George Pentheroudakis
Associate Professor of Oncology
Medical School, University of Ioannina

Cancer of Unknown Primary: Diagnosis and Treatment AND BIOLOGY

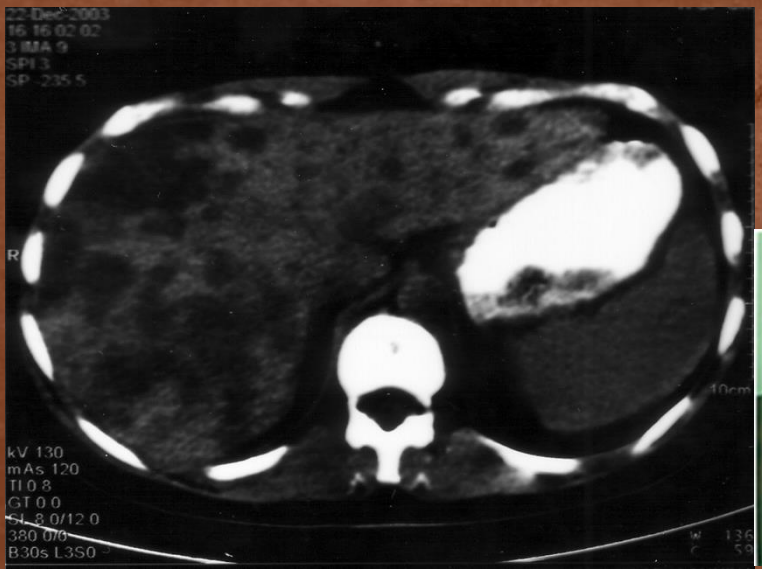
CYE Session
ESMO Conference, Madrid 2014

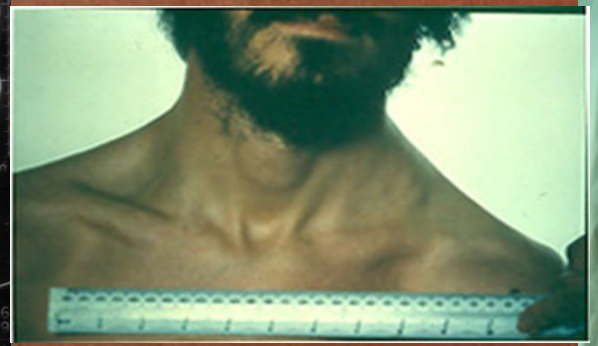
What we will talk about

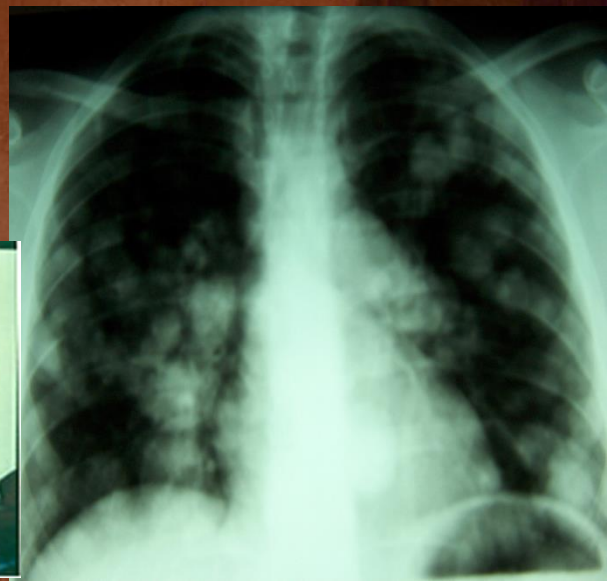
- **Definition of CUP**
- **CUP Epidemiology and Statistics**
- **CUP Pathology and Molecular Assays**
- **CUP Staging**
- **CUP Clinicopathologic Subsets**
- **CUP Prognostication**
- **CUP Therapy**
- **CUP Biology**
- **CUP Clinical Research**

Definition of CUP

- **Cytologic/pathologic diagnosis of malignancy (systemic metastases) in the absence of an identifiable primary tumour after a standardised diagnostic work up**

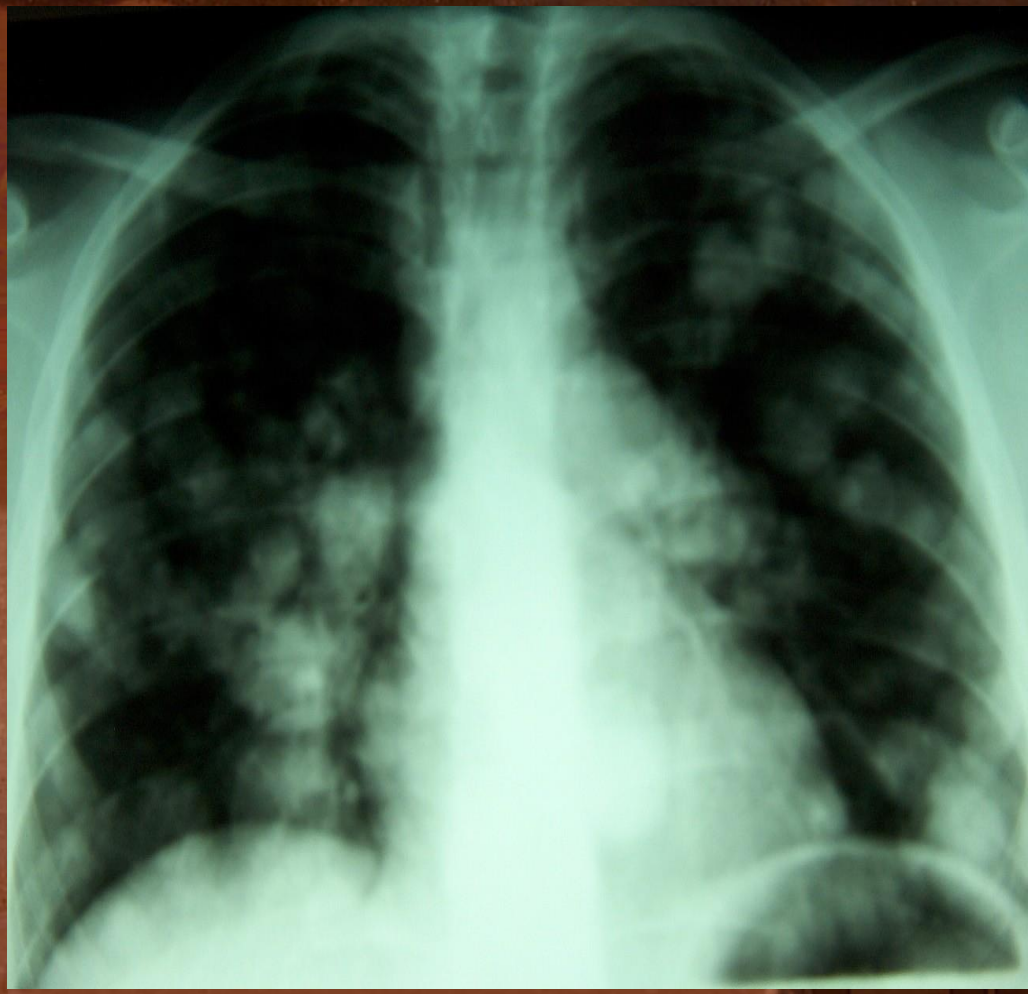






CUP: What is it?

- Metastases from a primary we simply cannot locate?
- Tumours with not only a primary tissue-specific biology but also with a distinct biological signature, common for most CUPs?



IS THERE EVIDENCE TO SUGGEST THAT CUP HAS PECULIAR AND DISTINCT BIOLOGY COMPARED TO METS FROM KNOWN PRIMARY TUMOURS (KPM)?

PROGNOSIS OF SUB-TYPES OF CUP COMPARED TO METASTATIC CANCER

Bishop JF et al [New South Wales, Australia] ASCO 2007 *(abs 21010)*

- ❖ Cancer Registry : 1980 – 2004
- ❖ 65.239 confirmed metastatic cancer patients

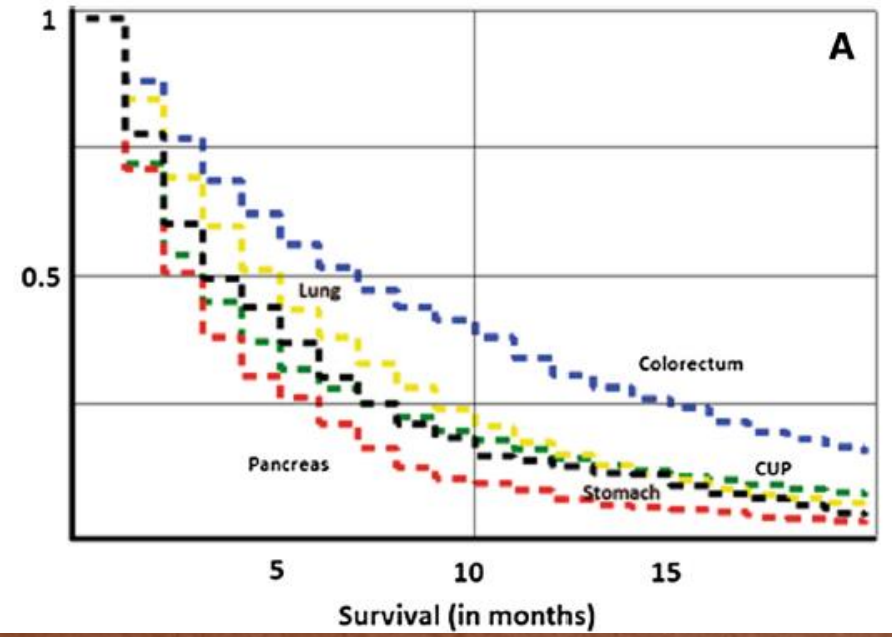
	46.435 (77%) Metastatic with known primary		13.280 (22%) CUP
Median Survival	7 (mos)	*(p< 0.0001)*	3 (mos)

Risk of dying by histology

Adenocarcinoma	80% greater (HR 1.8)
Squamous	50 % less (HR 0.49)
Small cell	20% less (HR 0.77)
Undifferentiated	15% less (HR 0.84)

Survival: CUP vs KPM

- Swedish Cancer Registry: 2881 CUP vs 6745 KPM



Primary site	N	HR
CUP (reference)	2881	1
Colorectal cancer	1438	**0.61**
Pancreatic cancer	460	**1.71**
Stomach cancer	322	**1.16**
Liver cancer	188	**1.58**
Lung cancer	2453	0.98
Kidney cancer	284	**0.71**
Bladder cancer	139	0.93
Prostate cancer	1259	**0.24**
Breast cancer	202	**0.53**
All known primaries	6745	**0.69**

Riihimäki et al. BMC Cancer 2013, 13:36

CUP characteristics

- Regression/dormancy of the primary

  Autopsies fail to identify the primary in 30-40% of cases or identify small nodules in lung, pancreas. Why does it not grow?

- Early uncommon systemic metastases

  High volume mets in multiple sites.

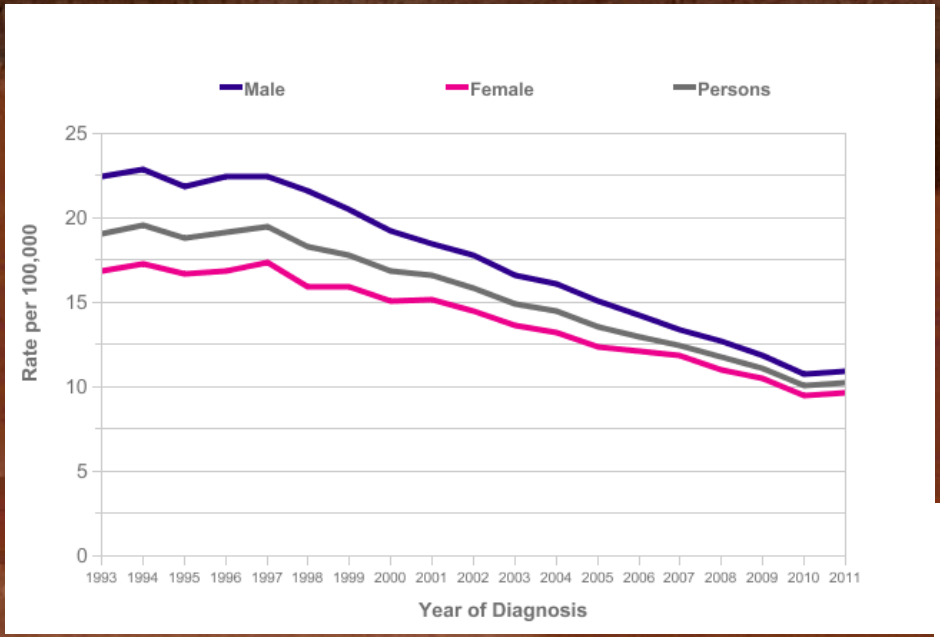
  Viscera, skin, heart, scalp, kidneys, distant nodes

Pentheroudakis et al, CTR 2009;35:221-7

EPIDEMIOLOGY OF CANCER OF UNKNOWN PRIMARY

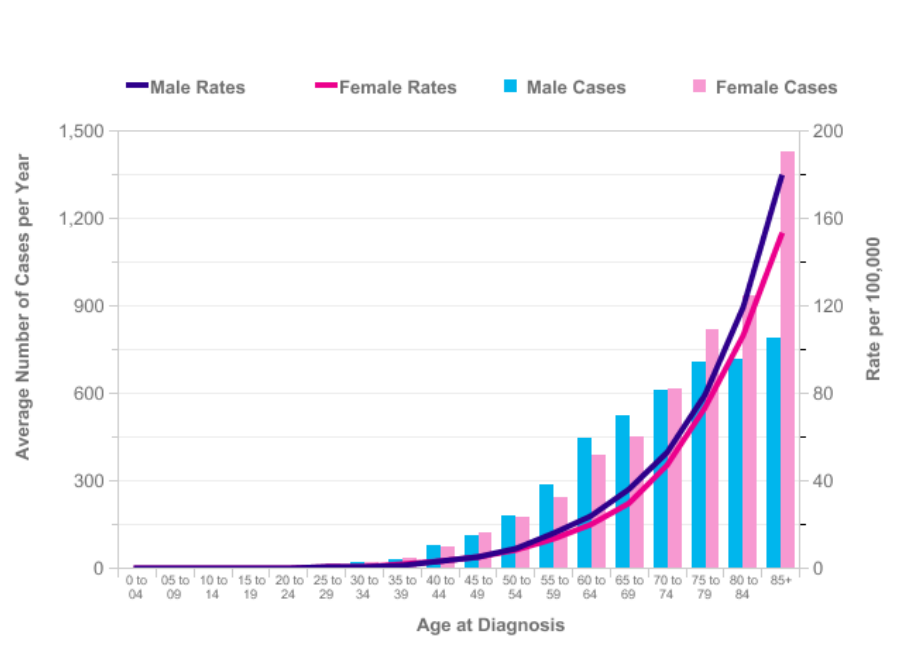
Geographical area	Source	Frequency (%)	Period
USA	SEER	2.3	1973-1987
Australia	New South Wales Registry	4.2	1970-1990
Netherlands	Eindhoven Cancer Registry	4.0	1984-1992
Finland	IARC	2.5	-
Germany	-	7.8	1968-1984
Russia	-	3.6	-
Switzerland	Local registries	2.3	1984-1993
Japan	IARC	3.0	-

Incidence



1993-2011: European Age-Standardised Incidence Rates per 100,000

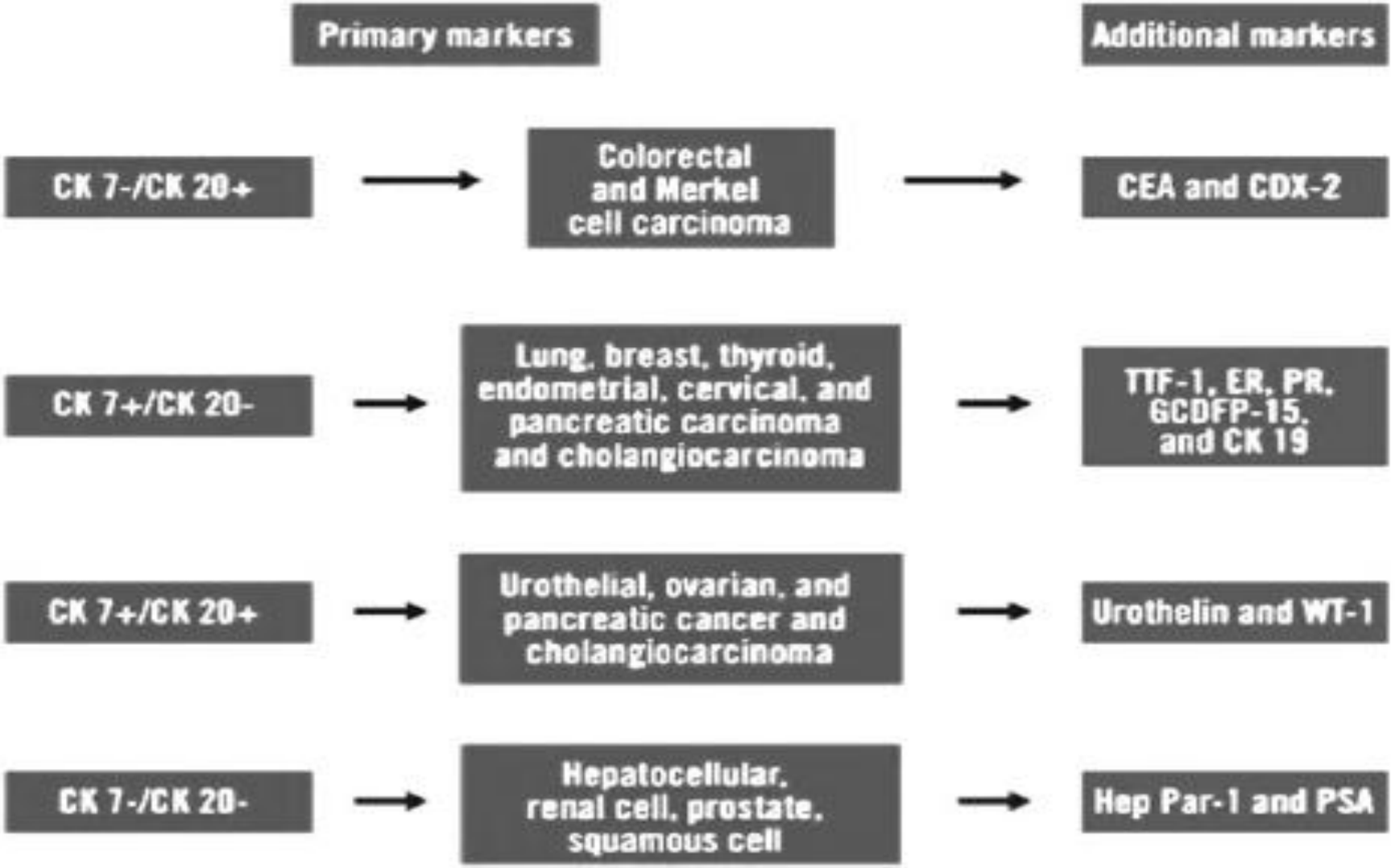
Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000, UK 2009-2011



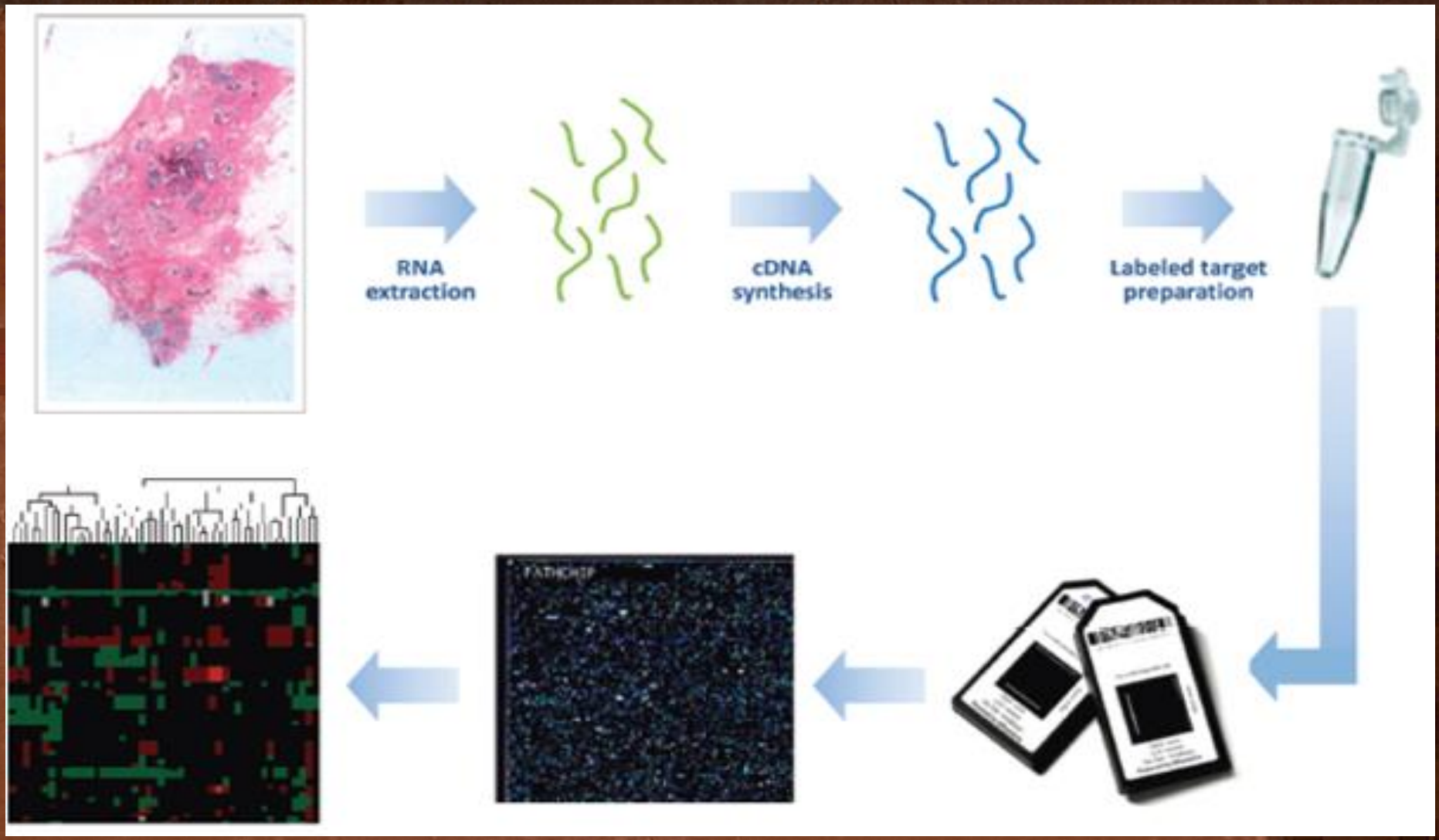
Prepared by Cancer Research UK - original data sources are available from http://www.cancerresearchuk.org/cancer-info/cancerstats/

CUP Pathology

- Biopsy needed
- Generous material wellcome (excisional biopsy or tru-cut rather than FNA)
- Classical histo work up with H&E stain


Primary markers
Additional markers
CK 7-/CK 20+
Colorectal and Merkel cell carcinoma
CEA and CDX-2
CK 7+/CK 20-
Lung, breast, thyroid, endometrial, cervical, and pancreatic carcinoma and cholangiocarcinoma
TTF-1, ER, PR, GCDFP-15, and CK 19
CK 7+/CK 20+
Urothelial, ovarian, and pancreatic cancer and cholangiocarcinoma
Urothelin and WT-1
CK 7-/CK 20-
Hepatocellular, renal cell, prostate, squamous cell
Hep Par-1 and PSA

Molecular Assays



Molecular assignment of primary: Gene expression arrays

Assays

Assay	Platform	Tissue	No. of Tumor types	Number of genes	Accuracy (%)
Veridex	RT-PCR mRNA	FFPE	6 and "other"	10	76
Pathwork Diagnostics Tissue of Origin test	cDNA microarray	Frozen/ FFPE	15	1500	89
Rosetta Genomics MiRview mets-2	Microarray miRNA	FFPE	42	64 miRNAs	92
bioTheranostics CancerType ID	RT-PCR mRNA	FFPE	39 (including subtypes)	92	86

IDENTIFICATION OF PRIMARY SITE BY GENETIC PROFILING (MICROARRAYS) FROM ALL PUBLISHED CUP SERIES

Years of Publications : 2005- 2007

No of Samples : > 500 (cDNA)

Biological Assignment of Primaries (Accuracy) : 50 – 87 %

Primary Sites Identified :

Breast	15 %
Pancreas	12.5 %
Bowel	12 %
Lung	11.5 %
Genital system	9 %
Liver/bile duct	8 %
Kidney / adrenals	6 %
Bladder / ureter	5 %
Stomach	3 %
Other	18 %

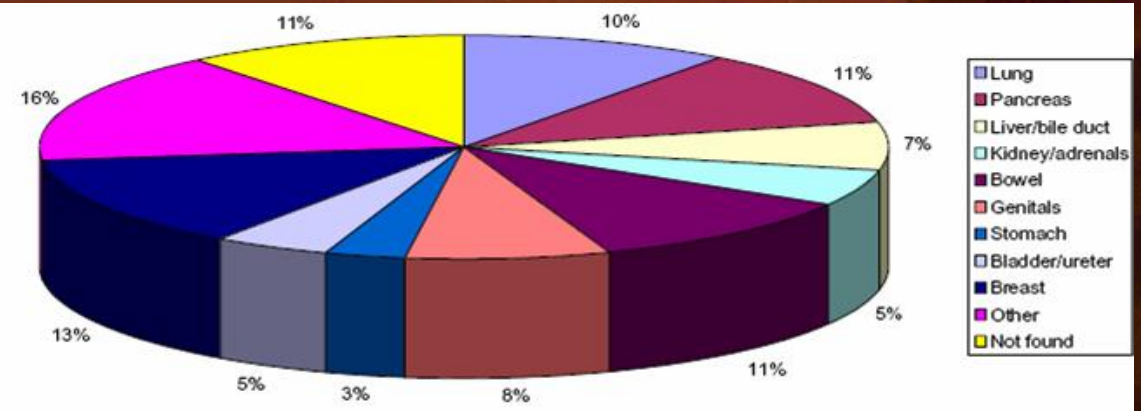
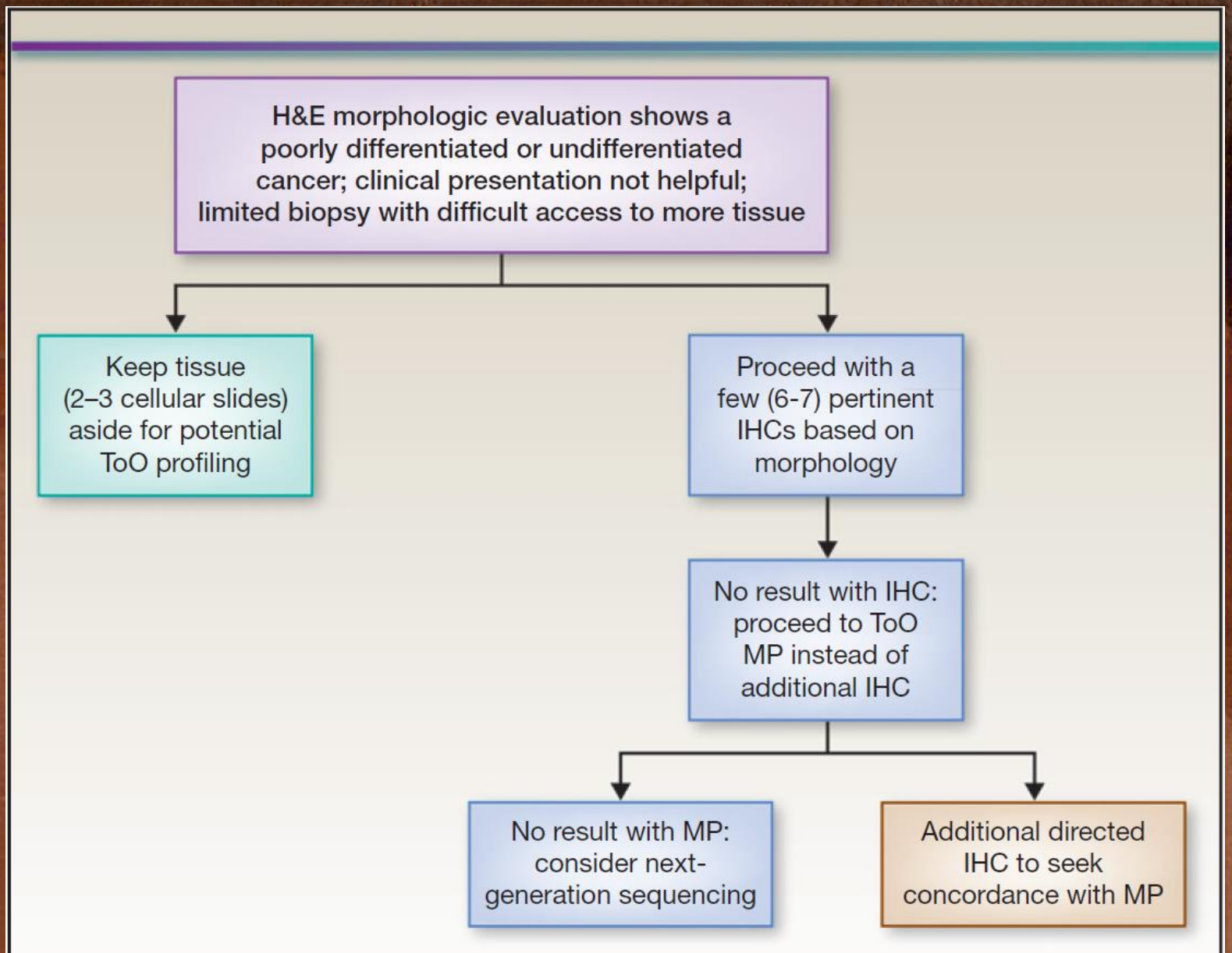


Fig. 2 – Relative proportion of molecularly-assigned primaries in published series.

Eur J Cancer 2026-36, 2007

Suggested use of Molecular Assays

Clin Cancer Res 2013;19:4027-4033



CLINICAL AND THERAPEUTIC UTILITY OF GENE AND PROTEIN MICROARRAY TECHNOLOGIES

QUESTION 1

DOES MOLECULAR ASSAYS, INCREASE THE ACCURACY OF IDENTIFYING THE PRIMARY SITE?

ANSWER 1

YES : UP TO 90% ACCURACY

QUESTION 2

DOES THIS DIAGNOSTIC AID RESULTS IN IMPROVEMENT OF PATIENT OUTCOME ?

ANSWER 2 **?**

CUP Staging

Assessment suggested	Target patient population
Thorough medical history and physical examination	All patients
Basic blood and biochemistry survey	All patients
CT scans of thorax, abdomen and pelvis	All patients
Mammography	Female patients
Work-up for CUP subsets	
Breast MRI	Female with axillary adenocarcinoma
Serum α-fetoprotein and human chorionic gonadotropin	Patients with midline metastastatic disease
Serum prostate-specific antigen	Male with adenocarcinomatous bony metastases
Head and neck CT/PET scan (optional)	Cervical squamous carcinoma
Endoscopies	Sign/symptom/lab-oriented
Octreoscan and plasma chromogranin A	Patients with neuroendocrine tumor CUP

SERUM TUMOR MARKERS

- Routine evaluation of current commonly used markers have not been proven of any prognostic or diagnostic assistance

- A non – specific multiple overexpression of the adenocarcinoma markers (CEA, CA 125, CA 15-3, CA 19-9) has been observed in the majority of CUP patients.

- Worthwhile to request :

PSA	in men with bone metastatic adenocarcinoma
B-HCG & AFP	in men with an undifferentiated tumor
AFP	in patients with hepatic tumors
CA 125	women with papillary adenocarcinoma of peritoneal cavity.
CA 15-3	women with adenocarcinoma involving only axillary lymph nodes.

CUP

FAVOURABLE *OR*
GOOD PROGNOSIS SUBSETS

20%

UNFAVOURABLE *OR*
POOR PROGNOSIS SUBSETS

80%

Pavlidis N & Pentheroudakis G.
The Lancet 379 : 1428-35, 2012

Favourable Subsets

1. Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome).
2. Women with papillary adenocarcinoma of peritoneal cavity.
3. Women with adenocarcinoma involving only axillary lymph nodes.
4. Squamous cell carcinoma involving cervical lymph nodes
5. Poorly differentiated neuroendocrine carcinomas.
6. Men with blastic bone metastases PSA+ (adenocarcinoma).
7. Adenocarcinoma with a colon-profile (CK 20^{+}, CK 7^{-}, CDX 2^{+})
8. Isolated inguinal adenopathy (squamous carcinoma).
9. Patients with a single, small, potentially resectable tumor.

CHARACTERISTICS OF PATIENTS WITH POORLY DIFFERENTIATED CUP

GENDER / AGE : Men / < 50 yrs

TUMOR INVOLVEMENT : Mediastinum
Retroperitoneum
Lungs
Lymph nodes

TUMOR MARKERS : Elevated serum levels of β-HGC or AFP

CLINICAL EVOLUTION : Rapid tumor growth

RESPONSE TO Rx : Favourable response to Cisplatin - based chemotherapy. RR 50% (CRs: 15-25%)

SURVIVAL : Median : 13 months
15% long – term survivors

PERITONEAL CARCINOMATOSIS IN FEMALES

THE NATURAL HISTORY

Incidence	10% of CUP patients
Mean Age (yrs)	60 (25 – 80)
Clinical Picture	Abdominal distension, pelvic masses, ascites
Surgical Picture	Abdominal masses, peritoneal disease, ascites, with normal ovaries
Histology	Papillary serous carcinoma (± psammoma bodies)
Serum CA-125	Often abnormal or markedly elevated.

WOMEN WITH PAPILLARY ADENOCARCINOMA OF PERITONEAL CAVILY

(Peritoneal Adenocarcinomatosis)

Treatment :

- **As FIGO III ovarian cancer.**
- **Surgical cytoreduction.**
- **Platinum – based chemotherapy.**

Response Rate : **40 – 60 % (CR : 30 %)**

Survival : **Median : 16 months**

Long – term survival : **5-yr: 10 %**

Breast Cancer Res Treat (2010) 119:1–11
DOI 10.1007/s10549-009-0554-3

REVIEW

Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence

George Pentheroudakis · George Lazaridis · Nicholas Pavlidis

Years : 1975 – 2006 (24 studies)

N : 689 patients

Mean Age : 52 yr

Menopause status : Postmenopausal 66%

Premenopausal 34%

Histology : Ductal adenocarcinoma 83%,

ER/PR 40 - 50/%, HER2 31%

Nodal status : N1 : 48% > N1 : 52

Treatment and Outcome

- ✓ **Mastectomy / axillary dissection : 59 %**
- ✓ **Primary breast irradiation : 26 %**
- ✓ **Observation : 15 %**

- ✓ **Logoregional recurrence rate : 25 % (mostly in observation cases)**
- ✓ **5-yr Survival : 72 % (similar to stage II-III breast cancer)**
- ✓ **No survival difference between conservative management (breast preservation + RT) and mastectomy**

SQUAMOUS CELL CANCER INVOLVING CERVICAL LYMPH NODES

Treatment :

- As locally advanced head-neck cancer.
- Surgery alone is inferior except pN1 neck disease with no extracapsular extension.
- Radiation : both sides of neck and mucosa (entire pharyngeal axis and larynx).
- Chemotherapy remains undefined (despite encouraging results with Platinum-based).

Survival :

- 5-year survival 35–50%.
- Documented long term disease – free survivors.

POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMAS

Treatment: **Platinum – based or paclitaxel / carboplatin – based chemotherapy**

Response : **50 – 70% (CR : 25%)**

Survival: **Median : 14.5 months**
3-yr : 24%

Pavlidis N & Pentheroudakis G.
The Lancet 379 : 1428-35, 2012

UNFAVOURABLE SUBSETS

1. Adenocarcinoma metastatic to the liver or other organs
2. Non-papillary malignant ascites (adenocarcinoma)
3. Multiple cerebral metastases (adeno or squamous Ca)
4. Multiple lung/pleural metastases (adenocarcinoma)
5. Multiple metastatic bone disease (adenocarcinoma)
6. Squamous – cell carcinoma of the abdominal cavity

Greco F, Pavlidis N. Semin Oncol, 2009

Table 4. Long-Term Survival in Patients With Unknown Primary Carcinoma and Unfavorable Prognostic Factors

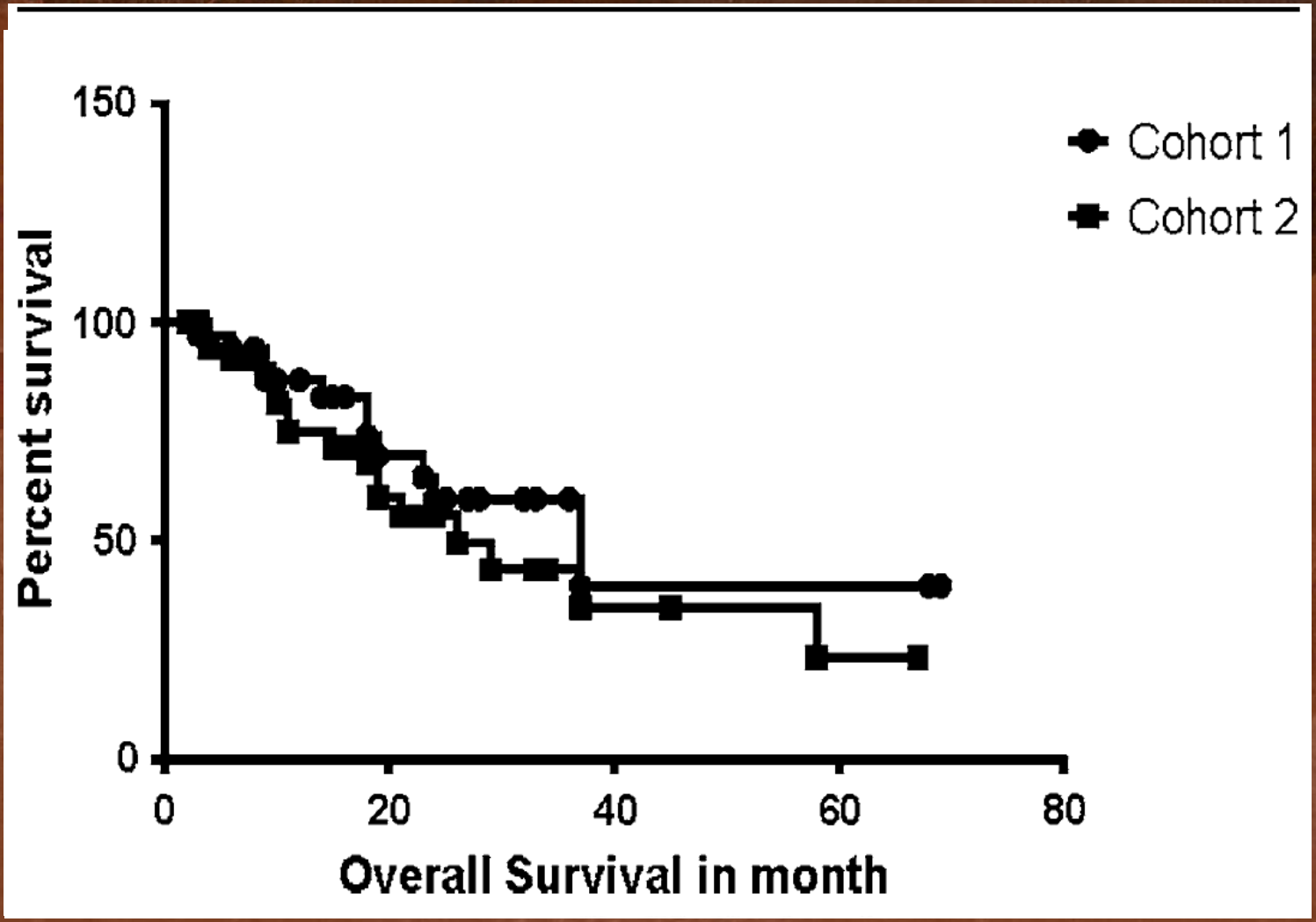
Author and Year of Publication	No. of Patients	Regimen	Median Survival (mo)	1-Year Survival (%)	2-Year Survival (%)	3-Year Survival (%)
Briasoulis et al, 2000[34]	33	PCb	10	25	5	NR
Dowell et al, 2001[35]	34	P5FUL (17)	8.3	26	NR	NR
		CbE (17)	6.4			
Balaña et al, 2003[38]	30	GCE	7.2	36	14	NR
Park et al, 2004[40]	37	PC	11	38	11	NR
Piga et al, 2004[39]	102	CbDoxE	9	35.3	18	11
Pouessel et al, 2004[41]	35	GD	10	43	7	NR
El-Rayes et al, 2005[43]	22	PCb	6.5	27	NR	NR
Pittman et al, 2006[36]	51	GCb	7.8	26	12	NR
Palmeri et al, 2006[44]	66	GPC (33)	9.6	30	NR	NR
		GVC (33)	13.6	52	NR	NR
Berry et al, 2007[46]	42	PCb	8.5	33	17	NR
Briasoulis et al, 2007[42]	47	OxIr	9.5	40	NR	NR
Schneider et al, 2007[45]	33	GCaCb	7.6	35.6	14.2	NR
MPCRN (5 trials) 1997-2008[1,21-24]	396	Multiple regimens (see text)	9.1	38	19	12
Total	928		8.9*	34.6*	13*	12*

OVERALL RESULTS OF CHEMOTHERAPY IN CUP PATIENTS WITH LIVER METASTASES

Nº of trials	:	5 (1991, 1998, 2002, 2005, 2008)
Nº of patients	:	711
Response rate	:	< 20%
Median survival	:	5.5 months

Bull Cancer 1991, J Clin Oncol 1998, Clin Radiol 2002, Gastroent Clin Biol 2005, Cancer Treat Rev 2008

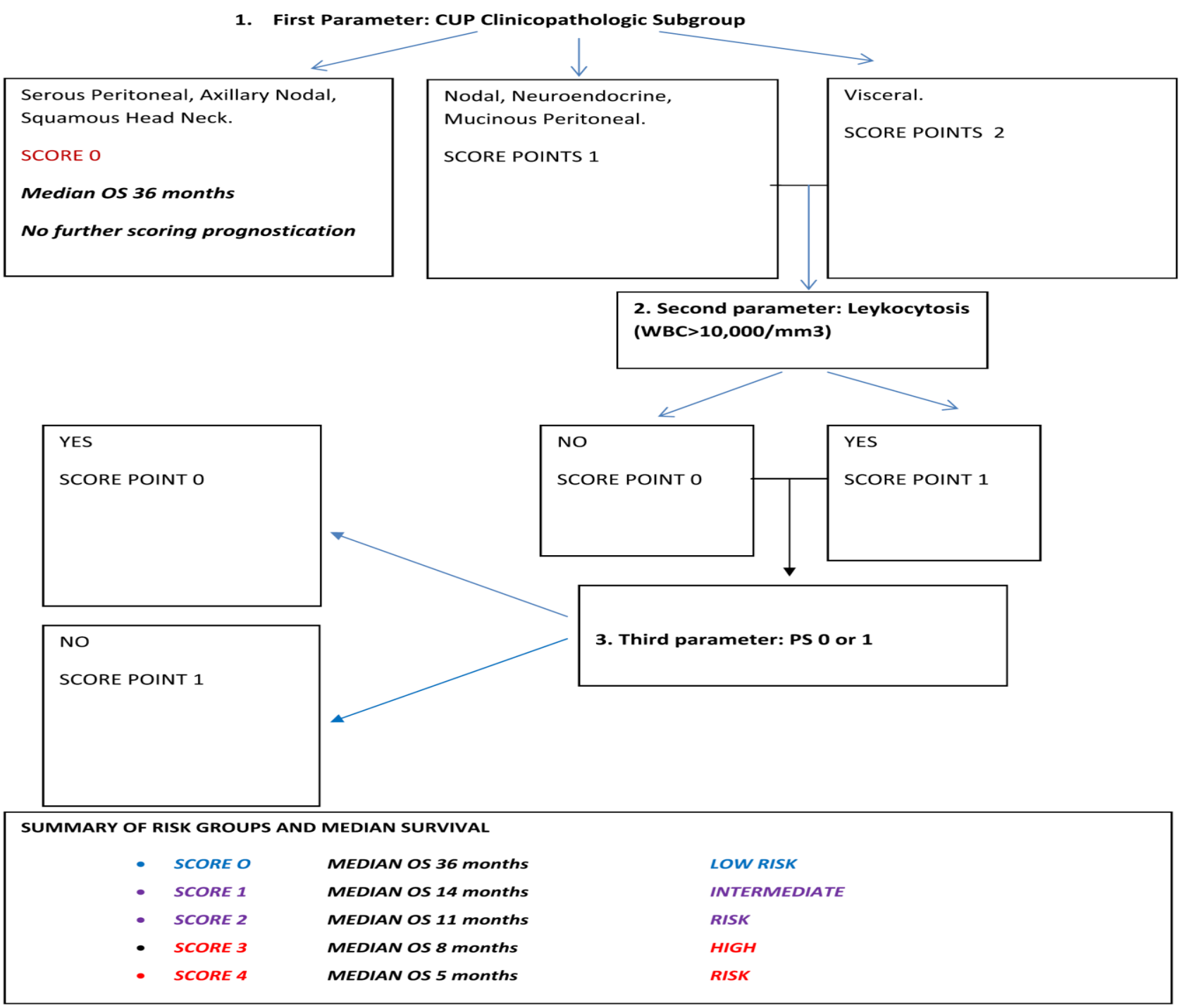
A poor-risk CUP subgroup that may not be so



MedOS
37 m
21 m

Varadhachary et al, Int J Clin Oncol 2013

PROGNOSTICATION AND TREATMENT


1. First Parameter: CUP Clinicopathologic Subgroup
Serous Peritoneal, Axillary Nodal, Squamous Head Neck.
SCORE 0
Median OS 36 months
No further scoring prognostication
Nodal, Neuroendocrine, Mucinous Peritoneal.
SCORE POINTS 1
Visceral.
SCORE POINTS 2
2. Second parameter: Leykocytosis (WBC>10,000/mm3)
YES
SCORE POINT 0
NO
SCORE POINT 0
YES
SCORE POINT 1
3. Third parameter: PS 0 or 1
NO
SCORE POINT 1
SUMMARY OF RISK GROUPS AND MEDIAN SURVIVAL
SCORE O MEDIAN OS 36 months LOW RISK
SCORE 1 MEDIAN OS 14 months INTERMEDIATE
SCORE 2 MEDIAN OS 11 months RISK
SCORE 3 MEDIAN OS 8 months HIGH
SCORE 4 MEDIAN OS 5 months RISK

Chemotherapy (mg/m^2)	Time	Interval	Comments
Cisplatin 60–75 Gemcitabine 1000	Day 1 Day 1 + 8	Q 3 weeks	Fit patients, adequate hydration
Cisplatin 75 Etoposide 100	Day 1 Days 1–3	Q 3 weeks	Fit patients with neuroendocrine feature-CUP, adequate hydration
Paclitaxel 175 Carboplatin AUC 5	Day 1	Q 3 weeks	Convenient outpatient regimen, monitor neurotoxicity
Docetaxel 75 Carboplatin AUC 5	Day 1	Q 3 weeks	Convenient outpatient regimen, monitor neurotoxicity
Irinotecan 160 Oxaliplatin 80	Day 1	Q 3 weeks	Outpatient regimen, monitor for neurotoxicity and diarrhoea
Oral Capecitabine 2000 ± Oxaliplatin 85–130	Days 1–14 Day 1	Q 3 weeks	Outpatient regimen, risk for diarrhea and neurotoxicity
Gemcitabine 1000/Irinotecan 100	Day 1+8	Q 3 weeks	Convenient outpatient regimen, monitor diarrhoea

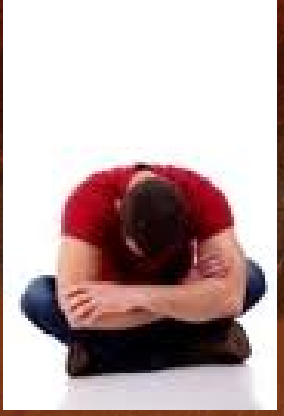
Meta-analysis

Golfinopoulos et al, Cancer Treat Rev 2009

Multiple-treatments meta-analysis results for death.

	HR[a]	95% CrI
nPnTc vs. nPnTm	1.01	0.59–1.72
Platinum vs. nPnTm	0.69	0.39–1.28
Taxane vs. nPnTm	0.66	0.22–2.08
Platinum plus taxane vs. nPnTm	0.81	0.34–1.89
Platinum vs. nPnTc	0.69	0.43–1.15
Taxane vs. nPnTc	0.66	0.23–2.00
Platinum plus taxane vs. nPnTc	0.80	0.39–1.67
Taxane vs. platinum	0.95	0.37–2.5
Platinum plus taxane vs. platinum	1.16	0.56–2.38
Platinum plus taxane vs. taxane	1.22	0.36–4.00

[a] A hazard ratio (HR) above one means that the risk of death is higher with the first rather than second listed regimen; nPnTm, non-platinum, non-taxane monotherapy; nPnTc, non-platinum, non-taxane combination.



- SHOULD WE TARGET CUP GENETIC ABERRATIONS?

  SHOULD WE ADMINISTER TARGETED THERAPY ACCORDING TO THE PRIMARY SITE?

Actionable genetic alterations in CUP-1

- **N=1350 patients with CUP**

- **Caris Life Sciences, Phoenix, USA**
- Mutational analyses, in-situ hybridisation, immunohistochemistry, (RT)-qPCR.

- Actionable biomarkers were identified in **77%:**

- **Steroid receptor IHC expression**
- **MET IHC expression**
- **PTEN loss of IHC expression,**
- **Activating mutations in EGFR, BRAF, PIK3CA**
- **Gene copy number variations in HER2, TOP2A and MET.**

Abstract E17-7084), ECCO/ESMO European Cancer Congress 2013

Targeted next-generation sequencing (NGS) of carcinoma of unknown primary site (CUP): Actionable genomic alterations (GA) and new routes to targeted therapies. Jeffrey S. Ross, Kai Wang, Geoff Otto, Gary A. Palmer, et al
J Clin Oncol 32:5s, 2014 (suppl; abstr 11048)

- Hybridization capture of exons/introns from 236 cancer-related genes was applied to DNA extracted from 200 CUP FFPE specimens.
- **169 (85%) CUP had at least 1 actionable GA (2.00 actionable GA/CUP).**

- The most common actionable GA were **KRAS (25%), CDKN2A (19%), MCL1 (8-10%), PTEN (8%), PIK3CA (8%), BRAF (6% in ACUP and 2% in non-ACUP) and NF1 (5%).**

- Mutations, amplifications and rearrangements of ERBB2 (10%), EGFR (8%) and BRAF (6%) were common in ACUP but not present in non-ACUP.

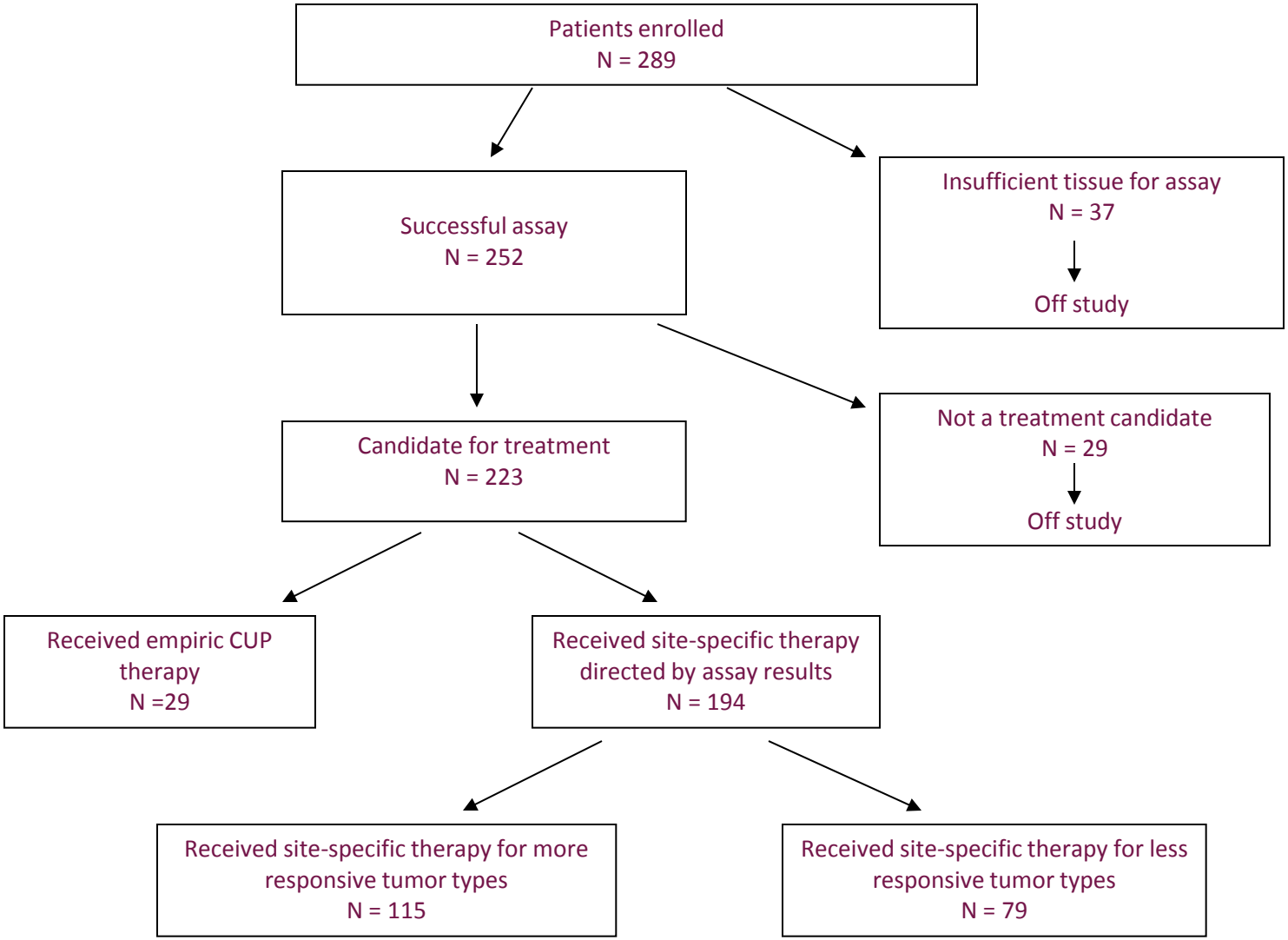
Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site (CUP): Results of a prospective Sarah Cannon Research Institute Trial

F. Anthony Greco, MD[1,2]; Mark S. Rubin, MD[1,3]; David R. Spigel, MD[1,2]; Samuel Raby[1]; Thabiso Chirwa[1]; Raven Quinn, MS[1]; Catherine A. Schnabel, Ph.D.[4]; Mark G. Erlander, Ph.D.[4]; John D. Hainsworth, MD[1,2]

[1]Sarah Cannon Research Institute (SCRI), Nashville, TN ; [2]Tennessee Oncology, PLLC, Nashville, TN; [3]Florida Cancer Specialists/SCRI, Ft Myers, FL; [4]bioTheranostics, Inc., San Diego, CA

bioTheranostics CancerTypeID 92-gene test

Patient Flow Diagram



Survival in 223 Treated Patients and in Subsets

Patient Group	Number	Median survival (mo.)
All treated	223	10.8
Assay-directed treatment	194	12.5, p=0.02
Empiric treatment	29	4.7
Tumor type*		
Treatment responsive	115	13.4, p=0.04
Less treatment responsive	79	7.6
Individual tumor types		
Biliary tract	45	6.8
Pancreas	12	8.2
Colorectal	26	12.5
NSCLC	23	15.9
Ovary	10	29.6
Breast	10	NYR (>24)

NYR = not yet reached; *Includes 194 patients who received assay-directed treatment

Real life questions

- Will Molecular Profling Assays improve patient outcome by administration of Primary Tissue-specific therapy?
- Does a CUP biologically assigned as X Cancer behave similarly to Typical Metastatic X cancer?
- What about comparing CUP metastases to matched Known Primary Metastases (KPM)?

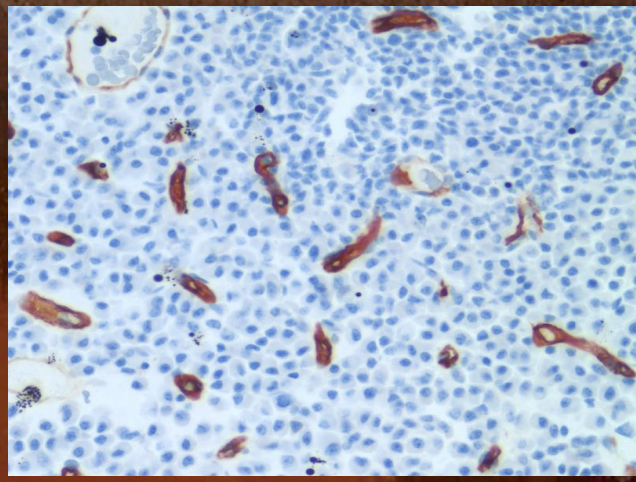
More

- Should we screen for actionable Genetic Aberrations in CUP?
- If we find such, how do we gain access to the targeted agents?
- Even if we have access to the targeted agents, how do we know they will work?
- How can we ignore the microenvironment and systems biology?

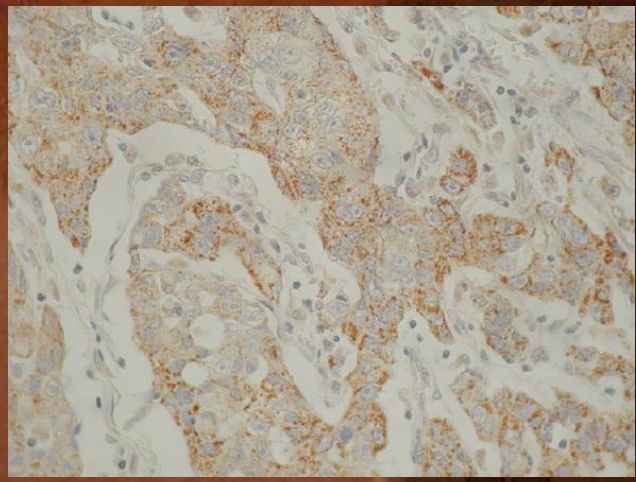
- Example: Targeting mutant BRAF in melanoma vs Colorectal Cancer

Angiogenesis in CUP

- Rashid et al, ASCO 2005:
  IHC VEGF expression in 49% of 76 CUP.



- Karavasilis et al, BMC Cancer 2005:
  N=81.
  IHC VEGF expression in 100%.



- **Angiogenesis is active in CUP, though this is a feature common for metastatic solid tumours in general.**

Mutational profiling in CUP

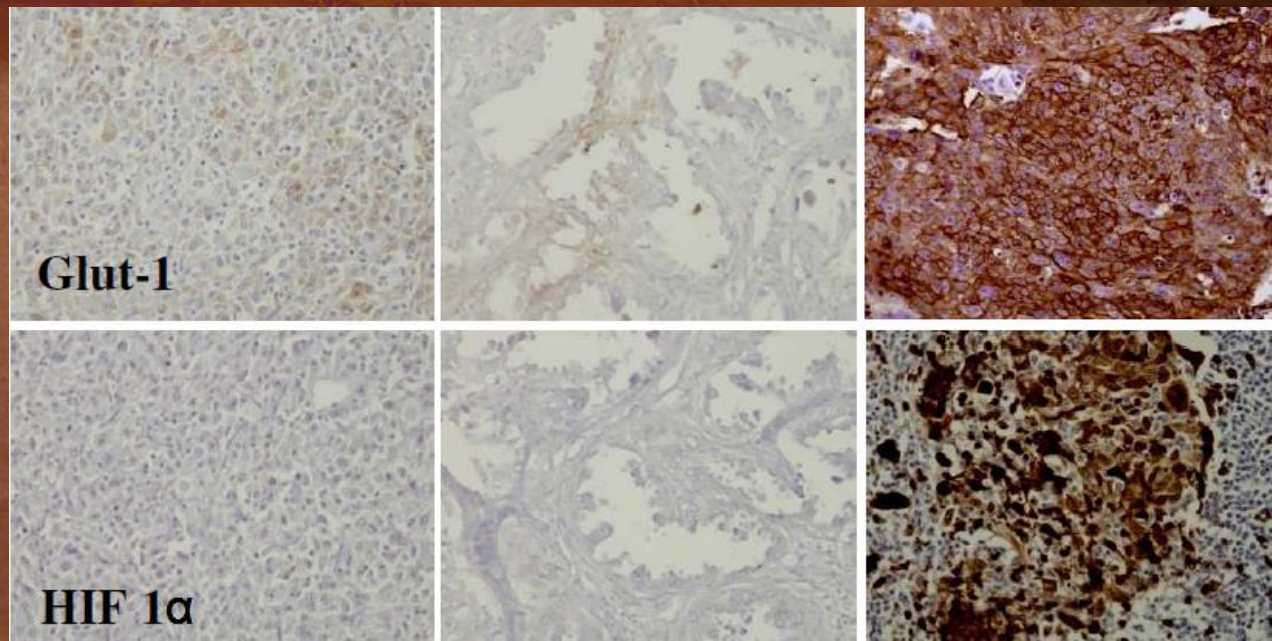
N=87	N (%
KRAS exon 2	Acti Inac
BRAF exon 15	Acti Inac
PIK3CA exons 9, 20	Acti Inac
CTNNB1 exons 1,3,5	Acti Inac
MET exon 18	Acti Inac

Parameter	Category (Reference: Activating mutation)	HR	p
MET_exon_18	inactivating mutation	0.43	0.34
	Wild type	0.20	**0.001**
CTNNB1_exons_1_3_5	inactivating mutation	0.46	0.46
	Wild type	0.70	0.27
Activating MET or CTNNB1 mutation	no activating mutation	0.47	**0.02**

Kotteas et al, Clin Exp Metas 2014, submitted

Hypoxia

- Koo J et al, Cancer Cell Biol 2010
- TMA IHC study of hypoxia related proteins in 69 CUP
- Hypoxia phenotype (GLUT1, HIF1a, COX2) present in 25% of CUP, associated with poor prognosis



Metabolic phenotypes of CUP

- N=77 CUP
- TMA IHC expression of metabolic enzymes

  GLYCOLYSIS Glut-1, CA IX, MCT4;

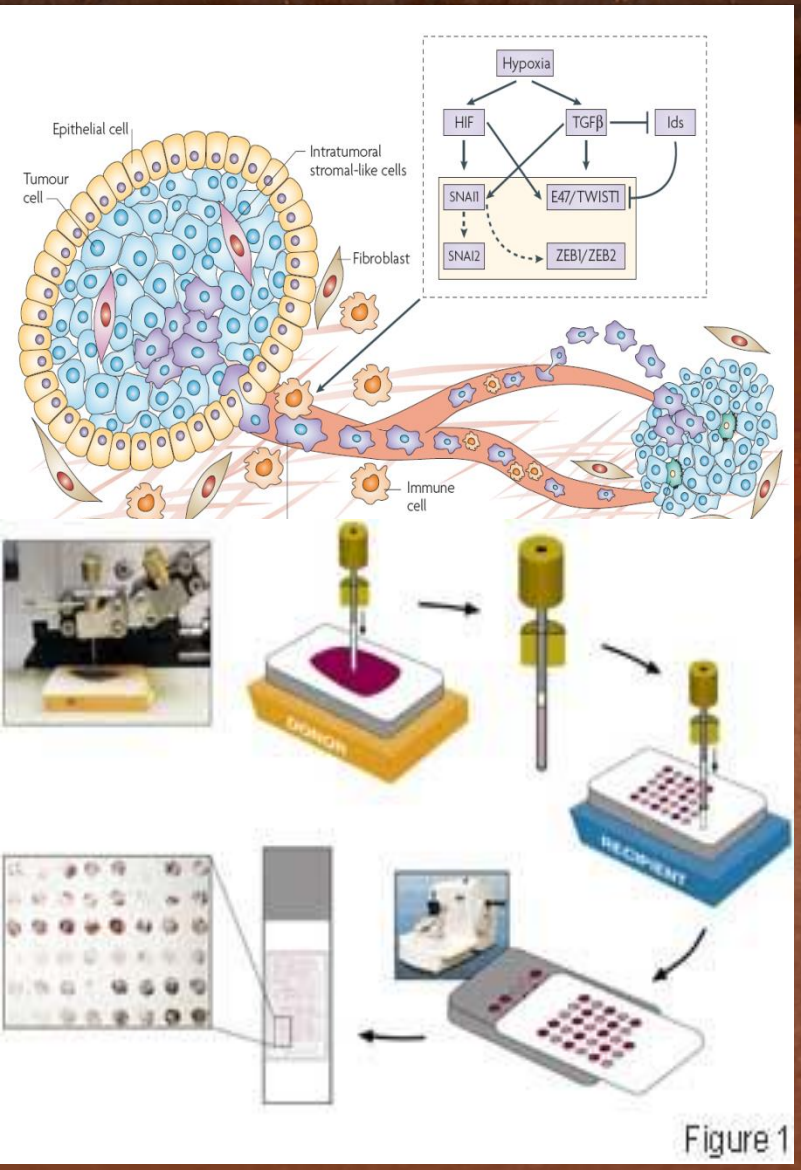
  GLUTAMINOLYSIS GLS1,GDH,ASCT2;

  MITOCHONDRIAL ATP synthase, SDHA,SDHB

- **More visceral metastases with glutaminolytic activity in tumour stroma (p=0.003)**

- **Kim HM,** *Journal of Translational Medicine* 2014, **12**:2

3. EPITHELIAL MESENCHYMAL TRANSITION AND STEMNESS in 100 CUP

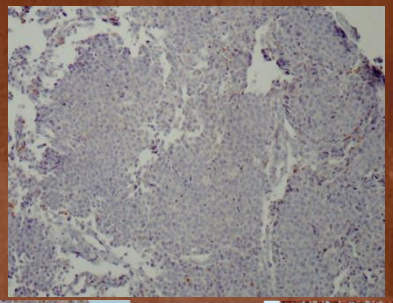


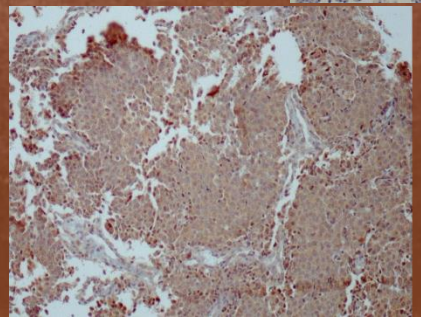
- IHC:

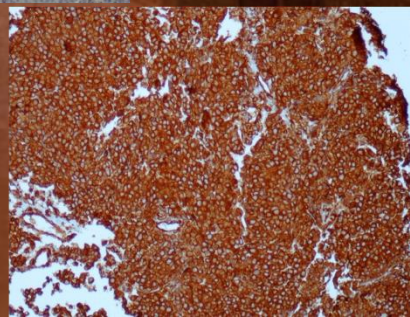
  EMT phenotype:

E-Cadherin,

Snail, N-Cadherin, Vimentin

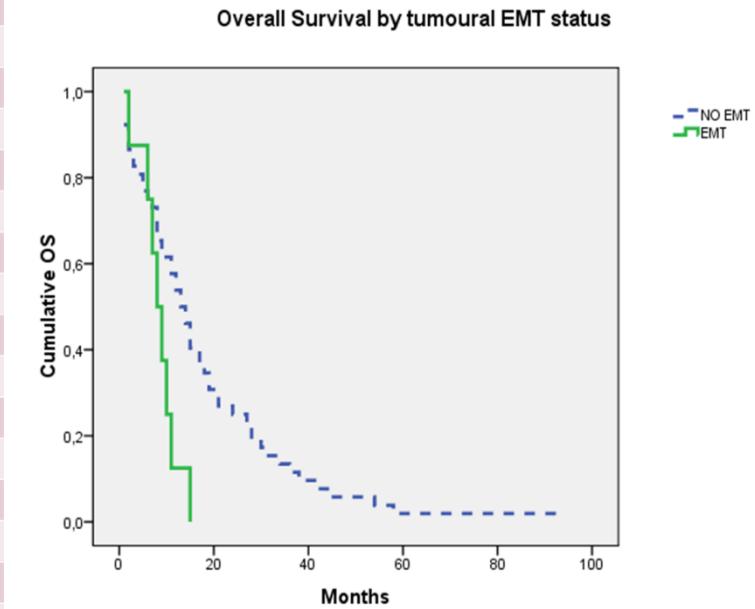






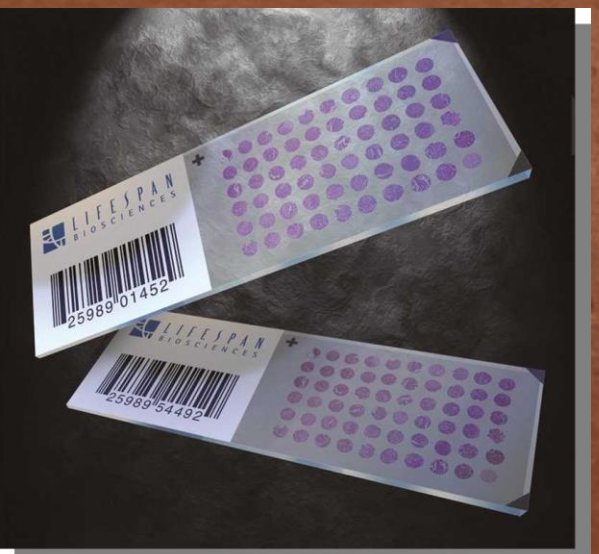
	EMT present	EMT absent	p
Characteristics			
Male gender	8(17.4)	38(82.6)	
Female gender	0 (0)	52 (100)	0.002
High grade	6(13.6)	38(86.4)	
Low grade	2 (4.5)	42 (95.5)	0.05
Visceral metastases	2(13.3)	13(86.7)	
Non-visceral mets	3 (5.1)	55 (94.9)	0.05
Response			
CR or PR	3(7.5)	37(92.5)	
NO CR or PR	3(8.3)	33(91.7)	0.893
PFS(months)			
Median	5	8	0.112
95% CI	3.0-7.0	5.3-10.7	
Survival(months)			
Median	8	13	0.023
95% CI	5.2-10.7	9.8-16.1	
1-year (%)	0	75	
EMT H-SCORE			
PFS			
Median (months)	5	8	0.541
95% CI	5.6-6.3	5.4-10.5	
Survival			
Median	9	14	0.074
95% CI	7.2-10.7	10.6-17.3	
1-year (%)	7.7	72.3	

Stoyianni A et al,
Anticancer Res.
2012;32(4):1273-81



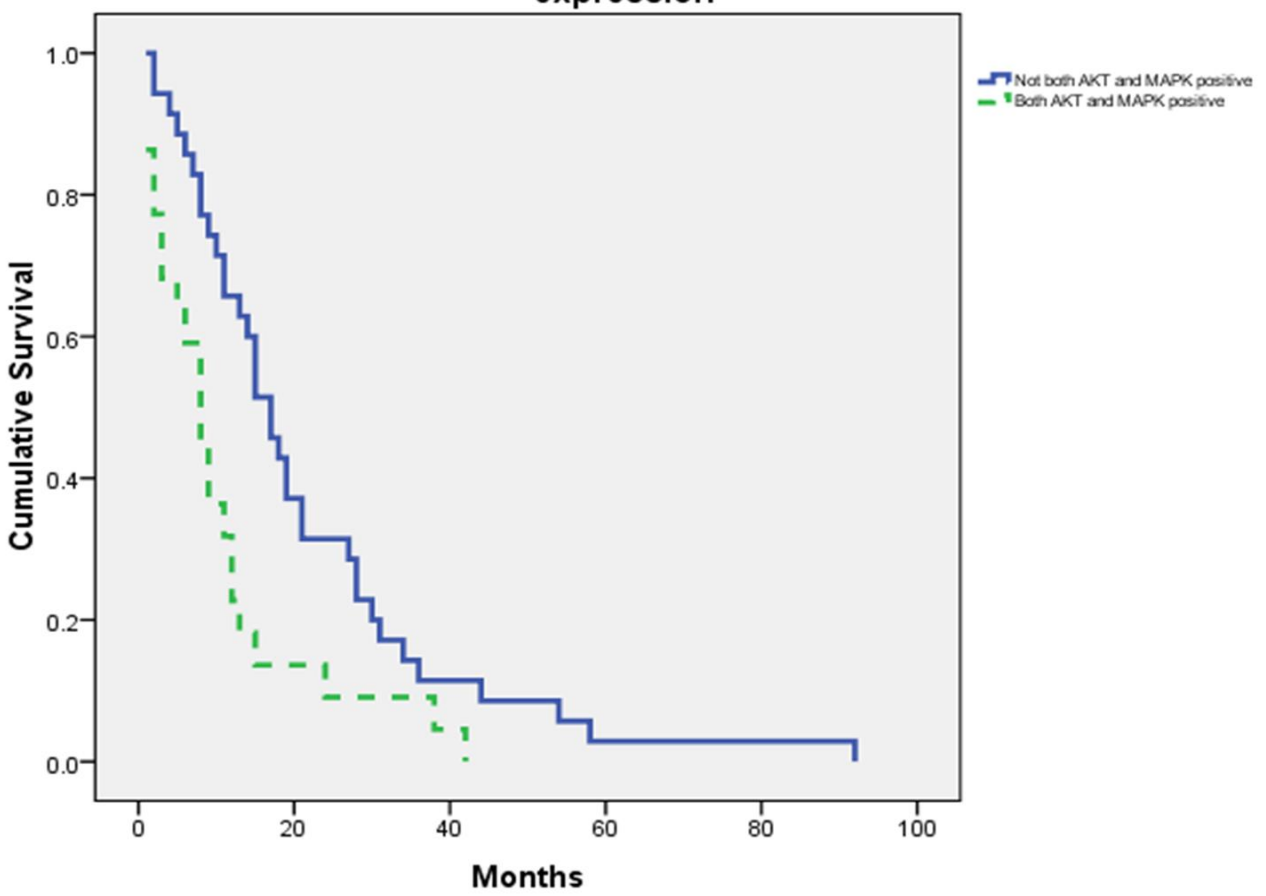
SHALL WE FIND ANYTHING WE DO NOT SEE IN METASTATIC TUMOURS?

TMA PROFILING

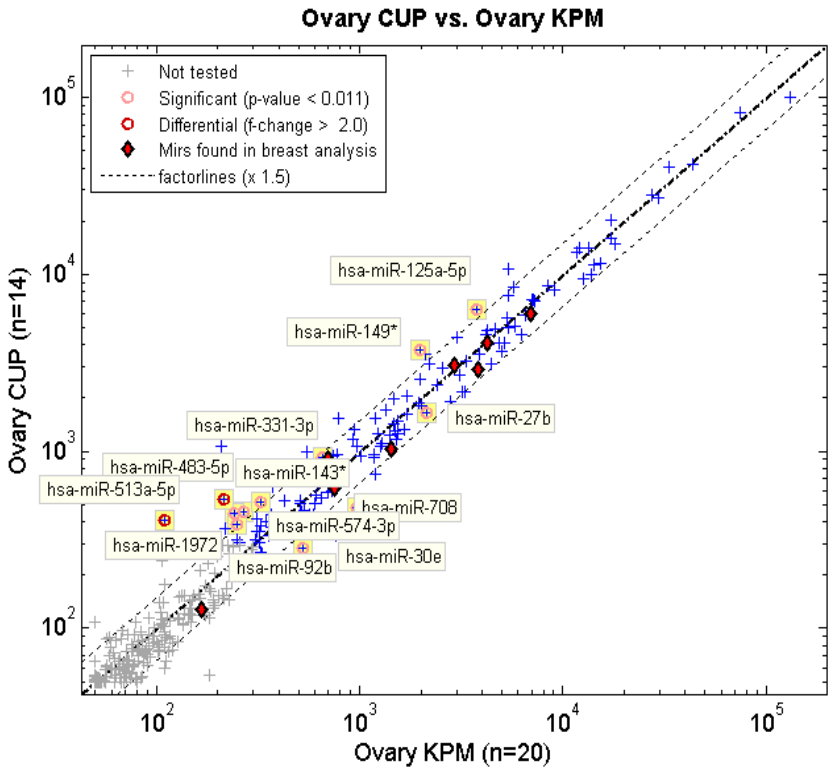


- Profiling 100 CUP cases for protein and phosphoprotein expression of **12 key membrane receptors, signal transducers, transcription factors hypoxia and cell cycle regulators**

Golfinopoulos et al, Ann Oncol. 2012;23(10):2725-30
Krikelis et al, Clin Exp Metastasis. 2012;29(6):603-14



Parameter	Hazard Ratio for risk of death	95% CI	2-sided p
P21	0.34	0.16 – 0.73	0.005
cMET	0.48	0.26-0.91	0.025
pAKT Thr308	2.39	1.23 – 4.66	0.01
pS6RP Ser235/236	2.76	1.31 – 5.84	0.008



GNATURE

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- Metastases from e
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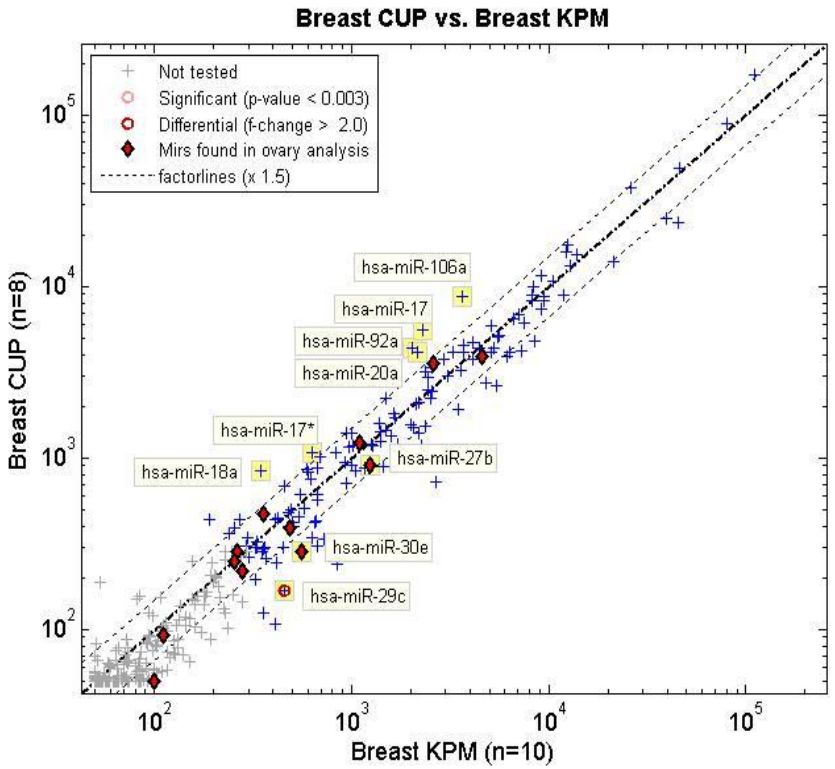
- IS THERE A miRNA C

Pentheroudakis et al, Clin Exp Metastasis 2013;30(4):431-9



Conclusions

- **No trace of a «CUP biologic signature», distinct from KPM**

- **Activated pathways in CUP:**
- Angiogenesis with concurrent hypoxia
- Stromal glutaminolytic activity
- AKT/S6RP axis with deficient apoptosis
- b-Catenin/Wnt axis
- MET axis
- EMT activity

Target them!

- ***Is it simply metastases from a missed primary?*** Find the primary, administer primary tumour-specific therapy.

- ***Or is it truly a disease with a unique molecular signature that defines its metastatic propensity?***
- Target the genetic aberrations.

Current Clinical Research: CUP Trials

Trial	Sponsor	Design	Arms
CUP ONE	*NCRI/CRUK*	*RCT Phase II*	**ECX vs ECX+Vandetanib**
MIRVIEW	*TEVA/ROSETTA*	*Parallel Cohort*	**ClinPath work up vs ClinPath work up+MirView**
UNKPRI20	*Sarah Cannon RC, USA*	*Single arm Phase II*	**Therapy based on molecular profiling**
UNKPRI21	*Sarah Cannon RC, USA*	*RCT Phase II*	**Carboplatin Paclitaxel vs CP+Belinostat**
GEFCAPI04	*GEFCAPI, France*	*RCT Phase III*	**CDDP+Gemcitabine vs Pathwork test-based therapy**
PACET-CUP	*Ruprecht-Karls-University of Heidelberg*	*RCT Phase II*	**Carboplatin Paclitaxel vs CP+Cetuximab**
CUP02	*CRUK*	*RCT Phase III*	**ECX vs Molecularly Assigned Therapy**

Evaluation and Management of Possible CUP Patient