Prospective study on incidence of bone metastasis (BM) and skeletal related events (SREs) in patients(pts) with stage IIIB and IV lung cancer (CSP-HOR13)

Haruko Daga[1], Nobuyuki Katakami[2], Keisuke Tomii[3], Hiroshi Kunikane[4],
Kenji Eguchi[5], Koichi Takayama[6], Toshiyuki Sawa[7], Hiroshi Saito[8],
Masao Harada[9], Souichiro Yokota[10], Kiyoshi Ando[11], Yasuo Ohashi[12]

1: Department of Clinical Oncology, Osaka City General Hospital, 2: Institute of Biomedical Research and Innovation Hospital, 3: Kobe City Medical Center General Hospital , 4: Yokohama Municipal Citizen's Hospital, 5: Teikyo University School of Medicine, 6: University of Kyushu School of Medicine, 7: Gifu Municipal Hospital, 8: Aichi Cancer Center-Aichi , 9: Hokkaido Cancer Center, 10: Toneyama National Hospital, 11: Tokai University; 12: University of Tokyo

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発表者・研究責任者の利益相反開示事項

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発表者氏名	耽賀　晴子	所属／身分	大阪市立総合医療センター臨床腫瘍科／副部長	
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企業の職員・法人の代表	☑			
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試験責任者氏名	江口　研二	所属／身分	臨床腫瘍科帝京大学医学部附属病院内科／教授	
	該当なし	該当有りの場合：企業名等		
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委受託研究（治験等）	☑			
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その他	☑			

BACKGROUND

- Although the overall incidence of BM is not known, BM are a frequent complication in patients with advanced lung cancer.
- BM can be associated with SREs, which include pathologic fracture, need for surgery or radiation to bone, spinal cord compression, and hypercalcemia of malignancy.
- As patients' quality of life deteriorates tremendously once SREs develop, it is important for investigators to treat patients with BM with an appropriate treatments as early as possible.

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PURPOSE

The aim of this study is to investigate prospectively the following items in patients with advanced lung cancer.

1) Incidence of BM and time interval of developing BM

2) Time interval between BM and developing of SREs, and incidence and types of SREs

3) Predictive factors of BM and SREs

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METHODS

Definition of SRE
- Pathologic fracture
- Radiation to bone lesion
- Surgery to bone
- Spinal cord compression
- Hypercalcemia of malignancy

Staging of lung cancer
- Chest and upper abdomen CT scan, bone scan or PET scan, brain CT or MRI scan were required.

METHODS

During the follow up period
- Chest CT scan : every 3 months
- Brain CT or MRI scan : every 6 months
- Bone scan or PET scan : every 6 months
- QOL questionnaire was carried out at enrollment, 3 months and 12 months
- Treatment for lung cancer and use of zoledronate were at the discretion of the investigator

Eligibility Criteria

Inclusion criteria

1. newly diagnosed SCLC in all stages and NSCLC in stage IIIB or stage IV
2. age $\geq$ 20 years old
3. enable to reply QOL questionnaire
4. written informed consent
5. treatment for lung cancer and use of zoledronate were at the discretion of the investigator

Exclusion criteria

1. patient who is judged to be inappropriate to enrollment by the investigator

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Schedule of examination

Visit	0	1	2	3	4	5	6	7	8	9 - 12
	Enrollment	1month	2months	3months	4months	5months	6months	9months	12months	24months
Allowance	≤1month	±2wks	±2wks	±2wks	±2wks	±2wks	±2wks	±6wks	±6wks	±6wks
Bone scintigram or PET	○						★		○	
X-ray (DV· L-spine)	○									
Chest CT	○(chest and abdomen)			☆			☆	☆	☆	
Patient background	○									
P.S.	○	○	○	○	○	○	○	○	○	
height	○						★		○	
weight	○	○	○	○	○	○	○	○	○	Repeat between 7 and 8
Blood biochemistry	○	○	○	○	○	○	○	○	○	
Tumor marker	○	○	○	○	○	○	○	○	○	
Bone marker (blood· urine)	○									
Bone metastasis	○	○	○	○	○	○	○	○	○	
Metastasis extra-bone	○	○	○	○	○	○	○	○	○	
Bisphosphonate	○	○	○	○	○	○	○	○	○	
Bone Pain	○	○	○	○	○	○	○	○	○	
Analgesic use	○	○	○	○	○	○	○	○	○	
SRE	○	○	○	○	○	○	○	○	○	
QOL· ADL	○			☆	← 4 wks after SRE (± 2 wks) →				○	
Outcome		← On demand →								

☆ : ±4wks ★ : ±6wks

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RESULTS

Total Enrollment : 277 pts

- Entry period : April 2007 to December 2009
- Participating institution : 12
- Follow-up : until December 2011
- Exclusion : delayed registration   2
  not eligible(stage IIIA NSCLC) 1

Analysis : 274 pts

- SCLC : 77
- NSCLC : 197 (Stage IIIB/IV : 73/124)

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RESULTS

- Analysis :   274 pts
  - ✓ Termination 249
    - 2yr completion 64
    - death 112
    - changing hospital 65
    - patient refusal 3
    - others 5
  - ✓ Under follow-up 25
- Follow-up duration(median): 12.7 months [range 0-27.4]
- Analysis for time data :   272 pts
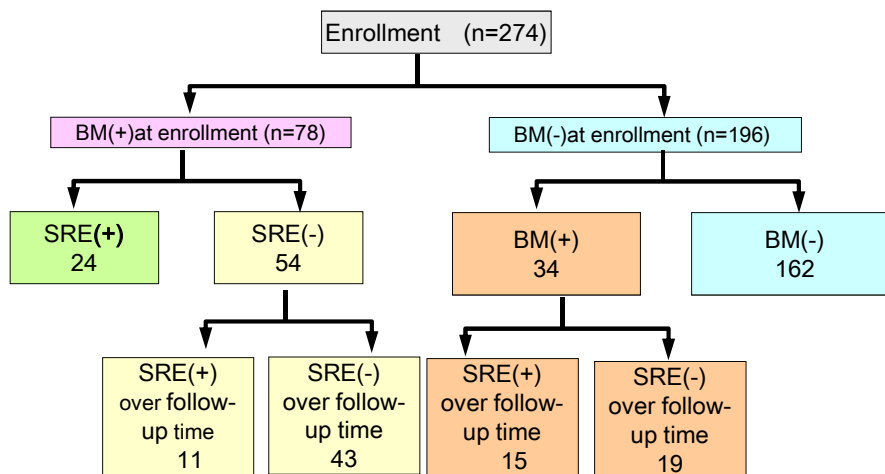 - 2 patients were excluded due to missing data.

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Patients characteristics at enrollment

		NSCLC		SCLC	Total
		Stage IIIB	Stage IV		
n		73	124	77	274
Gender（Male/Female）		57/16	79/45	57 /20	193/ 81
Age（Median）〔Range〕		69.0 〔35-86〕	67.0 〔41-89〕	69.0 〔45-82〕	68.0 〔35-89〕
PS (ECOG)	0	22 (30.1)	31 (25.0)	23 (29.9)	76 (27.7)
	1	43 (58.9)	82 (66.1)	46 (59.7)	171 (62.4)
	2	7 (9.6)	8 (6.5)	8 (10.4)	23 (8.4)
	≥3	1 (1.4)	3 (2.4)	0 (0)	4 (1.5)
Bone metastasis	-	73 (100.0)	65 (52.4)	58 (75.3)	196 (71.5)
	+	0	59 (47.6)	19 (24.7)	78 (28.5)
SRE	-	73 (100.0)	104 (83.9)	73 (94.8)	250(91.2)
	+	0	20 (16.1)	4 (5.2)	24 (8.8)

Tree Diagram of enrolled patients

Enrollment （n=274）

BM(+)at enrollment (n=78)　　　　BM(-)at enrollment (n=196)

SRE(+) 24　　SRE(-) 54　　　　BM(+) 34　　BM(-) 162

SRE(+) over follow-up time 11　　SRE(-) over follow-up time 43　　SRE(+) over follow-up time 15　　SRE(-) over follow-up time 19

Incidence and type of SRE (n=274)

|	SREs at enrollment		New SREs during follow up		Total	
	n	%	n	%	n	%
Any SRE	24	8.8	26	9.5	50	18.2
Pathologic fracture	9	3.3	4	1.5	13	4.7
Radiation to bone lesion	22	8	21	7.7	43	15.7
Surgery to bone	0	0	0	0	0	0
Spinal cord compression	2	0.7	1	0.4	3	1.1
Hypercalcemia of malignancy	1	0.4	5	1.8	6	2.2

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Time to bone metastasis from diagnosis of lung cancer

N=271
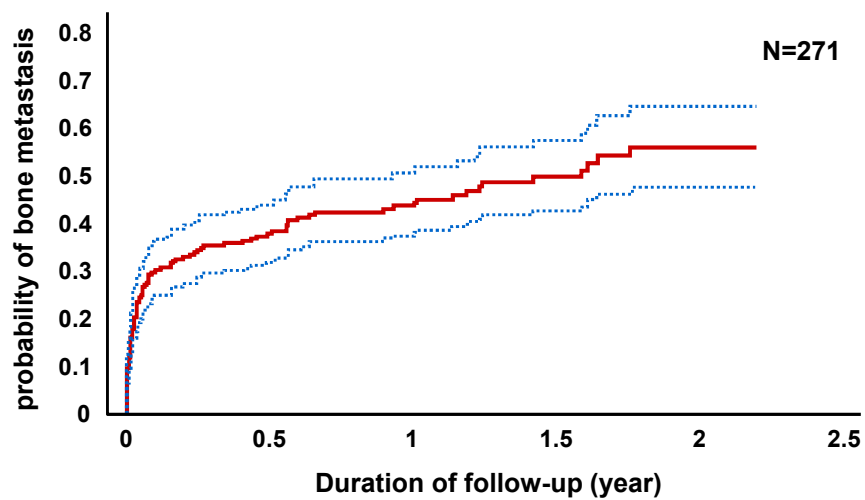
Day 0 : diagnosis date of lung cancer

Time to SRE from diagnosis of lung cancer

N=247

Day 0 : diagnosis date of lung cancer
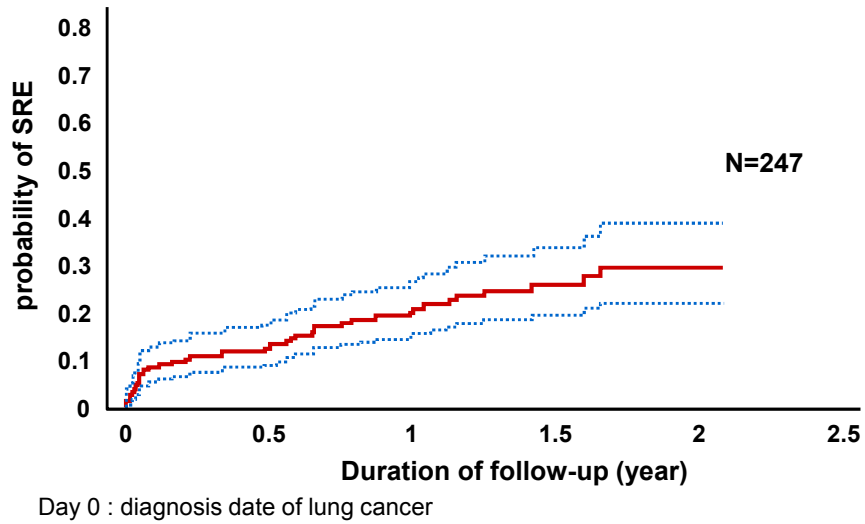
Time to SRE from bone metastasis

N=107

Day 0 : diagnosis date of BM
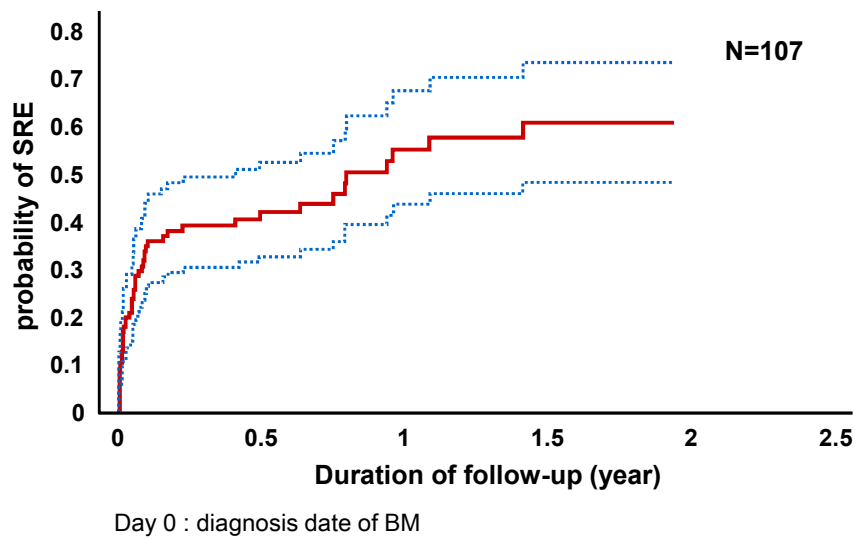
Analyses for subgroups by age
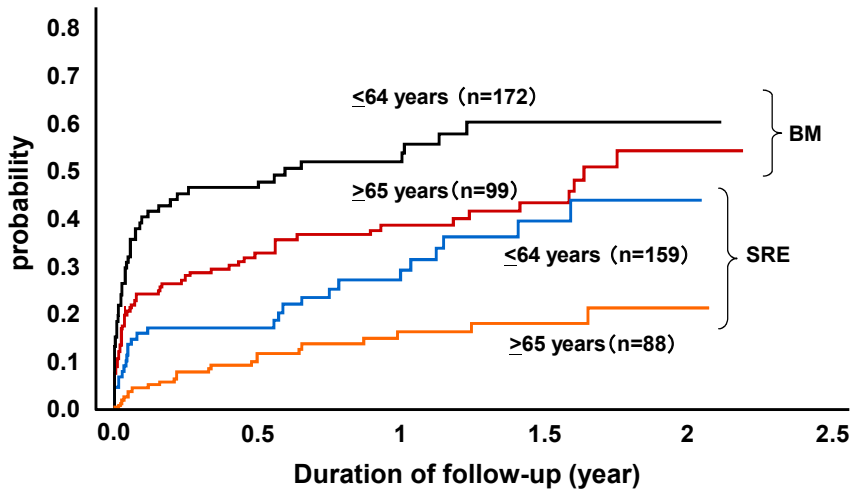
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Cox regression for BM incidence
<multivariable analysis>

Factor	HR	(95% CI)	p value
Stage III NSCLC/SCLC	0.31	(0.15-0.66)	0.002
Stage IV NSCLC/SCLC	2.23	(1.38-3.60)	<.0001
Gender (female/male)	1.03	(0.67-1.57)	0.895
Age ($\geq$65 / $\leq$64)	0.74	(0.49-1.11)	0.146
PS (>1 / 0)	1.70	(1.03-2.80)	0.037
LDH [1000 U]	2.72	(1.23-6.02)	0.014
Alb [g/dL]	0.76	(0.51-1.13)	0.175
Ca [mg/dL]	0.91	(0.69-1.19)	0.486
PTHrP [pmol/L]	0.90	(0.74-1.10)	0.308
BALP [100U/L]	1.94	(1.13-3.33)	0.016
NTx [1000nmolBCE/mmolCRE]	0.82	(0.31-2.14)	0.688

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Cox regression for SRE incidence
<multivariable analysis>

Factor	HR	(95% CI)	p value
Stage III NSCLC/SCLC	0.63	(0.22-1.81)	0.391
Stage IV NSCLC/SCLC	2.82	(1.34-5.97)	0.001
Gender (female/male)	0.82	(0.42-1.58)	0.545
Age (≥65 / ≤64)	0.44	(0.24-0.78)	0.005
PS (>1 / 0)	1.23	(0.60-2.52)	0.576
LDH [1000 U]	1.57	(0.46-5.32)	0.469
Alb [g/dL]	0.64	(0.38-1.09)	0.101
Ca [mg/dL]	0.88	(0.61-1.27)	0.500
PTHrP [pmol/L]	0.96	(0.75-1.23)	0.742
BALP [100U/L]	1.17	(1.89-1.54)	0.248
NTx [1000nmolBCE/mmolCRE]	0.79	(0.23-2.71)	0.703

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Summary of Results (1)

❖ Two hundred and seventy four pts were enrolled into the study between Apr. 2007 and Dec. 2009 from 12 institutions.

❖ Seventy eight of 124 pts with stage IV NSCLC (48%) already had BM at the time of enrollment .

❖ Twenty four of 78 pts with known BM (31%) had some kind of SREs concomitantly. Additional 11 pts developed SREs during follow up time and the total incidence of SREs was 45%.

❖ Thirty four of 196 pts without initial BM (17%) developed bone metastases, and 15 of these 34 pts developed SREs during the follow up period.

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Summary of Results (2)

❖ The type of SREs was radiation to bone 15.7%, pathologic fracture 4.7%, hypercalcemia 2.2% and spinal cord compression 1.1%.

❖ Multivariate analysis by Cox regression model showed that factors predicting subsequent BM at enrollment were NSCLC, stage IV, PS $\geq$1, LDH and BALP.

❖ Multivariate analysis by Cox regression model showed that factors predicting subsequent SREs at enrollment were NSCLC, stage IV and age $\leq$ 64.

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CONCLUSIONS

❖ The incidence of BM at initial diagnosis was 48% in patients with stage IV NSCLC and was higher than initially expected.

❖ Various SREs developed in 18% of all the patients during the follow up time.

❖ Forty percent of patients enrolled into the study had BM and half of the patients who had developed BM had SREs during the follow up time.

❖ Multivariate analysis revealed that factors predicting BM were NSCLC, stage IV, PS $\geq$1, LDH and BALP, and factors predicting SREs were NSCLC, stage IV and age $\leq$ 64.

❖ Quality of life assessment and other therapeutic factors affecting BM and SREs will be reported next year.

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参加施設・研究者一覧

＊：研究代表者（実行委員長）
＃：実行委員

- 愛知県がんセンター愛知病院　齋藤博、山本麻衣子
- 独立行政法人国立病院機構　刀根山病院　横田総一郎、上野智子
- 東海大学医学部附属病院　安藤潔、植田いずみ
- 財団法人先端医療振興財団　先端医療センター　片上信之＃、笹木美幸
- 独立行政法人国立病院機構　北海道がんセンター　原田眞雄、内藤義博
- 九州大学病院　高山浩一、平田麿梨
- 岐阜市民病院　呼吸器・腫瘍内科　澤祥幸、水井貴詞
- 浜松医科大学医学部附属病院　千田金吾、木村路子
- 神戸市立医療センター中央市民病院　富井啓介、桜川圭子
- 大阪市立総合医療センター　武田晃司、服部美千代
- 横浜市立市民病院　国兼浩嗣＃、吉田牧子
- 帝京大学医学部附属病院　江口研二＊、宮野千恵
- 独立行政法人国立病院機構　四国がんセンター　江口久恵＃
- 静岡県立静岡がんセンター　齊藤裕子＃

財団法人パブリックヘルスリサーチセンター支援研究　　　23