ONKOLOŠKI INŠTITUT LJUBLJANA
INSTITUTE OF ONCOLOGY LJUBLJANA

Onkološki inštitut Ljubljana
Sektor za internistično onkologijo

SLOVENSKO ZDRAVNIŠKO DRUŠTVO

Sekcija za internistično onkologijo

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

6th

Annual Meeting of the Slovenian Society for Medical Oncology

RARE TUMORS

Izročki predavanj

Kraj in datum srečanja:
predavalnica stavba C,
OIL, Ljubljana,
12. in 13.11.2010

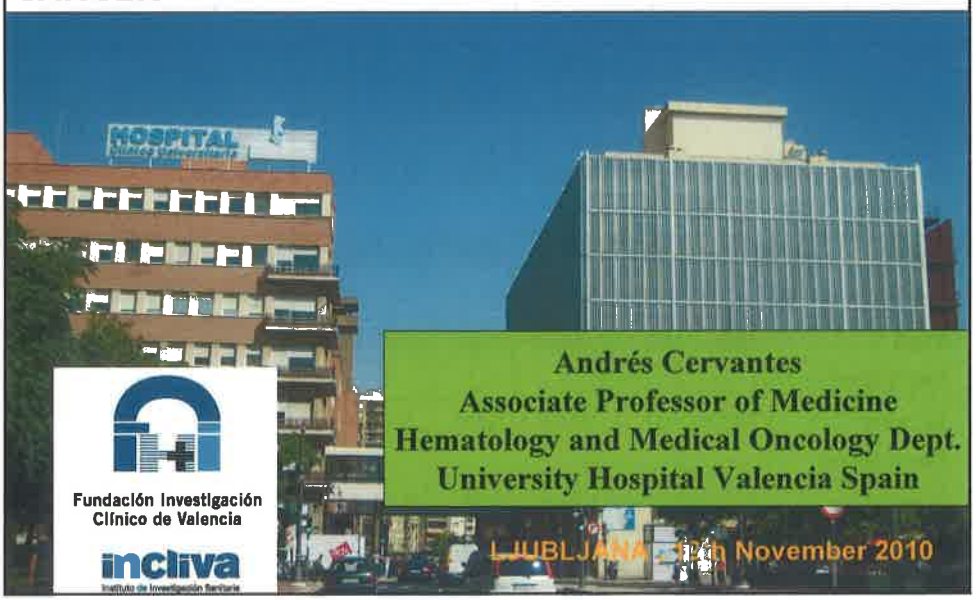
6th Annual Meeting of the Slovenian Society for Medical Oncology

Organizacijski in strokovni odbor:
Simona Borštnar, MD, PhD
Prof. Tanja Čufer, MD, PhD
Asist. prof. Barbara Jezeršek-Novaković, MD, PhD
Tanja Južnic, MD, Msc.
Erika Matos, MD, Msc.
Asist. prof. Janja Ocvirk, MD, PhD
Breda Škrbinc, MD, PhD
Assoc. prof. Branko Zakotnik, MD PhD

Izdajatelja: OIL in Sekcija za internistično onkologijo pri SZD

VSEBINA

STANDARDS AND FUTURE PERSPECTIVES IN SYSTEMIC TREATMENT OF OESOPHAGO-GASTRIC CANCER



CLASSICAL APPROACH TO LOCALISED GASTRIC CANCER

- Surgical resection
- Pathology assessment and estimation of risk
- Treatment based upon classical TNM stage
- Postoperative Chemotherapy of limited value
- Postoperative Chemoradiation

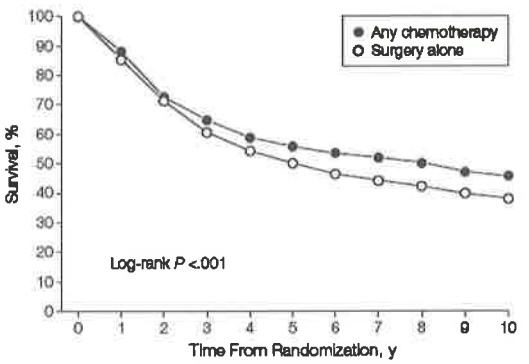
META-ANALYSIS OT TRIALS INVOLVING ADJUVANT CHEMOTHERAPY VERSUS SURGERY ALONE FOR GASTRIC CANCER-1

Meta-analysis	Year	No. Trials	No. Pts	Odds Ratio	95% CI	Conclusions
Hermanns J Clin Oncol	1993	11	2096	0.88	0.78-1.08	No benefit
Earle Eur J Cancer	1999	13	1990	0.80	0.66-0.97	Small survival benefit In N+ patients
Mari Ann Oncol	2000	20	3658	0.82	0.75-0.89	Small survival benefit
Januger Eur J Surg	2002	21	3962	0.84	0.74-0.96	Very heterogeneous group of trials
Western				0.96	0.83-1.12	
Asian				0.58	0.44-076	

META-ANALYSIS OT TRIALS INVOLVING ADJUVANT CHEMOTHERAPY VERSUS SURGERY ALONE FOR GASTRIC CANCER-2

Meta-analysis	Year	No. Trials	No. Pts	Odds Ratio	95% CI	Conclusions
Zhao et al Cancer Investigation	2008	15	3212	0.90	0.84-0.96	Marginal, though significant benefit P: 0.001
Liu et al Eur J Surg Oncol	2008	19	2286	0.85	0.80-0.90	Marginal, though significant benefit P< 0.0001
Gastric Group JAMA	2010	17	3871	0.82	0.76-090	P< 0.001

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years



No. at risk

Any chemotherapy	1924	1686	1385	1217	1080	929	709	526	390	297	243
Surgery alone	1857	1568	1300	1092	952	782	583	407	267	172	138

The GASTRIC GROUP *JAMA*. 2010; 303:1729

RECENTLY PUBLISHED TRIALS OF ADJUVANT CHEMOTHERAPY FOR LOCALIZED GASTRIC CANCER FROM WESTERN COUNTRIES

Trial	CT	Nr. Pts Control	Nr. Pts CT	5-year Survival Control	Median Survival CT	HR (CI at 95%)
Di Constanzo JNCI 2008	PELF	128 No CT	130	48.7%	47.6 %	0.90 0.64-1.26
Cascinu JNCI 2007	PELFw	196 FU-LV	201	50%	52%	0.95 0.70-1.29
De Vita Ann Oncol 2007	ELFE	113 No CT	113	43.5%	48%	0.91 0.69-1.21
Bajetta Ann Oncol 2002	EAP 5FU-LV	137 No CT	137	48%	52%	0.93 0.65-1.34

POSTOPERATIVE CHEMOTHERAPY IN LOCALIZED GASTRIC CANCER

- LIMITED VALUE, IF ANY
- HRs BY 0.90
- NON SIGNIFICANT EFFECT IN MOST SINGLE TRIALS
- BUT...
  - NONSTANDARDIZED SURGERY
  - MANY SINGLE TRIALS UNDERPOWERED
  - HYPOTETIC BENEFIT OVERESTIMATED
  - STRATIFIED BY MANY AND DIFFERENT CLINICAL OR PATHOLOGICAL FACTORS
  - HETEROGENEOUS POPULATION ACCRUED
  - N NEGATIVE PATIENTS PREDOMINATE
  - SELECTED POPULATION OF PATIENTS WELL ADAPTED TO TOTAL OR PARTIAL GASTRECTOMY
  - BIOLOGICAL PREDICTIVE FACTORS UNKOWN AND THEREFORE NOT APPLIED TO STRATIFICATION

D2 LYMPHADENECTOMY ALONE OR WITH PARA-AORTIC NODAL DISSECTION FOR GASTRIC CANCER

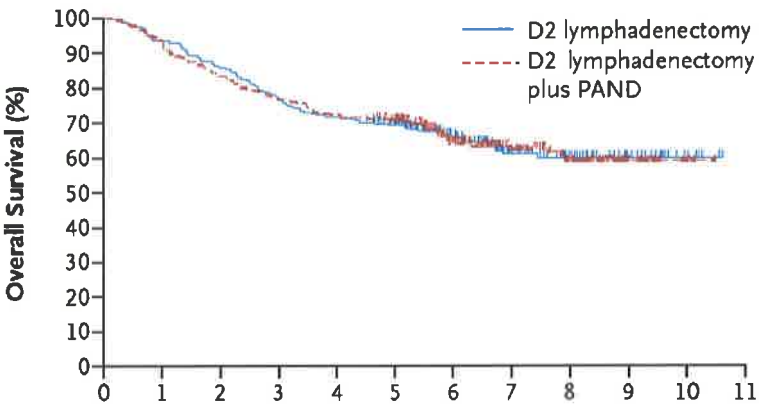
Table 2. Site of First Tumor Recurrence.*

Site	D2 Lymphadenectomy Alone (N=109)	D2 Lymphadenectomy plus PAND (N=106)
	no. (%)	
Peritoneum	43 (39.4)	39 (36.8)
Lymph nodes	24 (22.0)	23 (21.7)
Liver	21 (19.3)	24 (22.6)
Others	21 (19.3)	20 (18.9)

* In nine patients in the group assigned to D2 lymphadenectomy alone and seven patients in the group assigned to D2 lymphadenectomy plus para-aortic nodal dissection (PAND), more than one site was involved at the time of first recurrence.

Sasako et al. N Eng J Med 2008; ; 359; 453

D2 LYMPHADENECTOMY ALONE OR WITH PARA-AORTIC NODAL DISSECTION FOR GASTRIC CANCER



Sasako et al. N Eng J Med 2008; ; 359; 453

ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER WITH S1: AN ORAL FLUOROPYRIMIDINE

TRIAL DESIGN

SURGERY

RANDOMIZED
N= 1059
STRATIFIED
STAGE II, IIIA, IIIB

NO TREATMENT

S1 40 MG/M^2 BID
4 OUT OF 6 WEEKS 0NE YEAR

Sakuramoto et al N Eng J Med 2007; 357:1810

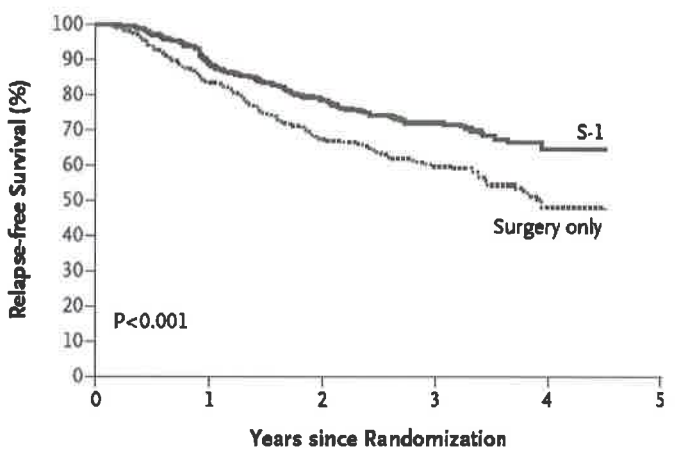
ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER WITH S1: AN ORAL FLUOROPYRIMIDINE

Table 3. Site of First Relapse, According to Treatment Group.*

Site	S-1 (N=529)	Surgery Only (N=530)	Hazard Ratio for Relapse in the S1 Group (95% CI)	P Value
	no. of patients (%)			
Total no. of relapses	133 (25.1)	188 (35.5)		
Local	7 (1.3)	15 (2.8)	0.42 (0.16–1.00)	0.05
Lymph nodes	27 (5.1)	46 (8.7)	0.54 (0.33–0.87)	0.01
Peritoneum	59 (11.2)	84 (15.8)	0.64 (0.46–0.89)	0.009
Hematogenous	54 (10.2)	60 (11.3)	0.84 (0.58–1.21)	0.35

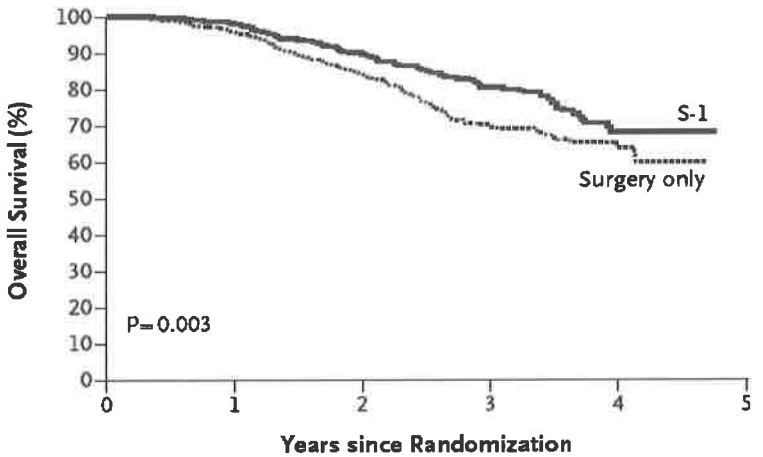
Sakuramoto et al N Eng J Med 2007; 357:1810

ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER WITH S1: AN ORAL FLUOROPYRIMIDINE



Sakuramoto et al N Eng J Med 2007; 357:1810

ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER WITH S1: AN ORAL FLUOROPYRIMIDINE



Sakuramoto et al N Eng J Med 2007; 357:1810

POSTOPERATIVE CHEMORADIOTHERAPY FOR LOCALISED GASTRIC CANCER

TRIAL DESIGN

SURGERY

RANDOMIZED
N= 556
STRATIFIED
T 1-4
NODES 0, 1-3, >3

NO TREATMENT

ChT+ ChRT + ChT

McDonald JS et al (N Engl J Med 2001;345:725-30.)

POSTOPERATIVE CHEMORADIOTHERAPY FOR LOCALISED GASTRIC CANCER

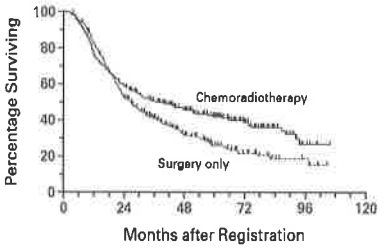


Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

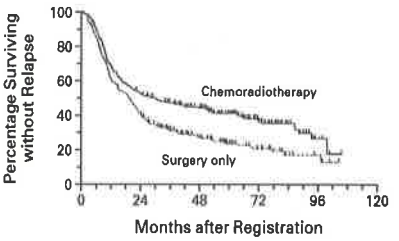


Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.

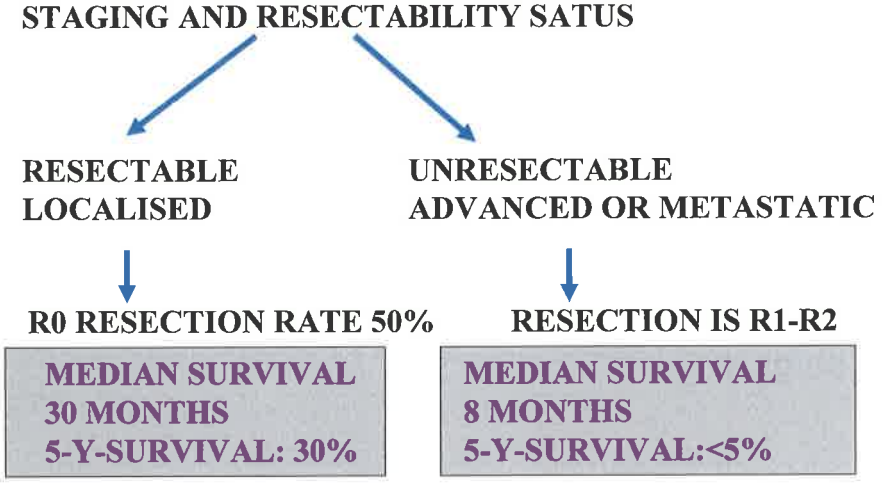
- **Clear benefit in disease free and overall survival with median follow-up of 6 years. Risk reduction of death by 24%.**
- **Type of surgery: D2 resection less than 10%**
- **Planning of Radiation to be modified after central review in 35% of cases due to minor/minor deviations**

McDonald JS et al (N Engl J Med 2001;345:725-30.)

DISADVANTAGES OF POST-OPERATIVE TREATMENT

- Efficacy of treatment used is unknown
- Treatment appears to be less well tolerated after major surgery
- Commencement of post-operative treatment may be delayed by slow recovery from surgery or peri-operative morbidity
- Important morbidity related with total gastrectomy, specially altered nutritional status

LOCALISED GASTRIC CANCER: Estimated median survival 10-14 months



RATIONALE FOR PRE-OPERATIVE TREATMENT

- Tumour downstaging/downsizing prior to surgery
  - Reduction of microscopic marginal involvement with tumour
  - Increase likelihood of curative resection
- Eliminating disseminated micrometastatic disease and achieving systemic control
- Demonstrates in vivo sensitivity to systemic treatment
- Improvement of tumour related symptoms
- Better tolerated than post-operative therapy
- More patients may benefit from therapy

DISADVANTAGES OF PRE-OPERATIVE TREATMENT

- Risk of progression of disease during pre-operative treatment
- ?Increased risk of peri-operative morbidity
- Pathological staging is difficult after a response to pre-operative treatment
  - Need for alternative prognostic or predictive factors
- Definitive surgery may be delayed if significant toxicity occurs
- Patients must be referred for treatment prior to surgery

Perioperative chemotherapy in operable gastric and lower oesophageal cancer: a randomised controlled trial (the MAGIC trial, ISRCTN 93793971)

D Cunningham, W Allum, S Stenning and S Weeden on behalf of the UK NCRI Upper GI Clinical Studies Group. Conducted by the UK Medical Research Council CTU.

NEJM 2006, 355(1): 11-20

STUDY DESIGN

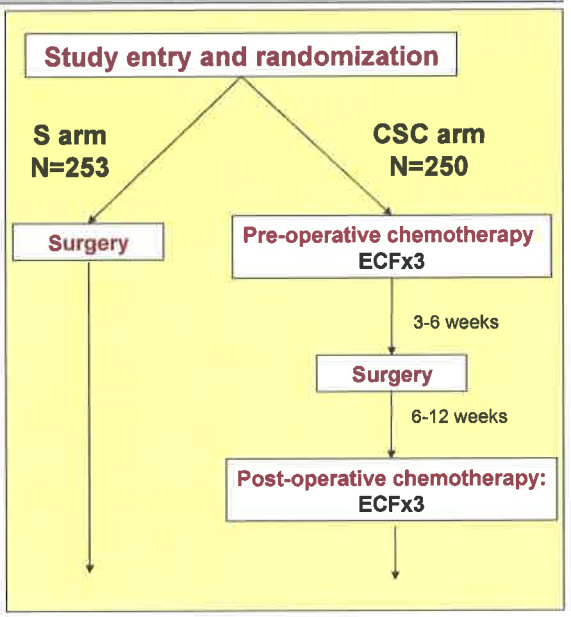
Eligible patients:
- Adenocarcinoma of the stomach or lower third of the oesophagus (from 1999), suitable for curative resection
- Non-metastatic disease
- Stage II or greater

Primary
Overall survival

Secondary
Progression-free survival
Surgical resectability
Quality of Life

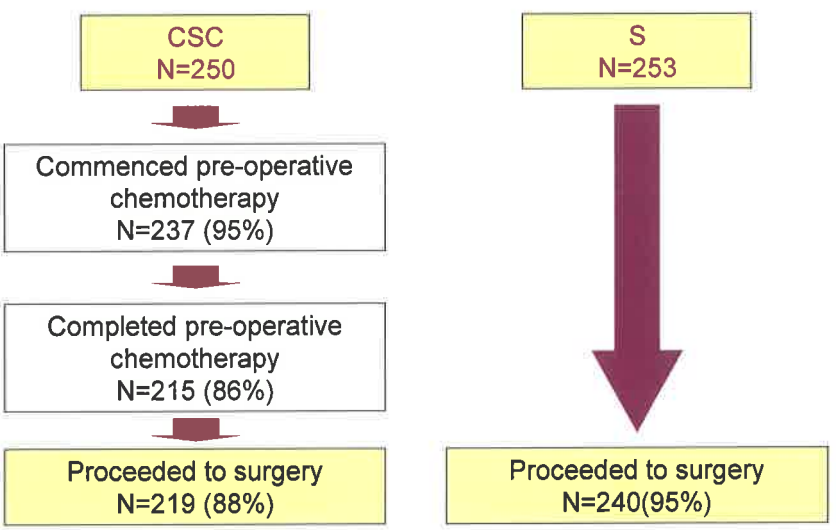
Chemotherapy (ECF):
Epirubicin 50mg/m2, IV day 1
Cisplatin 60mg/m2, IV day 1
5-FU 200mg/m2/day, continuous infusion, days 1-21
(cycles repeated every 3 weeks)

Recruitment: July 1994-April 2002



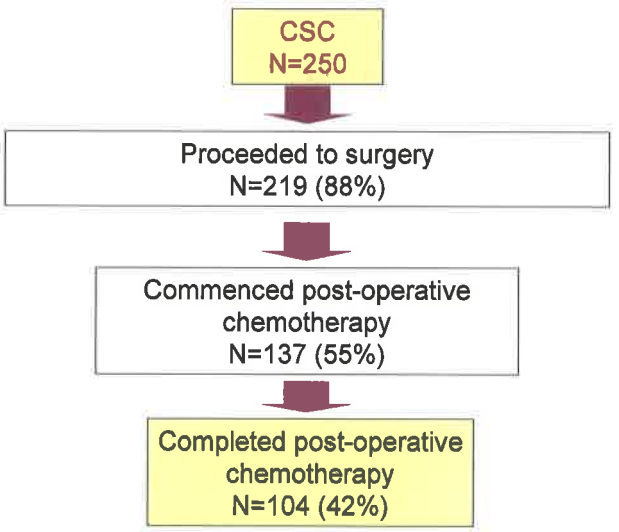
Cunningham et al NEJM 2006

PRE-OPERATIVE CHEMOTHERAPY AND SURGERY TRIAL PROFILE



Cunningham et al NEJM 2006

POST-OPERATIVE CHEMOTHERAPY TRIAL PROFILE



Cunningham et al NEJM 2006

REASON FOR NOT COMMENCING POST-OPERATIVE CHEMOTHERAPY

	N=	%
Early death/ progression of disease	34	52%
Never had surgery	15	
Surgery but did not complete pre-op chemo	10	11%
Patient request	11	12%
Post-op complications	9	10%
Toxicity from pre-op chemotherapy	6	6%
Hickman line complications	4	4%
Other	5	5%
TOTAL	94	100%

Cunningham et al NEJM 2006

GRADE 3/4 TOXICITIES

	Preop	Postop
Granulocytes	24%	28%
Lymphocytes	20%	17%
WBC Count	12%	11%
Haemoglobin	5%	1%
Platelets	< 1%	3%
Haemotological other	< 1%	2%

	Preop	Postop
Nausea	6%	12%
Vomiting	6%	10%
Neurological maximum	4%	4%
Skin	3%	2%
Stomatitis	4%	4%
Diarrhoea	3%	4%

No significant difference in toxicity between pre-operative and post-operative treatment.

Cunningham et al NEJM 2006

POSTOPERATIVE MORBIDITY/MORTALITY

	CSC	S
Postoperative deaths	6% (14/219)	6% (15/240)
Postoperative complications	46%	46%
Median duration of post-operative hospital stay	13 days	13 days

Cunningham et al NEJM 2006

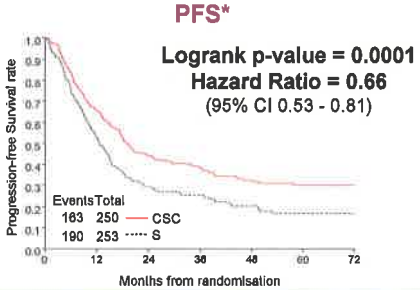
PATHOLOGY STAGING FOLLOWING SURGERY

	CSC	S	p-value
Maximum tumour diameter			
Median (IQR)	3.cm (2.0-5.0)	5.0cm (3.5-7.5)	<0.001, Mann-Whitney U test
Extent of tumour (gastric only)			
T1/T2	52%	38%	0.009, χ^2 test (trend)
T3/T4	48%	62%	
Nodal status (gastric only)			
N0/N1	84%	76%	0.01, χ^2 test (trend)
N2/N3	16%	29%	

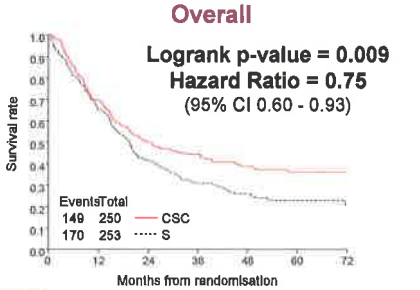
Cunningham et al NEJM 2006

SURVIVAL

PFS*



Overall



	2 year survival	5 year survival	Median survival
CSC	50%	36%	24 mo
S	41%	23%	20 mo
Benefit to CSC arm	9%	13%	4 mo

- On multivariate analysis, treatment effect unchanged after adjustment for age, performance status, site of primary and gender
- Hazard ratio for death
  - Adjusted: 0.74 (95%CI: 0.59-0.93)
  - Unadjusted: 0.75

*Included relapse, PD and death from any cause.

Cunningham et al NEJM 2006

MAGIC: Conclusions

In operable gastric and lower oesophageal cancer, perioperative chemotherapy:

- leads to downsizing of primary tumour
- significantly improves progression-free survival
- significantly improves overall survival

Cunningham et al NEJM 2006

CAN MAGIC BE COMPARED TO INT0116?

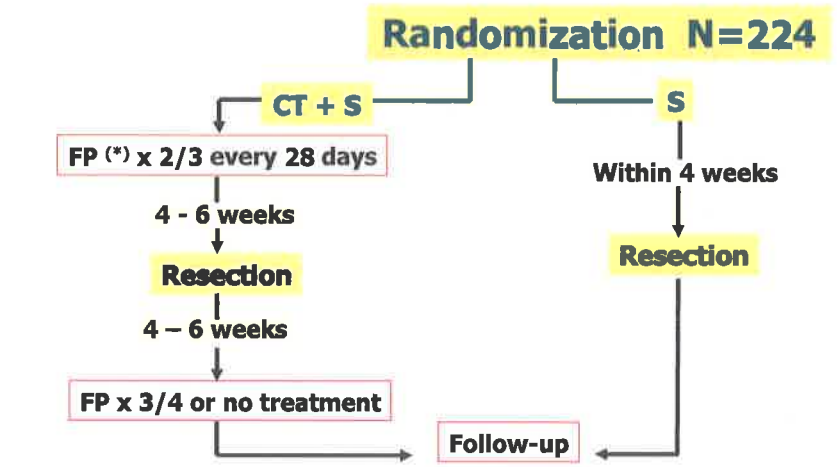
	MAGIC[1] (N=503)		INT116[2] (N=556)	
	Peri-op chemo + surgery N=250	Surgery only N=253	Post-op chemoRT + surgery N=282	Surgery only N=277
2 year survival	50%	41%	58%*	50%*
5 year survival	36%	23%	40%*	26%*
Median survival	24 months	20 months	35 months	27 months
Hazard ratio (95% CI)	0.75 (0.60-0.93) P=0.009		0.76 (0.62-0.93) P=0.006	

Direct comparison of results is difficult due to different inclusion criteria and different time of randomization.

[1] Cunningham NEJM 2006
[2] MacDonald NEJM 2001; 2004 GI Cancers Symposium

*Estimated from curve

PERIOPERATIVE CHEMO: FNLCC 94012-FFCD 9703 TRIAL



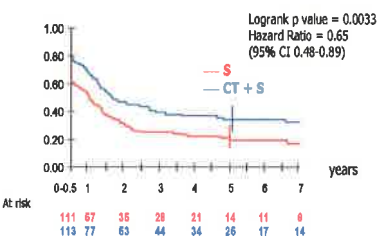
Trial accrual 1995-2003

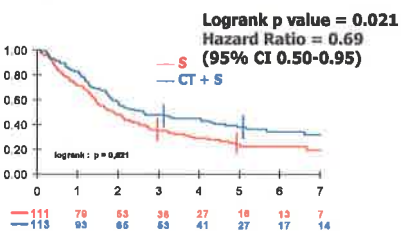
Median FU 5.7 yrs

5-Fluorouracil 800 mg/m2 d1-5
+ Cisplatin 100 mg/m2 day 1

BOIGE et al ASCO 2007

PERIOPERATIVE CHEMO: FNLCC 94012-FFCD 9703 TRIAL





	2 year survival	5 year survival	Median survival
Periop CT	58%	38%	29 mo
Surgery	47%	24%	20 mo
Benefit to CSC arm	10%	14%	9 mo

- On multivariate analysis, treatment effect unchanged after adjustment for age, performance status, site of primary and gender
- Prognostic variables in Cox multivariate analysis:
  - Preoperative CT
  - Gastric location

SUMMARY OF TRIALS OF PERIOPERATIVE CHEMOTHERAPY FOR LOCALIZED GASTRIC CANCER

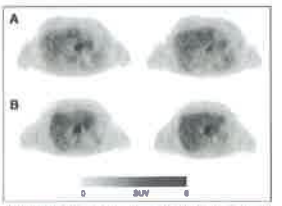
Trial	CT	Nr. Pts Control	Nr. Pts CT	5-year Survival Control	5-year Survival CT	HR (CI at 95%)
Cunningham NEJM 2006	ECF	253 No CT	250	23%	36 %	0.75 0.60-0.93 p=.009
Boige ASCO 2007	CDDP 5-FU	111 No CT	113	24%	38%	0.69 0.50-0.95 p=.021

FUTURE DIRECTIONS IN THE TREATMENT OF LOCALISED GASTRIC CANCER

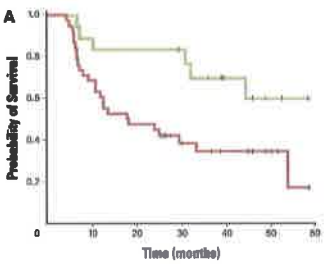
- More active systemic treatment combinations, including targeted therapies
- Defining role of radiotherapy in relation to systemic therapy
- Diagnostic/assessment
- Assessing response to treatment (i.e. role of PET)
- Translational: prognostic and predictive markers

TAILORING TREATMENT: METABOLIC RESPONSE

- 65 patients with locally advanced adenocarcinomas of the gastro-esophageal union
- Cisplatin-based chemo pre-op
- FDG-PET at baseline and day 14
- PET Response cut-off Δ35%
- Predictive of response and survival



	Metabolic response	
	Responder	Non-responder
Path Responder (<10% viable cells)	8	2
Path Non-responder (>10% viable cells)	10	36 χ^2 p=0.0002



Ott et al JCO 2006, 24

PET TO ASSESS EARLY METABOLIC RESPONSE AND TO GUIDE TREATMENT OF ADENOCARCINOMA OF THE GASTROESOPHAGEAL JUNCTION: THE NUNICON PHASE II TRIAL

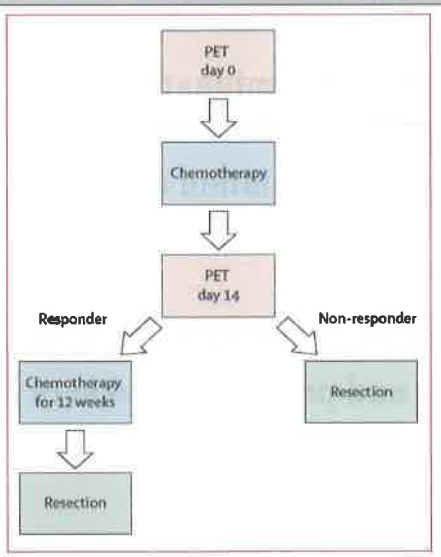


Figure 1: Study design

Lordick F. et al Lancet Oncol 2007;8:797

PET TO ASSESS EARLY METABOLIC RESPONSE AND TO GUIDE TREATMENT OF ADENOCARCINOMA OF THE GASTROESOPHAGEAL JUNCTION: THE NUNICON PHASE II TRIAL

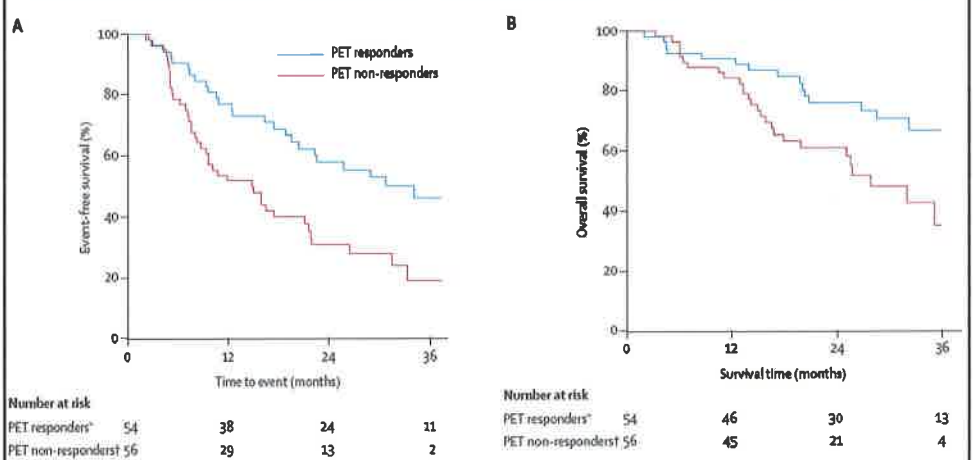
	Responder (n=50)	Non-responder (n=54)	p
Resection margin, n (%)			
R0	48 (96)	40 (74)	0·002
R1	2 (4)	14 (26)	..
Histopathological response*, n (%)			
Score 1 (a+b)	29 (58)	0	0·001
Score 2	10 (20)	2 (4)	..
Score 3	11 (22)	52 (96)	..
pT category, n (%)			
pT0	8 (16)	0	<0·0001
pT1	13 (26)	3 (6)	..
pT2	8 (16)	6 (11)	..
pT2b or pT3	21 (42)	44 (81)	..
pT4	0	1 (2)	..
pN category, n (%)			
pN0	31 (62)	11 (20)	0·001
pN1	19 (38)	43 (80)	..

*Histopathological response was scored according to that described by Becker and colleagues.[19] score 1a indicates complete remission and 0% residual tumour; score 1b indicates less than 10% residual tumour; score 2 indicates 10–50% residual tumour; and score 3 indicates more than 50% residual tumour.

Table 3: **Surgical and histopathological outcome in patients who showed a metabolic response versus those who did not show a metabolic response to neoadjuvant chemotherapy**

Lordick F. et al Lancet Oncol 2007;8:797

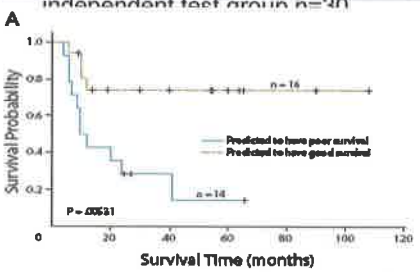
PET TO ASSESS EARLY METABOLIC RESPONSE AND TO GUIDE TREATMENT OF ADENOCARCINOMA OF THE GASTROESOPHAGEAL JUNCTION: THE NUNICON PHASE II TRIAL

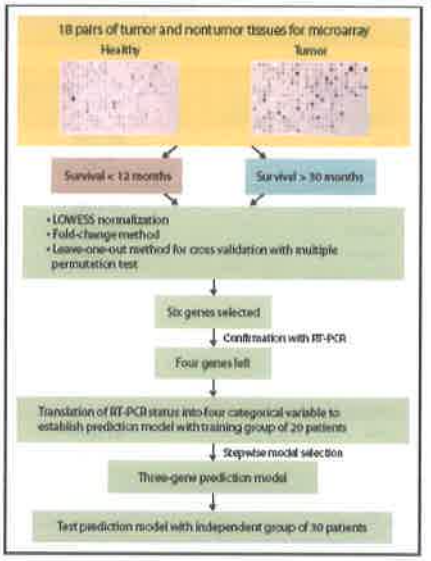


Lordick F. et al Lancet Oncol 2007;8:797

TAILORING TREATMENT: GENE EXPRESSION PROFILING

- 18 patients with gastric cancer undergoing D2 gastrectomy
- cDNA microarray-based gene expression profiling
- Identification of 3 genes for survival prediction model
- Validated by RT-PCR and tested in independent test group n=30





Chen et al JCO 2005, 23 :7286

A MULTIDISCIPLINARY TEAM APPROACH FOR GASTRIC: ANTICIPATED BENEFITS

- **Improved coordination of care**
- **To consider each case from a variety of perspectives.**
- **Patients are more likely to be offered a range of types of treatment at appropriate times**
- **A supportive environment where professionals can share their concerns**
- **Surgeons receive feedback from histopathologists and other team members on the results of their work**
- **Optimal setting for clinical research**

A MULTIDISCIPLINARY TEAM APPROACH FOR GASTRIC CANCER

- Discussion of all new cases before surgery
- Discussion of imaging data to determine optimal staging
- Selection of patients for preoperative therapy
- Discussion of pathology report, stressing on the assessment of resected lymph nodes after location
- Selection for postoperative therapy
- Detailed discussion of any relapse during follow up
- Yearly audits of all activities and results

CURRENTLY RECOMMENDED APPROACH TO LOCALISED GASTRIC CANCER

- Clinical assessment and staging
- Multidisciplinary team discussion
- Preoperative treatment in all patients with clinical stage II and III
- Surgical resection after chemotherapy
- Pathology assessment and estimation of risk
- Postoperative chemotherapy?
- Participation in trials

NEOADJUVANT CHEMOTHERAPY IN GASTRIC CANCER: CONCLUSIONS

- **Perioperative Chemotherapy:**
  - **Induces downstaging**
  - **May increase the R0 resection rate**
  - **Prolongs disease free survival**
  - **Improves overall survival**

- **Evidence level I based upon 2 well designed and properly conducted randomized trials**
- **Preoperative therapy is better tolerated than postoperative**
- **Localized gastric cancer requires a multidisciplinary team approach**
- **Further research on biological predictive factors is needed**

HAVE WE MADE ANY PROGRESS IN THE TREATMENT OF ADVANCED GASTRIC CANCER?

A. CERVANTES
HOSPITAL CLINICO
UNIVERSITY OF VALENCIA
SPAIN

Fundación Investigación Clínico de Valencia

incliva

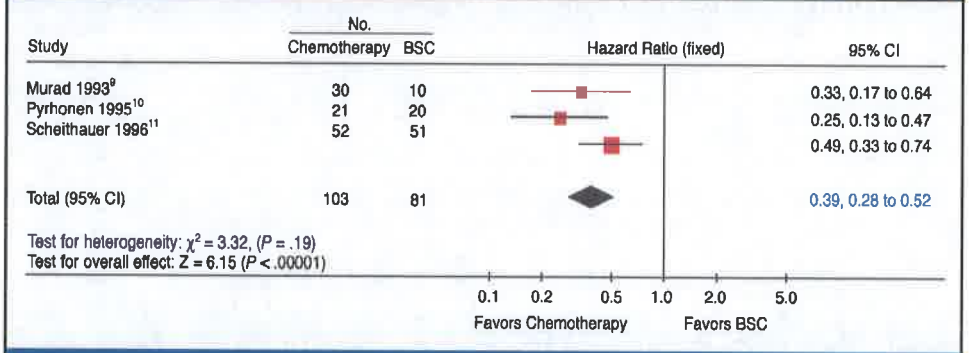
Current Questions in Advanced Gastric Cancer Management

- Which are the aims of therapy?
- Should patients with advanced gastric cancer receive chemotherapy and when?
- Which are the main prognostic factors?
- Is primary tumor location relevant for treatment decisions?
- Which are the active drugs?
- Is there any standard combination of drugs?
- Why haven't we been successful in getting better treatment for this disease?

Which are the aims of therapy?

- Symptomatic control
- Improve QoL or avoid its deterioration
- Delay tumor progression
- Prolong survival

Should patients with advanced gastric cancer receive chemotherapy?



Wagner A, et al. JCO 2006.

When should patients with advanced gastric cancer receive chemotherapy?

	INITIAL ELF-FULV	DELAYED CT AT PD
CT	100%	50%
TIME TO CT	8 DAYS	82 DAYS
QOL IMPROVEMENT	70%	25%
SURVIVAL	10 MONTHS	4 MONTHS

Glimelius B, et al. Ann Oncol 1994.

Is primary tumor location relevant for treatment decisions?

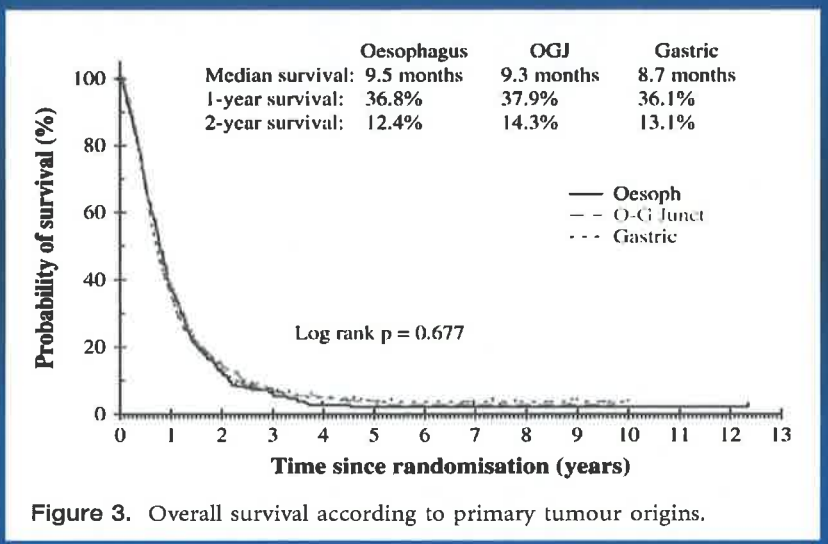


Figure 3. Overall survival according to primary tumour origins.

Chau I, et al. Ann Oncol 2009.

What are the main prognostic factors?

PS 2
Liver mets
Peritoneal mets
↑Alkaline Phosphatase

Chau I, et al. J Clin Oncol 2004.

What are the main prognostic factors?

Group	Score	median OS	1-year Surv
Good	0	11.8 m	48.5%
Moderate	1 o 2	7.4 m	25.7%
Poor	3 o 4	4.1 m	11.0%

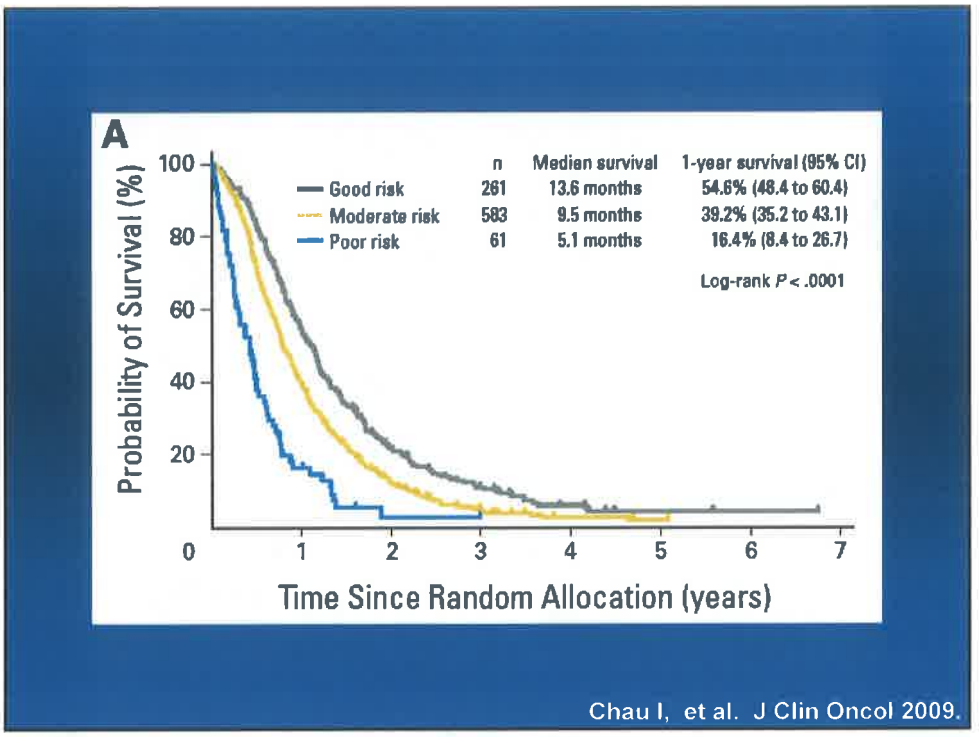
Chau I, et al. J Clin Oncol 2004.

What are the main prognostic factors?

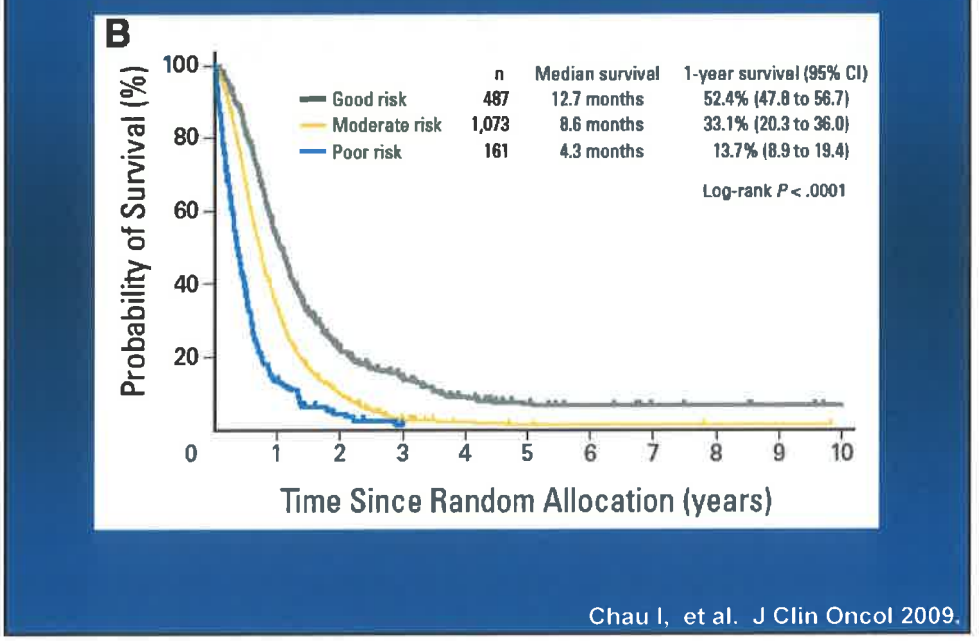
Table 1. Multivariate Baseline Prognostic Model for REAL 2 Study Patients

Factor	Hazard Ratio	99% CI	*P*
Performance status			
0-1	1		
2	2.044	1.533 to 2.725	< .0001
Liver metastasis	1.473	1.219 to 1.779	< .0001
Peritoneal metastasis	1.546	1.212 to 1.971	< .0001
Alkaline phosphatase ≥ 100 U/L	1.114	0.923 to 1.345	.14

Chau I, et al. J Clin Oncol 2009.



Chau I, et al. J Clin Oncol 2009.

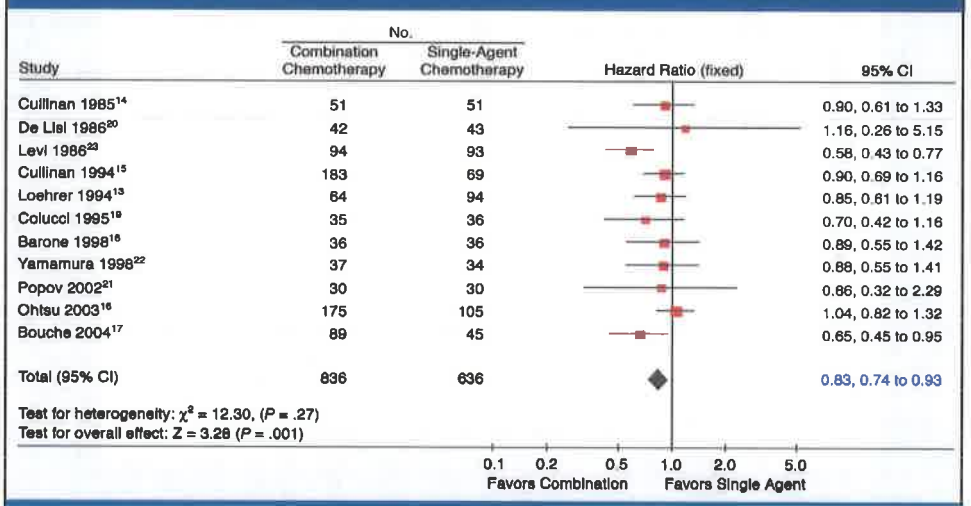


Chau I, et al. J Clin Oncol 2009.

Which are the active drugs?

- 5-Fluorouracil
- Oral Fluoropirymidines (capecitabine, S1, UFT)
- Anthracyclines?
- Cisplatin
- Oxaliplatin
- Docetaxel
- CPT-11
- Transtuzumab

Monotherapy or combination of drugs?

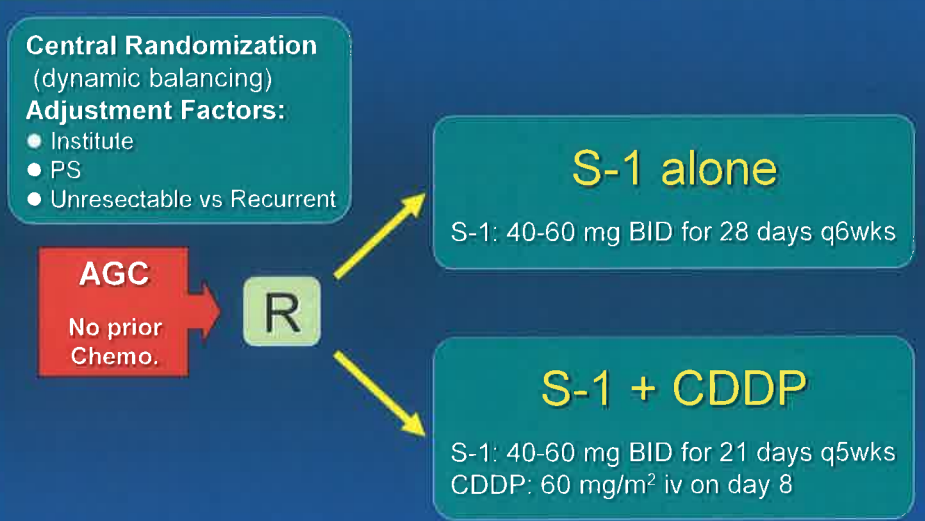


Wagner A, et al. JCO 2006.

What are the active drugs that have shown superiority in randomized trials?

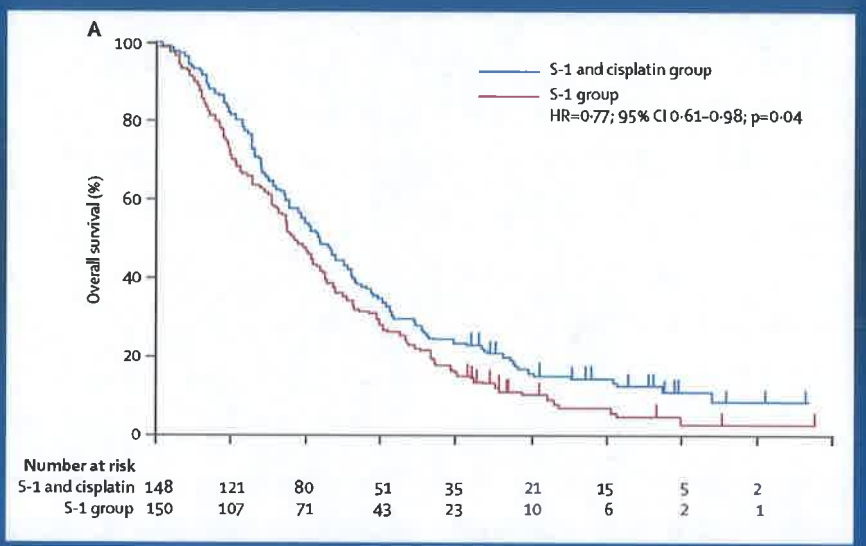
- 5-Fluorouracil
- Oral Fluoropirymidines (capecitabine, S1, UFT)
- Anthracyclines?
- **Cisplatin**
- Oxaliplatin
- **Docetaxel**
- CPT-11
- **Transtuzumab**

SPIRITS: Study Design



Koizumi W, et al. Lancet Oncol 2008

S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial



Koizumi W, et al. Lancet Oncol 2008

Docetaxel-based chemotherapy in advanced gastric cancer: Phase III trial

- Measurable/evaluable metastatic or measurable locally recurrent gastric adenocarcinoma
- Age ≥18 years
- KPS >70
- Adequate haematological/ biochemical parameters
- No prior palliative chemotherapy

→ RANDOMISATION

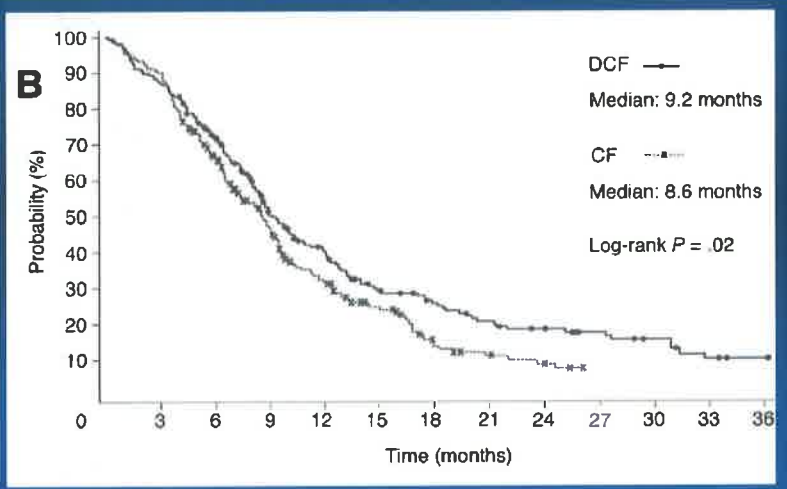
DCF
Docetaxel 75 mg/m^2 over 1 h, Day 1
Cisplatin 75 mg/m^2 over 1–3 h, Day 1
5-FU 750 mg/m^2/day over 5 days, q3w
(n=227)

Treatment until PD, consent withdrawn or unacceptable toxicity; tumour assessments q8w

CF
Cisplatin 100 mg/m^2 over 1–3 h, Day 1
5-FU 1000 mg/m^2/day over 5 days, q4w
(n=230)

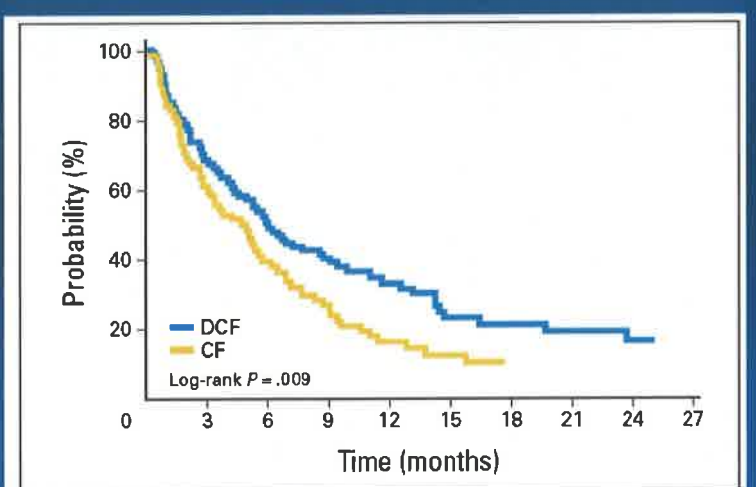
Van Cutsem E, et al. J Clin Oncol 2006

Docetaxel-CF vs CF in advanced gastric cancer: Overall survival



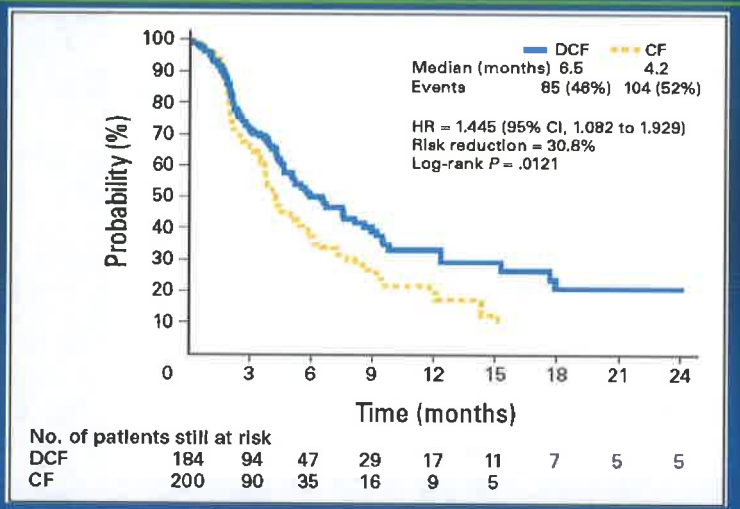
Van Cutsem E, et al. J Clin Oncol 2006

Docetaxel-CF vs CF in advanced gastric cancer: Time to definitive Karnofsky PS deterioration



Ajani JA, et al. J Clin Oncol 2007

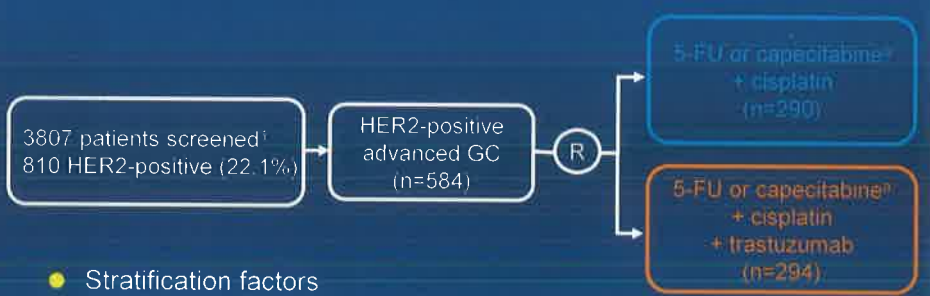
Docetaxel-CF vs CF in advanced gastric cancer: Time to 5% definitive Global Health status deterioration



Ajani JA, et al. J Clin Oncol 2007

ToGA trial design

Phase III, randomized, open-label, international, multicenter study

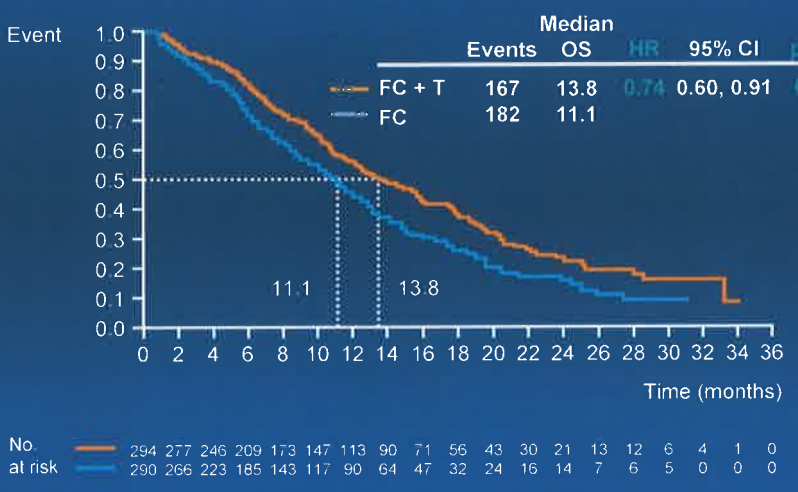


- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

[a]Chosen at investigator's discretion
GEJ, gastroesophageal junction

[1]Bang et al, Abstract 4556, ASCO 2009

Primary end point: OS



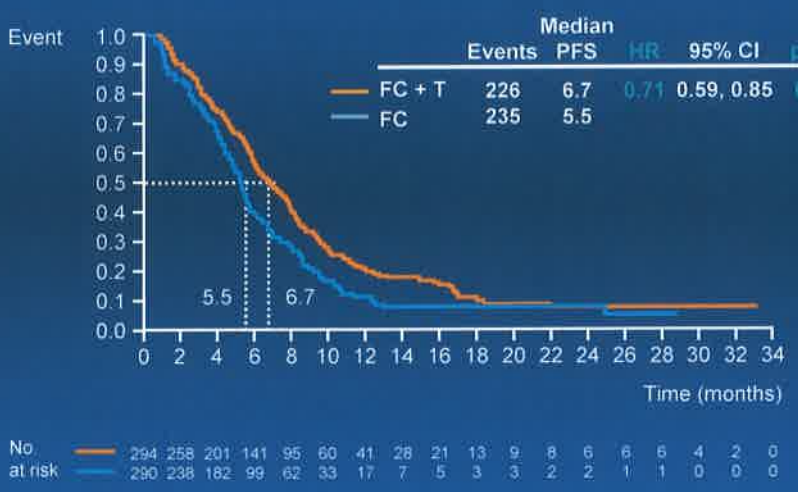
	Median Events	OS	HR	95% CI	p value
FC + T	167	13.8	0.74	0.60, 0.91	0.0046
FC	182	11.1			

No at risk																		
FC + T	294	277	246	209	173	147	113	90	71	56	43	30	21	13	12	6	4	1	0
FC	290	266	223	185	143	117	90	64	47	32	24	16	14	7	6	5	0	0	0

T, trastuzumab

Van Cutsem E, et al. ASCO 2009 abstract 4509

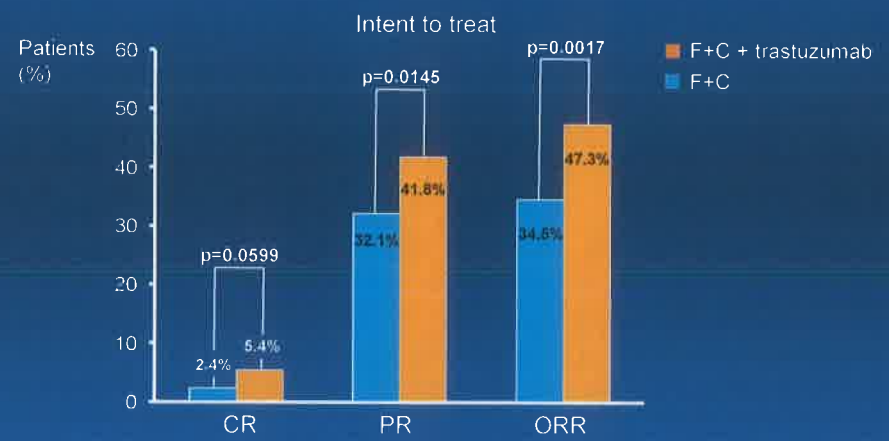
Secondary end point: PFS



	Median Events	PFS	HR	95% CI	p value
FC + T	226	6.7	0.71	0.59, 0.85	0.0002
FC	235	5.5			

No at risk																		
FC + T	294	258	201	141	95	60	41	28	21	13	9	8	6	6	5	4	2	0
FC	290	238	182	99	62	33	17	7	5	3	3	2	2	1	1	0	0	0

Secondary end point: tumor response rate



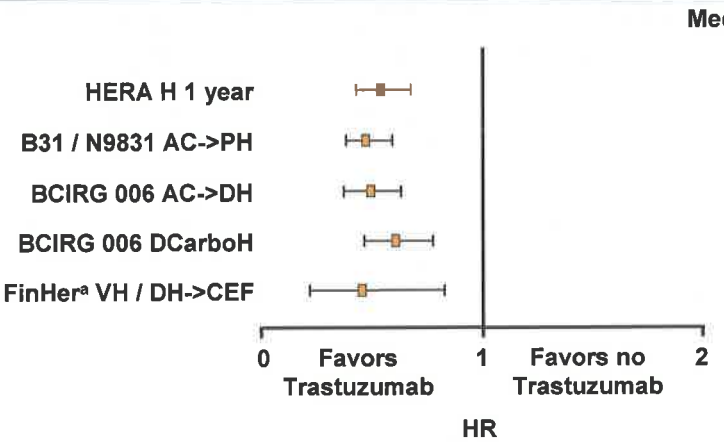
ORR= CR + PR
CR, complete response; PR, partial response

HER2: LESSONS FROM BREAST CANCER

- **HER2 is over-expressed in 15-25% of patients and indicates poor prognosis**
- **HER2 status is defined by ICH or FISH**
- **In HER2 positive patients, trastuzumab is active as single agent and in combination with CT[1], in advanced disease and in the adjuvant setting[2-3]**
- **Trastuzumab, when given concurrently with anthracyclines, increases cardiotoxocity to 27%, but can be given after anthracyclines with a better safety profile[3-4]**

1Vogel et al., JCO 2002; 2Slamon et al., NEJM 2001; 3Smith et al., Lancet 2007; 4Romond et al., NEJM 2005;

ADJUVANT TRASTUZUMAB IN EARLY BREAST CANCER: DISEASE FREE SURVIVAL



Piccart-Gebhart et al 2005; Romond et al 2005; Slamon et al 2005; Joensuu et al 2006

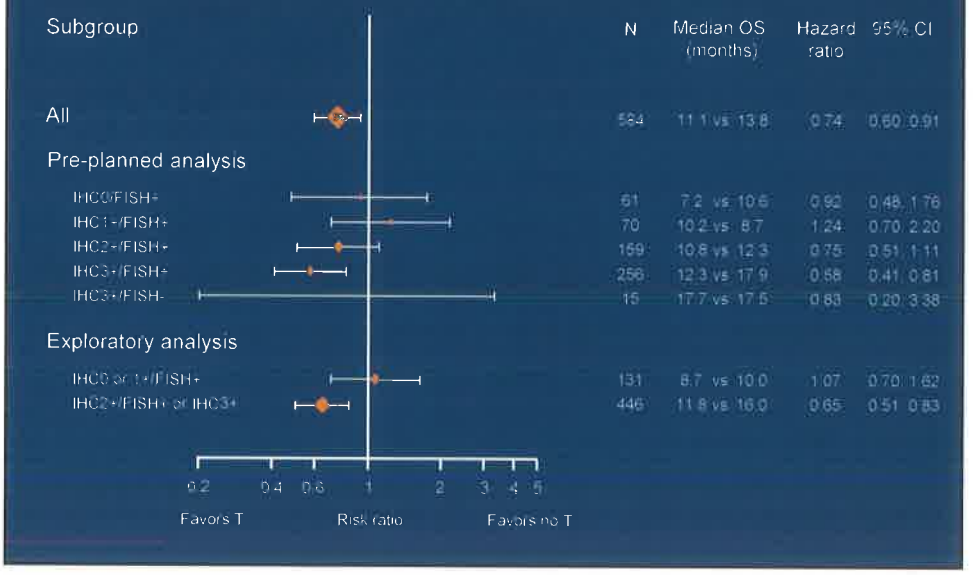
TRASTUZUMAB-RELATED CARDIAC DYSFUNCTION IN EBC TRIALS

EBC trials (1-year Herceptin)	Arm	n	Asymptomatic LVEF decline, %[a]	Severe CHF, %	Cardiac death, n
HERA[b]	H 1 year	1678	3.0	0.6	0
NSABP B-31	AC□PH	947	NR	3.8[cum (5 yr)]	0
NCCTG N9831	AC□PH	570	NR	3.3[cum (3 yr)]	0
BCIRG 006	AC□DH	1068	18.0	1.9	0
	DCarboH	1056	8.6	0.4	0

EBC, early breast cancer; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; [cum], cumulative incidence; Carbo, carboplatin
[a]Data not comparable due to different assessment criteria; [b]1-year median follow-up

Slamon et al 2006; Rastogi et al 2007; Smith et al 2007; Perez et al 2008

Efficacy: OS by HER2 status

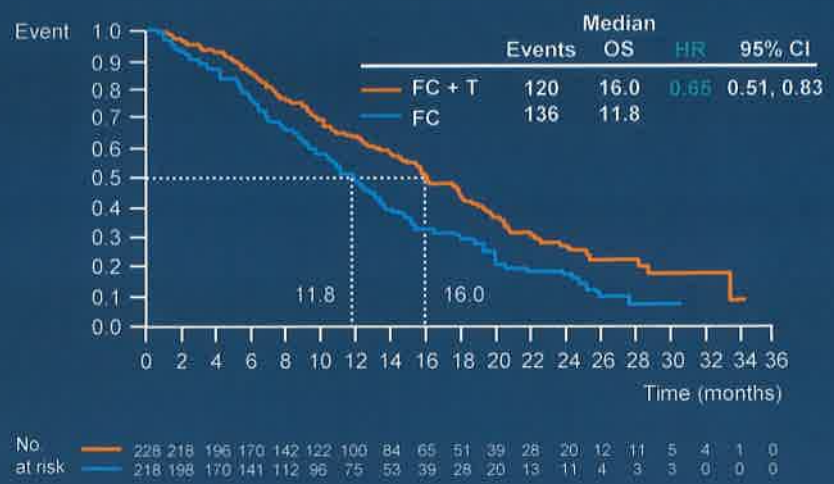


OPTIMAL THRESHOLD DEFINING HER-2 STATUS

- In the exploratory pooled analysis of patients with ICH 3+ and ICH 2+ with FISH +ve, median overall survival increased to 16 months from 11.8 months
- Those criteria are similar to those recommended in breast cancer guidelines[1]
- In ToGA, only 5% of eligible patients had ICH 2 or 1+ with FISH negative[2]
- Magnitude of the benefit of trastuzumab could be greater than observed in ToGA trial if those guidelines to define HER2 status were applied to gastric cancer

1 Wolff et al., JCO 2007; 2 Bang et al., ASCO 2008

OS in IHC2+/FISH+ or IHC3+
(exploratory analysis)



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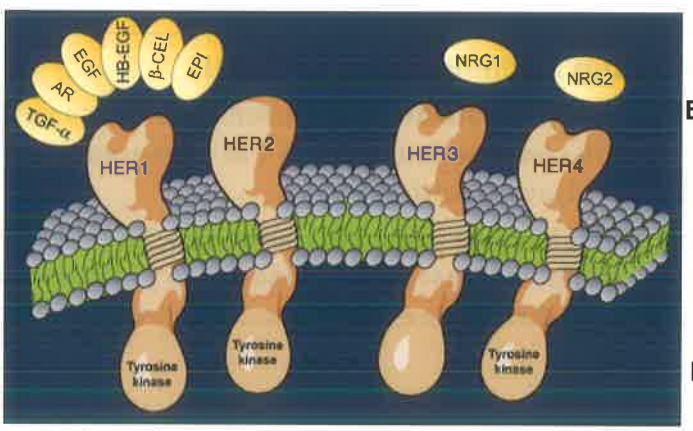
1Vogel et al., JCO 2002; 2Slamon et al., NEJM 2001; 3Smith et al., Lancet 2007; 4Romond et al., NEJM 2005;

ToGA TRIAL: TOXICITY DERIVED FROM THE ADDITION OF TRANSTUZUMAB

- **No increase in hematological or GI toxicity**
- **No increase in clinicaly detected cardiac events, but a higher rate of asymptomatic decrease of LVEF (4.6% vs 1,1 %)**
- **The median duration of transtuzumab treatment is shorter than in breast cancer trials (4.9 months)**
- **Cardiotoxicity might be more prevalent when used in other settings (perioperative, with anthracyclines or after second line therapy)**

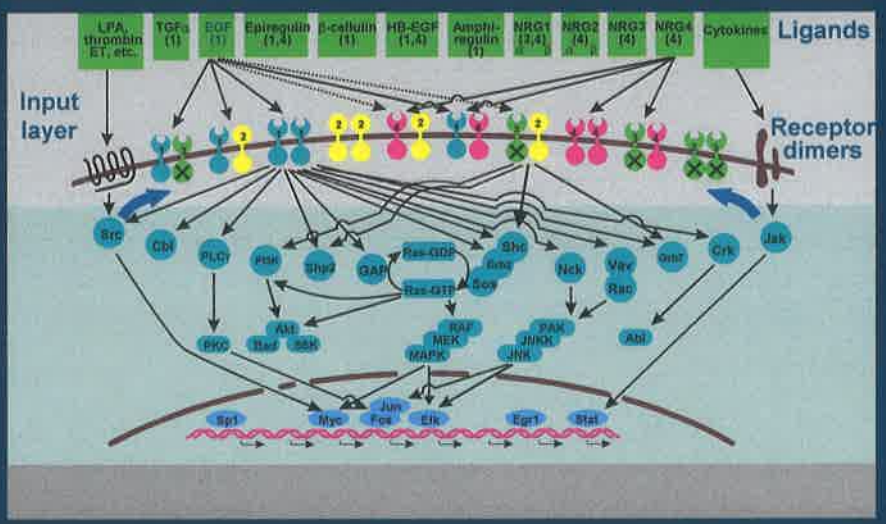
The HERs, a dysfunctional family of receptors

The epidermal growth factor family of receptors comprises 4 transmembrane proteins with distinct properties, which all regulate cell proliferation



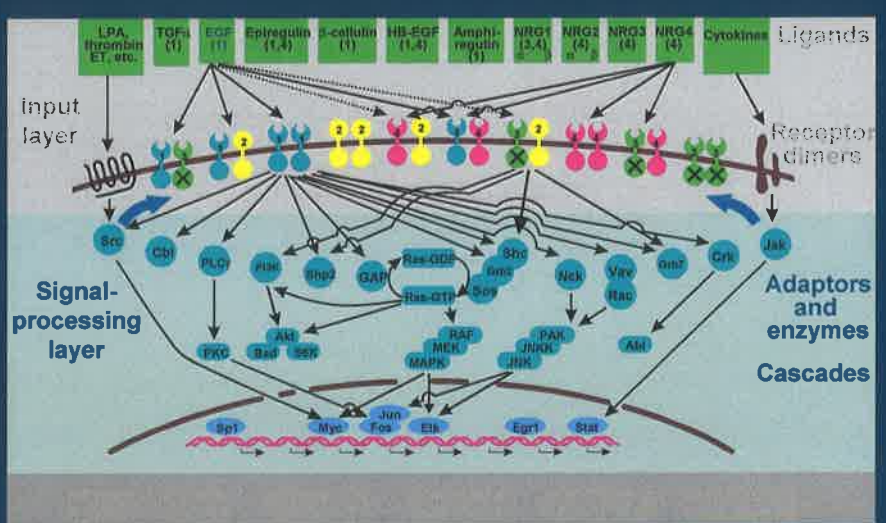
Adapted from Tzahar and Yarden. *Biochim Biophys Acta*. 1998;1377:M25.

The HER signalling network



Yarden Y, Sliwkowski M. Nat Rev Mol Cell Biol 2001;2:127–37

The HER signalling network (cont'd)



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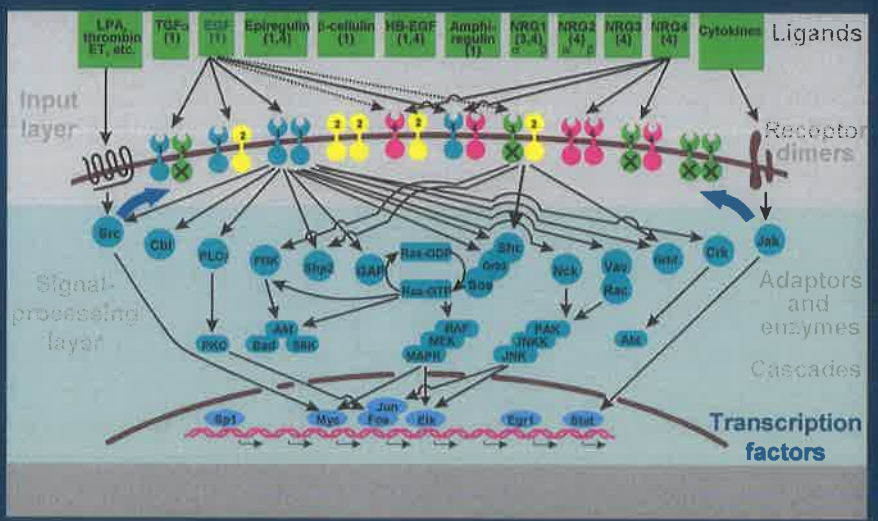
The HER signalling network (cont'd)



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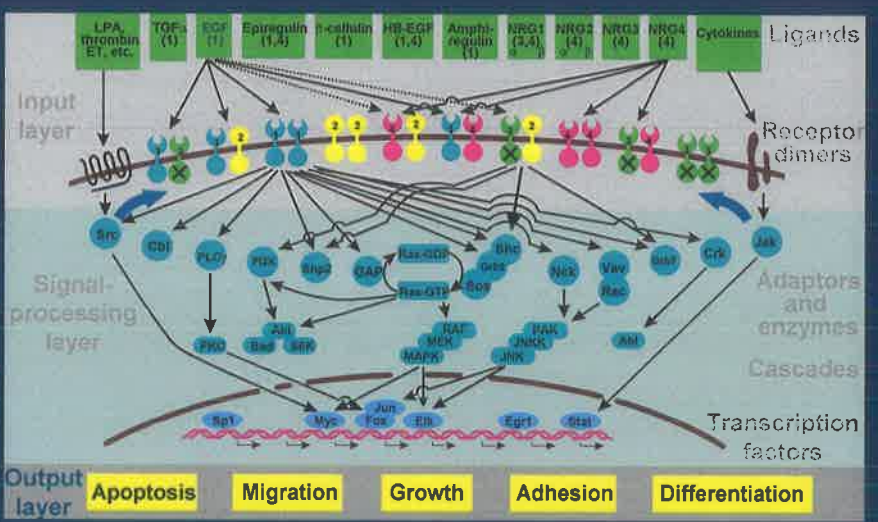
The HER signalling network (cont'd)



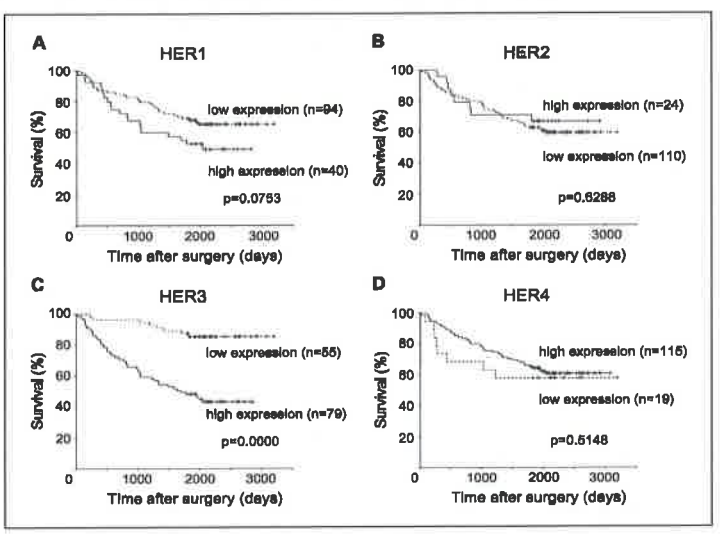
Yarden Y, Sliwkowski M. Nat Rev Mol Cell Biol 2001;2:127–37

HER2: LESSONS FROM BIOLOGY

- **MECHANISMS OF RESISTANCE TO TRANSTUZUMAB**
  - **PRESENCE OF HER2 C TERMINAL FRAGMENTS (p95HER2)**
  - **INCREASED SIGNAL FROM EGFR/ERBB3**
  - **PTEN LOSS OF FUNCTION AND ACTIVATION OF THE PI3K AKT m-TOR PATHWAY**
  - **LATERAL SIGNALING BY OTHER RECEPTOR FAMILIES**

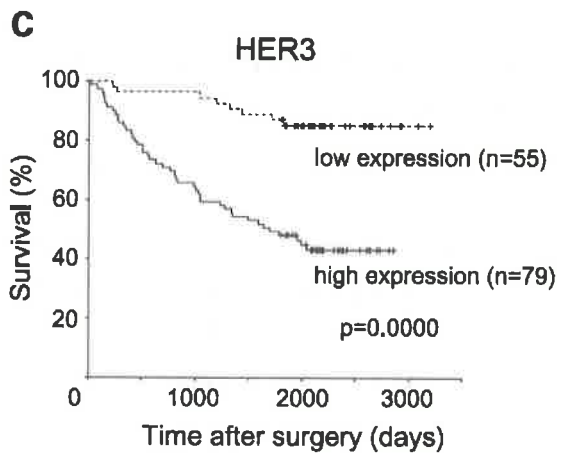
BASELGA J AND SWAIN SM CANCER NAT REV 2009

HIGH EXPRESSION OF HER3 IS ASSOCIATED WITH A DECREASED SURVIVAL IN GASTRIC CANCER



HAYASHI M, et al. Clin Cancer Res 2008

HIGH EXPRESSION OF HER3 IS ASSOCIATED WITH A DECREASED SURVIVAL IN GASTRIC CANCER



HAYASHI M, et al. Clin Cancer Res 2008

What are the active drugs that have shown non inferiority in randomized trials?

- 5-Fluorouracil
- Oral Fluoropirymidines (Capecitabine, S1, UFT)
- Anthracyclines?
- Cisplatin
- Oxaliplatin
- Docetaxel
- CPT-11
- Trastuzumab

REAL-2: First line phase 3 trial in oesophagogastric cancer

ITT=1002
PPP=961

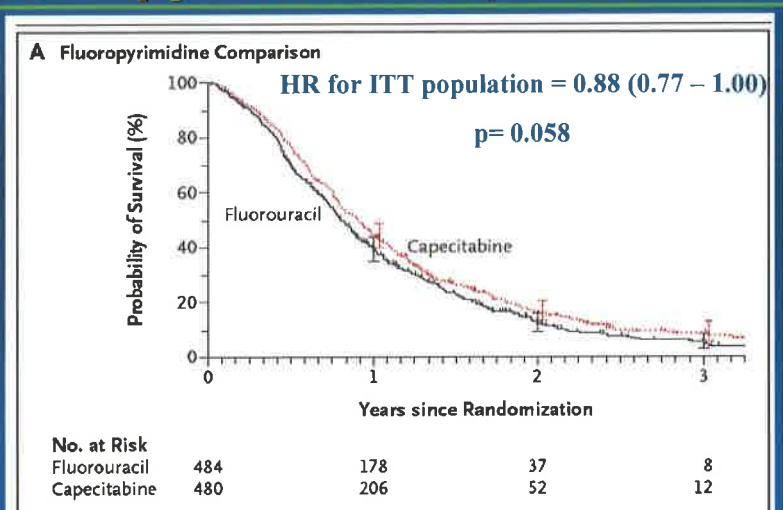
- ECF
- ECX
- EOF
- EOX

- Primary end point of demonstrating non-inferiority in both PPP comparisons for survival was met (upper limit of CI of HR<1.23)

Arm	No. (ITT)	OS		ORR, %
		Med, mo	1yr	
ECF	263	9.9	37.7%	40.7%
EOF	250	9.3	40.4%	42.4%
ECX	245	9.9	40.8%	46.4%
EOX	244	11.2	46.8%	47.9%

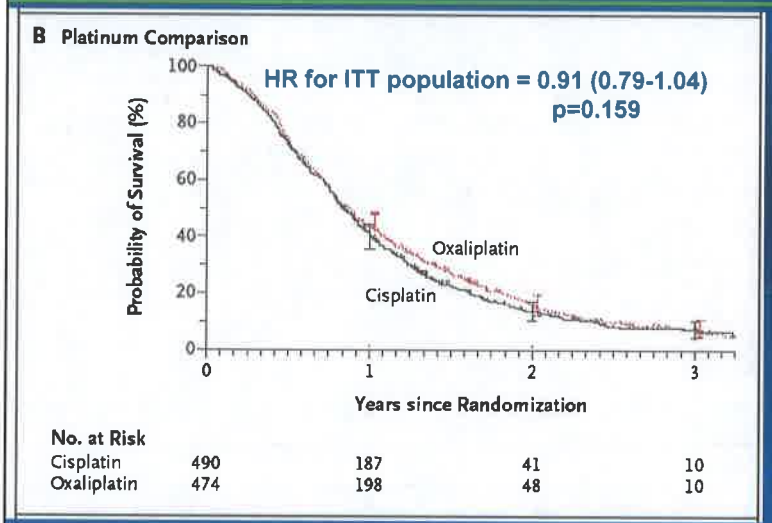
Cunningham et al, NEJM 2008

REAL-2: Overall survival fluoropyrimidin comparison



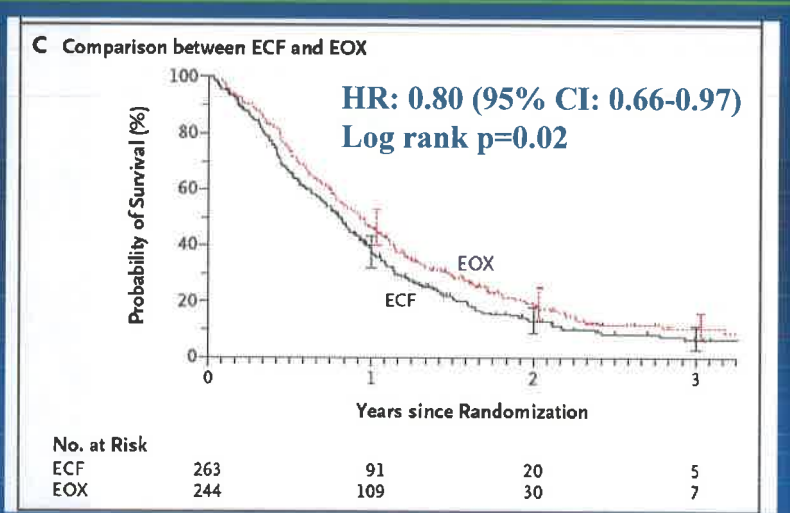
Cunningham et al, NEJM 2008

REAL-2: Overall survival platinum comparison



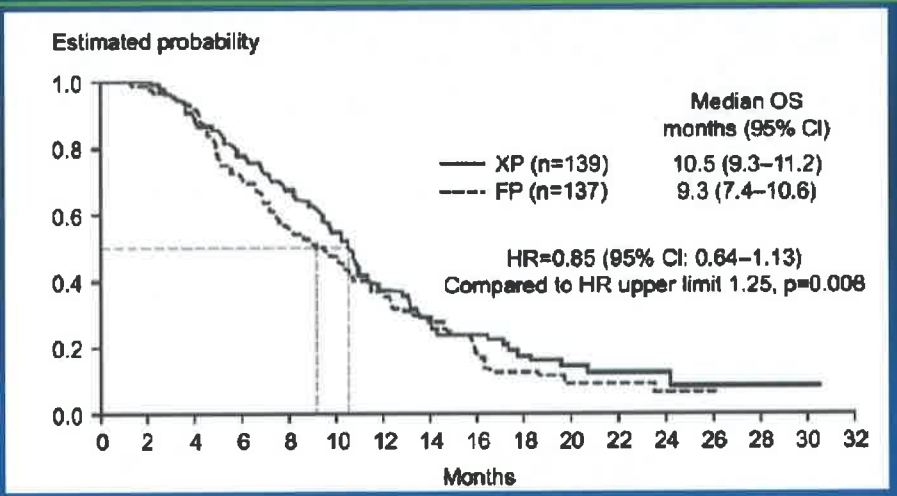
Cunningham et al, NEJM 2008

REAL-2: Overall survival: ECF vs EOX comparison



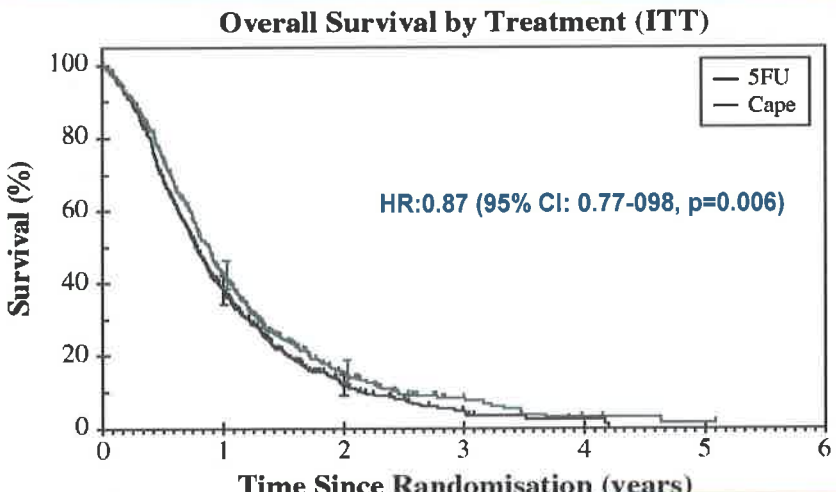
Cunningham et al, NEJM 2008

5-FU CDDP VERSUS CAPECITABINE-CDDP. A RANDOMISED PHASE III NONINFERIORITY TRIAL (ML17032)



Kang YK et al, Ann Oncol 2009

5-FU VERSUS CAPECITABINE
A META-ANALYSIS OF REAL2 AND ML17032



Okines AFC et al, Ann Oncol 2009

5-FU, LV, Oxaliplatin (FLO) vs. 5-FU, LV, Cisplatin (FLP) in Advanced Gastroesophageal Adenocarcinoma

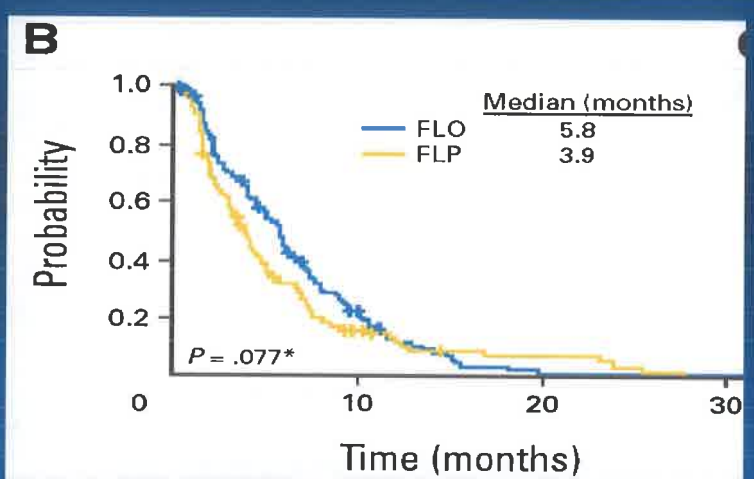
220 patients with advanced gastric cancer:

RANDOMIZE

- 5-FU 2,600mg/m²/24hr + Leucovorin 200mg/m² + Oxaliplatin 85mg/m² } Q 2 weeks
- 5-FU 2,000mg/m²/24hr + Leucovorin 200mg/m² + Cisplatin 50mg/m² } Q 2 weeks

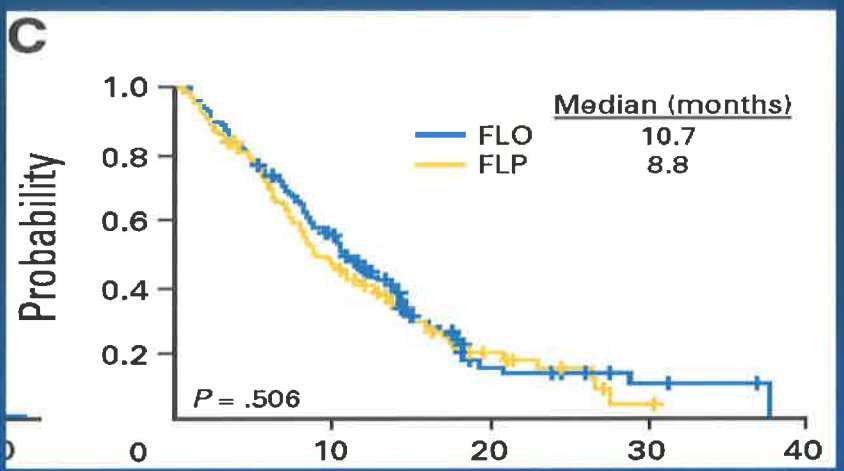
Al-Batran SE et al, J Clin Oncol 2009

OXALIPLATIN VERSUS CISPLATIN
A RANDOMISED PHASE III TRIAL OF FLO VS FLP PROGRESSION FREE SURVIVAL



Al-Batran SE et al, J Clin Oncol 2009

OXALIPLATIN VERSUS CISPLATIN
A RANDOMISED PHASE III TRIAL OF FLO VS FLP
OVERALL SURVIVAL



Al-Batran SE et al, J Clin Oncol 2009

Irinotecan and Gastric Cancer

CPT11 usually done in CRC (FOLFIRI):
Well known and managed drug

- Many phases II studies:
  - Anti-tumoral activity in gastric cancer
  - Usually combined with 5FU
  - Good safety profile
- One large randomized phase II study (LV5FU2 vs LV5FU2 – Platine vs FOLFIRI):
  - In favour of FOLFIRI regimen (RR, PFS, OS, tolerance)
- One large phase III study (IF vs Platine-5FU):
  - Non inferiority of IF vs PF

Bouché O et al. J Clin Oncol. 2004;22:4319-4328
Dank M et al. Ann Oncol. 2008;19(8):1450-7.
Curran D et al. Qual. Life Res. 2009;18:853-61.

FFCD-GERCOR-FNCLCC 03-07 Phase III Study

Stratification :

- Mesurable or not
- PS $_{WHO}$ 0-1 or 2
- Adj (R)CT or not
- Linitis or not
- Cardial or gastric
- Center

R

A: ECX until progression ; then **FOLFIRI** 2d line

B: FOLFIRI until progression ; then **ECX** 2d line

ECX : D1 = Epirubicin 50 mg/m² (15 min.), Cisplatin 60 mg/m² (1 h) ; D2 to 15 : Capecitabine 1 g/m² x 2/d. D1 = D21
Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)

FOLFIRI : D1 = Irinotecan 180 mg/m² (90 min) + LV 400 mg/m² (2h), 5FU b 400 mg/m², 5FU c.i. 2400 mg/m² (46h). D1 = D14

- **Objective I :** 1st line Time to Treatment Failure (**TTF**)

  Time between Randomisation and: 1/ Progression Or 2/ tt discontinuation Or 3/ Death

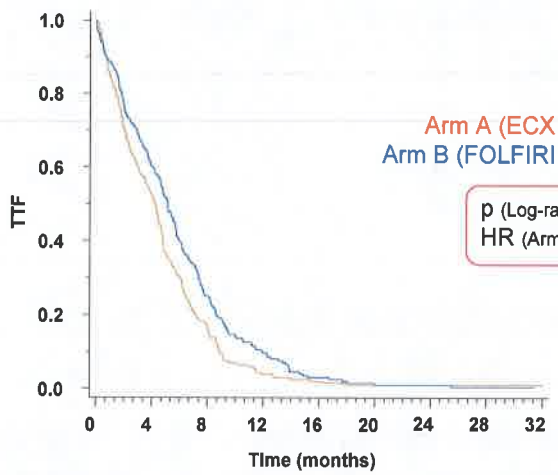
- **Objectives II :** - PFS, OS, (TTF 2d line)
  - Toxicity,
  - Response rate, QoL*

* *QLQC30 et STO-22*
* *Data not shown*

R Guimbaud et al, ESMO 2010

95

Primary end point :
1st line Time To Treatment Failure



Arm A (ECX 1st line) : 4.24 m [3.48; 4.65]
Arm B (FOLFIRI 1st line) : 5.09 m [4.53; 5.68]

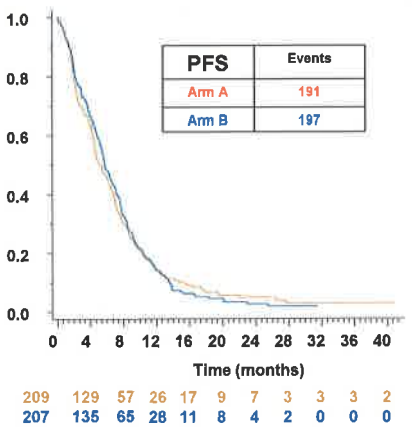
p (Log-rank)= **0.008**
HR (Arm B vs Arm A)= **0.77** [0.63;0.94]

	Events
Arm A	203
Arm B	203

96

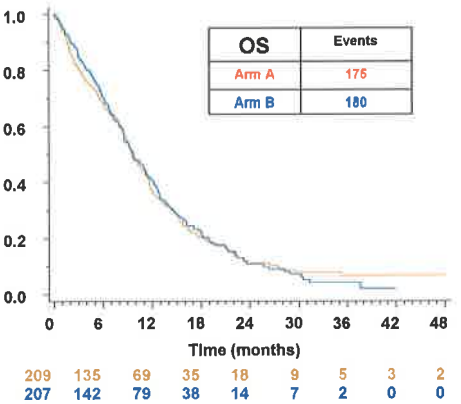
Progression Free Survival and Overall Survival

Arm A (ECX 1st line) : **5.29 m.** [4.53;6.31]
Arm B (FOLFIRI 1st line) : **5.75 m.** [5.19; 6.74]
p (Log-rank)= 0.96
HR (B vs A)= 0.99 [0.81; 1.21]



PFS	Events
Arm A	191
Arm B	197

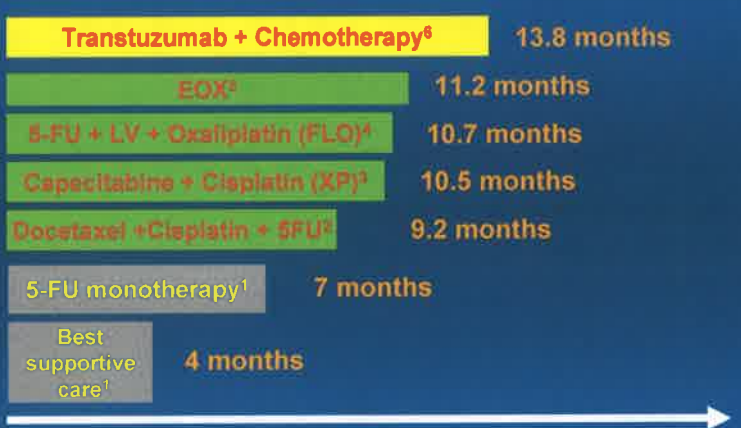
Arm A (ECX 1st line) : **9.49 m.** [8.77; 11.14]
Arm B (FOLFIRI 1st line) : **9.72 m.** [8.54; 11.27]
p (Log-rank)= 0.95
HR (B vs A)= 1.01 [0.82; 1.24]



OS	Events
Arm A	175
Arm B	180

97

HAVE WE MADE ANY PROGRESS IN THE TREATMENT OF ADVANCED GASTRIC CANCER?



MEDIAN OVERALL SURVIVAL IN ADVANCED GASTRIC CANCER

1. Wagner A, et al. JCO 2003, 2. van Cutsen E, et al. JCO 2006. 3.Kang YK et al. Ann Oncol 2009. 4. Al Batran SE, et al. JCO 2009. 5. Cunningham D, et al. NEJM 2007. 6.van Cutsen E, et al. ASCO 2009.

HAVE WE MADE ANY PROGRESS IN THE TREATMENT OF ADVANCED GASTRIC CANCER?

ABSOLUTE INCREASE IN MEDIAN SURVIVAL IN ADVANCED GASTRIC CANCER

1. Wagner A, et al. JCO 2003. 2. Kaizumi W,et al, Lancet Oncol 2008. 3 van Cutsen E, et al. JCO 2006. 4.Kang YK et al, Ann Oncol 2009. 5. Al Batran SE, et al. JCO 2009. 6. Cunningham D, et al. NEJM 2007. 7.van Cutsen E, et al. ASCO 2009.

HAVE WE MADE ANY PROGRESS IN THE TREATMENT OF ADVANCED GASTRIC CANCER?

RISK OF DEATH REDUCTION IN ADVANCED GASTRIC CANCER

1. Wagner A, et al. JCO 2003, 2. van Cutsen E, et al. JCO 2006, 3.Kang YK et al, Ann Oncol 2009. 4. Al Batran SE, et al. JCO 2009. 5. Cunningham D, et al. NEJM 2007. 6.van Cutsen E, et al. ASCO 2009.

AVAGAST: first phase III randomised trial with bevacizumab in gastric cancer

Inoperable locally advanced or metastatic cancer of stomach or GEJ (n=774)

R

XP* + bevacizumab 7.5mg/kg q3w

XP* + placebo q3w

Stratification factors
1. Geographic region
2. Chemotherapy backbone
3. Disease status

*5-FU also allowed
Capecitabine 1,000 mg/m² bid, days 1–21
Cisplatin 80 mg/m², day 1
Maximum of 6 cycles of cisplatin
Capecitabine and bevacizumab/placebo until PD

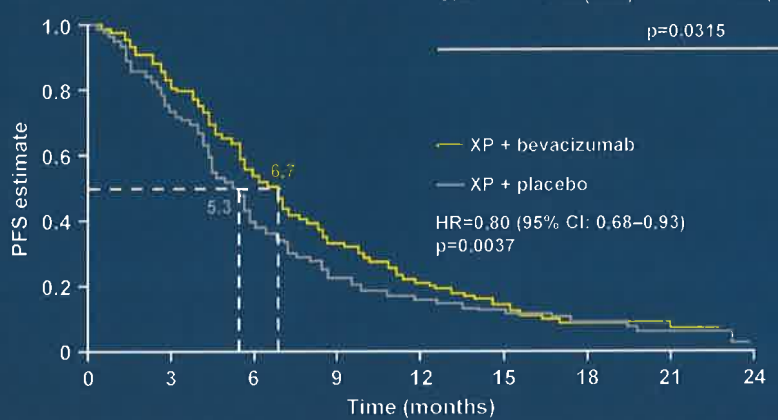
- Primary endpoint: OS
- Secondary endpoints:
  PFS, TTP, ORR, duration of response, safety, QoL, biomarkers

Available at:
http://clinicaltrials.gov/ct2/show/NCT00548548

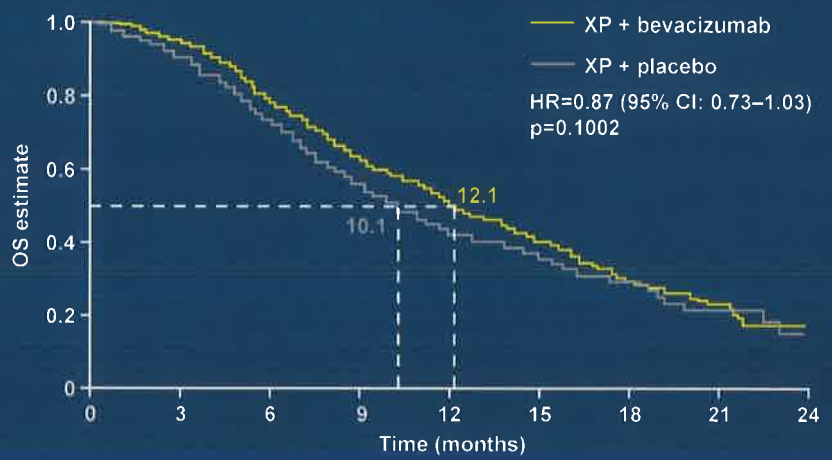
XP = capecitabine/cisplatin; GEJ = gastroesophageal junction

Secondary endpoints: PFS and RR

	XP + bevacizumab (n=387)	XP + placebo (n=387)
ORR	143 (46%)	111 (37%)
	p=0.0315	



Primary endpoint: OS



GASTRIC CANCER: SECOND LINE CHEMOTHERAPY

Irinotecan versus best supportive care (BSC) as 2nd-line therapy in gastric cancer

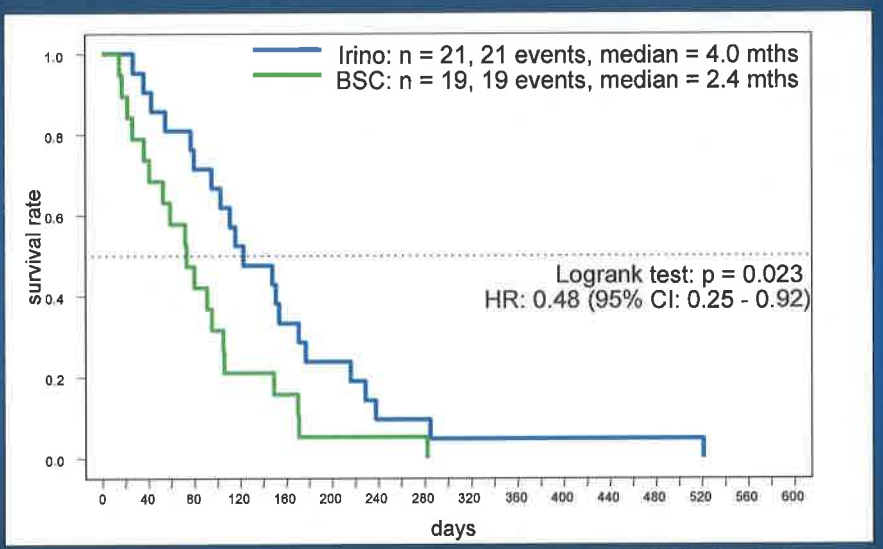
R

- Arm A: Irinotecan 250 mg/m² q3w (1st cycle) to be increased to 350 mg/m², depending on toxicity *
- Arm B: BSC

120 patients planned to be included
Trial closed due to poor accrual (40 patients in 50 months)

Thuss-Patience PC et al, ECCO/ESMO 2009 abstr 6504

Overall survival (ITT-Population)



Thuss-Patience PC et al, ECCO/ESMO 2009 abstr 6504

AIO CHARITÉ

Recommended approach to advanced gastric cancer patients

- Select patients with PS0-1 to participate in clinical trials
- CT should have a palliative role
- Patient reported otcomes of value
- Assess the risk of toxicity vs benefit
- TCF, ECF, EOX, XP or similar schedules of value
- Consider second line therapy for selected patients. More trials on this point are needed

Recommended approach to improve results on gastric cancer patients

- Design better clinical trials within academic and community centers
- International Cooperation
- Biological agents should be studied in randomized trials
- Further studies on better predictive and prognostic biomarkers

MULTIDISCIPLINARY TEAM FOR GASTRO-ESOPHAGEAL CANCER

UNIVERSITY HOSPITAL VALENCIA

- **Radiology**: Marta Rausell
- **Pathology**: Samuel Navarro
- **Surgery**: Fernando López, Roberto Martí, Blas Flor, Salvador Lledó, Vicente Tarrazona
- **Radiation Oncology**: Ana Hernández, Pepe López Torrecilla
- **Medical Oncology**: Desamparados Roda, Alejandro Pérez-Fidalgo, Susana Roselló, Andrés Cervantes

6° Annual Meeting of
Slovenian Medical Oncology Association
Ljubljana 12-13 November, 2010

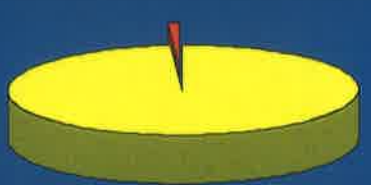
SYMPOSIUM
RARE TUMORS

THYROID CANCER

Rossella Elisei

Department of Endocrinology, University Hospital, Pisa, Italy

THYROID CANCER IS RARE TUMOR
AND REPRESENTS ONLY 1% OF ALL HUMAN TUMORS

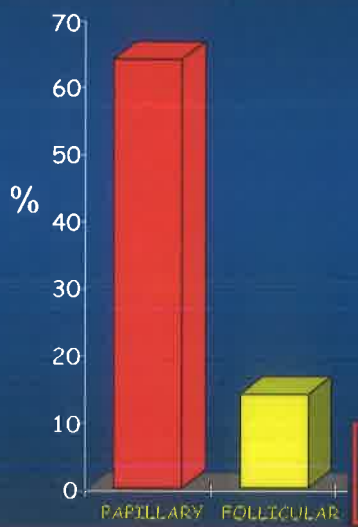


- All human cancer
- Thyroid cancer

MOST FREQUENT CANCER AMONG ALL ENDOCRINE TUMORS !!!

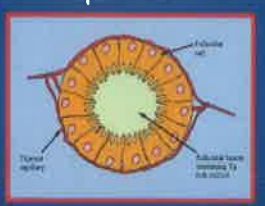
THYROID CANCER HISTOTYPE

(Department of Endocrinology, Pisa)



TSH dependance

Iodine uptake

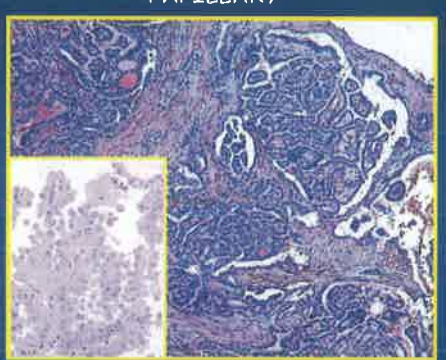


Tg secretion

DIFFERENTIATED THYROID CARCINOMA

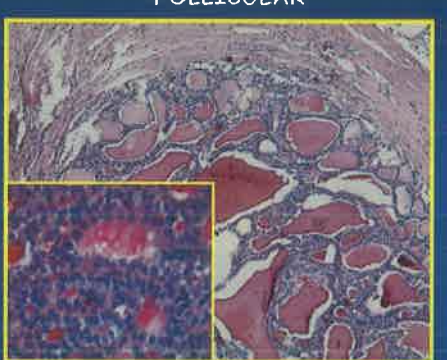
MORPHOLOGY

PAPILLARY



VARIANTS:
a) CLASSIC
b) FOLLICULAR
c) SOLID
d) TRABECULAR
e) COLUMNAR
f) TALL
g) WARTHIN LIKE

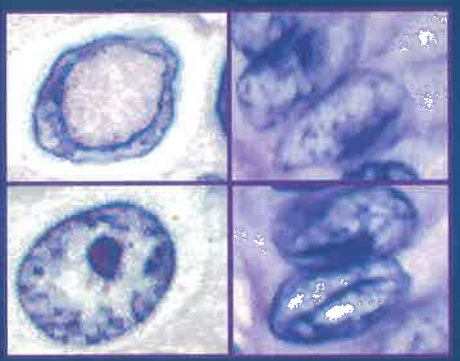
FOLLICULAR



VARIANTS:
a) MINIMALLY INVASIVE
b) WIDELY INVASIVE

PAPILLARY THYROID CARCINOMA
TYPICAL NUCLEAR FEATURES

Nuclear pseudoinclusions



Oval cells

Chromatin clearing margination along nuclear membrane

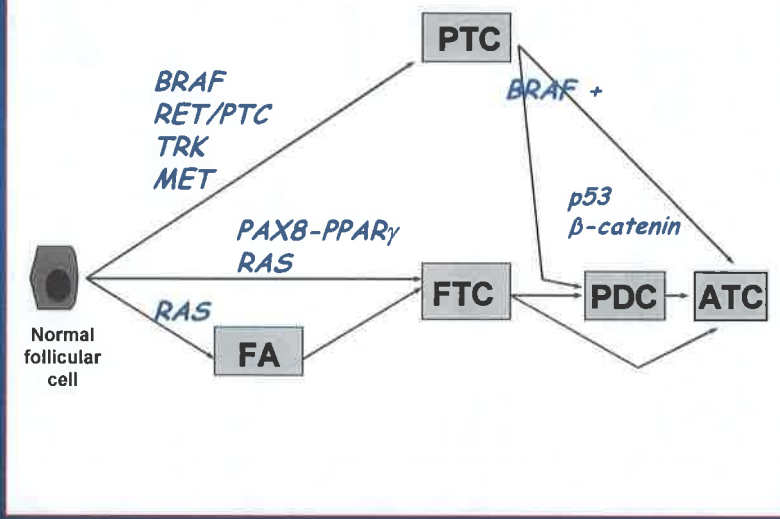
Grooves

GOOD CYTOLOGICAL DIAGNOSIS

FOLLICULAR CARCINOMA
AND
CAPSULAR INVASION

ONLY HYSTOLOGICAL DIAGNOSIS

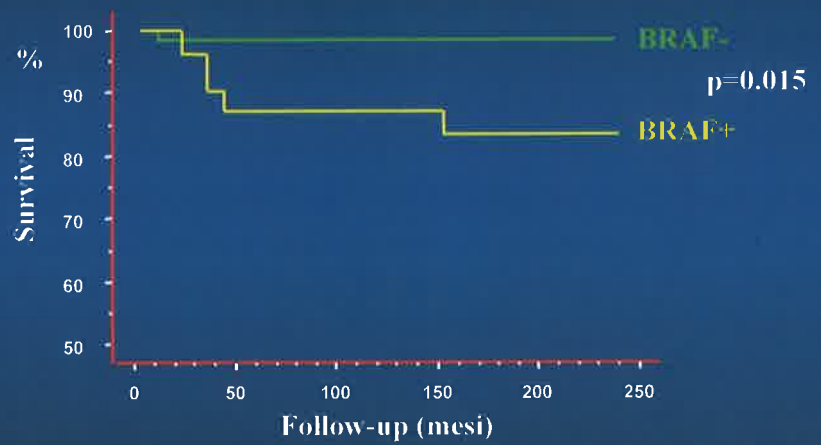
THYROID TUMORIGENESIS: MOLECULAR EVENTS



Meta-analysis (2003-2007) of *oncogene alterations* in thyroid tumors: prevalence in different hystotypes

	Benign nodules	FA	FTC	PTC	PDC and ATC
RET/PTC +	5-10%	5%	0	30%	5%
BRAF +	<1%	<1%	0	45%	20%
H-Ras +	5%	34%	45%	15%*	5%
PAX-8/PPARg +	0	7%	30%	11%	0

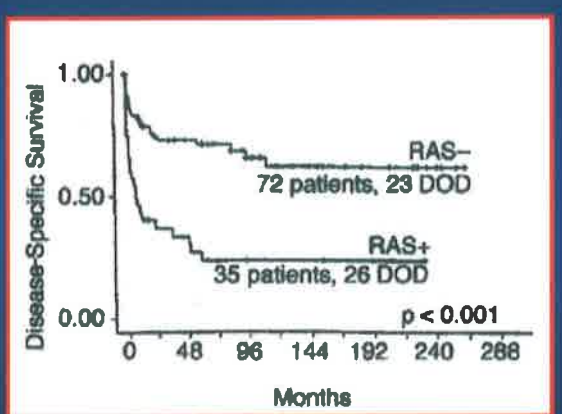
Kaplan-Meier survival analysis



Elisei R et al. JCE&M 2008

Ras mutations as prognostic factors

Survival of thyroid carcinoma patients with (n=35) and without (n=72) ras mutation



Modified from Garcia-Rostan et al J Clin Oncol 2003

THYROID CANCER

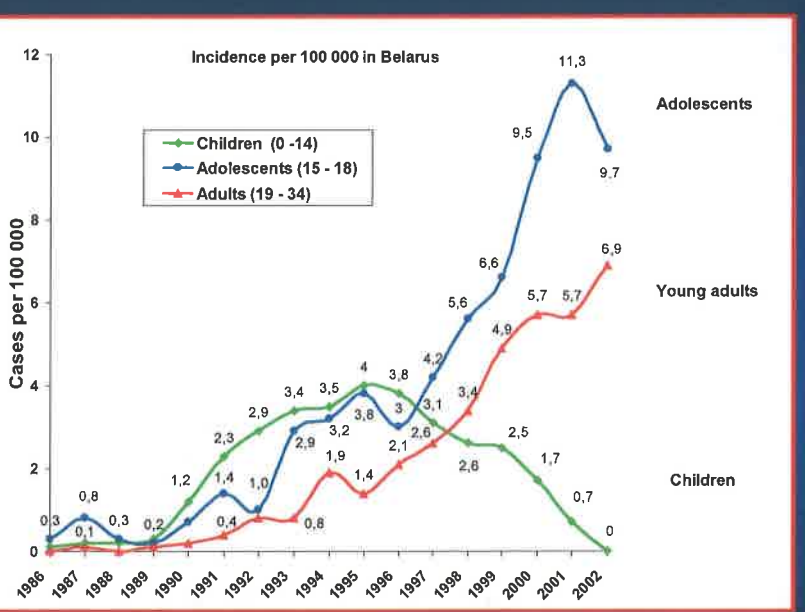
RISK FACTORS

RADIATION AND THYROID CANCER

The Chernobyl Experience

Thyroid cancer in Belarus before and after the Chernobyl accident

Age	1971-1985	1986-2000	Fold of increase
0-14	8	703	87.8
15-18	21	267	12.7
≥19	1465	6719	4.6
Total	1494	7689	5.1



Cardis E et al, J. Radiol Prot 26: 127-140, 2006

Estimated risk of developing thyroid cancer after radiation dose of 1 Gy, by level of soil iodine and potassium iodide supplementation at the time of Chernobyl accident

	OR at 1 Gy (95% CI)	
Consumption of potassium iodide	Highest two tertiles of soil iodine	Lowest tertiles of soil iodine
No	3.5 (1.8 to 7.0)	10.8 (5.6 to 20.8)*
Yes	1.1 (0.3 to 3.6)**	3.3 (1.0 to 10.6)

* Lowest risk

**Highest risk

From Cardis E et al, J Natl Cancer Inst, 97: 724-32, 2005

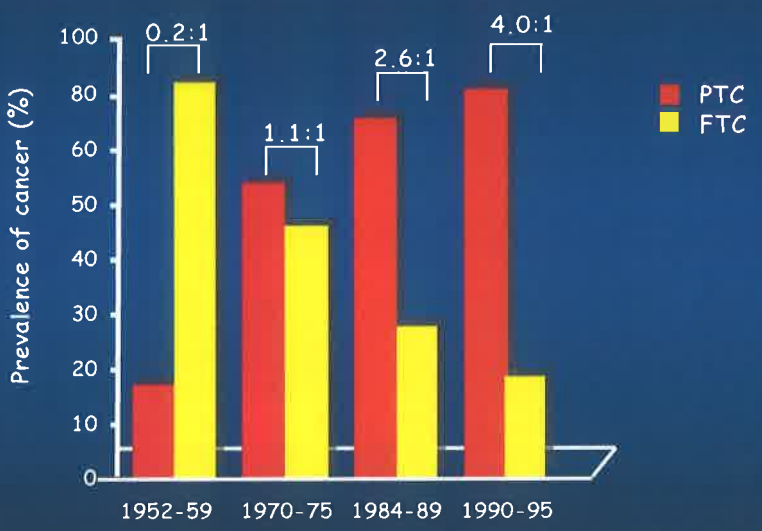
PREVALENCE OF THYROID NODULES AND THYROID CANCER IN 2 SICILIAN AREAS WITH DIFFERENT IODINE CONTENT

	IODINE DEFICIENT AREA (IDA)		IODINE SUFFICIENT AREA (ISA)
CANCER (n.)	27 (3.0%)		139 (5.5%)
NODULES (n.)	911 (4.3%)*		2537 (1.7%)
CANCER (inc)	127/10^5/yr		93/10^5/yr
PAP/FOL ratio	1:1	($p < 0.001$)	3.7:1

*IDA > ISA 2.5

from Belfiore A, Cancer 1987

PTC AND FTC PREVALENCE BEFORE AND AFTER IODINE PROPHYLAXIS IN AUSTRIA

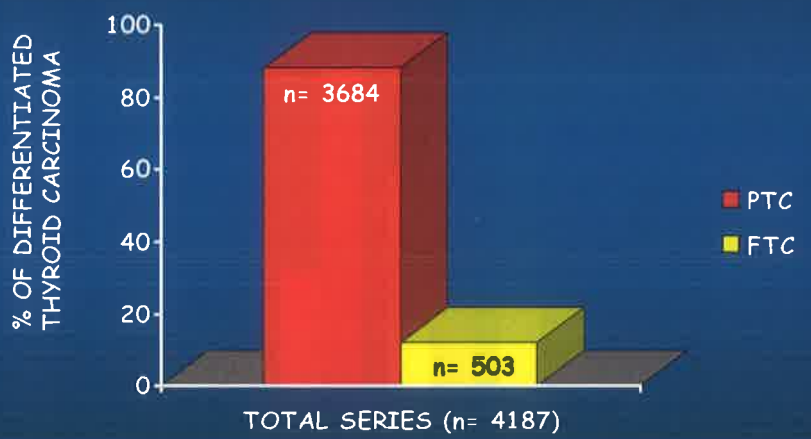


From Lind, Thyroid 2002

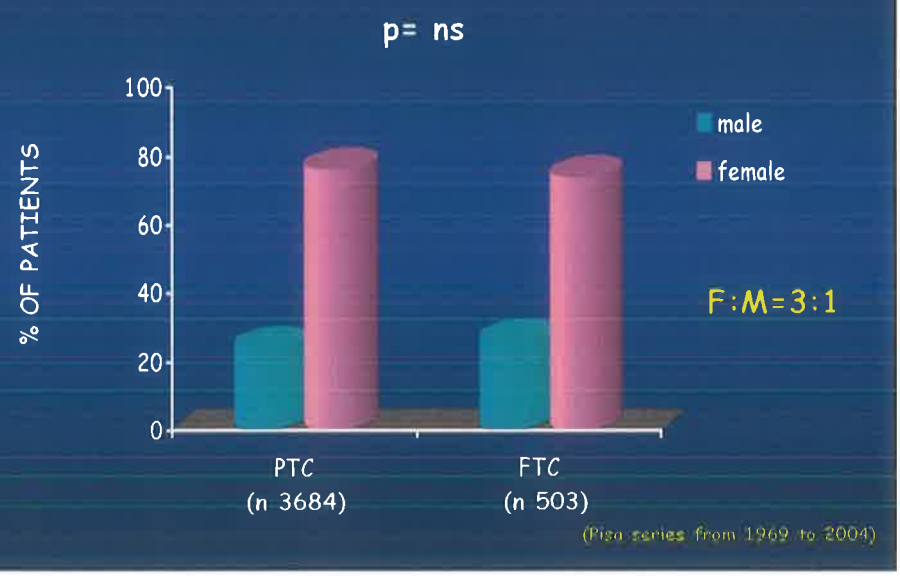
THYROID CANCER

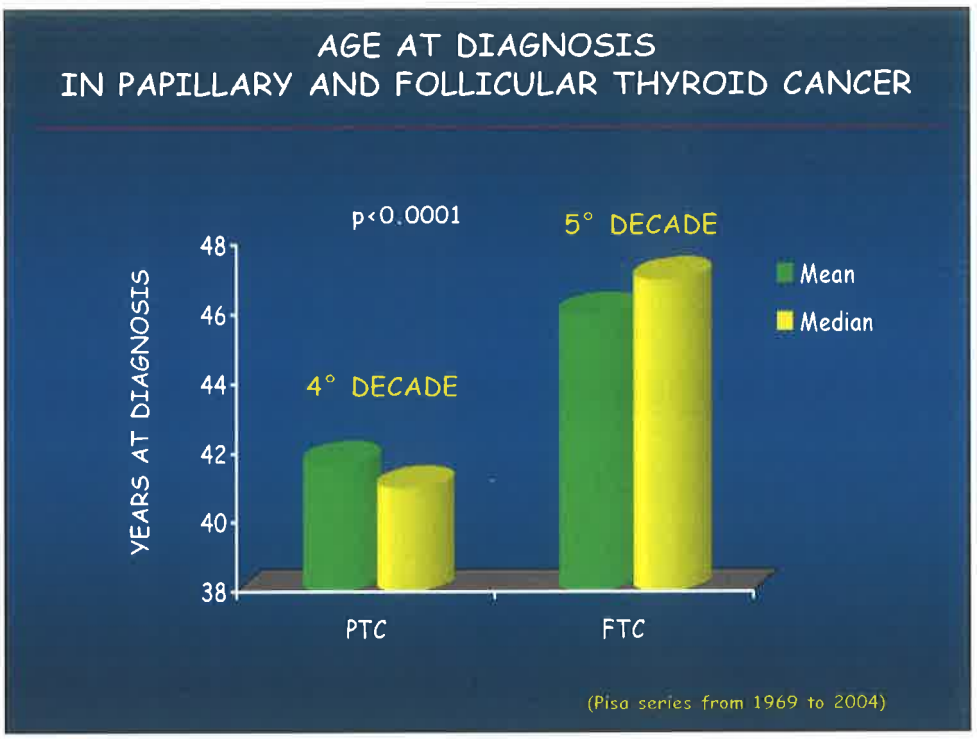
EPIDEMIOLOGY

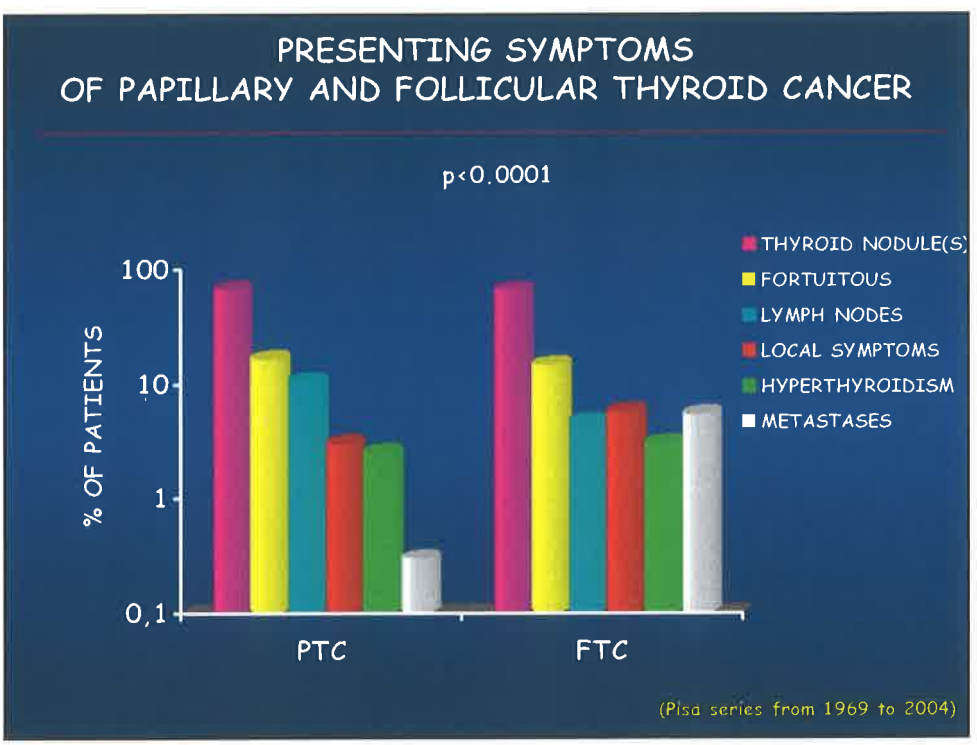
PAPILLARY AND FOLLICULAR HYSTOTYPES IN PISA SERIES 1969-2004



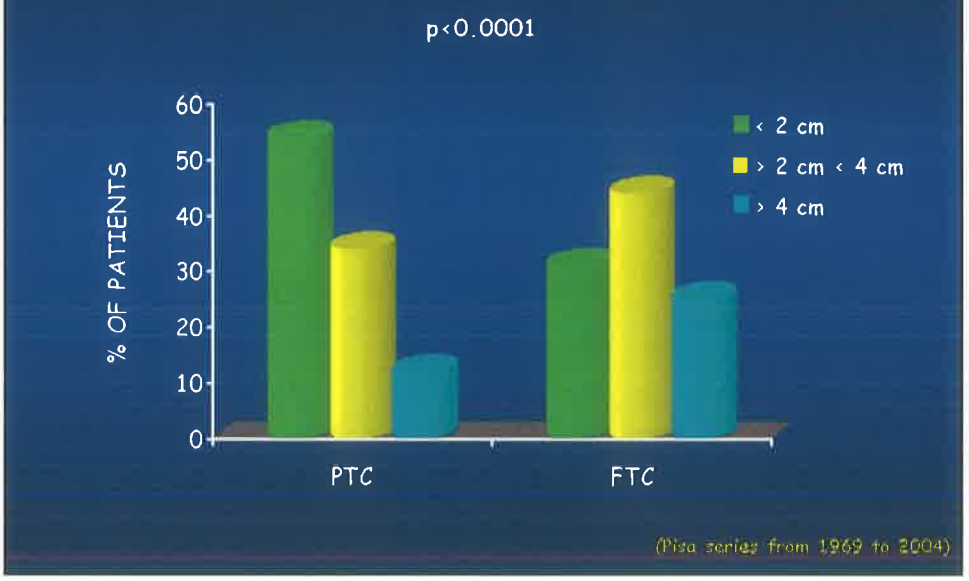
SEX DISTRIBUTION IN PAPILLARY AND FOLLICULAR THYROID CANCER



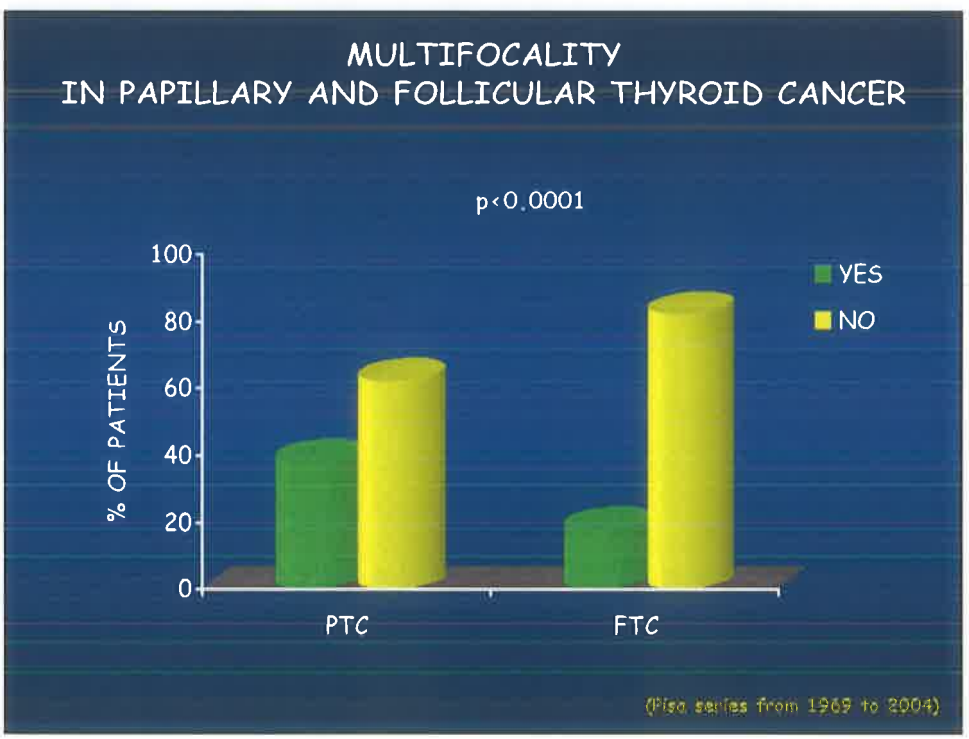

AGE AT DIAGNOSIS
IN PAPILLARY AND FOLLICULAR THYROID CANCER
p<0.0001
5° DECADE
4° DECADE
Mean
Median
YEARS AT DIAGNOSIS
48
46
44
42
40
38
PTC
FTC
(Pisa series from 1969 to 2004)


PRESENTING SYMPTOMS
OF PAPILLARY AND FOLLICULAR THYROID CANCER
p<0.0001
THYROID NODULE(S)
FORTUITOUS
LYMPH NODES
LOCAL SYMPTOMS
HYPERTHYROIDISM
METASTASES
% OF PATIENTS
100
10
1
0,1
PTC
FTC
(Pisa series from 1969 to 2004)

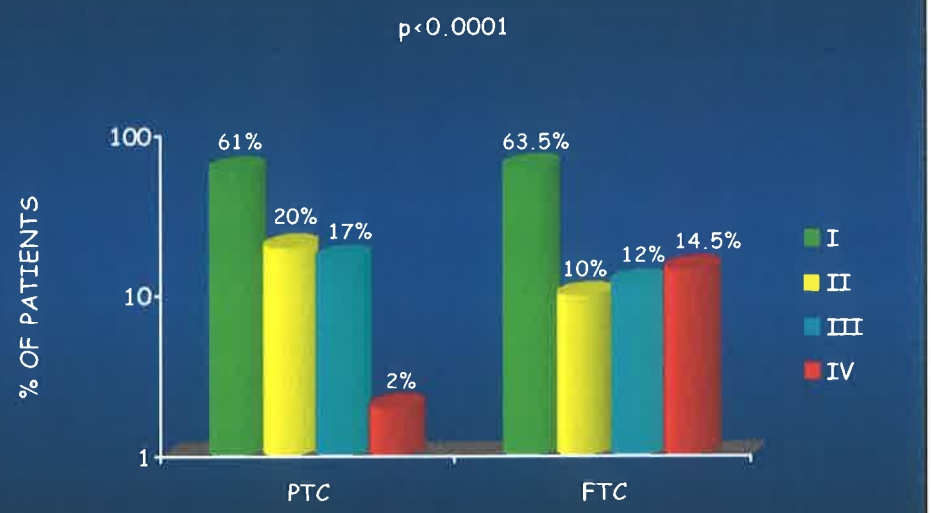
MAXIMUM TUMOR SIZE OF PAPILLARY AND FOLLICULAR THYROID CANCER



MULTIFOCALITY IN PAPILLARY AND FOLLICULAR THYROID CANCER



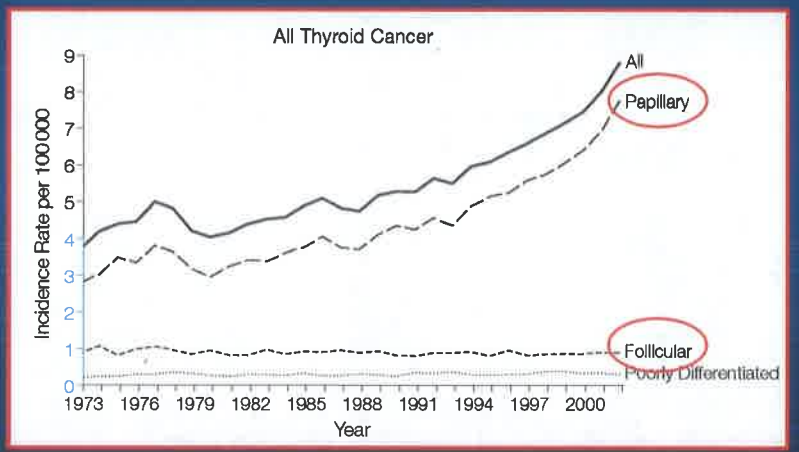
DE GROOT'S CLINICAL CLASSES AT DIAGNOSIS IN PAPILLARY AND FOLLICULAR THYROID CANCER



(Pisa series from 1969 to 2004)

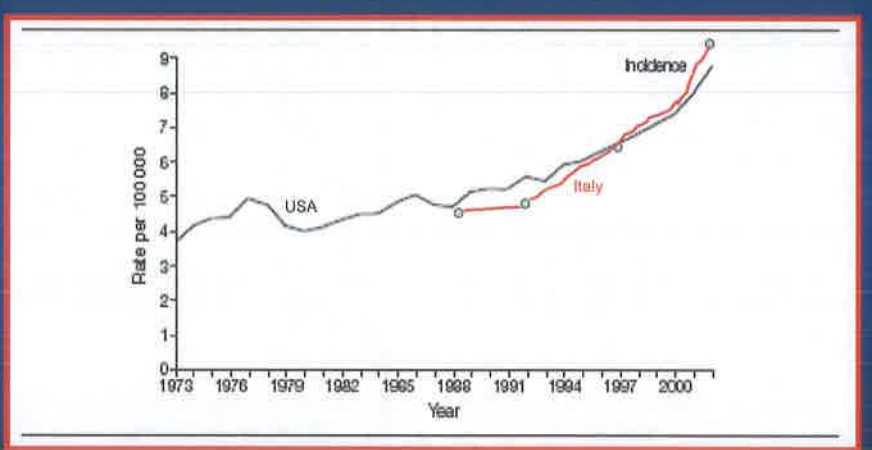
IS THYROID CANCER EPIDEMIOLOGY CHANGING ?

Incidence of thyroid carcinoma in U.S.A. (1973-2002)



Davies & Welch JAMA. 2006;295:2164-2167

Thyroid cancer incidence in USA (1973-2002) and Italy (1988-2002)



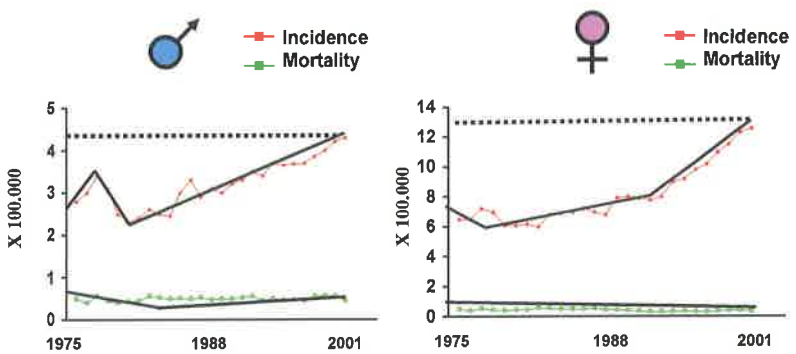
Davies L and Welch G, JAMA, May 10, 2006 compared with the data of the Italian Network of Cancer Registries

… thyroid cancer incidence, *in France*, has dramatically increased over the last 2 decades.

The increased incidence is *8.1% and 6.2 % per year* in females and males respectively.

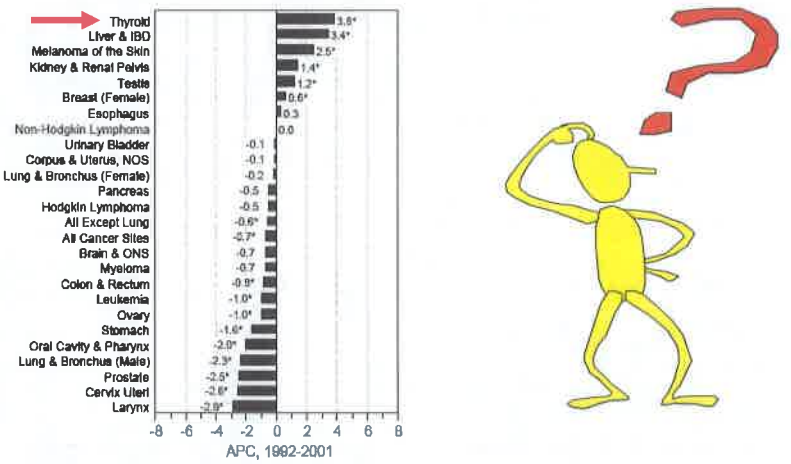
Laurence Leenhardt et al, Thyroid, 2004

Evidence of significant increase of thyroid cancer incidence but not of mortality



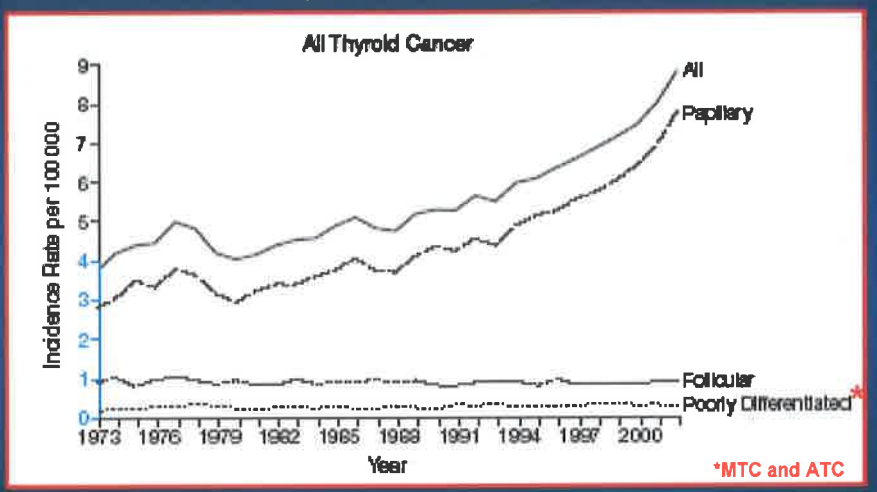
SEER 12 areas and NCHS public use data file

Trends in SEER Incidence by Primary Cancer Site 1992-2001



Source: SEER 12 areas and NCHS public use data file for the total US. Rates are per 100,000 and age-adjusted to the 2000 US standard population by 5-year age groups.
The APC is the Annual Percent Change over the time interval.
* The APC is significantly different from zero (p<.05).

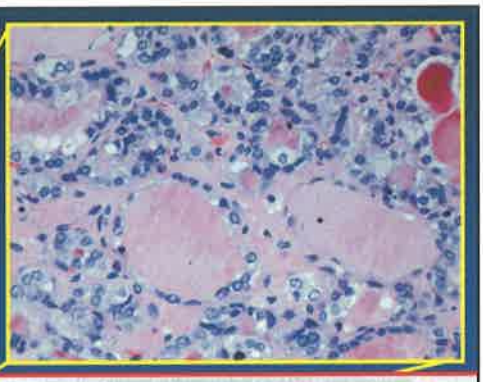
Thyroid cancer incidence in USA (1973-2002)



Davies L and Welch G, JAMA, May 10, 2006 modified with the data of the Italian Network of Cancer Registries

Papillary thyroid cancer Follicular variant

Increased incidence up to 173% according with Gemsenjager E. et al, Swiss Med Wkly 131:157, 2001.



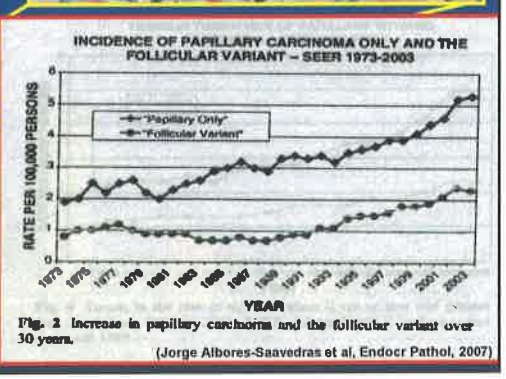
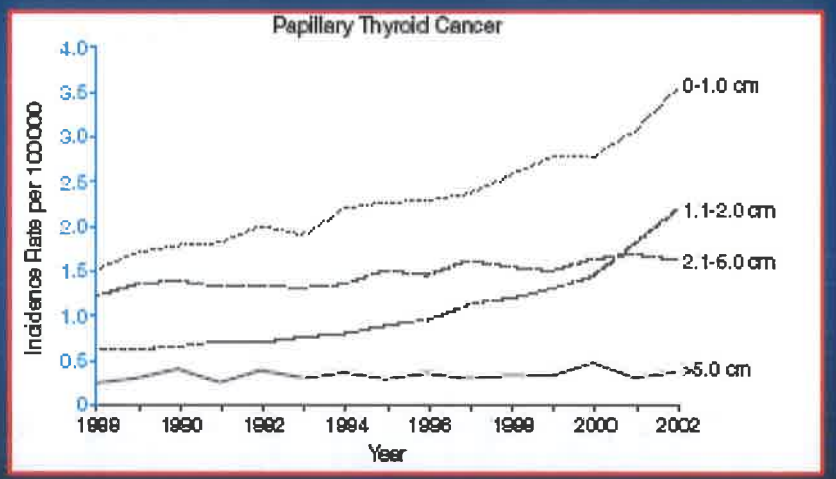


Fig. 2 Increase in papillary carcinoma and the follicular variant over 30 years.

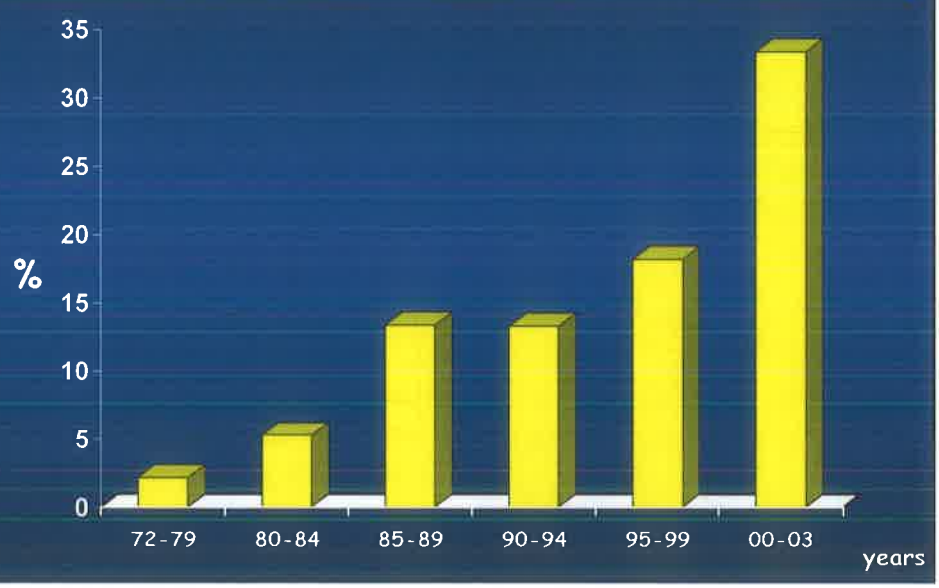
(Jorge Albores-Saavedras et al, Endocr Pathol, 2007)

Trend incidence of papillary thyroid cancer by size in USA (1988-2002)



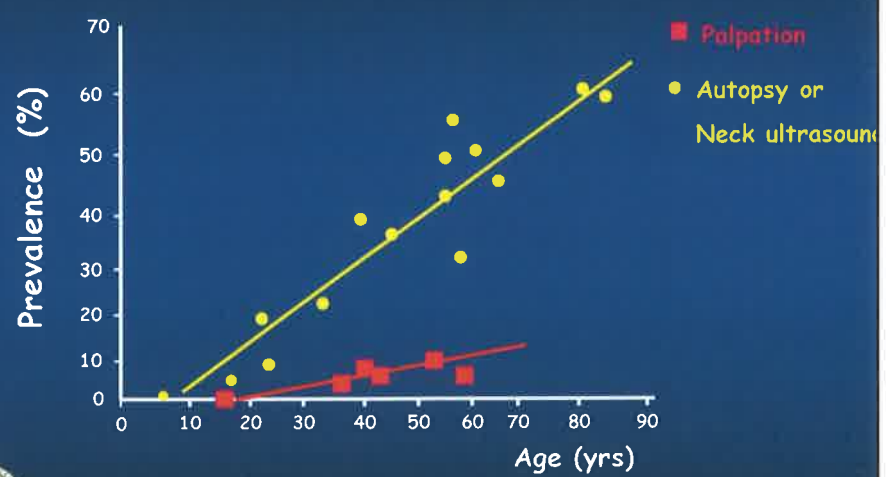
Davies L and Welch G, JAMA, May 10, 2006

Percentage distribution of mPTCs on the overall CTDs (793/4108) diagnosed in Pisa between 1972-2003



Possible reasons to explain this increase of thyroid cancer incidence

Thyroid nodule prevalence



(Mazzaferri et al. 1993)

About 50% of all thyroid nodules escape detection on clinical examination

Thyroid Nodule Prevalence at Autopsy

Author	Subjects (n)	Prevalence (%)	Age
Rice, 1932	390	57	11-75
Hellwig, 1935	100	51.3	5-85
Mortensen,1955	821	49.5	All ages

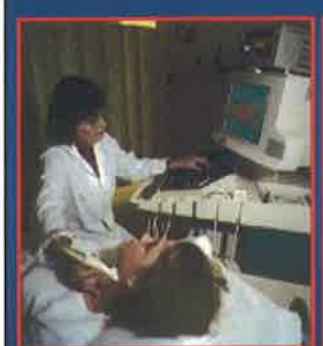
Burguera and Gharib 2000

Thyroid Nodule Prevalence by Palpation

Author	Subjects (n)	Prevalence (%)	Age
Vander, 1968	5127	4.2	30-59
Tunbridge, 1977	2979	3.2	18-75

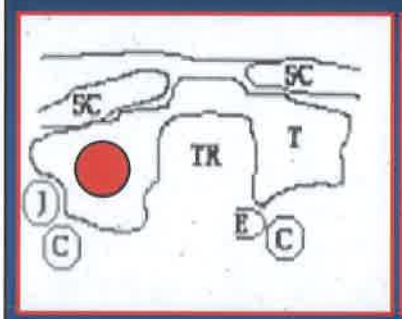
Wang and Crapo 1997

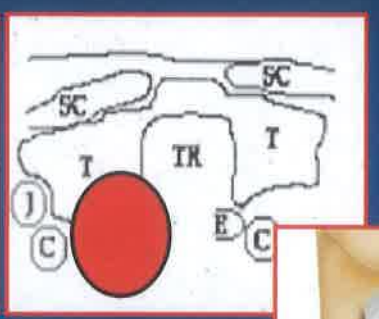
In the '80s: neck ultrasound

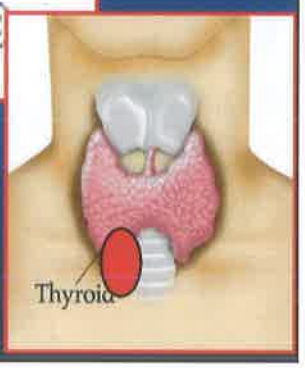


More and more thyroid nodules !!!

Thyroid nodule: not visible, not palpable

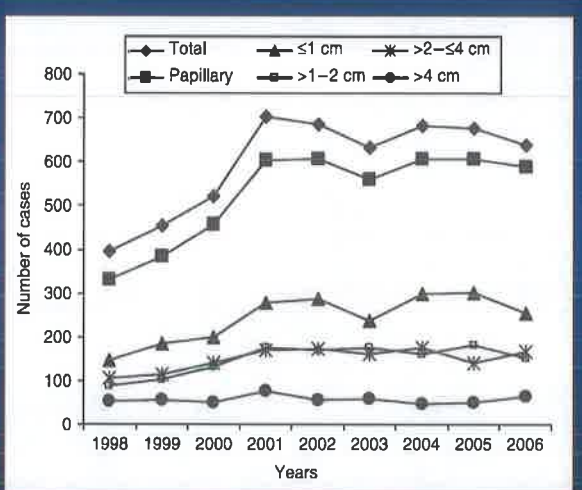






Incidental finding !

Number of cases per year of PTC in relationship to the tumor size
(Rhône-Alpes region tumor registry)



Sassolas G. et al Eur J Endocrinol 160: 71, 2009

Are the Clinical and Pathological Features of Differentiated Thyroid Carcinoma Really Changed over the Last 35 Years? Study on 4187 Patients from a Single Italian Institution to Answer this Question

Rossella Elisei,* Eleonora Molinaro,* Laura Agate, Valeria Bottici, Lucio Masserini, Claudia Ceccarelli, Francesco Lippi, Lucia Grasso, Fulvio Basolo, Generoso Bevilacqua, Paolo Miccoli, Giancarlo Di Coscio, Paolo Vitti, Furio Pacini, and Aldo Pinchera

J Clin Endocrinol Metab, 2010

Changing features of thyroid tumors

	Total series	1969-1989 Group1	1990-2004 Group2	p
N of patients	4187	1215 (29.0%)	2972 (71.0%)	
Sex				
Female	3166 (75.6%)	944 (77.7%)	2222 (74.8%)	0.04
Male	1021 (24.4%)	271 (22.3%)	750 (25.2%)	
Age at diagnosis	42.5 ±14.4 (5-88) Median 42 aa	42.2±15.8 (5-84) Median 41aa	42.6±13.9 (7-88) Median 42 aa	NS (0.56)
Histotype				
Papillary cancer (PTC)	3684 (88%)	979 (80.5%)	2705 (91.0%)	<0.0001
Follicular cancer (FTC)*	503 (12%)	236 (19.5%)	267 (9.0%)	

Changing features of thyroid tumors

	Total series	1969-1989 Group1	1990-2004 Group2	p
N of patients	4187	1215	2972	
Coexisting thyroid diseases				
None	2661 (63.6%)	882 (72.6%)	1779 (59.8%)	<0.0001
Nodular Goiter	1089 (26%)	271 (22.3%)	818 (27.5%)	0.0006
Autoim Thyroiditis		24 (2.0%)	292 (9.9%)	<0.0001
Graves' disease	91 (2.2%)	25 (2.1%)	66 (2.2%)	NS (0.8)
Toxic Adenoma	30 (0.7%)	13 (1.1%)	17 (0.6 %)	NS (0.1)
Neck irradiation	119/3898* (3.2%)	63/1021* (6.1%)	56/2877* (1.9%)	<0.0001

* Information on the radiation exposure was not available in 289 patients: 194 of Group 1 and 95 of Group 2.

Changing features of thyroid tumors

	Total series	1969-1989 Group1	1990-2004 Group2	p
N of patients	3997*	1175*	2822*	
Presenting symptoms				
thyroid nodule	2670 (66.8%)	772 (65.7%)	1898 (67.3%)	NS (0.3)
incidental finding	657 (16.4%)	94 (8.0%)	563 (20.0%)	<0.0001
cervical nodes	396 (9.9%)	200 (17.0%)	196 (7.0%)	<0.0001
local symptoms	134 (3.4%)	58 (5.0%)	76 (2.6%)	0.0005
hyperthyroidism	104 (2.6%)	30 (2.5%)	74 (2.6%)	NS (0.9)
distant metastases	36 (0.9%)	21 (1.8%)	15 (0.5%)	0.0003

Changing features of thyroid tumors

	Total series	1969-1989 Group1	1990-2004 Group2	p
Tumor size: N*	3996	1100	2896	
≤1 cm (mPTC)	923 (23.1%)	87 (7.9%)	836 (28.7%)	<0.0001
>1 cm ≤ 2 cm	1132 (28.3%)	389 (35.4%)	743 (25.8%)	<0.0001
>2 cm <4 cm	1409 (35.3%)	432 (39.3%)	977 (33.7%)	0.002
≥ 4 cm	532 (13.3%)	192 (17.4%)	340 (11.8%)	<0.0001
Local extension: N*	3625	824	2774	
No extrathyroid	2967 (81.8%)	673 (81.7%)	2267 (81.7%)	NS (0.4)
Extrathyroid	658 (18.2%)	151 (18.3%)	507 (18.3%)	
T3 (micro-invasion)	545 (15.0%)	93 (11.3%)	452 (16.3%)	0.002
T4 (macro-invasion)	113 (3.1%)	58 (7.0%)	55 (1.9%)	<0.0001

Changing features of thyroid tumors

Lymph nodes metastases: N*	4184	1213	2971	
	1081 (25.8%)	415 (34.2%)	666 (22.4%)	<0.0001
Distant Metastases: N*	4184	1213	2971	
	127 (3%)	66 (5.4%)	61 (2%)	<0.0001
Clinical Classes (De Groot's classification): N*	3995	1102	2893	
I	2450 (61.3%)	542 (49.2%)	1908 (65.9%)	<0.0001
II	764 (19.1%)	332 (30.1%)	432 (14.9%)	<0.0001
III	655 (16.4%)	163 (14.8%)	492 (17 %)	NS (0.1)
IV	126 (3.2%)	65 (5.9%)	61 (2.2%)	<0.0001
Multifocality: N*	3726	896	2830	
	1354 (36.0)	283 (31.5%)	1071 (37.8%)	0.0008
Bilaterality: N*	3662	873	2789	
	730 (19.9%)	134 (15.3%)	596 (21.4%)	0.0001

2 major considerations:

Finding of small papillary thyroid cancer (and of other changing features) as consequence of the widespread use of neck ultrasound

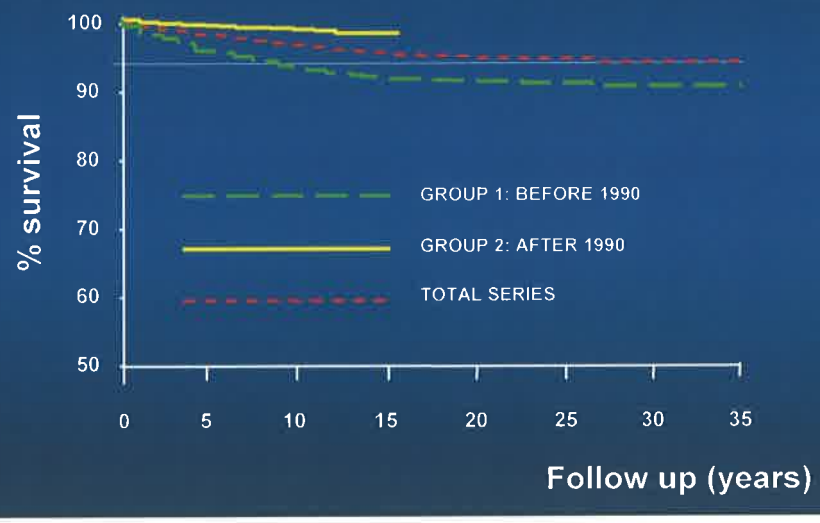
NO anticipation of diagnosis YES

Increased percentage of less advanced tumors (both for lymph nodes and distant metastases)

PROGNOSIS AND PROGNOSTIC FACTORS

SURVIVAL OF DTC PATIENTS (N=4187) AFTER A LONG TERM FOLLOW UP OF 35 YEARS

(Elisei R et al, JCE&M, 2010)



THERAPEUTIC STRATEGY

TOTAL THYROIDECTOMY

131-I THERAPY

80-85% "CURED"

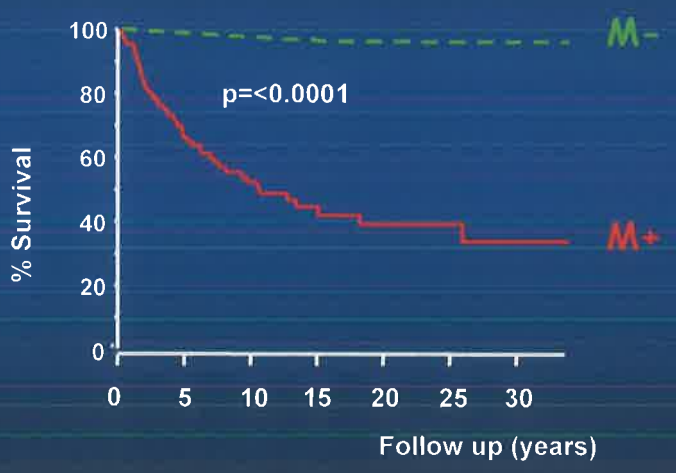
1% RISK OF RECURRENCE
UP TO 20 YEARS

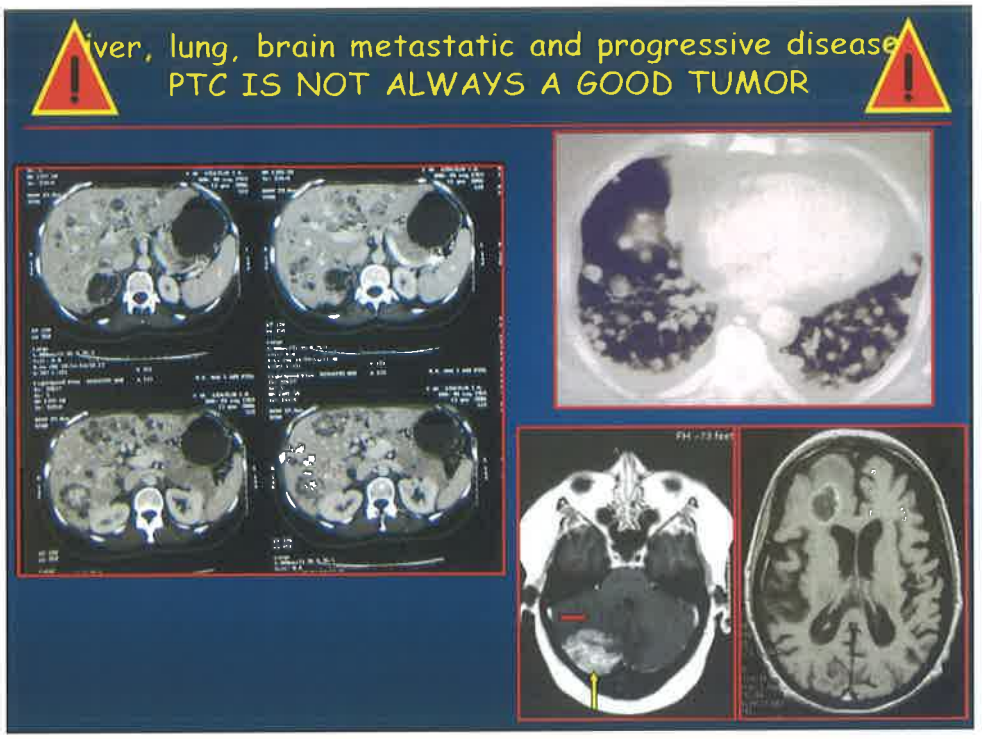
MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS IN THE TOTAL SERIES, GROUP 1 (1969-1989) AND GROUP 2 (1990-2004)

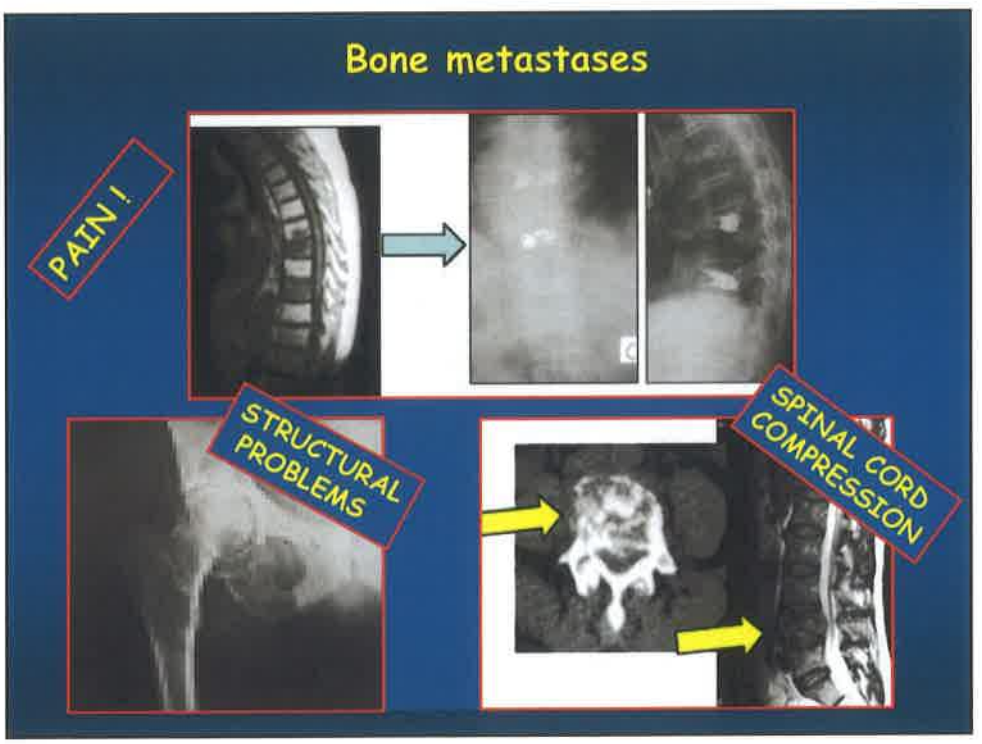
VARIABLES	TOTAL SERIES				BEFORE 1990				AFTER 1990			
	β	SE	p	OR	β	SE	p	OR	β	SE	p	OR
Gender: male vs female	0,44	0,26	0,095	1,55	0,57	0,36	0,113	1,77	0,43	0,42	0,300	1,55
Age (years):												
41-60 vs ≤ 40	2,42	0,62	< 0,0001	11,26	2,95	1,04	0,005	19,20	1,93	0,80	0,016	6,92
>60 vs ≤ 40	3,89	0,61	< 0,0001	49,20	4,53	1,03	< 0,0001	93,56	3,11	0,79	< 0,0001	22,52
Histotype: PTC vs FTC	-0,95	0,27	0,001	0,38	-1,44	0,35	<0,0001	0,23	0,05	0,56	0,919	1,06
Tumor size (cm):												
1-2 vs ≤ 1	-0,85	0,45	0,062	0,42	-0,40	0,66	0,543	0,66	-1,51	0,83	0,069	0,22
2-4 vs ≤ 1	-0,24	0,41	0,562	0,78	-0,10	0,63	0,870	0,90	0,01	0,59	0,978	1,01
≥ 4 vs ≤ 1	0,71	0,39	0,068	2,03	0,97	0,60	0,104	2,65	0,79	0,56	0,170	2,21
Local extrathyroidal extension (with vs without)	-1,09	0,54	0,045	0,33	-0,89	0,89	0,316	0,40	-1,47	0,73	0,045	0,22
Lymph node metastases (with vs without)	1,50	0,37	< 0,0001	4,51	1,08	0,52	0,041	2,9	1,42	0,57	0,014	4,1
De Groot's Class:												
2 vs 1	0,14	0,54	0,979	1,01	0,45	0,74	0,538	1,58	0,24	0,87	0,778	1,27
3 vs 1	1,78	0,59	0,003	5,96	1,80	0,90	0,045	6,05	2,21	0,90	0,015	9,17
4 vs 1	2,89	0,38	< 0,0001	18,07	2,38	0,47	< 0,0001	10,84	3,98	0,73	< 0,0001	53,54
Year of diagnosis : > 1990 vs < 1990	-0,88	0,26	0,001	0,41								

Survival of DTC patients with and without distant metastases at the diagnosis

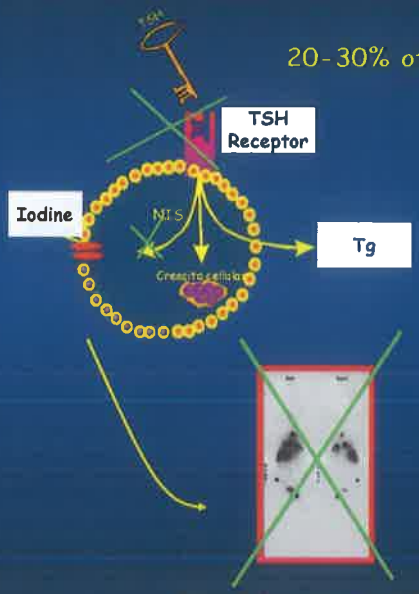
Department of Endocrinology, University of Pisa
4187 DTC from 1969 to 2004




iver, lung, brain metastatic and progressive disease
PTC IS NOT ALWAYS A GOOD TUMOR


Bone metastases
PAIN !
STRUCTURAL PROBLEMS
SPINAL CORD COMPRESSION

POORLY AND/OR DE-DIFFERENTIATED THYROID TUM



20-30% of thyroid carcinomas lose the capacity to uptake iodine

No Uptake of Iodine

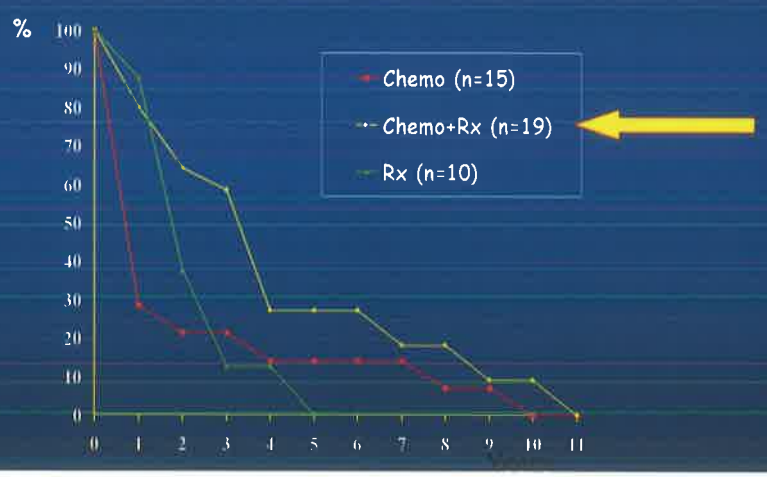
NIS

131-I useless

What to do?

DE-DIFFERENTIATED THYROID TUMORS ARE CANDIDATE TO CHEMOTHERAPY

10-year survival after chemotherapy, external Rx or both
(Dept. of Endocrinology, Pisa)



OVERALL RESULTS OF CHEMOTHERAPY

- VARIOUS COMBINATIONS OF DIFFERENT DRUGS PRODUCE SIMILAR RESPONSE RATES (20-30%), WITH SYMPTOMATIC IMPROVEMENT IN SOME PATIENTS BUT NO BENEFIT ON THE SURVIVAL RATE
- THE RESPONSES ARE USUALLY PARTIAL AND SHORT-LIVED.
- THE TOXICITY OF THE DRUGS IS USUALLY VERY HIGH

OTHER THERAPEUTIC TARGETS

Angiogenesis (2010) 13:1–14
DOI 10.1007/s10456-009-9160-6

REVIEW PAPER

Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action?

Kristy J. Gotink · Henk M. W. Verheul

Agent	Target	Clinical activity and/or study	Phase of development	Refs
Sunitinib (SU11248; Sutent)	VEGFR-1, -2, -3, PDGFR, KIT, FLT3, CSF-1R, RET	Kidney, breast, prostate, lung, liver, ovarian, colorectal, thyroid, head and neck, gastric, bladder, cervical and pancreatic cancer, GIST, melanoma, glioblastoma, myeloma, lymphoma	Approved for kidney cancer and GIST, phase II or III for other cancers	[7, 9]
Sorafenib (BAY439006; Nexavar)	VEGFR-2, -3, PDGFR, Raf, KIT	Kidney, liver, breast, prostate, lung, ovarian, colorectal, thyroid, head and neck, gastric and pancreatic cancer, GIST, melanoma, glioblastoma, lymphoma, leukemia	Approved for kidney and liver cancer, phase II or III for other cancers	[8, 11]
Pazopanib (GW786034; Votrient)	VEGFR-1, -2, -3, PDGFR, KIT	Kidney, breast, lung, cervical, liver, thyroid, prostate and colorectal cancer, melanoma, glioblastoma	Approved for kidney cancer, phase II or III for other cancers	[99, 100]
Vandetanib (ZD6474; Zactima)	VEGFR-2, EGFR, KIT, RET	Lung, kidney, thyroid, head and neck, prostate, ovarian, breast and colorectal cancer, glioma, neuroblastoma	Phase II or III	[53, 101, 102]
Axitinib (AG013736)	VEGFR-1, -2, -3, PDGFR-β, KIT	Kidney, lung, thyroid, pancreatic, colorectal and breast cancer, melanoma	Phase II or III	[103, 104]
Cediranib (AZD2171; Recentin)	VEGFR-1, -2, -3, PDGFR-β, KIT	Kidney, breast, lung, liver, ovarian, head and neck, prostate and colorectal cancer, GIST, glioblastoma, melanoma	Phase II	[105, 106]
Vatalanib (PTK787; ZK222584)	VEGFR-1, -2, -3, PDGFR-β, KIT	Prostate, colorectal, kidney and pancreatic cancer, melanoma, lymphoma, leukemia	Phase II or III	[107, 108]
Motesanib (AMG706)	VEGFR-1, -2, -3, PDGFR, KIT, RET	Lung, thyroid, gallbladder, breast and colorectal cancer, GIST	Phase II or III	[109, 110]

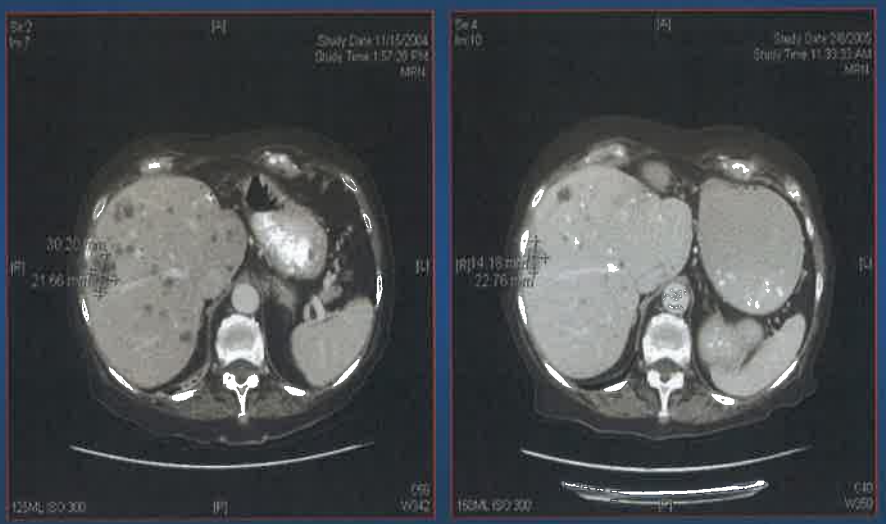
CSF-1R colony stimulating factor-1 receptor, *EGFR* epidermal growth factor receptor, *FLT3* fms-related tyrosine kinase 3, *GIST* gastro-intestinal stromal tumor, *PDGFR* platelet-derived growth factor receptor, *VEGFR* vascular endothelial growth factor receptor

THERAPEUTIC TARGETS

Papillary Carcinoma
- BRAF point mutations
- RAS point mutation
- RET/PTC rearrangement
- VEGFR, PDGFR, etc..

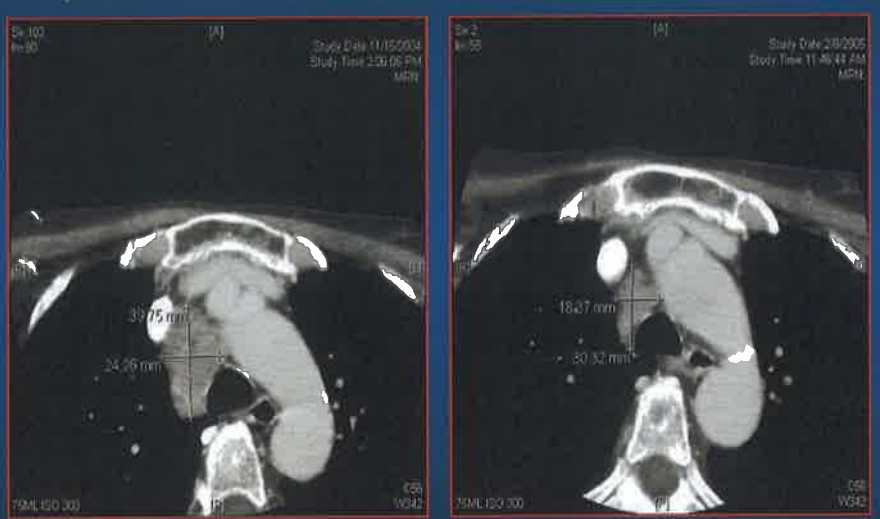
Follicular Carcinoma
- RAS point mutation
- PAX8-PPARγ rearrangement
- VEGFR, PDGFR, etc..

PHASE II STUDY: Patient 001: Liver Metastasis of thyroid cancer



Kindly provided by Dr Wells S, Duke University, USA

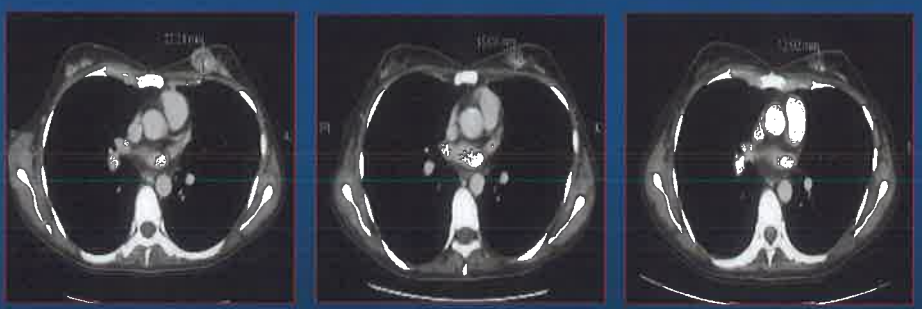
PHASE II STUDY: Patient 001: Lymph Node Metastasis of thyroid cancer



Kindly provided by Dr Wells S, Duke University, USA

PHASE II STUDY: Patient 002: Breast Metastasis of thyroid cancer

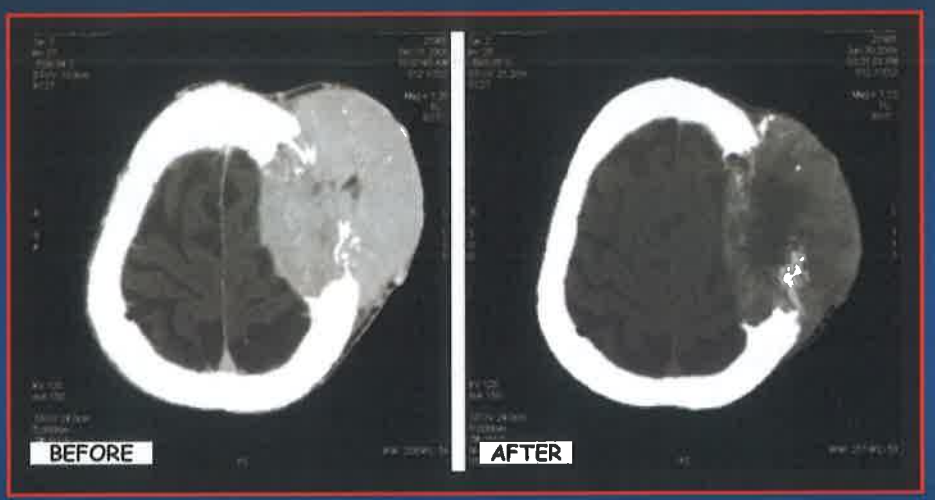
Lesion at Baseline | 3 Months | 7 Months



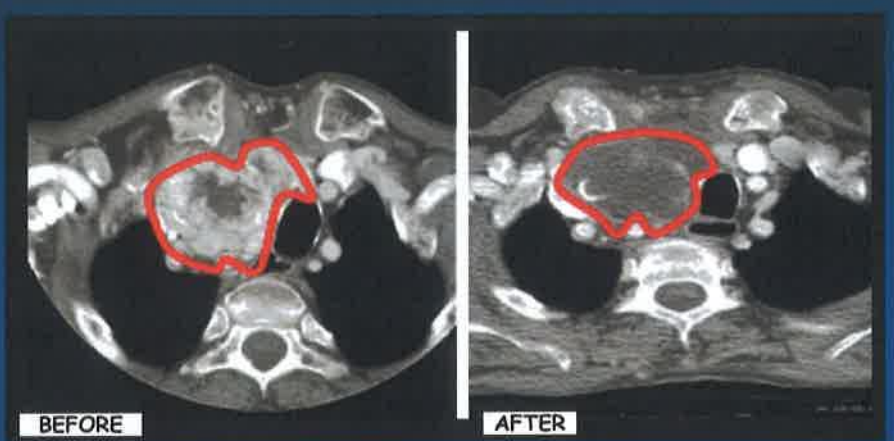
Kindly provided by Dr Wells S, Duke University, USA

BRAIN/BONE METASTASIS FROM UNTREATABLE FOLLICULAR THYROID CANCER

BEFORE THERAPY | AFTER 2 WEEKS OF THERAPY | AFTER 4 WEEKS OF THERAPY

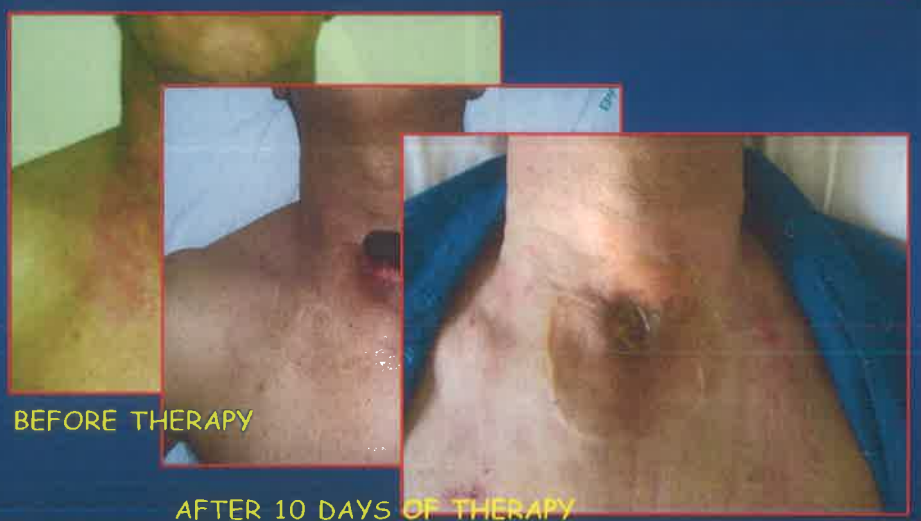


Follicular thyroid cancer: brain/bone metastasis



Follicular thyroid cancer: primary tumor

ANAPLASTIC THYROID CANCER



CONCLUSIONS

Thyroi cancer is a rare tumor but is the tumor with the highest rate of increase in incidence

With the exception of a significant increase of small tumors, all the other epidemiological features have been maintained over the years

The vast majority is curable with conventional therapy (i.e thyroidectomy and 131-I radiometabolic therapy)

New therapeutic strategies with TKI are under investigation for the treament of advanced/radioiodine refractory cases (15-20% of all cases): very promising results!!


GRAZIE PER L'ATTENZIONE!

GERM-CELL TUMORS

BredaŠkrbinc, MD, PhD
Institute of Oncology Ljubljana

Birth Defects Research (Part C) 87:96–112, (2009)

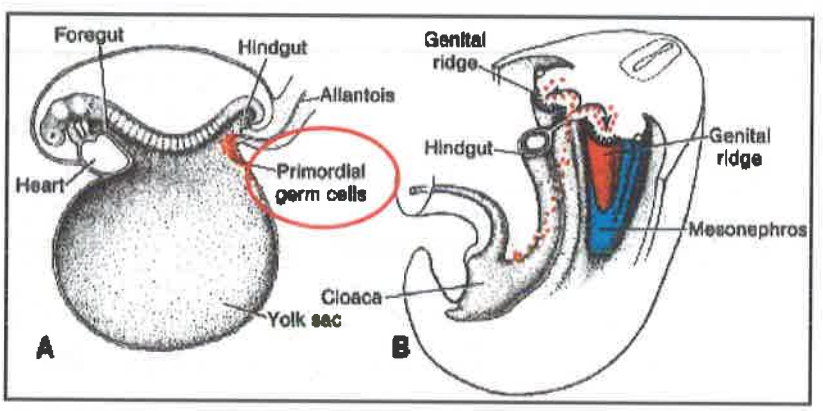
TABLE 1. Classification of the Five Different Types of Germ-Cell Tumors (Oosterhuis and Looijenga, 2005). See Text for Further Details

Type	Anatomical site	Phenotype	Age	Originating cell	Genomic imprinting	Genotype	Animal model
I	Testis/ovary/ sacral region/ retroperito-neum/ mediastinum/ neck/midline brain/other rare sites	(Immature) teratoma/yolk-sac tumor	Neonates and children	Early PGC/ gonocyte	Biparental, partially erased	Diploid (teratoma), Aneuploid (yolk-sac tumor): gain of 1q, 12(p11) and 20q, and loss of 1p,4 and 6q	Mouse teratoma
II	Testis	Seminoma/ nonseminoma	>15 years (median age 35 and 25 years)	PGC/gonocyte	Erased	Aneuploid (+/- triploid) gain of X, 7, 8, 12p, and 21, loss of Y, 1p, 11, 13 and 18	-
	Ovary	Dysgerminoma/ nonseminoma	>4 years	PGC/gonocyte	Erased	Aneuploid	-
	Dysgenetic gonad	Dysgerminoma/ nonseminoma	Congenital	PGC/gonocyte	Erased	Diploid/tetraploid	-
	Anterior mediastinum (thymus)	Seminoma/ nonseminoma	Adolescents	PGC/gonocyte	Erased	Diploid/tri-tetraploid	-
	Midline brain (pineal gland/ hypothalamus)	Germinoma/ nonseminoma	Children (median age 13 years)	PGC/gonocyte	Erased	Diploid/tri-tetraploid	-
III	Testis	Spermatocytic seminoma	Children/adults	Spermatogonium/ spermatocyte	Partially complete paternal	Aneuploid: gain of 9	Canine seminoma
IV	Ovary	Dermoid cyst	> 50 years	Oogonia/oocyte	Partially complete maternal	(Near) diploid, diploid/tetraploid, or triploid (gain of X, 7, 12, and 15)	Mouse gynogenote
V	Placenta/uterus	Hydatiform mole	Fertile period	Empty ovum/ spermatozoa	Completely paternal	Diploid (XX and XY)	Mouse androgenote

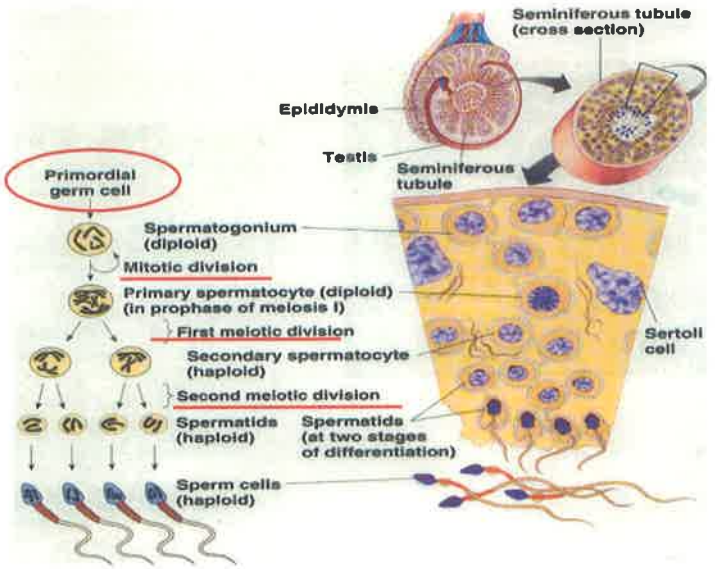
Epidemiology

- Germ-cell tumor type II - most common solid malignancy of Young Caucasian men between 15 and 40 years of age
- The incidence in Europe rising, with doubling every 20 years
- Current incidence 6.3 / 100 000 / year
- Highest incidence in Northern European Countries 6.8 / 100 000 / year

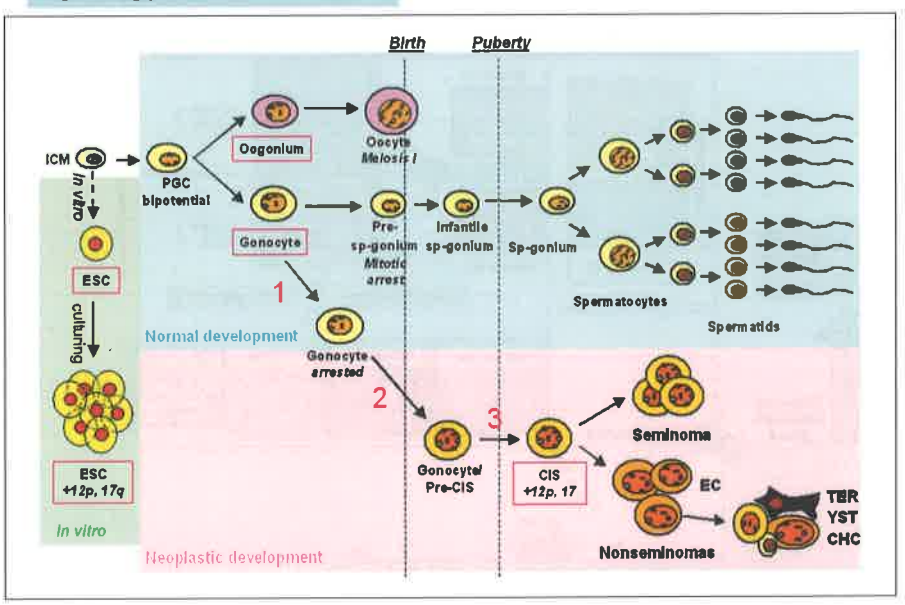
Byology of GCT II - 1



Byology of GCT II - 2

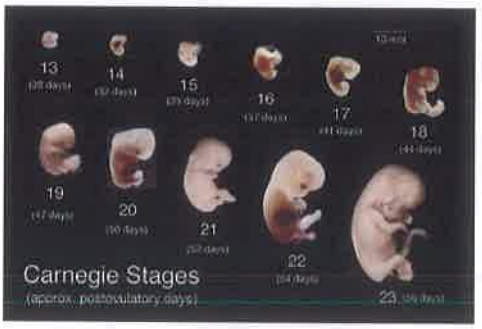


Byology of GCT II - 3

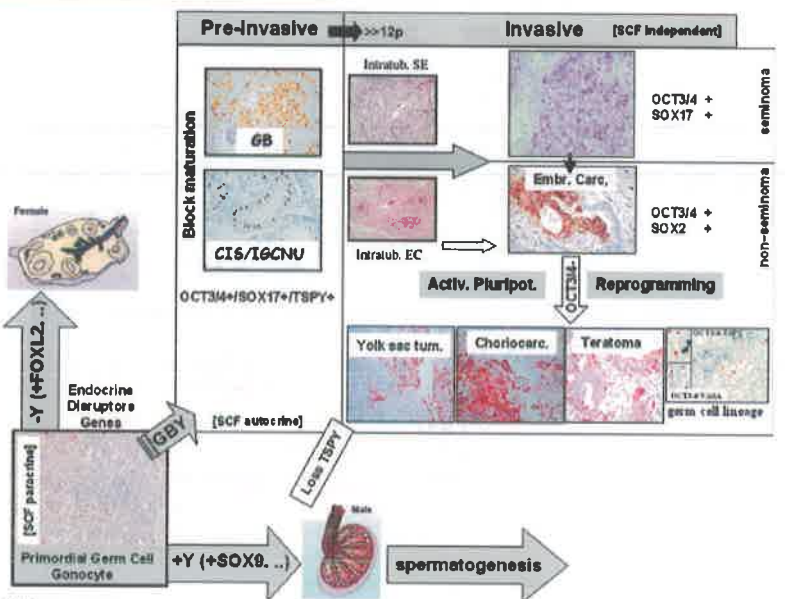


Cancer Res 2009;69:(12). June 15, 2009

Biology of GCT II - 4



Byology of GTC II - 5

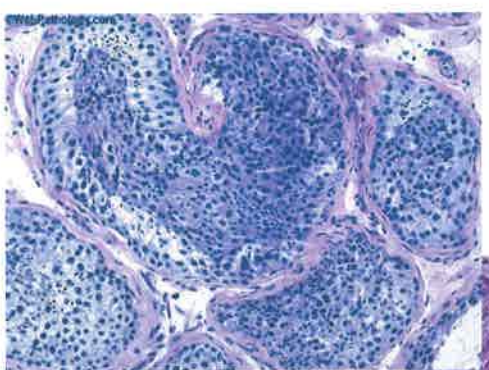


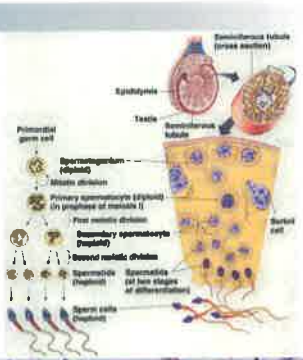
Looijenga LHJ 2009

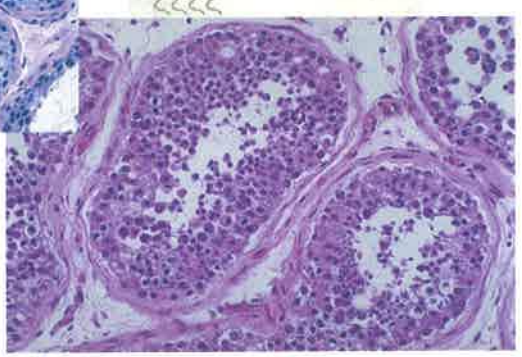
Histopathology 1

- CIS
- Seminoma (50 %)
- Nonseminoma (40 %)
  - Embrional carcinoma
  - Teratoma
  - Yolk sac tumor
  - Choriocarcinoma
- Mixed germ cell tumors (10 %)

Histopathology 2

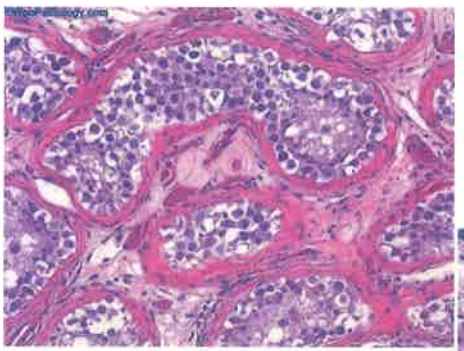


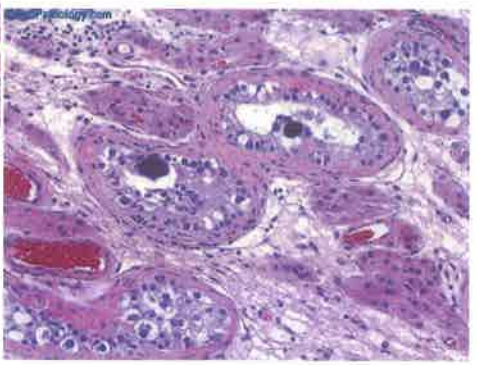




Normal testicle

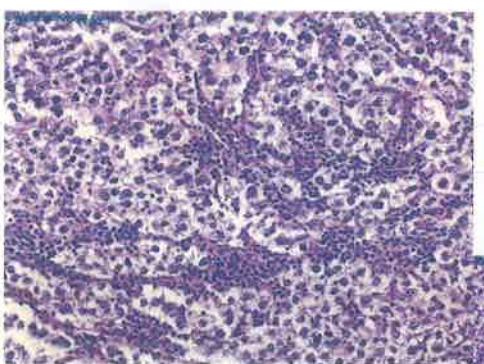
Histopathology 3

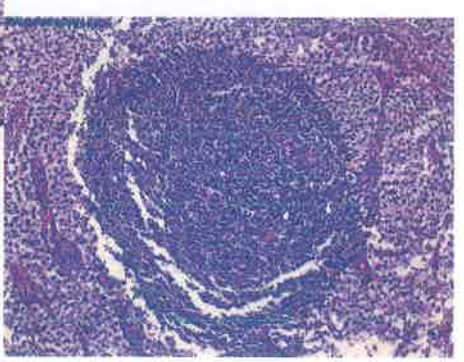




Carcinoma in situ

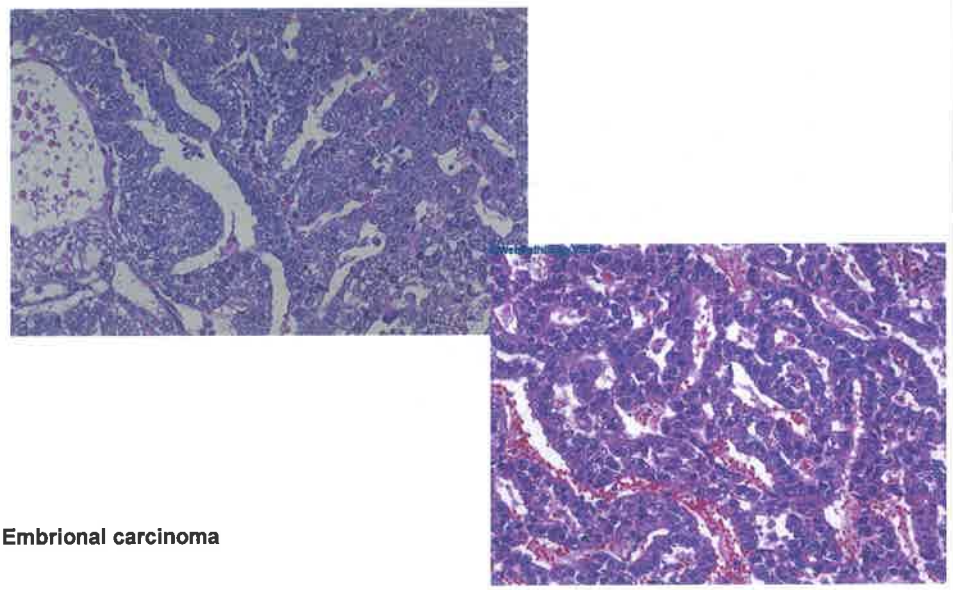
Histopathology 4





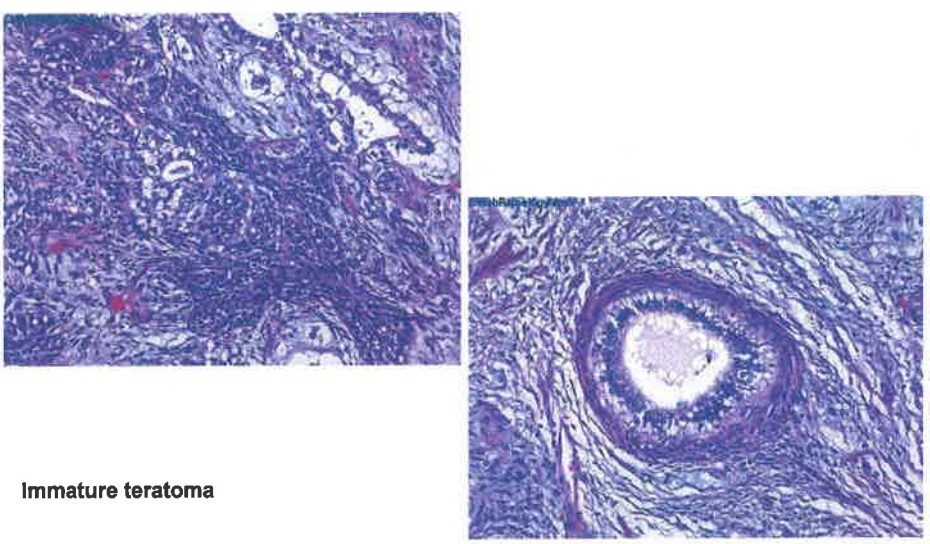
Seminoma

Histopathology 5



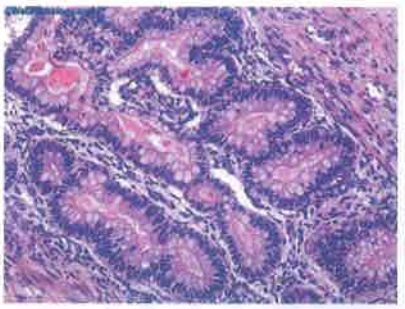
Embrional carcinoma

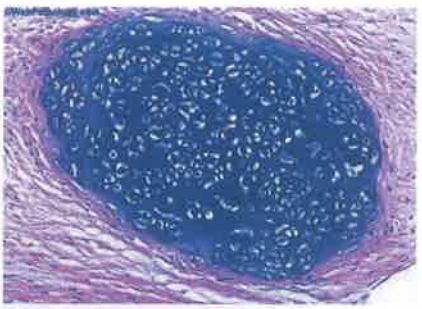
Histopathology 6

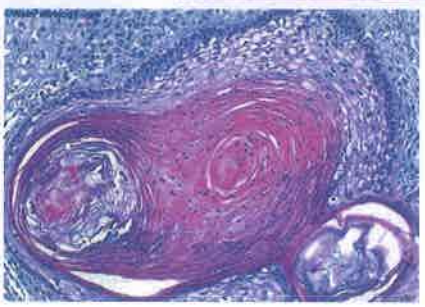


Immature teratoma

Histopathology 7

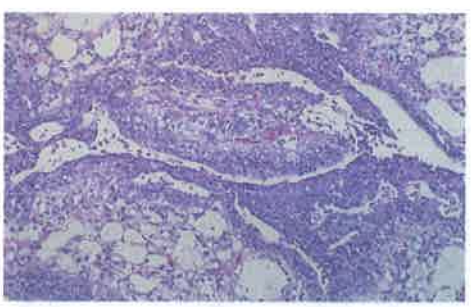




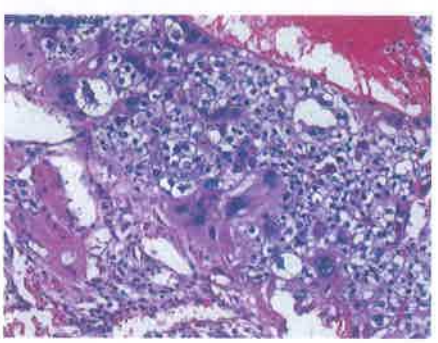


Mature teratoma

Histopathology 8

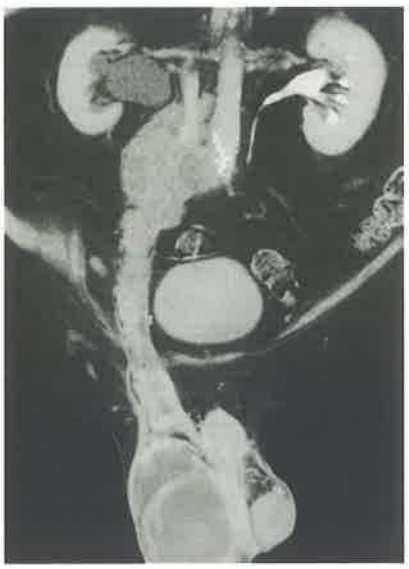


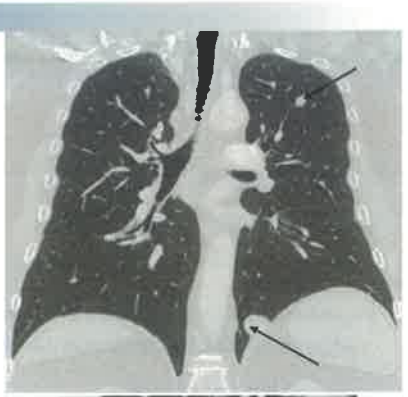
Yolk sac tumor

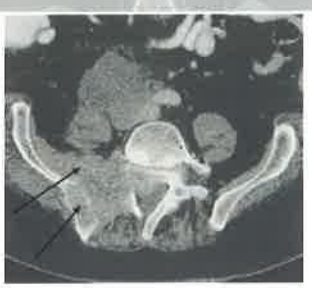


Choriocarcinoma

Clinical presentation







n engl j med 357;4 www.nejm.org july 26, 2007

Diagnostics and treatment

Testicular seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

H.-J. Schmoll1, K. Jordan1, R. Huddart2, M. P. Laguna Pes3, A. Horwich2, K. Fizazi4 & V. Kataja5
On behalf of the ESMO Guidelines Working Group*

Annals of Oncology 21 (Supplement 5): v140–v146, 2010

Testicular non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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Annals of Oncology 21 (Supplement 5): v147–v154, 2010

Diagnosis / staging / risk assessment 1

- **Histology of testicular mass**
  - Transinguinal orchyectomy
  - Testis-conserving surgery
  - No scrotal violation !

  In patients with advanced and rapidly progressive disease
  - urgent chemotherapy mandatory - no inicial orchiectomy

  - typical clinical picture
  - marker elevation
    pure clasic seminoma no AFP,
    ßHCG > 200 considered a non-seminoma

  Extrygonadal tumor syndrom

  - high tumor markers
  - biopsy

Diagnosis / staging / risk assessment 2

Extrygonadal tumor syndrom

- retroperytoneal or medistinal mass
- high tumor markers
- biopsy

- undifferentiated (adeno)carcinoma of unknown primary
- tipical TM elevation
- elevated copy number of cromosome i12p
  (specific for germ cell tumors)

- 1/3 CIS in testis
- 1/3 burned out tumor (scar in testicular tissue (
- 1/3 deffinitiveprimary extragonadal GCT without affecting the testicle

Diagnosis / staging / risk assessment 3

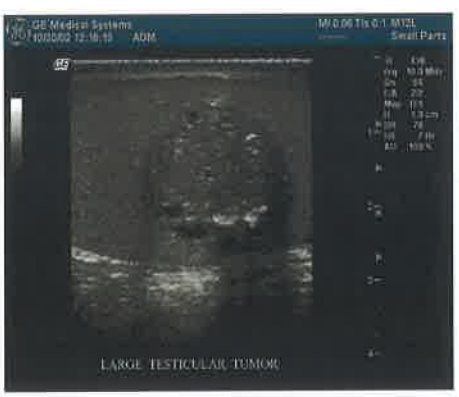
- blood tests
  - ► differentiation of stage and IGCCCG prognostic group:

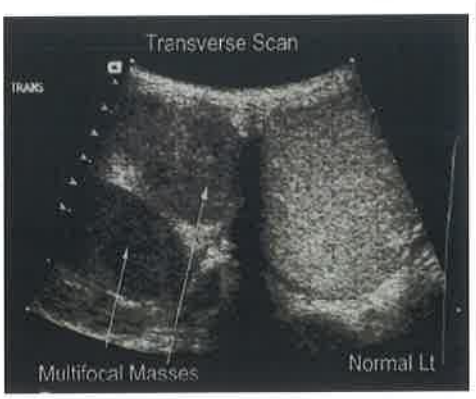
    TM determined

    - before orhiectomy
    - 7 days after orhiectomy

Diagnosis / staging / risk assessment 4

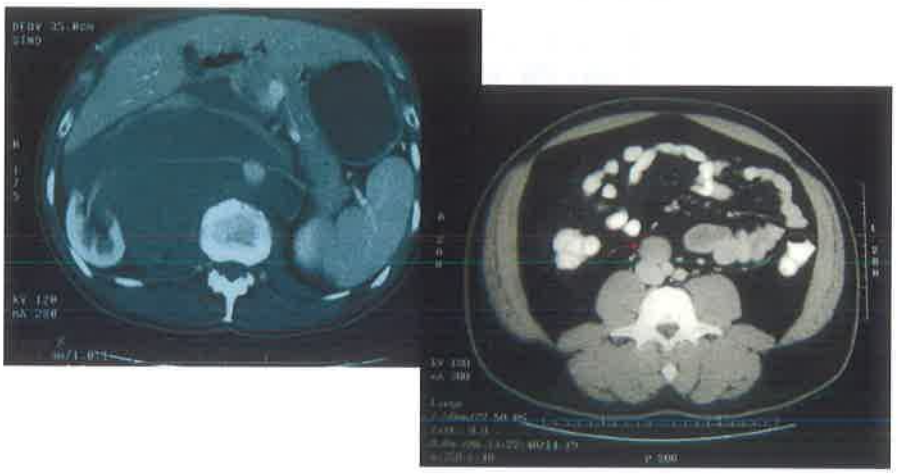
Testicular sonography of both testicles mandatory





Diagnosis / staging / risk assessment 5

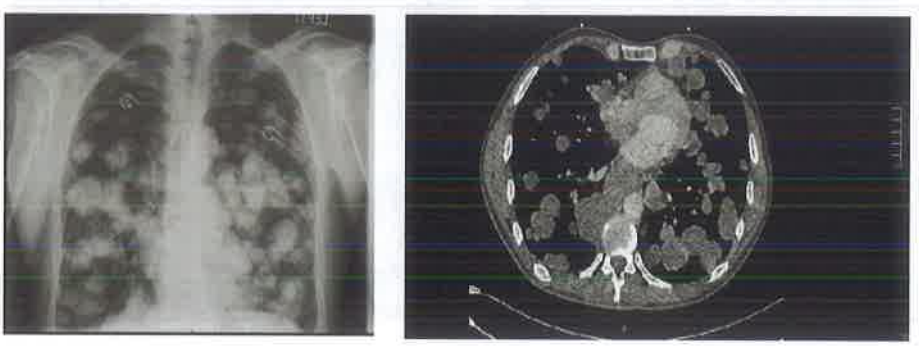
CT scan abdomen, pelvis mandatory



Diagnosis / staging / risk assessment 6

Ct scan of chest mandatory

exeption pure seminoma stage I



Diagnosis / staging / risk assessment 7

In case of borderline lymph node size, CT scan should be repeated in 6 weeks to define definitive treatment strategy

If imaging is normal TM decline monitoring until normalization

MRI of CNS only in advanced stages or with symptoms

Bone scan in case of symptoms

PET scan – no contribution in early stages

a possible option in seminoma stage II / III

for defining treatment strategies in case of residual leseions

staging of seminoma according to UICC/AJCC and IGCCCG classification

Clinical Stage	TNM (UICC/AJC) category					Serum tumor markers (S)			IGCCCG prognostic group[c]
	T		N	M	S	LDH[a]	ßHCG (mIU/ml)[b]	AFP (ng/ml)	
0	pTis	intratubular germ cell neoplasia	N0	M0	-	-	-	-	n.a.
IA	pT1	limited to testis and epididymis, without vascular/ lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis	N0	M0	S_{any}	any level	any level	normal	n.a.
IB	pT2	limited to testis and epididymis, with vascular/ lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis	N0	M0	S_{any}	any level	any level	normal	n.a.
	pT3	invasion of spermatic cord							
	pT4	invasion of scrotum							
IIA	T_{any}		N1 (≤ 2 cm)	M0	S_{any}	any level	any level	normal	n.a.
IIB	T_{any}		N2 (>2-5 cm)	M0	S_{any}	any level	any level	normal	n.a.
IIC	T_{any}		N3 (>5 cm)	M0	S_{any}	any level	any level	normal	good
IIA/B/C	T_{any}		N_{any}	M1a (non-regional nodal and/or pulmonary metastases)	S_{any}	any level	any level	normal	good
IIIC	T_{any}		N_{any}	M1b (liver, bone, CNS or other visceral metastases, e.g. intestinum or skin; ± pulmonary metastases)	S_{any}	any level	any level	normal	intermediate
IIIC	mediastinal primary		N_{any}	M_{any}	S_{any}	any level	any level	normal	intermediate

[a] N indicates the upper limit of normal for the LDH assay. [b] Caveat: BHCG levels are given in mIU/ml; to convert in ng/ml divide by factor 5
[c] poor prognosis is not applicable in seminoma
n.a.: not applicable

staging of non-seminoma according to UICC/AJCC and IGCCCG classification

Clinical Stage	TNM (UICC/AJCC) T		N	M	Serum tumor markers (S) to be determined after orchiectomy S	LDH*	HHCG	AFP (ng/ml)	Clinical prognostic classification
0	pTis	intratubular germ cell neoplasia	N0	M0	S0^/ SX^	normal	normal	normal	
IA	T1	limited to testis and epididymis, without vascular/ lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis	N0	M0	S0	normal	normal	normal	low risk (≥20%)
IB	T2	limited to testis and epididymis, with vascular/ lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis	N0	M0	S0	normal	normal	normal	high risk (≤80%)
IS	T2 T3 T4	limited to testis and epididymis, with vascular/ lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis invasion of spermatic cord invasion of scrotum	N0	M0	S0	normal	normal	normal	IGCCCG
IS	Tany		N0	M0	S1 S2 S3	<1.5xN and 1.5-10xN or >10xN or	<5000 and 5000-50 000 or >50 000 or	<1000 1000-10 000 >10 000	good intermediate poor
IIA	Tany		N1 (≤ 2 cm)	M0	S0 S1	normal <1.5xN and	normal <5000 and	normal <1000	
IIB	Tany		N2 (>2-5 cm)	M0	S0 S1	normal <1.5xN and	normal <5000 and	normal <1000	good
IIC	Tany		N3 (>5 cm)	M0	S0 S1	normal <1.5xN and	normal <5000 and	normal <1000	good
IIIA	Tany		N_{any}	M1a (non-regional nodal and/or pulmonary metastases)	S0 S1	normal <1.5xN and	normal <5000 and	normal <1000	good
IIIB	Tany		N1-3 N_{any}	M0 M1a	S2	1.5-10xN or	5000-50 000 or	1000-10 000	intermediate
IIIC	Tany		N1-3 N_{any}	M0 M1a M1b (liver, bone, CNS or other visceral metastases, e.g. intestinum or skin; a pulmonary metastasis)	S3 S3 S_{any}	>10xN or >10xN or any level	>50 000 or >50 000 or any level	>10 000 >10 000 any level	poor poor poor
IIIC	mediastinal primary		N_{any}	M_{any}	S_{any}	any level	any level	any level	poor

^ N indicates the upper limit of normal for the LDH assay. * Conc. HCG levels are given in mIU/ml; to convert in ng/ml divide by factor 5

Treatment algorithm for seminoma

Clinical stage	Standard treatment	Only, if standard is not applicable	Status after treatment	Further management	Management at relapse/ progression
I	Surveillance	Adjuvant treatment - Carboplatin, 1cycle AUC 7 or - Radiotherapy*		• Follow up	Chemotherapy as stage IICIII
IIA (1-2 cm) IIB "borderline" (2-2.5 cm)	Radiotherapy*	Chemotherapy - PEB x 3 cycles - If arguments against bleomycin: PE x 4 cycles	• CR • Residual tumour	• Follow up • Follow up	If previous radiotherapy: chemotherapy as stage IICIII If previous chemotherapy: salvage chemotherapy; consider radiotherapy for localized relapse
IIB (2.5-5 cm)	Chemotherapy • PEB x 3 cycles • If arguments against bleomycin: PE x 4 cycles	Radiotherapy*	• CR	• Follow up	
IICIII	Chemotherapy • Good prognosis (IGCCCG): PEB x 3 cycles (3 or 5 d)	Chemotherapy Good prognosis: - PE x 4 cycles	• CR • Residual tumour: < 3 cm: PET optional	• Follow up • no PET done: follow up • PET done and negative: follow up • PET done and positive: • consider resection or alternatively • follow up	• Relapse from CR/NED - Standard salvage chemotherapy • Small localized relapse: - consider radiotherapy • Progression under follow up, residual, non resected disease - salvage chemotherapy - exceptional: local (re-)irradiation
	• Intermediate prognosis (IGCCCG): PEB x 4 cycles (5 d)	Intermediate prognosis: - PEI = VIP x 4 cycles	• Residual tumour: > 3 cm: PET recommended	• no PET done: follow up or resection • PET done and negative: follow up • PET done and positive: consider resection	

* see table 3 radiotherapy

Treatment algorithm for non-seminoma stage I

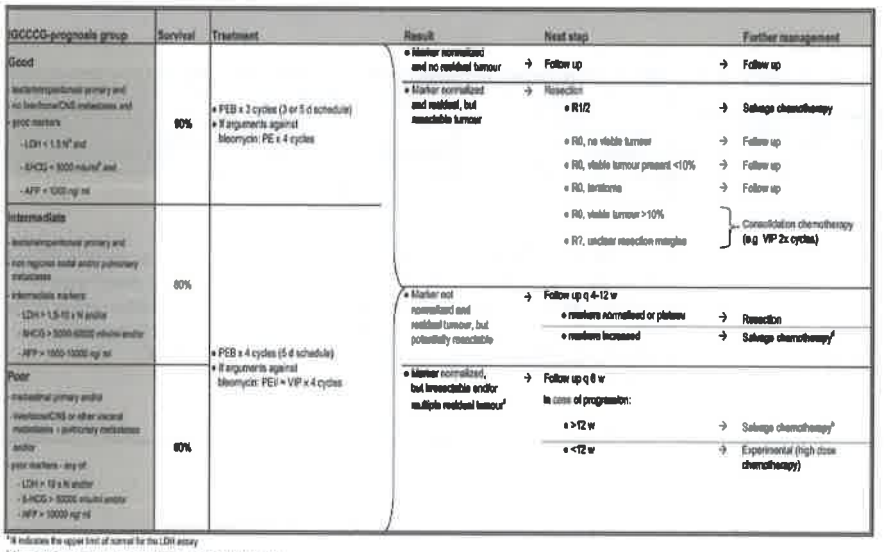
Clinical stage	Clinical prognostic classification	Treatment		
		1st choice	2nd choice	3rd choice
IA	"Low risk" (no vascular invasion)	Surveillance	Adjuvant chemotherapy (PEB x 2 cycles)	Only for very restricted cases (e.g. if chemotherapy or surveillance declined by the patient): nerve sparing-RPLND
IB	"High risk" (vascular invasion)	2 comparable options with same final outcome (> 98% survival) with different treatment/ follow up burden • adjuvant chemotherapy (PEB x 2 cycles) or • surveillance	• Surveillance or • adjuvant chemotherapy (PEB x 2 cycles)	

Treatmint algorithm for non-seminoma stage II A / B

Clinical stage	Treatment	Result		Further management
II A marker + II B marker +/-	Chemotherapy • standard: PEB x 3 cycles • option: PE x 4 cycles	• CR	→	Follow up
		• Residual tumor (> 1 cm)	→	Resection and follow up
II A marker -	**Strategy 1*** follow up only q 6 weeks	• PD, and marker ⊕	→	PEB x 3 cycles (or PE x 4 cylces, in case of residual tumour (> 1 cm): resection
		• PD, marker remains ⊖	→	PEB x 3 cycles (or PE x 4 cycles) or* Nerve sparing-RPLND
		• NC	→	Nerve sparing-RPLND
		• Regression	→	Further follow up
	Strategy 2* active treatment: biopsy or nerve sparing-RPLND	• Pathological stage I	→	Surveillance (independent of vascular invasion)
		•Pathological stage II A/B	→	• Follow up or* • PEB x 2 cycles or* • PE x 2 cycles

* equivalent options

Treatment algorithm for advanced non-seminoma stage IIC - III



[a] N indicates the upper limit of normal for the LDH assay

[b] Conv. S-HCG levels are given in mIU/ml, to convert in ng/ml divided by factor 5

[c] consider PET in individually patients for further planning of prognosis and management

[d] consider experimental chemotherapy in protocols for "refractory patients" (e.g. new drugs)

[e] consider also: local radiotherapy, if appropriate/applicable

Folow-up for seminoma

Clinical stage	Strategy		investigations (year)					
			1	2[b]	3	4	5[b]	6 to 10[b]
I	Surveillance	Exam/markers*	4x	4x	3x	2x	2x	1x
		Chest X-ray	2x	2x	1x	1x	1x	-
		CT abdomen	2x	2x	1x	1x	1x	-
	Carboplatin	Exam/markers*	4x	3x	2x	2x	2x	(1x)?[c]
		Chest X-ray	2x	2x	2x	1x	1x	(1x)?[c]
		CT abdomen	2x	2x	1x	-	1x	(1x)?[c]
	Radiotherapy	Exam/markers*	4x	3x	2x	2x	2x	-
		Chest X-ray	2x	2x	2x	1x	1x	-
		CT abdomen/pelvis	2x	2x	1x	-	1x	-
IIA/B	Radiotherapy	Exam/markers*	4x	3x	2x	2x	2x	-
		Chest X-ray	3x	1x	1x	1x	1x	-
	Chemotherapy	CT abdomen/pelvis	2x	1x	-	-	1x	-
IIC/III good IIC/III intermediate	Chemotherapy	Exam/markers*	6x	3x	2x	2x	2x	-
		Chest X-ray	3x	3x	1x	1x	1x	-
		CT abdomen/pelvis	CT 1-4x until CR with or without surgery, than according to chest X-ray plan					

[a] AFP, HCG, LDH

[b] Determination of late effects: Urea and electrolytes, fasting cholesterol (HDL, LDL), triglycerides, fastin glucose, FSH, LH, Testosterone

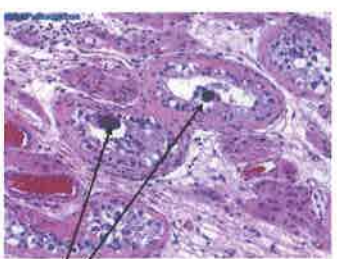
[c] Policies vary among countries and hospitals and there is no definitive evidence.

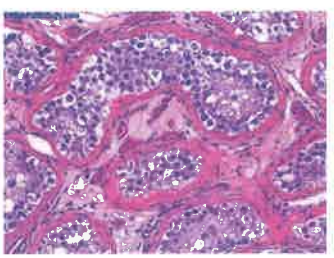
Follow-up for non-seminoma

IGCCCG-prognosis group	Survival	Treatment	Result	Next step	Further management
Good - testis/retroperitoneal primary and no liver/bone/CNS metastases and - good markers: - LDH < 1.5 N[1] and - b-HCG < 5000 mIU/ml[2] and - AFP < 1000 ng/ml	80%	• PEB x 3 cycles (3 or 5 d schedule) • If arguments against bleomycin: PE x 4 cycles	• Marker normalized and no resistant tumour	→ Follow up	→ Follow up
			• Marker normalized and residual, but resectable tumour	→ Resection	
				• R1/2	→ Salvage chemotherapy
				• R0, no viable tumour	→ Follow up
				• R0, viable tumour present <10%	→ Follow up
				• R0, teratoma	→ Follow up
				• R0, viable tumour >10%	→ Consolidation chemotherapy (e.g. VIP 2x cycles)
				• R?, unclear resection margins	
Intermediate - testis/retroperitoneal primary and - non regional nodal and/or pulmonary metastases - intermediate markers - LDH > 1.5-10 x N and/or - b-HCG > 5000-50000 mIU/ml and/or - AFP > 1000-10000 ng/ml	80%	• PEB x 4 cycles (5 d schedule) • If arguments against bleomycin: PEI = VIP x 4 cycles	• Marker not normalized and residual tumour, but potentially resectable	→ Follow up q 4-12 w	
				• markers normalized or plateau	→ Resection
				• markers increased	→ Salvage chemotherapy[3]
Poor - mediastinal primary and/or - liver/bone/CNS or other visceral metastases / pulmonary metastases and/or - poor markers - any of: - LDH > 10 x N and/or - b-HCG > 50000 mIU/ml and/or - AFP > 10000 ng/ml	60%		• Marker normalized, but irresectable and/or multiple residual tumour[4]	→ Follow up q 8 w in case of progression:	
				• >12 w	→ Salvage chemotherapy[3]
				• <12 w	→ Experimental (high dose chemotherapy)

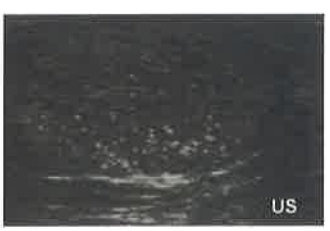
[1] N indicates the upper limit of normal for the LDH assay
[2] Caveat: b-HCG levels are given in mIU/ml. to convert in ng/ml divided by factor 5
[3] consider PET in individually patients for further planning of prognosis and management
[4] consider experimental chemotherapy in protocols for "refractory patients" (e.g. new drugs)
[5] consider also local radiotherapy, if appropriate/applicable

CIS



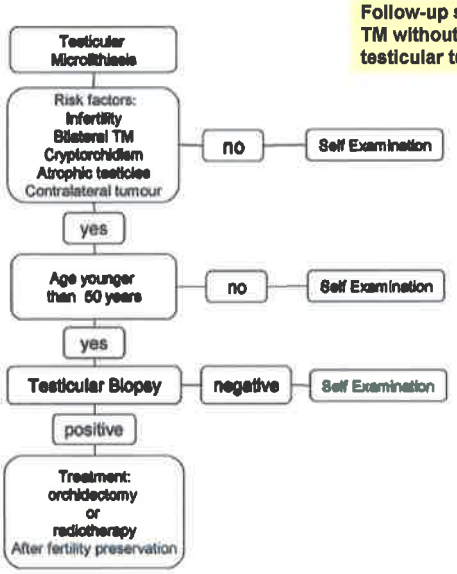


microlithiasis



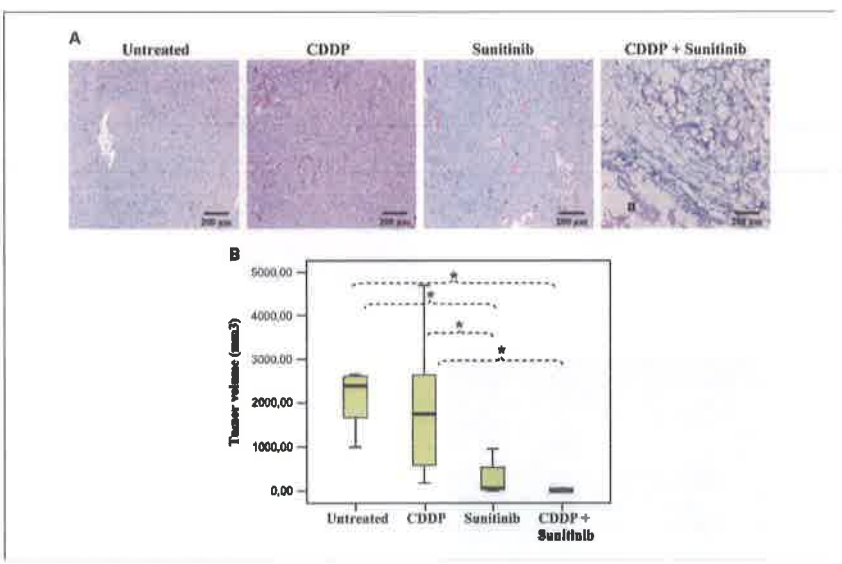
CIS

Follow-up scheme for patients with TM without a concomitant testicular tumour.



Int J Androl. 2009 Aug;32(4):279-87

new agents



Clin Cancer Res 2009;15(10) May 15, 2009

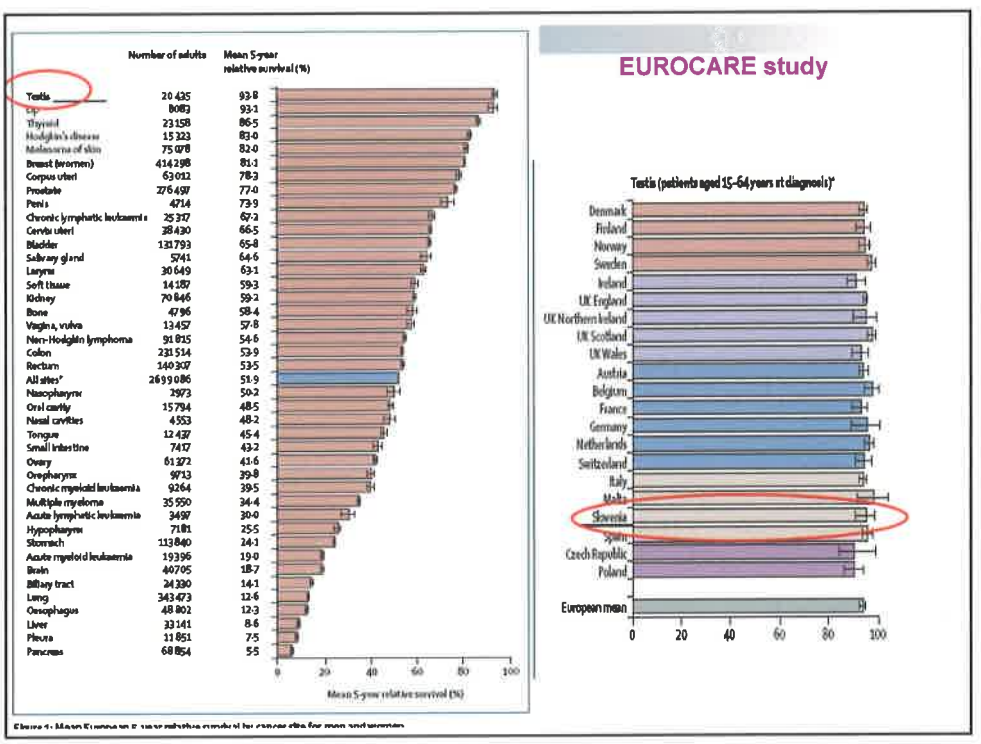
new agents

Phase II trial of sunitinib in patients with relapsed or refractory germ cell tumors

Darren R. Feldman & Stefan Turkula &
Michelle S. Ginsberg & Nicole Ishill & Sujata Patil &
Maryann Carousso & George J. Bosl & Robert J. Motzer

Invest New Drugs (2010) 28:523–528

- all patients progressive disease within three cycles of sunitinib
- some marker decline during the active treatment period with subsequent marker rise during the twoo-week off peroid → dosing scedule of sunitinib 37.5 mg / day cintuinously
- in general sunitinib well tolerated (no grade 4 toxicity)



EUROCARE study

Metastatic castration-resistant prostate cancer (mCRPC)

Boštjan Šeruga, MD
Sector of Medical Oncology
Institute of Oncology Ljubljana

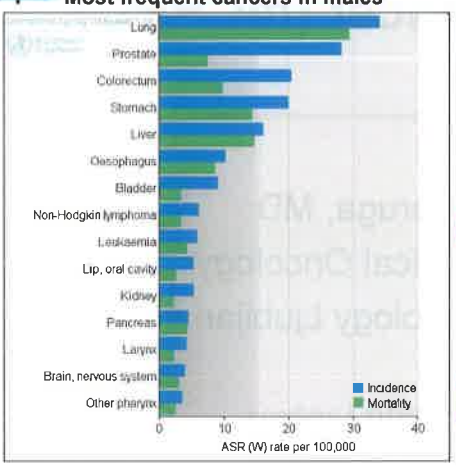
November 12, 2010; Ljubljana

Outline

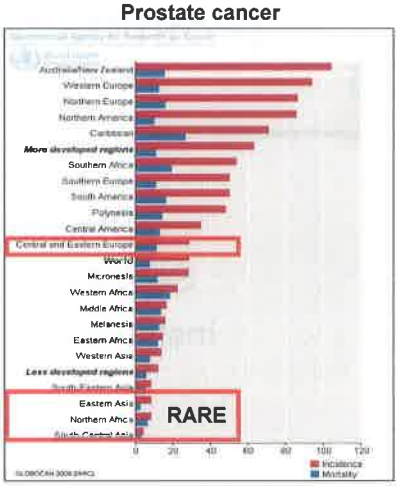
- How "rare" is CRPC?
- Biology of CRPC and mechanisms of resistance to standard therapies
- Current drug development in CRPC

Incidence and mortality rates for prostate cancer (World)

Most frequent cancers in males



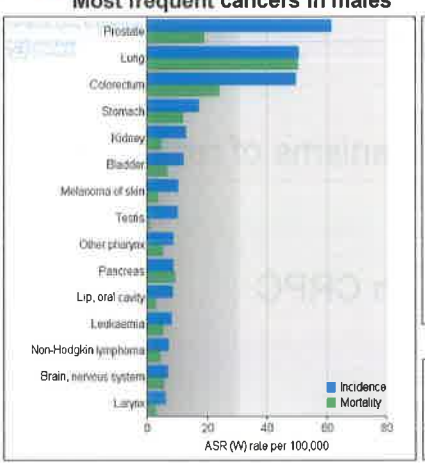
Prostate cancer

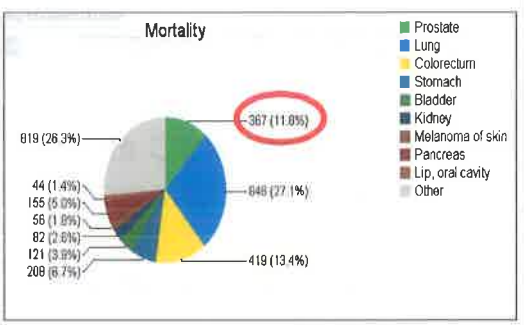


GLOBOCAN, 2008

Incidence and mortality rates for prostate cancer (Slovenia)

Most frequent cancers in males





- **367 men died of prostate cancer in Slovenia in 2008**
- **ASR (W): 19/100,000**
- **In Europe Denmark, Estonia, Lithuania, Latvia and Sweden have higher mortality rates**

GLOBOCAN, 2008

Current definition of CRPC

- **Castration-resistant prostate cancer (CRPC):**
  - Castrate levels of testosterone (< 0.50 ng/mL, 1.7 nmol/L)
  - Evidence of cancer progression (PSA or imaging)
- **It is not Hormone-resistant prostate cancer (HRPC)!**

What are the goals of any cancer treatment?

- To allow the patient to live **longer**

  and/or
- To allow the patient to live **better**

Pivotal phase III clinical trials with *Mitoxantrone* in mCRPC

Author/Year (Journal)	Experimental arm	Control arm	Results
Tannock/1996 (JCO)	Mitoxantrone + Prednisone	Prednisone	↑Quality of Life
Kantoff/1999 (JCO)	Mitoxantrone + Prednisone	Prednisone	↑Quality of Life

Mitoxantrone allowed patients with mCRPC to live better

Pivotal phase III clinical trials with *Docetaxel* in mCRPC

Author/Year (Journal)	Experimental arm	Control arm	Results
Tannock 2004 (NEJM)	Docetaxel +Prednisone	Mitoxantrone +Prednisone	↑Survival ↑Quality of Life
Petrylak 2004 (NEJM)	Docetaxel +Estramustine	Mitoxantrone +Prednisone	↑Survival

Docetaxel allowed patients with mCRPC to live longer and better

Outcome of patients with mCRPC

RCT (Drug)	Patient population	Median OS (mo)
NCIC (Mitoxantrone) Tannock,1996	Symptomatic	10.8
TAX327 (Docetaxel) Tannock, 2004	Symptomatic/ Minimally symp.	18.9
IMPACT (Provenge®) Kantoff, 2010	Asymptomatic/ Minimally symp.	25.8

How many patients with mCRPC do we treat with docetaxel?

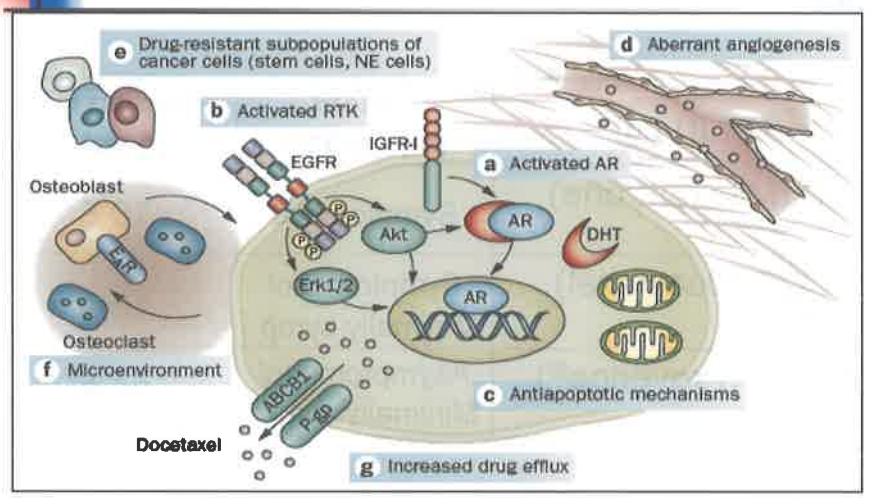
~ 370 men die of prostate cancer in Slovenia annually

Year	No. of patients treated with docetaxel
2007	16 (4,3%)
2008	17 (4,6%)
2009	43 (11,6%)
2010 (until 09/2010)	60 (16,2%)

Are our patients undertreated?

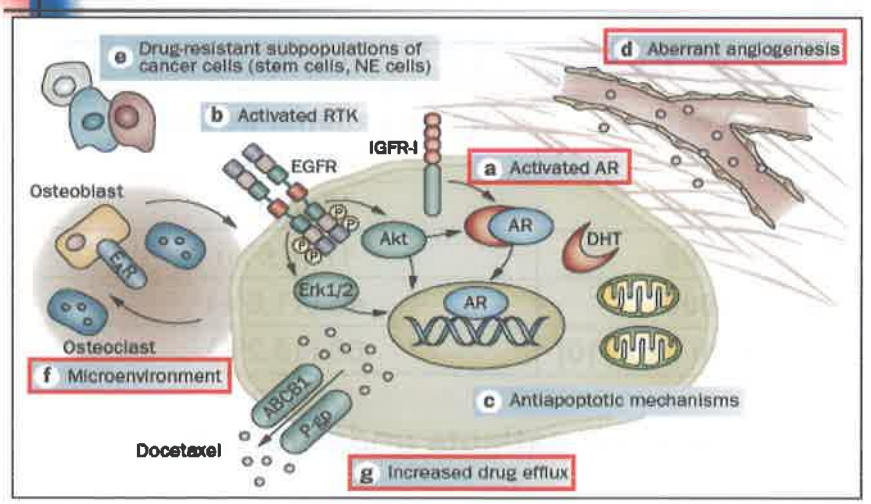
Courtesy of mag. Petra Tavčar & Samo Rožman

Mechanisms of drug resistance in CRPC



Seruga, Ocana & Tannock, Nat Clin Pract Oncol, 2010

Mechanisms of drug resistance in CRPC



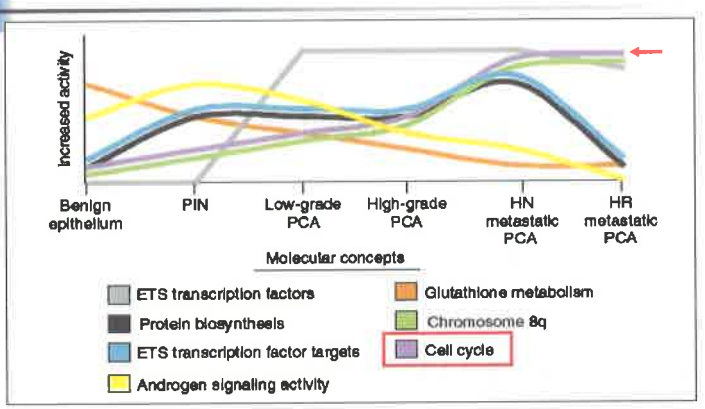
Seruga, Ocana & Tannock, Nat Clin Pract Oncol, 2010

Opportunities for drug development in mCRPC

- Drug "X" pre-Docetaxel
- Drug "X" and Docetaxel
- Drug "X" post-Docetaxel

New chemotherapeutic agents in CRPC

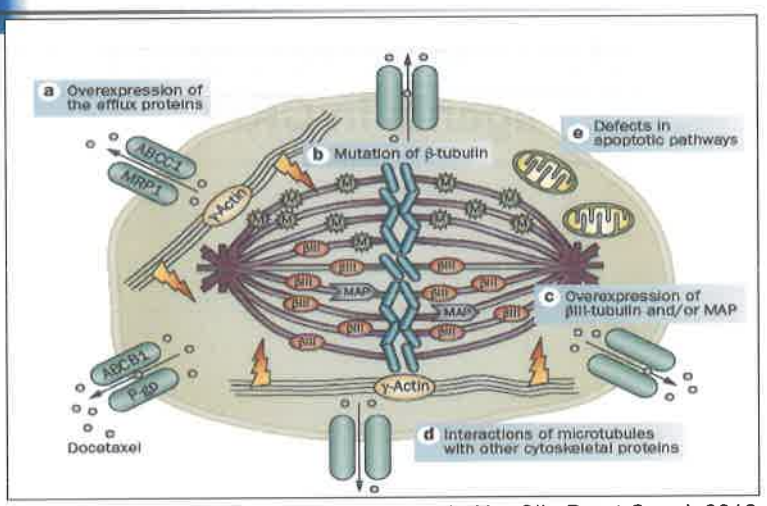
Molecular concept model of prostate cancer progression



With progression proliferative activity increases

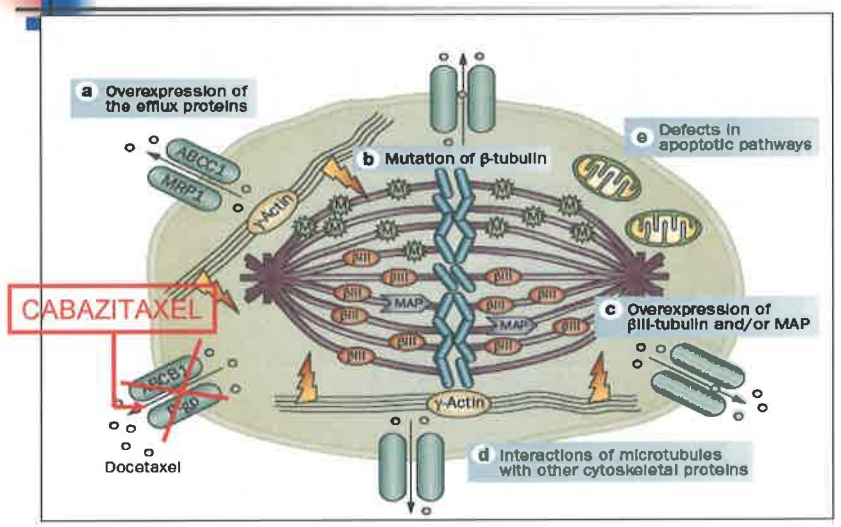
Tomlins, Nat Genet, 2007

Mechanisms of resistance to taxanes



Seruga, Ocana & Tannock, Nat Clin Pract Oncol, 2010

Evading resistance to taxanes



RCTs evaluating chemotherapeutic agents in mCRPC

RCTs	Experimental a. Control a.	Primary endpoint	Results
Drug X + Docetaxel			
Machielis, 2008	Estramustine+D+P D+P	PSA resp. N=150	Negative
Drug X post-Docetaxel			
TROPIC Sartor, 2010	Cabazitaxel+P Mitoxantrone+P	OS N=755	Positive
SPARC Sternberg, 2009	Satraplatin+P Placebo+P	PFS, OS N=950	Negative

TROPIC: Phase III Registration Study 146 Sites in 26 Countries

mCRPC patients who progressed after treatment with a docetaxel-based regimen (N=755)

Stratification factors
ECOG PS (0, 1 vs 2) • Measurable vs non-measurable disease

cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)	mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone 10 mg daily

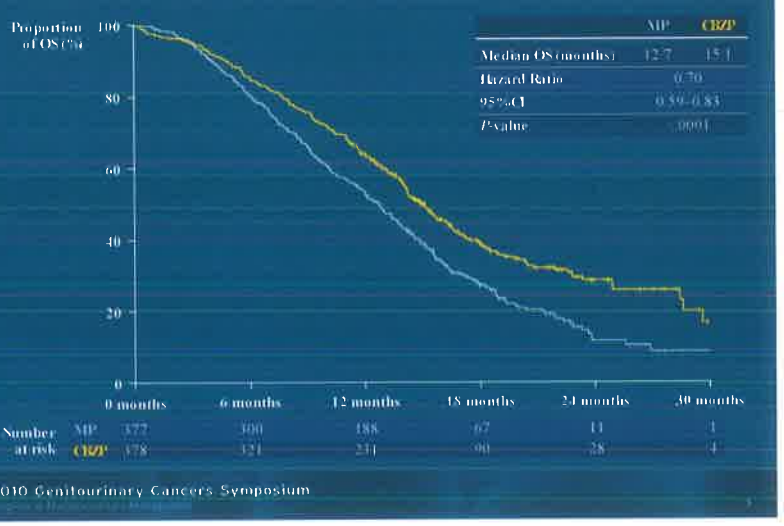
Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Final analysis: Significance level for OS 0.0452 to account for interim efficacy analysis

2010 Genitourinary Cancers Symposium

Primary Endpoint: Overall Survival (ITT Analysis)



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard Ratio	0.70	
95%CI	0.59–0.83	
P value	.0001	

2010 Genitourinary Cancers Symposium

Total Deaths During Study
Safety Population

	MP (n=371)	CBZP (n=371)
Total deaths during study	275 (74.1%)	227 (61.2%)
Due to progression	253 (68.2%)	197 (53.1%)
Due to AEs	7 (1.9%)	18 (4.9%)
Due to other reasons	15 (4.0%)	12 (3.2%)

Toxic deaths due to infections and diarrhea!

Targeting AR-associated signalling in CRPC

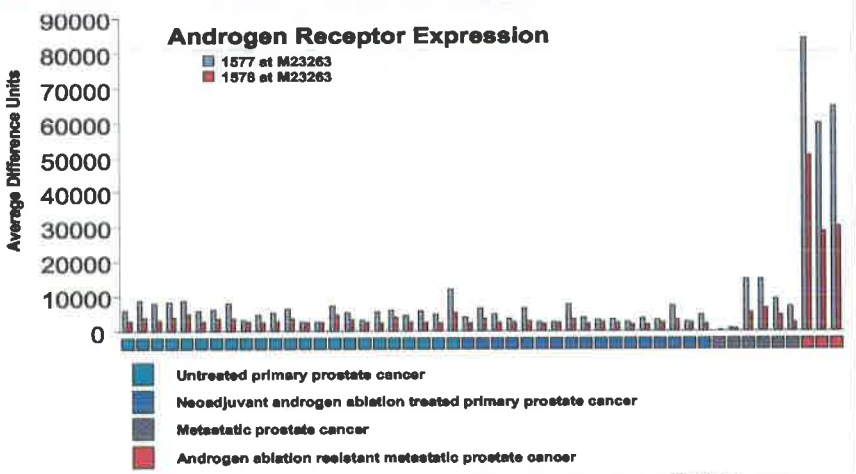
Molecular determinants of resistance to antiandrogen therapy

Charlie D Chen[1,5,8], Derek S Welsbie[3,5,8], Chris Tran[1,4], Sung Hee Baek[4,6], Randy Chen[1], Robert Vessella[7], Michael G Rosenfeld[4,6] & Charles L Sawyers[1–5]

- AR over-expression causes hormone refractory progression
- AR expression is necessary for hormone-sensitive to hormone-refractory progression
- AR-mediated progression occurs by a ligand-dependent mechanism
- Increased AR expression converts antagonists to agonists

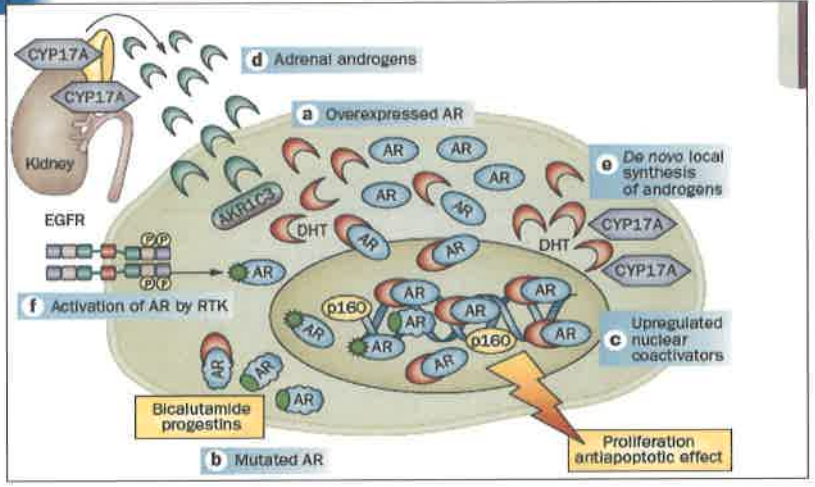
nature medicine 2004

AR is over-expressed in CRPC



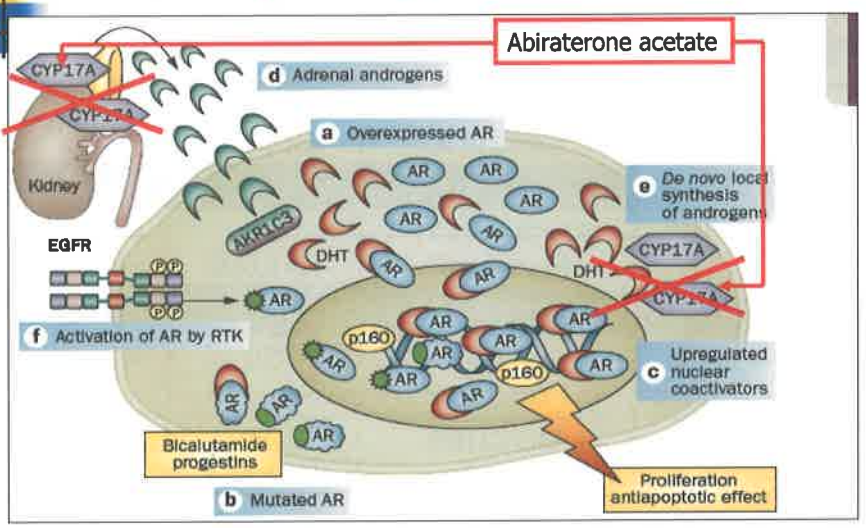
Holzbeierlein, Am J Pathol, 2004

AR-associated signalling in CRPC



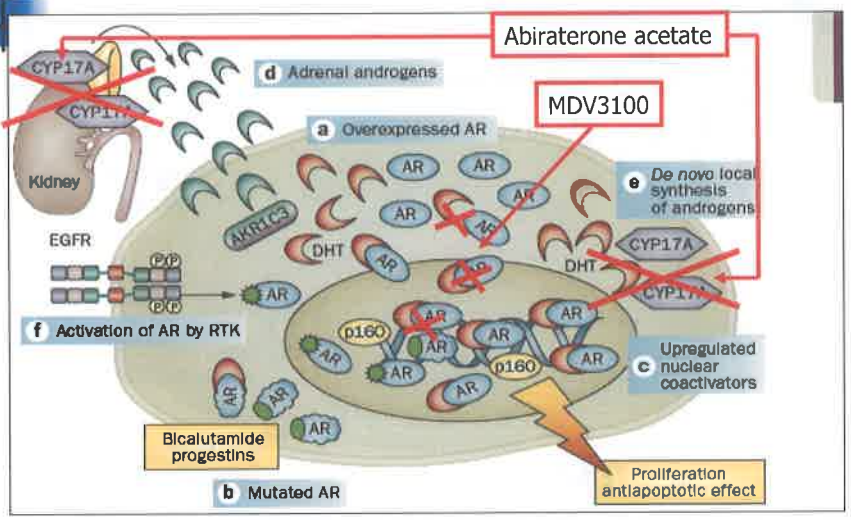
Seruga, Ocana & Tannock, Nat Clin Pract Oncol, 2010

Targeting AR-associated signalling in CRPC



Seruga, Ocana & Tannock, Nat Clin Pract Oncol, 2010

Targeting AR-associated signalling in CRPC



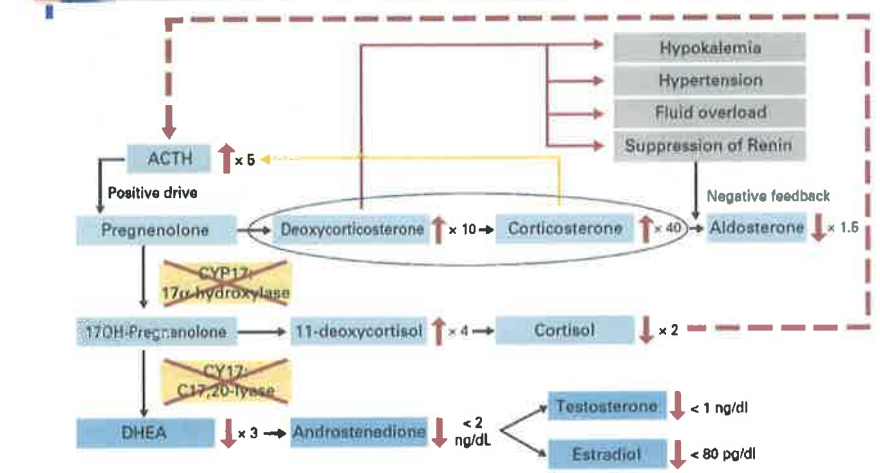
Seruga, Ocana & Tannock, Nat Clin Pract Oncol, 2010

RCTs evaluating agents targeting AR-associated signalling in mCRPC

Phase III RCT	Experimental a. Control a.	Primary endpoint	Results
Drug X pre-docetaxel			
COU-AA-302	Abiraterone+P Placebo+P	OS N=1,000	Recruitment complete
Drug X post-docetaxel			
COU-AA-301 De Bono, 2010	Abiraterone+P Placebo+P	OS N=1,185	Positive
AFFIRM	MDV3100 Placebo	OS N=1,170	Recruiting

OS: Overall Survival; P: Prednisone

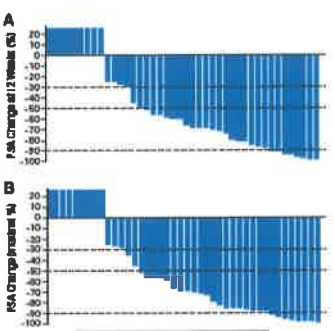
Abiraterone acetate: Inhibitor of Androgen Synthesis



Ryan, J Clin Oncol, 2010

Experience with abiraterone in early phase clinical trials

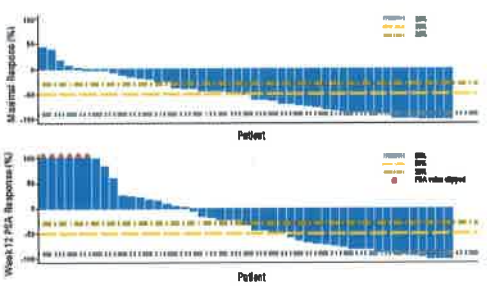
Pre-docetaxel



Phase I/II, n=54

Attard, JCO, 2009

Post-docetaxel

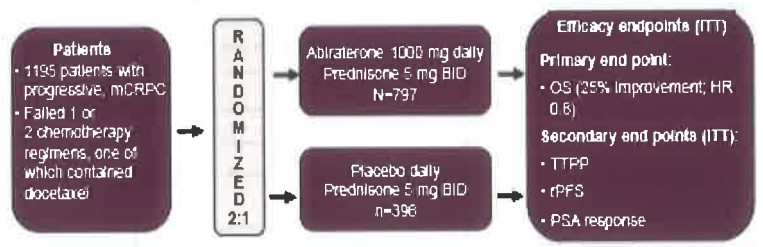


Phase II, n=47

Reid, JCO, 2010

ESMO congress Milan 2010

COU-AA-301 Study Design



- Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study (147 sites in 13 countries; USA, Europe, Australia, Canada)
- Stratification according to:
  - ECOG performance status (0-1 vs. 2)
  - Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs. 4-10 [present])
  - Prior chemotherapy (1 vs. 2)
  - Type of progression (PSA only vs. radiographic progression with or without PSA progression)

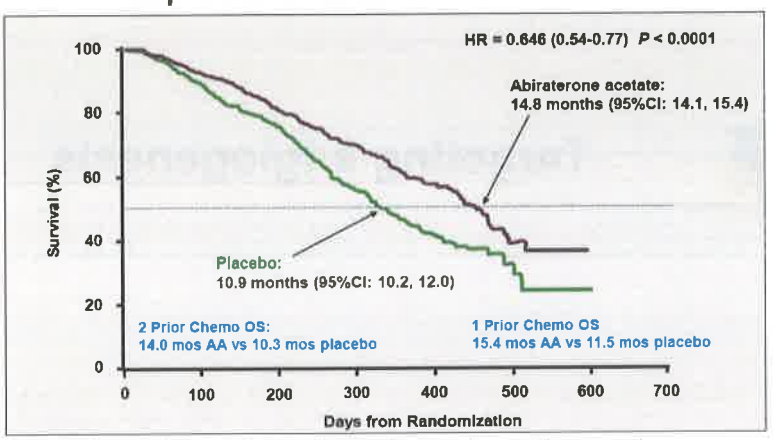
ESMO congress Milan 2010

COU-AA-301 Baseline Demographics

	AA (n = 797)	Placebo (n = 398)	Total (n = 1195)
Median age, years (range)	69.0 (42-95)	69.0 (39-90)	69.0 (39-95)
Race			
White	93.3%	92.7%	93.1%
Black	3.5%	3.8%	3.6%
Asian	1.4%	2.3%	1.7%
ECOG-PS 2	10.7%	11.1%	10.8%
Significant pain present	44.3%	44.0%	44.2%
2 Prior chemotherapies	28.2%	28.4%	28.3%
Radiographic Progression	70.1%	68.6%	69.6%

ESMO congress Milan 2010

COU-AA-301: Abiraterone Acetate Improves Overall Survival in mCRPC



AA	797	728	631	475	204	25	0
Placebo	398	352	296	180	69	8	1

14

ESMO congress Milan 2010

COU-AA-301: AEs of Special Interest

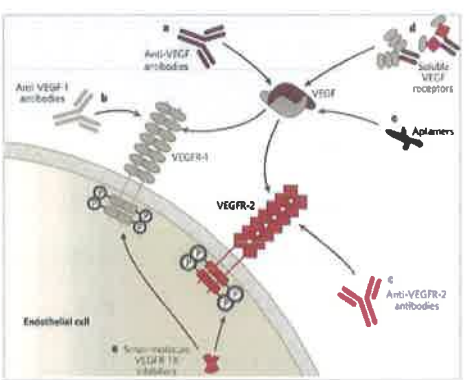
	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fluid retention	30.6%	2.3%	22.3%	1.0%
Hypokalaemia	17.1%	3.8%	8.4%	0.8%
LFT abnormalities	10.4%	3.5%	8.1%	3.0%
Hypertension	9.7%	1.3%	7.9%	0.3%
Cardiac disorders	13.3%	4.1%	10.4%	2.3%

LFT, liver function test

Targeting angiogenesis

VEGF-targeted strategies

- mAbs targeting VEGF-A (a)
- mAbs or small molecules VEGF receptors
- Aptamers that bind the heparin-binding domain VEGF165 (pegaptanib) (e)
- Chimeric soluble receptors such as VEGF-trap (domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused to a Fc fragment of an antibody) (d)



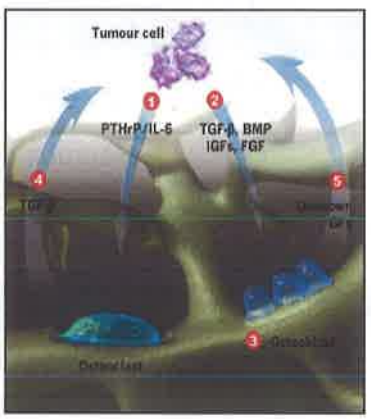
RCTs evaluating antiangiogenic agents in CRPC

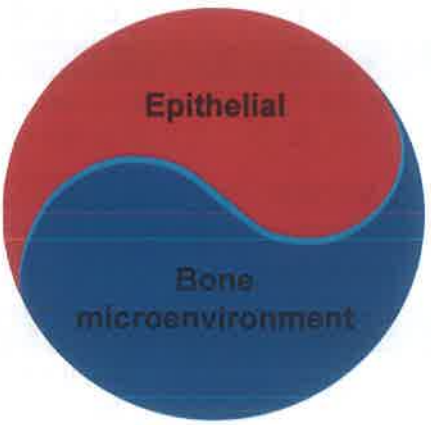
Phase III RCT	Experimental a. Control a.	Primary endpoint	Results
Drug X + Docetaxel			
CALGB 90401 Kelly,2010	Bevacizumab+D+P Placebo+D+P	OS N=1,020	Negative
VENICE	Aflibercept+D+P Placebo+D+P	OS N=1,200	Recruitment Complete
MAINSAIL	Lenalidomide+D+P Placebo+D+P	OS N=1,015	Recruiting
Drug X post-Docetaxel			
SUN 1120	Sunitinib+ P Placebo+P	OS N=819	Discontinued

Targeting bone microenvironment

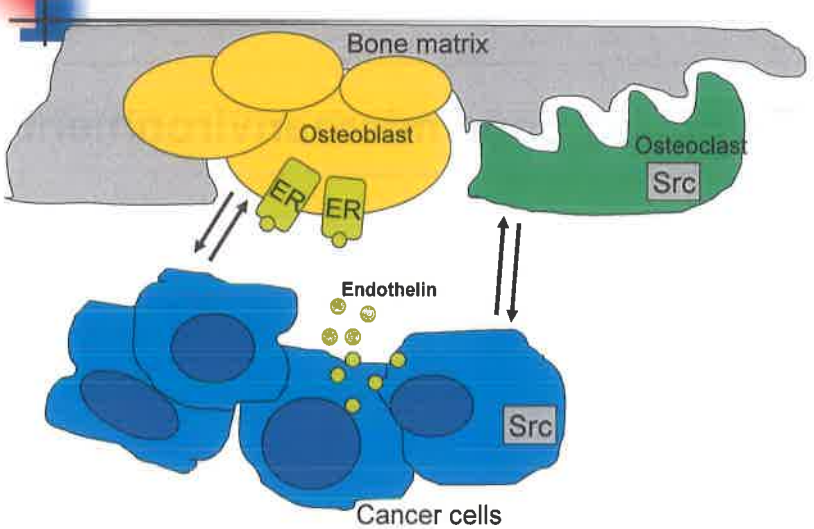
Bone-epithelial interaction central to prostate cancer progression

Osteoblastic Bone Disease

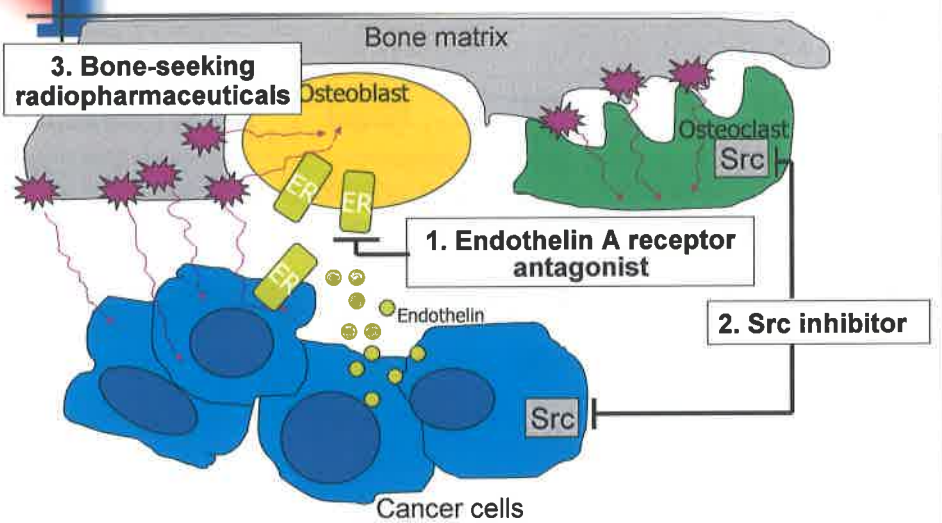




Bone microenvironment



Targeting bone microenvironment



RCTs evaluating agents targeting bone microenvironment

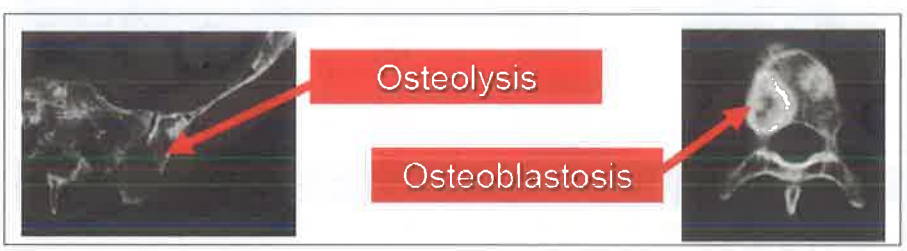
Phase III RCT	Experimental a. Control a.	Target	Primary endpoint	Results
Drug X pre-Docetaxel				
Carducci, 2007	Atrasentan Placebo	ER	TTP N=809	Negative
Enthuse M1	Zibotentan Placebo	ER	OS N=848	Recruitment complete
Drug X + Docetaxel				
SWOG SO421	Atrasentan+D+P Placebo+D+ P	ER	OS, PFS N=930	Recruitment complete
Enthuse M1c	Zibotentan+D+P Placebo+D+P	ER	OS N=1,044	Recruiting
CA180-227	Dasatinib+D+P Placebo+D+P	Src	OS N=1,380	Recruiting

RCTs evaluating agents targeting bone microenvironment (cont.)

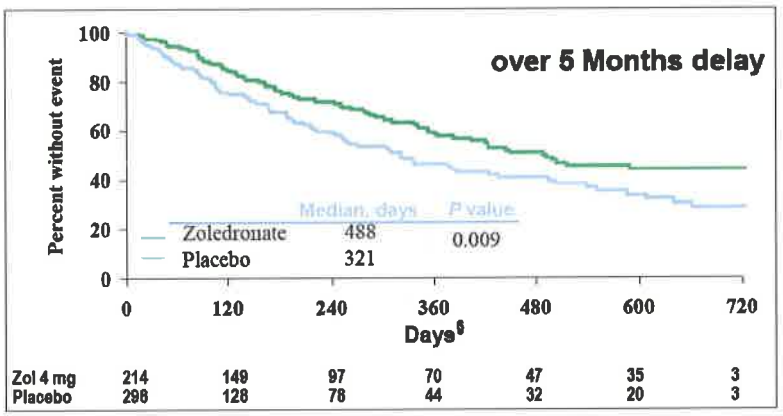
Phase III RCT	Experimental a. Control a.	Target	Primary endpoint	Results
Drug X + Docetaxel				
MD Anderson	D+P or KAVE— Sr+A D+P or KAVE	Bone matrix	OS N=480	Recruiting
Drug X post-Docetaxel				
ALSYMPCA	Alpharadin Placebo	Bone matrix	OS N=750	Recruiting

Alpharadin: Radium-223 (α-radiation)
Sr: Strontium-89 (β-radiation)

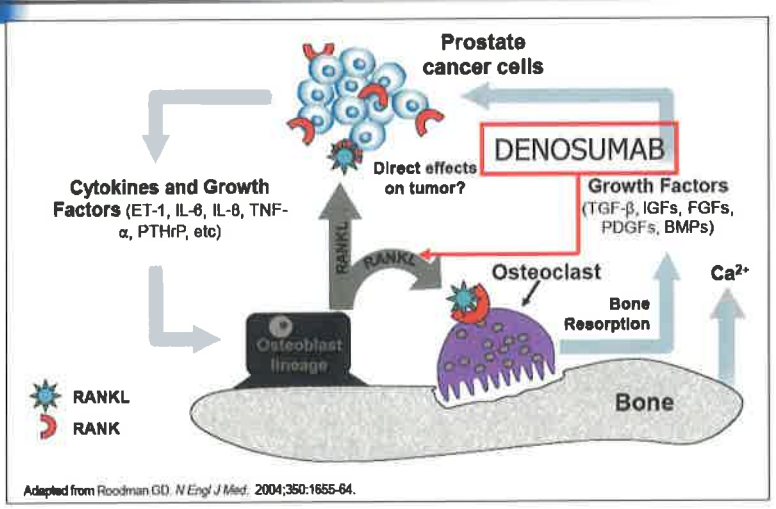
Osteoclasts present irrespective of radiology



Zoledronic acid in mCRPC



Role of denosumab in vicious circle



SRE Phase III study in mCRPC

Key Inclusion

- Castration-resistant prostate cancer and bone metastases

Key Exclusion

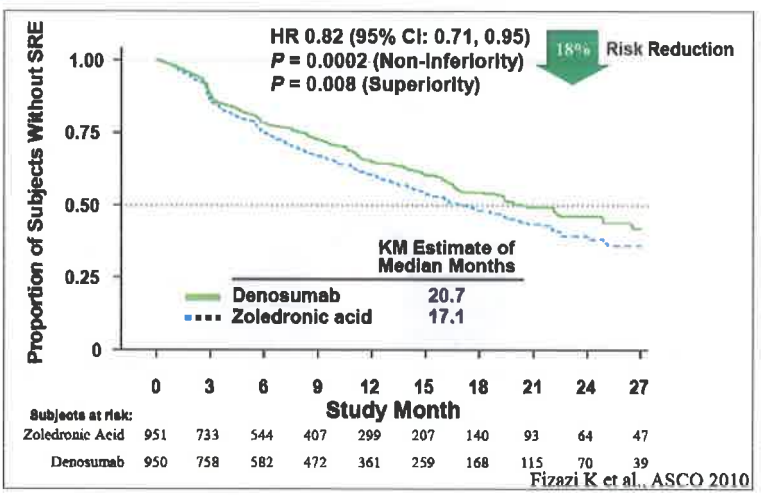
- Current or prior intravenous bisphosphonate administration

Denosumab 120 mg SC and Placebo IV* every 4 weeks

Zoledronic acid 4 mg IV* and Placebo SC every 4 weeks

Supplemental Calcium and Vitamin D

Time to first skeletal related event (SRE)



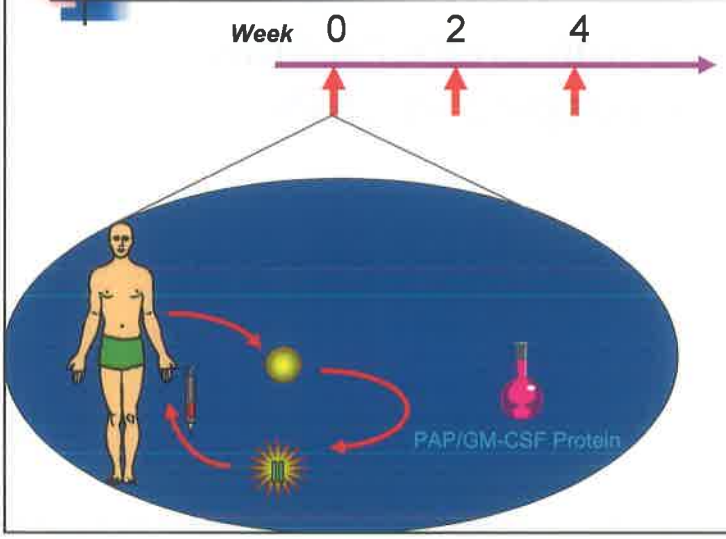
Fizazi K et al., ASCO 2010

New immunoherapeutic strategies in CRPC

Whole-Cell Prostate Cancer Vaccine (GVAX®)

- GVAX prostate cancer vaccine is a GM-CSF secreting whole-cell vaccine composed of prostate cancer cell lines (PC-3 and LN-CaP) genetically modified to secrete GM-CSF
- GM-CSF (sargramostim) can expand and activate APCs
- Whole-cell vaccines, unlike peptide vaccines, express multiple tumor antigens and are capable of eliciting a broad immune response; especially important if the "best" antigen target is unknown

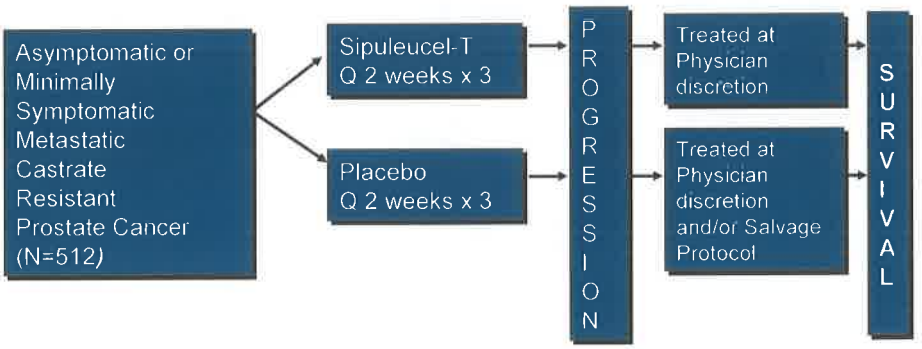
An Autologous Cellular immunotherapy Sipuleucel-T (Provenge®)



RCTs evaluating new immunotherapies

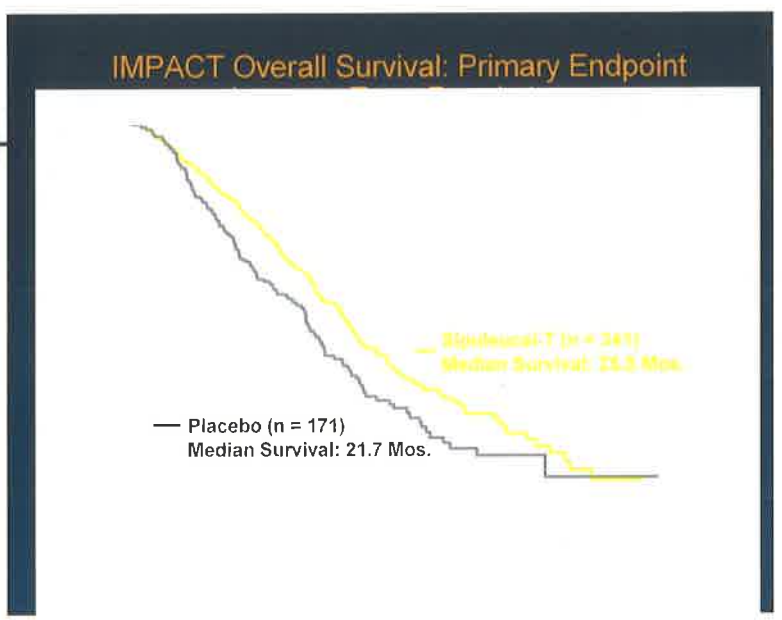
Phase III RCT	Experimental a. Control a.	Target	Primary endpoint	Results
Drug X pre-Docetaxel				
VITAL-1	GVAX® D+P	Multiple Antigens	OS N=626	Negative
IMPACT Kantoff, 2010	Provenge® Placebo	PAP	OS N=521	Positive
Drug X + Docetaxel				
VITAL-2	GVAX® +D+P D+P	Multiple Antigens	OS N=408	Negative

Phase III IMPACT Trial



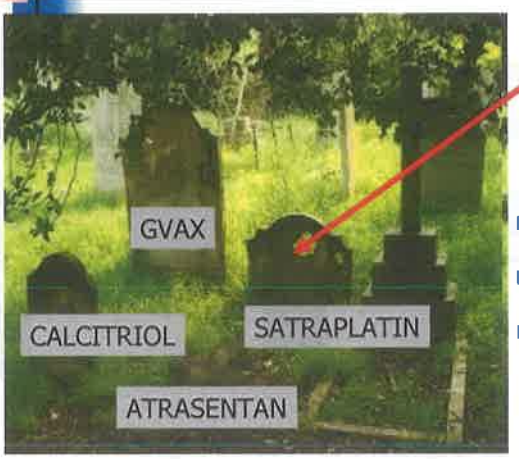
Primary endpoint: Overall Survival

Secondary endpoint: Time to Objective Disease Progression



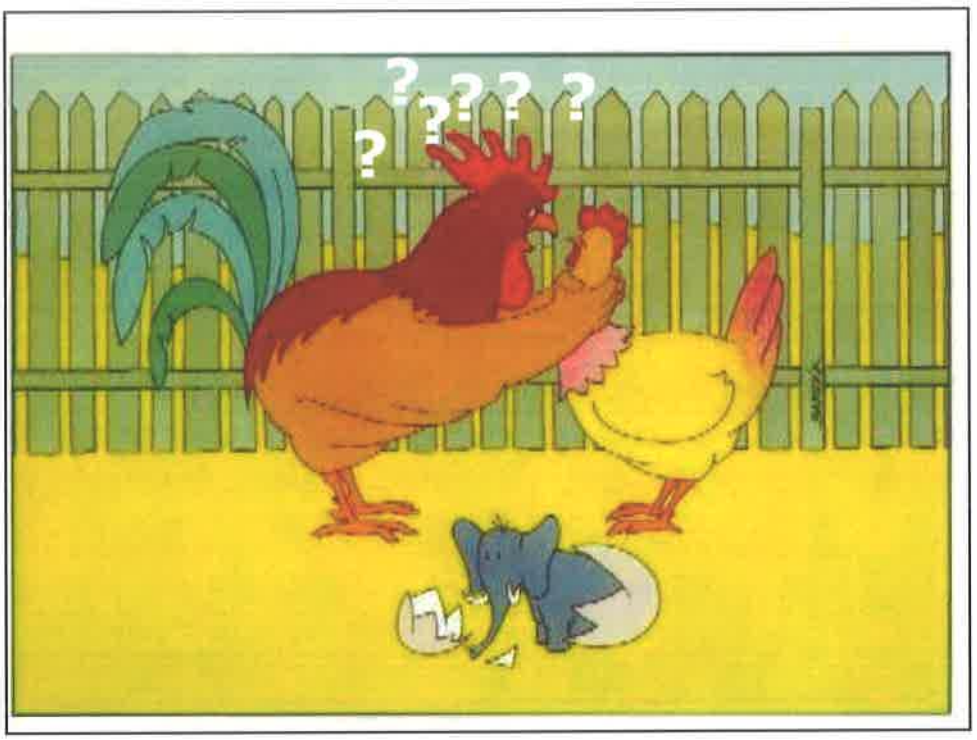
Kantoff, NEJM, 2010

The cemetery of dead drugs in struggle against CRPC



Negative RCTs

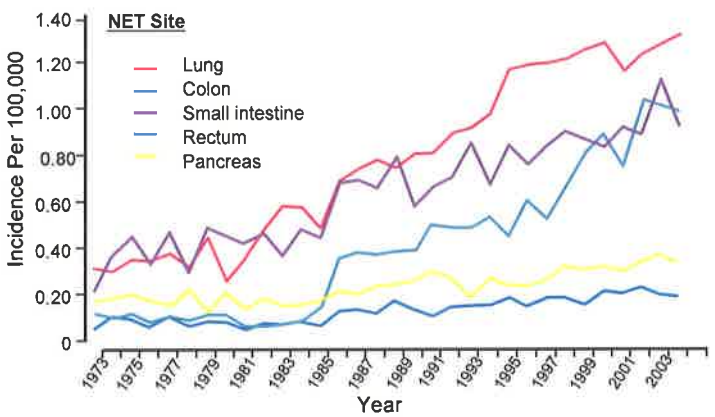
- Inactive drugs?
- Inappropriate target?
- Lack of appropriate patient selection?



Neuroendocrine tumors
Lung NET

Tanja Cufer, MD, PhD
University Clinic Golnik, Slovenia
Medical Faculty, University of Ljubljana, Slovenia

Incidence of NET is Increasing



SEER = Surveillance, Epidemiology, and End Results;

Approximate 5-fold increase between 1975 and 2004
Approximate 7-fold increase also evident in Norwegian registry

Yao J, Hassan M, Phan A, et al. *J Clin Oncol.* 2008;26:3063-3072.

NET Vary by Primary Tumor Site

- Generally characterized by their ability to produce peptides that may lead to associated syndromes (functional vs nonfunctional)
- Historically classified based on embryonic origin
  - Foregut tumors
  - Midgut tumors
  - Hindgut tumors
- Today, primary tumor location is recommended for NET classification

Foregut
- Thymus
- Esophagus
- Lung
- Stomach
- Pancreas
- Duodenum

Midgut
- Appendix
- Ileum
- Cecum
- Ascending colon

Hindgut
- Distal large bowel
- Rectum

1. Modlin IM, et al. *Lancet*. 2008;9:61-72. 2. Modlin IM, et al. *Gastroenterology*. 2005;128:1717-1751.

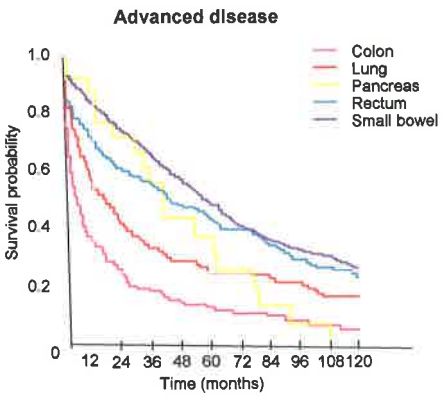
Diversity of NET Has Impacted Nomenclature

- Although some commonalities exist, NET include a diverse family of malignancies
- Range of behaviors/aggressiveness
  - Poorly vs. well differentiated
  - Tumor grade (G1, G2, G3)
  - Benign vs. malignant
- Extent of disease
  - Local vs. distant metastases
- Location of primary tumors
  - Lung, colon, small intestine, rectum, pancreas, etc
- Symptomatic vs. asymptomatic
  - Symptoms due to hormonal syndromes vs tumor mass

1. Klimstra DS, et al. *Am J Surg Pathol*. 2010;34(3):300-313. 2. Modlin IM, *Gastroenterology*. 2005;128:1717-1751. 3. Modlin IM, et al. *Lancet Oncol*. 2008;9(1):61-72.

Correlation of Primary Tumor Site with Survival

- Known prognostic factors include:
  - Location of primary tumor
  - Extent of disease
  - Tumor stage
  - Degree of differentiation/ proliferative index (PI)
  - Tumor grade
  - Patient age
  - Performance status

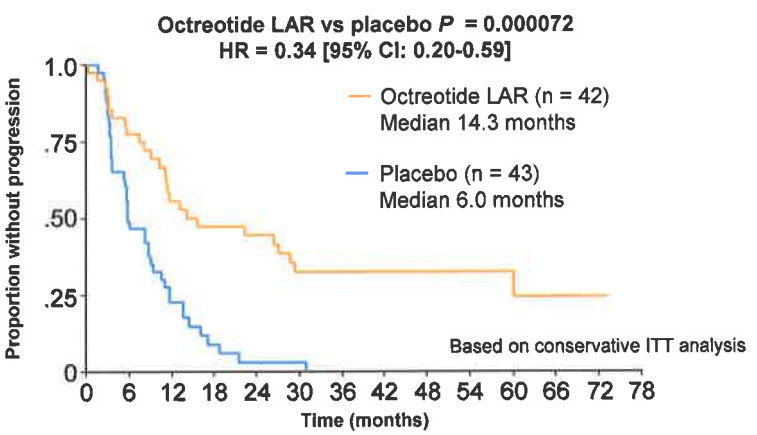


65% of patients with advanced NET will not be alive in 5 years !

Yao JC, et al. *J Clin Oncol.* 2008;26:3063–3072

New Treatment Modalities

PROMID: Octreotide LAR in advanced Midgut tumours

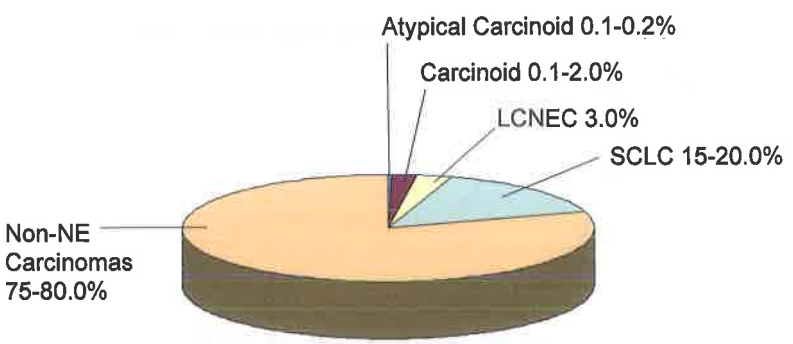


Rinke A, Barth P, Wied M, et al. *J Clin Oncol.* 2009;27:4656-4663.

Pulmonary NET Classification

- Low grade
  - Typical carcinoid
- Intermediate grade
  - Atypical carcinoid
- High grade
  - Large cell neuroendocrine carcinoma (LNEC)
  - Small cell carcinoma (SCLC)

Lung NET Frequency



Lung NET: Clinical Features: Japanese Registry

	TC	AC	LCNEC	SCLC
Age: Mean (Range) yr	52 (17–83)	63 (38–73)	67 (40-84)	65 (17-88)
Sex: % M	58,2	44,4	89,4	79,7
Paraneo-plastic %	1,8	0	0	2,7
% smokers	54,6	55,6	98,6	93,8

Asamura H et al: J Clin Oncol 24: 70,2006

Lung NET Pathologic Differential

	TC	AC	LCNEC	SCLC
Mitoses per 10 HPF	<2	2-10	>11 (median-70)	>11 (median-80)
Necrosis	No	Yes	Yes	Yes
Histologic heterogeneity	No	No	Yes	Yes
IHC tumor markers				
Neuroendocrine*	Yes	Yes	Yes	No
NSE	Yes	Yes	Yes	No
CD56	Yes/No	Yes/No	Yes	Yes
TTF1	No	No	Yes (40-70%)	Yes (70-80%)

* Chromogranin A, synaptophysin

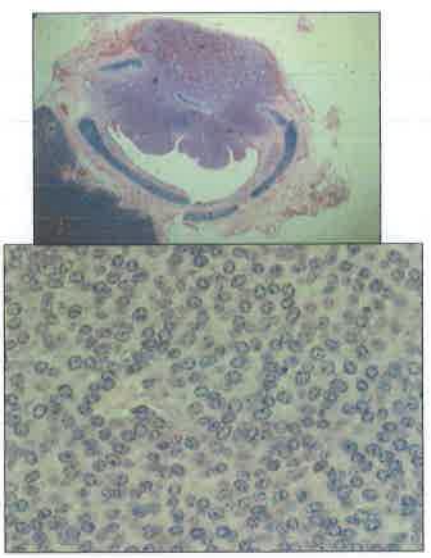
Typical and Atypical Carcinoid Diagnostic Criteria

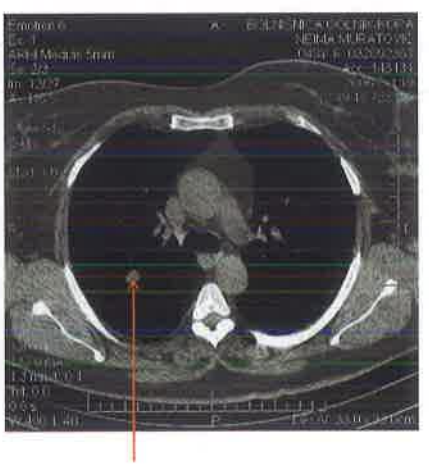
- Typical Carcinoid
  - Less than 2 mitoses per 10 HPF (2 mm^2) and no foci of necrosis
  - Centrally located tumors, endobronchial growth
- Atypical Carcinoid
  - 2-10 mitoses per 10 HPF (2 mm^2)

    OR
  - Foci of necrosis
  - Peripheral lessions

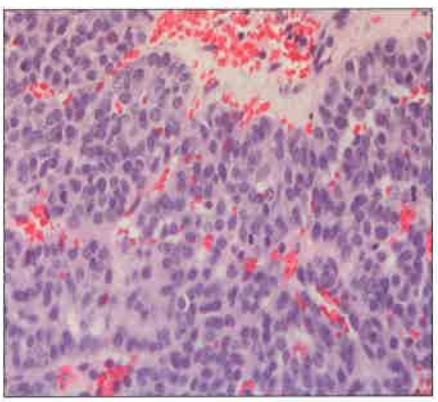
Travis WD, et al: Am J Surg Pathol 22: 934-44, 1988

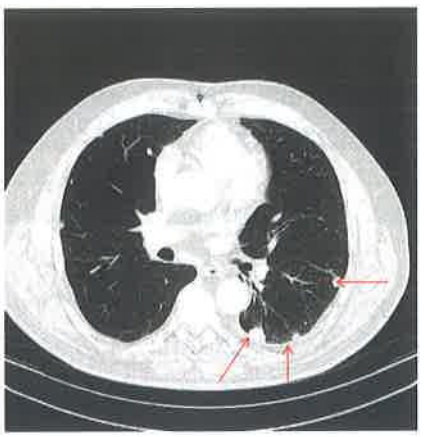
Typical Carcinoid



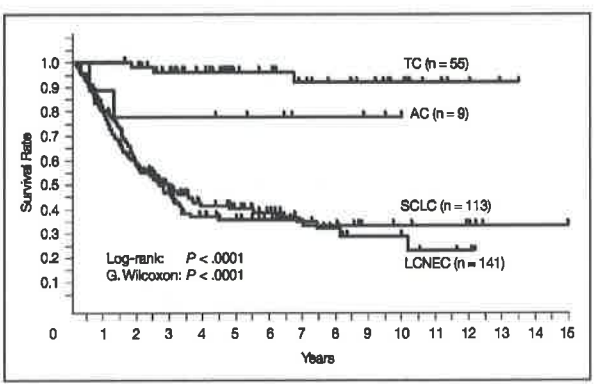


Atypical Carcinoid





Pulmonary NET
Survival rates of surgically resected disease



5 %-yr Survival

TC: 87%

AC: 56%

LCNEC: 27%

SCLC: 9%

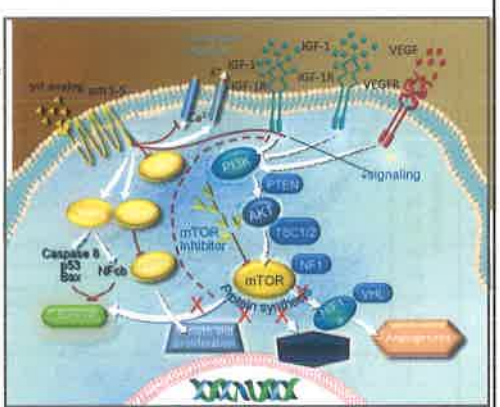
Asamura H et al: *J Clin Oncol* 24:70,2006

Typical and Atypical Carcinoid

- Most patients with TC are diagnosed with limited disease
  - Conventional surgery represents a standard treatment, with 5-year survival of 92%-100%
- AC patients have a significantly worse prognosis with reduced 5-year survival of 61%-88%
  - Most of the patients are diagnosed in advanced stage
  - Conventional chemotherapy has limited efficacy for patients with advanced NET
- Octreotide LAR, historically used for symptom control in GI-NET, prolongs time to progression and improves QoL
- New agents, like bevacizumab, sunitinib, everolimus might be beneficial in pts with in low -, intermediate grade NET tumors

Rationale for Combining Everolimus and Octreotide LAR

- mTOR is a central regulator of growth, proliferation, metabolism, and angiogenesis
- NET have been linked to genetic alterations that activate the mTOR pathway
- Everolimus inhibits mTOR
- Octreotide downregulates IGF-1, an upstream activator of the PI3K/AKT/mTOR pathway
- Everolimus + octreotide LAR has shown activity in a phase II trial



RADIANT-2: Study Design

Phase III Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial

Patients with advanced well,-moderately differentiated NET with a history of carcinoid syndrome,
N = 429
Lung N= 40

RANDOMIZE

1:1

Everolimus 10 mg/d + octreotide LAR 30 mg/28 days n =216

Crossover

Placebo + octreotide LAR 30 mg/28 days n =213

Treatment until disease progression

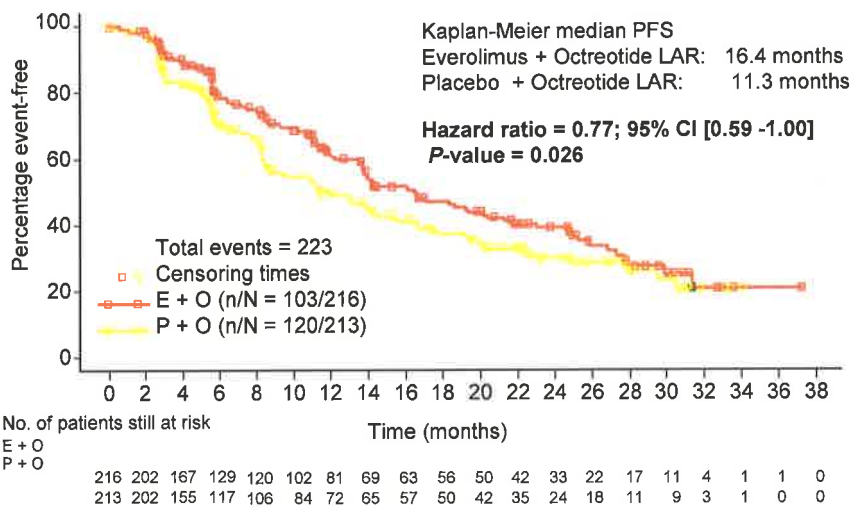
Multi-phasic CT or MRI performed every 12 weeks

Primary endpoint:
- PFS (RECIST)

Secondary endpoints:
- OS
- Safety and tolerability

Clinicaltrials.gov: NCT00412061

RADIANT 2: PFS by Central Review



No. of patients still at risk

E + O	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
P + O	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0

Pavel M et al,; ESMO 2010

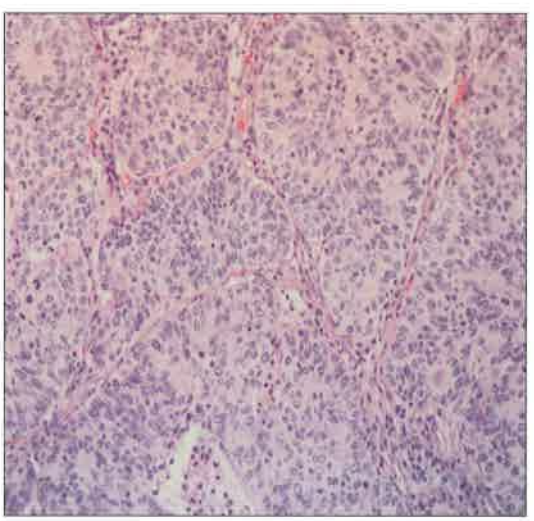
RADIANT 2: Treatment Related Adverse Events

Occurring in ≥10%	Everolimus + Octreotide LAR n = 216		Placebo + Octreotide LAR n = 211	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Stomatitis*	62	7	14	0
Rash	37	1	12	0
Fatigue	31	7	23	3
Diarrhea	27	6	16	2
Nausea	20	1	16	1
Infections*	20	5	6	1
Dysgeusia	17	1	3	0
Anemia	15	1	5	0
Weight decreased	15	1	3	0
Thrombocytopenia	14	5	0	0
Decreased appetite	14	0	6	0
Peripheral edema	13	0	3	0
Hyperglycemia	12	5	2	1
Dyspnea	12	2	1	0
Pulmonary events*	12	2	0	0
Vomiting	11	1	5	1
Pruritus	11	0	4	0
Asthenia	10	1	7	1

*Related toxicities grouped for calculations

Large Cell NE Carcinoma Diagnostic Criteria

- NE Morphology: Organoid nesting, trabecular, palisading, rosette-like patterns
- Increased Mitoses (11 or more per 10 HPE or mm^2)
- NE differentiation by immunohistochemistry or EM



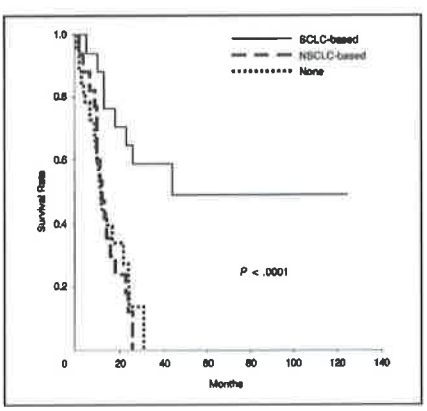
LCNEC: NCC Research Institute, Tokyo

- 87 cases (3,1% resected lung cancers)
- Sex: 77M (89%); Mean age 68 yr (37-82)
- Smoking: 98%; No paraneoplastic syndromes
- 5-yr survival – overall: 57%
  - Stage I: 67%; II: 75%; III: 45%; IV: 0%
  - Stage I LCNEC: 67%; PD NSCLEC: 88%; LCC: 92% (p=0,003)
  - No difference between Stage I SCLC and LCNEC

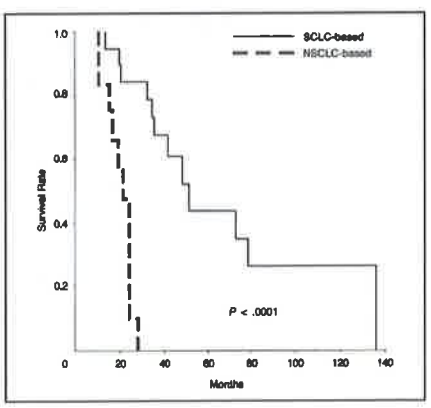
Takei H et al: J Thorac Cardiovasc Surg 24: 285, 2002

LCNEC: Chemotherapy

Adjuvant Setting
(Platinum/etoposide vs Gemcitabine/taxanes)



Metastatic Setting
(Platinum/etoposide vs Gemcitabine/taxanes)

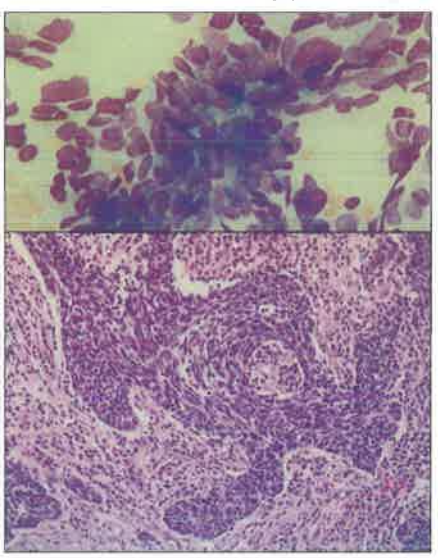


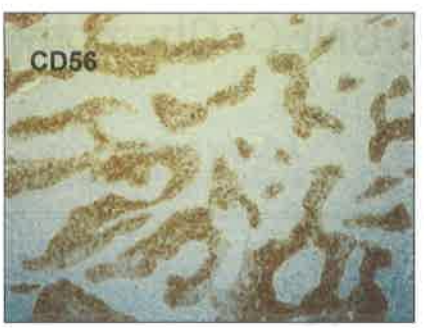
Rossi G eta al: *J Clin Oncol* 23: 8774,2005

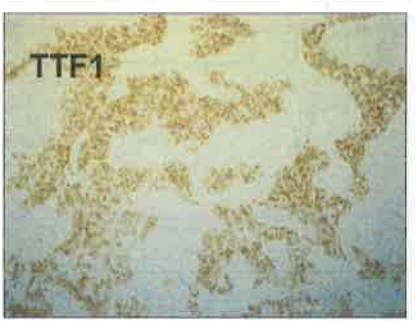
LCNEC: Chemotherapy

- Iyoda A: JTCVS 138: 446, 2009
  - 79 LCNEC; 36 recurred; Pts receiving platinum based chemo – significantly better DF survival (p>0,001)
- Saji H et al: Anticancer Drugs 21: 89-93, 2010
  - 45 LCNEN pts; 23 (41%) perioperative chemotherapy (mostly platinum based) – better survival (p=0,04)
- Igawa S et al: Lung Ca 68: 438-45, 2010
  - 14 HG NE carcinoma c/w LCNEN; clinical efficacy of chemo comparable to ED-SCLC

SCLC Pathology Criteria



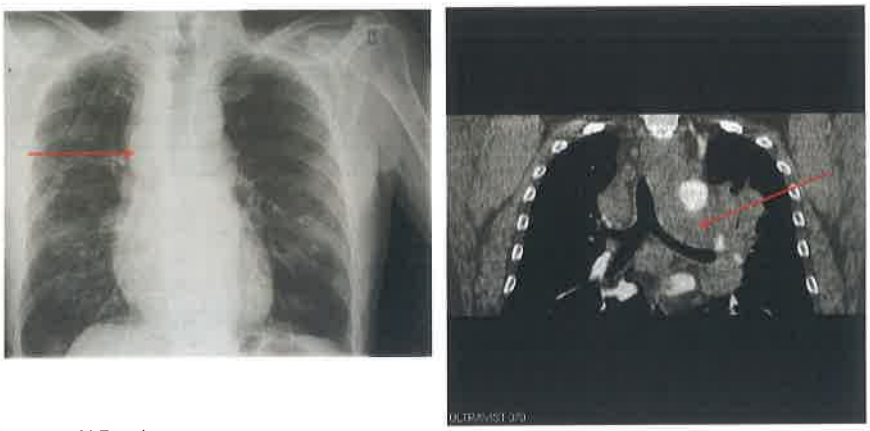




Courtesy of I Kern

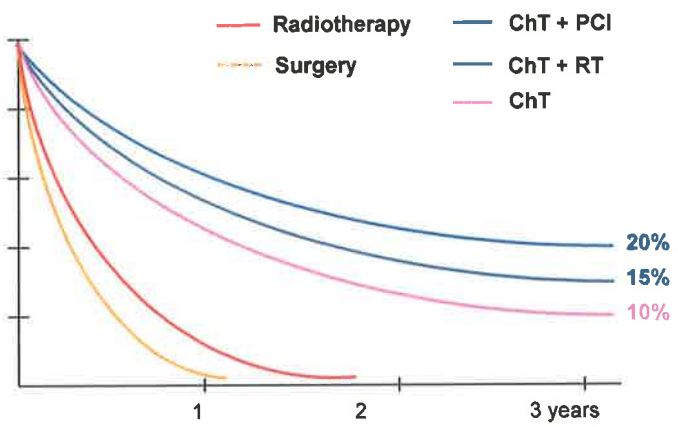
SCLC Radiologic Criteria

Bulky, widespread mediastinal disease



Courtesy of I Pozek

SCLC - Progress in Therapeutic Outcome



Courtesy of J Jassem

Cisplatin / Etoposide Versus CEV

	Cis/Etop	CEV
N	218	218
OS (all) 2-year 5-year	5%	2%
OS (LD) 2-year	15%	8%

- Cisplatin/Etoposide is superior to CEV
- Subset analyses revealed Cisplatin/etoposid superiority only in LD

Sundstrøm S *et al. J Clin Oncol* 2002; **20**(24): 4665–4672

Unmet Medical Needs in SCLC

- Topotecan improves survival and symptom control vs. BSC in second line therapy, thus representing a standard SL therapy
- New platinum based combinations (irinotecan/platinum, pemetrexed/carbo) failed to show superiority to cisplatinum/etoposide schema
- Amrubicin is a new agent of promising efficacy in relapsed SCLC, phase3 trial comparing amrubicin vs topotecan is underway
- So far, numerous targeted agents failed in SCLC
- To improve treatment results molecular predictor of response to either ChT or targeted agents need to be explored more profoundly in a near future (ERCC1, topo2, VEGF, ...)

Pulmonary NET Treatment

Pulmonary NET - Progress in Therapeutic Outcome

HISTOLOGY	SURGERY	SYSTEMIC THERAPY	RADIATION
TC	Primary approach	Not proven	Not proven
AC	Primary approach (N evaluation !)	Not yet proven Experimental approaches are encouraged	Not proven
LCNEC	If resectable	Probably needed	Effective locally
SCLC	Controversial	Primary approach	Effective locally

ESMO guidelines, Ann Oncol 2010; 21:v220-222; NCCN guidelines

In Summary

- Pulmonary NET include a wide spectrum of tumors, from low-grade TC, intermediate-grade AC to high-grade LCNEC and SCLC.
- Most of pulmonary NET express neuroendocrine markers, while paraneoplastic symptoms are quite rare.
- Nowadays, a proper anatomical staging (according to UICC7 edition) and sophisticated pathomolecular tumor classification are of upmost importance for effective therapy.
- Surgery, irradiation and chemotherapy still represent the mainstay of therapy. However, new treatment approaches based on better molecular markers identification and new targeted therapies are supposed to further improve survival rates and QoI of patients.

Multidisciplinary teams should take care of pulmonary NET patients!

Lymphomas in patients with HIV infection

Clinical cases

Doc.dr. Barbara Jezeršek Novaković,dr.med
Gregorič Brigita, Matej Horvat, Tanja Mesti

Clinical case 1

- M, 37 years old
- HIV-1+ patient; otherwise healthy and did not take any medications
- Presenting history:

  Upper abdominal pain and obstructive icterus since April 1998

  Despite the ERCP with an insertion of a stent into the dilatated d.choledochus there was no improvement
- Physical examination: PS (WHO) 3, icterus, no enlarged lymph nodes, ascites

INITIAL INVESTIGATIONS:

- Leu 9,19; Ery 5,5; Hb 164; Ht 0,46; MCV 83,7;Plt 619; neutro 77%; lymph 19%, mono 3%, eoz 0%, baso 0%; biochem.- pathologic liver tests (bilirubin 349; AP 12,30; gamaGT 32,48; AST 6,81; ALT 4,49); creatinine 137; urea 15,4; uric acid 849; LDH 25,58; CRP 6
- HIV-1 RNA (PCR) 8902 copies/ml, CD-4 count 114/mm^3
- CXR: minimal pleural effusion in right interlobar fissure
- XR of paranasal sinuses: normal

INITIAL INVESTIGATIONS:

- CT of abdomen: extensive ascitic fluid (3-4 L), infiltration of peritoneum, atrofic left hepatic lobe probably due to the occlusion of the left branch of venae portae and left hepatic vein. Larger tumor mass in the left hepatic lobe and in porta hepatis, marked dilatation of intrahepatic ducts, stent in d.choledochus
- CT of thorax showed minimal pleural fluid left and hiatal hernia, but was otherwise normal

OTHER INVESTIGATIONS:

- Ascites - cytology: diffuse large B cell lymphoma (CD10+, FMC7+, CD52+, CD38+, MIB-1 50%)
- Biopsy of bone marrow: no lymphoma infiltrates

Conclusion: diffuse large B-cell lymphoma, cytological diagnosis, stage IV.A.E.
Involved regions: liver (left lobe), peritoneum, ? pleura left, IPI 4.

- Diagnosis of lymphoma and HIV infection was made simultaneously

TREATMENT:

- Treatment in April 2008: methylprednisolone in increasing dosages (16 mg→125 mg) from the first day of hospitalization; an attempt to treat the patient with modified CVP on the day 4 (50% dosages)
- However, the patient's condition was irreversible, his hepatic and liver function progressively deteriorated (hepatorenal syndrome) during hospitalization and the patient died on day 6.

Clinical case 2

- M, 54 years old
- HIV-1+ patient, otherwise healthy and did not take any medications
- Presenting history:

  Swelling in the right parotid region for the last 2 months growing rapidly to a mass with 15 cm in diameter (spreading down to neck, behind the ear and up to the temple), headache, troubles with opening of his mouth, weight loss of 4 kg, no constitutional (B) symptoms
- Physical examination: PS (WHO) 1, large mass in the right parotid region (15 cm), other lymph nodes not enlarged, white coating of tongue

INITIAL INVESTIGATIONS:

- Leu 5,9; Ery 4,95; Hb 158; Ht 0,433; MCV 87; Plt 365; neutro 69%; lymph 22%, mono 8%, eoz 1%, baso 0%; biochem.- gamaGT 1,1, s-proteins 100, otherwise normal biochemistry (LDH 3,28)
- HIV-1 RNA (PCR) 250.000 copies/ml, CD-4 count 231/mm^3
- CXR: normal
- XR of paranasal sinuses: normal
- ORL examination: protrusion of pharyngeal wall on the right side
- US of abdomen: normal

OTHER INVESTIGATIONS:

- Cytology of the tumor under the right ear: morphologically and immunocytochemically Burkitt's lymphoma
- Biopsy of bone marrow: no lymphoma infiltrates, moderate to marked siderosis

Conclusion: Burkitt's lymphoma, cytological diagnosis, stage I.A.X, risk group (Murphy) 2.
Involved regions: lymph nodes in the right parotid region extending down to the right side of the neck.

- Diagnosis of HIV infection was made prior to the diagnosis of lymphoma

TREATMENT:

- Treatment from May 1998:
  Cytoreduction (5 days) with methylprednisolone and cyclophosphamide according to BFM protocol
- First A cycle (MD MTX, Ifosfamide, VP-16, Ara-C and dexamethasone) and prophylactic intrathecal chemotherapy from day 5 onwards
  Complication: 9 days after the first cycle the patient developed febrile neutropenia and stomatitis (Leu 0,42; Hb107; Plt 66) and needed to be hospitalized
- Clinically CR after the first cycle, US (neck) showed lymph node in parotid region (14X7mm) and on the right side of neck (15x6 mm)

TREATMENT:

- Second B cycle (MD MTX, Cyclophosphamide, Adriamycin, Vincristine) and prophylactic intrathecal chemotherapy in June 1998

  Complication: 6 days after the second cycle the patient had to be hospitalized because of febrile episode and stomatitis (Leu 1,9; neutro 75%, Hb 85, Plt 146)
- The third and the last fourth B cycle with prophylactic intrathecal chemotherapy were applied in July 1998

  Complication: stomatitis after third and fourth cycle
- No prophylactic antimicrobial therapy during chemotherapy
- Prophylactic G-CSF (3 -5 days) after every chemotherapy cycle

FOLLOW UP:

- The control US of neck in September 1998 showed reactive lymph nodes on the right side of neck (0,7 cm)
- In September 1998 the patient refused to take anti-retroviral medications adviced by the infectologist and would not start them until 1999
- The patient was followed by regular medical examinations for the first 5 years, no relapse of lymphoma had been confirmed (since July 1998)

Retrospective clinical trial

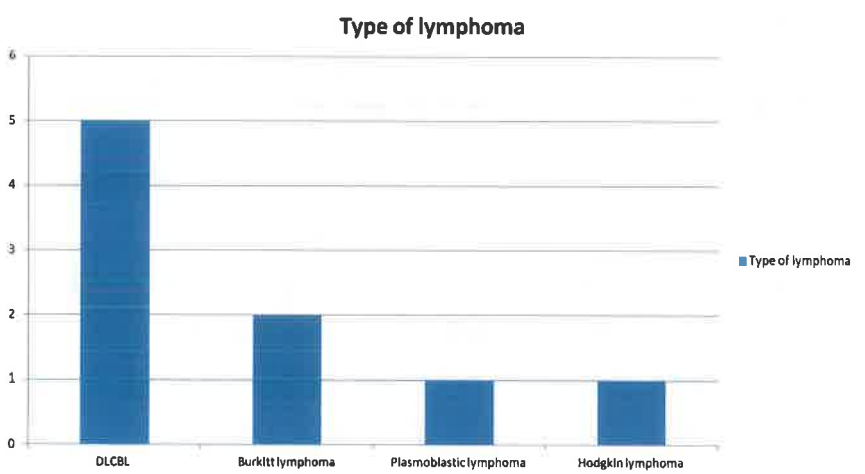
- Inclusion criteria:
  diagnosis of malignant lymphoma
  diagnosis of HIV infection or AIDS
- Patients treated at the Institute of Oncology Ljubljana
- Period 1998-2009
- 9 consecutive patients

Patients

- 9 male patients, 0 female patients
- Mean age at the discovery of lymphoma 48,0 years (range 24,0-59,5)
- Mean age at the discovery of HIV infection 47,2 years (range 20,0-59,5)
- 4 patients diagnosed with HIV infection at the time of diagnosis of lymphoma
- 5 patients diagnosed with HIV infection prior to the diagnosis of lymphoma

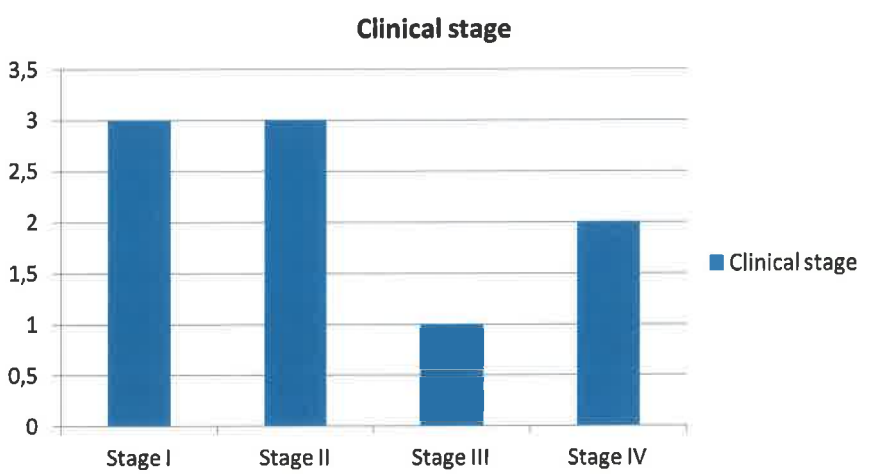
Patients

- 8 diagnosed with NHL:
  5 diffuse large B cell lymphoma (DLCBL)
  2 Burkitt's lymphoma
  1 plasmoblastic lymphoma
- 1 diagnosed with HL:
  mixed cell type



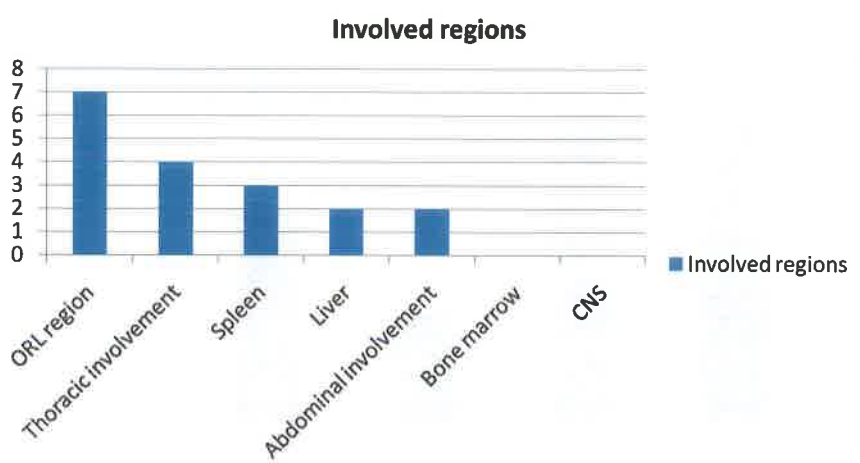
Patients

- Clinical stage of lymphoma:
  Stage I: 3
  Stage II: 3
  Stage III: 1
  Stage IV: 2



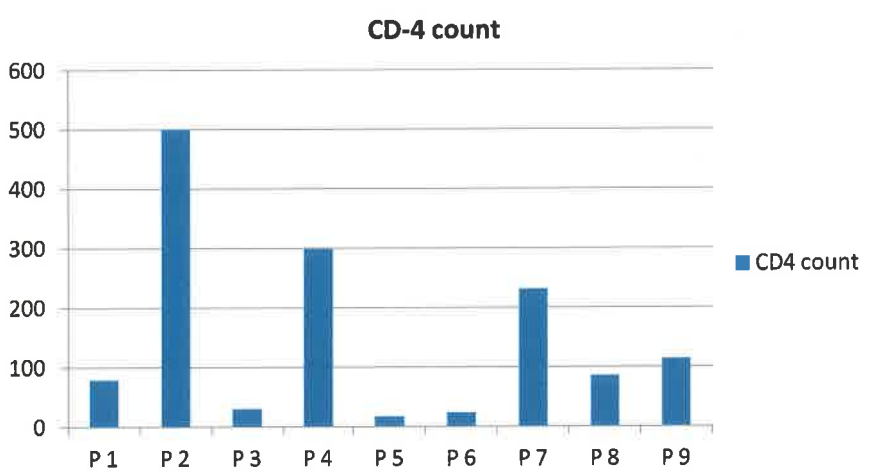
Patients

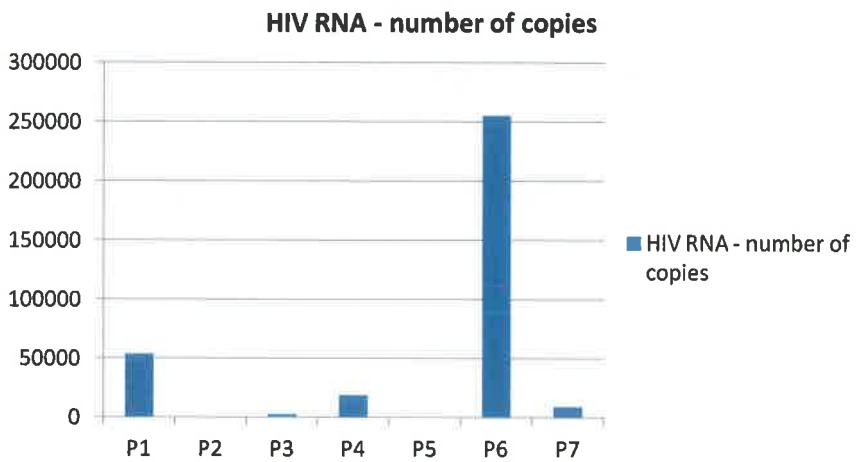
- Involved regions:
  Head and neck region: 7
  Thoracic involvement: 4
  Spleen: 3
  Liver: 2
  Abdominal involvement: 2
  Bone marrow: 0
  CNS: 0



Patients

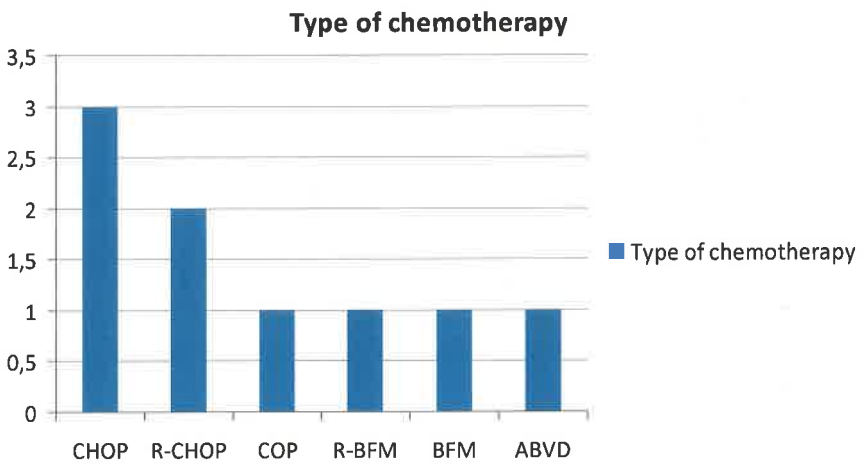
- Mean CD4 count: 153,3 cells/mm^3 (all 9 patients, range: 17-501 cells/mm^3)
- Mean number of HIV RNA copies: 48,408 copies/ml (7 patients, range: 40-255,000 copies/ml)





Treatment

- All 9 received chemotherapy:
  3 patients CHOP
  2 patients R-CHOP
  1 patient COP
  1 patient R-BFM
  1 patient BFM
  1 patient ABVD
  2 patients prophylactic i.t. chemotherapy
- Median number of chemotherapy cycles 4,5 (range: 1-8)



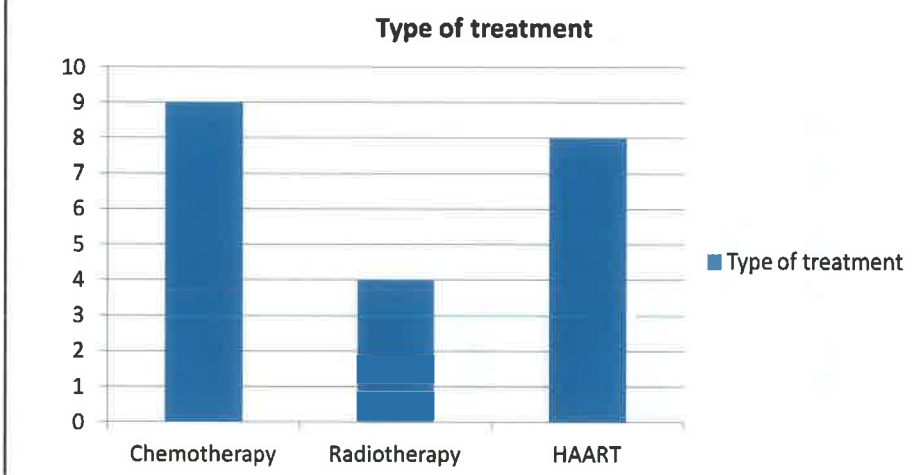
Treatment

- Radiotherapy:

  4 patients had additional radiotherapeutical treatment with 30,6 Gy

- HAART:

  8 patients received HAART, 7 simultaneously with chemotherapy, 1 after chemotherapy



Comorbidities

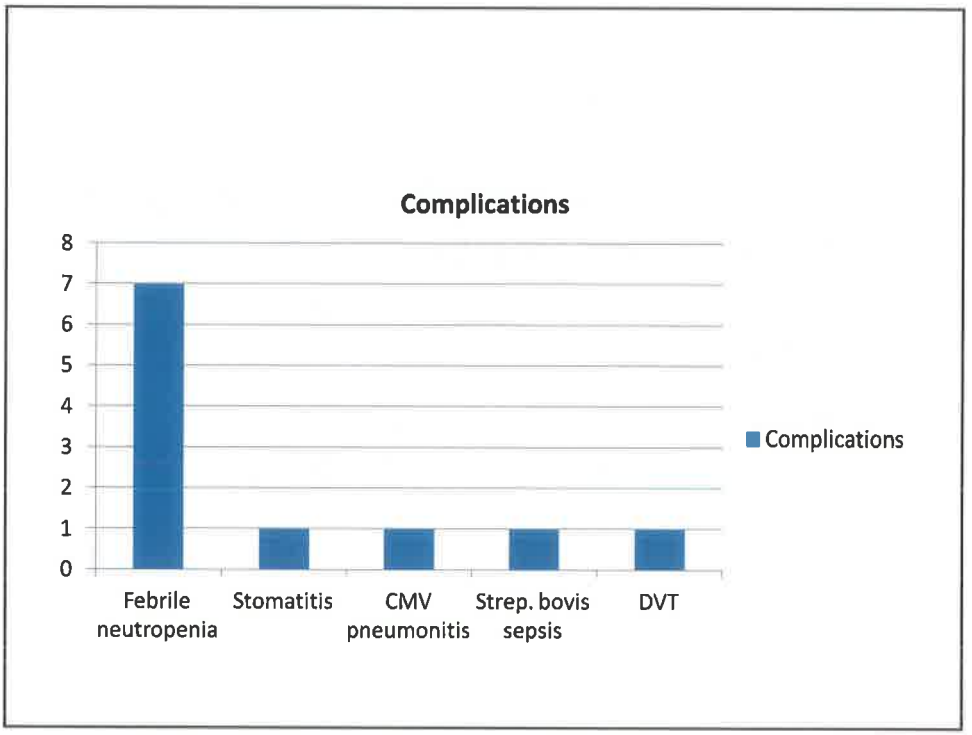
- 1 reactivation of CMV infection
- 1 latent TBC infection
- 3 hepatitis B infection in their clinical history
- 1 patient had 2 other types of cancer (invasive papilary carcinoma of urothelial epithelium, laryngeal carcinoma)

Supportive treatment

- 6 patients received prophylactic antibiotics and antimicotics (combination of trimetoprim-sulfamethoxazol and fluconazole)
- 6 patients received prophylactic granulocyte colony-stimulating factor

Complications

- 7 had febrile neutropenia
- 1 had stomatitis
- 1 had CMV pneumonitis
- 1 had Streptococus bovis sepsis
- 1 had DVT



Conclusion

- 8 patients completed planned chemotherapy treatment
- 4 patients received additional radiotherapy treatment
- 7 patients who completed planned chemotherapy treatment achieved CR
- 1 patient died after 1st cycle of chemotherapy
- 1 patient died after completed chemotherapy treatment

Conclusion

- 7 patients are still in CR on regular follow up, mean time of their survival is 65 months (range 16-150 months)
- Mean time of survival of all patients is 52 months (range 0-150 months)
- 1 patient died after 1st cycle of chemotherapy, because of spread of lymphoma
- 1 patient died after completed chemotherapy treatment, because of an opportunistic infection

Conclusion

- Patients were treated with the same chemotherapeutic regimen as non-HIV lymphoma patients
- Patients received HAART treatment
- Most patients received antibiotic and G-CSF prophylaxis
- Patients in our clinical trial had lower stage of lymphoma and different regions of involvement than AIDS related lymphoma patients

AIDS related lymphomas

Mesti Tanja,MD; Gregoric Brigita,MD; Horvat Matej,MD

Mentor: doc.dr.Jezersek Barbara, MD, PhD

Objective

- Discuss the most important issues in AIDS related lymphomas – what we, as oncologists, should be aware of

Incidence of AIDS - related and AIDS - Non related cancers

4194 patients included; 251 cancers diagnosed

Cancer type	Number of cases	%	Men	Age (median)	CD4 (median)
AIDS-defining cancer	109	43	78%	41.5	209
Non-Hodgkin's Lymphoma	61	24			
Kaposi's sarcoma	41	16			
Cervix uteri's carcinoma	7	3			
Non-AIDS-defining cancer	142	57	84%	46.8	329
Bronchopulmonary cancer and URT*	41	16			
Skin cancer	20	8			
Hodgkin's disease	18	7			
Hepatoma	16	6			
Anal cancer	14	6			
Other hemopathy	6	3			
Other solid tumors	27	11			

* Upper Respiratory Tract

The 15th Conference on Retroviruses and Opportunistic Infections, 2008, Abstract 15, Fabrice Bonnet Immunodeficiency and Risk of AIDS-defining and Non-AIDS-defining Cancers: ANRS CO3 Aquitaine Cohort, 1998 to 2006

Categories of HIV-associated Lymphomas: WHO Classification

- Lymphomas also occurring in immunocompetent patients
  - Burkitt's lymphoma
    - Classic
    - With plasmacytoid differentiation
    - Atypical
  - Diffuse large B-cell lymphoma
    - Centroblastic
    - Immunoblastic
  - Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue lymphoma (rare)
  - Peripheral T-cell lymphoma (rare)
  - Classic Hodgkin's lymphoma

Categories of HIV-associated Lymphomas: WHO Classification

- Lymphomas occurring more specifically in patients who are HIV* positive
  - Primary effusion lymphoma
  - Plasmablastic lymphoma of the oral cavity
- Lymphomas occurring in other immunodeficiency states
  - Polymorphic B-cell lymphoma

*HIV, human immunodeficiency virus

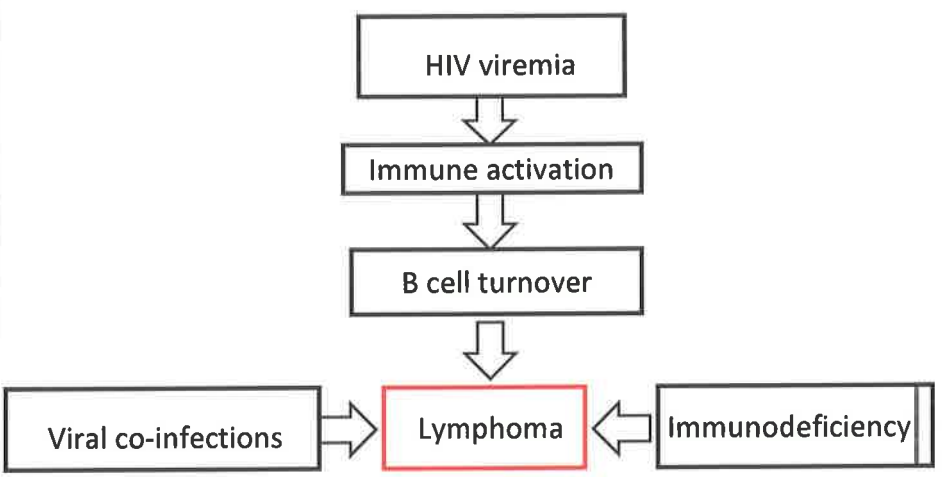
AIDS related lymphomas

- Burkitt's lymphoma
- Large cell lymphomas
- Primary effusion lymphoma
- Plasmablastic lymphoma of the oral cavity

AIDS related lymphomas

- NHLs are the most common lymphomas
- DLBCL comprises 30% of AIDS related disease and is usually seen when CD4<100
- 70% of lymphomas in HIV have mutations resulting in deregulation of BCL-6 proto-oncogene (pathway normally leading to B cell proliferation)

Hypothesis



Clinical characteristics of ARL

- 80% present with Stage IV disease
- Diffuse lymph node involvement is considered much less common
- Gastrointestinal HIV related lymphomas are the most common localization (45%)
- Marrow involvement 30% of time thus consider marrow biopsy if no other sites
- CNS involvement 10-20%

Discussion

- Risk factors
- The importance of HAART
- The role of rituximab
- Treatment

Alexander Zoufaly Insufficient Virus Suppression during HAART Is a Strong Predictor for the Development of AIDS related Lymphoma: German CLINSURV Cohort

Known associations with lymphoma risk

Study	Associated
Grulich et al,AIDS,2000	Increased risk: Prolonged immunodeficiency B-cell stimulation
Kirk et al,Blood,2001	Increased risk: Age, male sex Lower CD4 count Higher VL
Bonnet et al,CID,2006	Protective: HAART > 6 months VL nadir < 500 cop/ml

The 15th Conference on Retroviruses and Opportunistic Infections, 2008, Abstract 16

Alexander Zoufaly Insufficient Virus Suppression during HAART Is a Strong Predictor for the Development of AIDS related Lymphoma: German CLINSURV Cohort

Results [6364pts]

All lymphomas(n69)		Burkitt's (n11)	Non Burkitt high grade(n32)	PCNSL(n8)
Risk factor	HR p	HR p	HR p	HR p
Significant in a multivariate analysis				
Age <0.01	1.4(1.1-1.7)	1.4(0.8-2.3) ns	1.4(1.0-1.9) 0.04	1.8(1.0-3.2) 0.05
Cum.viremia <0.01	1.4(1.1.-1.7)	3.0(1.6-5.3) <0.01	1.5(1.1.-2.0) <0.01	0.9(0.4-1.9) ns
Latest CD4<200 <0.01 201-350 <0.01	8.6(4.2-17.5) 5.0(2.4-10.3)	3.1(0.7-13.6) ns 1.2(0.2-7.3) ns	10.0(3.2-31.6) <0.01 7.8(2.5-24.2) <0.01	15.2(1.6-141.4) 0.02 4.8(0.4-54.8) ns

The 15th Conference on Retroviruses and Opportunistic Infections, 2008, Abstract 16

Alexander Zoufaly Insufficient Virus Suppression during HAART Is a Strong Predictor for the Development of AIDSrelated Lymphoma: German CLINSURV Cohort

Conclusion

- Age, latest CD4 count, cumulative viremia are strong risk factors for the development of lymphoma
- Higher impact of viremia for Burkitt's lymphoma
- Viremia is the only directly modifiable factor
- Optimization of HAART might reduce the incidence of lymphoma

The 15th Conference on Retroviruses and Opportunistic Infections, 2008, Abstract 16

Non Hodgkin Lymphomas

International Prognostic Index

Risk factors:

- Age
- Stage
- Serum LDH
- ECOG performance status
- Extranodal site

Prognosis

- Low risk (0-1 points) - 5-year survival of 73%
- Low-intermediate risk (2 points) - 5-year survival of 51%
- High-intermediate risk (3 points) - 5-year survival of 43%
- High risk (4-5 points) - 5-year survival of 26%

Marc Bower, Prognostic index in ARNHL on HAART, Chelsea and Westminster cohort

- 9621 HIV seropositive; 111 ARNHL
- Two independent predictors of death
- IPI
- CD4 count
- 1 y survival: low risk 82%;
  low intermediate 47%;
  high intermediate 20%;
  high 15%

Bower M et al; A Prognostic Index for Systemic AIDS-Related Non-Hodgkin Lymphoma Treated in the Era of Highly Active Antiretroviral Therapy; Annals of Internal medicine; August 16, 2005vol. 143 no. 4 265-273

HAART

- Reverse transcription inhibitors (viral RNA-viral DNA)

  Nucleoside reverse transcriptase inhibitor (NRTI);interfering with nucleotides

  Non nucleoside reverse transcriptase inhibitor (NNRTI); reverse transcriptase enzyme
- Viral assembly inhibitor

  Protease inhibitors (PI); protease enzyme

Studies showing the impact of HAART on response rate and survival

Study (date)	Population	Study design	Main findings
Antinori (2001)	Two Italian centers n=65	Retrospective: HAART was administered concomitantly with chemotherapy and followed for 27 months	CR 71% of HAART respond and 30% of non respond Virolog.R to HAART associated with tumor R and ↑ surv
Tam (2002)	United States Multicenter AIDS Cohort (MAC) n=100	Retrospective observational: 100 men with a diagnosis of NHL	HAART associated with ↑surv for NHL pts And 8% reduced risk of death
Vaccher (2003)	Italy n=235	Retrospective single institution analysis	CR 49%; ↑ risk for ↓OS with no HAART use
Hoffmann (2003)	Germany multicenter cohort study n=203	Retrospective observational	HAART R associated with ↑ CR and OS

Soon TL et al, Recent Advances in Acquired Immunodeficiency Syndrome (AIDS) related Lymphoma, CA Cancer J Clin 2005; 55:229-241,doi: 10.3322/canjclin.55.4.229 © 2005 American Cancer Society

Selected Regimens and Outcomes for AIDS associated NHL

Regimen	Evaluable Patients	Median Baseline CD4c/mm3	CRR (%)	PFF 1y	PFF 2y	Study (Reference)
Infusional CDE	48	70	46		36	Spudich et al
Dose-adjusted EPOCH (HAART deferment until chemotherapy completion)	39	198	74		73	Lebrette et al
Three pooled Phase II trials of R-CDE	74	161	70		59	Spina et al
Randomized R-CHOP vs.CHOP	99 51	130 147	57.6 47	50 48		Kaplan et al
Randomized R-DA-EPOCH vs.DA-EPOCH followed by rituximab	38 38	190 180	65 38	80 72		Sparano et al

CRR (Complete response rate); PFF (Percent Failure Free); CDE(Cyclophosphamide,doxorubicin,etoposide); EPOCH (Etoposide,doxorubicin and vincristine with oral prednisone and bolus cyclophosphamide); HAART (Higly active antiretroviral therapy); R-CDE (Rituximab with CDE); R-CHOP (Rituximab with cyclophosphamide,doxorubicin,vincristine and prednisone (CHOP)); R-DA-EPOCH (Rituximab with dose adjusted (DA) EPOCH)

Sparano J et al; Phase II Trial of infusional cyclophosphamide, doxorubicin and etoposide in patients with HIV associated non Hodgkin's lymphoma: an Eastern Cooperative Oncology Group Trial (E 1494); J Clin Oncol 2004; 22:1491-1500; Little RF et al; Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology; Blood 2003; 101: 4653-4659; Spina M et al; Rituximab and infusional cyclophosphamide, doxorubicin and etoposide in HIV associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials; Blood 2005;105:1891-1897; Kaplan LD et al; Rituximab does not improve clinical outcome in a randomized phase III trial of CHOP with or without Rituximab in patients with HIV associated non Hodgkin lymphoma: AIDS malignancies consortium trial 010; Blood 2005; 106:1538- 1543; Sparano J et al; Randomized phase II trial of infusional EPOCH chemotherapy given either concurrently with or sequentially followed by rituximab in HIV associated lymphoma: AIDS Malignancy Consortium Trial 034; in 10th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies: Bathesda, October 16-17, 2006

RITUXIMAB

	Schedule	Sample size	CR (%)	2y OS (%)
Boue,2006	R-CHOP	61	77	75
Kaplan,2005	R-CHOP	99	58	55
Spina,2005	R-CDE	74	70	64
Ribera,2008	R-CHOP	81	69	56

Abbreviations: NHL, non-Hodgkin lymphoma; CR, complete response; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicine, vincristine and prednisone; R-CDE, rituximab,cyclophosphamide,doxorubicine and etoposide

Jean-Phillppe Spano, Dominique Costagliola, Christine Katlama, Nicolas Mounier, Eric Oksenhendler, David Khayat; AIDS-Related Malignancies: State of the Art and Therapeutic Challenges; *Journal of Clinical Oncology*, Vol 26, No 29 (October 10), 2008: pp. 4834-4842

Conclusion

- Factors related with neoplasms rather than HIV variables are the main predictors of treatment response and outcome
- All HIV patients with lymphomas (Hodgkin's and non-Hodgkin's) have to be treated with HAART and chemotherapy simultaneously
- As in HIV-negative counterparts, R-CHOP should be recommended as treatment for non-Hodgkin's lymphomas. ABVD should be provided for treating Hodgkin's disease

Conclusion

- Rituximab significantly improves survival of patients with HIV-related non-Hodgkin's lymphomas, without increasing mortality from infections
- Prophylaxis of opportunistic infections has to be done while patients are receiving chemotherapy, even when $CD4^+$ counts are > 200 cells/ml
- Primary prophylaxis of FN (20% risk) with hGFs

Conclusion

- Central nervous system prophylaxis should only be done in subjects with the highest risk for developing neurologic disease, such as in patients with Burkitt's lymphoma, those with stage IV, and those with lymphomas of the ORL area
- In HIV patients with refractory or relapsed lymphomas, if the clinical situation is good enough and it is decided to proceed with salvage therapy, special consideration should be given to autologous hematopoietic cell transplantation
- In HIV-infected individuals, there is an increased incidence

MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Mojca Unk
Domen Ribnikar
Jana Pahole Goličnik
Branko Zakotnik

1

Question 1

The correct statement is:

MPM is

1. a frequent tumor (incidence > 20/100000)
2. affects mostly older than 60 years
3. good prognosis
4. most patients are treated with surgery
5. mainly detected in early stages

2

Etiology and epidemiology

- Rare tumor, incidence about 1 - 2/100000
- Males
- Mesothelial surfaces of coelomic cavities (pleura, peritoneum, pericardium, tunica vaginalis)
- Poor survival (1 year)
- Azbestos (occupational exposure)
- Latency 40 years (15-67)

3

Azbestos fibres

- Primary (~ occupational) and secondary exposure
- Diseases: azbestosis, MPM, lung, ...

- Dose effect relatonship but there is no treshold of cummulative exposure below which there is no risk
- All asbestos fibers are cancerogenic

- Chrysotile - white azbestos
  - 99% products
  - 2-4x more cancerogenic than other typs of fibers
- Crocidolite

4

Slovenia

- Oscilating incidence in recent years (between 24 and 33 /100000)
- 29 new patients in year 2007 (26m,3f)
- 28% of patients from the Primorska region

Rak v Sloveniji 2007. Ljubljana: Onkološki inštitut Ljubljana, Epidemiologija in register raka, Register raka Republike Slovenije, 2010.

5

Clinical presentation

- *Symptoms*: shortness of breath, pain, cough, fatigue, weight loss, sweating, fever, palpable masses of the chest, paraneoplastic syndromes
- Occupational exposure to asbestos
- *signs* of pleural effusion

6

Diagnosis

- *Chest x-ray*: unilateral pleural effusion or thickening
- *CT of the chest*: ring like tumour along the pleural cavity, diffuse or nodular pleural thickening
- *Thoracocentesis* for cytology conformation (diagnostic error)
- *Pleural biopsy* (thoracoscopic- video asssisted thoracoscopy-VATS, open surgery) for histology conformation (4 histological subtyps- epitheloid 60%, sarcomatoid, mixed, desmoplastic)
- *Serum mesothelin related peptid (SMRP) and osteopontin*

7

Question 2

The correct statement is:

Serum mesothelin related peptid is

1. A very sensitive biomarker
2. A specific biomarker
3. Useful in screening

8

Staging (IMIG classification)
international mesothelioma interest group

Stage I	Ia	TlaNO
	Ib	TlbNO
Stage II		T2N0
Stage III		AnyT3, any N1 or any N2
Stage IV		Any T4, any N3 or any M1

Rusch et al. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. Chest 1995;108:1122-8.

Travis et al. WHO classification of tumours. Tumours of the lung, pleura, thymus and heart. Lyon, France:IARC;2004

9

Treatment: surgery

extrapleural pneumonectomy (EPP)- radical, but R1 or debulking
pleurectomy/decortication- R2

- Stage I-III: adequate cardiac- pulmonary function and technical possibilities
  - Stage I: surgery or follow up until disease progression
  - Stage II-III: technically resectable are treated with trimodality regiment (OP+RT+ChT), unresectable ChT only
- Stage IV and sarcomatoid subtype: ChT only

→ Palliative pleurodesis or PleuRx® and parietal pleuretomy

10

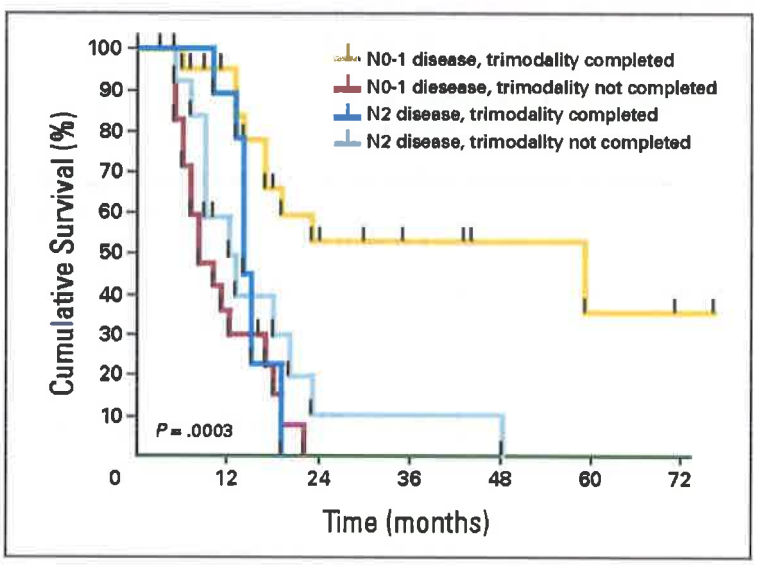
Question 3

Survival of patients following completed trimodality treatment is equal for patients with N0-1 and N2 disease.

1. YES
2. NO

11

Survival according to mediastinal nodal status (N2 disease) and completion of the entire trimodality regimen.



de Perrot M et al. JCO 2009;27:1413-1418

12

Treatment- radiotherapy

- Adjuvant radiotherapy to whole hemithorax after EPP for local disease control (80% local reccurence rate after EPP only and 13% after RT following EPP)(50-60 Gy)
- significant improvement in overall survival after EPP+RT (33.8 months vs. 10 months; p = 0.04) in early stages (I-II) but not in stages III-IV

Rusch et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Thorac Cardiovasc Surg. 2001 Oct;122(4):788-95.

- Prophylactic drain site radiotherapy (21 Gy) ???

O'Rourke et al. A randomised controlled trial of intervention site radiotherapy in malignant pleural mespthelioma. Radiother Oncol 2007;84:18-22.

- No improvement after adjuvant radiotherapy following debulking pleurectomy (R2), more toxicity

Baldini. Radiation therapy options for malignant pleural mesothelioma. Seminar Thorac Cardiovascular Surg. 2009; 21:159-163.

- Palliative radiotherapy for pain relief (RR 60%, duration of response 2-3 months)

13

Treatment- chemotherapy

- As neoadjuvant or adjuvant therapy (platinum based doublets)
- Unresectable patients stage II in III, sarcomatoid subtype and stage IV
- Platinum analogues, folate antimetabolites (pemetreksed, ralitreksed), gemcitabin, vinorelbine and doksorubicin

14

Question 4

- The wrong statement is:

  1. Combination cis/pem is more effective than monotherapy with cisplatinum.

  2. Platinum based doublets are comparable in terms of efficiency.

  3. Response rates to chemotherapy are higher than 45%.

  4. Patients without dispnoe do not need drainage of pleural effusion before application of pemetrexed.

Dickgreber et al. Pemetrexed safety and pharmacokinetics in patients with third-space fluid. Clin Cancer Res. 2010 May 15;16(10):2872-80

15

Treatment- chemotherapy
1st line

- Combination pemetreksed/cisplatinum in 1st line improves overall survival;

  - 12.1 m vs. 9.3 m (p=0.02) compared to single agent cisplatinum

  - RR 41 % vs. 16.7% compared to single agent cisplatinum

Vogelzang et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003.; 21:2636-2644.

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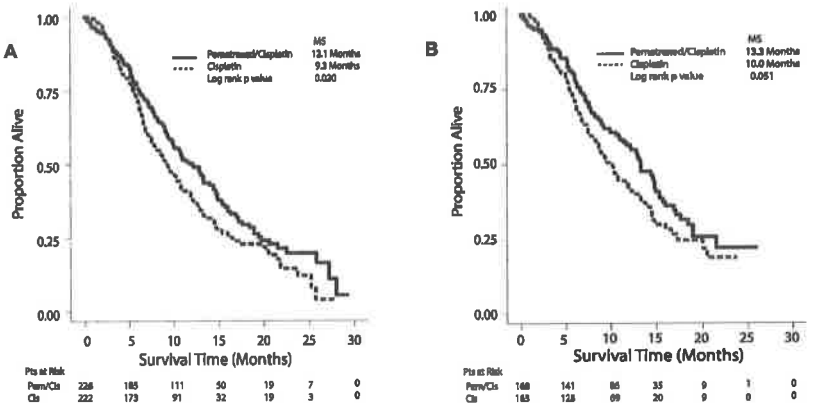

Kaplan-Meier estimates of overall survival time for all patients (Pts) (A) and for fully supplemented patients (B). Overall survival was significantly longer for the pemetrexed/cisplatin-treated patients (Pem/Cis) in the group of all patients (*P* .020) and approached significance for the group of fully supplemented patients (*P* .051). MS, median survival; Cis, cisplatin alone.

Vogelzang N J et al. JCO 2003;21:2636-2644

17

Treatment- chemotherapy
1st line

- Combination pemetreksed/carboplatin:
- Ceresoli: median survival 12.7 months and RR 18.6%
- Castagneto: median survival 14 months and RR 25%

Ceresoli et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. J Clin Oncol. 2006;24:1443-1448.
Castagneto et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma. Ann Oncol. 2008;19:370-373.

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Treatment- chemotherapy
1st line

- Combination gem/cis:
- van Haarst: median survival 9.6 months and RR 16%
- Nowak: median survival 11.2 months and RR 33%)

van Haarst et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. Br J Cancer. 2002;86:342-345.
Nowak et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer. 2002;87:491-496.

19

Question 5

Cisplatinum and carboplatinum are comparably effective.

1. YES
2. NO

20

Chemotherapy
cisplatinum or carboplatinum

Comparison of cis/pem and carbo/pem in 1704 patients confirmed similar activity (DFS and 1-year survival); combination carbo/pem is a better choice for patients with poorer performance status and comorbidity.

Santoro et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol. 2008;3:756-763.

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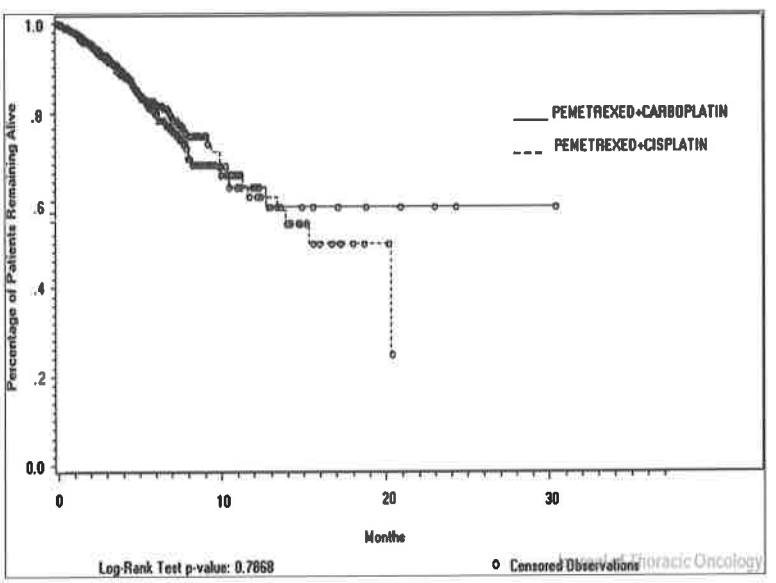

Santoro et al. J Thorac Oncol. 2008.

22

Treatment- targeted therapies

Different drugs have been or are being evaluated (alone or in combination with chemotherapy) → targeting:

- EGFR: gefitinib, erlotinib, cetuximab
- PDGFR
- VEGF and VEGFR: bevacizumab, sorafenib, vatalanib, pazopanib, sunitinib, talidomid
- histone deacetylase (HDAC): vorinostat
- proteosome: bortezomib

vanMeerbeeck et al. Malignant pleural mesothelioma: The standard of care and challenges for future management. Crit Rev Oncol/Hematol (2010).doi:10.1016/j.critrevonc.2010.04.004

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Question 6

There is no benefit with 2nd line chemotherapy.

1. YES
2. NO

24

Treatment- chemotherapy

2nd line

Phase III study compared pemetreksed single agent in 2nd line chemotherapy to best supportive care in pemetreksed naive patients:

- significantly better RR (18 vs. 1.7%)
- significantly longer time to progression (3.7 vs. 1.5 month; p=0.015)
- no improvement in overall survival (8.4 vs. 9.7 months; p=0.74).

Jassem et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin Oncol. 2008;26:5139-40.

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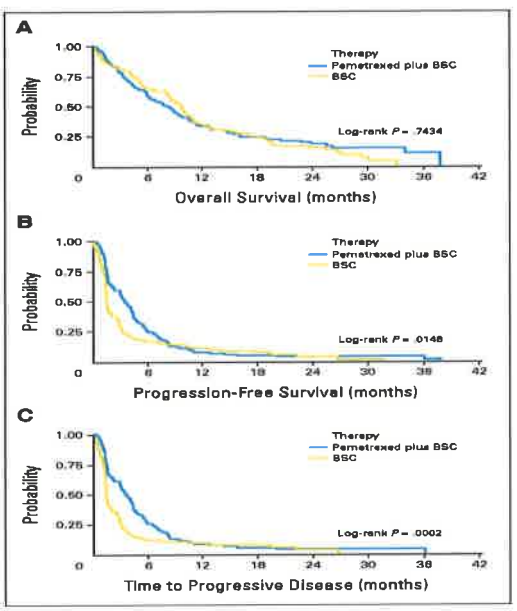

Jassem J et al. JCO 2008;26:1698-1704

26

Treatment- chemotherapy

2nd line

Gemcitabine and vinorelbine show some efficacy in the 1st line chemotherapy → an option for a 2nd line:

- 63 patients treated with weekly vinorelbin: RR 16%, median survival 9.6 months

Stebbing et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer. 2009;63:94-7.

- 30 patient treated with vinorelbin-gemcitabin (day 1.,8;Q3): disease control in 43% (10% PR and 33% stable disease), median survival 10.9 months

Zucali et al. Gemcitabine and vinorelbine in pemetrexed-pretreated patients with malignant pleural mesothelioma. Cancer;112:1555–1561.

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Evaluation

- Clinical examination
- CT of the thorax after 2 to 3 cycles of chemotherapy (modified RECIST criteria*)

* Byrne et al. Modified RECIST criteria for assessement of response in malignant pleural mesothelioma. Ann Oncol 2004:15;257-260.

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Conclusions

- Only a small proportion of patients might benefit from aggressive interventions with radical or curative intent
- Effective, albeit palliative chemotherapy, increases life expectancy and helps to relieve symptoms
- Relieving symptoms is the cornerstone in the management of patients with MPM at all stages of disease
- Enroll the patient in clinical (prospective) study
- Primary prevention and targeted treatments are the future in management of MPM

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Modified RECIST criteria

- Growth pattern of MPM (on CT of the thorax sferical changes for two- dimensional measurements are ussually not seen)
- Combination of one- and two- dimensional measurements:

  - pleural plaque at the thoracic or mediastinal wall is measured in two places, at least 1 cm interval, three cuts on the CT chest examination, the sum of the six measurements is defined as one-dimensional measurements of pleural changes
  - two-dimensional lesion are measured using conventional RECIST criteria
  - pleural effusion is not measurable lesion
  - regression in lesions by 30% in 4 weeks: partial response
  - increase in lesions by 20% in 4 weeks: progres

  Conclusion: The modified RECIST criteria coincide with the survival (15.1 m to 8.9 m, p = 0.03) and pulmonary function, but require further research to integrate them into regular clinical practice

Byrne et al. Modified RECIST criteria for assessement of response in malignant pleural mesothelioma. Ann Oncol 2004:15;257-260.

30

Malignant pleural mesothelioma Clinical case report

Domen Ribnikar, MD
Jana Pahole Goličnik,MD
Mojca Unk, MD
Mojca Juvan, MD
Mentor: prof.dr. Branko Zakotnik, MD

N.B., ♀, 1973

September 2006:

- 2 months dyspnea on exertion, epigastric blunt pain
- family history: no malignant disease
- no (family) exposure to asbestos, ex smoker

Physical examination:

- PS (WHO) 1, subfebrile
- auscultatory dullness on the left, up to 6th rib

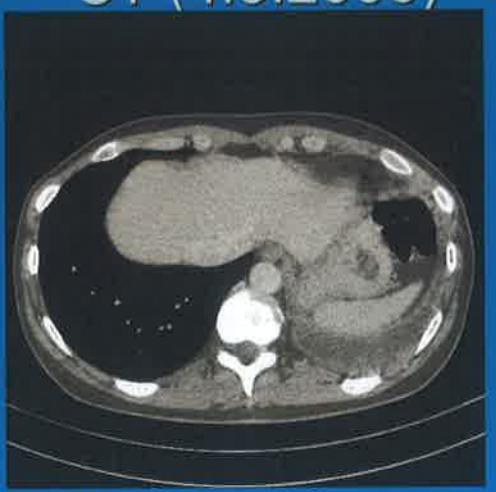
Diagnostic procedures

- blood count: WBC 11,0 G/l, platelets 411 G/l, normal Hb, CRP 54 U, normal renal and liver function tests, no electrolite disturbances
- chest X-ray: pleural effusion up to 6th rib
- diagnostic pleural paracentesis: exudate, no evidence of malignant cells

Diagnostic procedures

- blind needle biopsy of the parietal pleura: non specific chronical pleuritis with hyperplastic mesothelium
- VATS → histology: mesothelioma, epitheloid type
- CT of the thorax (4.9.2006):

CT (4.9.2006)



T3N0M0 – stage 3 (IMIG)

Treatment

- ***Multidisciplinary tumor board opinion*: chemotherapy with gemcitabine and cisplatinum, then operation**
- Planned: 4-6 cycles of gemcitabine (250mg/m2 in 6h infusion, day 1 and 8) and cisplatinum (80mg/m2, day 1) Q3W
- Recieved: cisplatinum 3x, gemcitabine 10x
- <u>Toxicity:</u>
  - transient hepatotoxic effect of chemotherapy (AST, ALT elevation 4 x IULN)
  - alopecia G2
  - mielosupression (neutropenia)

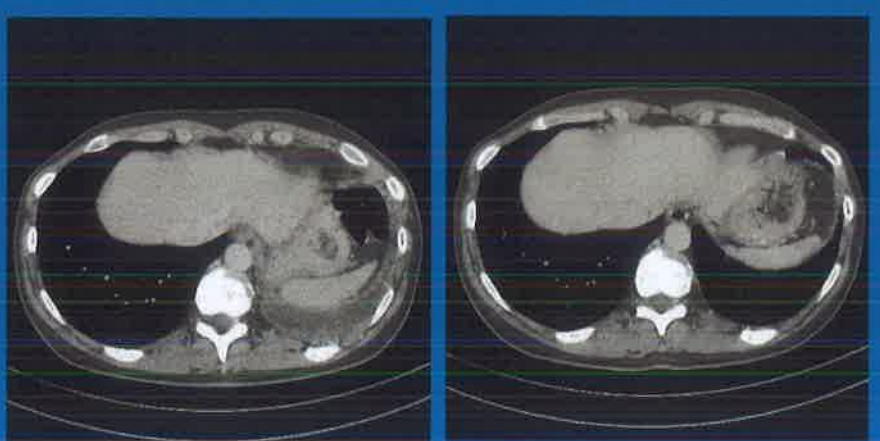
Treatment evaluation

January 2007:

- Clinically – absence of symptoms
- CT (17.1.2007): Partial response (almost complete regression of the tumour mass)

- ***Multidisciplinary tumor board opinion*:** **technically inoperable - follow up**

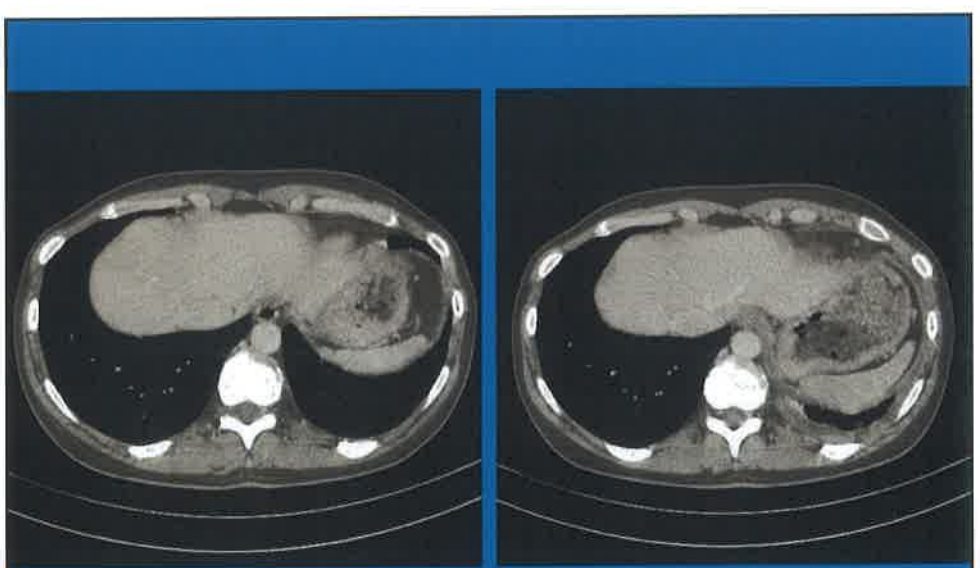
CT 4.9.2006 CT 26.10.2006



Follow-up

July 2007:

- constant thoracic pain on the left (asymptomatic with NSAIDs)
- CT (September 2007): left sided pleural effusion, visceral + parietal pleura thickening
  ⇒ progression

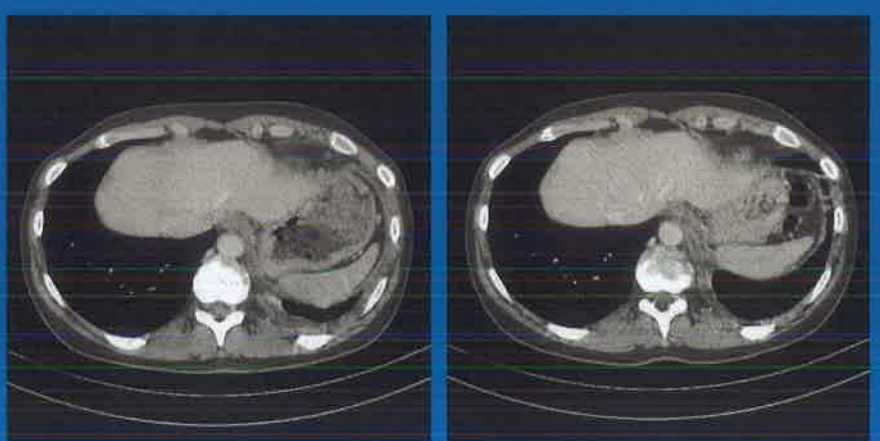


26.October 2006 19. September 2007

Treatment decision:

- 1. radiotherapy
- 2. second-line chemotherapy
- 3. best supportive care

CT 19.9.2007 CT 22.2.2008



Follow-up

- the patient did not decide for treatment immediately → follow up and supportive care
- CT (February 2008): spontaneous remission
- May 2008: pleuropneumonia with pericardial effusion → antibiotics
- December 2009: Horner's syndrome, pain in her left shoulder

Second line chemotherapy?

- 1. reinduction gemcitabine-cisplatinum
- 2. pemetrexed-single agent
- 3. pemetrexed-cisplatinum
- 4. vinorelbine
- 5. gemcitabine
- 6. None of the above

Second line treatment

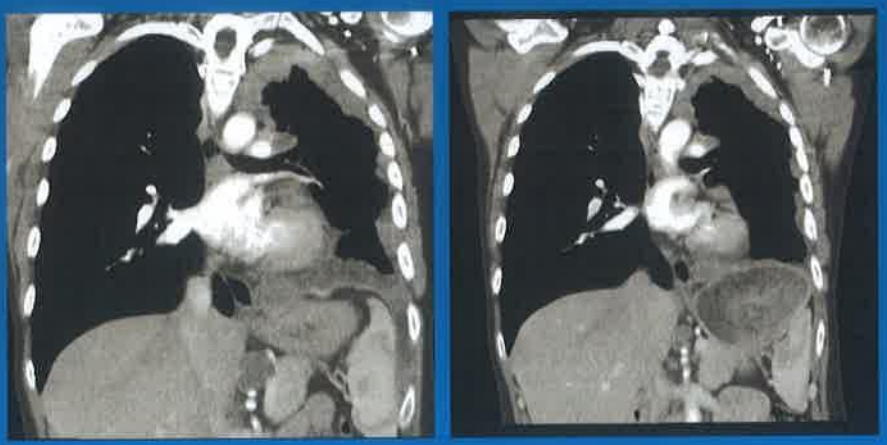
January 2010:

- 5 cycles pemetrexed + cisplatinum, 6th cycle pemetrexed only
- side effects of cisplatinum (hearing loss and paresthesias of the hands)
- cummulative dose of cisplatinum: 1070 mg

Treatment evaluation after 2nd line ChT

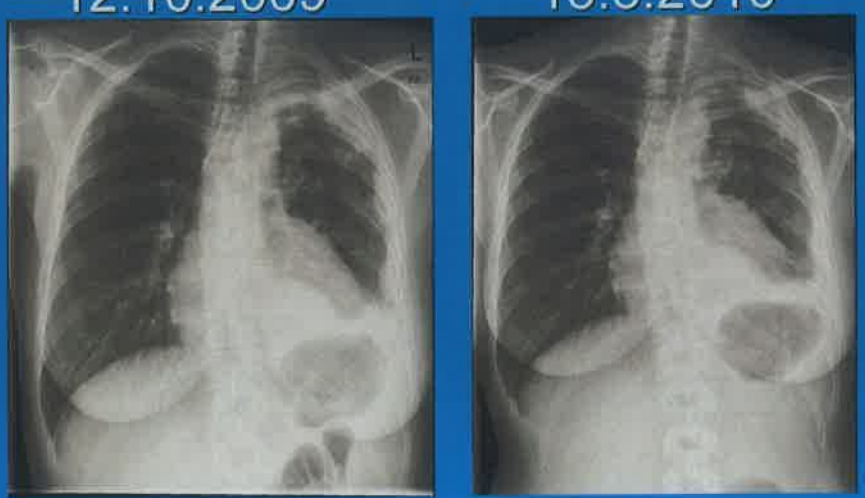
- clinically: no pain, no use of NSAIDs, persisting Horner's sy and auscultatory dullness
- radiologically:

CT 3.11.2009 CT 18.5.2010



Chest X-ray

12.10.2009 15.3.2010



Follow up

September 2010:

- progressive pain, Horner's sy
- raising platelet count, Hb levels stable
- Ultrasound of the abdomen: minimal ascites, celiac lymph nodes susp. enlarged

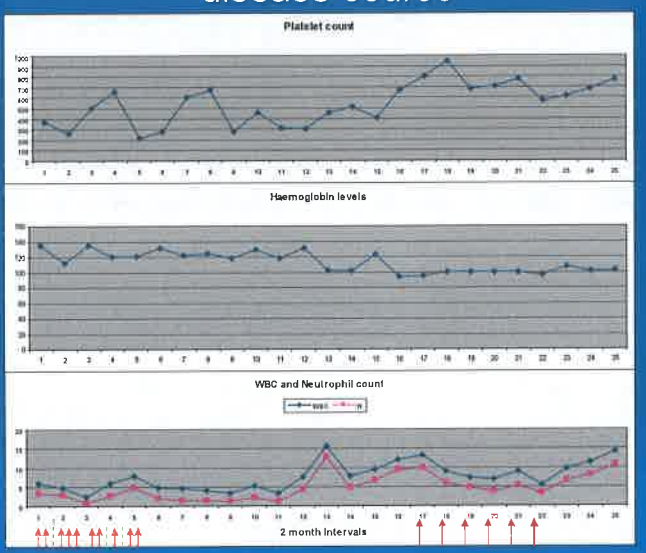
Thrombocytosis

1) toxic effect of gemcitabine

2) paraneoplastic

3) reactive - due to anemia

Platelets, Hb, WBC and Neutrophils during her disease course



Sept. 2006

6 DIO, 12 ,13 11 20010

Sept. 2010

21

Next step?

- 1. best supportive care
- 2. radiotherapy
- 3. 3rd line chemotherapy
- 4. targeted therapy

6 DIO, 12 ,13 11 20010

22

Conclusions

- Benefit of 1st line chemotherapy
- Unpredictable course of disease – spontaneous regression, infections
- Benefit of 2nd line chemotherapy
- The aim: to keep the quality of life (throughout disease course part time job, physically active)

TIME SAVINGS ASSOCIATED WITH ONCE-MONTHLY C.E.R.A.: A TIME AND MOTION STUDY CONDUCTED IN DIALYSIS CENTERS IN ITALY, FRANCE AND POLAND

W Klatko,[1] G Villa,[2] JC Glachant,[3] E De Cock[4]

[1]Nephrology Department, Specjalistyczny Szpital Wojewódzki, Ciechanów, Poland; [2]Fondazione Salvatore Maugeri, Pavia, Italy; [3]Service Néphrologie – Hémodialyse, Bourg en Bresse, France; [4]United Biosource Corporation

TH-PO471

INTRODUCTION

- Anemia is a common complication of chronic kidney disease (CKD) contributing to morbidity, mortality, and reduced quality of life in these patients.[1]
- Erythropoiesis-stimulating agents (ESAs) have been a key development in the treatment of anemia in patients with end-stage renal disease (ESRD) on hemodialysis. ESAs such as epoetin alfa, epoetin beta, and darbepoetin alfa have relatively short half-lives and require frequent administration, ranging from three times a week up to once every 2 weeks to maintain patients' hemoglobin (Hb) levels within the recommended target range.[2]
- The continuous erythropoietin receptor activator (C.E.R.A.®) has been proven to smoothly correct anemia and maintain Hb levels within the desired target range when administered once monthly (Q4W) in patients with CKD both on or not on dialysis.[1,3–6]
- Anemia management in CKD is time consuming both for healthcare professionals and patients. A major challenge for hemodialysis centers is to improve efficiency while maintaining high standards of quality and care for patients.

OBJECTIVES

- To quantify and compare healthcare personnel time for frequent routine anemia management-related tasks in hemodialysis centers for maintenance therapy with both shorter-acting ESAs and C.E.R.A. Q4W.
- To model time savings for a 100% uptake of C.E.R.A. Q4W in centers across three European countries.

SAMPLE

- This study was conducted in nine dialysis centers across three European countries: three centers each in Italy, France, and Poland.

METHODS

- This was a multi-country, multicenter, prospective, observational study using time and motion methodology to describe processes and document the time taken by healthcare staff to perform frequent ESA administration-related activities.
- The study was non-interventional as patients were treated according to individual center practice.
- No patient demographics were collected and all data were blinded to preserve the anonymity of individuals participating in the study.

Anemia management activities

- The processes associated with current anemia management were identified through interviews with center healthcare staff.
  - Observed tasks were frequent and observable activities associated with ESA treatment for which time could be clearly measured and was not intertwined with hemodialysis-related activities.
  - Observed tasks included preparation, distribution, and injection of ESAs, as well as record keeping.
- For selected anemia management tasks separate samples were collected for patients receiving traditional ESAs or C.E.R.A. Target sample sizes of 40 observations for activities per patient (eg injection) and 20 observations for activities per group of patients (eg preparation) were collected.
- Tasks were observed by trained designated observers using a stopwatch and time was recorded onto case report forms.
- A weighted number of ESA administrations per patient per year were calculated in each center based on the distribution of ESA products used and injection frequency by ESA product (obtained from interviews with healthcare staff).
- Time data were analyzed using SAS software assuming a gamma distribution and statistics were calculated for each task sample.

Modeling the impact of once-monthly C.E.R.A.

- Average time per ESA-treated patient and the frequency distribution of injections at each center were used to estimate the total time savings that could be achieved with a 100% uptake of C.E.R.A. Q4W.
- The main study end point, time per patient per ESA session, was used to calculate the annual time per patient per center.

RESULTS

Characteristics of hemodialysis centers

- The number of patients with ESRD receiving ESA treatment at the time of interviews ranged from 56–90 in Italian, 39–87 in French, and 60–136 in Polish centers (Table 1).
- The proportion of C.E.R.A. uptake across hemodialysis centers in three European countries at time of interviews ranged from 24–48% in Italian, 26–49% in French, and 22–34% in Polish centers (Table 1).
- The number of ESA injections per country per week categorized by ESA type and route of administration are shown in Figure 1.
- The average number of ESA injections per patient per year for traditional ESA products was 103 in Italian, 89 in French, and 93 in Polish centers.
- The average number of C.E.R.A. injections per patient per year was 12 across Italy and France, and 13 in Poland.

Figure 1. Number and type of ESA injections per center per week

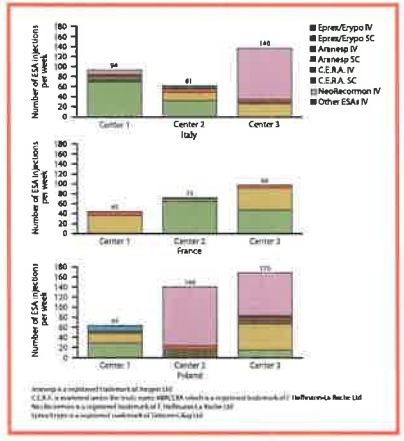


Table 1. Characteristics of ESA administration per center per country

	Italy				France				Poland			
	1	2	3	Average	1	2	3	Average	1	2	3	Average
Total no. pts receiving ESAs*	56	62	90	69	59	39	87	62	60	85	136	94
C.E.R.A. uptake, %*	29	48	24	34	49	26	30	35	22	34	30	29
Average no. ESA administrations/pt/year (excluding pts receiving C.E.R.A.)*	118	88	103	103	66	125	76	89	68	124	88	93
No. ESA administrations avoided/pt/year by switching to C.E.R.A. Q4W	106	76	91	91	53	113	64	77	54	111	76	81
Observed time/pt/year, min												
ESAs	103	231	165	166	95	194	91	127	380	176	239	265
C.E.R.A.	12	31	20	21	24	26	24	25	68	21	28	39
Calculated time savings for observed tasks at 100% C.E.R.A. uptake, %	88	87	88	87	75	86	74	79	92	88	88	86

*Data from interviews at time of observation.
ESA: erythropoiesis-stimulating agent; pt: patient; Q4W: once monthly.

Observed time per patient per year

- Estimated observed time per patient per year across three European countries ranged from 91 to 380 min for ESAs and from 12 to 68 min for C.E.R.A. (Figure 2).

Figure 2. Percentage reduction in time per patient per year by center (min)

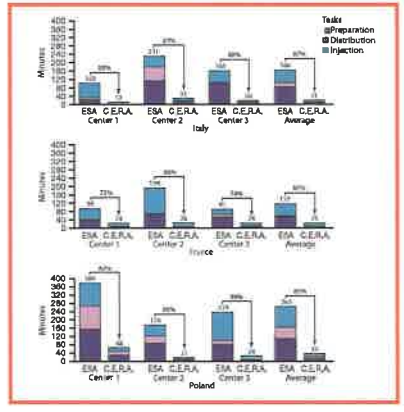
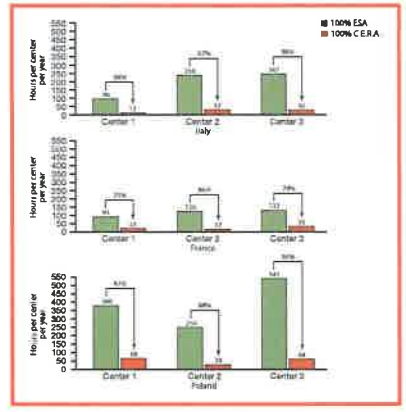


Figure 3. Estimated time savings with 100% uptake of C.E.R.A. Q4W per center



Time savings per patient converting to once-monthly C.E.R.A.

- Average reductions in time when converting a patient from traditional ESAs to C.E.R.A. Q4W were similar across all countries. Average annual time savings of 87% in Italian, 81% in French, and 85% in Polish centers were found (Figure 2).

Modeling the impact of once-monthly C.E.R.A. at the center level

- The reductions in observed task frequencies following conversion of a 100% uptake of C.E.R.A. Q4W produced estimated annual time savings of 87–88% (84–217 hours) in Italian, 74–86% (70–109 hours) in French, and 82–88% (221–477 hours) in Polish centers (Figure 3).

CONCLUSIONS

- Data from hemodialysis centers across three European countries showed that a 100% uptake of C.E.R.A. Q4W maintenance therapy could offer substantial annual time savings on frequent anemia management tasks.
- The per country results for time savings ranged from 87–88% in Italian, 74–86% in French, and 82–88% in Polish centers.
- Administration of 12 injections of C.E.R.A. per patient per year would allow scarce healthcare resources to be reallocated to other important CKD therapy needs and improve overall patient care.
- These results are in line with findings from other countries where this observational study was conducted, showing estimated annual time savings following a 100% uptake of C.E.R.A. Q4W of 69–84% across three centers in Spain and of 79–91% across four centers in Germany.
- These results confirm data from previous time and motion studies carried out in centers across Germany, the USA, and the UK which showed that an ESA administered Q4W would offer annual time savings of 79–84%.[7,8]

ACKNOWLEDGMENTS

The authors take full responsibility for the scope, direction and content of the poster and have approved the submitted poster. They would like to thank Tanya Chaudry at Complete HealthVizion for her assistance in the preparation of this poster. Editorial assistance was funded by F. Hoffmann-La-Roche Ltd.

*C.E.R.A. is marketed under the trade name MIRCERA® (methoxy polyethylene glycol-epoetin beta) which is a registered trademark of F. Hoffmann-La Roche Ltd.

REFERENCES

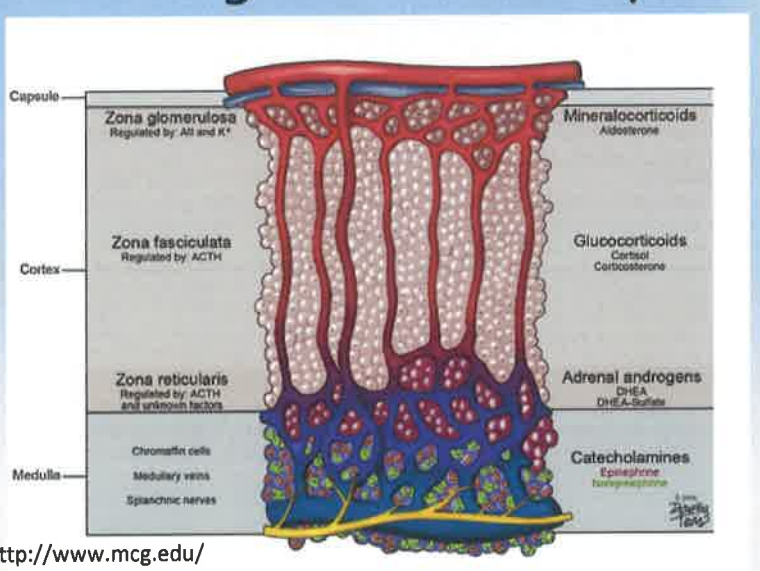
1. Carrera F et al. Nephrol Dial Transplant 2010; epub ahead of print.
2. Locatelli F et al. Nephrol Dial Transplant 2004; 19 (Suppl 2): ii1–47.
3. Kessler M et al. Hemodial Int 2009; 14: 233–239.
4. Macdougall IC et al. Clin J Am Soc Nephrol 2008; 3: 337–347.
5. Roger SD. Poster SaS35 presented at the ERA-EDTA, Munich, Germany, 25–28 June, 2010.
6. Sulowicz W et al. Clin J Am Soc Nephrol 2007; 2: 637–646.
7. Dellanna F et al. Poster SuS04 presented at the ERA-EDTA, Munich, Germany, 25–28 June, 2010.
8. Raluy M et al. Poster PUK27 presented at the ISPOR, Prague, Czech Republic, 6–9 November, 2010.

Poster presented at ASN Renal Week, Denver, Colorado, USA, 16–21 November 2010

Adrenal gland tumors

Rok Devjak ,Tanja Ovčariček, Ksenija Strojnik
Mentor: Simona Borštnar

Adrenal gland - anatomy



Vir: http://www.mcg.edu/

Adrenal gland tumors

- Tumors of adrenal gland are relatively common: incidence of incidentalomas is 4% of population and rises with age.
- 20% of those have clinical significance. Most of those are functioning adrenal adenomas and malignant **tumors are only sporadic.**

Incidentalomas

TABLE. Differential diagnosis of incidentalomas

Benign adrenal (cortical and medullary)

- Adrenal cortical tumors
- Adrenal adenoma (nonfunctioning)
- Adrenal adenoma functioning (cortisol-secreting)
- Adrenal adenoma functioning (androgen-secreting)
- Adrenal nodular hyperplasia
- Pheochromocytoma
- Ganglioneuroma
- Neuroblastoma
- Ganglioneuroblastoma

Miscellaneous benign lesions

- Cysts and pseudocysts
- Myelolipoma
- Schwannoma
- Hemorrhage
- Hemangioma
- Granulomatosis and infections
- Pseudoadrenal masses (stomach, kidney, pancreas, liver, lymph nodes)

Malignant

- Carcinoma
- Pheochromocytoma
- Neuroblastoma
- Metastatic tumors (breast, kidney, lung, ovarian, melanoma, leukemia)

Adrenal gland tumors

- Tumors of adrenal cortex
  - Malignant: Adrenocortical carcinoma
- Tumors of adrenal medulla:
  - Pheocromocytomas

Adenocortical carcinoma (ACC)

- Epidemiology: 1-2 per million population
  - Slovenia: 3 patients in 2007
  - Two peak incidences are in childhood and between 40-50 years
  - Ratio of incidences women against men is 1.5

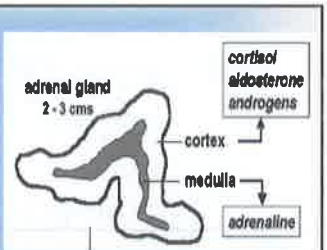
ACC- Pathology

- Table: Diagnosis of Malignancy in ACC

(Cancer, DeVitta et al. page 1529)

Reliability	Clinical Criteria	Pathologic and Genetic Criteria
Diagnostic of malignancy	Weight loss, feminization, nodal and distant metastases	Tumor weight> 100g, tumor necrosis, fibrous brands, vascular invasion, number of mitoses per high-power field, p53 mutations
Consistent with malignancy	Virilism, Cushing's virilism, no hormone production	Nuclear pleomorphism, aneuploidy
Suggestive of malignancy	Elevated urinary 17-ketosteroids	Capsular invasion, inhibin, 21-hydroxylase deficiency
Unreliable	Hypercortisolism, hyperaldosteronism	Tumor giant cells, cytoplasmic size variation, ratio between compact and clear cells

ACC-Clinical presentation:



- adrenal steroid hormone excess in 60% cases: rapidly progresing Cushing syndrome
- Androgen secreting
- Estradiol secreting in males: gynecomastia
- High DHEA-S suggests ACC
- Aldosteron secreting (rare)

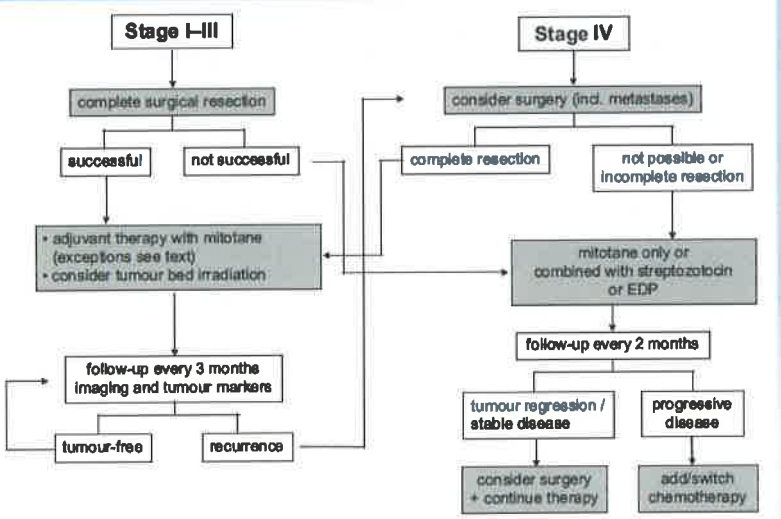
ACC: Staging

Table 2
Staging systems for adrenocortical carcinoma (ACC) proposed by the Union Internationale Contre Cancer (UICC) 2004 and European Network for the Study of Adrenal Tumours (ENSAT) 2008.[57,60]

Stage	UICC/WHO 2004	ENSAT 2008
I	T1, N0, M0	T1, N0, M0
II	T2, N0, M0	T2, N0, M0
III	T1-2, N1, M0	T1-2, N1, M0
	T3, N0, M0	T3-4, N0-1, M0
IV	T1-4, N0-1, M1	T1-4, N0-1, M1
	T3, N1, M0	
	T4, N0-1, M0	

T1, tumour ≤5 cm; T2, tumour >5 cm; T3, tumour infiltration in surrounding tissue; T4, tumour invasion in adjacent organs (ENSAT: also venous tumour thrombus in vena cava/renal vein); N0, no positive lymph nodes; N1, positive lymph node(s); M0, no distant metastases; M1, presence of distant metastasis.

ACC: Treatment flow chart



ACC: Prognosis

- 5-year survival rate:
  - Stage I: 60%
  - Stage II: 58%
  - Stage III: 24%
  - Stage IV: 0%

Allolio B and Fassnaht M, Adrenocortical carinoma, Clinical update. J Clin Endocrinol Metab 2006, 91: 2027-2037

Pheocromocytoma

- Epidemiology: 2-8 per million per year, ≈10% of them malignant
  - Few cases in last decade (no case in year 2007 in Slovenia)
  - Similar incidence in women and men
  - Peak incidence between 30-50
- 30% patiens with genetic background
- 5-year survival rate for malignant pheochromocytoma is 40 - 50%

Genetic syndromes with pheochromocytoma risk

Syndrome	Type of mutation	Tumors
MEN 2A and 2B (50% inherited as autosomal dominant trait, 50% new mutations)	Δ RET proto-oncogene	2A: medullary thyroid cancer + **pheochromocytoma (20-50%, benign, bilateral, adrenalin secreting)** + parathyroid hyperplasia 2B: medullary thyroid cancer + **pheochromocytoma (50%, benign, bilateral, adrenalin secreting)** + ganglioneuromatosis
Von Hippel – Lindau disease (80% inherited as autosomal dominant trait, 20% new mutations)	Δ VHL tumor suppressor gene	hemangioblastomas + angiomatosis + renal cell carcinoma + cafe au lait spots + pancreatic cysts + **pheochromocytoma (10-30%, benign, bilateral, noradrenalin secreting)**
PGL 1,3 and 4 (Familial paraganglioma syndromes)	Δ SDHB, C and D (genes for different subunits of succinate dehydrogenase)	**pheochromocytoma + extra-adrenal paragangliomas (>50% malignant, dopamine or noradrenalin or adrenalin secreting)**
Neurofibromatosis type 1 (formerly von Recklinghausen disease,– **50% autosomal dominant trait)**	Δ gene for neurofibromin (negative regulator of RAS oncogene)	Neurofibromas + schwannomas + neurofibrosarcomas + cafe au lait spots + optic gliomas + astrocytomas + **pheochromocytoma (0,1 -5,7%, benign, adrenalin secreting)** ...
Carney triad (autosomal dominant syndrome)		**extra-adrenal paraganglioma** + GIST + pulmonary chondroma
Carney – Stratakis dyad (autosomal dominant syndrome)		**extra-adrenal paraganglioma** + GIST

Pheocromocytoma- Pathology

- 90% in the adrenal medulla, 10 % extraadrenal - paragangliomas
- Ectopical presence of chromaffin cells is the strongest sign of malignancy
- pathologic distinction between benign and malignant is not entirely clear:
  - Commonly larger and **weigh more**
  - **Less** nuclear pleomorphism, **more mitoses**
  - **MIB-1** positivity, **aneuploidy, high S-phase fraction**
  - **Gene expression profiling**

Pheocromocytoma – Clinical manifestations and Diagnosis

- Clinical manifestations:
  - Pressure (elevated blood pressure),Pain (headache), Perspiration, Palpitations, Pallor
- Biochemical investigations: 24-hour urine collection for free catecholamines and metanephrines, plasma metanephrines
- Imaging: CT, MRI, ^{123}I-MIBG scanning, octreoscan, PET

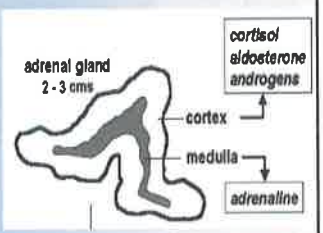
Adrenal gland tumors:

Adrenocortical carcinoma (case report 1)

Tanja Ovčariček, Ksenija Strojnik, Rok Devjak
Mentor: Simona Borštnar

JANUARY 2000

- **History:** 29-years old women presented with signs *of hypersecretion of cortisol and androgens* (Cushing syndroma, hirsuitism, thinning of the skin with bruising, virilisation with deepening of the voice and amenorrhea, psyhological disturbances)

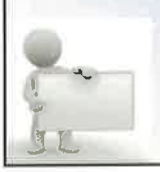


Physical examination: acne, male hair pattern,multiple bruises of the skin, otherwise b.p.

Lab.findings: complete blood count, renal and liver tests:normal, K: 3.4 mmol/l ↓

MORPHOLOGIC EVALUATION

- *Chest X-ray:* normal
- *US/CT abd.:* 8 cm heterogeneous tumor in the right suprarenal gland with irregular margins, poorly circumscribed, with some calcifications, displacing v.cava inf., pancreatic head and duodenum, but without local invasion or lymph node involvement or other metastases: *ACC susp*
- *CT thorax:* no signs of metastases



·Lung and liver predominant metastatic sites of ACC, abdominal and thoracic scans integral of the staging ACC

Hormonal work-up and imaging in patients with suspected or proven ACC recommendation of the ACC working group of the European Network for the Study of Adrenal Tumors (ENSAT), May 2005

Hormonal work-up:

Glucocorticoid excess

Dexamethasone suppression test (1 mg, 2300 h)
Excretion of free urinary cortisol (24 h urine)
Basal cortisol (serum)
Basal ACTH (plasma)

Sexual steroids and steroid precursors

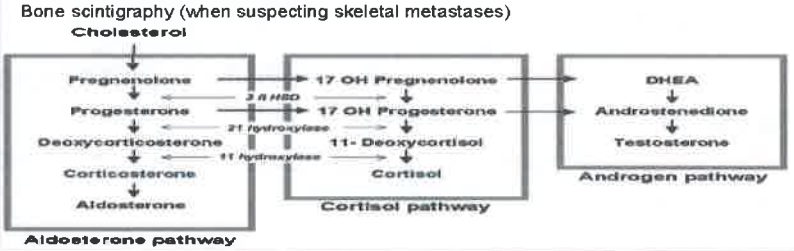
DHEA-S (serum)
17-OH-progesterone (serum)
Androstendione (serum)
Testosterone (serum)
17-estradiol (serum, only in men and postmenopausal women)

Mineralocorticoid excess

Potassium (serum)
Aldosterone to renin ratio (only in patients with arterial hypertension and/or hypokalemia)
Exclusion of a pheochromocytoma (1 of 2 tests) Catecholamine excretion (24 h urine)
Meta- and normetanephrines (plasma)

Imaging

CT or MRI of abdomen and thorax
Bone scintigraphy (when suspecting skeletal metastases)



HORMONAL WORK-UP

1. Assessement of glucocorticoid excess:

* *dexametason suppresion test (2 mg): no cortisol suppresion*
* *basal cortisol level (serum): ↑465 nmol/l*
* *basal ACTH level (plasma): normal 5.2 pmol/l*

2. Assessment of sexual steroids and steroid precursors:

* *DHEA-S:↑24.0 µmol/l*
* *17-OH progesteron: ↑32.7 nmol/l*
* *Androstendion: ↑14.5 nmol/l*
* *Testosteron: ↑ 58.7 pmol/l*

Autonomous secretion of cortisol and androgens from adrenal tumor

3. No mineralocorticoide excess

4. Exclusion of pheocromocitoma

WHAT KIND OF PRIMARY LOCOREGIONAL TREATMENT WOULD YOU RECOMMEND?

- 1. Laparoscopic adrenalectomy
- 2. Open surgery with adrenalectomy
- 3. Adrenalectomy with radiotherapy of the tumor bed

PRIMARY TREATMENT

28.1.2000: right adrenalectomy

Histology: (Weiss classification): 8x6x4 cm large tumor, the cancer cells with marked nuclear polymorphism, atipya, high mitotic rate, atypical mitoses, diffuse architecture with capsular and angiolymphatic invasion and extensive necrosis

Hormonally active ACC :pT3, N0, M0, (st III), R0 resection

Postsurgical hormonal work-up: indicated radical resection

suppression of cortisol level to 15nmol/l

1. Assessement of glucocorticoid excess:

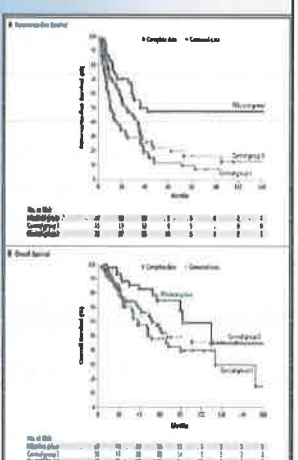
* *dexametason supp.test: no suppression* → ↓Bas.cortisol level 41.69nmol/l (norm.)
* *Basal cortisol level (serum):↑465nmol/l* →
* *Basal ACTH level (plasma) normal:4.6 pmol/l* → Basal ACTH: 5.8 pmol/l

2. Assessment of sexual steroids and steroid precursors:

* *DHEAS:↑22.5µmol/l* → ↓ basal DHEAS: 0.4 µmol/l
* *17-OH progesteron: ↑32.7 nmol/l* → ↓Basal 17-OHP: 0.24 nmol/l
* *Androstendion: ↑14.5nmol/l* → ↓basal androstendion: 0.1 nmol/l
* *Testosteron: ↑58.7pmol/l* → ↓basal testosteron: 0.2 pmol/l

ADJUVANT THERAPY?

- The risk of recurrence after R0 resection is 60%
- Due to the rarity of ACC, there are no published randomized prospective trials of adjuvant therapy, majority retrospective reports examined the use of adjuvant mitotane, an oral adrenocorticolytic agent
- The largest retrospective study (controlled) of 177 patients with resected ACC (stage I-III) with 2 cohort (Italy, Germany)
- In Italian cohort 47/102 pts received adjuvant mitotane(median treatment duration 29 months), German none out of 75 pts
- Radiaton Th of tumor bed recommended for R1 or Rx resection



*mDFS (42 months vs 10, p<0.001, 42 vs 25, p=0.005)
*mOS (110 months vs 52 , p=0.001, 110 vs 67, p=0.10)

Terzolo M, et al. N Engl J Med 2007

ADJUVANT MITOTANE (recommendations)

- The optimal dose and duration of adjuvant treatment with mitotane have not been standardised, but blood levels of mitotane should be monitored and kept at about 14-20 mg/ml
- The daily dosage needed to achieve and maintain blood levels greater than 14 mg/l is variable
- Treatment usually initiated with 1.5 g/d, rapidly increasing dose depending on tollerability to 5-6 g/d
- Measurement of plasma mitotane levels 14 d after initiation of treatment
- Due to adrenolityc effects of mitotane, replacement doses of corticosteroids (hydrocortisone or prednisolone) should be prescribed in order to prevent adrenal insufficiency
- Mitotane has narrow therapeutic window, more than 80% of the pts experience at least one undesirable side effect

TREATMENT(cont)

* *Adjuvant mitotane (jan 2000):* 1.5 g daily with glucocorticoide replacement with hydrocortisone (15 g daily)
* Rapidly improving symptoms, gain of menstruation, male hair pattern almost disappeared
* No serious mitotane adverse effects
* After 7 months patient decided to stop with mitotane therapy
* CT abdomen+thorax:normal, hormonal levels normal

FOLLOW-UP (recommendation)

- Follow-up with CT scans of the abdomen and thorax and hormonal work-up is recommended every 3-6 months

FOLLOW UP: OCTOBER 2001 (10 months after initiation of treatment)

- *History, clinical status, lab.findings:* normal
- *Hormonal tests:* ↑cortisol, DHEAS, 17-OHP, testosteron and androstendion, ↓ACTH
- *CT and MRI of the abdomen:* adrenal bed recurrence
- *CT thorax:* 2 metastatic lung nodes (4 mm) in left lower lung lobe

TREATMENT OF THE 1.st. RECURRENCE (recommendations)

- Surgery should be performed if complete surgical removal of local recurrence is feasible and the interval to a previous complete resection is >4 months. In these pts adjuvant therapy is mandatory
- If complete resection of metastatic sites is feasible, it should be done (even if 2 steps are needed) followed by adjuvant mitotane therapy
- **If surgery is not feasible, pts should be treated like pts with metastatic disease (mitotane+/-cytotoxic therapy)**

WHICH TREATMEN IS THE MOST APPROPRIATE IN THIS SETTING?

(1.recurrence: 2 metastases in left lung, adrenal bed recurrence)

- 1. systemic therapy (mitotane)
- 2. systemic therapy (mitotane +/- other cytotoxic regimen)
- 3. surgery of local recurrence and metastatic lesions
- 4. surgery of local recurrence and metastatic lesions and adjuvant mitotane therapy

TREATMENT OF 1. st RECURRENCE

- 18.10.2001: *resection of metastase in right adrenal bed*
- 7.11.2001: *resection of metastases in left lower lung lobe*
- *After resection decrease in cortisol, androgen, 17-OH and normalisation of ACTH level*
- 3.12.2001: *mitotane* ressumed adjuvantly (10 g 1 month, 5 g 5 months, 3 g 3 months, followed by 1 g daily)+ hydrocortisone replacement therapy (20+10 mg)
- **Regular 3 monthly follow-up**

JUNE 2003
(1 year, 7 months after initiation of treatment of 1.st recurrence)

- Symptoms free, CT scan abdomen and thorax negative, hormonal work-up normal
- Mitotane therapy stopped

JUNE 2005

- Asymptomatic, regular follow-up: CT scan thorax: Small (1cm) lesion in the right lower lung lobe

THE ONLY METASTATIC LESION

- US abdomen, bone scan: without metastatic lesions

WHAT KIND OF TREATMENT WOULD YOU RECOMMEND?

(2.nd recurrence after 2 years disease free interval,single metastasis in the lung, prior adjuvant mitotane th 7 mths, 1year+7mths)

- 1. mitotane
- 2. mitotane in combination with chemotherapy
- 3. resection of metastasis
- 4. resection of metastasis and adjuvant mitotane
- 5. resection of metastasis and chemotherapy

TREATMENT OF 2.nd RECURRENCE

- 30.6.2005: resection of lung metastasis
- CT scan of the thorax 4 weeks after the surgery: no radiological evidence of the disease
- 15.7.2005 reinstitution of mitotan therapy (2 g, titrated to 5 g daily), hydrocortisone replacement (30+20 mg)

REASONS FOR "ADJUVANT" MITOTAN THERAPY

- Retrospective case-controlled study demonstrated survival benefit of mitotane in the adjuvant setting (Berutti et al J Clin Oncol 2005, Terzolo M et al N Engl J Med 2007)
- Patient was disease free after metastatectomy-expected potential benefit from "adjuvant" therapy
- The role of postoperative cht with streptozocin after metastatectomy is less evident and the toxicity profile may outweigh any potential benefit
- Patient benefited from previous mitotane treatments by possible lengthening of previous recurrences with postoperative use in the past (after initial resection 2000, after metastatectomy in 2001)

FOLLOW-UP AFTER 3 MONTHS

- Hormonal assessement: increased levels of androgens
- CT thorax: pleural metastases in the right lung-radical with no suspicious changes in the pleura of the left pulmonary lobe and no pathological masses in lung parenchima-Only right pleuropneumectomy feasible
- No other metastatic lesions

METASTATIC UNRESECTABLE DISEASE

*in metastatic setting mitotane is the backbone of the therapy
*studies with different mitotane-cytotoxic Th combinations, no randomized trials
*2 imporatnt phase II trials: International consensus conference of the management of adrenal cancer (2003):

Recommended first-line cytotoxic drug regimens:

Etoposide, doxorubicin and cisplatin (EAP) plus mitotane (EAP/M) (adapted from Berruti et, Endocr Relat Cancer 2005) every 21-28 days:

day 1 40 mg/m2 D
day 2 100 mg/m2 E
day 3 + 4 100 mg/m2 E + 40 mg/m2 P
plus oral mitotane aiming at a blood level between 14 and 20 mg/L

Streptozotocin (Sz) plus mitotane (Sz/M) (Khan et al, Ann of Oncology 2000)

induction: day 1-5: 1 g Sz/d
afterwards 2 g/d Sz every 21 days
plus oral mitotane aiming at a blood level between 14 and 20 mg/L

*ongoing first randomised, phIII trial in ACC (FIRM-ACT)
*consider enrollment in a clinical trial!

METASTATIC UNRESECTABLE DISEASE(cont)

- Several new treatment options were also investigated
- Targeted therapies are of particular interest (gefitinib, erlotinib+gemcitabin, bevacizumab+capecitabin), no response was seen
- Occasional tumor responses have been reported for the antiangiogenic coumpound thalidomide (Chacon R et al. Journal of Clinical Oncology 2005)

TREATMENT(metastatic disease) (16.11.2005-5.1.2006)

- Mitotan (5g/dan) + chemotherapy regimen EAP: doxorubicin (40 mg/m2 D1) + etoposide (100 mg/m2 D 2-4) + cisplatin (30 mg/m2, D 2-4)/4 week
- Evaluation after 2 cycles: CT thorax: progression of pleural metastases in the right lung, no signs of other metastatic lesions
- Surgical procedure recomended

SECOND OPINION

- Results of IHC staining of the tumor: positive for expression of PDGFR alpha and beta, EGFR, VEGFR and COX-2
- phaseI clinical trial: DTIC/dacarbazin 250 mg/m2 D 1-3, capecitabin 1000 mg/m2 D 1-14, imatinib 400 mg/daily D 1-21, 3 week cycles in attempt to reduce tumor mass followed by surgery

TREATMENT (DTIC+capecitabin+imatinib) (18.1.2006-8.3.2006)

- After 1. cycle grade III neutropenia, otherwise no serious adverse affects
- Evaluations after 3 cycles: CT thorax: progression of pleural metastases, without evidence of other metastatic sites
- 12.4.2006: pleuropneumonectomy and RT of right thorax (60 Gy)

FOLLOW -UP (5 months later)

- US abd: progression in the abdomen with a bulky metastatic masses in the abdomen (retroperitoneum, peritoneum, omentum)
- Trial with thalidomide 200 mg/daily and mitotane (4g/daily) (Chacon R et al. Journal of Clinical Oncology 2005)
- Control US: progression in the abdomen and new lesions in the liver (37x 30 mm in VII segment, 33 mm v II segment), citologically confirmed
- 24.11.2006: Surgery with excision of bulky masses in the abdomen and RFA of liver metastases

TREATMENT (cont)

- After 1 month: CT thorax and abdomen: progress in the left lung, mediastinum, thoracic wall, abdominal progression
- Therapy with thalidomide and mitotane stopped
- 6.2.2007: exploratory laparotomy with adhesiolisis, metastatectomy in the liver, mesenterium, pelvis, colon
- After surgery: acute respiratory distress with citologically negative pleural effusion with mediastinal displacement
- Patient was put on supportive therapy

FUTURE PERSPECTIVES

Currently active clinical trials:

AGENTS	RATIONALE
EAP-M vs Sz-M	establishment of a first line cytotoxic drug regimen (phase III)
mitotane vs observation	adjuvant mitotane after R0 resection (phase III)
sunitinib	multiple TKI (phase II)
sorafenib and metronomic paclitaxel	multiple TKI in combination with metronomic cht (phase II)
mitotane vs mitotane+IMC-A12	IGF-R1 antibody in addition to mitotane in first line systemic treatment (randomized phase III)

Tumors of adrenal gland: Metastatic pheochromocytoma

Case report 2

Ksenija Strojnik, Rok Devjak, Tanja Ovčariček
Mentor: Simona Borštnar

Initial diagnosis (october 1992):

32-year-old female with incidental tumor of adrenal gland:

- Family diseases: no malignant or benign tumors;
- Past medical history: mumps and acute pancreatitis (at the age of 11), acute myocarditis (at the age of 29), no personal history of malignant or benign tumors;
- History and physical examination: ocassional left back pain, no abnormal physical findings
- Diagnostics:

CT abdomen: 8x5 cm inhomogeneous tumor in left adrenal gland with small cysts and calcinations, without local invasion into adjacent organs or tissue, no enlarged lymph nodes

Hormonal testing:

- 3 samples of metanephrines, catecholamines and VMA in 24h urine: normal
- plasma free metanephrines: not done
- plasma aldosteron and renin: normal
- suppression test with 2 mg of dexamethasone: **no denivelation of** cortisol

Treatment:

- **Surgical treatment:** open left adrenalectomy
- Histopathological report: 8x5cm pheochromocytoma, small-cell, with high mitotical activity and vascular invasion, R0 resection
- Staging with CT abdomen and chest x-ray: no distant metastases

Adjuvant treatment:

Which of the following would you recommend?

1. Adjuvant chemotherapy
2. Adjuvant targeted therapy
3. Adjuvant radiotherapy
4. No adjuvant therapy, follow-up for 5 years
5. No adjuvant therapy, follow-up for lifetime

Recommendations on primary treatment and surveillance in pheochromocytoma:

	PRIMARY TREATMENT[8]	SURVEILLANCE[9]
		3-12 mo postresection: • H&P, blood pressure, and markers[8]
Resectable →	Resect (laparoscopic preferred when safe and feasible) →	Long term: • H&P, blood pressure, and markers,[8] ▸ Years 1-3: every 6 mo ▸ Years 4+: annually • Imaging studies as clinically indicated

www.nccn.org. NCCN Clinical Practice Guidelines in Oncology

Genetic testing:

Would you recommend genetic testing to this patient?

1. Yes
2. No

Genetic syndromes with pheochromocytoma risk:

Syndrome	Type of mutation	Tumors
MEN 2A and 2B (50% inherited as autosomal dominant trait, 50% new mutations)	Δ RET proto-oncogene	2A: medullary thyroid cancer + **pheochromocytoma (20-50%, benign, bilateral, adrenalin secreting)** + parathyroid hyperplasia 2B: medullary thyroid cancer + **pheochromocytoma (50%, benign, bilateral, adrenalin secreting)** + ganglioneuromatosis
Von Hippel – Lindau disease (80% inherited as autosomal dominant trait, 20% new mutations)	Δ VHL tumor suppressor gene	hemangioblastomas + angiomatosis + renal cell carcinoma + cafe au lait spots + pancreatic cysts + **pheochromocytoma (10-30%, benign, bilateral, noradrenalin secreting)**
PGL 1,3 and 4 (Familial paraganglioma syndromes)	**Δ SDHB, C and D (genes for different subunits of succinate dehydrogenase)**	**pheochromocytoma + extra-adrenal paragangliomas (>50% malignant, dopamine or noradrenalin or adrenalin secreting)**
Neurofibromatosis type 1 (formerly von Recklinghausen disease - 50% autosomal dominant trait)	**Δ gene for neurofibromin (negative regulator of RAS oncogene)**	**Neurofibomas + schwannomas + neurofibrosarcomas + cafe au lait spots +** optic gliomas + astrocytomas + **pheochromocytoma (0,1 -5,7%, benign, adrenalin secreting) ...**
Carney triad (autosomal dominant syndrome)		**extra-adrenal paraganglioma +** GIST + pulmonary chondroma
Carney – Stratakis dyad (autosomal dominant syndrome)		**extra-adrenal paraganglioma +** GIST

All should be reffered to a genetic counselor!

Genetic testing is recommended in patients:

- less than 40 years old
- bilateral or multifocal tumors
- sympathetic or malignant extra-adrenal paragangliomas
- personal or family history of clinical features suggestive of a hereditary pheochromocytoma-paraganglioma syndrome

www.nccn.org. NCCN Clinical Practice Guidelines - v2.2010
www.cancer.gov. NCI Pheochromocytoma and Paraganglioma Treatment.

Follow-up november 1996 (4 years after operation):

- On follow-up ultrasound: 4 cm hepatic lesion (fine-needle biopsy: blood)
- CT chest: multiple round lesions 0,5 - 1,5 cm (transthoracic fine-needle biopsy: metastases of pheochromocytoma)
- History and physical examination: asymptomatic, no abnormal physical findings
- Hormonal testing: metanephrines, catecholamines and VMA in 24h urine - normal

Management of metastatic pheochromocytoma:

Which treatment would you recommend?

1. Surgery
2. Chemotherapy
3. Clinical trial
4. ^{131}I-MIBG radiation therapy
5. none

Recommendations on treatment of metastatic pheochromocytoma:

	PRIMARY TREATMENT[a]	SURVEILLANCE[g]
Locally unresectable	Cytoreductive (R2) resection, if possible ± RT + alpha-blockade ± alpha-methyltyrosine ± beta-blockade	Every 3–4 mo • H&P, blood pressure, and markers[e] • Imaging studies as clinically indicated
Distant metastases	Cytoreductive (R2) resection when possible + continuous alpha-blockade ± alpha-methyltyrosine ± beta-blockade (optional) or Clinical trial or Systemic chemotherapy (eg, dacarbazine, cyclophosphamide, vincristine) or 131I MIBG as compassionate use on clinical trial[f] (requires prior MIBG scan with dosimetry)	

www.nccn.org NCCN Clinical Practice Guidelines in Oncology

Treatment success with CVD (cyclophosphamide, vincristine, dacarbazine) for metastatic pheochromocytoma:

TABLE 1. CVD chemotherapy for malignant PCC (selected reports)

Publication year (ref.)	No. of patients	Biochemical response (%)		Tumor response (%)		Stable disease (%)	Progression (%)
		Complete	Partial	Complete	Partial		
1988 (52)	14	21	57	14	43	36	7
1996 (55)	2	0	50	50	0	50	0
1998 (44)	3	NE	NE	0	0	33	67
1999 (86)[a]	4[b]	0	0	0	50	0	50
2001 (87)[c]	3	33	0	0	33	67	0
2003 (26)	4	ND	ND	25	25	25[d]	25
% of evaluable cases		20	45	14	32	36	18

Scholtz et al. Malignant pheochomocytoma therapy. J Clin Endocrinol Metab, april 2007, 92 (4): 1217-1225
52. Averbuch et al. Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine and dacarbazine. Ann Intern Med 1988. 109; 267-273.
55. Noshiro et al. Two cases of malignant pheochromocytoma treated with cyclophosphamide, vincristine and dacarbazine in a combined chemotherapy. Endocr J 1996. 43; 279-284.
44. Tada et al. Three cases of malignant pheochromocytoma treated with cyclophosphamide, vincristine and dacarbazine combination chemotherapy and α-methyl-p-tyrosine to control hypercathecholaminemia. Horm Res 1998. 49: 295-297.
86. Sisson et al. Treatment of malignant pheochromocytoma with 131-I metaiodobenzylguanidine and chemotherapy. Am J Clin Oncol 1999. 22: 264-370.
87. Hartley et al. Management of malignant pheochromocytoma: a retrospective review of the use of 131-I MIBG and chemotherapy in the West Midlands. Clin Oncol 2001. 13: 361-366.
26. Edstrom et al. The management of benign and malignant pheochromocytoma and abdominal paraganglioma. Eur J Surg Oncol 2003: 29: 278-283.

Treatment success with ^{131}-I MIBG radiation therapy for metastatic pheochromocytoma:

TABLE 2. MIBG radiotherapy for malignant PCC (selected reports)

Publication year (ref.)	No. of patients	Biochemical response (%)		Tumor response (%)		Stable disease (%)	Progression (%)
		Complete	Partial	Complete	Partial		
1997 (88)[a]	116[b]	18	32	4	26	57	13
1999 (89)[a]	137[c]	43[d]	43[d]	6	16	55	21
1999 (86)	6	17	17	0	33	33	33
2001 (87)[e]	6[f]	0	20	0	0	67	33
2003 (96)[g]	12[h]	33	50	18	18	45	18
% of evaluable cases[i]		13	32	4	25	56	15

Scholtz et al. Malignant pheochomocytoma therapy. J Clin Endocrinol Metab, april 2007, 92 (4): 1217-1225
88. Loh et al. The treatment of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine (131-I MIBG): a comprehensive review of 116 reported patients. J Endocrinol Invest 1997. 20: 648-658.
89. Troncone et al. Nuclear medicine therapy of pheochromocytoma and paraganglioma. Q J Nucl Med 1999. 43: 344-355.
86. Sisson et al. Treatment of malignant pheochromocytoma with 131-I metaiodobenzylguanidine and chemotherapy. Am J Clin Oncol 1999. 22: 264-370
87. Hartley et al. Management of malignant pheochromocytoma: a retrospective review of the use of 131-I MIBG and chemotherapy in the West Midlands. Clin Oncol 2001. 13: 361-366.
96. Rose et al. High dose 131-I metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. Cancer 2003. 98: 239-248.

1-line treatment of metastatic disease (january - may 1997):

- ^{123}-I MIBG scintigraphy: negative
- She was treated with **6 cycles of CVD** (cyclophosphamide, vincristine and dacarbazine)

↓

stable disease in the lungs and liver

September 1998 (1 year and 4 months after chemotherapy):

- Severe pain in upper abdomen
- CT scan: progression of lung and liver metastases

2-line treatment of metastatic disease (october 1998 - january 1999):

- ^{111}-In pentetreotide scintigraphy: neg.

- 3 cycles of **etoposide and cisplatin**

↓

progression of disease in lung

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External beam irradiation of the whole lung (january 1999)

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Stable disease

February 2000 (1 year and 1 month after RT of lung):

- Medical history and physical examination: headache and left arm weakness
- CT scan: 1,5 cm metastasis in CNS

Surgery of brain metastasis

Radiotherapy of the whole brain

October 2000 (1 year and 9 month after RT of lung):

- Medical history and physical examination: dyspnea, cough, hemoptysis; painful induration in the left upper arm and under nail on the left thumb
- CT scan: progression in the lungs and liver
- Fine needle biopsy: metastases in soft tissue

Radiotherapy of painful soft tissue lesions

Bronchoscopic electrocautèrisation of lung metastases

3-line treatment of metastatic disease (october 2000 - july 2001):

- **Thalidomide:** stable disease for 9 months

progression

symptomatic treatment

died after 2 months (5 years after diagnosis of metastatic disease)

Novel agents and clinical trials in pheochromocytoma:

Theoretical backround	Drugs	Results and ongoing clinical trials
PI3/Akt/mTOR pathway	everolimus	Case-reports of monotherapy with dissapointing results; ongoing phase II: everolimus + erlotinib
PDGF-R, VEGF and EGF-R overexpressed	imatinib	Case-reports of monotherapy with dissapointing results
	sunitinib	Case -reports with CR and PR; ongoing ph. II trial monotherapy
	fostamatanib	Positive in preclinical trials; ongoing ph. II monotherapy
	bevacizumab	Positive in preclinical trials; ongoing ph. II with capecitabine and ocreotide LAR
	pertuzumab	Ongoing ph.II pertuzumab + erlotinib
HSP90 overexpressed	geldanamycine	Positive preclinical trials; ph. II trials in the near future

www.cancer.gov. National Cancer institute – Clinical Trials.