Bone neoplasms and Antiosteoporotic treatment

Andreas F. Mavrogenis, MD
First Department of Orthopaedics
National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

The Breast 41 (2018) 42–50

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Link between estrogen deficiency osteoporosis and susceptibility to bone metastases: A way towards precision medicine in cancer patients

F. Salamanna [a], V. Borsari [a, *], D. Contartese [a], N. Nicoli Aldini [a], M. Fini [b]

[a] Laboratory of Preclinical and Surgical Studies, Rizzoli RIT Department, IRCCS Rizzoli Orthopedic Institute, Via di Barbiano 1/10, Bologna, 40136, Italy
[b] Laboratory of Biomechanics and Technology Innovation, Rizzoli RIT Department, IRCCS Rizzoli Orthopedic Institute, Via di Barbiano 1/10, Bologna, 40136, Italy

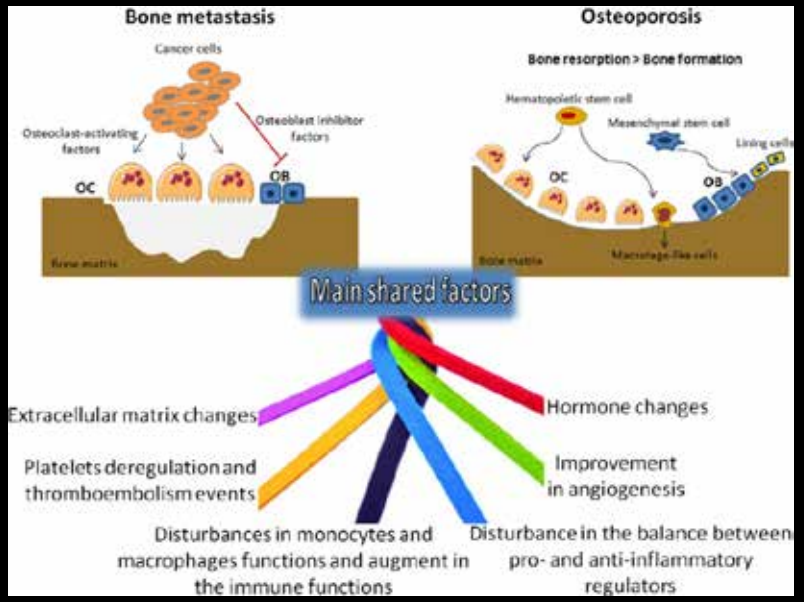
Design

- Systematic review
  - Studies of previous decade

- Study question: Could pre-existing estrogen deficiency osteoporosis promote and/or influence cancer cell homing and tumor growth in bone?

Main sharing factors between estrogen deficiency osteoporosis and bone metastases

- Numerous
- Disturbances in monocytes and macrophages functions and consequent alteration in the immune functions
- Disturbance in the balance between pro and anti-inflammatory regulators
- Improvement in angiogenesis
- Platelets deregulation
- Thromboembolism events
- ECM and hormonal changes



Alterations shared between estrogen deficiency osteoporosis and bone metastases

Disturbances in monocytes and macrophages functions	↑osteoclasts
	↑ IL-1, IL-3, IL -6, IL -11, TGF, GCS-F, MCS-F, LIF and stem-cell factor
	Osteolytic lesions
Alteration in the immune functions	↑osteoclastogenesis
	↑activated T cells
	↑bone-resorbing cytokines (as TNF-α and RANKL)
Disturbance in the balance between pro and anti-inflammatory regulators	↑IL-1
	↑IL-3
	↑IL-6
	↑IL-11
	↑TGF-α
	↑TNF
Improvement in angiogenesis	↓blood vessel volume
	↑HIF-1a, HIF-2a, VEGF
	↑platelets release
Platelets deregulation	Platelet degranulation
	↑growth factors and chemoattractants that affect bone metabolism
	↑TGF-β, TNF-α and IL-6
Thromboembolism events	↑blood coagulation
Alteration in extracellular matrix components	Changes in collagen fibril organization
	↑collagen cross-link ratio
	Alterations in type I collagen C-telopeptide isomerisation
	↑in MMP-9, MMP-1, MMP -2
	Alteration in matricellular proteins
Hormone changes	↑PTH
	↓glucocorticoid, progesterone and androgen
	↑ERα and ERβ

Zoledronic acid

- Completely prevented tumor growth in bone
  - OVX-mice with breast cancer cells inocculation
- Reduce the risk of invasive disease in women at least 5 years post-menopause

Kraemer et al. Anticancer Res. 2011
Ottewell et al. Clin Canc Res 2014

Conclusion

- BMD monitoring in combination with the detection of disseminated tumor cells can be a strategy to define a population more at risk of metastasis
- Zoledronic acid possibly effective

Exp Oncol 2018
40, 2, 136–139

Experimental ONCOLOGY

THE STATE OF BONE METABOLISM IN LUNG CANCER PATIENTS

*Y.V. Dumanskyy[1,] *, O.V. Syniachenko[1], Ph.A. Stepko[1], G.S. Taktashov[1], O.Y. Chernyshova[1], O.Y. Stoliarova[2]*

[1]*Donetsk National Medical University, Lyman 84400, Ukraine*

[2]*National Cancer Institute, Kyiv 03022, Ukraine*

Design

- Case series
- 32 patients with LC without distant metastases (mean age, 55.6 yrs), not received chemo- or radiotherapy previously
- Study question: the correlation of malignant tumor process, ongoing chemotherapy and radiation therapy with the development of osteoporosis

Methods

- DEXA of proximal part of femoral bone
- Osteopontin (OP), osteocalcin (OC), alkaline phosphatase (AP) and osteo-associated biochemical elements in blood

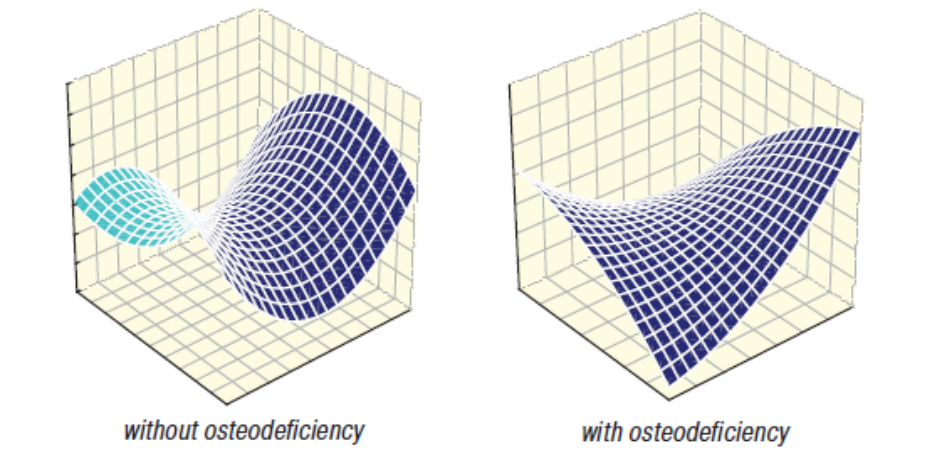


Fig. 3. Three-dimensional histograms of integral BMM parameters (OC + OP + AP) in patients with LC

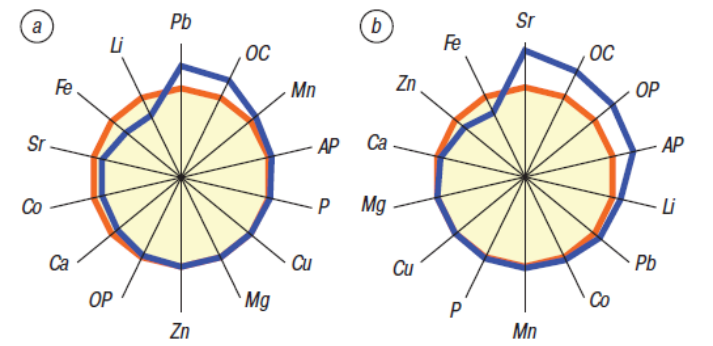


Fig. 1. The changes of the parameters of BMM and chemical elements in patients: *a*) with small cell and non-small cell LC which are taken as 100%; *b*) with osteodeficiency and without it which are taken as 100%

Results

- Osteodeficiency (osteopenia, osteoporosis) has been diagnosed in 46.9% of the LC patients
- More frequent in women with LC

Table. Indices of bone metabolism in blood of healthy people and patients with LC (M ± SE)

Indices	Groups of surveyed		Differences between groups	
	Control group (n = 40)	Patients with LC (n = 32)	*t*	*p*
OC, ng/ml	5.3 ± 0.4	13.8 ± 0.7	12.04	< 0.001
OP, ng/ml	22.0 ± 0.9	39.8 ± 1.3	10.86	< 0.001
AP, U/l	90.0 ± 5.3	121.1 ± 7.0	3.62	0.001
Ca, mg/l	100.0 ± 0.6	53.8 ± 1.3	35.57	< 0.001
Co, mg/l	6.6 ± 0.4	8.2 ± 0.1	3.45	0.001
Cu, mg/l	1.0 ± 0.03	1.0 ± 0.02	0.84	0.402
Fe, mg/l	439.9 ± 3.5	398.6 ± 23.8	1.92	0.060
Li, mg/l	2.3 ± 0.04	4.0 ± 0.3	6.11	< 0.001
Mg, mg/l	412.2 ± 5.8	35.9 ± 0.3	58.01	< 0.001
Mn, mg/l	18.4 ± 2.2	12.6 ±0.6	2.32	0.023
P, mg/l	27.8 ± 0.4	398.4 ± 2.7	153.71	< 0.001
Pb, mg/l	39.5 ± 2.6	64.2 ± 4.7	4.85	< 0.001
Sr, mg/l	32.4 ± 1.5	49.9 ± 3.2	5.22	< 0.001
Zn, mg/l	6.1 ± 0.1	6.3 ± 0.2	1.07	0.289

Conclusion

- Osteodeficiency (osteopenia, osteoporosis) in 46.9% of LC patients
  - More frequent in women
- Need for the development of antiosteoporosis treatment for cancer patients

GCT of bone

Spectrum of biologic behavior

- Controversial and confusing
- Benign or low grade malignant?

Latent GCT

Aggressive GCT

Typical benign

Benign metastasizing

Primary malignant

Secondary malignant

GCT of bone

Spectrum

- Recurrence up to 0-50%
  - 5 mos to 20 yrs
- Malignant GCT 5-10%
  - previous RT
- Lungs metastases 1-9%
  - resectable

Campanacci M, et al., JBJS Am. 1987

GCT of bone

- 4-10% of benign bone tumors
- M=F
- 80% in pts 15-30 yrs

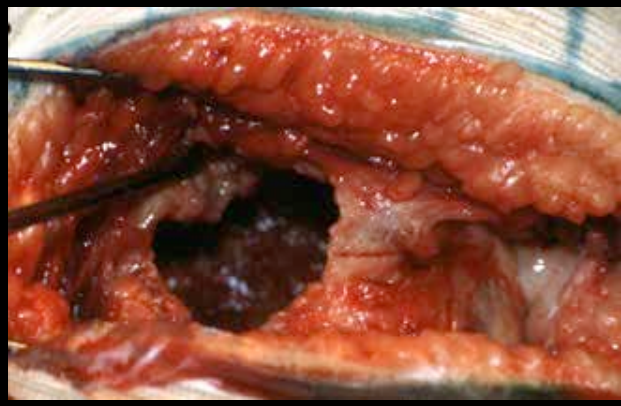
GCT of bone

Location

- Epiphysis
- >50% around the knee
- Radius, sacrum

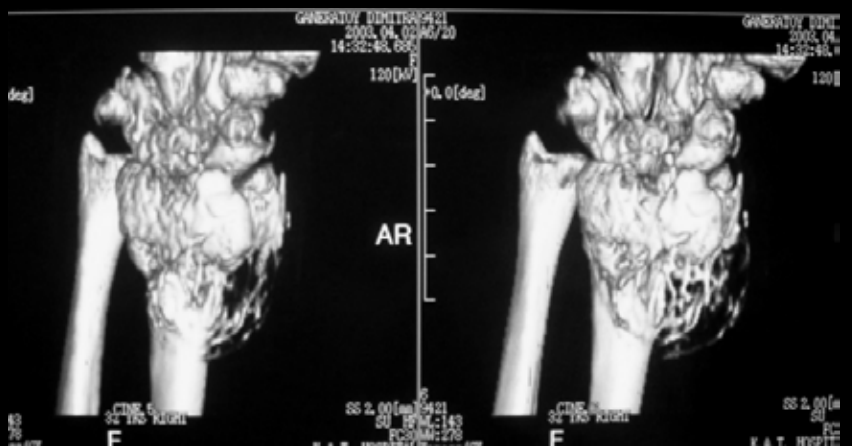


GCT of bone



Treatment

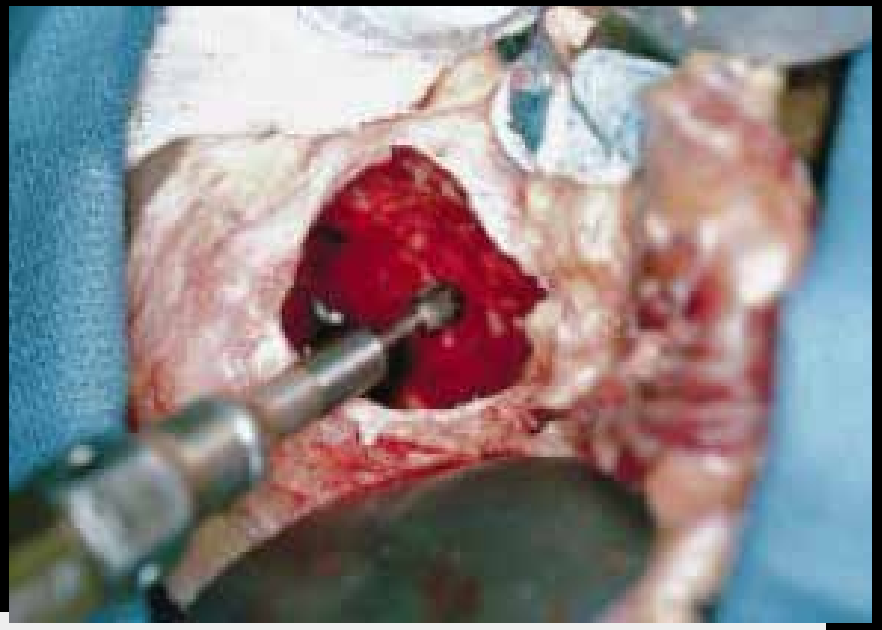
- Curettage
  - If the joint surfaces can be saved
- Resection/reconstruction
  - If the joint surfaces cannot be saved

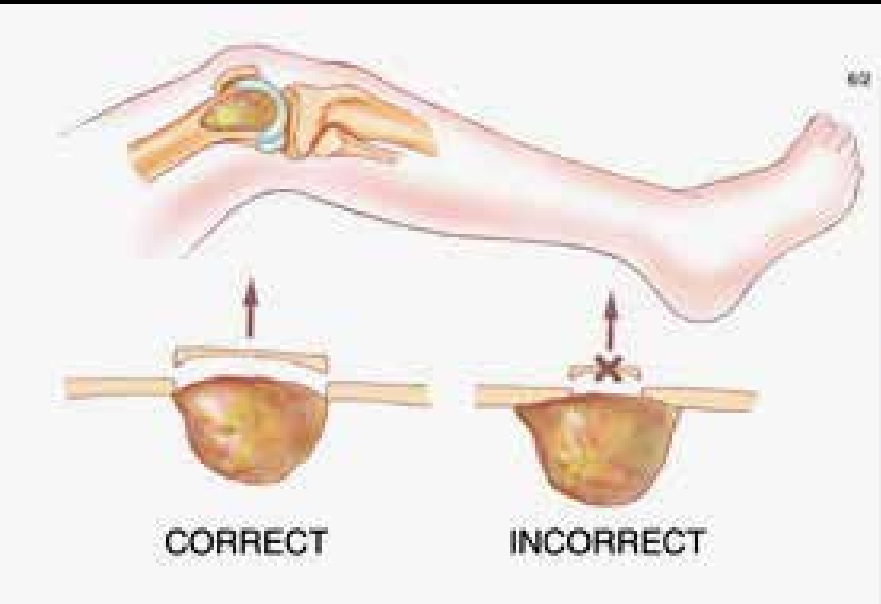


GCT of bone

Curettage

- Wide decortication
- sharp curette, burr
- Recurrence 35%-42%





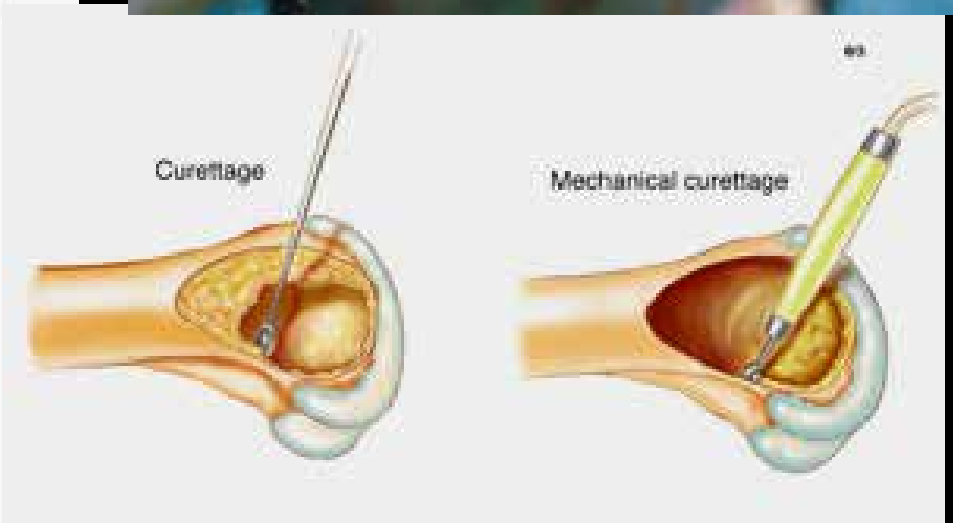


Table I. The rate of recurrence after different intralesional treatments of primary GCT of bone (minimum follow-up ≥ 2 years)

Author/s	Number of patients	Adjuvant treatment	Rate of local recurrence (%)
Goldenberg et al[17] (multicentre)	120	None	*43*
Campanacci et al[12]	128	None	*30*
Capanna et al[52] (multicentre)	490	None	*45*
Lausten et al[85]	18	None/radiotherapy	*56*
Richardson and Dickinson[62]	16	(Burr) none	*0*
Blackley et al[51]	59	Burr, none	*12*
McDonald et al[35]	85	Burr, phenol, alcohol	*34*
Capanna et al[52] (multicentre)	187	PMMA,* phenol, liquid nitrogen	*17*
Szendröi[29]	11	Phenol, PMMA	*9*
Komiya and Inoue[63]	11	Burr, PMMA	*0*
Gitelis et al[46]	16	Burr, phenol, alcohol, PMMA	*0*
O'Donell et al[49]	60	PMMA/Burr, phenol	*25*
Bini et al[57]	38	PMMA	*8*
Malawar and Dunham[59]	102	(Burr)+liquid nitrogen	*7.9*
Labs et al[48]	15	PMMA	*12*

* polymethylmethacrylate

McGough et al, CORR 2005

GCT of bone

- Local adjuvants
  - Embolization
  - Alcohol
  - Phenol
  - Nitrogen
- ***Facilitate curettage***
- PMMA
  - Supports the subchondral plate
  - Exothermic reaction (thermal ablation)
- RT
  - No role
- Denosumab

Ruggieri P, Mavrogenis AF, Mercuri M. CORR, 2010

Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study

David Thomas, Robert Henshaw, Keith Skubitz, Sant Chawla, Arthur Staddon, Jean-Yves Blay, Martine Roudier, Judy Smith, Zhishen Ye, Winnie Sohn, Roger Dansey, Susie Jun

Lancet Oncol 2010; 11: 275–80

- Further investigation of denosumab as a therapy for GCT is warranted

Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study

Sant Chawla, Robert Henshaw, Leanne Seeger, Edwin Choy, Jean-Yves Blay, Stefano Ferrari, Judith Kroep, Robert Grimer, Peter Reichardt, Piotr Rutkowski, Scott Schuetze, Keith Skubitz, Arthur Staddon, David Thomas, Yi Qian, Ira Jacobs

Lancet Oncol 2013; 14: 901–08

- Denosumab represents a new treatment option for patients with GCTB
  - tumour responses and reduced need for morbid surgery
- Adverse events were consistent with the known safety profile of denosumab

A Translational Study of the Neoplastic Cells of Giant Cell Tumor of Bone Following Neoadjuvant Denosumab

Isabella W.Y. Mak, MSc*, Nathan Evaniew, MD*, Snezana Popovic, MD, Richard Tozer, MD, and Michelle Ghert, MD

Investigation performed at the Departments of Surgery, Pathology and Molecular Science, and Oncology, McMaster University, Hamilton, and the Juravinski Cancer Centre, Hamilton Health Sciences, Hamilton, Ontario, Canada

- Treatment with denosumab only partially addresses the therapeutic need of patients with a GCTB
  - wipes the osteoclasts but leaves the neoplastic stromal cells proliferative
  - almost complete loss of RANKL expression

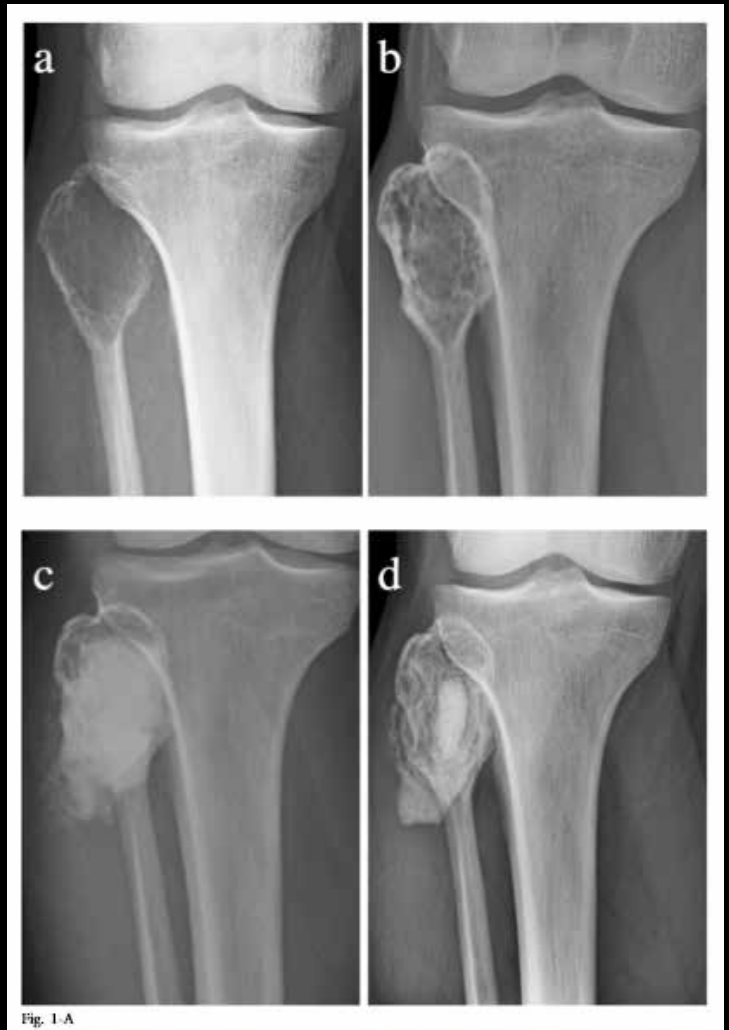


Fig. 1-A

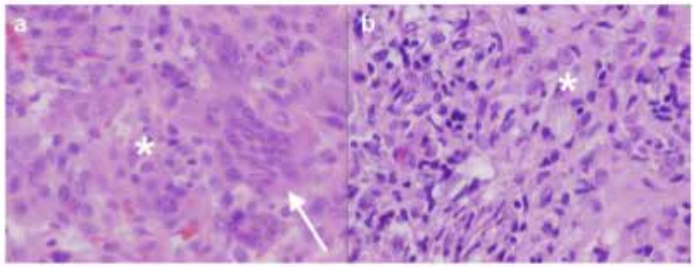
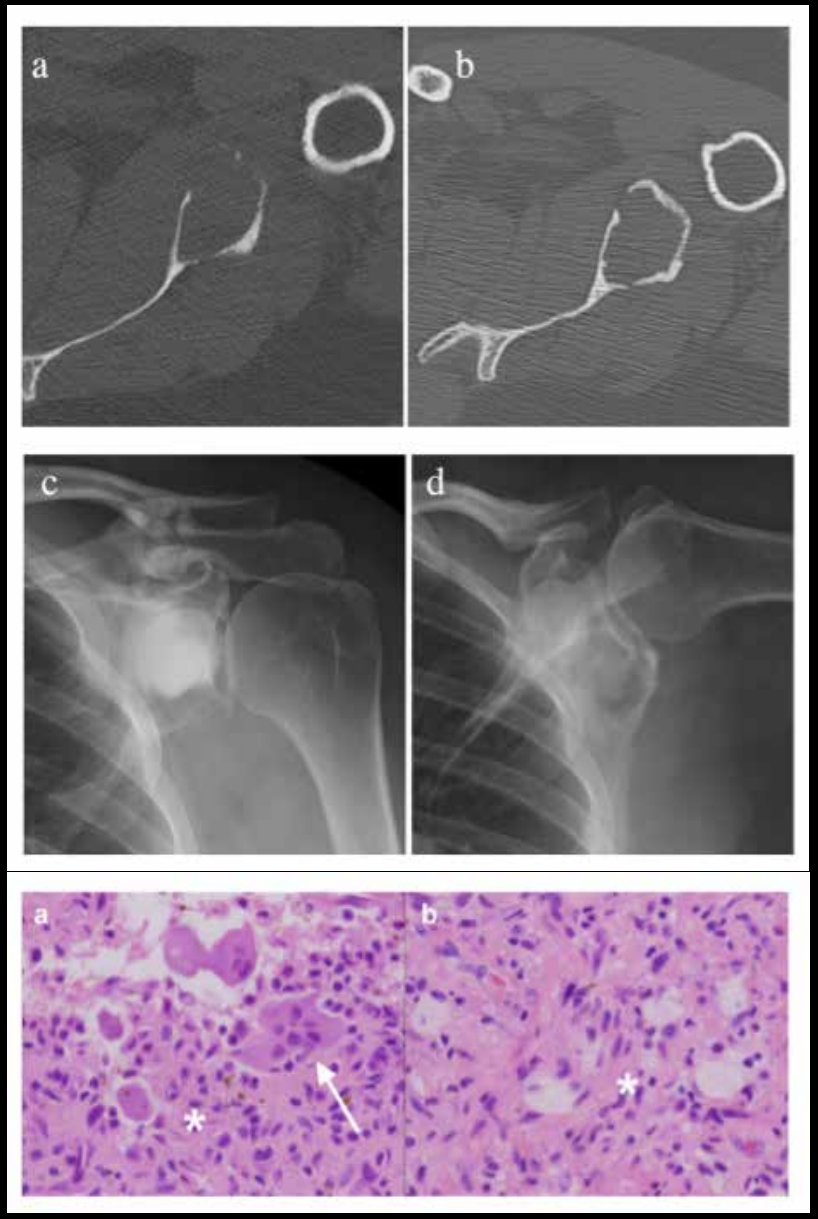


Fig. 1-B

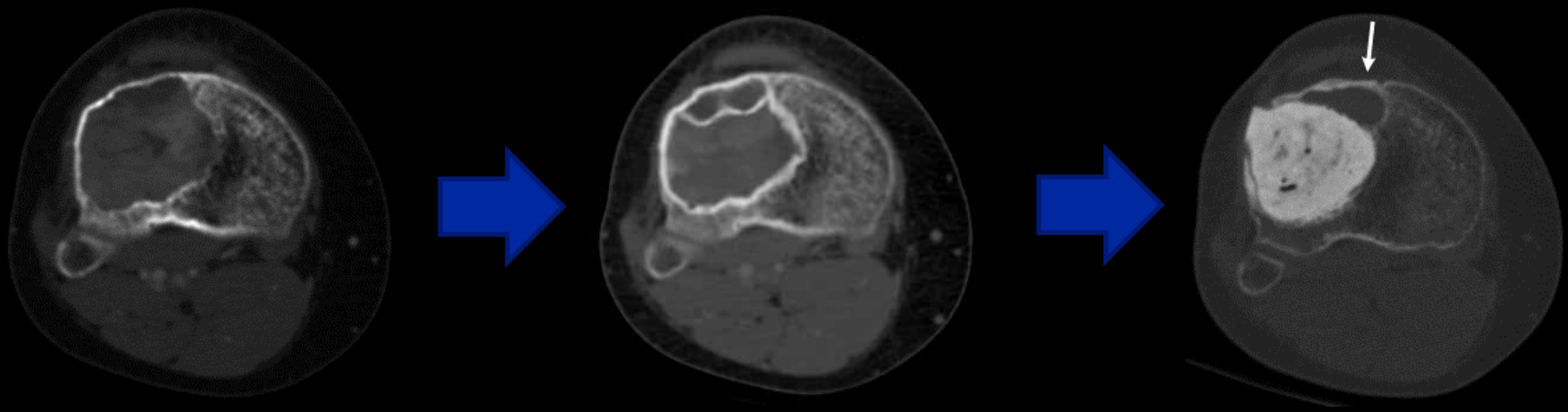
- Once the giant cell tumor tissue was no longer exposed to denosumab, the stromal cells continued to proliferate in vitro, albeit to a lesser degree



GCTB
before
denosumab

GCTB
after
denosumab

Local
Recurrence
GCTB



Ann Surg Oncol (2015) 22:2860–2868
DOI 10.1245/s10434-015-4634-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – CTOS – BONE AND SOFT TISSUE SARCOMAS

Surgical Downstaging in an Open-Label Phase II Trial of Denosumab in Patients with Giant Cell Tumor of Bone

Piotr Rutkowski, MD, PhD[1], Stefano Ferrari, MD[2], Robert J. Grimer, MB, BS[3], Paul D. Stalley, MB, BS[4], Sander P. D. Dijkstra, PhD[5], Andrzej Pienkowski, MD, PhD[1], Gualter Vaz, MD[6], Jay S. Wunder, MD[7], Leanne L. Seeger, MD[8], Amy Feng, PhD[9], Zachary J. Roberts, MD, PhD[10], and Bruce A. Bach, MD, PhD[10]

- For patients with resectable GCTB, neoadjuvant denosumab therapy resulted in beneficial surgical downstaging, including either no surgery or a less morbid surgical procedure


Before Denosumab
After Denosumab
a
b
c
d

European Journal of Cancer 59 (2016) 1–12

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone

Frank Traub [a], Janith Singh [a], Brendan C. Dickson [c], Stephanie Leung [d], Rakesh Mohankumar [d], Martin E. Blackstein [e], Albiruni R. Razak [e], Anthony M. Griffin [a], Peter C. Ferguson [a,b], Jay S. Wunder [a,b,*]

- Denosumab facilitates less aggressive surgical treatment, especially joint preservation
- However, the local recurrence rate for GCTB following resection does not seem to be affected by denosumab and remains a concern

- The new osseous tumor matrix and the thickened cortical bone that develop following denosumab treatment raises a new surgical challenge by not allowing the surgeon to delineate the true extent of the tumor

Observational Study

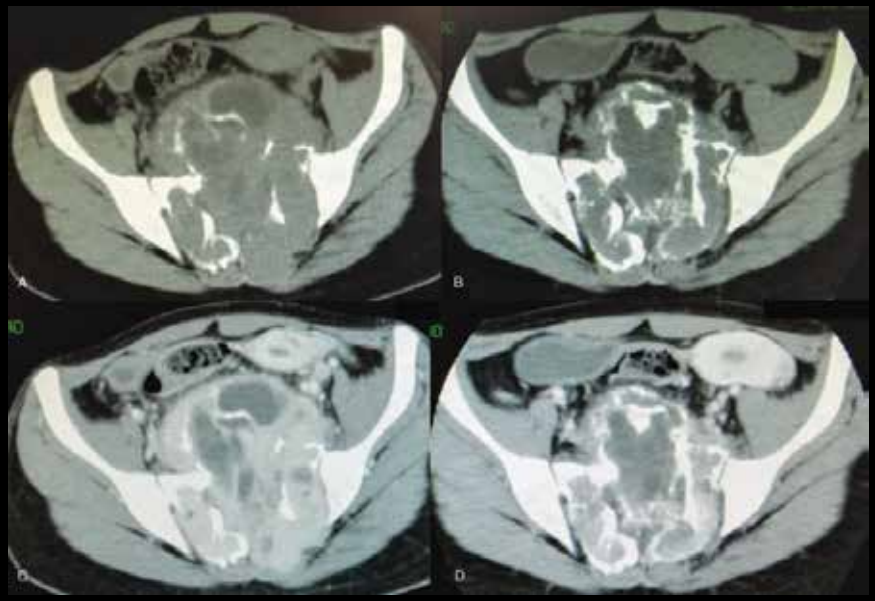
Medicine®

OPEN

A nonrandomized controlled study of sacral giant cell tumors with preoperative treatment of denosumab

Yongkun Yang, MD*, Yuan Li, MD, Weifeng Liu, MD, Hairong Xu, MD, Xiaohui Niu, MD*

- Preoperative denosumab treatment has the tendency to reduce blood supply and intraoperative bleeding of sacral GCT
- But the sclerosis and bony separation can increase the difficulty of tumor curettage and lead to high recurrence rate after denosumab treatment.



International Orthopaedics (SICOT)
DOI 10.1007/s00264-017-3536-9

REVIEW ARTICLE

How safe and effective is denosumab for bone giant cell tumour?

Costantino Errani [1] · Shinji Tsukamoto [2] · Andreas F. Mavrogenis [3]

- Nine cases of malignant transformation of GCT during denosumab therapy without previous radiation exposure have been reported
- Inhibition of RANKL may increase the risk of new malignancies due to immunosuppression

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2017, 47(11) 1090–1096
doi: 10.1093/jjco/hyx112
Advance Access Publication Date: 9 August 2017
Case Report

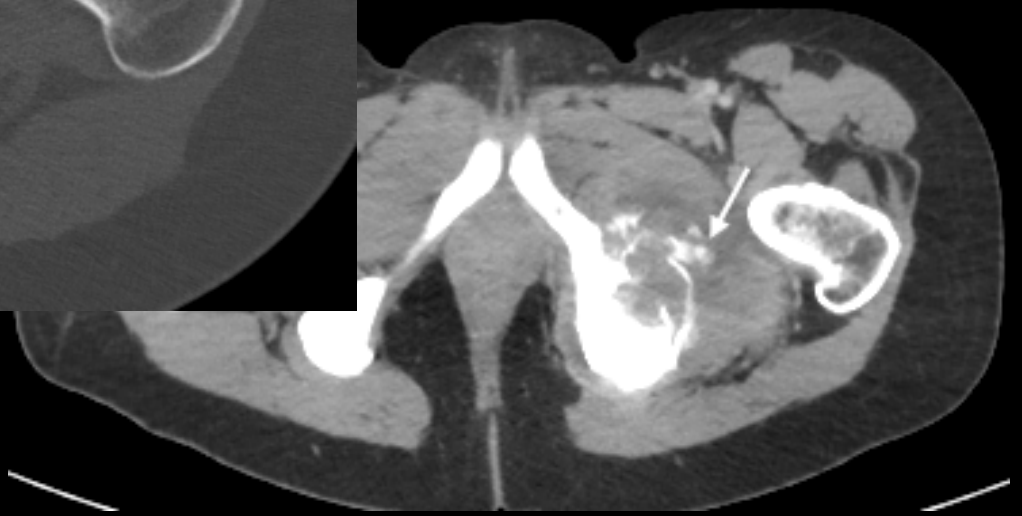
OXFORD

Case Report

Development of high-grade osteosarcoma in a patient with recurrent giant cell tumor of the ischium while receiving treatment with denosumab

Shinji Tsukamoto[1,*], Alberto Righi[2], Daniel Vanel[2], Kanya Honoki[1], Davide Maria Donati[3], and Costantino Errani[3]


R
10 cm



Clin Orthop Relat Res (2018) 476:1783-1790
DOI 10.1007/s11999.0000000000000104

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

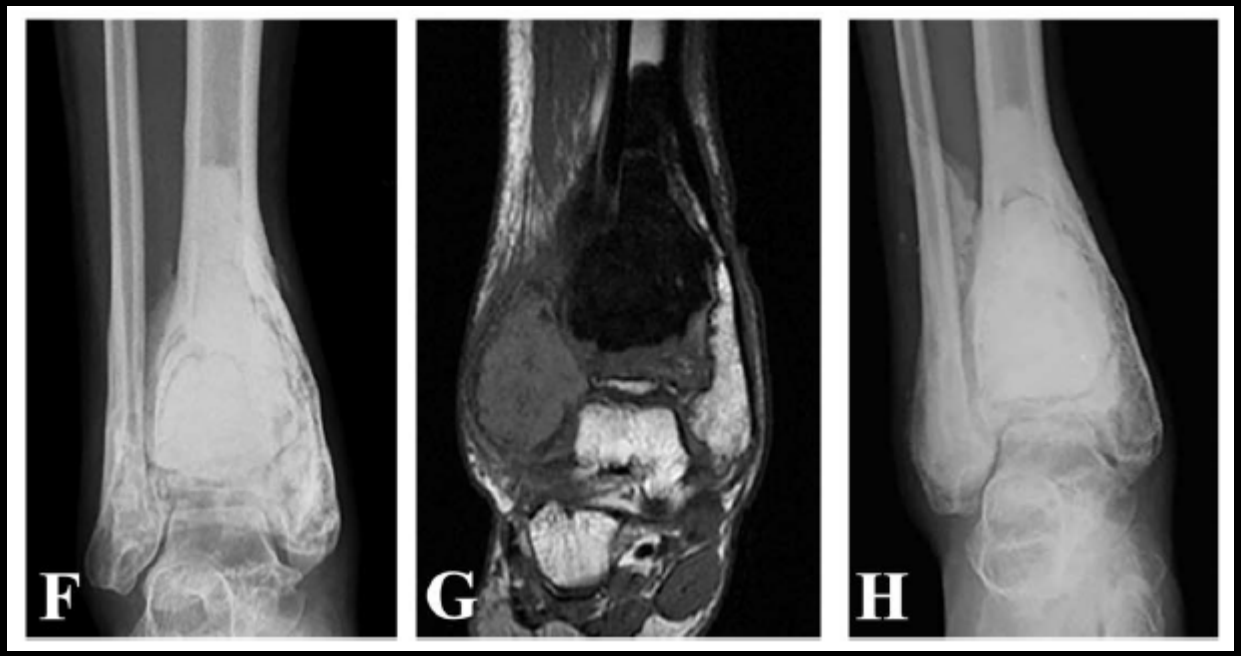
2017 International Society of Limb Salvage Proceedings

Preoperative Denosumab With Curettage and Cryotherapy in Giant Cell Tumor of Bone: Is There an Increased Risk of Local Recurrence?

Guido Scoccianti MD, Francesca Totti MD, Maurizio Scorianz MD, Giacomo Baldi MD, Giuliana Roselli MD, Giovanni Beltrami MD, Alessandro Franchi MD, Rodolfo Capanna MD, Domenico Andrea Campanacci MD

- Perhaps facilitates curettage in some patients
- No decrease in the risk of local recurrence
- No adverse effects with denosumab
  - we caution readers that this study was underpowered to detect even relatively common complications
- Primary intralesional surgery without denosumab seems more prudent when curettage is feasible at presentation


A
B
C
D


F
G
H

Clin Orthop Relat Res (2018) 476:1773-1782
DOI 10.1007/s11999.0000000000000243

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

2017 International Society of Limb Salvage Proceedings

Does Denosumab Change the Giant Cell Tumor Treatment Strategy? Lessons Learned From Early Experience

Manish G. Agarwal MS Orth, Manit K. Gundavda DNB Orth, Rajat Gupta MS Orth, Rajeev Reddy DNB Orth

- We advise caution in its routine use for intralesional procedures
  - Local recurrence
  - Malignant degeneration

- It may be important to curette up to margins on pretreatment imaging owing to the potential residual tumor within the denosumab-mediated thick bony shell, which may result in local recurrence

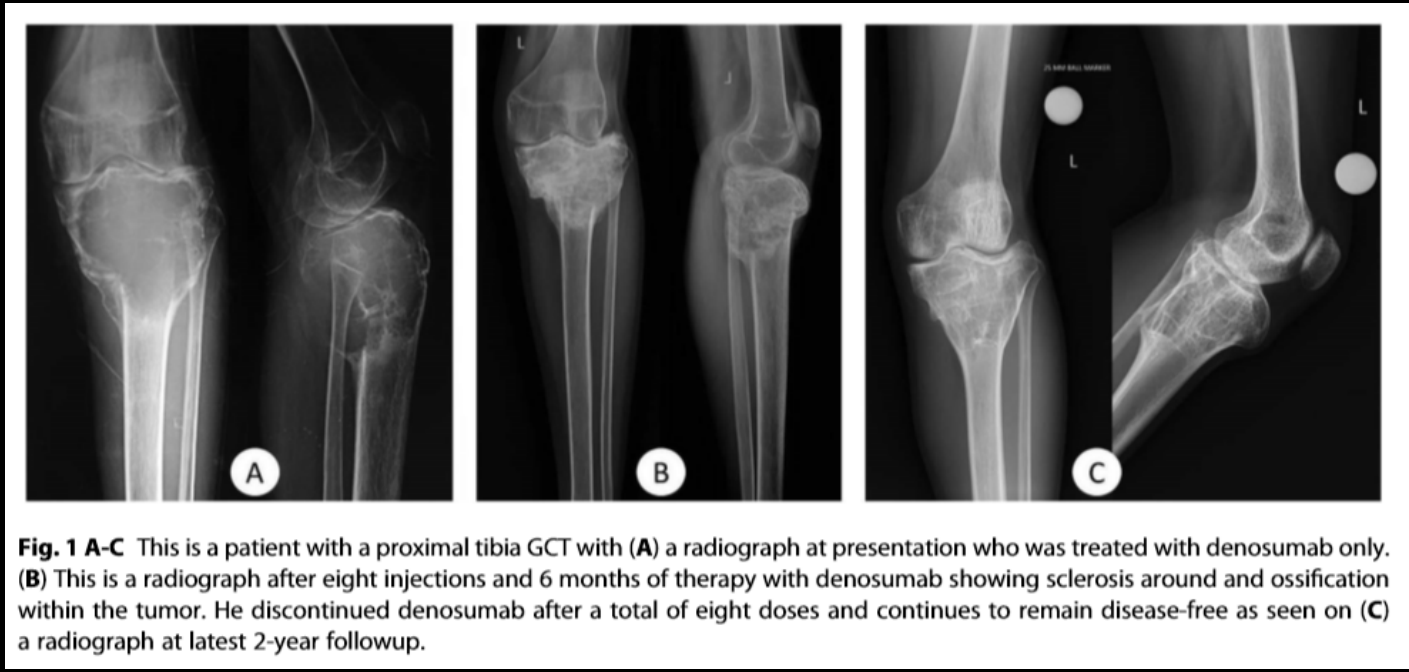


Fig. 1 A-C This is a patient with a proximal tibia GCT with (**A**) a radiograph at presentation who was treated with denosumab only. (**B**) This is a radiograph after eight injections and 6 months of therapy with denosumab showing sclerosis around and ossification within the tumor. He discontinued denosumab after a total of eight doses and continues to remain disease-free as seen on (**C**) a radiograph at latest 2-year followup.

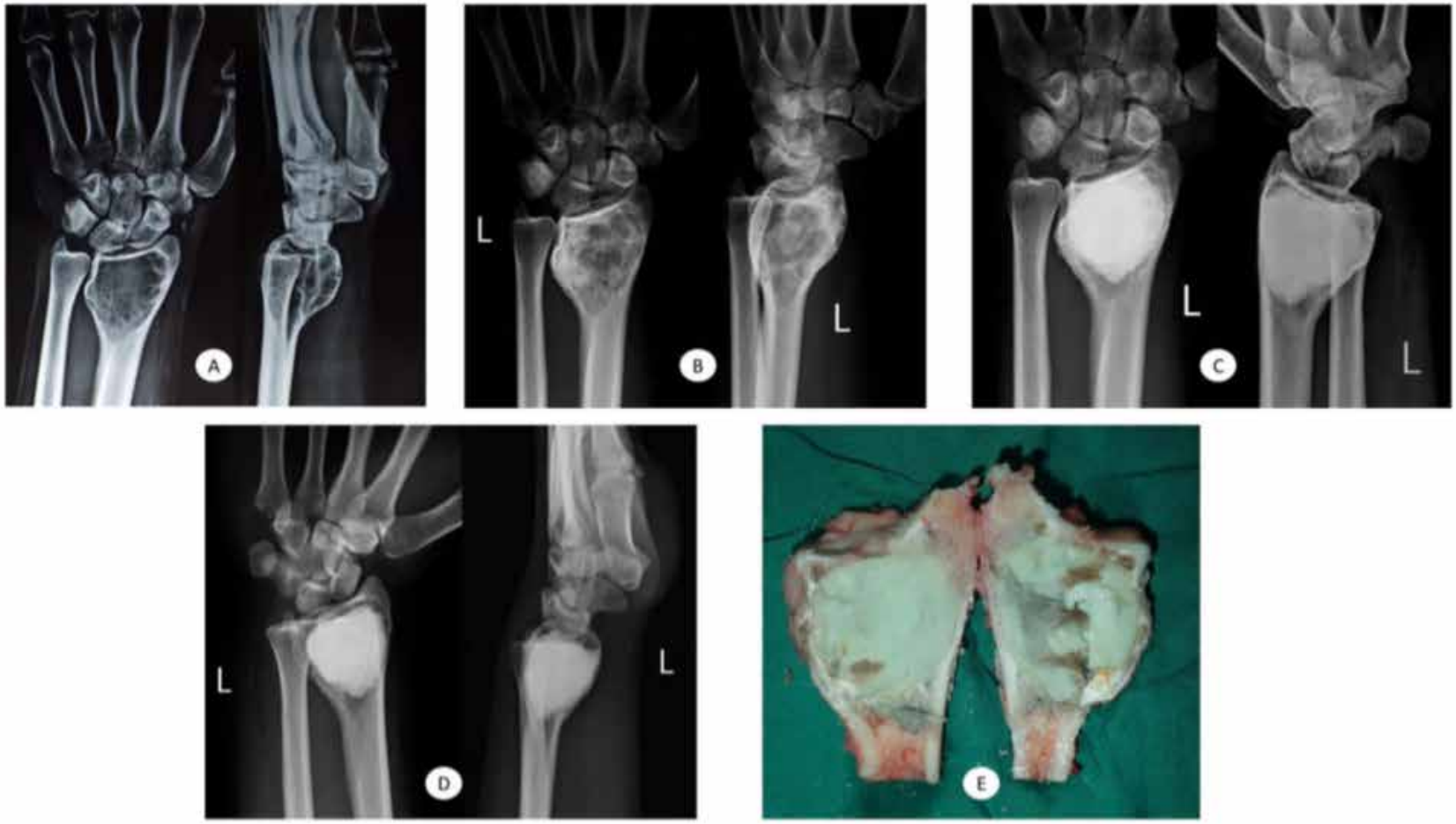


Fig. 3 A-E This is a (**A**) radiograph of a patient with a distal radius GCT who was treated with denosumab to allow formation of a (**B**) bony shell and sclerosis to solidify the tumor to allow joint salvage intralesional surgery, but we observed on the (**C**) postoperative radiograph that margins of curettage (space filled with bone cement) are confined within the bony shell formed postdenosumab and have not been extended beyond the pretreatment tumor. Ten months postsurgery, a radiograph (**D**) with presence of pericement lysis was suggestive of local recurrence and the patient underwent resection for local recurrence; (**E**) split section of the resected specimen showing disease in the subchondral area beyond the cement.

- Malignancy-causing potential from our observation in one patient as well as reports of this by others and recommend judicious use of this drug in patients with GCT

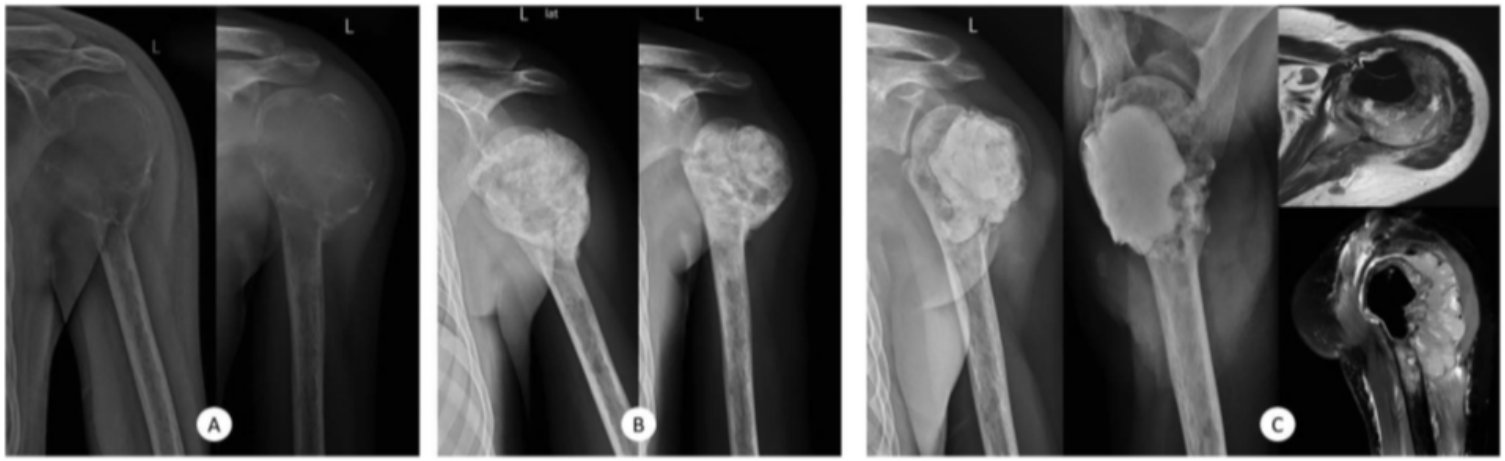


Fig. 2 A-C This shows a patient with a proximal humerus GCT with (**A**) a radiograph at presentation who was treated with eight injections of denosumab, which led to (**B**) bony shell formation and sclerosis within the lesion after which the patient underwent intralesional surgery for disease clearance. Eight months postoperatively the patient presented with a local recurrence, which as seen on (**C**) radiography and MRI suggested aggressive malignant transformation. Biopsy confirmed osteosarcoma.

Denosumab May Increase the Risk of Local Recurrence in Patients with Giant-Cell Tumor of Bone Treated with Curettage

Costantino Errani, MD, PhD, Shinji Tsukamoto, MD, PhD, Giulio Leone, MD, Alberto Righi, MD, PhD, Manabu Akahane, MD, PhD, Yasuhito Tanaka, MD, PhD, and Davide Maria Donati, MD, PhD

Investigation performed at the Departments of Orthopaedic Oncology and Pathology, Rizzoli Institute, Bologna, Italy

- Viable tumor was present in all 30 specimens from patients treated with denosumab
- There was a higher rate of recurrence in the cohort exposed to denosumab

Pathology

- Tumour cells may hide within the thickened cortex and subchondral bone that develop after denosumab administration, where the neoplastic cells may initiate proliferation once the microenvironment is free of denosumab
- The new osseous tumor matrix and the thickened cortical bone that develop with denosumab administration raise a new surgical challenge through not allowing the surgeon to delineate the true extent of the tumour, thereby increasing the risk of local recurrence

International Orthopaedics
https://doi.org/10.1007/s00264-018-4085-6

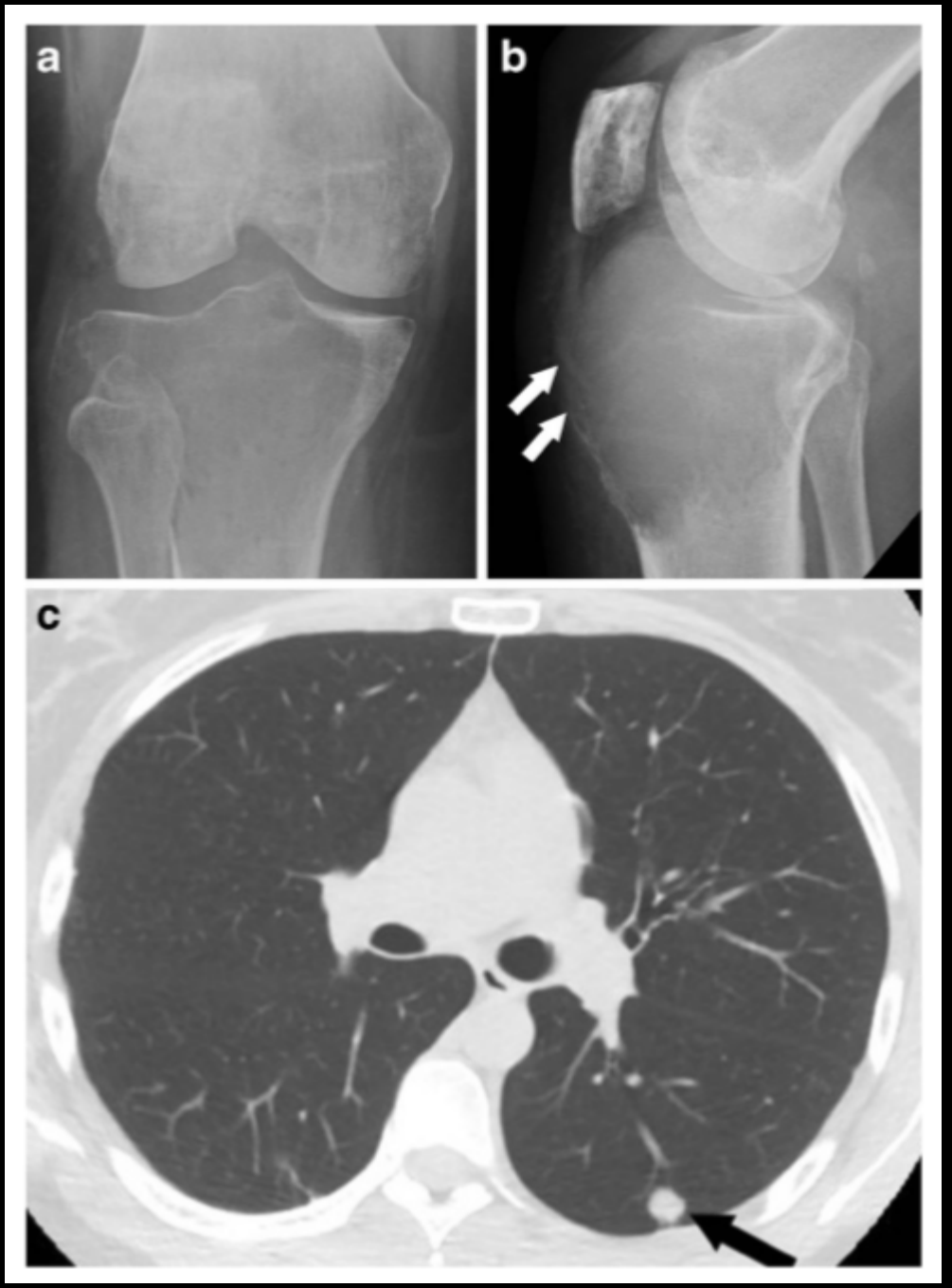
ORIGINAL PAPER

Denosumab does not decrease the risk of lung metastases from bone giant cell tumour

Shinji Tsukamoto[1] · Andreas F. Mavrogenis[2] · Giulio Leone[3] · Alberto Righi[4] · Manabu Akahane[5] · Tanzi Piergiuseppe[6] · Akira Kido[1] · Kanya Honoki[1] · Yasuhito Tanaka[1] · Davide Maria Donati[6] · Costantino Errani[6]

- Denosumab does not decrease the risk for GCT lung metastases

- Campanacci stage and type of surgery were the only univariate predictors for lung metastases
- Type of surgery and local recurrence were the only multivariate predictors for lung metastases



The Lancet Oncology
Manuscript Draft

Manuscript Number: THELANCETONCOLOGY-D-19-00403

Title: Safety and efficacy of denosumab in patients with giant cell tumour of bone: results of an open-label phase 2 study

Article Type: Article (Clinical Trials)

- Unpublished data

- 532 pts
- hypophosphataemia, osteonecrosis of the jaw (ONJ), pain in extremity, atypical femur fracture, hypercalcaemia, sarcomatous transformation (20 cases, 4%)
- Clinical benefit (80%)
- Recurrence was higher for curettage (34%) than excision (12%)

Journal of Bone Oncology 15 (2019) 100217

Contents lists available at ScienceDirect

Journal of Bone Oncology

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

Research Paper

Denosumab versus zoledronic acid in cases of surgically unsalvageable giant cell tumor of bone: A randomized clinical trial

Shenglong Li*, Peng Chen, Qiankun Yang

Department of Bone and Soft Tissue Tumor Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, No 44 of Xiaoheyan Road, Dadong District, Shenyang, Liaoning Province 110042, China

- Denosumab and zoledronic acid had similar tumor responses (*p= 0.18*) and clinical benefits (*p= 0.476*)

Evaluation parameters at the end of the treatment.

Parameters	Disease status	Groups		Comparison between groups
		DB	ZA	
	Intervention	Denosumab	Zoledronic acid	
	Sample size	125	125	*p*-value
Clinical benefits	[a]Pain reduction	38 (30)	35 (28)	0.476
	Improved mobility	28 (23)	22 (18)	
	Improved functional activity	26 (21)	24 (19)	
	Slight or no significant clinical improvement	33 (26)	44 (35)	
Disease status	[b]Disease progression	1 (1)	2 (2)	0.18
	[c]Stable disease	69 (55)	73 (58)	
	[d]Fractional response	41 (33)	45 (36)	
	[e]Complete response	14 (11)[f]	5 (4)	

- Side effects
  - Denosumab caused fatigue ($p = 0.0004$) and back pain ($p < 0.0001$), while zoledronic acid caused hypo-calcemia ($p < 0.0001$),flu-like symptoms ($p = 0.021$), hypotension ($p = 0.021$), and hypokalemia ($p = 0.021$)
- Cost
  - Denosumab treatment was markedly more expensive than zoledronic acid treatment ($p < 0.0001$)
  - The cost to manage treatment adverse effects was higher for the ZA group than the DB group ($p = 0.0425$)