La gestione del paziente con metastasi ossee da carcinoma del polmone mutato e riarrangiato

Elisa Roca
Oncolgia Medica
Spedali Civili di Brescia
elisaroca@gmail.com

INTRODUCTION

Bone metastases in NSCLC

- Worldwide, lung cancer is the leading cause of cancer-related death
- Overall 5 year survival rate for NSCLC is around 15%
- For patients which bone M+ median OS is <6 months and 5 years OS rate is <5%
- NSCLC = third most common cause of bone metastases (I:breast, II:prostate cancer)

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-tieulent J, Jemal A. Global Cancer Statistics, 2012. *CA a cancer J Clin*. 2015;65(2):87-108.
Yu JL, Simmons C, Victor JC, et al. Impact of new chemotherapeutic and targeted agents on survival in stage IV non-small cell lung cancer. *Oncologist*. 2011;16(9):1307-1315.
Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev*. 2001;27(3):165-176.

INTRODUCTION

Bone metastases in NSCLC

- About 80% of patients with bone M+ will experience significant pain and a reduction of QoL
- Over 60% of patients with BM will develop skeletal-related events (SREs)

✓ **Bone surgery**
✓ **Radiotherapy**
✓ **Pathological fractures**
✓ **Spinal cord compression**
✓ **Hypercalcemia**

- SREs → pain, decreased quality of life, declines in physical, functional and emotional well being and negatively affect survival

Kuchuk M, Kuchuk I, Sabri E, Hutton B, Clemons M, Wheatley-Price P. The incidence and clinical impact of bone metastases in non-small cell lung cancer. *Lung Cancer*. 2015;89(2):197-202.

INTRODUCTION

Bone metastases in NSCLC

- Incidence of bone metastasis in NSCLC
  - 30–40% during the clinical course
  - 60% at the time of diagnosis
- MST (bone Metastasis Survival Time) → 7 months
- Presence of bone metastases → negative prognostic
- Bone metastases have a greater negative impact on the OS and the QoL

Rosen, Cancer. (2004).
Price, N., Clin Lung Cancer. (2004)

Kosteva, J. Lung Cancer. (2004)
Coleman, Cancer. (1997)

Weinfurt, K. P. Ann Oncol. (2005)
Lipton, A. Cancer. (2000).

The Past…

The Past…

Bone M+ in NSCLC

Reference	Total number of patients	BM+ at diagnosis	ADK BM+	Squamo BM+	Treatment of NSCLC	Treatment of BM	PFS	OS
Rosen, 2003	280	280 (100%)	nd	nd	nd	Biphosphonates	nd	6.7 vs 6.1 (zoledronic acid vs placebo)
Hendriks, 2014	186	64 (34,4%)	162	nd	CT vs TKI (119 vs 48)	nd	nd	15.5 vs 9.0 vs 3.2 (EGFR+ vs KRAS+ vs WT)
Murakami , 2014	100	100 (100%)	77	12	Docetaxel (after one or two prior line of CT)	Zoledronic acid	2.7 vs 2.6 (docetaxel+zoledronic acid vs docetaxel)	10.4 vs 9.7 (docetaxel+zoledronic acid vs docetaxel)
Huang , 2015	114	62 (54,4%)	62	0	TKI	Biphosphonates	15.0 vs 7.3 (TKI+biphosponates vs TKI)	25.2 vs 10.4 (TKI+biphosponates vs TKI)
Santini, 2015	2003	661 (33%)	436	nd	CT vs TKI (564 vs 199)	Biphosphonates	nd	9.5
Chen, 2016	1510	234 (15,5%)	292	nd	nd	nd	nd	10.5
Zhang, 2017	2975	1560 (52,4%)	552	nd	CT	Biphosphonates	5.5 vs 5.6 (CT+biphosphonates vs CT)	13.7 vs 13.6 (CT+biphosphonates vs CT)

The Past…

Bone M+ in Mutated NSCLC

Lung Cancer 84 (2014) 86–91

Contents lists available at ScienceDirect

Lung Cancer

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

EGFR mutated non-small cell lung cancer patients: More prone to development of bone and brain metastases?

L.E.L. Hendriks[a,*], E.F. Smit[b], B.A.H. Vosse[a], W.W. Mellema[b], D.A.M. Heideman[c], G.P. Bootsma[d], M. Westenend[e], C. Pitz[f], G.J. de Vries[g], R. Houben[h], K. Grünberg[c], M. Bendek[i], E.-J.M. Speel[i], A.-M.C. Dingemans[a]

The Past…

Bone M+ in Mutated NSCLC

Mutation status and bone/brain metastases.

	EGFR+ N = 62	KRAS+ N = 65	Wildtype N = 62	p-Value
Bone metastases				
Imaging at 1st diagnosis of mNSCLC N (%)				
PET-CT	38 (61.3)	46 (70.8)	48 (77.4)	0.232
CT[a]	17 (27.4)	13 (20.0)	11 (17.7)	
Bone scintigraphy[b]	5 (8.1)	4 (6.2)	2 (3.3)	
Missing	2 (3.2)	2 (3.0)	1 (1.6)	
Bone mets N (%)				
Yes	37 (59.7)	34 (52.3)	31 (50.0)	0.528
At diagnosis	20 (54.1)	26 (76.5)	18 (58.1)	0.121
During follow up	17 (45.9)	8 (23.5)	13 (41.9)	
No	25 (40.3)	31 (47.7)	31 (50.0)	
Time to bone mets months [SD]	13.4 [±10.6]	23.3 [±19.4]	16.4 [±9.6]	0.201
SRE+ N (%)	19 (51.4)	22 (64.7)	15 (48.4)	0.361
Time to 1st SRE months [95% CI]	12.9 [5.0–20.7]	7.3 [0.0–14.9]	3.5 [0–7.7]	0.213
Post bone mets survival months [95% CI]	15.5 [10.6–20.3]	9.0 [5.2–12.9]	3.2 [0–6.9]	EGFR/KRAS 0.049 EGFR/WT 0.004

EGFR: epidermal growth factor receptor; 95% CI = 95% confidence interval; SD = standard deviation; SRE = skeletal related event; EGFR-TKI = epidermal growth factor receptor; WBRT = whole brain radiotherapy; SRS = stereotactic radiosurgery.

[a] Ct-thorax/upper abdomen.

[b] When both PET-CT and bone scintigraphy were performed, patients were scored for "PET-CT".

[c] Only low dose CT brain during PET-CT was scored as "none".

Hendriks L.E.L. Lung Cancer 2014

The Past…

Bone M+ in Mutated NSCLC

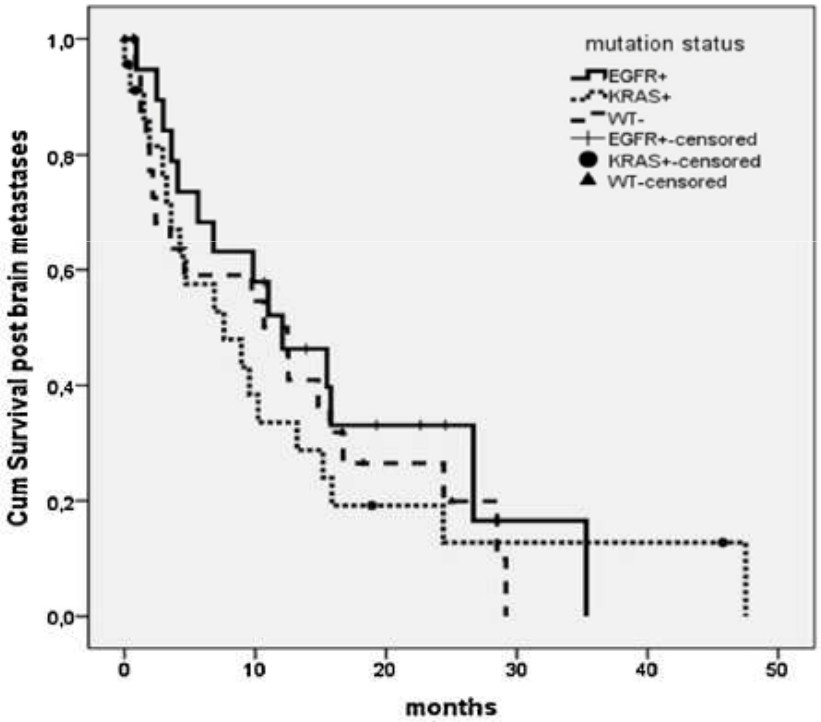

Fig. 2. survival post brain metastases for EGFR+, KRAS+ and WT patients.

5. Conclusion

Incidence of metastatic bone disease and brain metastases was not different between EGFR+, KRAS+ and WT patients. Furthermore, survival post metastatic bone disease was significantly longer in the EGFR+ group, which stresses the impact of bone management especially in these patients and probably warrant more intense screening for metastatic bone disease.

Hendriks L.E.L. Lung Cancer 2014

The Past…

Bone M+ in Mutated NSCLC

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 41

Research Paper

Bisphosphonates enhance EGFR-TKIs efficacy in advanced NSCLC patients with EGFR activating mutation: A retrospective study

Chu-Ying Huang[1,3,*], Li Wang[1,4,*], Cheng-Jun Feng[1,*], Ping Yu[2,*], Xiao-Hong Cai[2], Wen-Xiu Yao[2], Yong Xu[1], Xiao-Ke Liu[1], Wen-Jiang Zhu[1], Yan Wang[1,5], Jin Zhou[2], You Lu[1], Yong-Sheng Wang[1]

The Past…

Bone M+ in Mutated NSCLC

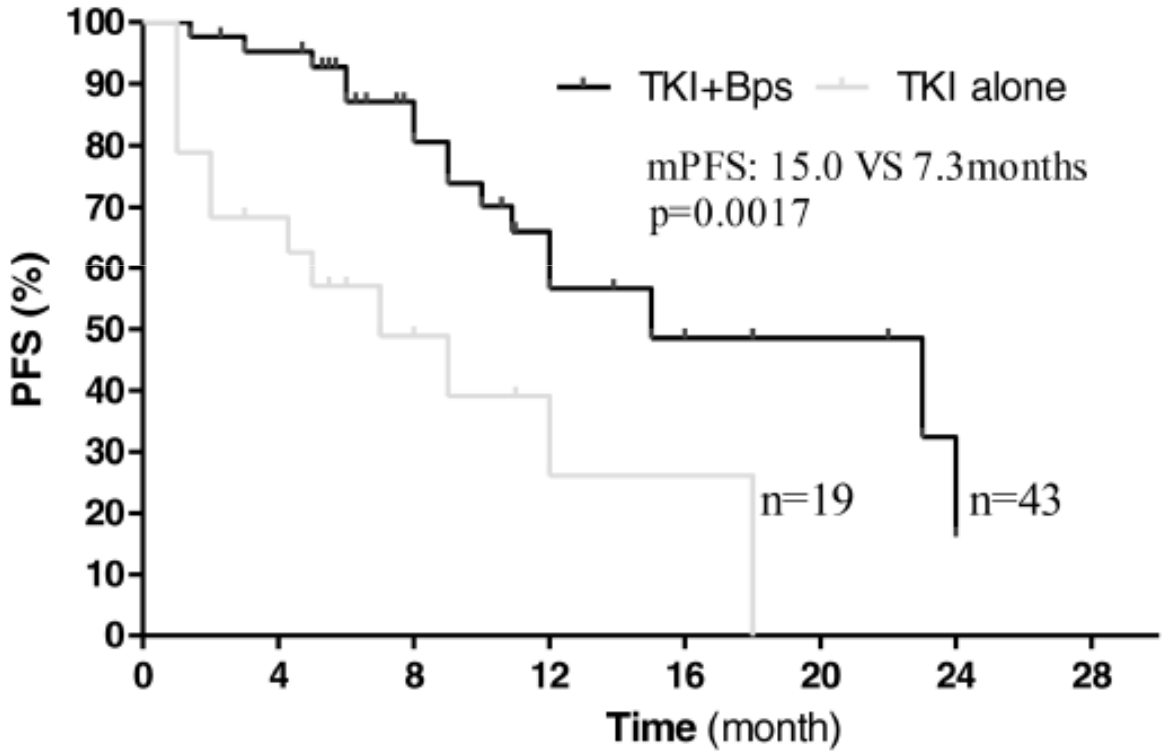

Figure 1: Kaplan–Meier curves showing progression-free survival, stratified by the use of bisphosphonates.

Huang C.Y., Oncotarget. 2015

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Bone M+ in Mutated NSCLC

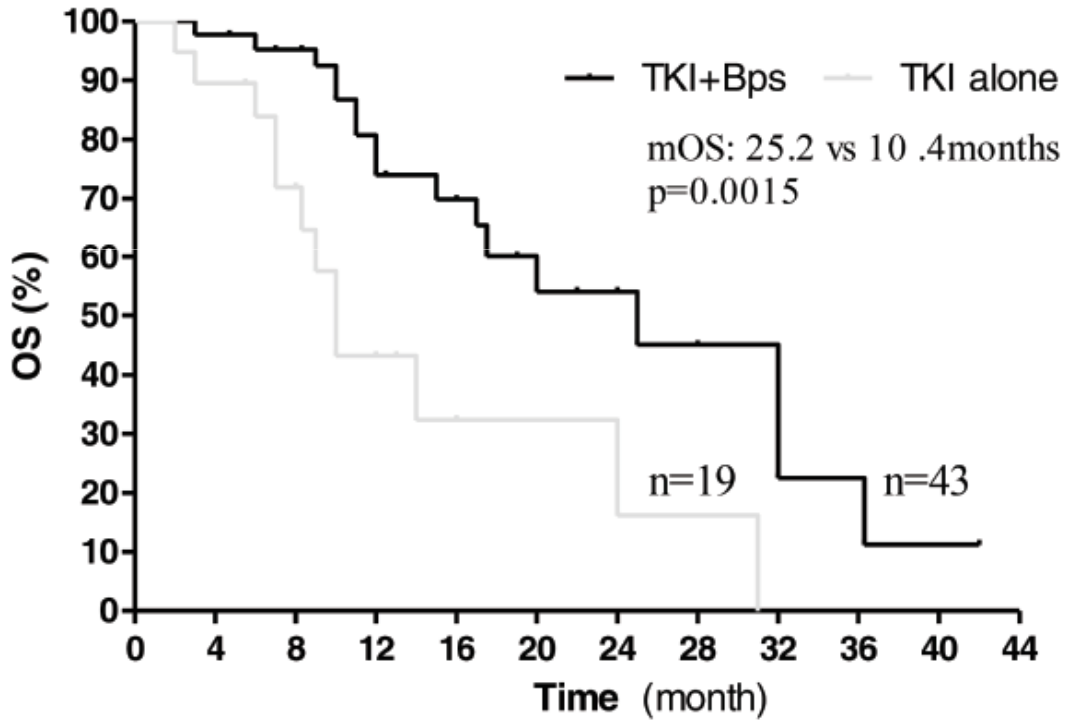

Figure 2: Kaplan–Meier curves showing overall survival, stratified by the use of bisphosphonates.

Huang C.Y., Oncotarget. 2015

The Past…

Bone M+ in Mutated NSCLC

Conclusions: Concomitant use of bisphosphonates and EGFR-TKIs improves therapeutic efficacy and brings survival benefits to NSCLC patients with EGFR mutation and bone metastases.

Huang C.Y., Oncotarget. 2015

The Past…

Bone M+ in Mutated NSCLC

SCIENTIFIC REPORTS

OPEN

Natural History of Non-Small-Cell Lung Cancer with Bone Metastases

Santini Daniele[1], Barni Sandro[2], Intagliata Salvatore[1], Falcone Alfredo[3], Ferraù Francesco[4], Galetta Domenico[5], Moscetti Luca[6], La Verde Nicla[7], Ibrahim Toni[8], Petrelli Fausto[2], Vasile Enrico[3], Ginocchi Laura[3], Ottaviani Davide[9], Longo Flavia[10], Ortega Cinzia[11], Russo Antonio[12], Badalamenti Giuseppe[12], Collovà Elena[13], Lanzetta Gaetano[14], Mansueto Giovanni[15], Adamo Vincenzo[16], De Marinis Filippo[17], Satolli Maria Antonietta[18], Cantile Flavia[19], Mancuso Andrea[20], Tanca Francesca Maria[21], Addeo Raffaele[22], Russano Marco[1], M Sterpi[1], Pantano Francesco[1], Vincenzi Bruno[1] & Tonini Giuseppe[1]

Received: 13 July 2015
Accepted: 18 November 2015
Published: 22 December 2015

The Past…

Bone M+ in Mutated NSCLC

Tumor Characteristics And Treatments	N° Patients
Surgery	
No	81,4% (531)
Yes	18,6% (121)
First-Line Treatment	
Chemotherapy	
No	5,7% (34)
Yes	94,3% (564)
Platinum-based	54,9% (388)
Other Therapies	45,1% (265)
Tkis	
No	69.4% (452)
Yes	30,6% (199)
Gefitinib	22,1% (44)
Erlotinib	77,9% (155)

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The Past…

Bone M+ in Mutated NSCLC

- 57.5% bone M+ at diagnosis
- 57.7% SRE

- **9 months** = time to bone M+
- **6 months** = time to first SRE

- **9.5 m** = survival after bone M+ diagnosis
- **7 m** = survival after the first SRE

- **6 m** = survival if SRE as onset of bone M+
- **10 m** = survival if SRE after diagnosis of bones M+

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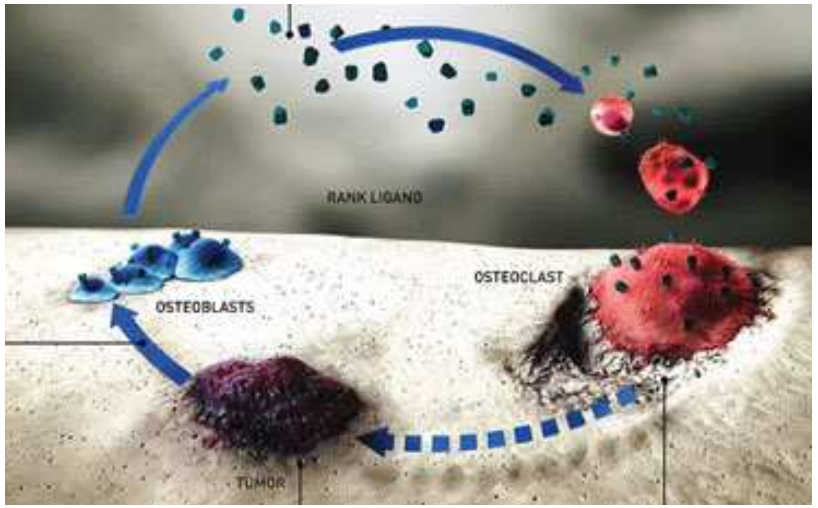
The Past…

Bone M+ in Mutated NSCLC

Most frequent first, second, third and subsequent SREs

SREs	First SRE	Second SRE	Third and subsequent SREs
Radiotherapy	71.4% (262)	79.2% (76)	61.9% (13)
Pathologic fractures	16.3% (60)	9.4% (9)	19% (4)
Spinal cord compression	6% (22)	2.1% (2)	9.5% (2)
Hypercalcemia	4.1% (15)	4.2% (4)	9.5% (2)
Surgery	3.3% (12)	5.2% (5)	14.3% (3)



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The Past…

Bone M+ in Mutated NSCLC

Univariate Analysis

Parameters		Median OS (months)	P-value	95% CI
Age	>64	7	0.008	6.253–7.747
	<64	8		7.161–8.839
ECOG PS at diagnosis	0–1	8	0.001	7.457–8.543
	>2	3.5		3.080–3.920
Histology	Adenocarcinoma	8	0.001	7.099–8.901
	Others	6		5.312–6.688
Stage at diagnosis	I	14	0.004	9.639–18.631
	II	6		2.412–9.588
	IIIa	9		7.075–10.925
	IIIb	9		5.720–12.280
	IV	7		6.437–7.563
First-line treatment	CT	8	0.001	7.463–8.537
	TKIs	3		2.324–3.676
Platinum-based chemotherapy	Yes	8	0.001	7.081–8.919
	No	5		4.089–5.911
First-line TKIs	Yes	12	0.001	10.466–13.534
	No	6		5.395–6.605
ECOG PS at bone metastasis diagnosis	0–1	8	0.001	7.510–8.490
	>2	4		3.104–4.896
Number of SREs	0	6	0.001	5.403–6.597
	1	8		7.117–8.883
	2	10		7.330–12.670
	3	12		7.268–17.932
Pathologic fracture	Yes	7	0.040	5.026–8.974
	No	8		6.744–9.256
Spinal cord compression	Yes	7	0.008	4.740–9.260
	No	9		7.864–10.136
Use of Biphospho	Yes	9	0.001	8.046–9.954
nates	No	5		4.244–5.756
Use of Zoledronic acid	Yes	9	0.001	8.120–9.880
	No	5		4.202–5.798
Use of Zoledronic acid before the first SRE onset	Yes	10	0.001	8.594–11.406
	No	7		6.358–7.642
Concomitant presence of visceral metastases	*Yes*	7	0.001	6.383–7.617
	No	10		8.277–11.722

Overall survival from bone metastasis diagnosis

Multivariate Analysis

Parameters		Median OS (months)	HR	P-value	95% CI
Histology	*Adenocarcinoma*	8	1,296	0.049	1.001–1.677
	Others	6			
Stage at diagnosis	*I*	14	1,17	0,01	1.039–1.327
	II	6			
	IIIa	9			
	IIIb	9			
	IV	7			
Platinum-based chemotherapy	*Yes*	8	0,66	0.002	0.511–0.861
	No	5			
Use of Zoledronic acid before the first SRE onset	*Yes*	10	0,77	0,046	0,609–0,995
	No	7			
Concomitant presence of visceral metastases	*Yes*	7	1.354	0.002	1.114–1,647
	No	10			

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The Past…

Bone M+ in Mutated NSCLC

Time to first bone metastasis onset

Univariate Analysis				
Parameters		**Median Time to bone met (months)**	**P-value**	**95% CI**
Age	>64	5	0.046	3.021–6.979
	<64	7		5.503–8.497
ECOG PS at diagnosis	0–1	7	0.012	5.928–8.072
	>2	2		0.000–4.191
Stage at diagnosis	I	16	0.001	9.426–22.574
	II	19		2.197–35.803
	IIIa	12		9.739–14.261
	IIIb	7		4.863–9.137
	IV	4		3.363–4.637
Surgical resection	Yes	11	0.004	6.051–15.949
	No	6		4.788–7.212
First-line treatment	CT	6	0.008	5.142–6.858
	TKIs	12		4.160–19.840
Pelvic bone metastasis	Yes	4.2	0.023	2.495–5.905
	No	8		5.835–10.165
Limb bone mestastasis	Yes	5	0.019	2.326–7.674
	No	7		5.447–8.553

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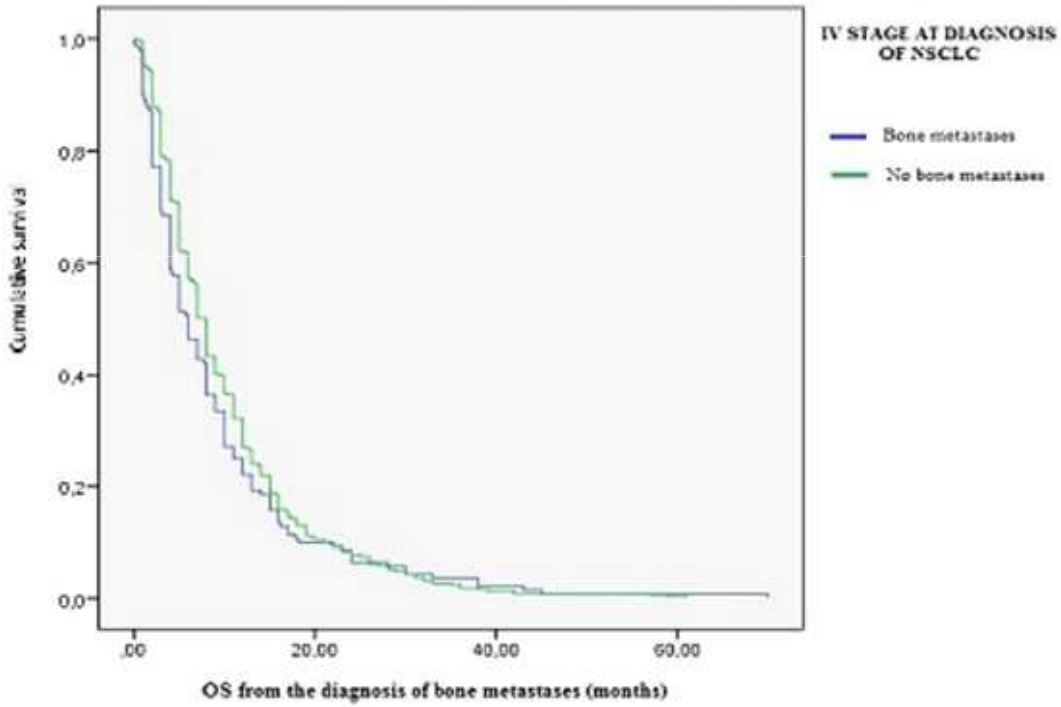
The Past…

Bone M+ in Mutated NSCLC



"The selective evaluation of patients with stage IV at diagnosis of NSCLC has **NOT** shown **statistically significant differences in OS** between **patients with bone metastases and patients without bone metastases at diagnosis**."

"**Not even** the **time to the onset of bone metastases** appears to be a **factor able to predict differences in overall survival from diagnosis of bone metastases**"

Figure 1. IV stage at diagnosis: patients with or without bone metastases. Kaplan-Meier survival analysis.

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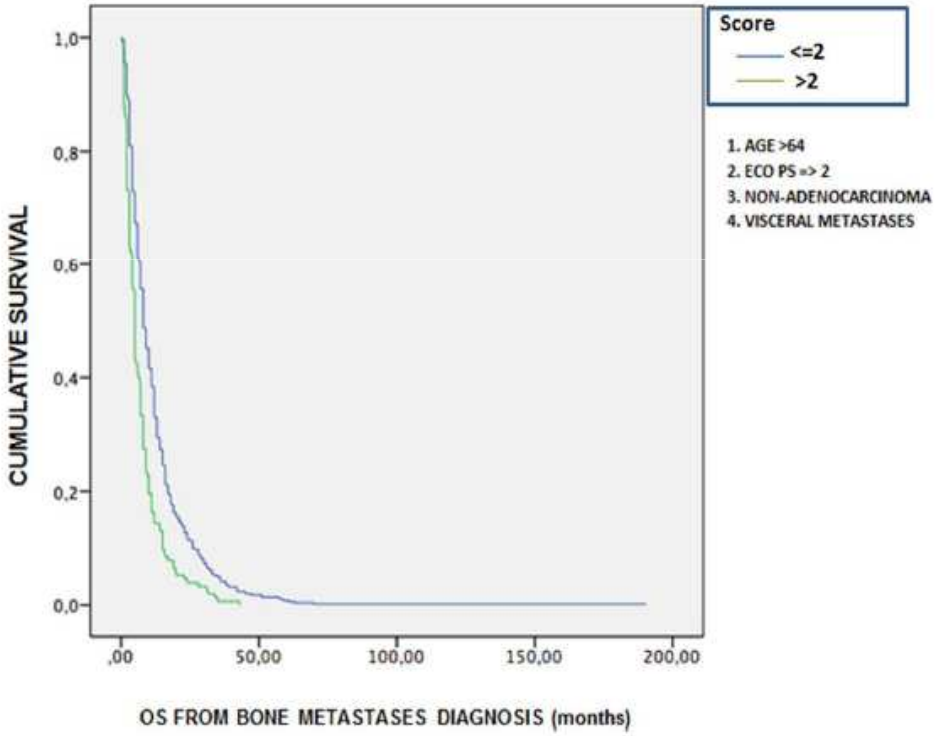
The Past…

Bone M+ in Mutated NSCLC



4 factors significant in the univariate analysis to **predict the OS from the diagnosis of bone metastases**:

- age >65 years,
- non-ADK,
- ECOG >2,
- concomitant presence of visceral M+

"The presence of >2 of these 4 factors is associated with a **worse prognosis**: median survival was 5m vs 8 m"

Figure 2. Score to predict a different prognosis at diagnosis of bone metastases. Kaplan-Meier survival analysis.

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The Past…

NSCLC EGFR+ and ALK+… Bone M+?

Reference	Trial Phase	Trial Name	TKI	Bone M+ EGFR wt (%)	Bone M+ EGFR+ (%)
Mok TS et al. NEJM 2009	III	IPASS	Gefitinib	nd	nd
Maemondo M et al. NEJM 2010	III	NEJ02	Gefitinib	nd	nd
Mitsudomi T et al. The Lancet 2010	III	WJTOG 3405	Gefitinib	nd	nd
Zouh C et al. The Lancet 2011	III	OPTIMAL	Erlotinib	nd	nd
Rossel R et al. The Lancet 2012	III	EURTAC	Erlotinib	nd	57 (32.94%)
Han JY et al. JCO 2012	III	First-SIGNAL	Gefitinib	nd	nd
Miller Va et al. The Lancet 2012	II	LUX-Lung 1	Afatinib	nd	nd
Sequist LV et al. JCO 2013	III	LUX-Lung 3	Afatinib	nd	nd
Shaw AT et al. NEJM 2013	III	PROFILE 1007	Crizotinib	nd	nd
Wu JL et al. The Lancet 2014	III	LUX-Lung 6	Afatinib	nd	nd
Solomon BJ et al. NEJM 2014	III	PROFILE 1014	Crizotinib	nd	nd
Blackhall F et al. ESMO Open 2017	II	PROFILE 1005	Crizotinib	nd	nd

The Present...

The Present...

Bone M+ in NSCLC EGFR+ and ALK+

PATIENT CHARACTERISTICS		
Total number of patients	124	
Gender	**N/124**	**%**
Male	47	37,90%
Female	77	62,09%
Age		
Median	70	
Range	34-99	
Performance Status	**N/124**	**%**
0	65	17,24%
1	53	79,31%

The Present...

Bone M+ in NSCLC EGFR+ and ALK+

Molecular biology at diagnosis	N/124	%
EGFR +	109	87,9%
Exon 18	2	1,61%
Exon 19	52	41,93%
Exon 20	2	1,61%
Exon 21	39	31,45%
Exon 18+20	1	0,8%
Exon 20+21	1	0,8%
Exon not available	27	21,77%
ALK rearrangement	15	12,09%
TKI	**N/124**	**%**
Erlotinib	12	9,67%
Gefitinib	79	63,7%
Afatinib	18	14,51%
Crizotinib	15	12,09%

The Present...

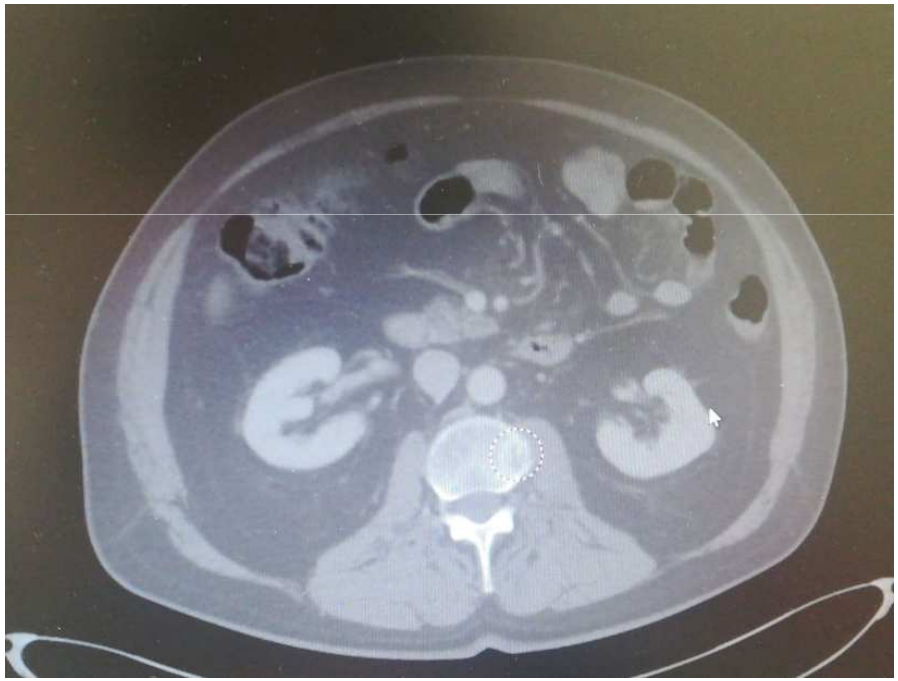
Bone M+ in NSCLC EGFR+ and ALK+

Bone metastases at diagnosis	N/124	%
Presents	60	48,38%
Absents	64	51,61%
Treatment of bone metastases	**N/60**	**%**
No specific therapy	28	46,66%
Biphosponates/Denosumab	9	15%
RT	23	38,33%

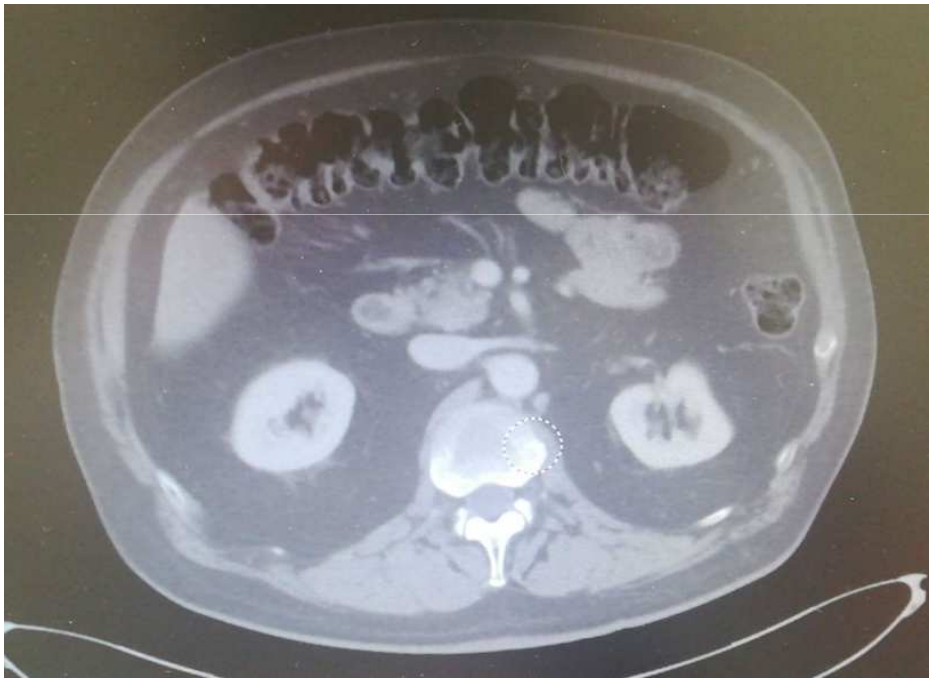
PFS	Months	
Median	14	
OS	**Months**	
Median	17,5	

The Present…

Bone M+ in NSCLC EGFR+ and ALK+



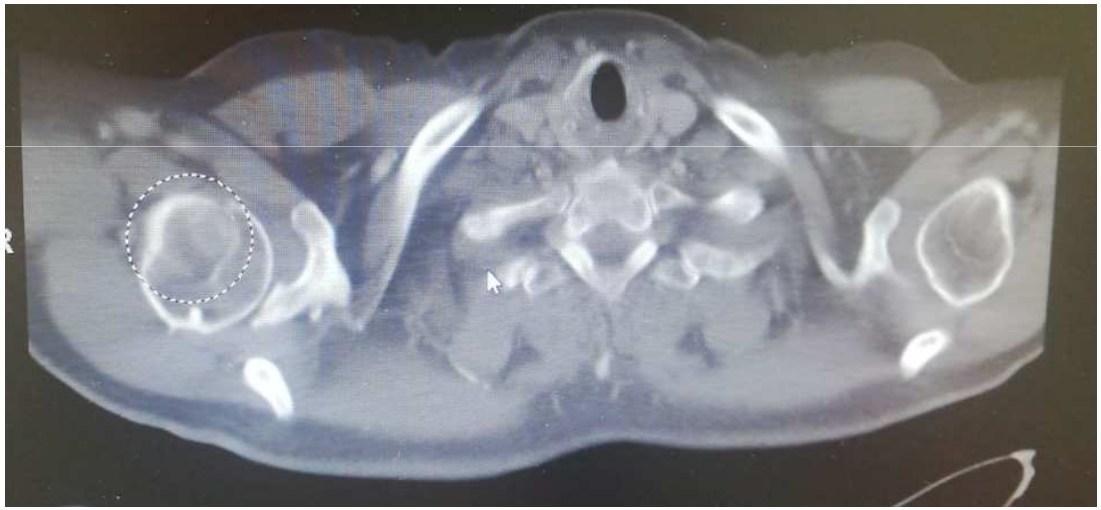
L1 Pre-treatment



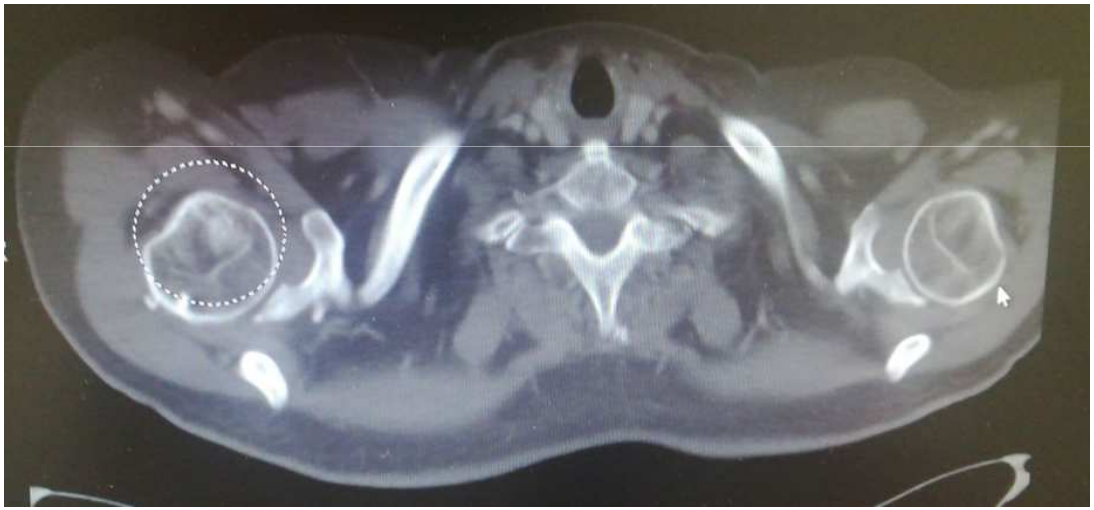
L1 Post-treatment

The Present…

Bone M+ in NSCLC EGFR+ and ALK+



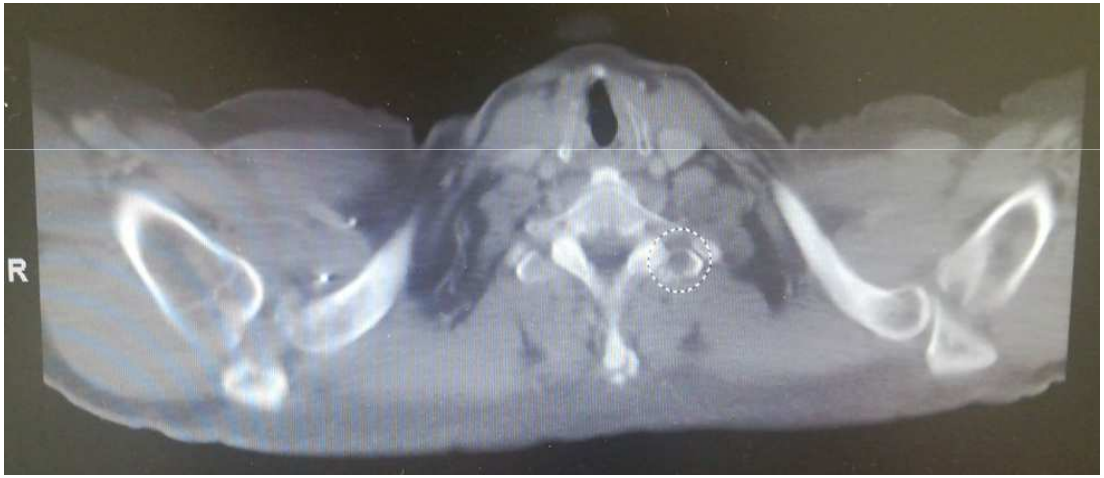
Right homerus pre-treatment



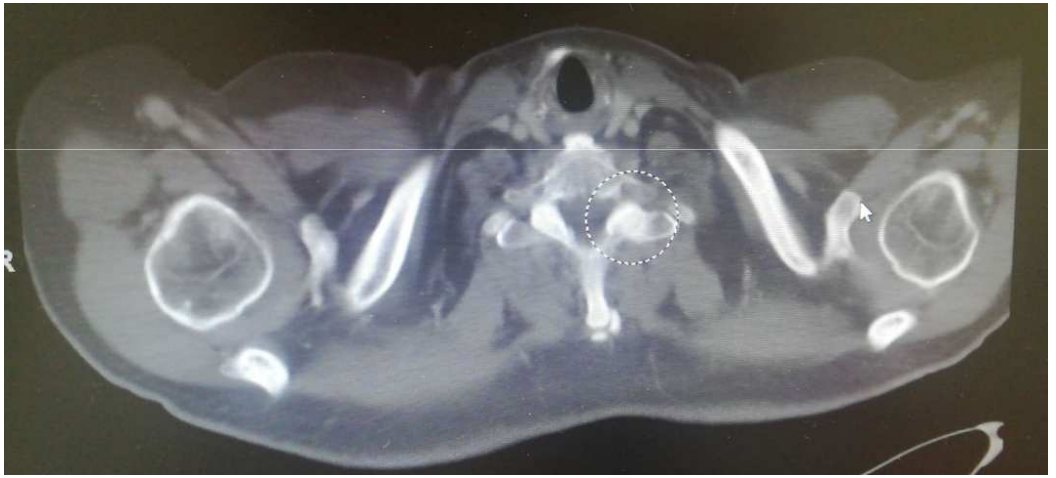
Right homerus Post-treatment

The Present…

Bone M+ in NSCLC EGFR+ and ALK+



C7 Pre-treatment



C7 Post-treatment

The Future…

The Future…

Bone M+ in NSCLC EGFR+ and ALK+

The Future…

Bone M+ in NSCLC EGFR+ and ALK+

- Retrospective, observational multicenter study: all Italian hospital centers are welcome!
- EGFR+/ALK+ NSCLC patients with bone metastasis
- All ages
- Never enrolled in any clinical trials or experimental protocols
- Ar least one bone metastasis during the course of disease
- Death caused by NSCLC or cancer-related complications
- Record proved the use of therapy for the bone for palliative purposes
- Data of the whole course of the disease and all cancer treatments

The Future…

Bone M+ in NSCLC EGFR+ and ALK+

Società Italiana di Osteoncologia

Thank for your attention