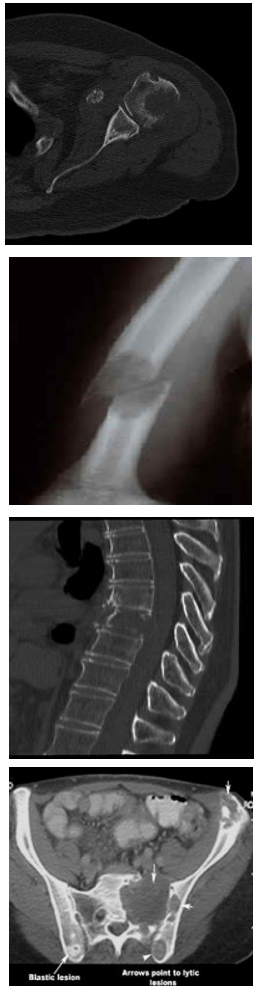
Clinical needs M1

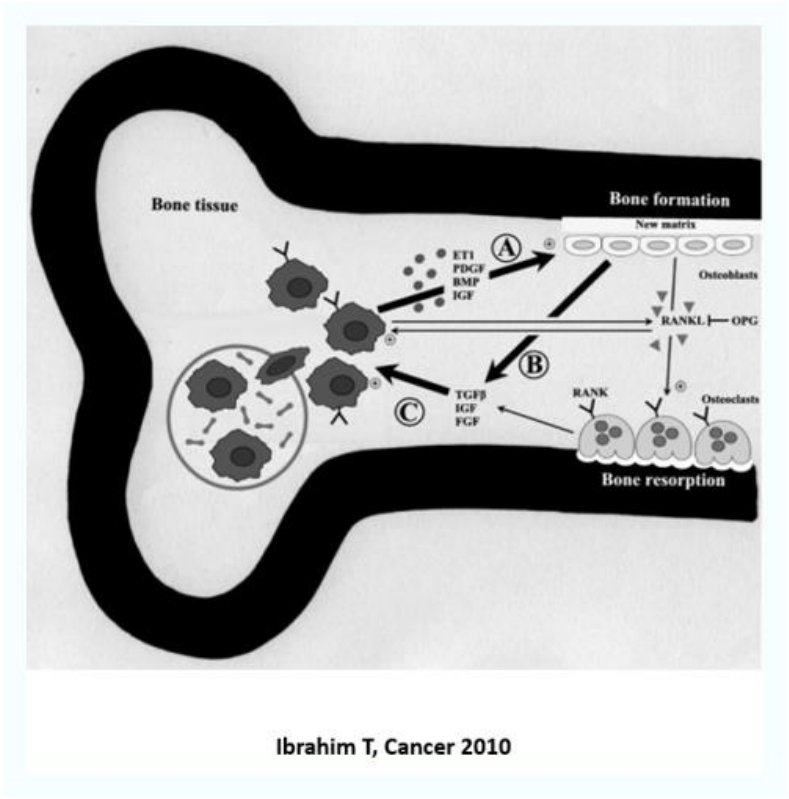
Physiopathological needs

Clinical needs M0/M1

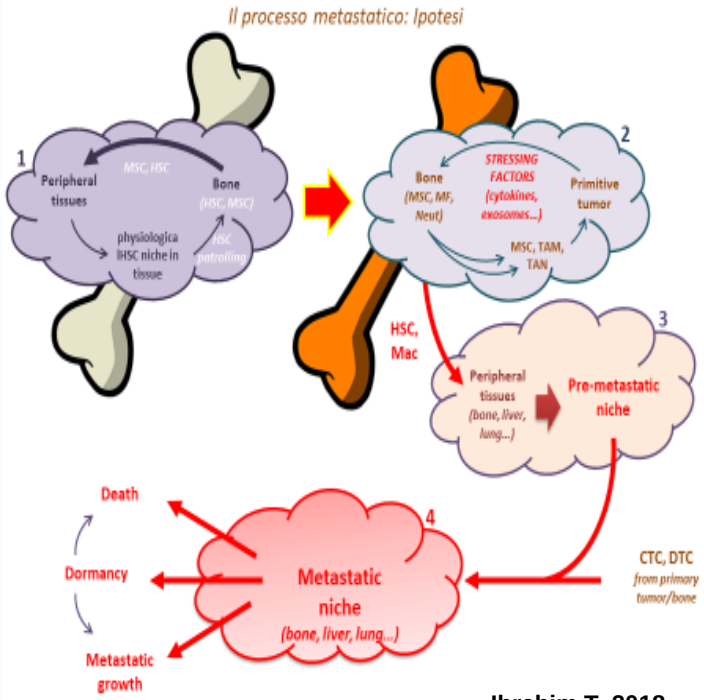
2000 — Professional needs — 2024

The Osteoncology





Ibrahim T, Cancer 2010



Ibrahim T, 2018

2000 — 2010 — 2024

Clinical needs M1 | **Physiopathological needs** | **Clinical needs M0/M1**

2000 — **Professional needs** — 2024

Bone Metastases

Responsible for high morbidity in patients with cancer for two reasons:

- Epidemiologi
-

INCIDENCE

Tumor type

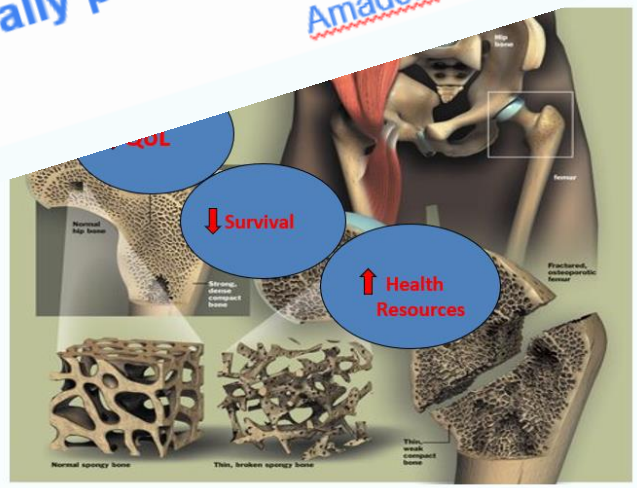
Frequency of serious complications depends on:

- Tumor site: more frequent in sites under dynamic stress, e.g. femur.
- Lesion type: more frequent in lytic than in blastic lesions.
- Treatment, especially preventive

Amadori D, Ibrahim T, Osteoncologia, Ed. Exc. Med. 2003

...arrow suppression

... D, Ibrahim T, Osteoncologia, Ed. Exc. Med. 2003




Oncologist
Dedicated Nurse
Radiotherapist
Lab Reasearchers
Orthopedic Specialist
Data Manager
Neurological surgeon
The Osteoncology model
Pathologist
Palliative Care Expert
Clinical Pathologist
Radiologist
Endocrinologist
Nuclear Medicine Physician
Psicologist
Physiatrist

Prof. Dino Amadori

OSTEONCOLOGY: New discipline in Oncology

(IRST-IRCCS, Meldola; AUSL Romagna;Istituto Ortopedico Rizzoli-IRCCS)

Prof Mario Mercuri

Italian Project: Multidisciplinary approach of Bone Metastases

2000 ..... **2024**

National training courses

2002 Bologna, Rome 2003 Naples, Bologna 2004 Naples, Florence

Publications: 3 books

2003 - 2021

National training and practical courses in Osteoncology

(Modena – Forlì- Meldola- Roma- Verona- others)

→ **Course in Osteoncology**

2003 - 2005

II level University Masters in Osteoncology (Modena/Bologna/Forlì)

2009-2021

PhD in Osteoncology (Campus Biomedico Roma)

→ **Masters/PhD in Osteoncology**

Establishment of Osteoncology field

Establishment of Osteoncology Center

2008

Italian Society of Osteoncology — ISO — Società Italiana di Osteoncologia

2014

National Bone Metastases Data Base

2016

Multidisciplinary Osteoncology School (MOS)

Treatment of Bone Metastases

Treatment of Bone Metastases	
Medical treatment	✓ Chemotherapy ✓ Endocrine therapy ✓ Bio-immunotherapy ✓ Bone target therapy: o Bisphosphonates o RANK-L antibody (denosumab) o Cathepsin K inhibitor o Src inhibitor o PTH-rP antibody o CXCR-4 antagonist o HDAC inhibitors o Proteosome inhibition o Anti-integrin o TGF-β inhibitors o ETRA inhibitor o Wnt inhibitor ✓ Palliative care: o Analgesic drugs o Best Supportive Care
Radiotherapy	
Radiometabolic treatment	
Orthopedic surgery	
Interventional radiology	
Rehabilitation	

RANK-L, receptor activator of nuclear factor-kb ligand; PTH-rP, parathyroid hormone-related peptide; CXCR-4, chemokine receptor type 4; HDAC, histone deacetylase;TGF-β, tumor growth factor β; ETRA, endothelin receptor A

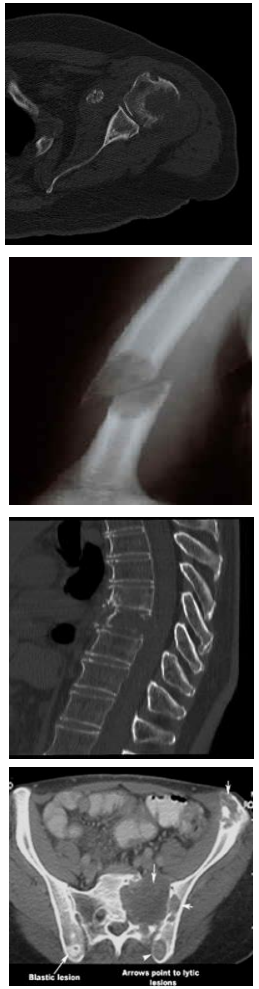
Medical treatment of bone metastases has become progressively complex and currently includes:

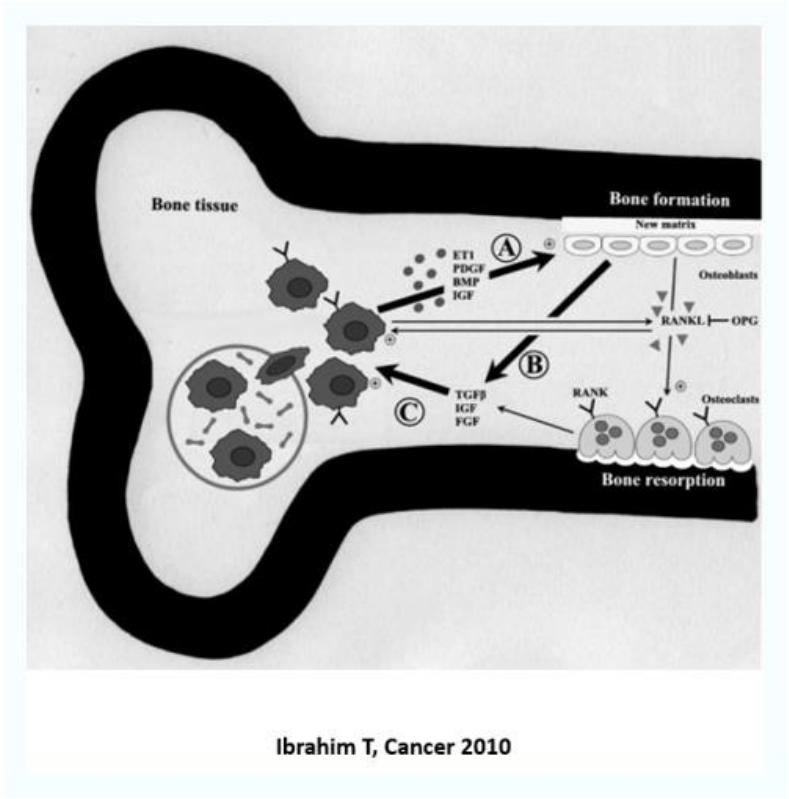
✓ well known antitumor agents

✓ Bone targeted agents = Bone modifyng agents

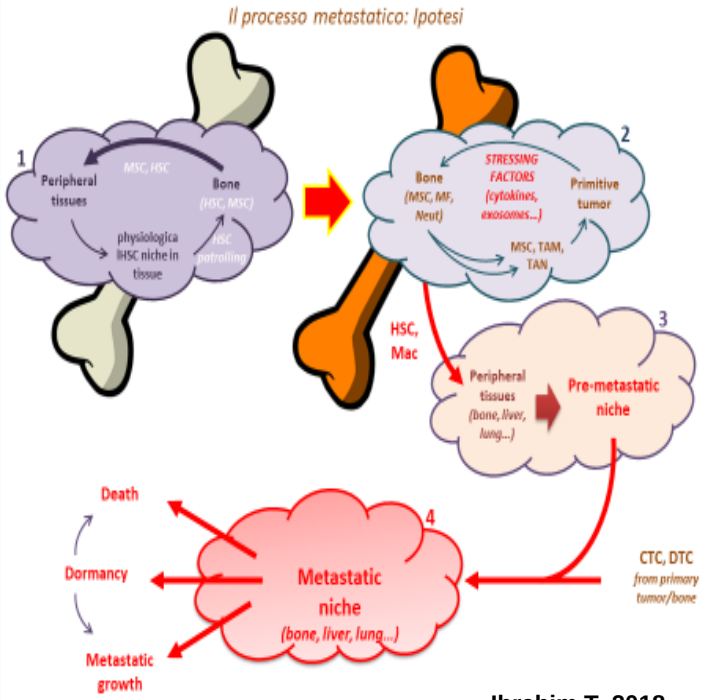
Ibrahim T, Tumori 2013

The Osteoncology





Ibrahim T, Cancer 2010



Ibrahim T, 2018

2000 — 2010 — 2024

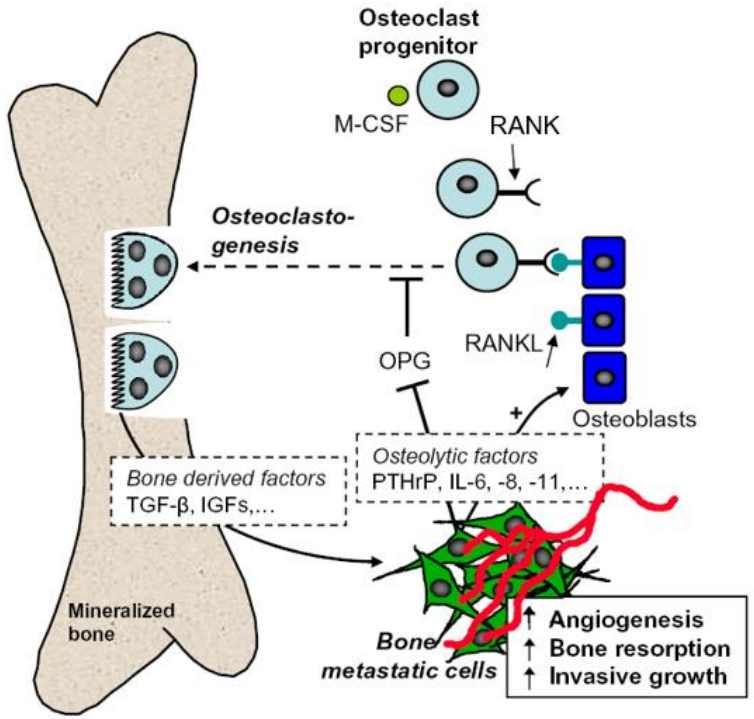
Clinical needs M1

Physiopathological needs

Clinical needs M0/M1

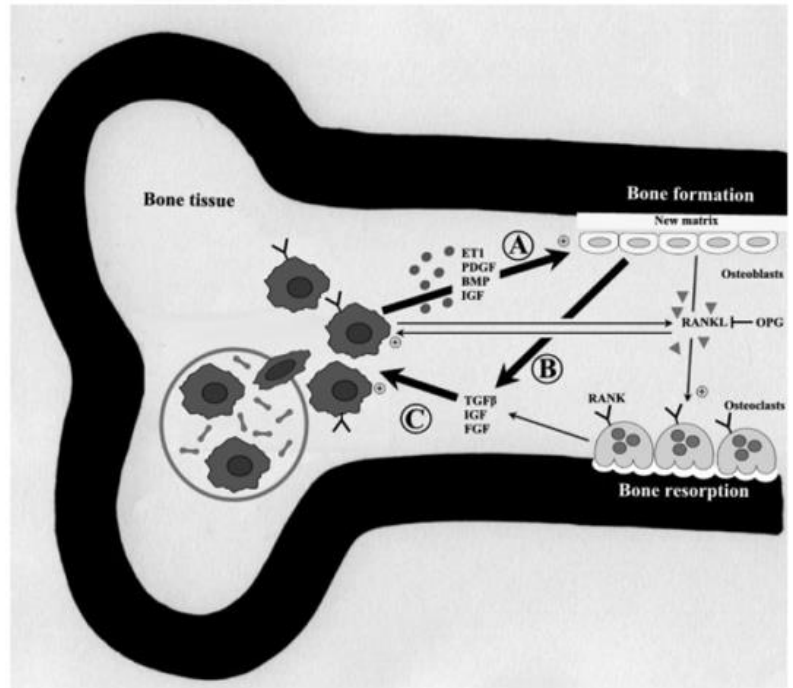
2000 — Professional needs — 2024

OSTEOLYTIC MODEL: a vicious cycle



Buijs, The prostate,2009

OSTEOBLASTIC MODEL: a vicious cycle



Ibrahim T, Cancer 2010

Evolving cancer–niche interactions and therapeutic targets during bone metastasis

Reviews Nature 2021

Robert L. Satcher[1] *and Xiang H.-F. Zhang*[2,3,4]✉

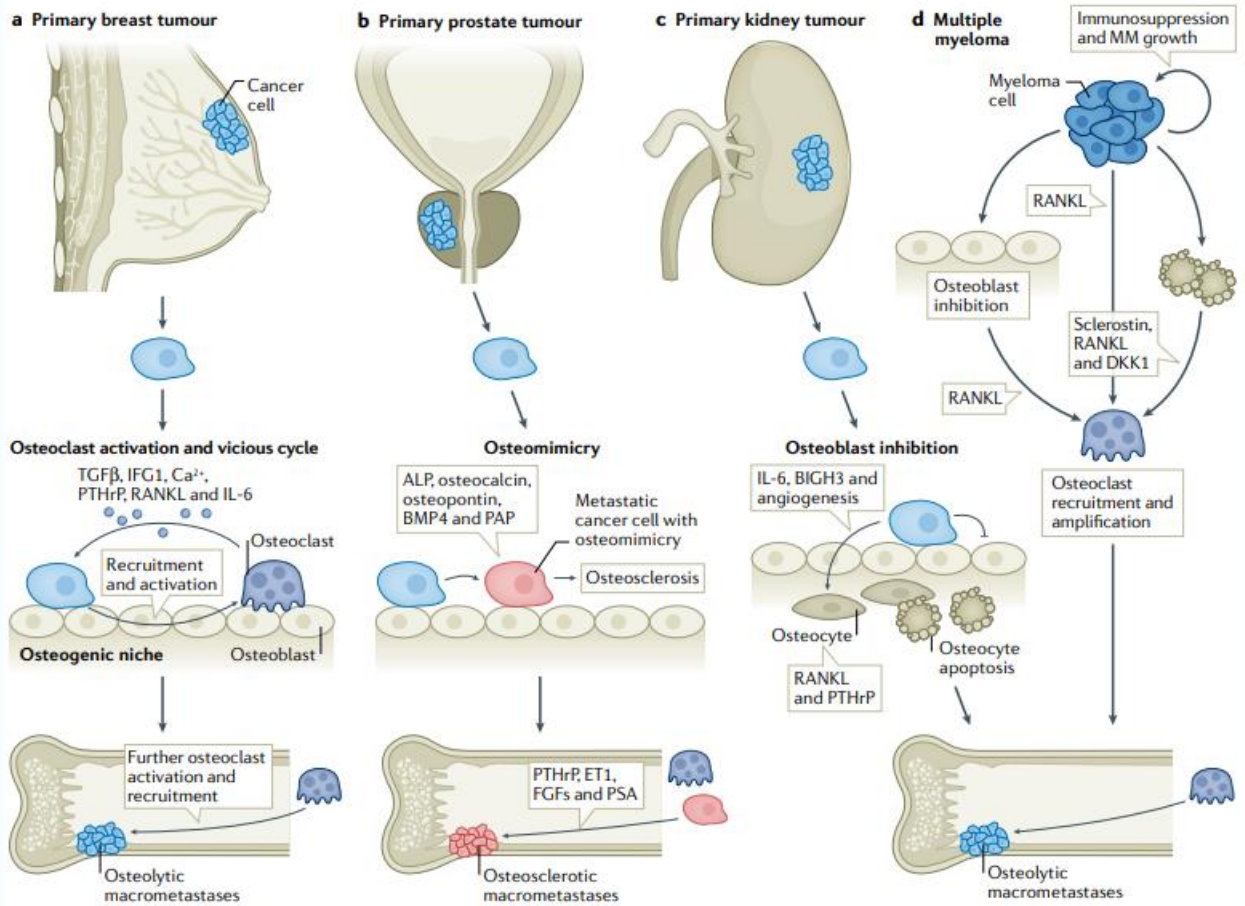
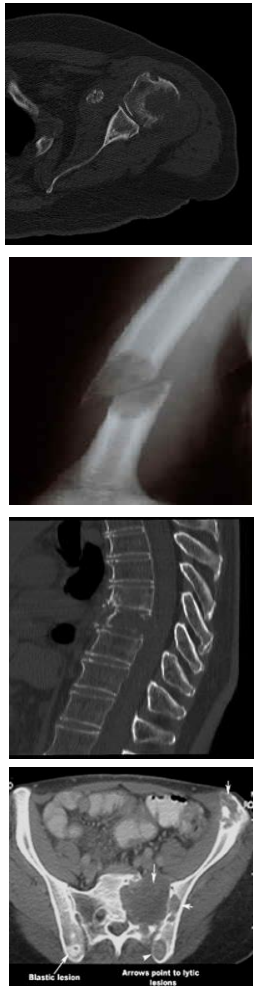
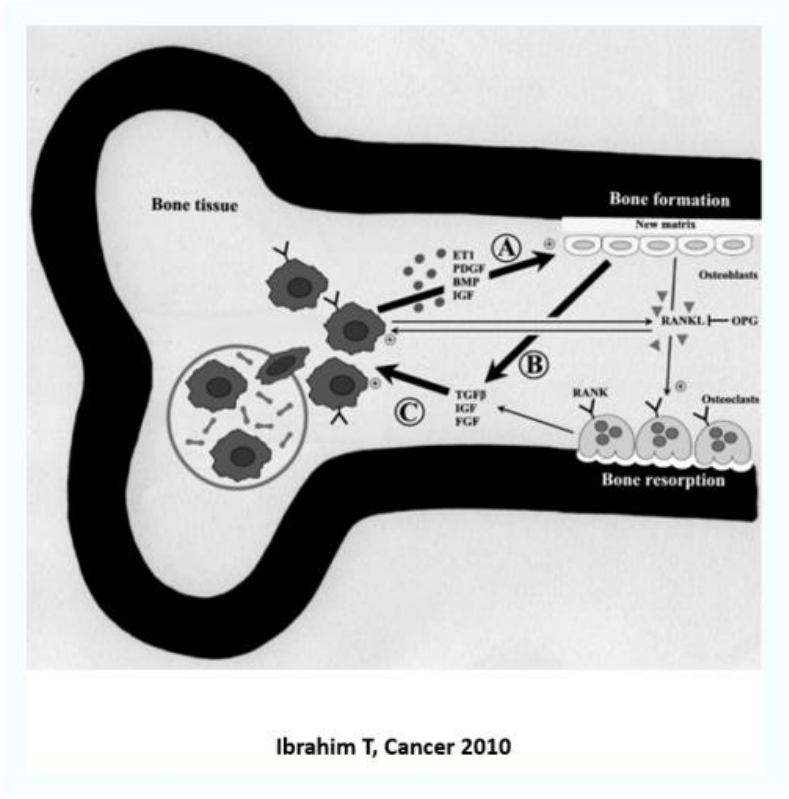


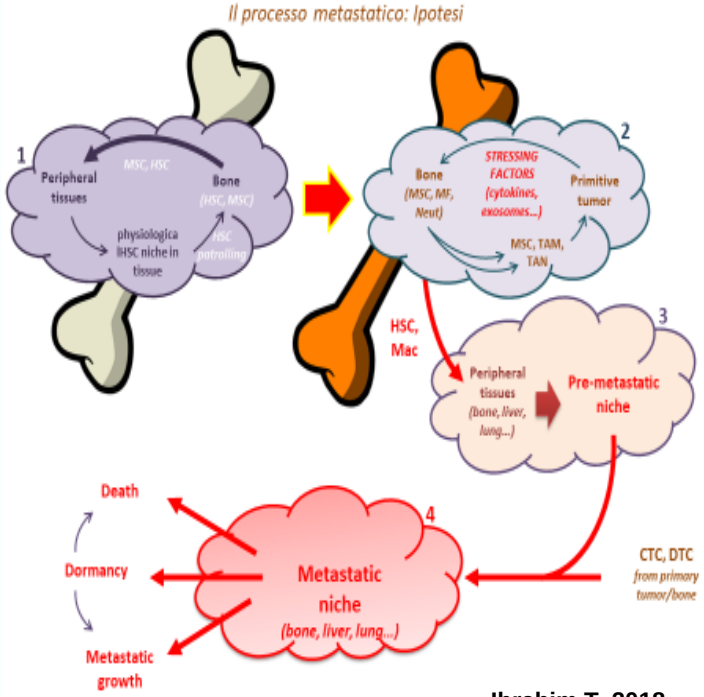
Fig. 3 | **The relationship between primary tumour and the vicious cycle of late-stage bone metastasis in various cancer types. a** | For breast cancer, disseminated tumour cells (DTCs) awaken from dormancy to create osteolytic macrometastases by both paracrine and heterotypic adherens junction and gap junction interactions in the osteogenic niche, which directly and indirectly stimulate osteoclast recruitment and activation. Osteoclast activity, in turn, releases TGFβ, IGF1, Ca^{2+} and other growth factors from bone that further stimulate tumour proliferation. This is the classic 'vicious cycle'. **b** | For prostate cancer, osteomimicry of DTCs in the osteogenic niche harnesses both the anabolic and lytic components of normal bone homeostasis, leading to osteolysis (PSA) and/or osteosclerosis (PAP). Tumour cells induce osteosclerosis via secretion of osteogenic factors such as ALP, osteocalcin, osteopontin and bone morphogenic protein 4 (BMP4). Osteolysis is induced via secretion of PTHrP, ET1 and IGF1. This global alteration towards bone-like phenotypes may be driven by RUNX2. The underlying genomics of osteomimicry and why it is not as predominant in other tumour types are not known. **c** | For kidney cancer, the road to bone destruction is more indirect than for breast or prostate cancer, and resembles that for multiple myeloma (MM). DTCs create a vicious cycle via paracrine inhibition of osteoblast function and osteocyte apoptosis. Consequently, the adverse impact on the anabolic component of the osteogenic niche creates an environment that increases the RANKL to OPG ratio, promoting osteoclast recruitment and activity that creates predominantly lytic macrometastases. The details of interactions in the perivascular and osteogenic niches are likely tightly linked, as neovascular induction is a prominent component of kidney cancer bone metastasis. **d** | MM is almost exclusively bone organotropic. Interactions in the osteogenic niche are driven by crosstalk between MM cells and osteocytes, osteoblasts and osteoclasts. Osteolysis is induced via secretion of RANKL by MM cells, and amplified by RANKL from apoptotic osteocytes and inhibited osteoblasts. Immunosuppression enabling MM proliferation and progression is provoked by immune dysregulation, influencing T cell immunity, natural killer cell function and the antigen-presenting capacity of dendritic cells; and via myeloid derived suppressor cell amplification by osteoclasts. DKK1, Dickkopf-related protein 1.

The Osteoncology





Ibrahim T, Cancer 2010



Ibrahim T, 2018

2000 — 2010 — 2024

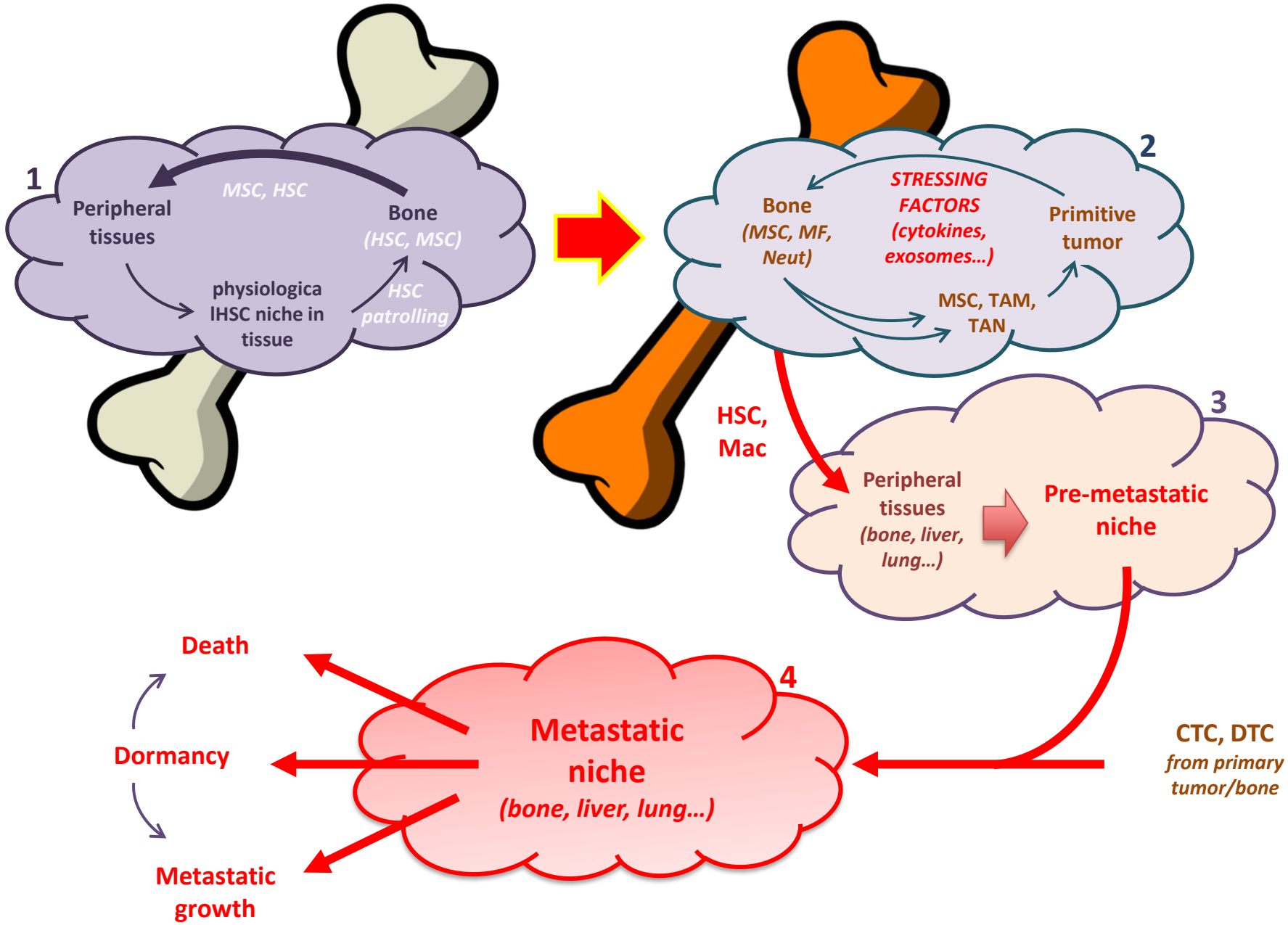
Clinical needs M1

Physiopathological needs

Clinical needs M0/M1

2000 — Professional needs — 2024

The Metastatic Process: hypothesis



Ibrahim T, 2018

Bone tropism

IRST DATA: RANK expression in primary breast cancers of patietns with/without bone relapse

Table 3 Frequency of Marker-expressing Tumors

	NED Patients (n = 10)		Relapsed Patients: Overall (n = 30)		Relapsed Patients: VM (n = 10)		Relapsed Patients: BM (n = 20)		*P* BM vs NED Patients	*P* BM vs VM Patients
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)		
OPG	20	(6-52)	23	(12-41)	20	(6-52)	25	(11-47)	1.000	1.000
RANK	20	(6-52)	17	(7-34)	0	0	25	(11-47)	1.000	.140
CXCR4	10	(0-29)	30	(14-46)	0	0	45	(23-67)	.101	.013

Abbreviations: BM = bone metastasis; CI = confidence interval; NED = no evidence of disease; VM = visceral metastasis.

❖The CXCR4+RANK combination was an independent predictive marker of relapse to bone, increasing the RR of bone relapse 9.3-fold in the BM group with respect to NED-VM patients (*P* =008).

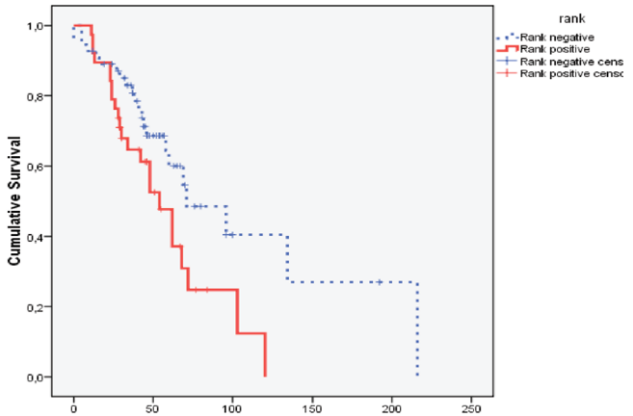
❖Considering only patients who relapsed to viscera as control group, the RR of bone relapse increased 16.1-fold.

Ibrahim, Clin breast cancer 2011

IRST DATA: The role of gene profiling: tissue and circulating markers in the prediction of bone metastases in breast cancer patients

Marker	Expression in cases	Expression in Controls	Expression in VM	Expression in NEDP
B2m	27	3	0	6
CTGF	30	7	12	3
HPSE	18	3	4	3
SPARC	9	0	0	9
TFF1	63	22	23	21
RANK	18	2	4	0
CXCR4	35	6	13	0
IBSP	20	0	0	0
TFF1/B2m CTGF/RANK	79	28	30	26

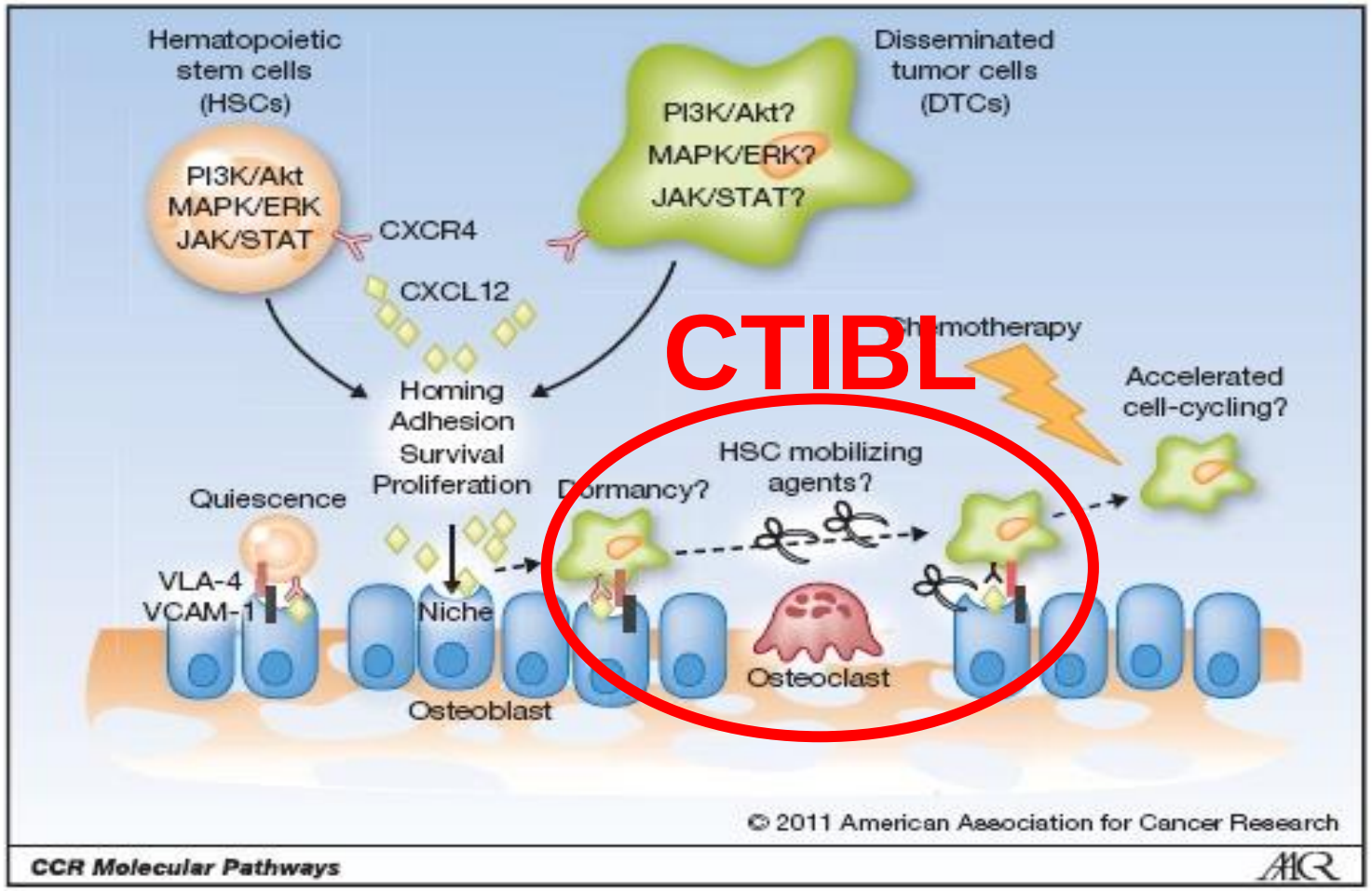
Receptor activator of NF-kB (RANK) expression in primary tumors associates with bone metastasis occurrence in breast cancer patients.



▪Immunohistochemical analysis of RANK showed a positive correlation with the development of bone metastases (P=0.023)
▪"RANK-negative" and "RANK-positive" patients had a SDFS of 105.7 months (95% CI: 73.9-124.4) and 58.9 months (95% CI: 34.7-68.5), respectively

Santini D et al *PlosOne 2011*

Bone Microenvironment



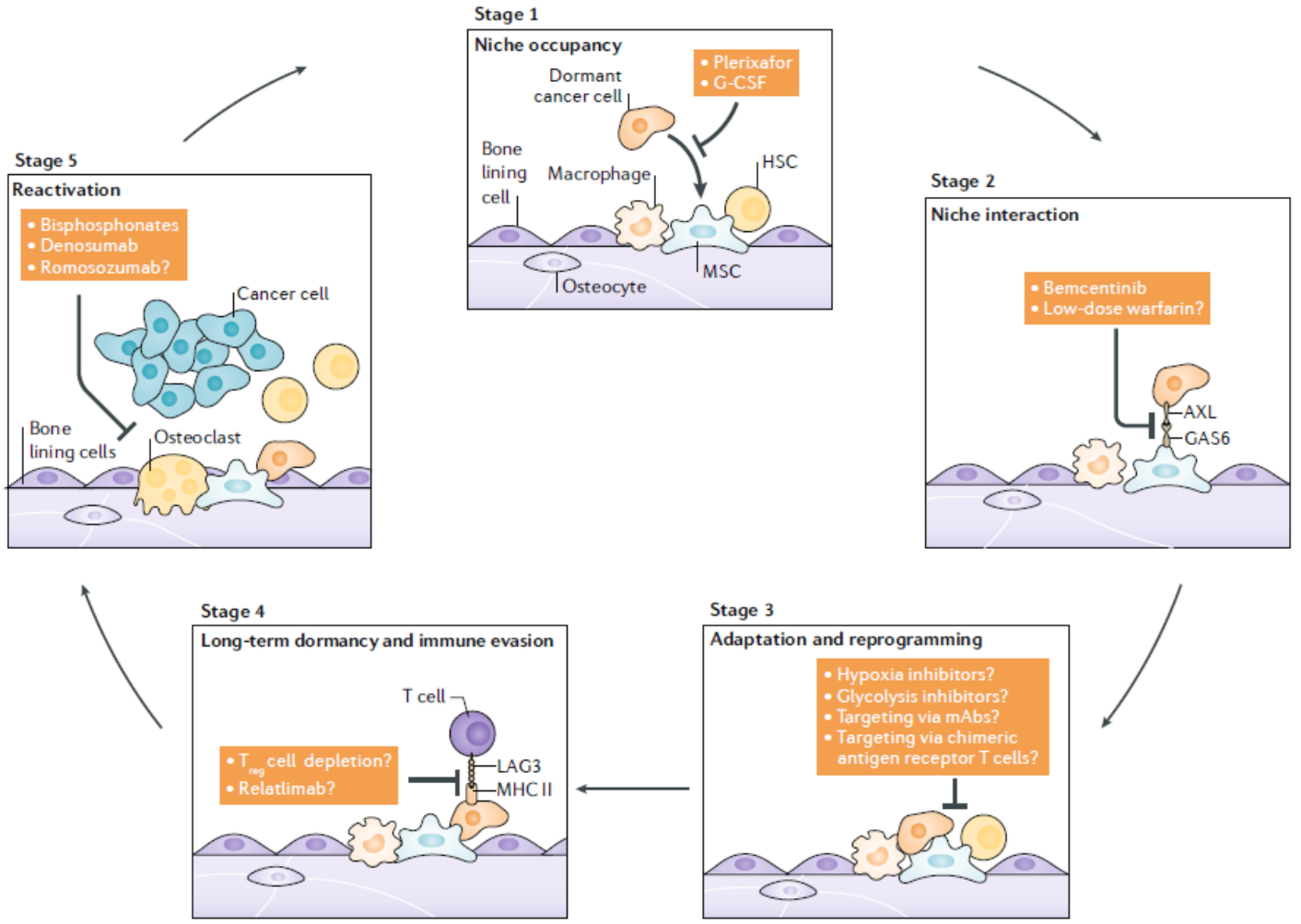
Shiozawa Y, Clinical Cancer Research, 2011

Bone Targeted Therapy
(Bone modifying agents)

Advanced setting

Adjuvant setting

Niche-targeted therapies to prevent bone metastasis



Croucher, Nature Reviews 2020

J BONE ONCOL 45 (2024) 100597

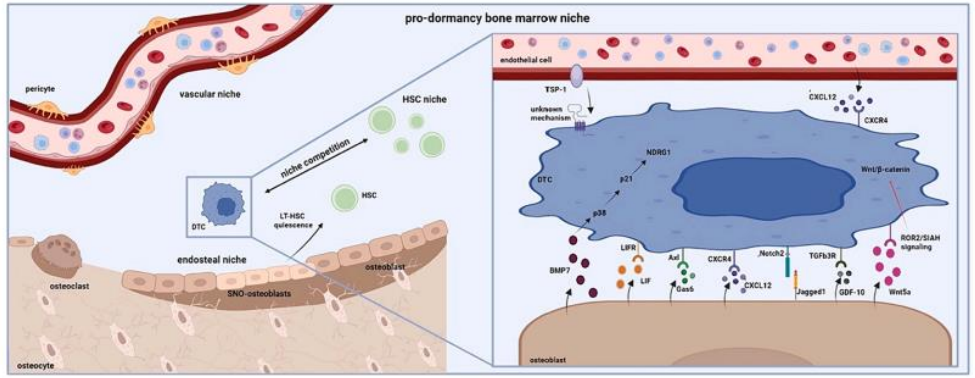
Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

The osteoblast in regulation of tumor cell dormancy and bone metastasis

Jennifer Zarrer [a,b], Hanna Taipaleenmäki [a,b,*]



Regulation of the disseminated tumor cell pro-dormant milieu by osteogenic cells. Disseminated tumor cells (DTCs) have been found

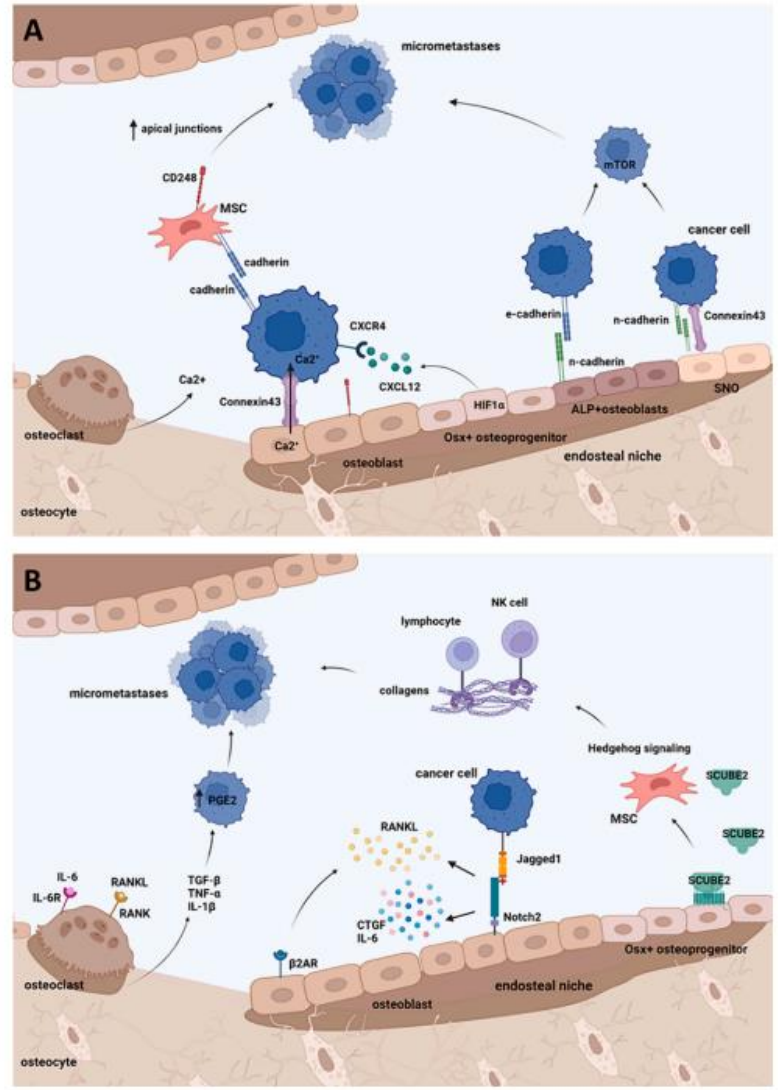
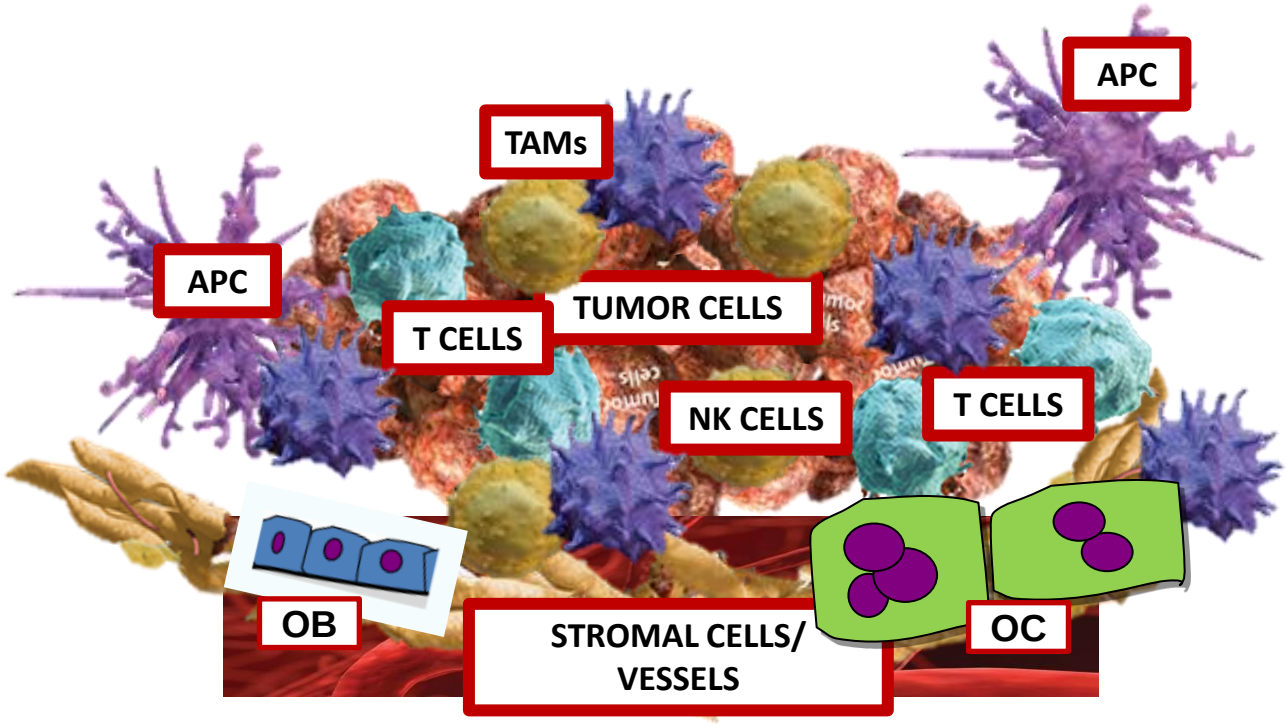
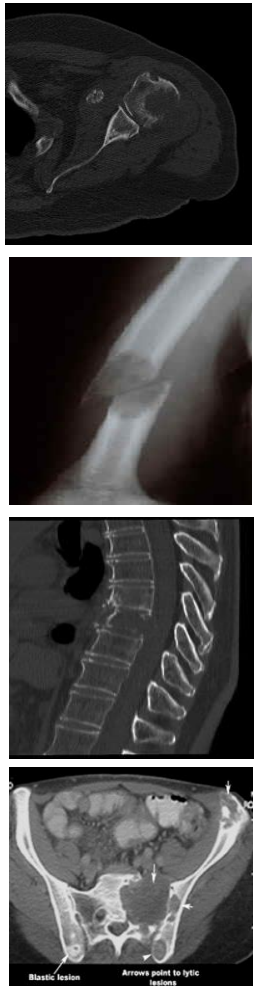


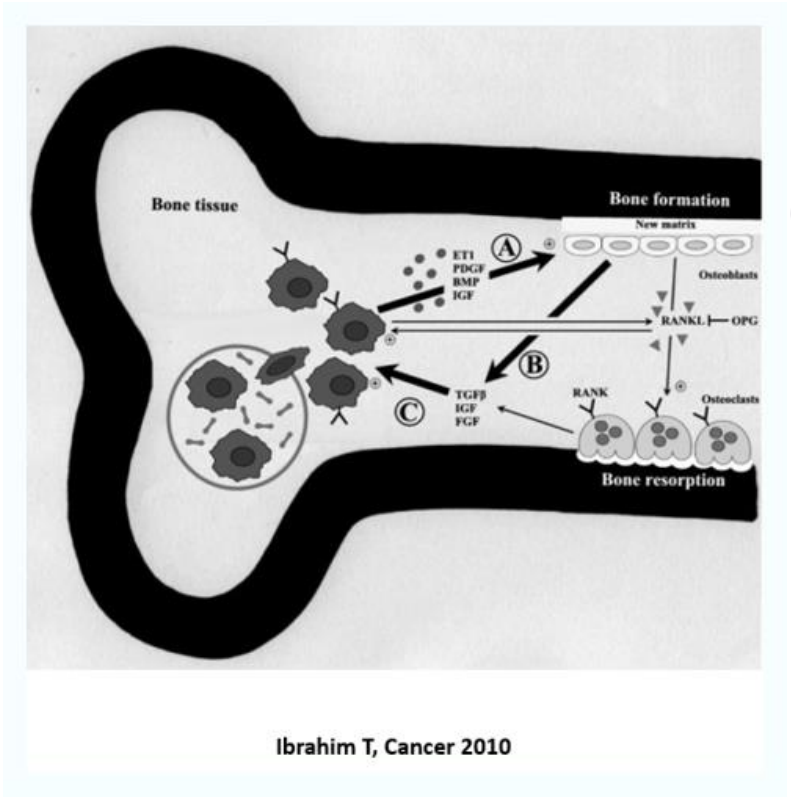
Fig. 2. Osteoblast lineage cells drive cancer cell colonization and proliferation in the metastatic niche. Triggered by microenvironmental cues, DTCs

Cancer and Tumor Microenvironment

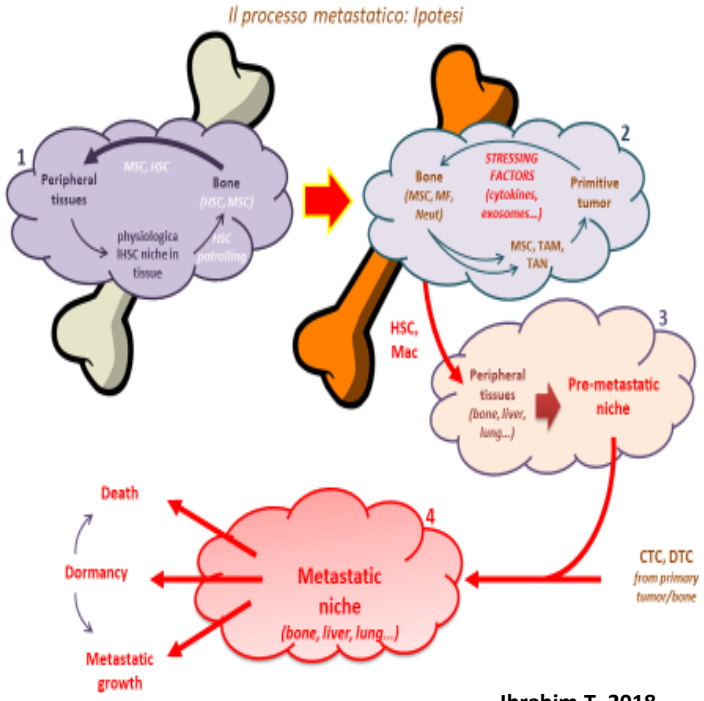


The Osteoncology





Ibrahim T, Cancer 2010



Ibrahim T, 2018

2000 — 2010 — 2024

Clinical needs M1

Physiopathological needs

Clinical needs M0/M1

2000 — Professional needs — 2024



















Vision of The Osteoncology on 2024

Clinical and Lab Researchers

Networks

Dialogue = Cross Talk

Patients

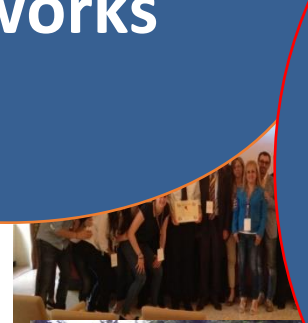
Multi/ Interdisciplinarity

Volunteer Associations













I.S.O. ETS

Società Italiana di Osteoncologia
I.S.O.

www.osteoncology.it

C.F. 92068610408

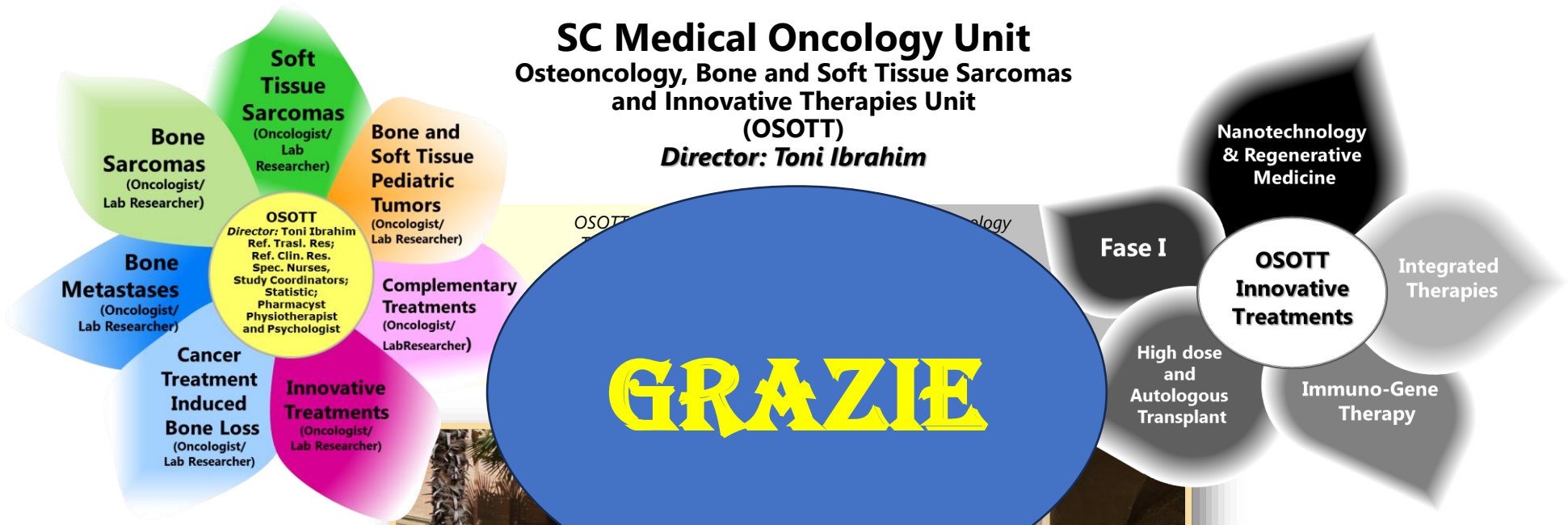
ISTITUTO ORTOPEDICO RIZZOLI 1896-2021 40 ANNI DI IRCCS

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Ortopedico Rizzoli di Bologna
Istituto di Ricovero e Cura a Carattere Scientifico

SC Medical Oncology Unit

Osteoncology, Bone and Soft Tissue Sarcomas and Innovative Therapies Unit (OSOTT)

Director: Toni Ibrahim



GRAZIE

Oncologists:
Cesari Marilena, Hakim Rossella, Longhi Alessandra,
Paioli Anna, Palmerini Emanuela, Marrari Andrea, Frega Giorgio
Nurse Head:
Coluccino Paola
Nurses: Boccomino Riccardo, Borri Chiara, Boschi Rita, Brruku Eugenio, Cazal Diana, Cosme Magdalena, Gironi Sonia, Napolano Mariamaddalena, Panzeri Paola, Polo Dolores, Raucci Giovanni,
Rychter Renata, Sabbi Daniela, Spadaro Concetto, Verdoliva Viviana
Support Professionals: Coirazza Marina, Ferla Monica, Minerbi Carla, Oliva Vincenza
Psychologist: Biscardi Giulia **Physiotherapists:** Cotti Marco, Morri Mattia
Segretary: Gilli Giulia

Strudy Coordinators: Pierini Michela, Molendini Lara, Giostra Chiara
Project Manager: Paglia Simona
Scientific Secretary: MarikaSciandra

Lab Researchers
SS Pharmacogenomics & Pharmacogenetics Unit: Casotti Chiara, Leonardo Fantoni, Claudia Hattinger, Massimo Serra

SS Regenerative Therapies in Oncology Unit: Chiara Bellotti, Ania Naila Guerrieri, Micaela Pannella, Enrico Lucarelli

SS Advanced Models and Innovative Therapies Unit: Laura Mercatali

toni.ibrahim@ior.it

SAVE THE DATE

VIII CONGRESSO NAZIONALE
SOCIETÀ ITALIANA DI OSTEONCOLOGIA
PADOVA, 24-25 OTTOBRE 2024

PRESIDENTI
T. Ibrahim, S. Zovato

COMITATO SCIENTIFICO:
A. Brunello, M. Maruzzo, L. Mercatali, G. Lanzetta, R. Casadei, S. Severi, A. Berruti