UNIMORE
UNIVERSITÀ DEGLI STUDI DI
MODENA E REGGIO EMILIA

Metastasi ossee e tumori gastrointestinali:
Attualità e prospettive

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Metastasi ossee

Terza sede di metastasi dopo polmone e fegato

L'80% è dovuto a secondarismi da:

- Mammella
- Prostata
- Polmone
- Rene
- Tiroide

Metastasi ossee da tumori GI, davvero un problema?

- Epidemiologia
- Panoramica sulle diverse neoplasie
  - Comportamento clinico
  - Significato prognostico
  - Terapia
  - Implicazioni biologiche
    - Il carcinoma gastrico come modello

Epidemiologia

Neoplasia	Incidenza metastasi ossee	Tipologia delle elsioni	Isolate (1° sede)
Esofago	1%	miste	rare
Pancreas	1%	miste	no
HCC	3-20%	Osteolitiche/ miste	si
Vie biliari	3-5%	miste	si
Colon	5%	osteolitiche	rare
Retto	5-10%	miste	si
Stomaco	1-2% (autopsia 20%)	Osteoblastiche/miste	si

HCC and bone metastases

Asian patients	Western patients
• More frequent • Mixed 90% • Multiple 70% • mOS 11 months • Prognostic factors for S Child/PS • VEGF mediated • Moderately aggressive	• osteolytic 80% • Soft tissue expansion • Hypervascolaerized • Aggressive • Median survival a few months • No utility of bone scan

Radiotherapy effective
Good response to bifosfonates (embolization)

PDAC and bone metastases

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/ World J Gastroenterol 2017 March 14; 23(10): 1872-1880

DOI: 10.3748/wjg.v23.i10.1872 ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Prognostic value of site-specific metastases in pancreatic adenocarcinoma: A Surveillance Epidemiology and End Results database analysis

Hani Oweira, Ulf Petrausch, Daniel Helbling, Jan Schmidt, Meinrad Mannhart, Arianeb Mehrabi, Othmar Schöb, Anwar Giryes, Michael Decker, Omar Abdel-Rahman

7% incidence

- Associated with squamous subtype (smokers)
- c-myc alteration

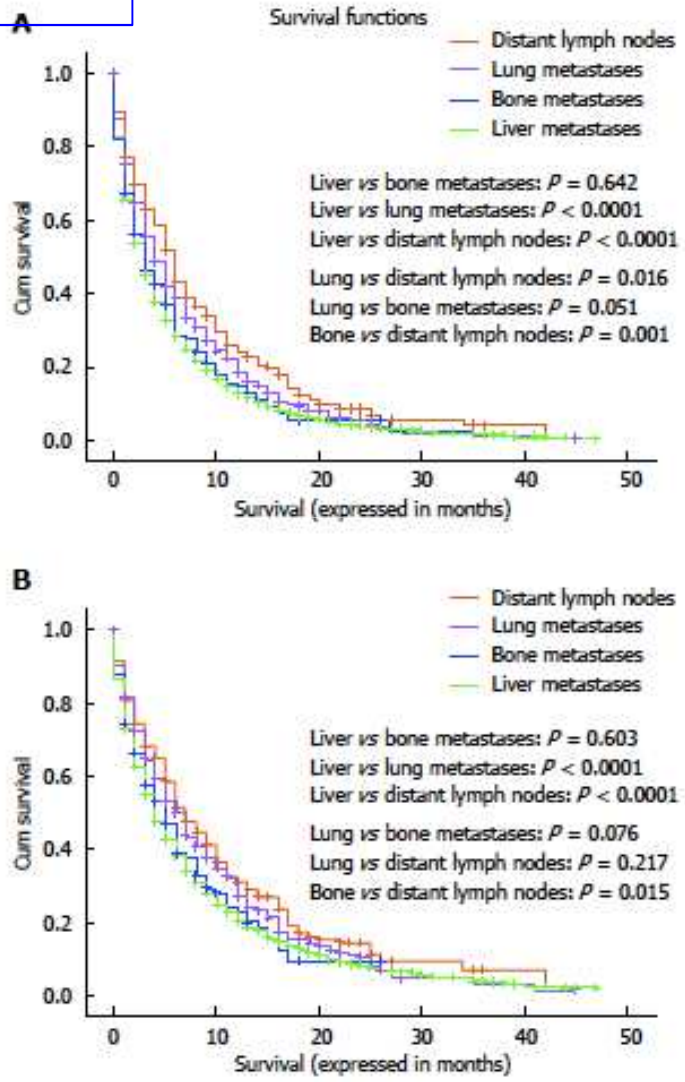
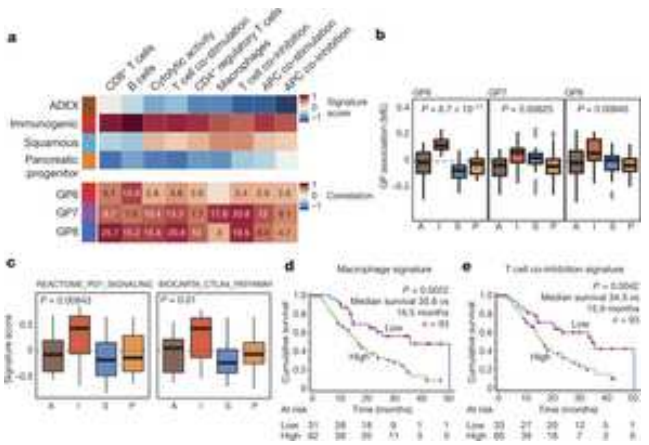
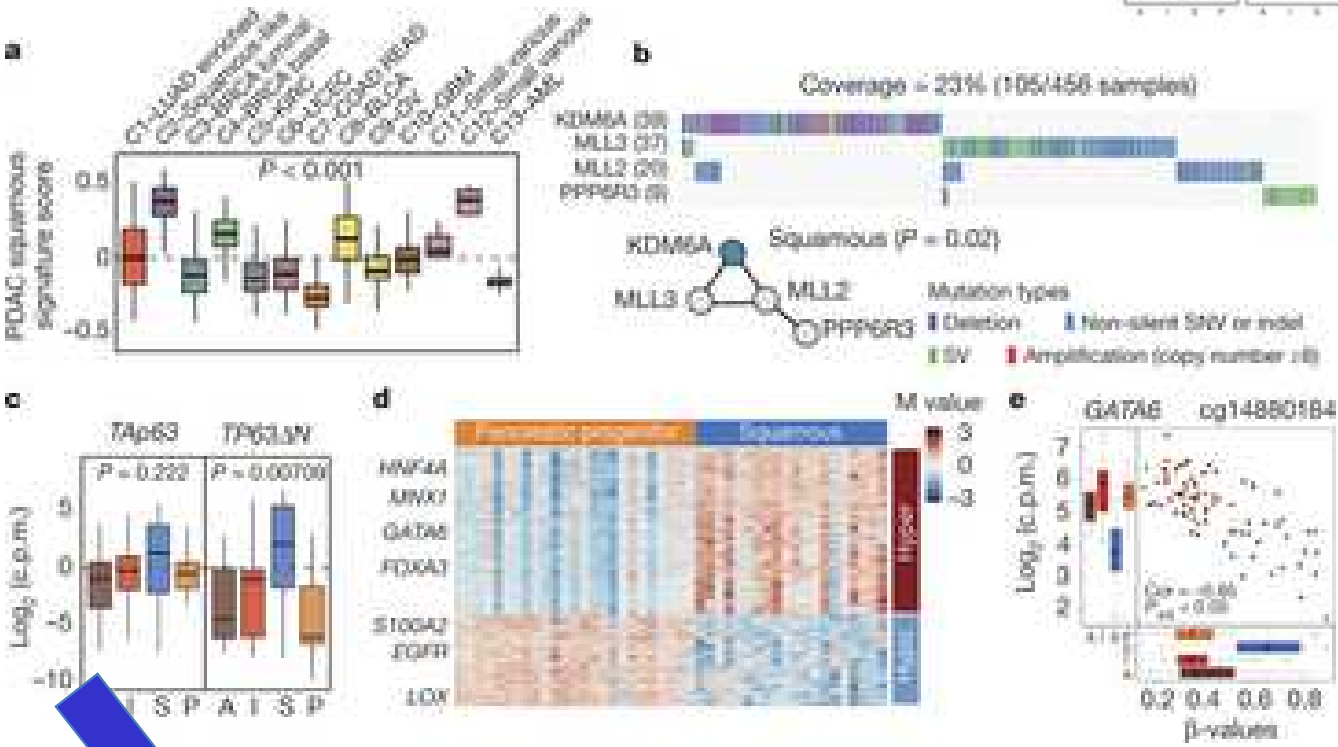


Figure 1 Kaplan-Meier curve of: overall survival (A), and pancreatic cancer-specific survival (B) according to the site of single site metastases.

nature

Genomic analyses identify 4 molecular subtypes of pancreatic cancer *Nature* 2016





Smokers
C-MYC mut

Natural history of bone metastasis in colorectal cancer: final results of a large Italian bone metastases study

D. Santini[1*], M. Tampellini[2], B. Vincenzi[3], T. Ibrahim[4], C. Ortega[4], V. Virzì[1], N. Silvestris[5], R. Berardi[6], C. Masini[7], N. Calipari[8], D. Ottaviani[9], V. Catalano[10], G. Badalamenti[11], R. Giannicola[12], F. Fabbri[13], O. Venditti[1], M. E. Fratto[1], C. Mazzara[1], T. P. Latiano[13], F. Bertolini[7], F. Petrelli[14], A. Ottone[2], C. Caroti[15], L. Salvatore[16], A. Falcone[16], P. Giordani[10], R. Addeo[17], M. Aglietta[4,18], S. Cascinu[6], S. Barni[2,4], E. Maiello[11,3] & G. Tonini[1]

Table 1. Patient demographics and baseline disease characteristics

Characteristic	Patients, n (%) (N = 264)	No ZOL[a] (N = 31)	ZOL (N = 126)	Unknown (N = 107)
Tumor site				
Colon	148 (56)	21 (68)	79 (63)	48 (45)
Rectum	98 (37)	9 (29)	47 (37)	42 (39)
Unknown	3 (1)	1 (3)	1 (<1)	1 (<1)
Tumor histology				
Neoplasia	178 (67)	24 (77)	95 (75)	59 (55)
Mucinous	56 (21)	7 (23)	31 (25)	18 (17)
Unknown	30 (11)	0	0	30 (28)
Tumor grade				
1	10 (4)	1 (3)	4 (3)	5 (5)
2	139 (53)	20 (65)	74 (59)	45 (42)
3	91 (34)	10 (32)	48 (38)	33 (31)
Unknown	24 (9)	0	0	24 (22)
Tumor stage				
T1	3 (1)	0	0	3 (3)
T2	22 (8)	3 (9)	12 (10)	7 (7)
T3	130 (50)	27 (90)	64 (51)	39 (37)
T4	94 (36)	NA	NA	NA
Unknown	15 (6)	NA	NA	NA
Nodal status				
N0	51 (19)	6 (19)	31 (25)	14 (13)
N+	130 (49)	21 (68)	75 (60)	34 (32)
Unknown	83 (32)	4 (13)	20 (16)	59 (55)
Metastatic status				
M0	106 (40)	11 (36)	60 (48)	35 (33)
M1	132 (50)	15 (48)	55 (44)	62 (58)
Unknown	26 (10)	5 (16)	11 (9)	10 (9)
Adjuvant chemotherapy				
Yes	62 (23)	10 (32)	30 (24)	22 (21)
Stage II	8 (3)	NA	NA	NA
Stage III	48 (18)	NA	NA	NA
No	134 (51)	11 (36)	68 (54)	75 (70)
Unknown	68 (26)	6 (19)	28 (22)	10 (9)
Stage at diagnosis				
Stage I	9 (3)	1 (3)	4 (3)	3 (3)
Stage II	31 (12)	4 (13)	15 (12)	12 (11)
Stage III	46 (18)	10 (32)	38 (30)	35 (33)
Stage IV	122 (46)	11 (36)	68 (54)	43 (40)
Unknown	56 (21)	1 (3)	1 (1)	14 (13)
Number of bone metastases, n[b]	NA	31	126	NA
Location of lesion				
Spine	—	13 (37)	66 (46)	—
Pelvis	—	10 (28)	34 (24)	—
Long bone	—	7 (20)	32 (22)	—
Other	—	5 (14)	14 (10)	—
Lesion type				
Osteolytic	—	20 (65)	116 (92)	—
Osteoblastic	—	4 (13)	11 (8)	—
Mixed	—	4 (13)	14 (11)	—
Unknown	—	3	5 (3)	—

[a]Patients were known not to receive any bisphosphonate therapy.
[b]Includes patient who had bone metastases at more than one site. Percentages are based on total number of metastases not number of patients.

Table 2. Median time from primary cancer diagnosis to diagnosis of bone metastasis

Baseline characteristic	Patients, n (%) (N = 264)	Time, months	95% CI	P value
Tumor site				
Rectum	163 (62)	12.00	6.8–17.2	0.516
Colon	98 (37)	11.00	8.75–13.25	
Tumor histology				
Neoplasia	174 (66)	11.00	7.65–14.35	0.069
Mucinous	56 (21)	9.00	6.56–11.44	
Tumor stage[a]				
2	22 (8)	13.00	0–28.98	0.216
3–4	207 (78)	13.00	10.23–15.78	
Tumor grade				
1	10 (4)	33.00	9.76–56.24	<0.001
2	119 (45)	16.00	11.49–20.52	
3	91 (34)	6.00	4.63–7.39	
Nodal status				
N-	51 (19)	10.00	13–37	0.116
N+	107 (59)	13.00	10.43–15.58	
Adjuvant chemotherapy				
Yes	62 (23)	33.00	9.43–36.57	0.402
No	154 (58)	10.00	15.26–34.75	
Overall	264 (100)	11.00	4.67–13.08	

[a]At initial diagnosis.
CI, confidence interval; N, node.

The median overall survival after diagnosis of bone metastases was 7.00 months (95% CI 5.75–8.70 months). In univariate analyses (Table 3), osteoblastic lesions ($P = 0.008$) or the presence of only one bone lesion ($P = 0.004$) correlated with longer median survival compared with osteolytic lesions or the presence of two or more bone lesions. Neither the occurrence of SREs ($P = 0.88$) nor use of zoledronic acid ($P = 0.161$) significantly correlated with survival after diagnosis of bone metastases.

Bisphosphonate therapy

Of the 264 patients with confirmed bone metastases, 107 did not have data on bisphosphonate use. These patients were excluded, and a subgroup analysis was carried out on the patients with well-documented bisphosphonate treatment history. In this subset, 126 patients had received zoledronic acid (4 mg every 4 weeks via 15-min i.v. infusion, with dose adjustment based on creatinine clearance) and 31 patients had not received an i.v. bisphosphonate.

Baseline demographics and disease characteristics were generally similar between patients receiving zoledronic acid and those not receiving zoledronic acid (Table 1). Patients who received zoledronic acid had a significantly longer time to first SRE than patients who did not receive zoledronic acid (2.00

Table 3. Median survival after bone metastasis diagnosis

Variable	Time, months	95% CI	P value[a]
Bone metastasis type			
Osteolytic	7.00	5.87–8.13	0.008
Osteoblastic	21.00	5.90–36.11	
Number of bone metastases			
1	9.00	6.34–11.67	0.004
>1	6.00	4.9–7.1	
SREs			
No	7.00	5.43–8.57	0.88
Yes	7.00	5.58–8.43	
Bisphosphonate treatment			
ZOL	10.00	8.09–11.91	0.161
No ZOL	6.00	4.46–7.54	
Overall	7.00	5.75–8.70	

[a]Log-rank test.
CI, confidence interval; SRE, skeletal-related event; ZOL, zoledronic acid.

Figure 2. Comparison of time to first SRE in colorectal cancer patients receiving zoledronic acid ($n = 126$) and those who did not receive zoledronic acid ($n = 31$, $P = 0.009$). SE, standard error; SRE, skeletal-related event; ZOL, zoledronic acid.

Metastasi ossee e carcinoma del colon-retto: prognosi

Attenzione
PS importante!!

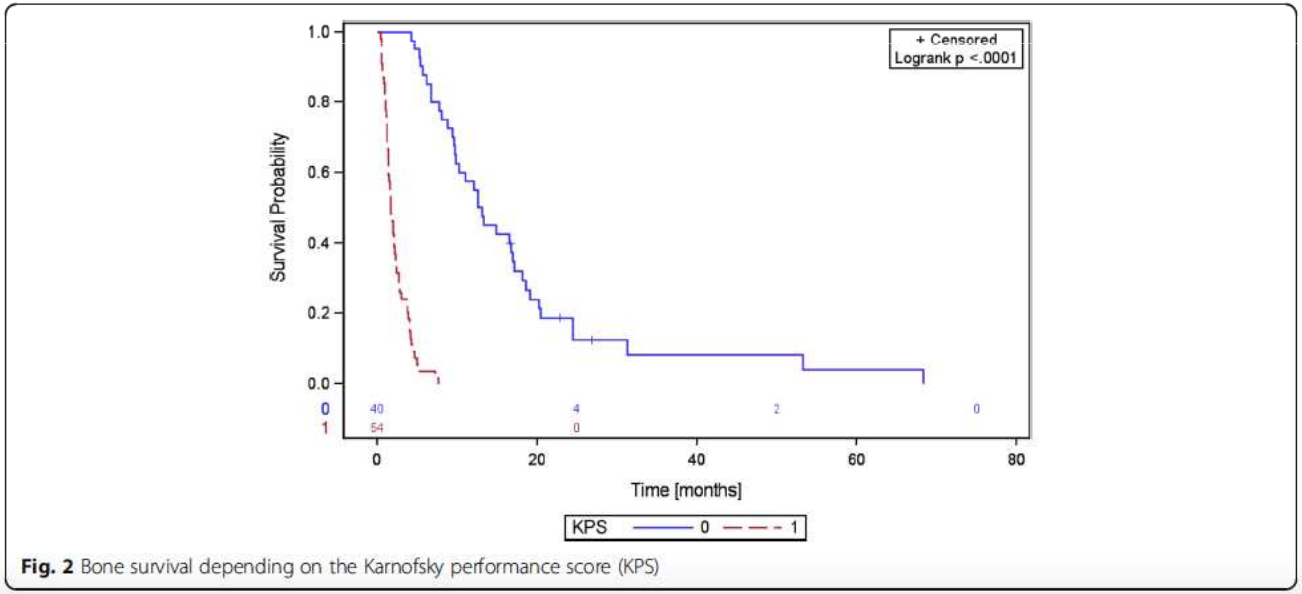


Fig. 2 Bone survival depending on the Karnofsky performance score (KPS)

Carcinoma del colon-retto e metastasi epatiche

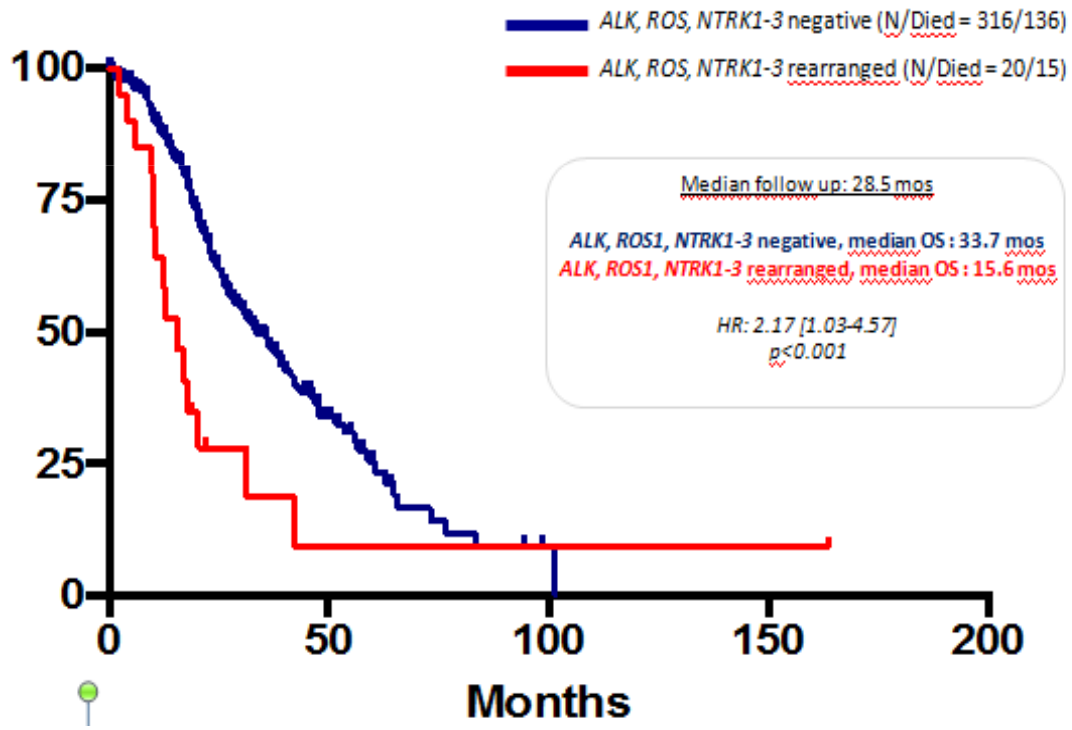
- Fattori prognostici per sviluppo di meta ossee: metastasi polmonari e neoplasie rettali.
- Seguire il paziente con ca del retto e i pazienti operati per lesioni polmonari
- Sono più spesso eventi tardivi e cattiva prognosi (osteolitiche) (mOS 7 mesi, D. Santini)
- Zoledronato efficace nel ritardare SRE ma impatto anche su sopravvivenza
- No mutazione specifica ma attenzione a ALK

Characteristics of *ALK/ROS/NTRK* rearranged mCRC

Female
Elderly

Right colon
Nodal mets

***RAS&BRAF* wt**
MSI-high



Pietrantonio …Cremolini, JNCI '17

Natural History of Malignant Bone Disease in Gastric Cancer: Final Results of a Multicenter Bone Metastasis Survey

Nicola Silvestris[1*], Francesco Pantano[2], Toni Ibrahim[3], Teresa Gamucci[4], Fernando De Vita[5], Teresa Di Palma[6], Paolo Pedrazzoli[7], Sandro Barni[8], Antonio Bernardo[9], Antonio Febbraro[10], Maria Antonietta Satolli[11], Paola Bertocchi[12], Vincenzo Catalano[13], Elisa Giommoni[14], Alessandro Comandone[15], Evaristo Maiello[16], Ferdinando Riccardi[17], Raimondo Ferrara[18], Antonio Trogu[19], Rossana Berardi[20], Silvana Leo[21], Alessandro Bertolini[22], Francesco Angelini[23], Saverio Cinieri[24], Antonio Russo[25], Salvatore Pisconti[26], Anna Elisabetta Brunetti[1], Amalia Azzariti[27], Daniele Santini[2]

Table 7. Patients survival parameters according bone metastasis onset.

PATIENTS SURVIVAL PARAMETERS	TIME, MO	95% C.I
ALL PATIENTS		
OVERALL SURVIVAL	14	12,025–15,975
SURVIVAL AFTER BONE METASTASIS DIAGNOSIS	6	5,068–6,932
TIME TO SRE AFTER BONE METASTASIS DIAGNOSIS	2	1,536–2,464
SURVIVAL AFTER SRE	3	2,049–3,951
TIME TO BONE METASTASIS	8	6,125–9,875
BONE METASTASIS SYNCRHONOUS		
SURVIVAL AFTER BONE METASTASIS DIAGNOSIS	5	3,461–6,539
TIME TO SRE AFTER BONE METASTASIS DIAGNOSIS	1	0,530–1,470
SURVIVAL AFTER SRE	4	3,156–4,844
BONE METASTASIS METACHRONOUS		
SURVIVAL AFTER BONE METASTASIS DIAGNOSIS	5	3,830–6,170
TIME TO SRE AFTER BONE METASTASIS DIAGNOSIS	2	1,333–2,667
SURVIVAL AFTER SRE	3	2,074–3,000
ONLY BONE METASTASIS		
SURVIVAL AFTER BONE METASTASIS DIAGNOSIS	5	1,679–8,321
TIME TO SRE AFTER BONE METASTASIS DIAGNOSIS	1	0,000–2,283
SURVIVAL AFTER SRE	3	1,829–4,171

CI, confidence interval; SRE, skeletal-related event.
doi:10.1371/journal.pone.0074402.t007

Table 2. Patient bone disease characteristics in the entire population.

BASELINE CHARACTERISTICS	FREQUENCY	PERCENTAGE (%)
BONE LESION TYPE		
OSTEOLYTIC	105/202	52,0
OSTEBLASTIC	46/202	22,8
MIXED	51/202	25,2
BONE METASTASIS NUMBER		
1	65/207	31,4
>1	142//207	68,6
BONE METASTASIS SPINE		
YES	42/207	20,3
NO	165/207	79,7
BONE METASTASIS LONG BONES		
YES	109/207	52,7
NO	98/207	47,3
BONE METASTASIS HIP		
YES	79/207	38,3
NO	127/207	61,7
ZOLEDRONIC ACID TREATMENT		
NO	105/186	56,5
YES	81/186	43,5
SRE TYPE (ALL) a		
PATHOLOGICAL FRACTURE	19/85	22,4
HYPERCALCEMIA	4/85	4,7
SPINAL CORD COMPRESSION	9/85	10,6
SURGERY TO BONE	13/85	15,3
RADIATION TO BONE	40/85	47,1

[a]included first, second and third; SRE, skeletal-related event.
doi:10.1371/journal.pone.0074402.t002

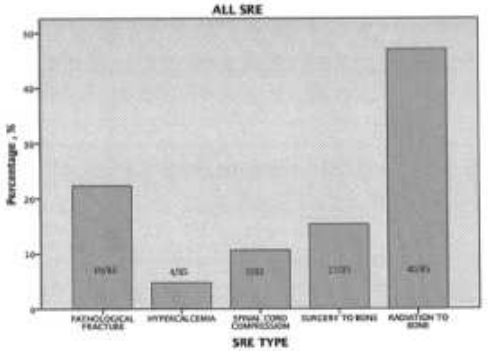


Figure 1. Percentage of skeletal-related events (SREs) occurring in patients with bone metastases from gastric cancer.
doi:10.1371/journal.pone.0074402.g001

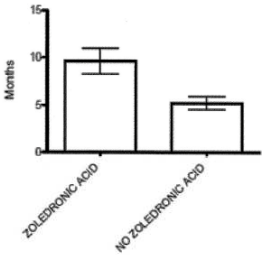


Figure 2. Comparison of time to first SRE in patients receiving zoledronic acid before SRE (n = 31) and those who did not receive zoledronic acid (n = 85, p = 0.0005). Data are presented as mean ± SEM Statistical significance was determined by Mann-Whitney test.

Research Paper

Metastatic spread in patients with gastric cancer

Matias Riihimäki[1,2], Akseli Hemminki[3,4], Kristina Sundquist[2], Jan Sundquist[2], Kari Hemminki[1,2]

Table 2: Multivariable logistic regression model for ORs of specific metastases in gastric cancer patients with a single metastasis ($N = 1,945$)

Patient characteristics	Any metastasis			Thorax				Peritoneum				Liver				Other Gastro-intestinal				Bone				Other			
	OR	95 % CI		%	OR	95 % CI		%	OR	95 % CI		%	OR	95 % CI		%	OR	95 % CI		%	OR	95 % CI		%	OR	95 % CI	
All				5%				29%				44%				5%				7%				10%			
Sex																											
Men	1			5%	1			26%	1			48%	1			4%	1			8%	1			8%	1		
Women	1.0	0.9	1.1	3%	0.6	0.4	0.9	34%	1.1	1.0	1.4	37%	0.8	0.7	0.9	7%	1.5	1.0	2.2	6%	0.7	0.5	1.0	13%	1.8	1.3	2.4
Age at diagnosis																											
< 60	1			3%	1			37%	1			29%	1			6%	1			12%	1			14%	1		
60 – 69	0.9	0.8	1.1	5%	1.7	0.9	3.4	33%	0.9	0.7	1.1	40%	1.3	1.0	1.6	5%	0.8	0.5	1.5	8%	0.7	0.4	1.0	8%	0.6	0.4	0.9
70 – 79	0.7	0.6	0.9	4%	1.4	0.7	2.7	26%	0.5	0.4	0.7	48%	1.4	1.1	1.7	6%	0.8	0.5	1.4	5%	0.4	0.2	0.6	10%	0.7	0.5	0.9
> 79	0.4	0.3	0.5	6%	1.1	0.6	2.3	23%	0.3	0.2	0.4	55%	1.0	0.8	1.2	5%	0.5	0.2	0.8	4%	0.2	0.1	0.3	7%	0.3	0.2	0.4
Anatomical site																											
Cardia	1			7%	1			18%	1			51%	1			3%	1			8%	1			11%	1		
Fundus/ Corpus	0.9	0.8	1.1	3%	0.4	0.2	0.7	33%	1.7	1.3	2.2	46%	0.9	0.7	1.1	4%	1.1	0.5	2.1	5%	0.6	0.4	1.1	8%	0.6	0.4	0.9
Antrum/ Pylorus	0.9	0.8	1.1	4%	0.5	0.3	0.9	34%	1.8	1.3	2.3	40%	0.7	0.6	0.9	7%	1.7	0.9	3.2	9%	0.1	0.7	1.9	7%	0.5	0.3	0.8
Unknown	1.2	1.0	1.4	4%	0.7	0.4	1.1	33%	2.0	1.6	2.7	38%	0.9	0.7	1.1	6%	0.9	1.1	3.3	6%	0.9	0.6	1.5	12%	1.1	0.8	1.6
Histology																											
Adenocarcinoma	1			5%	1			26%	1			48%	1			5%	1			6%	1			9%	1		
Signet ring	1.2	1.0	1.4	2%	0.4	0.2	1.1	56%	2.5	2.0	3.1	11%	0.3	0.2	0.4	7%	1.4	0.8	2.5	12%	2.1	1.3	3.2	12%	1.3	0.9	2.0
Mucinous	0.7	0.5	1.0	2%	0.3	0.0	2.3	27%	0.8	0.5	1.5	45%	0.7	0.4	1.1	16%	2.7	1.2	5.8	0%				9%	0.8	0.3	2.1

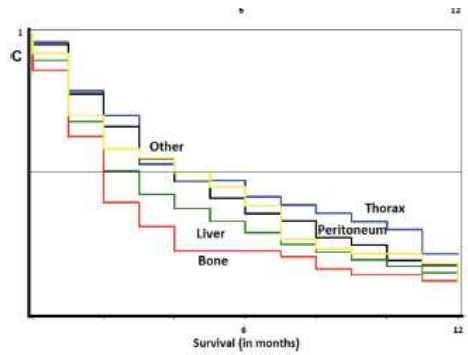


Figure 2: Survival curves in metastatic gastric cancer. In panel (A) comparison by T stage. In panel (B) comparison by N stage. In panel (C) comparison by site of metastasis.

Table 4: Location of second metastasis in gastric cancer patients with one or multiple metastases (two or more)

Site of metastasis	*Total amount*	*As one of N listed metastases*				*% multiple*	*Lung*	*Pleura/ Mediastinum*	*Peritoneum*	*Liver*	*Other GI*	*Nervous system*	*Bone*	*Ovary**	*Other*
		1	*2*	*3*	*4+*										
ALL															
Lung	440	89	191	111	49	80%	100%	9%	16%	55%	8%	5%	13%	1%	16%
Pleura/Med.	161	9	50	50	52	94%	25%	100%	32%	25%	3%	3%	16%	6%	18%
Peritoneum	934	570	209	104	51	39%	8%	6%	100%	16%	7%	1%	4%	5%	12%
Liver	1416	848	381	136	51	40%	17%	3%	11%	100%	6%	2%	7%	1%	10%
Other GI	279	102	112	50	15	63%	12%	2%	23%	30%	100%	2%	7%	2%	13%
Nervous system	98	37	32	15	14	62%	21%	5%	9%	27%	6%	100%	18%	1%	16%
Bone	350	136	109	64	41	61%	16%	7%	11%	29%	6%	5%	100%	4%	21%
Ovary	82	20	29	18	15	76%	7%	12%	56%	12%	7%	1%	18%	100%	21%
Other	445	134	163	93	55	70%	16%	7%	26%	31%	8%	4%	17%	4%	100%
CARDIA															
Lung	188	35	85	46	22	81%	100%	8%	13%	60%	7%	6%	14%	0%	15%
Pleura/Med.	55	5	17	19	14	91%	27%	100%	16%	40%	2%	5%	13%	0%	15%
Peritoneum	168	90	42	25	11	46%	14%	5%	100%	26%	4%	1%	6%	1%	12%
Liver	481	253	151	56	21	47%	23%	5%	9%	100%	5%	4%	10%	0%	10%
Other GI	59	17	25	11	6	71%	24%	2%	12%	37%	100%	7%	10%	0%	15%
Nervous system	54	19	21	6	8	65%	22%	6%	4%	33%	7%	100%	13%	2%	17%
Bone	123	40	42	25	16	67%	22%	6%	8%	38%	5%	6%	100%	1%	24%
Ovary	4	1	0	3	0	75%	0%	0%	50%	25%	0%	25%	25%	100%	25%
Other	125	34	39	30	22	73%	23%	6%	16%	40%	7%	7%	24%	1%	100%
NONCARDIA															
Lung	139	25	60	39	15	82%	100%	7%	21%	56%	9%	3%	11%	2%	21%
Pleura/Med.	53	2	17	18	16	96%	19%	100%	42%	21%	2%	0%	15%	9%	15%
Peritoneum	428	259	100	46	23	39%	7%	5%	100%	17%	7%	1%	4%	7%	12%
Liver	544	336	137	50	21	38%	14%	2%	13%	100%	8%	1%	5%	1%	10%
Other GI	123	43	47	26	7	65%	11%	1%	24%	35%	100%	1%	9%	2%	15%
Nervous system	25	9	7	6	3	64%	16%	0%	12%	20%	4%	100%	36%	0%	20%
Bone	122	53	32	23	14	57%	12%	7%	15%	23%	9%	7%	100%	5%	21%
Ovary	41	9	16	7	9	78%	7%	12%	68%	15%	7%	0%	15%	100%	15%
Other	170	39	72	42	17	77%	17%	5%	31%	33%	11%	3%	15%	4%	100%

Percentages indicate how many of all patients with site-specific metastases have multiple metastases to other sites.

Gastric cancer and bone metastases

The majority of bone metasese are asymptomatic

Sites: Spine; pelvis

Methacronous met median time to met 16 months

Bone metastases prognostic factors for survival: 8.7 vs 4 months

Better survival for patients with bone only vs bone + other sites

PS prognostic factor for survival

Cardia > incidence; PD >

Synchronous vs metachronosus prgonsotic

S-1 or irinotecan better?

	Bone metastasis		
	synchro-nous (n = 126)	meta-chronous (n = 77)	total (n = 203)
Median age (range), years	52 (24–83)	51 (28–71)	51 (24–83)
Sex			
Male	71 (56)	46 (60)	117 (57)
Female	55 (44)	31 (40)	86 (43)
Performance status			
0–2	99 (79)	67 (87)	166 (82)
3–4	27 (21)	10 (13)	37 (18)
Histology			
WD-MD	25 (20)	13 (17)	38 (20)
PD-SRC	91 (72)	56 (73)	147 (72)
Unknown	10 (8)	8 (10)	16 (8)
Gross type			
EGC	9 (8)	3 (4)	12 (6)
Type 1	3 (2)	0	3 (2)
Type 2	13 (10)	10 (13)	23 (11)
Type 3	63 (50)	40 (51)	103 (51)
Type 4	19 (15)	19 (25)	38 (19)
Unclassified	19 (15)	5 (7)	24 (11)
Location			
Upper 1/3	1 (1)	1 (1)	2 (1)
Middle 1/3	41 (33)	37 (49)	78 (38)
Lower 1/3	31 (25)	24 (31)	55 (28)
Diffuse	39 (31)	8 (10)	47 (23)
Unknown	14 (10)	7 (9)	21 (10)
Operation			
Yes	8 (6)	69 (90)	77 (38)
No	118 (94)	8 (10)	126 (62)
Aim of surgery			
Curative	0	59 (77)	59 (29)
Palliative	6 (5)	6 (8)	12 (6)
Bypass	2 (2)	4 (5)	6 (3)

Anaplastic lymphoma kinase (ALK) gene alteration in signet ring cell carcinoma of the gastrointestinal tract

Olatunji B. Alese, Bassel F. El-Rayes, Gabriel Sica, Guojing Zhang, Dianne Alexis, Francisco G. La Rosa, Marileila Varella-Garcia, Zhengjia Chen, Michael R. Rossi, Nazim V. Adsay, Fadlo R. Khuri and Taofeek K. Owonikoko

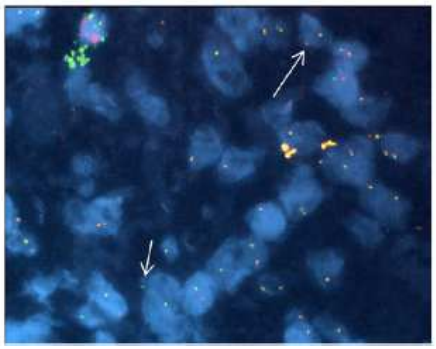
Ther Adv Med Oncol

2015, Vol. 7(2) 56–62

DOI: 10.1177/1758834014567117

Tipico dello stomaco distale
Istotipo mucinoso
Raro nella giunzione EG

3-5% incidenza



Identification of ROS1 Rearrangement in Gastric Adenocarcinoma

Jeeyun Lee, MD, PhD[1]; Seung Eun Lee, MD, PhD[2]; So Young Kang, MS[2]; In-Gu Do, MD, PhD[3]; Sujin Lee, MD[1]; Sang Yun Ha, MD[2]; Jeonghee Cho, PhD[3]; Won Ki Kang, MD, PhD[1]; Jiryeon Jang, MS[1]; Sai-Hong Ignatius Ou, MD, PhD[4]; and Kyoung-Mee Kim, MD, PhD[2]

4% incidenza

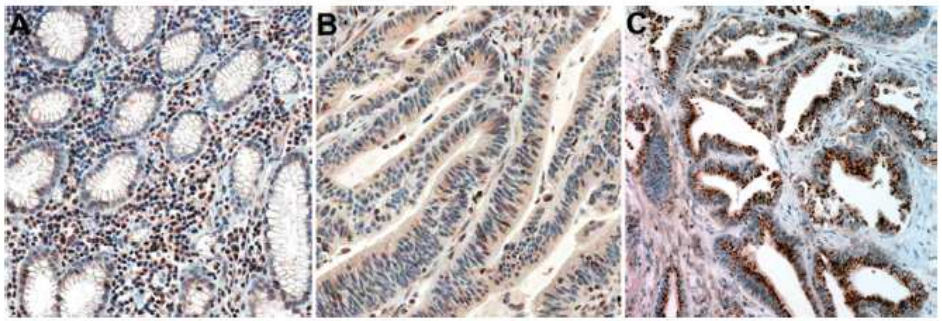


Figure 1. Representative staining patterns of c-ros oncogene 1, receptor tyrosine kinase (*ROS1*) are observed in (A) non-neoplastic gastric mucosa and in gastric carcinoma that was (B) negative and (C) positive for ROS1. Note the perinuclear, dot-like, cytoplasmic staining in C.

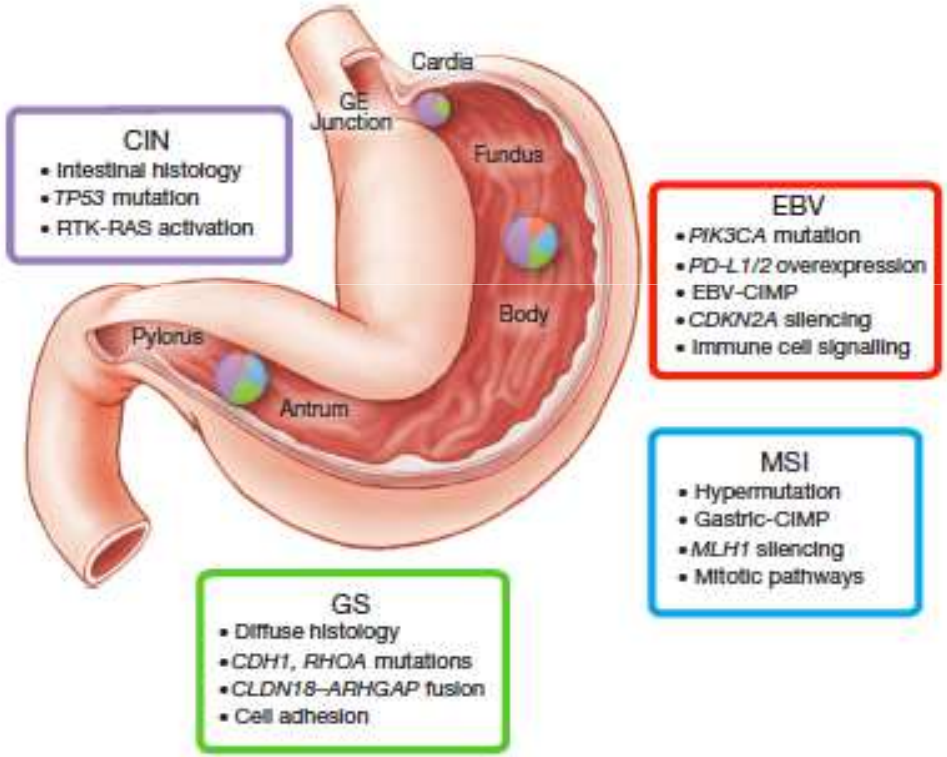
ARTICLE

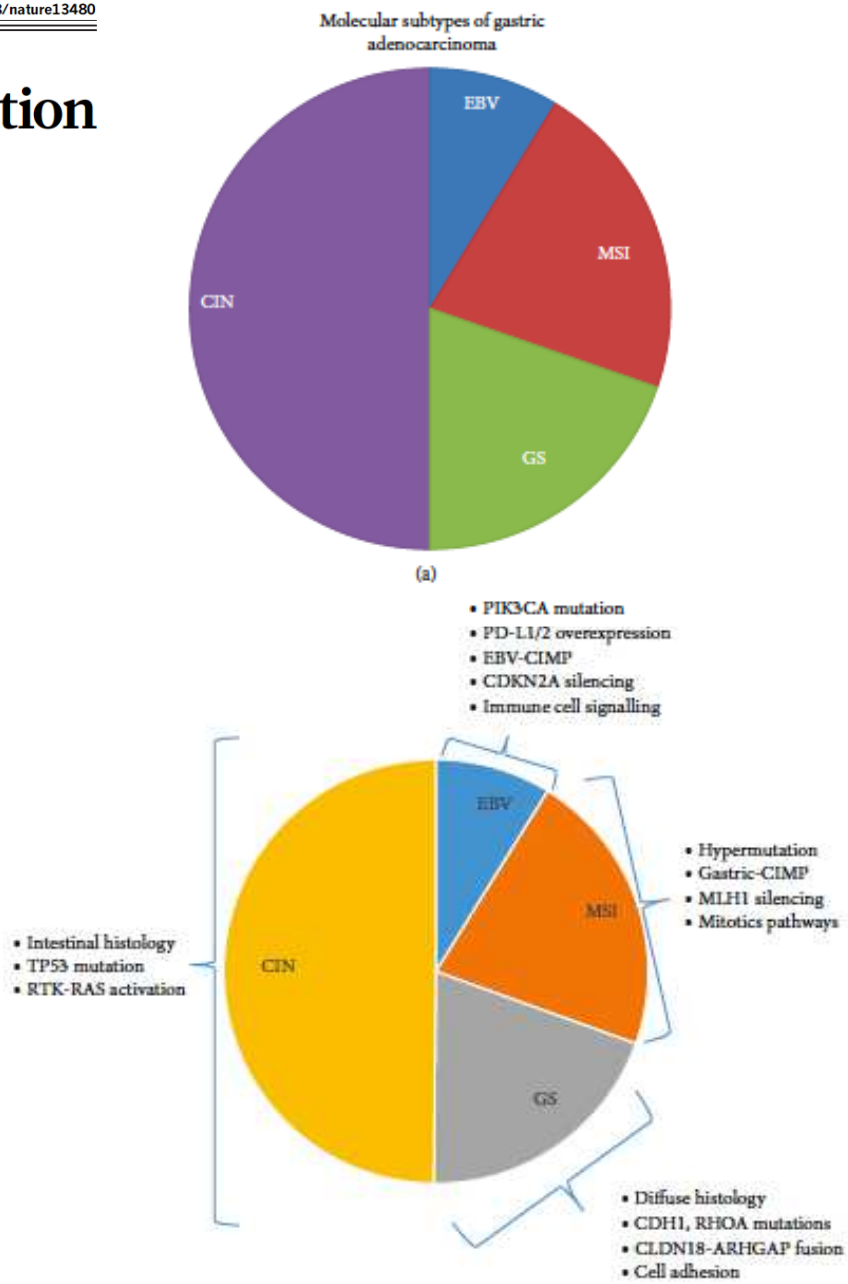
OPEN

doi:10.1038/nature13480

Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network*





The Journal of NUCLEAR MEDICINE

Bone Marrow and NOT Bone Metastases is What 21st Century Diagnostic Imaging Must Focus upon when Looking for Skeletal Metastases

Poul Flemming Høilund-Carlsen, Søren Hess and Abass Alavi

J Nucl Med.
Published online: September 15, 2017.
Doi: 10.2967/jnumed.117.201848

noma) and described in detail in a succeeding editorial [6]. In short, the main massage is that skeletal metastasis occurs by seeding in the red bone marrow of circulating tumor cells, retrograde venous flow or direct extension, and that proliferating cancer cells at some unknown time point give rise to reactive bone formation, which is what can be detected by the four modalities compared in the Löfgren study. Opposite to FDG-PET imaging, all four modalities bear only indirect evidence of metastatic dis-

Metastasi ossee e midollari: l'esempio del carcinoma gastrico

- Attenzione è diversa la situazione fra metastasi ossee e coinvolgimento midollare.

- Coinvolgimento midollare può rispondere bene e avere una buona prognosi.

Cancer Medicine

Open Access

ORIGINAL RESEARCH

Presence of bone marrow micro-metastases in stage I-III colon cancer patients is associated with worse disease-free and overall survival

Carsten T. Viehl[1,2], Benjamin Weixler[2,3], Ulrich Guller[4,5], Salome Dell-Kuster[2,6], Rachel Rosenthal[2], Michaela Ramser[2], Vanessa Banz[5], Igor Langer[7], Luigi Terracciano[8], Guido Sauter[8,9], Daniel Oertli[2] & Markus Zuber[3]

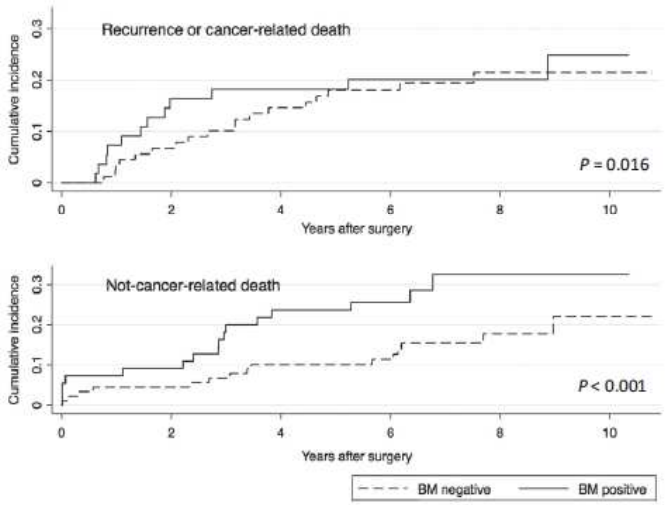
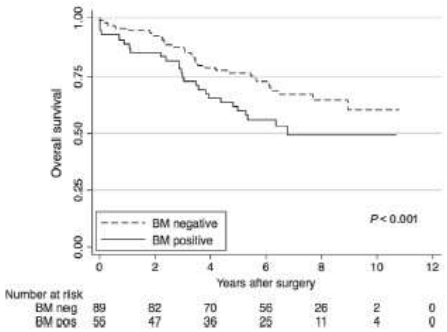


Figure 2. Cumulative incidence of recurrence or cancer-related death (top) and not-cancer related death for the covariates bone mar negative and positive.



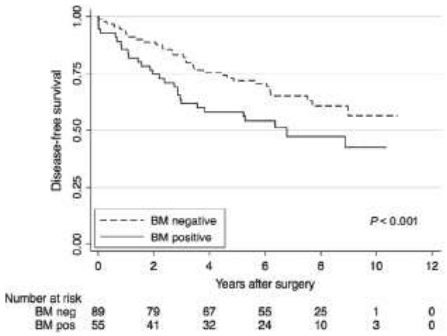


Figure 3. Kaplan-Meier survival curves for overall survival and disease-free survival for the covariates bone marrow (BM) negative and positive.

12-15% incidence

Rectal cancer 16% vs 30% pre vs no prechemoradiotherapy

Hepatogastroenterology. 2013 Mar-Apr;60(122):273-6.

Clinical study of disseminated tumor cells in bone marrow of patients with gastric cancer.

Wang G[1], Wang S, Li Y, Yu Y, Song Z, Zhao Q, Tian Z.

BACKGROUND/AIMS: Tumor micrometastasis usually occurs at early stage. Therefore, we aimed to investigate the morphology of disseminated tumor cells (DTCs) and its clinical significance in bone marrow (BM) of patients with gastric cancer.

METHODOLOGY: Forty patients with gastric cancer were enrolled and mononuclear cells were separated from BMs. After labeled by MACS microbeads conjugated with human epithelial antigen (HEA) antibodies, tumor cells were viably enriched twice by MS+/RS+ positive separation column. Parts of the cells from the patients were stained with CK-FITC, DAPI and EB. Then, morphology of the stained tumor cells was observed under fluorescence microscope.

RESULTS: Six hundred and eighty eight CK positive cells in 18 cases (45%) were detected, including 384 (55.8%) medium-sized cells, 102 (14.8%) large-sized cells, 46(6.7%) stem-cell-like cells, 8 (1.2%) M-phase cells, 84 (12.2%) nuclear debris and 64 (9.3%) non-nuclear debris. The number of tumor cells in BM was significantly correlated with TNM stage (p=0.038), but not with gender, age, histological differentiation and lymph node metastasis.

CONCLUSIONS: The DTCs in BM of patients with gastric cancer show various morphological characteristics. The existence of these tumor cells suggests a poor prognosis.

Invasione midollare e metastasi ossee

- Perché i tumori GI hanno una bassa incidenza di metastasi ossee ma una alta incidenza di invasione midollare?
  - Occasionale crocevia di passaggio?
  - Qualche significato biologico nascosto?
- Caratteristiche delle cellule tumorali o degli esosomi?
- L'esempio del carcinoma gastrico

The bone metastasis: the marrow invasion as the first step

- Pre-metastatic niche formation
- Chemotactic attraction of malignant cells
- Homing of malignant cells to **bone marrow**
- Acquisition of an osteomymetic cell phenotype

After a latency period (months to years) malignant cells can proliferate into tumors that alter bone remodeling processess by inducing activation of osteoblasts and osteoclasts function.

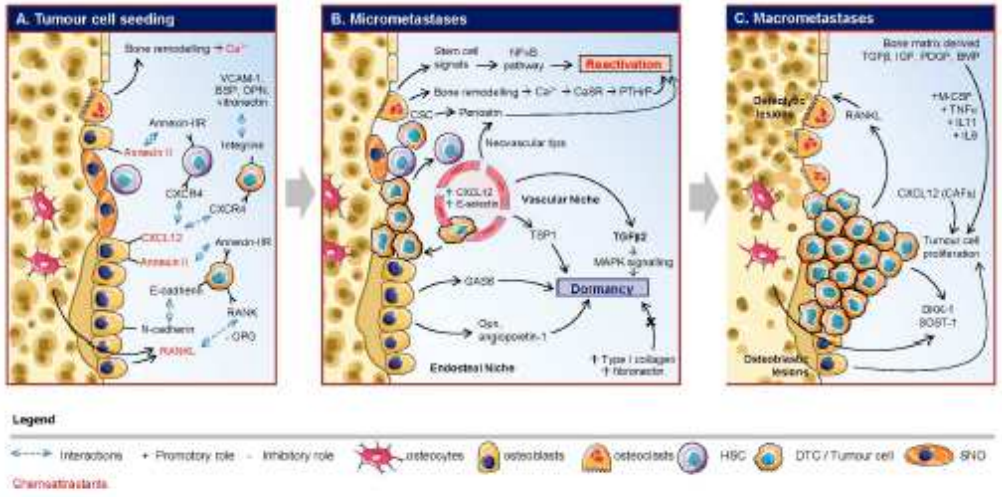
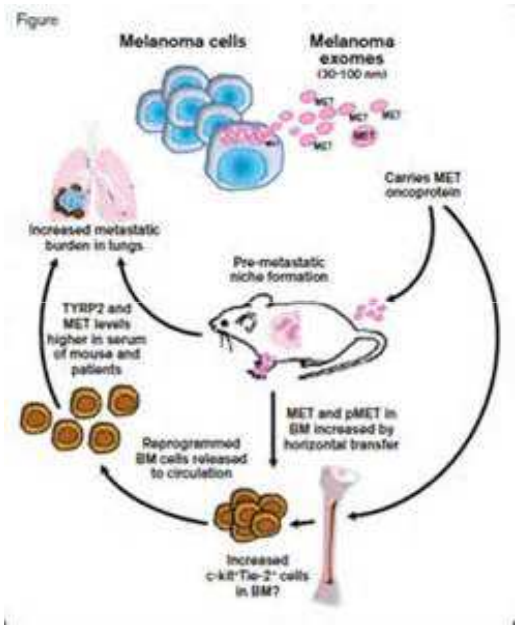


Figure 1. Stages of cancer cell colonisation of the bone. (**A**) Tumour cells are attracted to the high levels of chemoattractants in the bone marrow (red), such as Ca^{2+}, CXCL12 (C–X–C motif chemokine

The bone marrow invasion: really a first step only?

The role of exosomes: new actors in the play



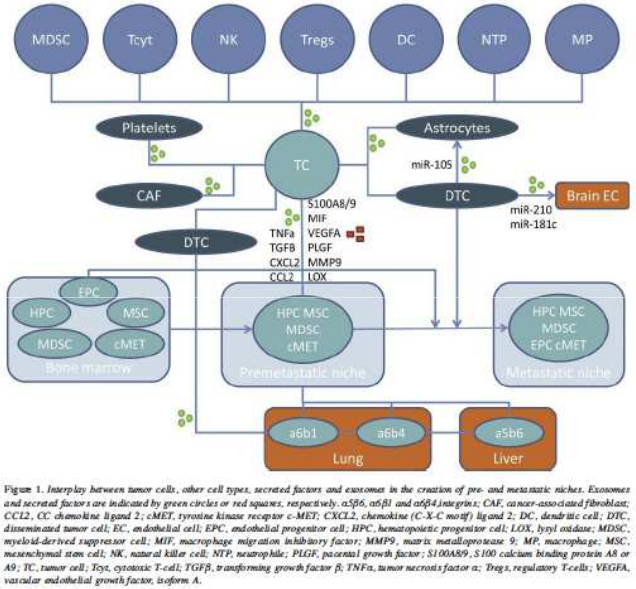


Figure 1. *Interplay between tumor cells, other cell types, secreted factors and exosomes in the creation of pre- and metastatic niches. Exosomes and secreted factors are indicated by green circles or red squares, respectively. α5β6, α6β1 and α6β4 integrins; CAF, cancer-associated fibroblast; CCL2, CC chemokine ligand 2; cMET, tyrosine kinase receptor c-MET; CXCL2, chemokine (C-X-C motif) ligand 2; DC, dendritic cell; DTC, disseminated tumor cell; EC, endothelial cell; EPC, endothelial progenitor cell; HPC, hematopoietic progenitor cell; LOX, lysyl oxidase; MDSC, myeloid-derived suppressor cell; MIF, macrophage migration inhibitory factor; MMP9, matrix metalloprotease 9; MP, macrophage; MSC, mesenchymal stem cell; NK, natural killer cell; NTP, neutrophile; PLGF, placental growth factor; S100A8/9, S100 calcium binding protein A8 or A9; TC, tumor cell; Tcyt, cytotoxic T-cell; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α; Tregs, regulatory T-cells; VEGFA, vascular endothelial growth factor, isoform A.*

- exosomes (small vesicles surrounded by a membrane similar to cellular membrane with a few cytosol); express integrin (avB5 liver, a6B4 lung, …….) responsible for cell to cell comunication

The bone marrow invasion: really a first step only?

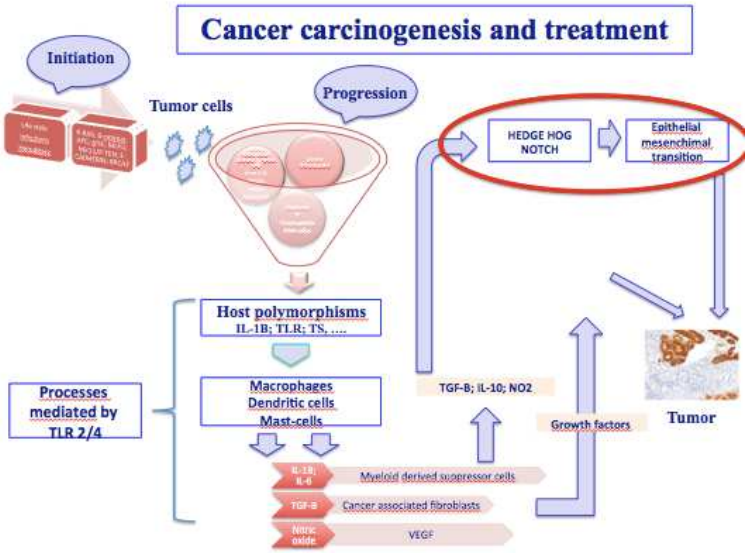
What really happens:

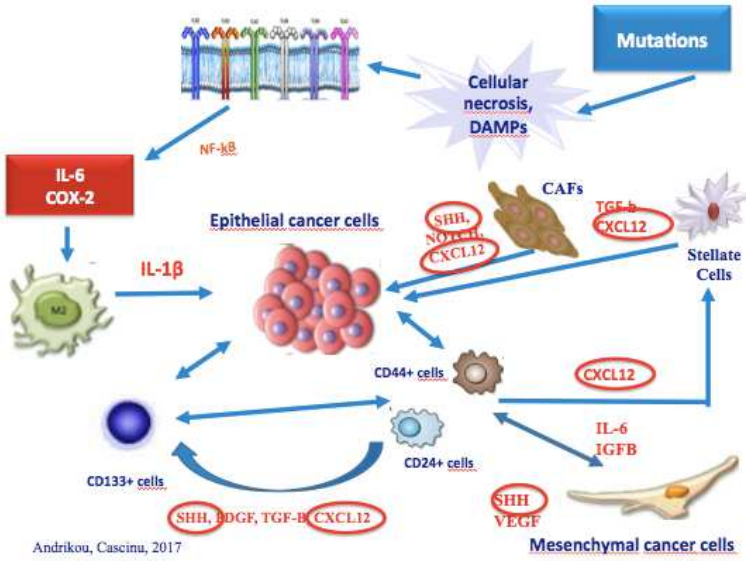
- tumour cells present EMT and release exosomes
- exosomes (small vesicles surrounded by a membrane similar to cellular membrane with a few cytosol); express integrin (avB5 liver, a6B4 lung, …….)
- CXCL12 attract cells expressing CXCR4
- soluble RANKL attract cells expressing RANK

The bone marrow invasion: really a first step for bone metastases or a connecting point?

Bone marrow:
the bad father of the metastatic process?

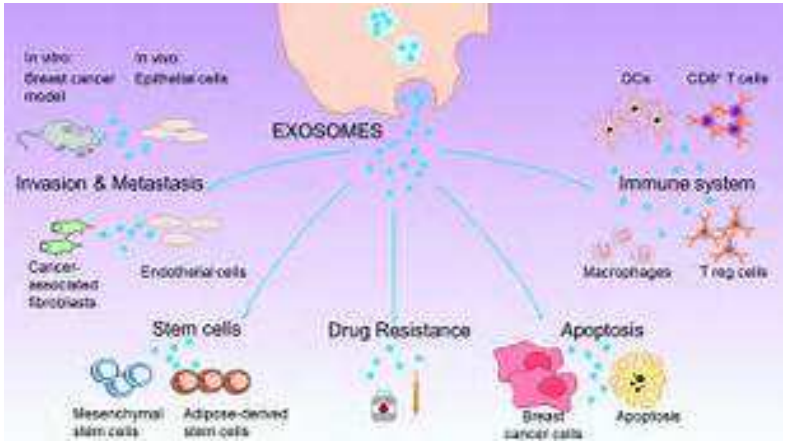
- Initiated tumor cells (KRAS, c_myc, ….)
- inflammation (IL-6; IL1B, IL-8, COX-2,…)
- Hedge Hog activation
- Epithelial mesenchymal transition





Bone marrow:
the bad father of the metastatic process?

- Initiated tumor cells (KRAS, c_myc, ….)
- inflammation (IL-6; IL1B, IL-8, COX-2,…)
- Hedge Hog
- Epithelial mesenchymal transition
- Mesenchymal cells release exosomes to bone marrow



OncoTargets and Therapy

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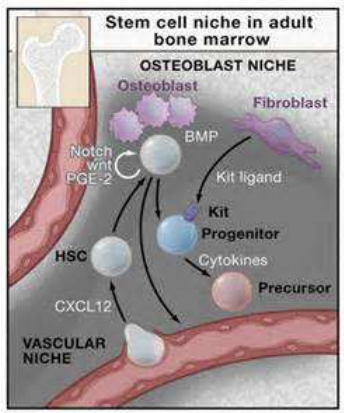
ORIGINAL RESEARCH

miRNA-221 of exosomes originating from bone marrow mesenchymal stem cells promotes oncogenic activity in gastric cancer

This article was published in the following Dove Press journal:
OncoTargets and Therapy
22 August 2017
Number of times this article has been viewed

Bone marrow:
the bad father of the metastatic process?

- Initiated tumor cells (KRAS, c_myc, ….)
- inflammation (IL-6; IL1B, IL-8, COX-2,…)
- Hedge Hog
- Epithelial mesenchymal transition
- Mesenchymal cells release exosomes to bone marrow
- **Recruitment of bone marrow stromal cells by exosomes, leaving bone marrow to tumor and in part creating the tumoral niche. They release exosomes to find the specific metastatic sites**



OPEN ACCESS Freely available online PLOS ONE

Sonic Hedgehog Mediates the Proliferation and Recruitment of Transformed Mesenchymal Stem Cells to the Stomach

Jessica M. Donnelly[1], Ambreesh Chawla[1], JeanMarie Houghton[2], Yana Zavros[1]*

Cellular Physiology and Biochemistry

Cell Physiol Biochem 2017;42:2242-2254
DOI: 10.1159/000479998
Published online: August 16, 2017
Accepted: May 24, 2017

Original Paper

Exosomes Derived from Human Bone Marrow Mesenchymal Stem Cells Promote Tumor Growth Through Hedgehog Signaling Pathway

Jin Qi[a,b,c] Yali Zhou[b] Zuoyi Jiao[b] Xu Wang[c] Yang Zhao[b] Yangbin Li[b] Huijuan Chen[b] Luxi Yang[b] Hongwen Zhu[b] Yumin Li[a,b]

[a]The Second Hospital of Lanzhou University, Lanzhou, Gansu, China, [b]Key Laboratory of Digestive System Tumors of Gansu Province, [c]Key Laboratory of Orthopedics of Gansu Province, Lanzhou, China

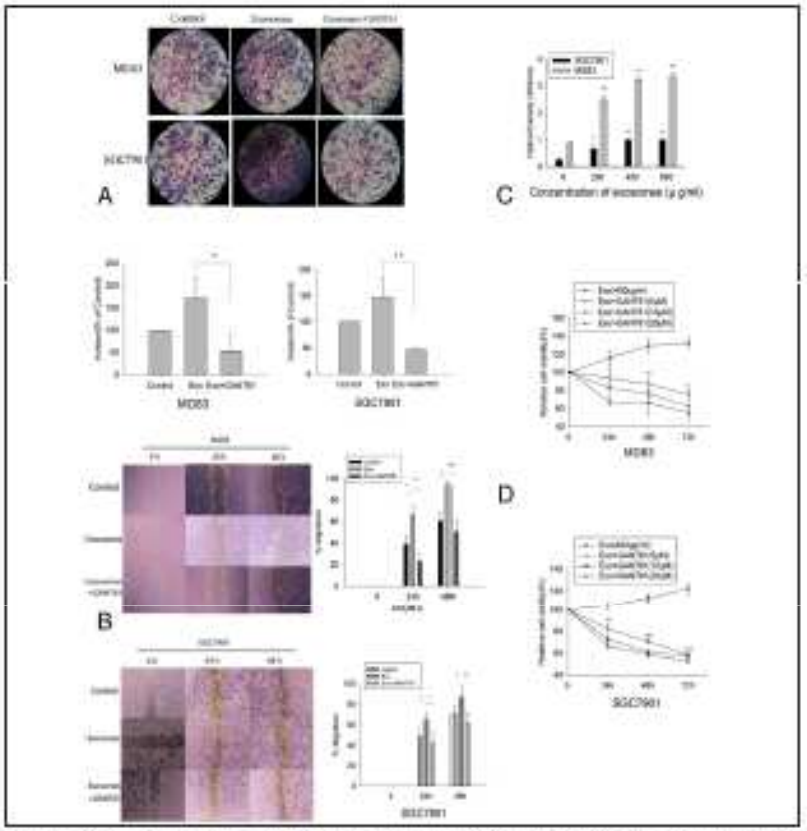


Fig. 4. hBMSC-exosomes induce viability and proliferation in MG63 and SGC7901 cells. (A) an amounts of MG63 cells and SGC7901 cells were respectively added to the upper chamber of transwell with matrigel coated membrane. Cancer cells were treated with exosomes (400μg/ml) or treated with exosomes (400μg/ml) and GANT-61(10μM), an equal volume of exosome-depleted medium was used as a control. After 24 hours the number of cells migrated to the lower chamber of the 8 μm pore-sized membrane were analyzed by taking photos and counting the number of cells per visual field. n=3 per group; *P <0.05, **P <0.01. (B) Scratch migration assay test of interfering hBMSC-exosomes group, interfering GANT61 group and control group in 24 hours and 48 hours. The wound healing assay demonstrated a stronger migration ability of cells in interfering hBMSC-exosomes group. Compared with control group and interfering GANT61 group, there were significant difference in percentage of wound closed(n=3 per group; *P <0.05, **P <0.01).a weaker migration ability of cells in the blank control and GANT61 group. (C) MG63 and SGC7901 cells were respectively co-cultured with different concentrations of hBMSC-exosomes (0, 200, 400 and 800μg/ml) for 24 hours and then subjected to CCK-8 analyses. n=3 per group; *P <0.05, **P <0.01. (D) MG63 or SGC7901 cells in serum-free medium were treated with 400μg/ml hBMSC-exosomes or hBMSC-exosomes and different concentrations of GANT-61(0, 5, 10, 20 μM) in a 96-well plates. Cell viability was measured using CCk-8 analyses at 24, 48 and 72 hours after exosomes and GANT-61 treatment. n=3 per group; *P <0.05, **P <0.01, ***P<0.001.

Bone marrow:
the bad father of the metastatic process?

- Initiated tumor cells (KRAS, c_myc, ….)
- inflammation (IL-6; IL1B, IL-8, COX-2,…)
- Hedge Hog
- Epithelial mesenchymal transition
- Mesenchymal cells release exosomes to bone marrow
- Recruitment of bone marrow stromal cells by exosomes, leaving bone marrow to tumor and in part creating the tumoral niche. They release exosomes to find the specific metastatic sites
- **Mesenchymal tumor cells migrate to tumoral niches where they convert to epithelial (to proliferate) and then again to mesenchymal to go to the specific metastatic site on the basis of exosomes messages**

Ann Surg Oncol. 2010 Sep;17(9):2526-33. doi: 10.1245/s10434-010-1041-0. Epub 2010 Apr 1.

The clinical significance of vimentin-expressing gastric cancer cells in bone marrow.

Iwatsuki M[1], Mimori K, Fukagawa T, Ishii H, Yokobori T, Sasako M, Baba H, Mori M.

⊕ Author information

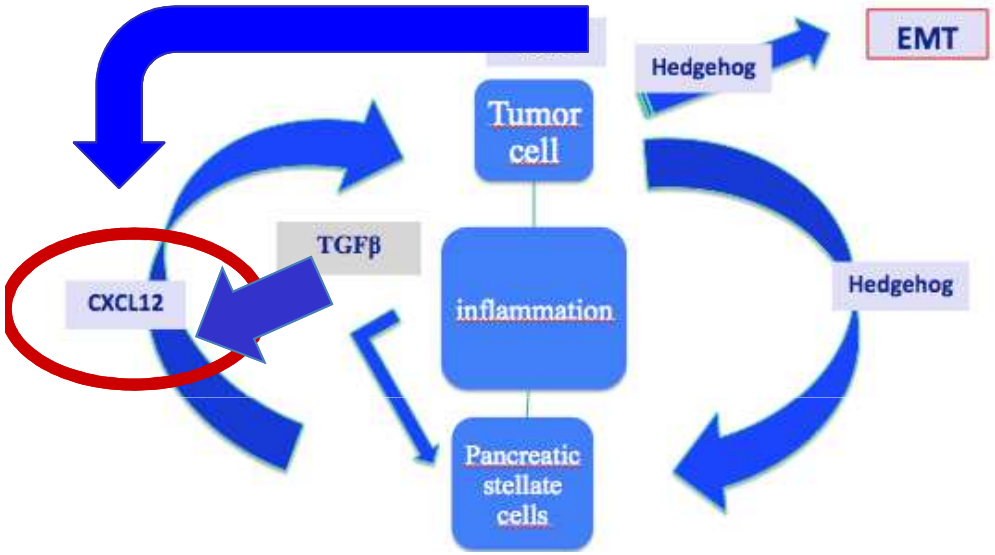
BACKGROUND: Expression of the mesenchymal marker gene vimentin (VIM) in gastric cancer is associated with a more aggressive form of the disease and poor prognosis. Because epithelial mesenchymal transition (EMT) plays a critical role in the progression of gastric cancer, VIM expression was examined in the bone marrow (BM) of gastric cancer patients.

METHODS: BM samples from 437 gastric cancer patients were collected and analyzed by quantitative RT-PCR. Expression of VIM protein in the primary lesions of resected gastric cancers was evaluated using immunohistochemistry. Furthermore, induction of VIM expression by TGF-beta1 and hypoxia was evaluated in gastric cancer cells.

RESULTS: VIM mRNA expression increased concordantly with clinical staging and was significantly associated with tumor invasion and lymph node metastasis ($P < .0001$). Though cancer cells in the primary lesions did not stain with VIM antibody, some of the cells invading the intratumoral vessels were strongly positive for VIM, but were negative for E-cadherin. Hypoxic conditions and treatment with TGF-beta1 induced VIM expression and repressed E-cadherin in gastric cancer cells, coupled with an alteration of cellular morphology.

CONCLUSIONS: We found that gastric cancer cells undergo EMT in BM to survive and metastasize. These findings suggest that isolated tumor cells have the potential to undergo EMT, which could increase the malignancy of gastric cancer.

“HH and CXCL12 and the others”: the bad company



Published in final edited form as:
Mol Cancer Res. 2011 November ; 9(11): 1462–1470. doi:10.1158/1541-7786.MCR-11-0190.

SDF-1α induces PDGF- B expression and the differentiation of bone marrow cells into pericytes

Randala Hamdan, Zhichao Zhou, and Eugenie S. Kleinerman[1]
[1]Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Theranostics 2013, Vol. 3, Issue 1 11

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2013; 3(1):11-17. doi: 10.7150/thno.4806

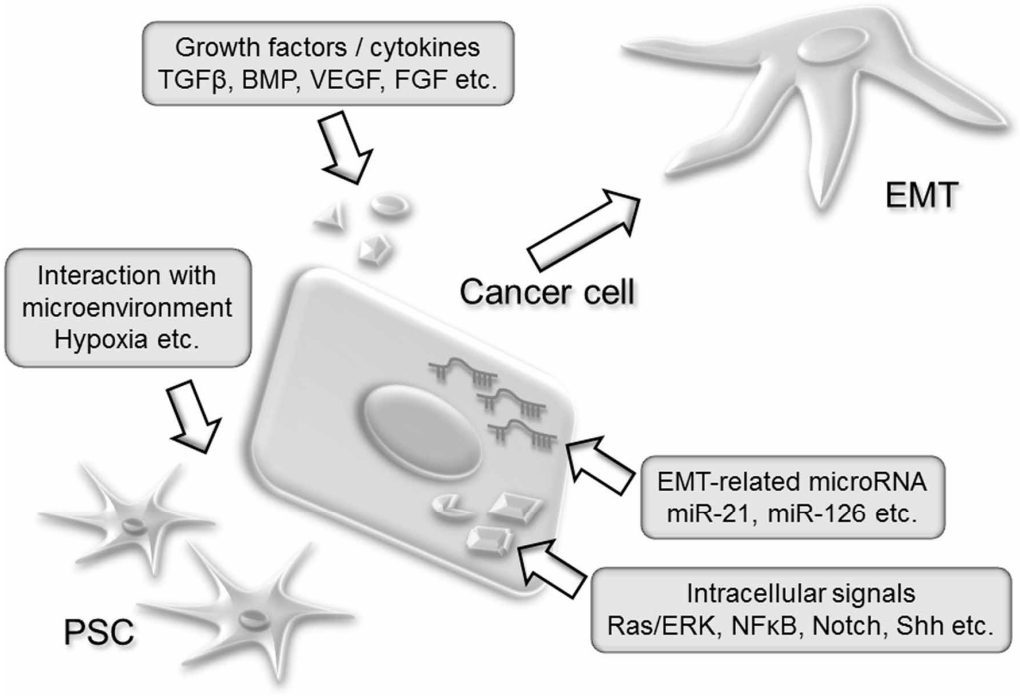
Review

The Role of CXCL12-CXCR4 Signaling Pathway in Pancreatic Development

Keiichi Katsumoto [1,2,3] and Shoen Kume [2,3]

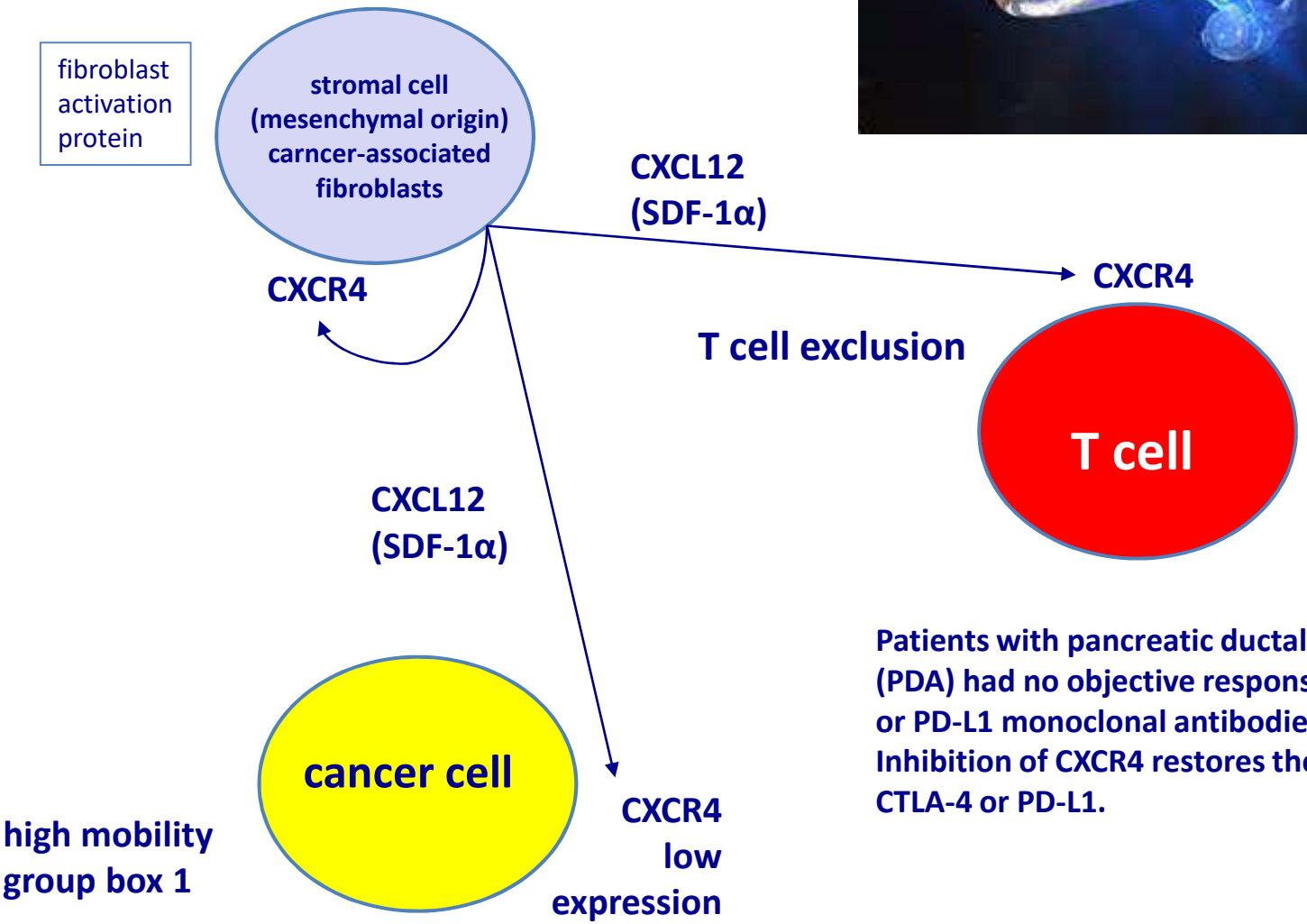
1. The Danish Stem Cell Center (DanStem), University of Copenhagen, 3B Blegdamsvej, Copenhagen N, DK-2200, Denmark.
2. Department of Stem Cell Biology, Institute of Molecular Embryology and Genetics (IMEG), Kumamoto University, Honjo 2-2-1, Kumamoto 860-0811, Japan;
3. The Global COE ‘Cell Fate Regulation Research and Education Unit,’ Kumamoto University, Honjo 2-2-1, Kumamoto 860-0811, Japan.

Epithelial mesenchymal transition



IGURE 1 | A schematic view of EMT regulators in pancreatic ancer development. Secreted cytokines such as TGFβ or BMP ctivates intracellular signal which leads to the EMT induction. Activating mutation such as *Kras G12D* constitutively stimulates intracellular signal and amplifies extracellular signal. Endogenous alteration of microRNA expression modifies cancer cell function. Stromal cells including PSCs establish protective microenvironment for cancer cells such as desmoplasia.

Exclusion of T cells in PDAC: the Startrek effect



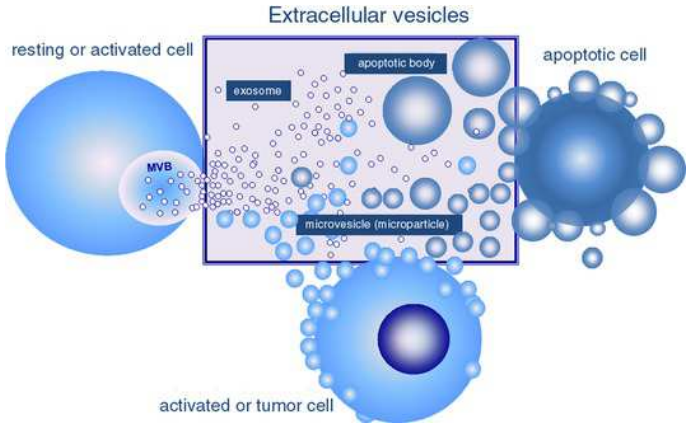
Patients with pancreatic ductal adenocarcinoma (PDA) had no objective responses to anti CTLA-4 or PD-L1 monoclonal antibodies.
Inhibition of CXCR4 restores the response to CTLA-4 or PD-L1.

Courtesy by Prof F. Piva

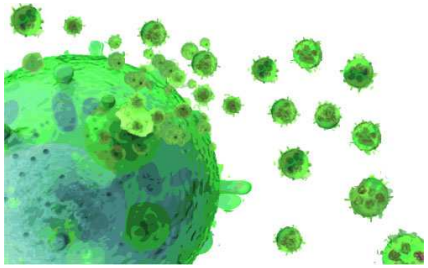
Prospettive terapeutiche

- Interferire con HH e somministrare agenti differenzianti (da mesenchimale a epiteliale) o capaci di colpire le cellule nella fase mesenchimale (eribulina)
- Inibire l'effetto immunosoppressivo di CXCL12 sia per rendere meno ospitale la nicchia metastatica che per far funzionare meglio l'immunoterapia in ogni sede anche dove potrebbero esserci dei santuari.

Esosomi come target terapeutico?



Francesco Piva



CXCL12

CXCR7

Cancer cell

Activated

CXCR4

Cancer cell

Non activated

Francesco Piva
Giovanni Principato

Fabio Gelsomino
Andrea Spallanzani
Katia Di Emidio
Massimiliano Salati

Kalliopi Andrikou
Giulia Orsi
Monica Barbolini
Giuseppe Pugliese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