

SIGNATURES OF METASTATIC BEHAVIOUR IN LUNG ADENOCARCINOMA

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Background

- **Lung cancer is the most common cause of cancer death in western countries**
- **Lung metastases are the most common intracranial malignancy**
- **30-70% of all solitary brain metastasis will be from a lung primary**

Brain Metastases in NSCLC: Epidemiology

- **10% of NSCLC patients have brain metastases at diagnosis**
- **Approximately 10% of completely resected NSCLC relapse only in the brain**
- **Up to 40% of NSCLC patients eventually develop brain metastases**
- **Incidence continues to rise as systemic therapy improves**

Prevention

- **Chemotherapy is ineffective in micrometastatic disease due to the intact blood brain barrier**
- **50% of locally advanced NSCLC subjects will develop brain mets, 30% as site of first failure**

Prophylactic Cranial Irradiation

Study	Patients	Incidence of brain metastases (PCI vs. no PCI)	Median survival (PCI vs. no PCI)
RTOG (8) 1991	187 patients adenocarcinoma or large-cell carcinoma confined to the chest	9% vs. 19%, $p = 0.10$	8.4 vs. 8.1 months $p = 0.36$
SWOG (9) 1998	254 patients Stage III inoperable NSCLC	1% vs. 11%, $p = 0.003$	8 vs. 11 months $p = 0.004$
Umsawasdi (10) 1984	97 patients NSCLC; 13% Stage I/II, 87% stage III	4% vs. 23%, $p = 0.02$	NA
VALG (11) 1981	281 male patients inoperable NSCLC	6% vs. 13%, $p = 0.038$	35.4 vs. 41.4 weeks $p = 0.5$

Predicting Brain Metastasis

- **Clinical Predictors**

- **Histology**
- **Stage**
- **Age**

- **Biological Predictors:**

- **Markers of proliferation and evading apoptosis**
- **Cell-cell interaction: E-Caderin**
- **Matrix metalloproteases**
- **Angiogenesis: VEGF**
- **Chemokines**

ONCOBELL Trial: Patient Characteristics

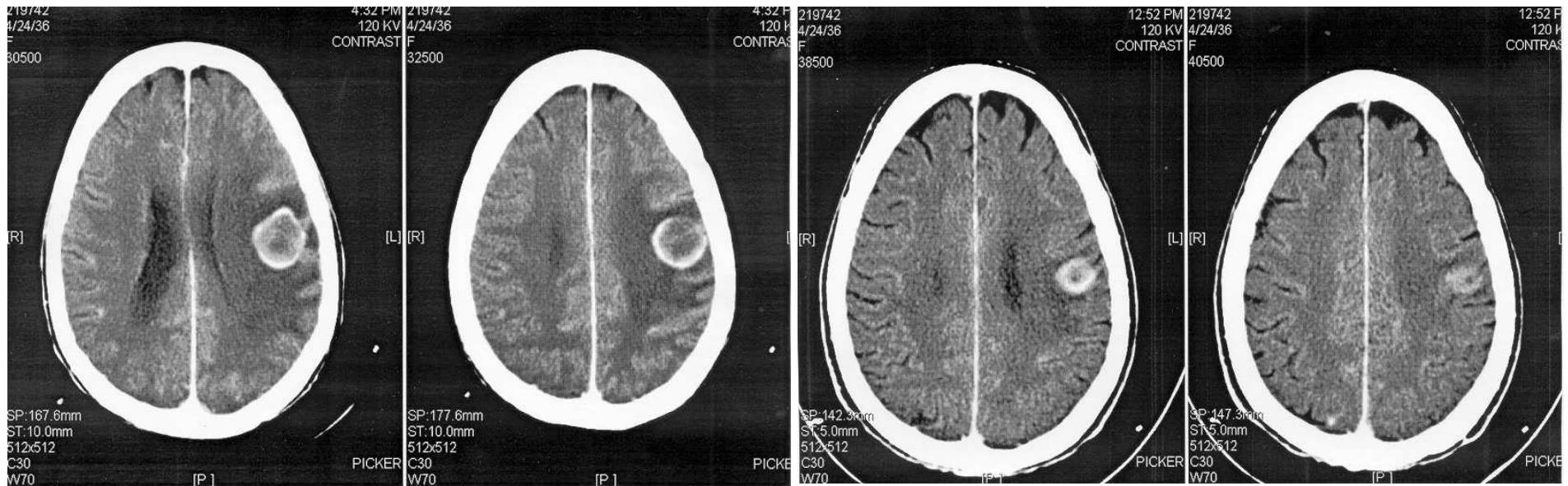
	Total	%
Total	42	100
Gender:M/F	11/31	26.2/73.8
Age:Median	60.9	
Histology:ADC/BAC/SCC/other	32/4/1/5	76.2/9.5/2.4/11.9
Smoking:Never/Former/Current	36/4/2	85.7/9.5/4.8
Previous chemotherapy lines: 0/1/2+	16/16/10	38.1/38.1/23.8
Previous platinum	22	52.4
Number metastatic sites:1/2/3/4+	11/10/7/14	26.2/23.8/16.7/33.4
Main metastatic sites:		
➤ Brain	17	40.5
➤ Lung	41	97.6
➤ Liver	5	11.9
➤ Bone	19	45.2

Characteristics	Total Number	Response Rate		p value
		N	%	
Male	11	4	36.4	0.4
Female	31	16	51.6	
Brain Metastases	17	9	52.9	0.6
No Brain Metastases	25	11	44.0	
Never Smokers	36	17	47.2	1.0
Current/Former Smokers	6	3	50.0	
<i>EGFR</i> FISH+	25	17	68.0	<0.001*
<i>EGFR</i> FISH-	11	1	9.1	
P-Akt+	18	9	50.0	0.9
P-Akt-	17	8	47.1	
<i>EGFR</i> FISH+/P-Akt+	12	7	58.3	0.4
Other	21	9	42.9	
Never Smokers <i>EGFR</i> FISH+	19	14	73.7	0.001*
Never Smokers <i>EGFR</i> FISH-	11	1	9.1	
<i>EGFR</i> Mutation (all)	24	15	62.5	0.02*
<i>EGFR</i> Wild type	13	3	23.1	
<i>EGFR</i> Mutation (19 and/or 21)+	21	15	71.4	0.001*
<i>EGFR</i> Mutation (19 and/or 21)-	16	3	18.8	

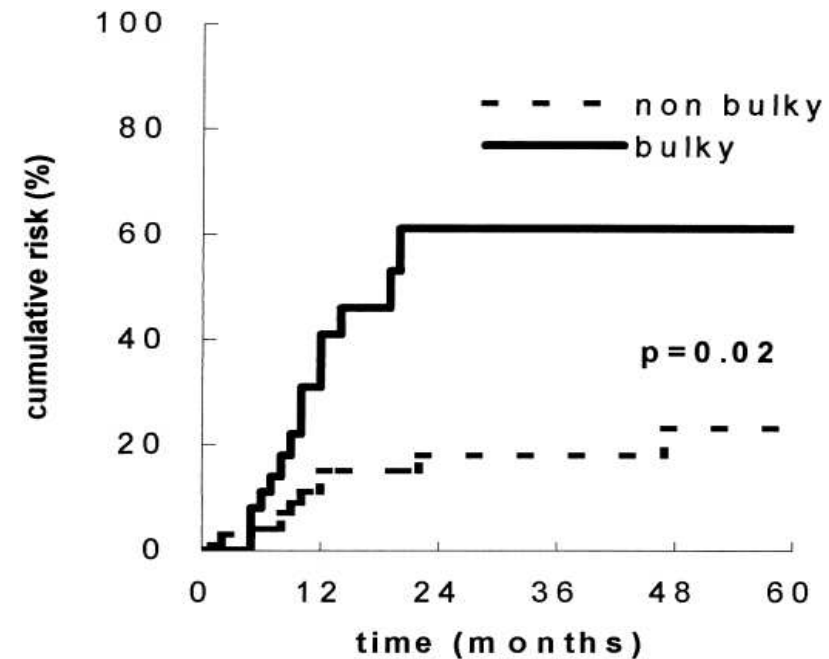
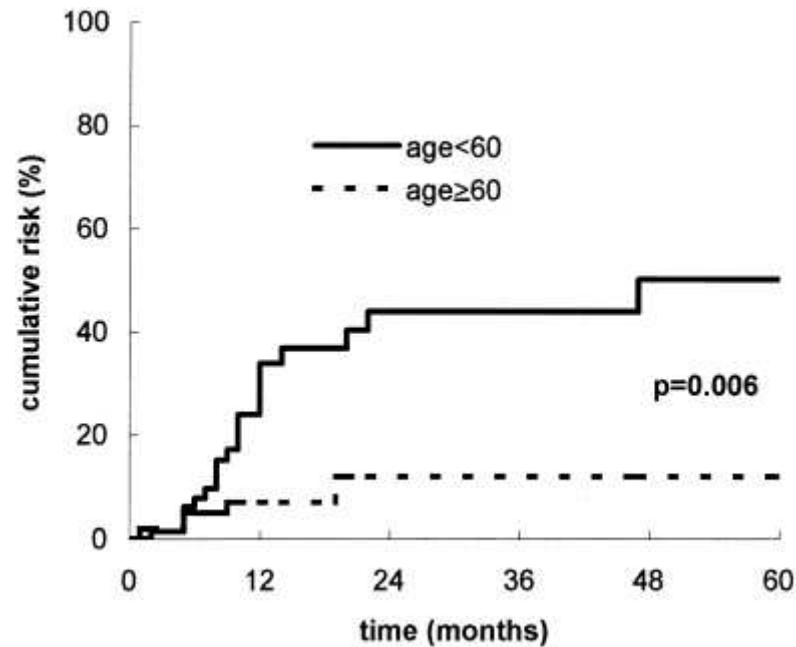
Brain Metastases Respond to EGFR-TKI Therapy

Baseline

After 3 months of gefitinib



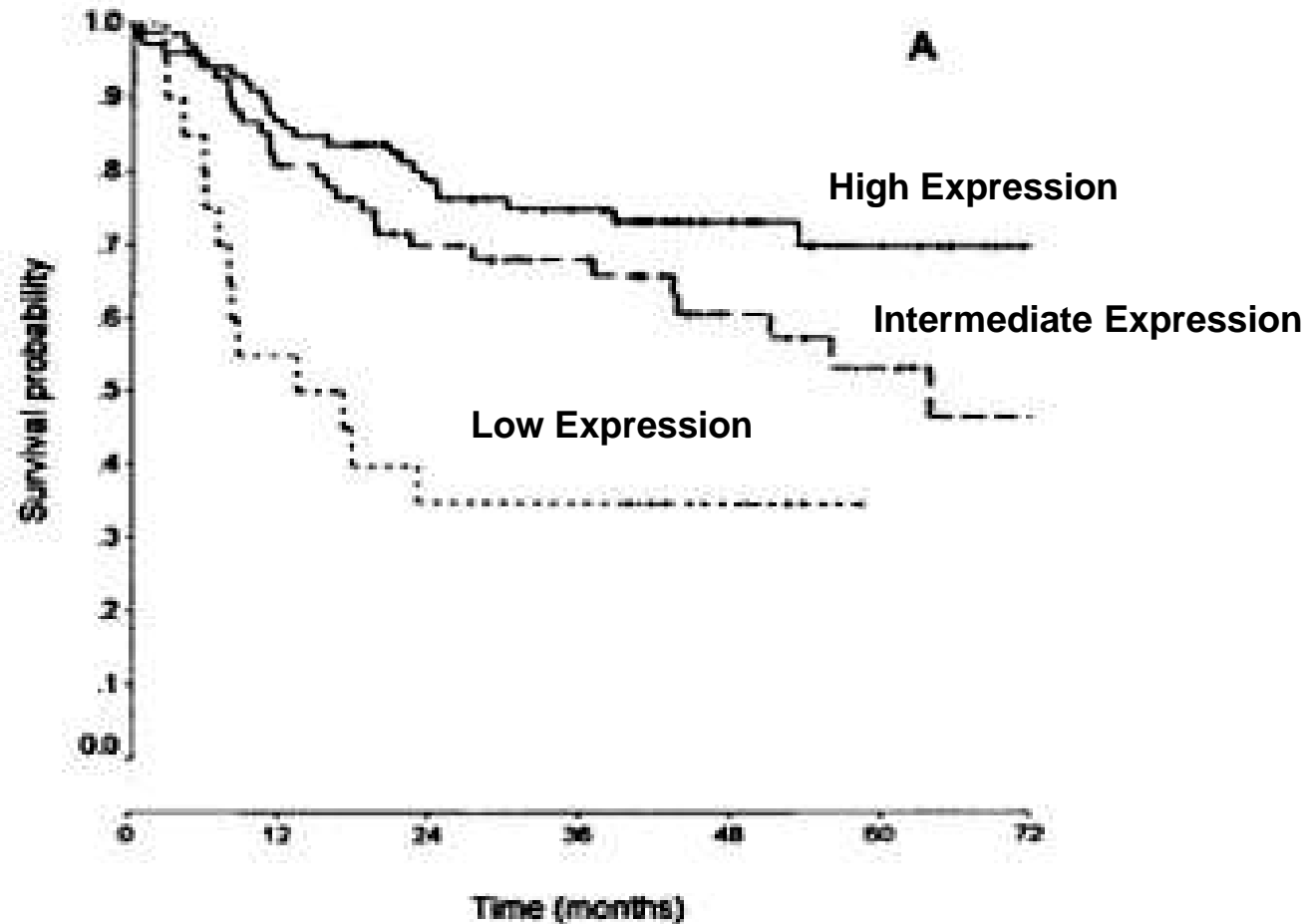
Clinical Predictors of Brain Metastases: Incidence According to Age and N Status



Proliferation and Evading Apoptosis: Ki-67, p53, and bcl2 in Primary Tumor and Corresponding Brain Metastasis

Reference	N	Bcl-2 positive staining		p53 positive staining		ki 67 positive staining	
		Primary (%)	Brain (%)	Primary (%)	Brain (%)	Primary (%)	Brain (%)
Arnold	17	24	29	100	91	-	-
Bubb	29	14	11	52	66	31	41

E-Cadherin Overexpression Associated with Longer Survival in Resected NSCLC



E-Cadherin is Expressed in Brain Metastases

Reference	N	E-Cadherin Positive Staining
		Brain (%)
Arnold	35	86
D'Amico	25	100

E-Cadherin is Expressed in Brain Metastases

- **202 stage I NSCLC subjects.**
- **IHC for p53, erbB2, angiogenesis factor viii, EphA2, E-cadherin, uPA, uPA receptor**
- **25 subjects had isolated brain mets, all had strong expression of E-cadherin (25/109)**
- **None of the 92 patients with low expression of E-cad developed brain metastases.**

Urokinase Plasminogen Activator (uPA) and Brain Metastases

- **uPA expression was also independently associated with brain metastases in NSCLC.**
- **92% of brain mets vs. 59% of other sites. (p=.002)**
- **Only 4% of uPA negative subjects had brain mets compared to 15% of uPA positive.**

Matrix metalloproteases (MMP) and Brain Metastases

- In mice overexpressing tissue inhibitor of metalloproteinase 1 (TIMP-1), brain metastases were reduced by 75%.¹
- MMP2 has been shown to have high expression rates in resected brain mets.²

1 Oncogene 1998

2 Clin Cancer Res 1999

Angiogenesis: VEGF

- **An animal model of brain mets with breast cancer cells showed increased VEGF expression correlated with brain metastases.¹**
- **Another mouse model studying VEGF isoforms showed that VEGF expression was necessary but not sufficient for the production of brain metastases.²**

Chemokines and Metastasis

- **Chemokines superfamily includes a large number of proteins regulating the trafficking of leukocytes to inflammatory sites.**
- **>50 chemokines are known: the majority belongs to CC and CXC chemokine subfamilies.**
- **Chemokines are involved in metastatic process**
- **Chemokines are expressed by tumor cells and their corresponding ligands are expressed at the site of metastasis.**

Chemokines and Metastasis

- **CXCR4 is the major chemokine receptor expressed on cancer cells**
- **CXCR4 is an important regulator of breast cancer metastasis**
- **In NSCLC high CXCR4 expression associated with metastasis**
- **Data only from retrospective studies**

Can we identify a biologically high risk group ?

- **High expression of E-cadherin.**
- **High expression of uPA and MMP.**
- **High expression of VEGF.**
- **More studies needed.**

Conclusions

- **Brain mets are increasingly responsible for a large part of the morbidity and mortality from NSCLC.**
- **Prophylactic cranial radiation is effective but the appropriate population is not defined.**
- **High E-cadherin and uPA expression are strongly associated with isolated brain metastases.**
- **VEGF and the metastasis suppressor genes are strong candidates for further investigation.**
- **Biologic risk stratification would allow the design of better trials of prevention strategies.**