

CANCER OF UNKNOWN PRIMARY SITE

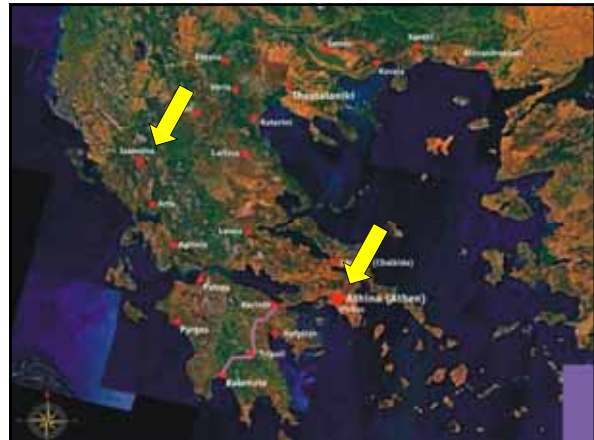
THE UNFAVOURABLE SUBSET WITH LIVER METASTASES

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Barcelona, June 2009



CANCER OF UNKNOWN PRIMARY (CUP)

- 1) DEFINITION
- 2) EPIDEMIOLOGY
- 3) BIOLOGY
- 4) PATHOLOGY
- 5) NATURAL HISTORY
- 6) DIAGNOSTIC APPROACH
- 7) TREATMENT

IS THERE A DEFINITION FOR
CANCER OF UNKNOWN
PRIMARY ORIGIN ?



THE DEFINITION

In 1970's

All patients presented with histologically confirmed metastatic carcinoma in whom a complete medical history, careful physical examination, chest x-ray, full blood count, stool occult blood testing and urinalysis did not identify the primary site.

WHAT IS THE INCIDENCE OF CANCER OF UNKNOWN PRIMARY SITE ?



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	-

DON'T FORGET THAT

- ✓ CUP represents the 7th – 8th most frequent type of cancer and the 4th commonest cause of cancer death.
- ✓ It is considered to be more common than non-Hodgkin's lymphoma

THE BIOLOGY OF CANCER OF UNKNOWN PRIMARY



TRANSLATION RESEARCH ON

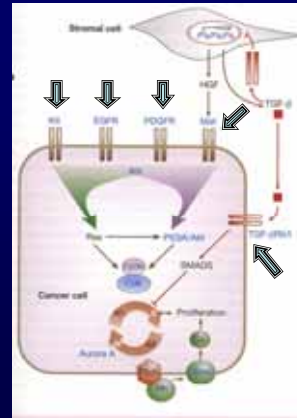
- Oncogenes
- Oncoproteins
- Tumor Suppressor Genes
- Angiogenesis
- Proteolysis

Oncogenes / Oncoproteins in CUP

Author	N	Method	Results	Correlations with clinicopathological parameters and outcome
Pavlidis et al <i>Anticancer Res</i> 1995	26	IHC	C-myc expression 96%, overexpression 23% Ras expression 92%, overexpression 23% HER2 expression 65%, overexpression 27%	None
Brisoult et al <i>Anticancer Res</i> 1998	40	IHC	BCL2 expression in 65%, overexpression in 40%	None

Tumour Suppressor Genes in CUP

Author	N	Method	Results	Correlations with clinicopathological parameters and outcome
Briassoulis et al <i>Antic. Res. 1998</i>	40	IHC	P53 expression 70%, overexpression 53%	Co-expression of BCL2 and p53 predictive for response to platinum
Dova et al <i>[in press, 2008]</i>	50	PCR - SSCP	Ki67-1: One case with exon 4a 242C>G mutation (P811R)	Not reported



Oncogenes / Oncoproteins in CUP

Author	N	Method	Results	Correlations with clinicopathological parameters and outcome
Dova et al <i>Clin Exp Metastasis [2007]</i>	50	IHC	EGFR expression 74%, overexpression 12%	None
		PCR - SSCP	Wild-type exon 18 19 21 EGFR gene in 96% 1 case with exon 21 SNP R836R 1 case with exon 19 intronic splicing variant: IVS19+24G>A.	
		qPCR	No exon 18, 19, 21 EGFR gene amplification.	
Dova et al <i>J Cancer Res Clin Oncol [2007]</i>	50	IHC	c-KIT expression 81%, overexpression 13% PDGFRa expression 50% overexpression 2%	None
		PCR - SSCP	No exon 11 c-KIT gene mutations No exon 12, 18 PDGFRa gene mutations	

Angiogenesis and Proteolysis in CUP

Author	N	Method	Results	Correlations with clinicopathological parameters and outcome
Karavasilis et al <i>BMC Cancer 2005</i>	80	IHC	CD34 microvessel density 59 microvessels/mm ² VEGF expression 100%, overexpression 83% Stromal TSPI expression 83%, overexpression 20%	Positive correlation of VEGF and inverse correlation of TSPI with microvessel density. Increased microvessel density in unfavourable group CUP.
Karavasilis et al <i>Cancer 2005</i>	75	IHC	MMP2 expression 69%, overexpression 49% MMP9 expression 49%, overexpression 36% TIMP1 expression 79%, overexpression 44%	Correlation of MMP2 and MMP9 expression. Adverse prognostic significance of TIMP1 expression.

THE NATURAL HISTORY OF CANCER OF UNKNOWN PRIMARY SITE



FUNDAMENTAL CHARACTERISTICS

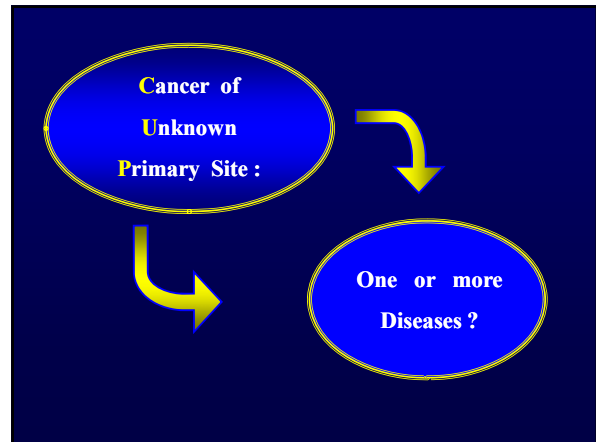
- ❖ Early dissemination
- ❖ Clinical absence of primary at presentation
- ❖ Aggressiveness
- ❖ Unpredictable metastatic pattern

UNPREDICTABLE METASTATIC PATTERN

❖ Refers to the differences in the incidence of metastatic sites at diagnosis between known and unknown primary carcinomas

Examples

- (1) Lung cancer presenting as CUP involves the bones in 4%, while presenting as a known primary the osseous involvement is 30-50%
- (2) Pancreatic cancer presenting as CUP has 4-fold higher incidence to affect bones, and 30% incidence to appear with lung metastases.
- (3) Prostate cancer presenting as CUP has a 3-fold less incidence to affect bones compared to the known primary prostate cancer.



HISTOLOGICAL CLASSIFICATION

HISTOLOGY

INCIDENCE

Adenocarcinoma

Well to moderately differentiated	50 %
Poorly or undifferentiated	35 %

Squamous cell carcinoma 10 %

Undifferentiated neoplasms 5 %

Not specified carcinoma
Neuroendocrine tumors
Lymphomas
Germ cell tumors
Melanomas
Sarcomas
Embryonal malignancies

CLINICOPATHOLOGICAL ENTITIES OF CUP

ORGAN

HISTOLOGY

Liver (mainly)
and/or other organs

AdenoCa M or P diff

Lymph nodes

Mediastinal – Retroperitoneal
(midline distribution)

U or P diff Ca

Axillary

AdenoCa W to P diff

Cervical

SCC Ca

Inguinal

U Ca, SCC, mixed SCC / adenoCa

W = well, M = moderately, P = poorly, U = undifferentiated

Peritoneal cavity

Peritoneal adenocarcinomatosis
in females

Papillary or serous adenoCa
(± psammoma bodies)

Malignant ascites of other
unknown origin

Mucin adenoCa M or P diff
(± signet ring cells)

Lungs

Pulmonary metastases

AdenoCa various diff

Pleural effusion

AdenoCa M or P diff

W = well, M = moderately, P = poorly, U = undifferentiated

Bones

(solitary or multiple)

AdenoCa of various diff

Brain

(solitary or multiple)

AdenoCa of various diff or
squamous cell Ca

Neuroendocrine tumors

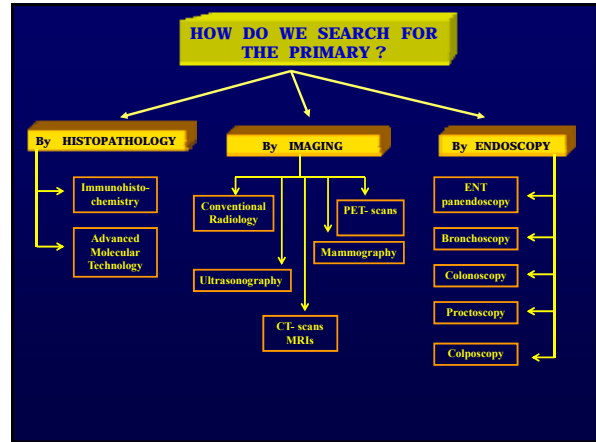
P diff Ca with neuroendocrine
features (mainly), low-grade
neuroendocrine Ca, small cell
anaplastic Ca

Melanoma

U neoplasm with melanoma features.

W = well, M = moderately, P = poorly, U = undifferentiated

WHAT IS THE OPTIMAL INVESTIGATIONAL DIAGNOSTIC APPROACH FOR THE IDENTIFICATION OF THE PRIMARY TUMOR ?



By HISTOPATHOLOGY

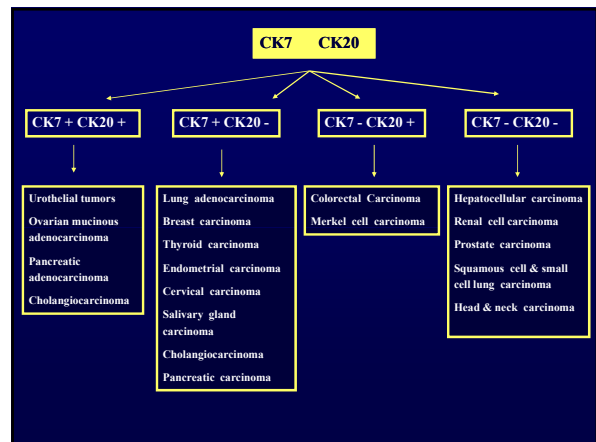


IMMUNOHISTOCHEMISTRY IN CUP DIAGNOSTIC ALGORITHM FOR ADENOCARCINOMA Clin Cancer Res 11:3766,2005

Marker	THE 10 MARKERS	Site of Origin
◊ PSA (Prostate - specific antigen)		Prostate
◊ TTF1 (Thyroid transcription factor 1)		Lung
◊ GcDFP-15 (gross cystic disease fluid protein 15)		Breast
◊ CDX2		Colon
◊ CK20		Ampullary, Colon, Esophageal, Ovarian
◊ CK7		Lung, Pancreas, Breast, Cholangio, Ovarian
◊ ER (Estrogen receptor)		Breast, Ovarian, Endometrial
◊ Mesothelin		Ovarian, Cholangio, Mesothelioma, Endometrial
◊ CA 125		Ovarian, Endometrial, Cholangio, Pancreas
◊ Lysozyme		Cholangio, Stomach, Colon, Pancreas, Lung

CYTOKERATINS (CKS)

Monoclonal antibodies against cytokeratin polypeptides **CK7** and **CK20**




PANELS OF IMMUNOHISTOCHEMICAL MARKERS HELP DETERMINE PRIMARY SITES OF METASTATIC ADENOCARCINOMA

Arch Pathol Lab Med 131: 1561-7, 2007

MARKERS


TTF-1	MUC 2
CDX 2	MUC 5AC
CK 7	SMAD 4
CK 20	ER
CEA	GCDFP - 15

COLON CA




CDX 2	+	OR	CDX 2	+	or MUC 2
CK 20	+		CEA	+	
CK 7	-		CK 7	-	
CK 20	-		CK 20	-	
TTF-1	-		TTF-1	-	

PANCREATOBILIARY



CK 7	+
CEA	+
MUC 5AC	+
CDX 2	-
TTF-1	-


STOMACH CA



CDX 2	+
CK 7	+
CK 20	-
TTF-1	-


TUMOUR TYPES

BREAST CA




GCDFP-15	+	OR	ER	+
CK 7	-		CDX 2	-
CDX 2	-		CK 20	-
CK 20	-		CEA	-
TTF-1	-		MUC 5AC	-

LUNG CA



TTF-1	+	OR	CK 7	+
CK 7	-		TTF-1	-
CDX 2	-		CDX 2	-
CK 20	-		CK 20	-
GCDFP-15	-		GCDFP-15	-
ER	-		ER	-
CEA	-		CEA	-

OVARIAN CA



CK 7	+
MUC 5AC	+
CDX 2	-
CEA	-
GCDFP-15	-
TTF-1	-

MOLECULAR ANALYSIS [Microarray Platforms]

around 80% accuracy

VALIDATION OF A MICROARRAY-BASED DIAGNOSTIC TEST FOR CUP (GENE EXPRESSION PROFILING)

Reference	Microarray platform (tissue)	Validation in metastases from CUP (N)	Primary Sites
AACR 2007	eDNA/ Frozen + FFPE	> 50 % (> 500)	B (16%), P (12%), C (11%), Lb (9%), G (8.5%), L (8%), S (4%), R (5%), O (20.5%)
Cancer Res 2005	eDNA/Frozen	84.5 % (11/3)	L (31%), B (23%), R (15%), C (7.5%), O (18%)
J Mol Diagn 2006	eDNA/FFPE	77 % (37/48)	L (19%), R (17%), B (10%), C (8%), P (4%), Ov (4%), Pr (4%), O (10%)
ASCO 2007	Veridex 10-gene qRT-PCR	61 % (42/69)	L (22%), P (16%), C (17%), O (6%)
ASCO 2007	eDNA/FFPE	87 % (34/39)	

B = breast, P = pancreas, C = colon, L = lung, Lb = liver/bile, G = genital, S = stomach, R = renal, O = others, Ov = ovary, Pr = prostate

MicroRNAs accurately identify cancer tissue origin

Nature Biotechnology 26, 462 - 469 (2008)

Abstract

"..... they may be used in identifying the tissue in which cancers of unknown primary origin arose, We measured miRNA expression levels in 400 paraffin-embedded and fresh-frozen samples Two-thirds of samples were classified with high confidence, with accuracy >90%. Our findings demonstrate the effectiveness of miRNAs as biomarkers for tracing the tissue of origin of cancers of unknown primary origin."

7

By IMAGING



IMAGING STUDIES

Chest X-ray

- ✓ A prerequisite test

Barium Studies

- ✓ Non contributory to the detection of 1st (very low sensitivity)
- ✓ Should only rarely if ever be used

CT - scans

- ✓ Offers an additional diagnostic accuracy of 40%
- ✓ Provides guidance to biopsy procedure

Mammography

- ✓ Basic test in women with metastatic adenoCa in axillary nodes
- ✓ However, sensitivity was found to be low

FREQUENCY OF MRI-DETECTED BREAST CA IN PATIENTS WITH CUP AXILLARY ADENOPATHY

Author, Year	N	N (%) with MRI –Detected Ca
Stomper, 1999	8	2 (25.0 %)
Henry-Tillman, 1999	8	8 (100 %)
Orel, 1999	22	19 (86.4%)
Obdeijn, 2000	20	8 (40.0%)
Olson, 2000	40	28 (70%)
Buchanan, 2005	64	31 (48.4%)
Total	162	96 (59.3%)

FDG - PET SCAN

(18 - F - FLUORODEOXYGLUCOSE)

- ✓ Diagnostic accuracy : 26% - 45%
- ✓ More sensitive for occult head - neck and lung tumors

J. Nucl. Med. 2003

- ✓ Meta-analysis (1994-2001) on 298 patients
- ✓ FDG PET showed detection of the primary in 43% of pts
- ✓ Occult : lung 42%, head-neck 36%, GI 6%, Others 17%

By ENDOSCOPY



ENDOSCOPY

✓ *Should always be symptoms - or signs oriented investigational procedures*

- ❖ **ENT panendoscopy** : in cervical node involvement
- ❖ **Bronchoscopy** : in radiographic indications or symptoms
- ❖ **Colonoscopy** : in relevant symptoms and signs
- ❖ **Proctoscopy** : in inguinal node involvement
- ❖ **Colposcopy** : in inguinal node involvement

SERUM TUMOR MARKERS

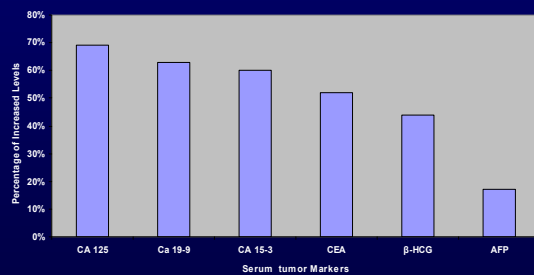
❖ Routine evaluation of current commonly used markers have not been proven of any prognostic or diagnostic assistance

❖ 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.

Fig 1. FREQUENCY OF TUMOR MARKER ELEVATIONS IN 85 CUP PATIENTS



Pavlidis et al, *Med. Ped. Oncology*, 22:162-167, 1994.

Published Clinical Experience on Serum Tumour Marker use in CUP

Author	Number of CUP patients N	Markers studied	Diagnostic utility	Predictive /prognostic utility	
Koch	1981	32	CEA	Yes	No
Varadhachary	2004	147	CEA	No	No
Fritsche	1993	41	CEA	No	No
Gupta	1985	15	CEA, CA 19-9	No	No
Pavlidis	1994	85	CEA, CA 19-9, CA 125, CA 15-3, β-HCG, AFP	No	No
Milovic	2002	46	CEA, CA 19-9, CA 15-3, CA 125	No	No
Yonemori	2006	93	CEA, CA 19-9, CA 15-3, CA 125, PSA, AFP, βHCG	No	No

HOW OFTEN CAN THE PRIMARY TUMOR BE IDENTIFIED ?

IDENTIFICATION OF PRIMARY SITE BY EXTENSIVE DIAGNOSTIC WORK - UP

The antemorten frequency of detection of primary site by imaging, endoscopy or immunohistochemistry studies **remains around 30%**.

Pavlidis et al, *Eur J Cancer* 39:1990-2005, 2003



EUROPEAN JOURNAL OF CANCER 43 (2007) 2026-2036

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com

ELSEVIER

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Review

Switching benchmarks in cancer of unknown primary: From autopsy to microarray

George Pentheroudakis, Vassilios Golfopoulos, Nicholas Pavlidis*

Department of Medical Oncology, Ioannina University Hospital, Niarxou Avenue, 45500 Ioannina, Greece

IDENTIFICATION OF PRIMARY SITE AT AUTOPSY FROM ALL PUBLISHED SERIES

Years of Publications : 1944 - 2000
 No of Autopsies : 884
 Primary Site Found : 73 % (644 / 884)

Primary Sites Identified :

Lung	27 %
Pancreas	24 %
Liver/bile duct	8 %
Kidney /adrenals	8 %
Bowel	7 %
Genital system	7 %
Stomach	6 %
Bladder / ureter	0.01 %
Breast	0.007 %
Other	10 %

Fig. 1 - Relative proportion of autopsy-found primaries to published series.

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 microarray-assignable primaries to published series.

WHAT IS THE OPTIMAL THERAPEUTIC APPROACH OF CANCER OF UNKNOWN PRIMARY ?

HISTORICAL OVERVIEW 1960 - 2008

DECADE	REGIMEN (based)	RESPONSES (%)	SURVIVAL (months)
1960 - 1970	5-Fluorouracil	8 (5-12)	6 (4-9)
1970 - 1980	Anthracyclines	16 (0-37)	7 (3-13)
1980 - 1990	Platinum	30 (17-79)*	8 (5-72)**
1990 - > 2000	Taxanes / Platinum	39 (7 - 50)*	8 (6-48)**

*CRs were seen ** Long survivors

HELLENIC COOPERATIVE ONCOLOGY GROUP EXPERIENCE WITH PHASE II TRIALS

References	N	Regimens	Favourable Subsets		Unfavourable Subsets	
			ORR /CR (%)	Survival (mos)	ORR/CR (%)	Survival (mos)
Ann Oncol 1992	48	Platinum-containing	32 (32)	15	14 (0)	4
Oncology 1998	62	Carbo/Epi/Eto	65 (18)	15.5	26 (2)	8
J Clin Oncol 2000	77	Carbo/Taxol	58 (36)	14	15 (0)	10
Cancer Chemo Pharmacol 2007	47	Oxal/CPT-II	---	---	13 (0)	9.5
Acta Oncologica 2008	47	Carbo/Docet	46 (21)	22.6	17 (0)	5.3

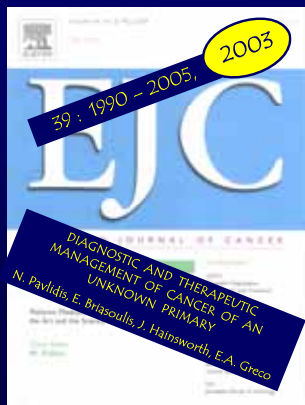
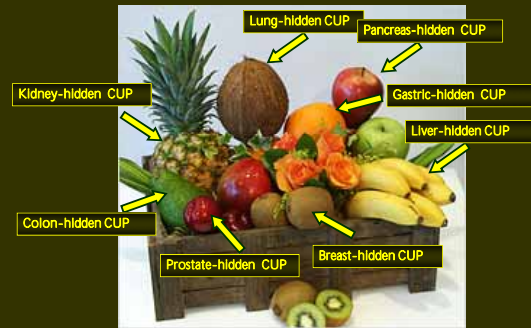
DO WE HAVE **EFFECTIVE DRUGS**
FOR CANCER OF UNKNOWN
PRIMARY

OR

WE JUST HAVE **RESPONSIVE**
SUBSETS OF PATIENTS ?



WHAT IS CANCER OF UNKNOWN PRIMARY ?



CUP

FAVOURABLE OR
GOOD PROGNOSIS SUBSETS

UNFAVOURABLE OR
POOR PROGNOSIS SUBSETS

THE FAVOURABLE SUBSETS
OR
GOOD PROGNOSIS SUBSETS

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 and elevated PSA (adenocarcinoma).
7. Isolated **inguinal** adenopathy (squamous carcinoma).
8. 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 -HCG 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 invasive serous ovarian Ca, 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 (\pm psammoma bodies)
Serum CA-125	Often abnormal or markedly elevated.

WOMEN WITH PAPILLARY ADENOCARCINOMA OF PERITONEAL CAVITY (Peritoneal Adenocarcinomatosis)

Treatment :	<ul style="list-style-type: none"> • 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 %

ISOLATED AXILLARY NODAL METASTASES FROM AN OCCULT PRIMARY BREAST CANCER

THE NATURAL HISTORY

Incidence	0.3 % of all breast cancer
Mean Age (yr)	52 (66% postmenopausal)
Imaging Accuracy	Mammography 20% U/S 20% MRI 70%
Nodal Status	60 % N1
Histology	83 % invasive ductal
Receptors	43% ER (+) 41% PR (+) HER-2 : ?
Simultaneous Distant Mets	2%



Excerpta Medica

The American Journal of Surgery 190 (2005) 609–613
Presentation

The American Journal of Surgery*

Therapeutic options for occult breast cancer: a survey of the American Society of Breast Surgeons and review of the literature

Anjay K. Khandelwal, M.D.^{a,*}, Gerard A. Garguilo, M.D., F.A.C.S.^{a,b}

✓ A survey was sent by mail to **1837** members of ASBS

✓ A total of **776 (42%)** responses were received

BREAKDOWN OF ALL RESPONSES [776 Surgeons]

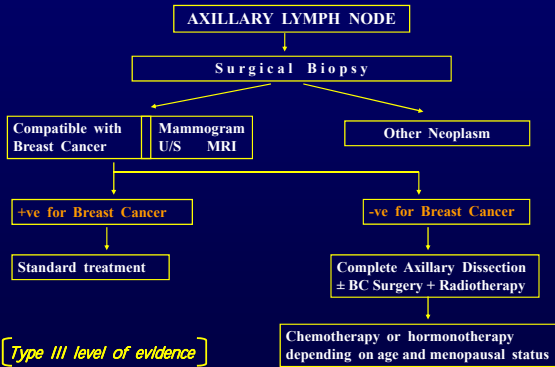
<u>Therapeutic Option</u>	<u>N</u>	<u>(%)</u>
Mastectomy	338	43%
Whole breast radiation	285	37%
Other*	153	20%

* Other

Observation	46
Mastectomy + radiation	36
PET only	23
Chemotherapy or ALND	22
Non-Contributable replies	26

Am J Surg 190:609-613, 2005

TREATMENT RECOMMENDATIONS



ISOLATED AXILLARY NODAL METASTASES FROM AN OCCULT PRIMARY BREAST CANCER

SURVIVAL RATES

- Similar to **stage II or III breast cancer**
- Locoregional recurrence rate : **25%**
- Overall survival : **75%** at 5yrs **68%** at 10yrs
- **No survival difference** between conservative management (breast preservation + RT) and mastectomy.
- **N₂ disease** has worse prognosis than N₁.

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%**

OTHER FAVOURABLE CUP SUBSETS

- ✓ Men with adenocarcinoma blastic bone metastases (and elevated PSA)
Rx = Treat as metastatic prostate cancer
- ✓ Isolated inguinal lymphadenopathy from squamous cell carcinoma
Rx = Dissection ± radiotherapy
- ✓ Single metastatic site
Rx = Dissection ± radiotherapy

THE UNFAVOURABLE SUBSETS OR POOR PROGNOSIS SUBSETS

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)

Results of Empiric Therapy with Cisplatin - containing Regimens for Adenocarcinoma of Unknown Primary Site

First Author	Regimen	No Pts	Response (%)	Survival (m)
Bedikian 1983	CAP	13	15	-
Jadeja 1983	FACP	23	17	6
Pastez 1986	CAFP	47	28	7
Eagan 1987	AMP	27	19	5
Milliken 1987	PVeB	50	39	5
Becouam 1989	FAPH	85	21	6
Raber 1991	PEF	36	22	11
Lenzi 1991	PFL	31	32	-
de Campos 1994	CAV/PE	16	19	5
Pouessel 2005	Pl-based	118	19	8
	Non-Pl-based		20	5

THE SUBSET OF ADENOCARCINOMA METASTATIC TO THE LIVER

HISTOLOGIC SPECTRUM OF LIVER METASTASES

Histology	Moussau et al [Bull Cancer 1991]	Ayoub et al [JCO 1998]	Hogan et al [Clin Radiol 2002]	Poussel et al [Gastro Clin Biol 2005]	Lazaridis et al [Cancer Treat Rev 2008]	Total
	(N=91)	(N=365)	(N=88)	(N=118)	(N=49)	(N=711)
Adenocarcinoma	78%	61%	79.5%	58%	69%	69%
Undifferentiated	12%	27%	3.5%	20%	24%	20%
Neuroendocrine	-	9%	9%	14%	6%	9%
Squamous	6%	2%	4.5%	4%	0%	4%
Others	4%	1%	3.5%	4%	-	3%

OVERALL RESULTS OF CHEMOTHERAPY IN CUP PATIENTS WITH LIVER METASTASES

N° of trials : 5 (1991, 1998, 2002, 2005, 2008)
 N° of patients : 711
 Response rate : < 20%
 Median survival : 5.5 months

HOW SHOULD WE TREAT PATIENTS WITH UNFAVOURABLE CUP?

- Patients with relatively young age and good P.S. could offer a chance of platinum - based chemotherapy
- Alternatively, best supportive care should be recommended.

IRINOTECAN-CONTAINING REGIMENS IN CUP

Reference	N	Regimen	ORR	Med. Survival
ASCO 2002	80	Cisplatin/Gemcitab	42 %	22%
		vs	vs	vs
		Cisplatin/IRINO	25 %	23%
} 1-yr				
JCO 2003	80	Cisplatin/Gemcitab	55 %	8 mos
		vs	vs	vs
		Cisplatin/IRINO	38 %	6 mos
Oncologist 2004	132	Taxol/Carbo/VP-16 → IRINO	30 %	9.1 mos
Cancer Chem Pharm 2007	47	Oxaliplatin/IRINO	13 %	9.5 mos

COMPARATIVE ACTIVITY OF CHEMOTHERAPY BETWEEN PTS WITH METASTATIC BREAST OR COLORECTAL CANCER & CUP PTS

Pentheroudakis et al, Cancer Treat Rev, 2008

	N Studies	N Pts	Rx	ORR	OS (median)
Metastatic Colorectal Cancer	7 (R)	2978	FU-based Oxal-based Irin-based	39%	19 months
CUP and Colorectal Type of CX	8 (II + R)	673	FU-based Oxal-based Irin-based	14%	5.5 months
Metastatic Breast Cancer	5 (R)	2802	A-based T-based	41%	22 months
CUP and A-based CX	10 (II+R)	679	A-based	29%	7 months

CX = Chemotherapy, A= Anthracycline, T= Taxane

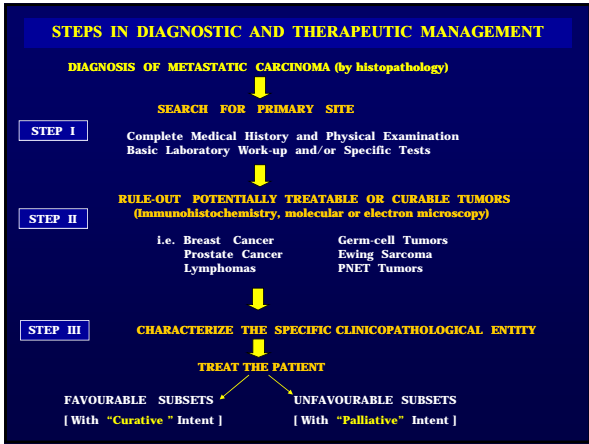
DOES THE IDENTIFICATION OF PRIMARY SITE BY MOLECULAR PROFILING IMPROVE PATIENTS' OUTCOME ?

?



- ### THE SUPPORTERS
- Gene profiling can detect the primary site in up to **85%** of the cases
 - The assigned tissue of origin is compatible with **response to relevant chemotherapy** regimens, i.e. hidden colorectal cancer
 - These patients merit a **survival benefit** after systemic chemotherapy

- ### THE NON-SUPPORTERS
- The distinction between **favourable** and **unfavourable** subsets can be adequately performed by **clinicopathological approach**
 - Favourable** subsets can be treated accordingly and **responses are almost similar** to the corresponding primary tumours
 - Although gene profiling can detect the primary site in up to **85%** of the cases, **responses and survival** to relevant cytotoxic combinations **are not similar** to those with known primary tumours.
 - CUP patients, especially those with unfavourable subsets, carry a **unique biological and clinical behaviour** (genetic signature ?)
 - High cost**



CARCINOMA OF UNKNOWN PRIMARY

A HUMAN MODEL FOR METASTATIC DISEASE

