Clinical Presentation and Treatment - an Overview

Prof. Nicholas Pavlidis, MD, PhD, FRCP (Edin)

London , September 2015

What is Cup ?

CUP represent a heterogenous group of metastatic tumours for which a standardized work-up fails to identify the site of origin at the time of diagnosis. It accounts for 3% - 5% of all malignancies.

The Natural History of Cancer of Unknown Primary Site

FUNDAMENTAL CHARACTERISTICS

- **Early dissemination**
- **Clinical absence of primary at presentation**
- **Aggressiveness**
- **Unpredictable metastatic pattern,** ***ie***

  Pancreatic cancer presenting as CUP has 4-fold higher incidence to affect bones, and 30% incidence to appear with lung metastases.

Cancer of Unknown Primary Site :

One or more Diseases ?

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

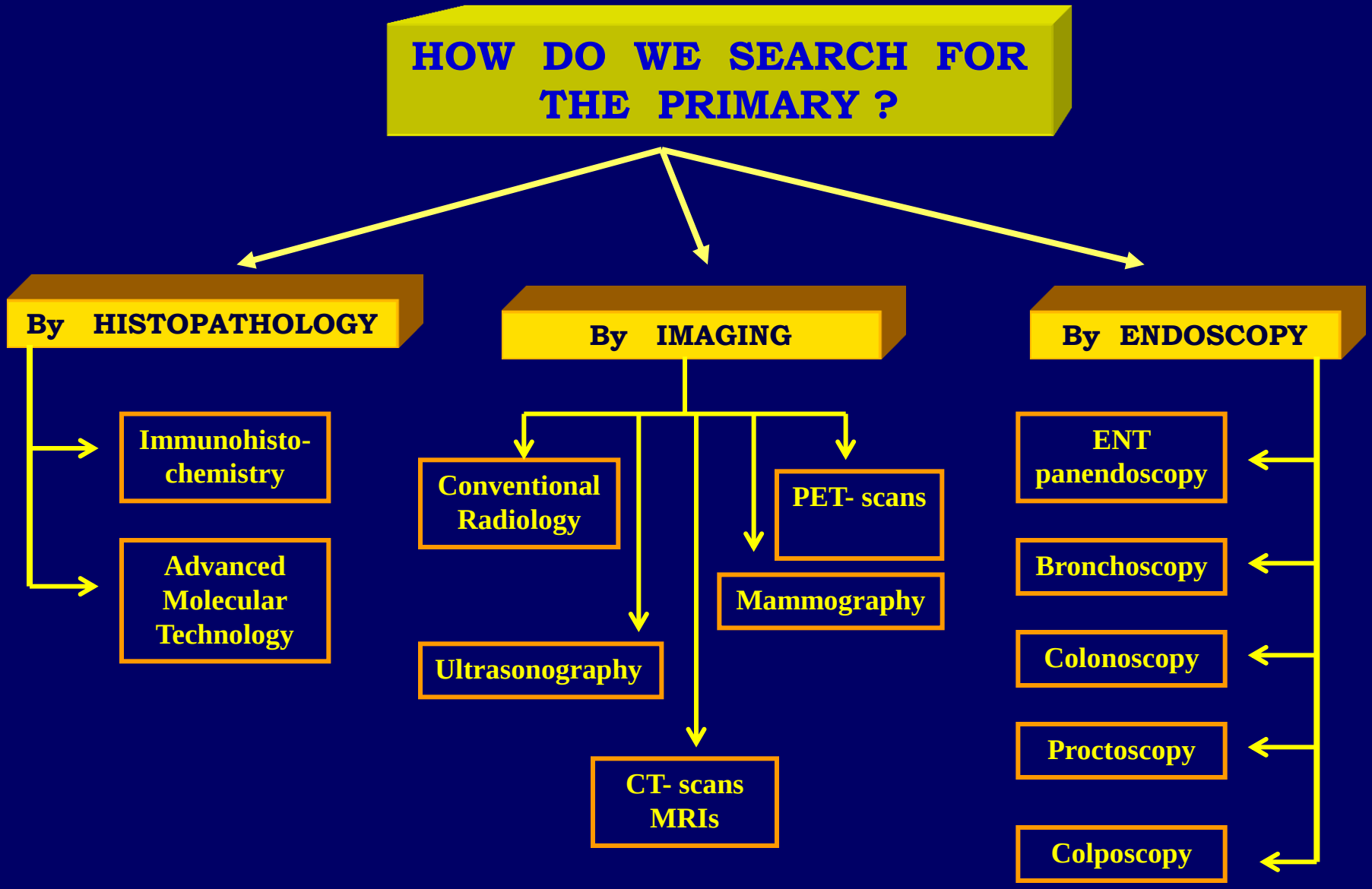
Pulmonary metastases	**AdenoCa various diff**
Pleural effusion	**AdenoCa M or P diff**

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

Bones	
(solitary or multiple)	**AdenoCa of various diff**
Brain	
(solitary of 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 ?

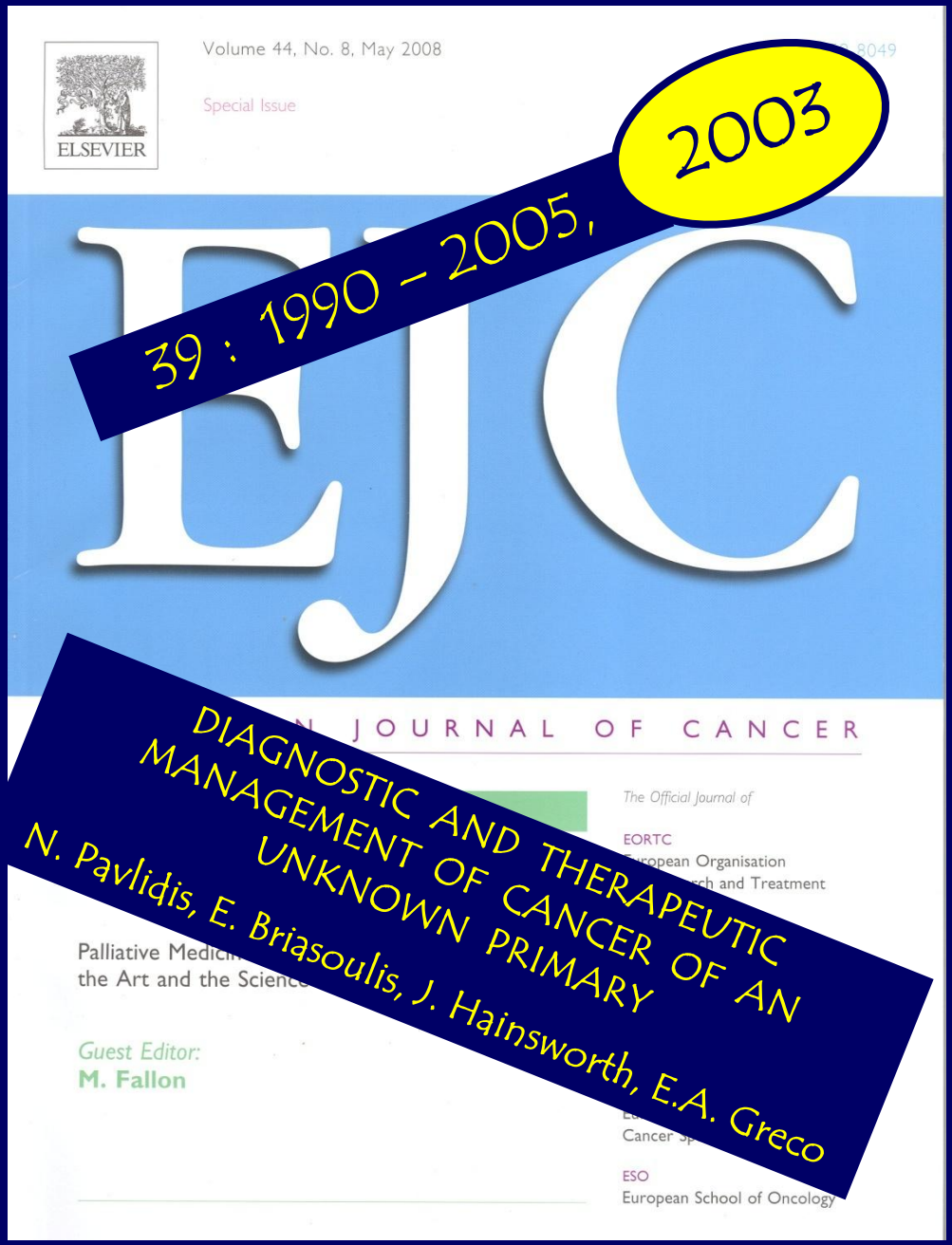

HOW DO WE SEARCH FOR THE PRIMARY ?
By HISTOPATHOLOGY
Immunohisto-chemistry
Advanced Molecular Technology
By IMAGING
Conventional Radiology
PET- scans
Mammography
Ultrasonography
CT- scans MRIs
By ENDOSCOPY
ENT panendoscopy
Bronchoscopy
Colonoscopy
Proctoscopy
Colposcopy

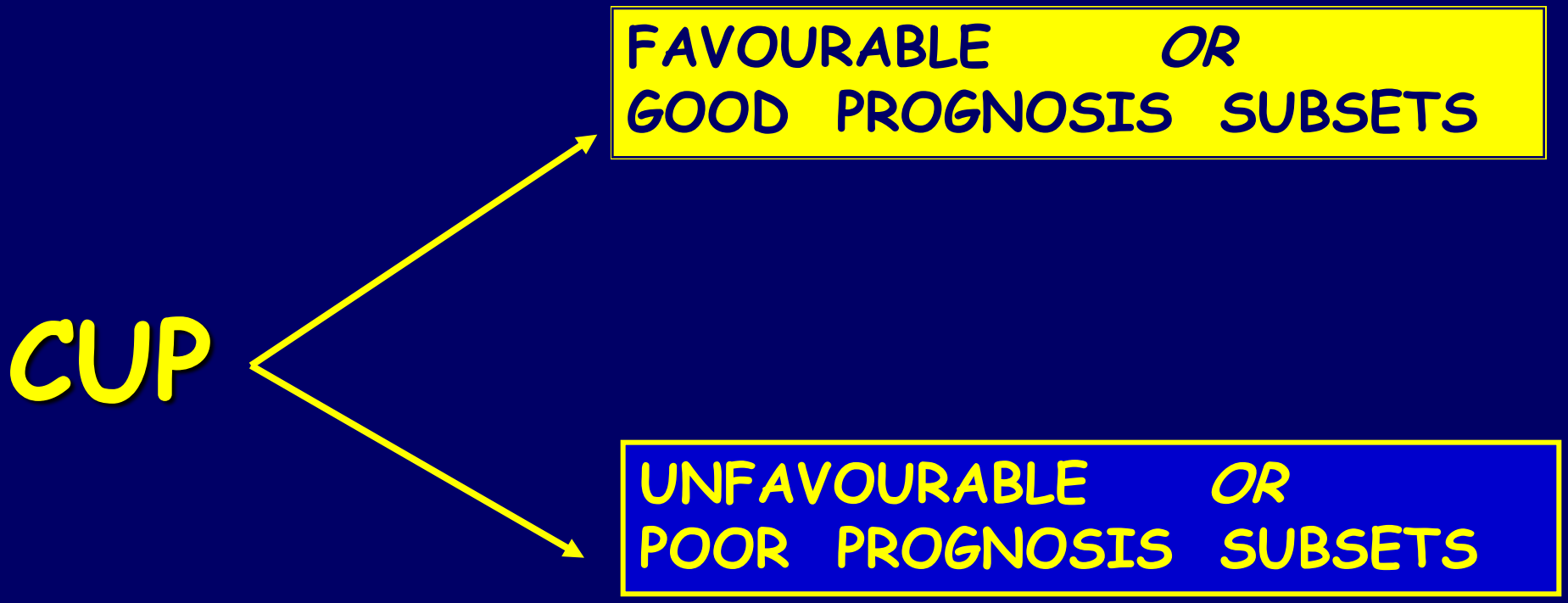
WHAT IS THE OPTIMAL THERAPEUTIC APPROACH OF CANCER OF UNKNOWN PRIMARY ?

DO WE HAVE EFFECTIVE DRUGS FOR CANCER OF UNKNOWN PRIMARY

OR

WE JUST HAVE RESPONSIVE SUBSETS OF PATIENTS ?


Volume 44, No. 8, May 2008
Special Issue
ELSEVIER
2003
39 : 1990 – 2005,
EJC
JOURNAL OF CANCER
DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF CANCER OF AN UNKNOWN PRIMARY
N. Pavlidis, E. Briasoulis, J. Hainsworth, E.A. Greco
The Official Journal of
EORTC
European Organisation
Palliative Medici
the Art and the Science
Guest Editor:
M. Fallon
Cancer
ESO
European School of Oncology


CUP
FAVOURABLE OR
GOOD PROGNOSIS SUBSETS
UNFAVOURABLE OR
POOR PROGNOSIS SUBSETS

Favourable Subsets

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

1. **Women with adenocarcinoma involving only axillary lymph nodes.**
2. **Women with papillary adenocarcinoma of peritoneal cavity.**
3. **Squamous cell carcinoma involving cervical lymph nodes**
4. **Poorly differentiated neuroendocrine carcinomas.**
   Merkel cell carcinoma of unknown primary (localized disease)
5. **Adenocarcinoma with a colon-profile (CK 20^{+}, CK 7^{-}, CDX 2^{+})**
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.**

Subset 1

WOMEN WITH OCCULT PRIMARY BREAST CARCINOMA PRESENTING AS AXILLARY LYMPHADENOPATHY

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

Therapeutic options applied :

1. Mastectomy and axillary dissection (M + ALND) : 59 % of pts
2. Primary breast irradiation : 26 % of pts
3. Observation : 15 % of pts

Outcomes :

1. Observation group : 42 % locoregional relapse rate
2. M + ALND or breast irradiation : adequate locoregional control and 72 % 5-year survival
3. No survival difference between M + ALND or irradiation alone

Masinghe SP et al [UK], *Clinical Oncology 23: 95-100, 2011*

N : 53 pts TxN1-2M0

Rx : 100 % axillary surgery

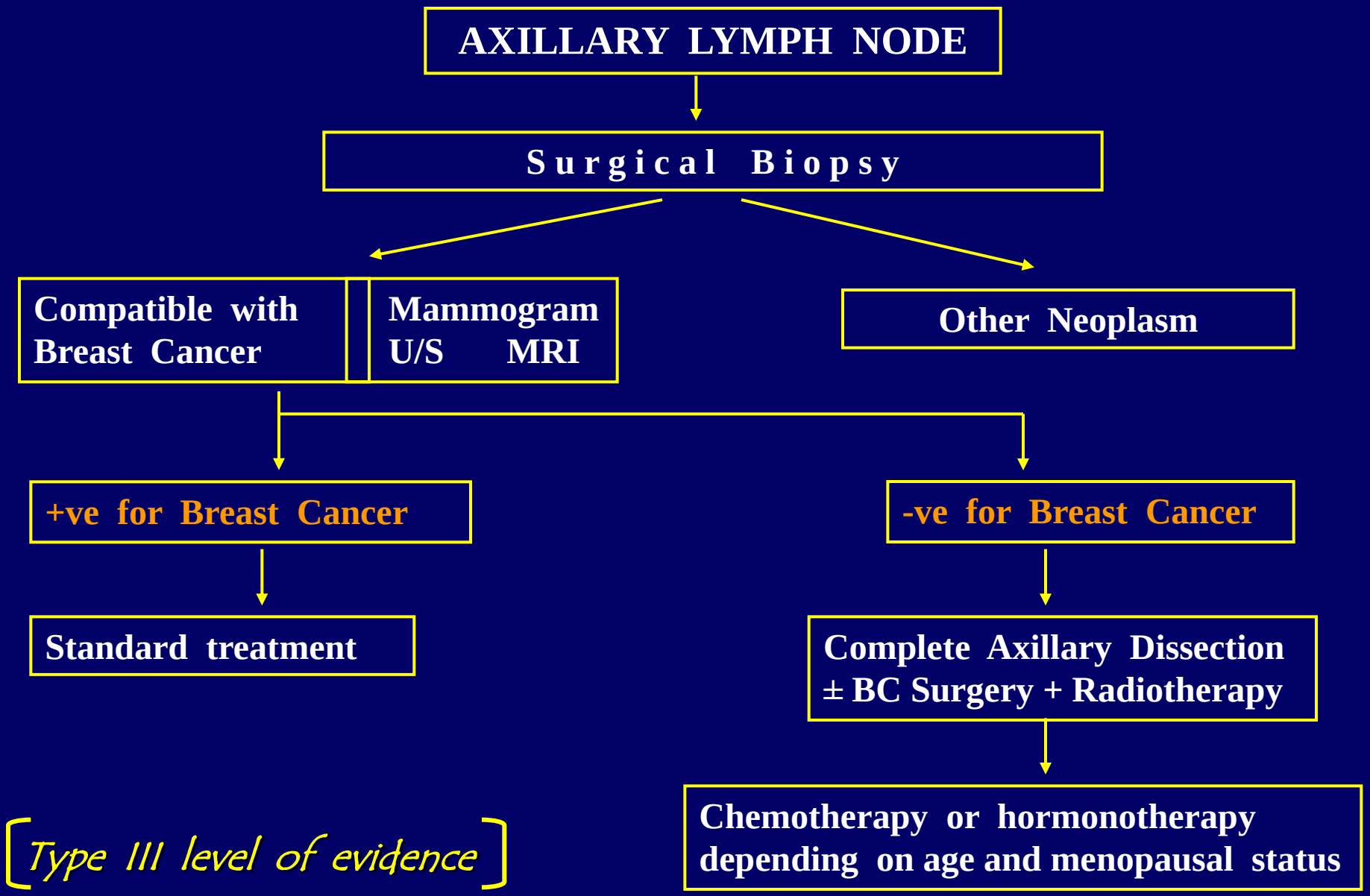
77% ipsilateral breast radiotherapy

[32 % adjuvant systemic treatment]

Outcome	Irradiated pts	Non-irradiated pts
	5 - yrs : 16%	5 - yrs : 36%
Local recurrence at		
[p = 0.001]	10 – yrs : 23%	10 – yrs : 52 %

	5 – yrs : 72%	5 – yrs : 58%
Breast Cancer specific survival at		
[p = 0.0073]	10 – yrs : 66 %	10 – yrs : 15 %

TREATMENT RECOMMENDATIONS



Type III level of evidence

Subset 2

WOMEN WITH SEROUS PAPILLARY PERITONEAL CARCINOMA (Primary Peritoneal Carcinoma)

ELSEVIER

Critical Reviews in Oncology/Hematology 75 (2010) 27–42

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Serous papillary peritoneal carcinoma: Unknown primary tumour, ovarian cancer counterpart or a distinct entity? A systematic review

George Pentheroudakis, Nicholas Pavlidis*

Years : 1980 – 2008 (25 studies)

Nº Pts : SPPCs 579

SOCs 1408

	SPPCs	SOCs
ORR	71%	70%
OS (median)	24,4 mos	29 mos

SPPC = Serous Papillary Peritoneal Carcinoma **SOC = Serous Ovarian Carcinoma**

Available online at www.sciencedirect.com
SciVerse ScienceDirect
ELSEVIER
Taiwanese Journal of Obstetrics & Gynecology 52 (2013) 81–84
www.tjog-online.com

Original Article

Prognosis for advanced-stage primary peritoneal serous papillary carcinoma and serous ovarian cancer in Taiwan

N : SPPCs : 38 pts SOCs : 52 pts

High grade tumors : SPPCs 100 % (p < 0.001)
SOCs 68 %

Rx : Platinum - paclitaxel combination (92 – 94 % of pts)

Outcome		SPPCs	SOCs
	PFS	12 mos	16.7 mos (p = 0.470)
	OS	62 mos	77.5 mos (p = 0.006)

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v133–v138, 2015
doi:10.1093/annonc/mdv305

Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

K. Fizazi[1], F. A. Greco[2], N. Pavlidis[3], G. Daugaard[4], K. Oien[5] & G. Pentheroudakis[3], on behalf of the ESMO Guidelines Committee*

Table 3. Therapy of patients with favorable risk cancers of unknown primary site (CUPs)

CUP subtype	Proposed treatment	Potential equivalent tumor
Peritoneal adenocarcinomatosis of a serous papillary histological type in female	Optimal surgical debulking followed by platinum –taxane-based chemotherapy	Ovarian cancer

Subset 3

SQUAMOUS CELL CARCINOMA OF AN UNKNOWN PRIMARY SITE INVOLVING CERVICAL LYMPH NODES

Treatment Modalities

[1] Surgery

1. **Excisional biopsy**
2. **Neck dissection**

   Radical (removal of levels I-IV neck nodes, spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle)

   Modified radical (removal of levels I-IV neck nodes and spares rest of neck structures)

3. **Bilateral tonsillectomy** (for hidden primaries)

Indications

1. Pts with N1 or N2a disease **without** extraxapsular extension could be treated with surgery alone.
2. Locoregional control : 80 % - 90 %
3. 5 – year overall survival : **up to 65%**

[II] Postoperative Radiation Therapy

Indications

1. Excisional or incisional biopsy
2. Extracapsular extension of the tumor
3. Multiple positive nodes (stage N2b or higher)

but also in

4. Initial stage N2b or N3 as a sole treatment
5. Large nodes fixed to the adjacent structure (ie carotid)
5. Pts with low PS and comorbidities

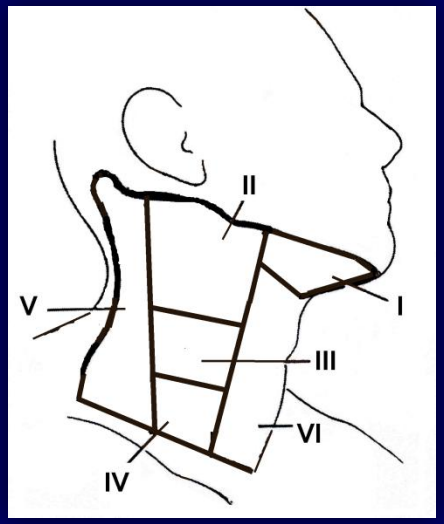
Sites

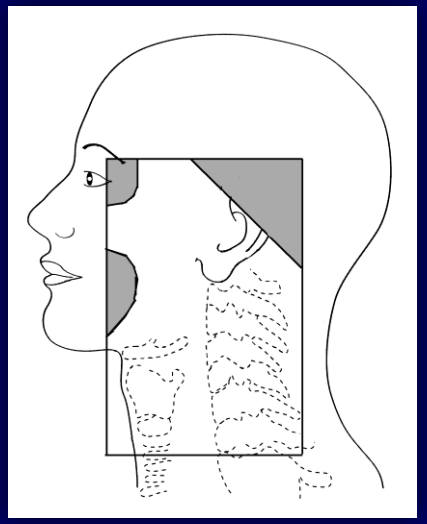
Levels of the neck	Sites to be irradiated
I	Oral cavity, Waldeyer's ring, oropharynx, both sides of the neck. Protection of larynx
II, III (upper) V	Nasopharynx, oropharynx, hypopharynx, larynx, both sides of the neck, to the level of the clavicles
IV only	Waldeyer' s ring, larynx, hypopharynx, both sides of the neck
Lower level V	Larynx, hypopharynx, both sides of the neck, generous regional portal to include adjacent apex of the axilla

Dosage

a. The neck, 65-70 Gy to the involved nodal stations and 50 Gy for the uninvolved sites.

b. The mucosal sites usually 50 – 60 Gy





[III] CHEMORADIATION

1. **Lack of data** from prospective randomized studies

2. **Probably no benefit** for patients with pN1 neck disease without extracapsular extension

3. **For more advanced disease** (N2 or N3) chemoradiotherapy might be required (similarly to the known head / neck locally advanced disease) although they still have some negative voices.

4. **Drugs used**: cisplatin, fluorouracil , paclitaxel, cetuximab

5. Chemoradiation could be associated with significant **grade 3 toxicities** (i.e. mucositis, esophagitis, skin desquamation, laryngeal edema).

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v133–v138, 2015
doi:10.1093/annonc/mdv305

Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

K. Fizazi[1], F. A. Greco[2], N. Pavlidis[3], G. Daugaard[4], K. Oien[5] & G. Pentheroudakis[3], on behalf of the ESMO Guidelines Committee*

Table 3. Therapy of patients with favorable risk cancers of unknown primary site (CUPs)

CUP subtype	Proposed treatment	Potential equivalent tumor
Squamous carcinoma involving non-supraclavicular cervical lymph node	Neck dissection and/or irradiation of bilateral neck and head – neck axis. For advanced stages induction chemotherapy with platinum – based combination or chemoradiation	Head and neck cancer

Subset 4

POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMA OF AN UNKNOWN PRIMARY SITE

Cancer Treatment Reviews 37 (2011) 358–365

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Tumor Review

Neuroendocrine carcinoma of unknown primary: A systematic review of the literature and a comparative study with other neuroendocrine tumors

Aikaterini Stoyianni [a], George Pentheroudakis [a], Nicholas Pavlidis *

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

Data : **1988 – 2010**

Nº pts : **515** ***[Low grade = 231 (45%)]***

Chemotherapy ***(Platinum based)*** : **65%**

Response rate : **50-60% (CR: 20 - 30%)**

Median survival : **15.5 months (11.6 – 40)**

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v133–v138, 2015
doi:10.1093/annonc/mdv305

Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

K. Fizazi[1], F. A. Greco[2], N. Pavlidis[3], G. Daugaard[4], K. Oien[5] & G. Pentheroudakis[3], on behalf of the ESMO Guidelines Committee*

Table 3. Therapy of patients with favorable risk cancers of unknown primary site (CUPs)

CUP subtype	Proposed treatment	Potential equivalent tumor
Poorly differentiated neuroendocrine carcinomas of an unknown primary	Platinum + etoposide combination chemotherapy	Poorly differentiated NET with a known primary
Well differentiated NET of unknown primary	Somatostatin analogs, streptozocin + 5-FU, sunitinib, everolimus	

J Am Acad Dermatol
March 2013

Unknown primary Merkel cell carcinoma: 23 new cases and a review

Tina I. Tarantola, MD,[a] Laura A. Vallow, MD,[c] Michele Y. Halyard, MD,[d] Roger H. Weenig, MD,[f] Karen E. Warschaw, MD,[e] Amy L. Weaver, MSc,[b] Randall K. Roenigk, MD,[a] Jerry D. Brewer, MD,[a] and Clark C. Otley, MD[a]

Rochester and Minneapolis, Minnesota; Jacksonville, Florida; and Scottsdale, Arizona

- At 2 years, overall survival of patients with stage IIIB unknown primary MCC was significantly improved compared with patients with stage IIIB known primary MCC: 76.9% to 36.4% (P = .028).

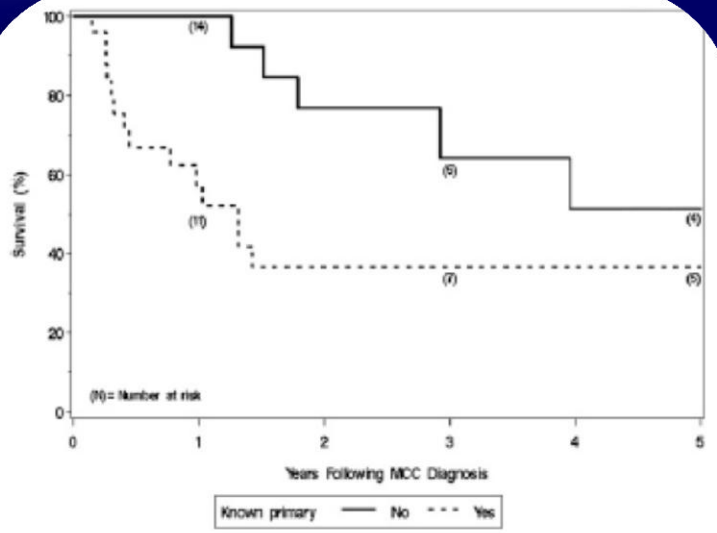


Fig 1. Overall survival among 18 patients with stage IIIB unknown primary Merkel cell carcinoma (*MCC*) and 27 patients with stage IIIB known primary MCC from same time period. Kaplan-Meier estimates are provided at 1, 2, 3, and 5 years. Number at risk are included in parenthes

Subset 5

ADENOCARCINOMA WITH A COLON – PROFILE (CK 20^{+}, CK 7^{-}, CDX 2^{+}, CEA $^{+}$) OF AN UNKNOWN PRIMARY SITE

Original Study

Clinical Colorectal Cancer, Vol. 11, No. 2, 112–8 © 2012

A Retrospective Study of Treatment Outcomes in Patients With Carcinoma of Unknown Primary Site and a Colorectal Cancer Molecular Profile

John D. Hainsworth,[1,2] Catherine A. Schnabel,[3] Mark G. Erlander,[3]
David W. Haines III,[1] F. Anthony Greco[1,2]

Int J Clin Oncol
DOI 10.1007/s10147-013-0583-0

ORIGINAL ARTICLE

Carcinoma of unknown primary with gastrointestinal profile: immunohistochemistry and survival data for this favorable subset

G. R. Varadhachary · S. Karanth · W. Qiao ·
H. R. Carlson · M. N. Raber · J. D. Hainsworth ·
F. A. Greco

CUP ADENOCARCINOMA WITH A COLON-PROFILE

Cases reported : **74**

Gender M/F : **36 % / 64 %** ***Median Age*** : **57 years**

IHC : **CK 20^{+} , CK 7^{-} , $CDX2^{+}$, ± CEA^{+}**

Molecular Profiling : **83 – 97 % sensitivity for colon Ca**

Disease extension **(Intraabdominal) :**

- **Abdominal nodes = 51 %**
- **Carcinomatosis = 50%**
- **Liver mets = 30%**
- **Ascites = 27%**

Overall RR to site specific regimen : **50% [CR: 15%, PR : 35% , SD: 25%]**

Overall RR to empirical Rx : **17% [(CR: 0%, PR : 17% , SD: 33%]**

Median Survival : **21 – 37 months**

Int J Clin Oncol (in press), Clin Colorectal Cancer 11: 112-8, 2012

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

OTHER FAVOURABLE SUBSETS

- **Men with blastic bone metastases from an adenocarcinoma and elevated serum PSA ⇒ treat as advanced prostate cancer**

- **Isolated inguinal adenopathy from squamous cell carcinoma ⇒ local excision ± radiation**

- **Patients with a single, small, potentially resectable tumours ⇒ local excision ± radiation**

THE UNFAVOURABLE SUBSETS
OR
POOR PROGNOSIS SUBSETS

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

UNFAVOURABLE SUBSETS

1. Adenocarcinoma metastatic to the liver or other organs
2. Poorly differentiated carcinoma
3. Non-papillary malignant ascites (adenocarcinoma)
4. Multiple cerebral metastases (adeno or squamous Ca)
5. Multiple lung/pleural metastases (adenocarcinoma)
6. Multiple metastatic bone disease (adenocarcinoma)
7. 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*

THE SUBSET OF ADENOCARCINOMA METASTATIC TO THE LIVER

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

Cancer Treatment Reviews xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Prognostication in cancer of unknown primary (CUP): Development of a prognostic algorithm in 311 cases and review of the literature

Dimitrios Petrakis, George Pentheroudakis, Evangelos Voulgaris, Nicholas Pavlidis *

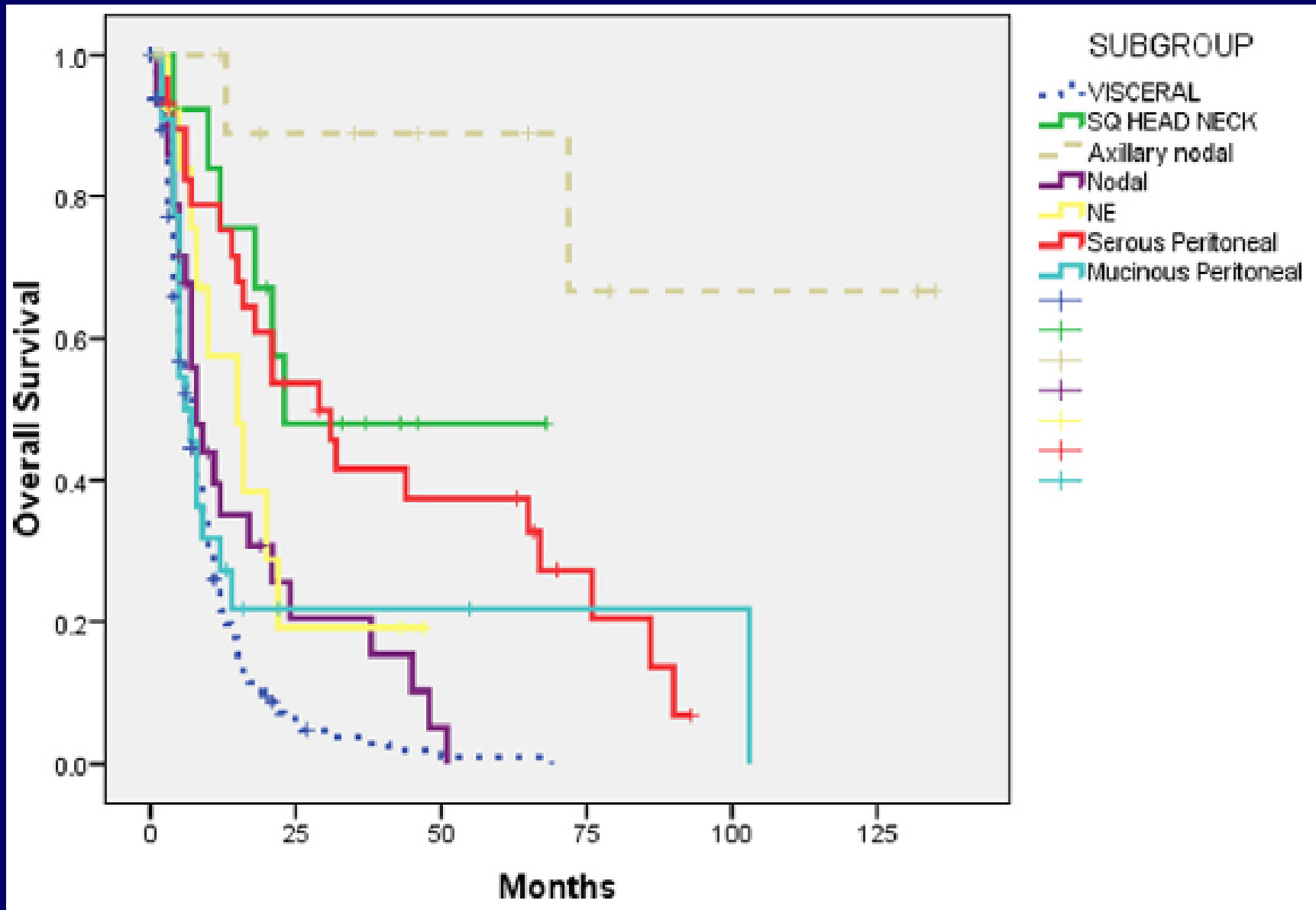


Fig. 1. Overall Survival by CUP Clinicopathologic Subgroups in univariate analysis.

Table 5
Prognostic factors in multivariate analysis.

Parameter	Hazard Ratio for death	95% CI	p-value
PS 0–1	0.56	0.39–0.81	0.002
CUP Subgroup Visceral	1.75	0.98–3.5	0.001
WBC up to 10.000/mm3	0.512	0.34–0.76	0.001
Total Bilirubin >1 mg/dl	0.67	0.45–1.001	0.054

DOES THE IDENTIFICATION OF PRIMARY SITE BY MOLECULAR PROFILING FOLLOWING SITE-SPECIFIC THERAPY IMPROVE PATIENTS' OUTCOME ?

WHAT IS THE EVIDENCE TODAY ?

STEPS IN DIAGNOSTIC AND THERAPEUTIC MANAGEMENT

DIAGNOSIS OF METASTATIC CARCINOMA (by histopathology)

↓

SEARCH FOR PRIMARY SITE

STEP I

Clinical, immunohistochemistry, imaging, endoscopy studies

↓

RULE-OUT POTENTIALLY TREATABLE OR CURABLE TUMORS
(Immunohistochemistry or other studies)

STEP II

i.e. Breast Cancer, Germ-cell Tumors, Lymphomas

↓

STEP III

CHARACTERIZE THE SPECIFIC CLINICOPATHOLOGICAL ENTITY

↓

TREAT THE PATIENT

↙ ↘

FAVOURABLE SUBSETS

[Similarly to relevant primaries with "Curative Intent"]

UNFAVOURABLE SUBSETS

[With empirical chemotherapy with "Palliative Intent" or with specific Rx following gene profiling]


THANK YOU