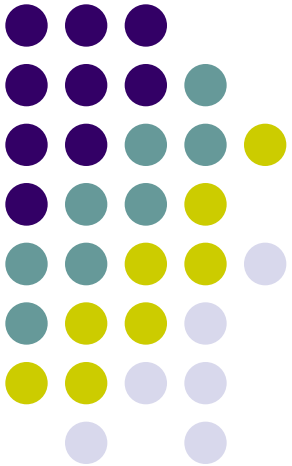
First Line Chemotherapy Overview of Trends

1st International Workshop on Gynaecologic Oncology



Dr Chia Yin Nin
MBBS, MRCOG, FAMS, DGO
Consultant and Head
Gynaecological Cancer Unit
KK Women's and Children's Hospital
Singapore

1970s - 2010

Future ?

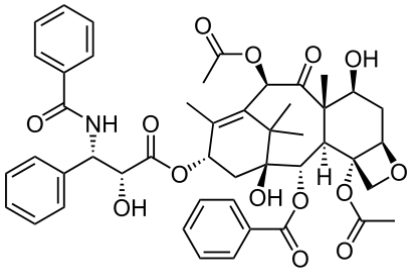
Taxanes

Platinums

Any Chemo

Surgery alone

Cisplatin - Taxol



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Letters to Nature

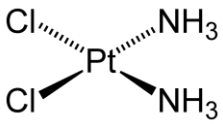
Nature **205**, 698-699 (13 February 1965) | doi:10.1038/205698a0

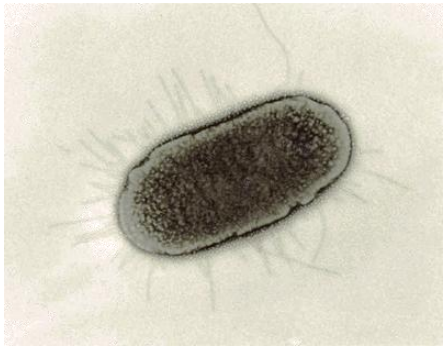
Inhibition of Cell Division in *Escherichia coli* by Electrolysis Products from a Platinum Electrode

BARNETT ROSENBERG, LORETTA VAN CAMP & THOMAS KRIGAS

1. Biophysics Department, Michigan State University, East Lansing.

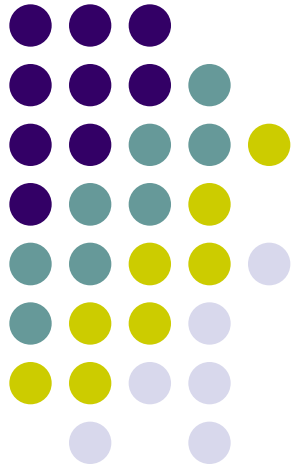
IN an investigation of the possible effects of an electric field on growth processes in bacteria, we have discovered a new and interesting effect. In *E. coli*, the presence of certain group VIII*b* transition metal compounds in concentrations of abou parts per million of the metal in the culture medium causes inhibition of the cell division process. The bacteria form lon filaments, up to 300 times the normal length, which implies the growth process is not markedly affected.





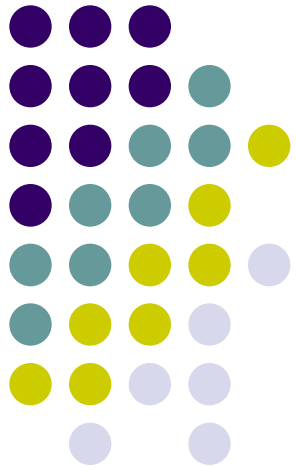
Studies in Early Ovarian Cancer

Evidence for observation in Early Stage Low Risk EOC (stage 1a,b, grade 1,2)				
Young et al GOG 1990	81	Stage 1a,b, grade 1,2	Melphalan vs observation	No difference 94% vs 96% 5 yr survival
Guthrie et al	656	Early stage	Observation	No untreated stage1a, grade 1 died of disease.
Bolis et al Italian Cooperative 1995	83	Stage1a,b grade 2,3 (included grade 3)	Cisplatin vs observation	No difference (not significant, small sample size)



Studies in Early Ovarian Cancer

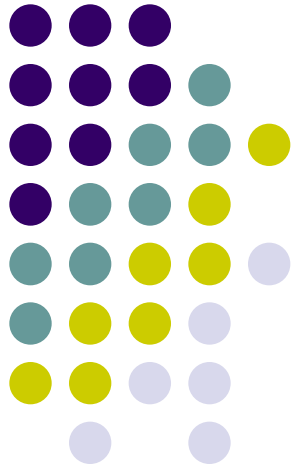
Evidence for Adjuvant Chemotherapy for **Early Stage High Risk EOC** (stage 1c, grade 3, clear cell, stage 2)				
ICON 1 2003	477	Stage 1 to 3, mostly 1 to 2 Optimal staging not required. Flaws: 1. Vague entry criteria 2. Likely an unquantified no are infact stage 3 and would hence benefit from adjuvant chemotherapy.	Platinum based vs observation	**DFS (5yr) 73% vs 62%,** HR 0.65, (0.46-0.91 CI), p=0.01
ACTION 2003	488	Stage 1a, b, grade 2,3 Stage1c, any grade Stage 2a, any grade Clear cell histology Flaws: 1. Only 1/3 optimally staged. 2. The analysis comparing optimally staged to nonoptimally staged was not included in the original study design and was underpowered to detect a clinically significiant difference in outcome. The information is therefore hypothesis generating than definitive. 3. ACTION trial filaed to detect an overall survival difference between the arms when results of both optimally and suboptimaly staged women were analysed togerther.	Platinum based vs observation	**Improved survival in nonoptimally staged patients only.**
ICON1/ACTION metanalysis	925	Flaws: 1. >90% were unstaged. Hence conclusion: platinum based chemotherapy should be given to patients who have not been optimally staged.	Platinum based vs observation	**82% vs 72% 5 yr survival.** HR 0.67 CI(0.50-0.90, p=0.008)



Evidence for Adjuvant Chemotherapy in Advanced EOC

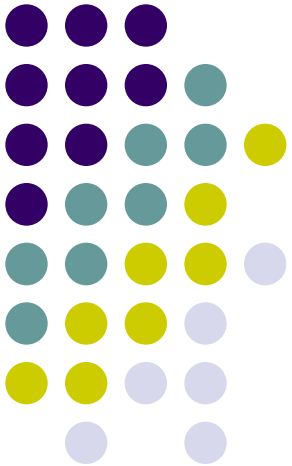
Studies in Advanced Ovarian Cancer

Evidence for Platinum based chemotherapy				
Advanced Ovarian Cancer Trialist Gp 1991	Meta-analysisPooled data 9 RCTs	Stage III and IV	Platinum based vs nonplatinum based	Absolute improvement in survival rates of 5% at 2 to 5 yrs. N.B. Difference disappear by 8 yrs.



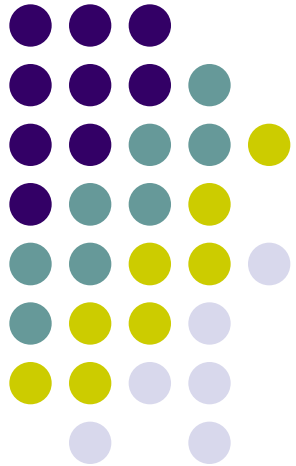
Evidence for Platinum and Taxanes

Evidence for **Platinum and Taxanes combination chemotherapy**				
GOG 111 1996 McGuire et al	386	Stage 3 and 4 Suboptimal	Paclitaxel 135mg/m2 over 24 hrs) + cisplatin 75mg/m2 vs Cyclophosphamide + cisplatin	Median survival 38 vs 24 mths RR 0.6 (0.5-0.8 CI), p<0.001
Intergroup 2000 Piccart et al	680	Stage 2b-IV	Paclitaxel 175mg/m2 over 3 hrs + cisplatin75mg/m2 vs Cyclophosphamide + cisplatin	Median survival 36 vs 26 mths. RR 0.73 (0.60-0.89) p=0.0016
Evidence for **cisplatin = carboplatin**				
GOG 158 2003 Ozols et al	792	Stage III	Paclitaxel 175mg/m2 over 3 hrs+ carboplatin (AUC7.5) vs Paclitaxel 135mg/m2 over 24 hrs + cisplatin75mg/m2	No difference in PFS or OS Caboplatin: Less toxicity (nephrotoxicity,ototoxicity,neurolotoxicity and nausea/vomiting) More myelosuppression esp thrombocytopenia
AGO-OVAR3 Du Bois et al 2003	798	Stage Iib-IV	Paclitaxel 185mg/m2 over 3 hrs+ carboplatin (AUC 6) vs Paclitaxel 185mg/m2 over 3 hrs + cisplatin75mg/m2	No difference in PFS or OS



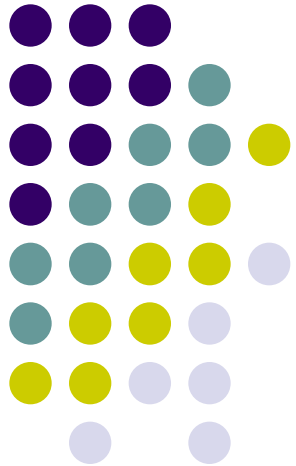
Cisplatin/Taxol as the Standard of Care

Year	Patient No.	Findings
1986	227	Doxo/Cyclo /Platin > Doxo/Cyclo
1989	349	Doxo/Cyclo/Platin = Cyclo/Platin
GOG111 1996	410	Taxol/Platin >> Cyclo/Platin
OV 10 2000	680	Taxol/Platin >> Cyclo/Platin



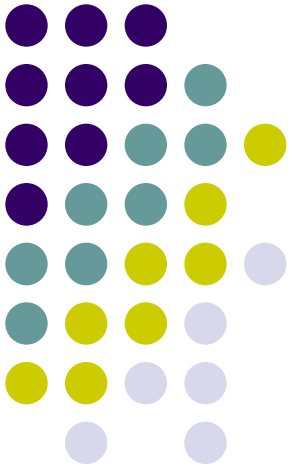
Equivalance of Cisplatin and Carboplatin

Year	Patient No.	Findings
2000	208	Taxol/Cisplatin = Taxol/Carboplatin (Dutch)
AGO-OVAR3 2003	798	Taxol/Cisplatin = Taxol/Carbo
GOG 158 2003	792	Taxol/Cisplatin = Taxol/Carbo (GOG)

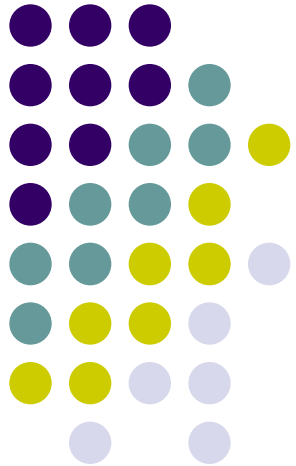


Taxol / Carboplatin :

The Current Gold Standard for First Line Chemotherapy for EOC

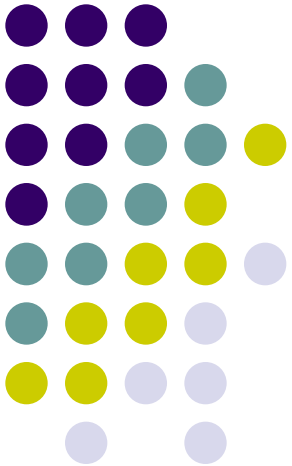


Improving on Standard Taxol / Carboplatin



Trends

- Additional of A Third Agent
- Use of Higher Doses
- Maintenance Chemotherapy
- Alternative Taxanes
- Use of Avastin
- IP Chemotherapy
- Dose Dense Chemotherapy

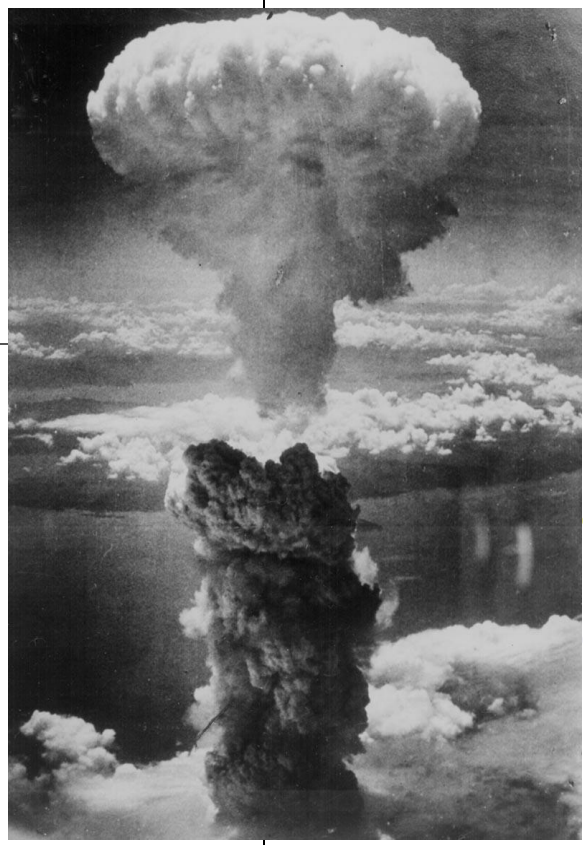


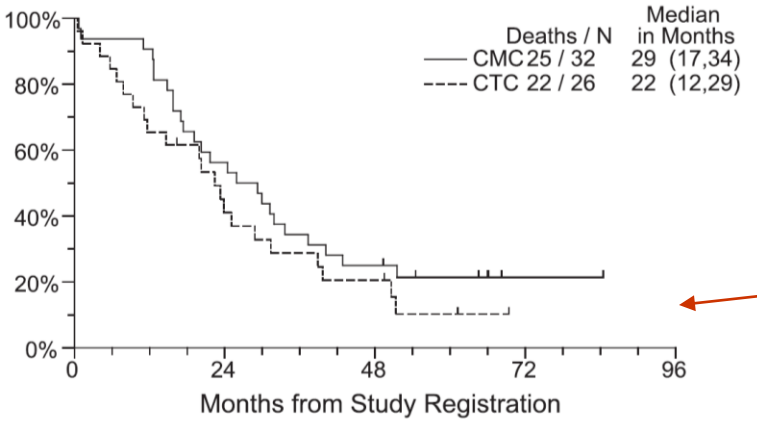
Addition of 3rd Agent – More is not better

Year	Pat No.	Agent
2006	1282	Toptecan
2008	847	Interferon-g
2008	451	Doxorubicin
2009	1742	Gemcitabine

Higher Chemotherapy doses Ineffective

Year	Pat No.	Findings
2004	502	Taxol (175) vs Taxol (225)
1994	798	- Taxol (250) vs Taxol (135)
		- 3hr vs 24 hr
2003	792	Carboplatin AUC 7.5
2001	523	Carboplatin AUC 9
Transplant		6 negative Trials

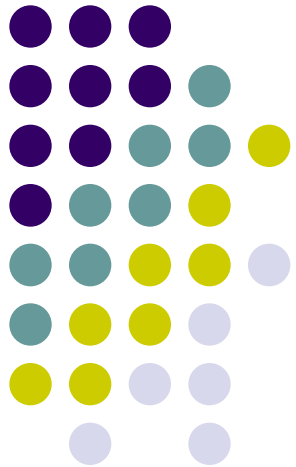




Bone Marrow Trpt is Ineffective!

Maintainance Chemotherapy

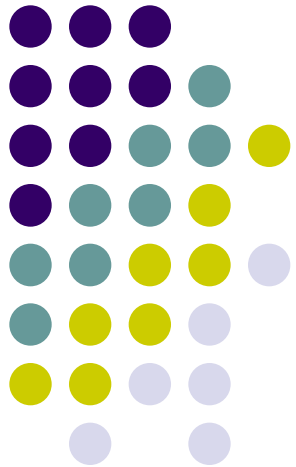
Year	Pat No.	Intervention
2003	277	12 mths vs 3 mths Taxol
2004	273	Topotecan x 6
2006	1308	Topotecan x 4
2004	145	Ca125 monoclonal Antibody
1992	202	12 vs 6 cycles Cyclophos/Doxo/Plat
1997	255	8 vs 5 Cisplatin



Hormones – also no benefit!

Alternative First Line: ? Docetaxel

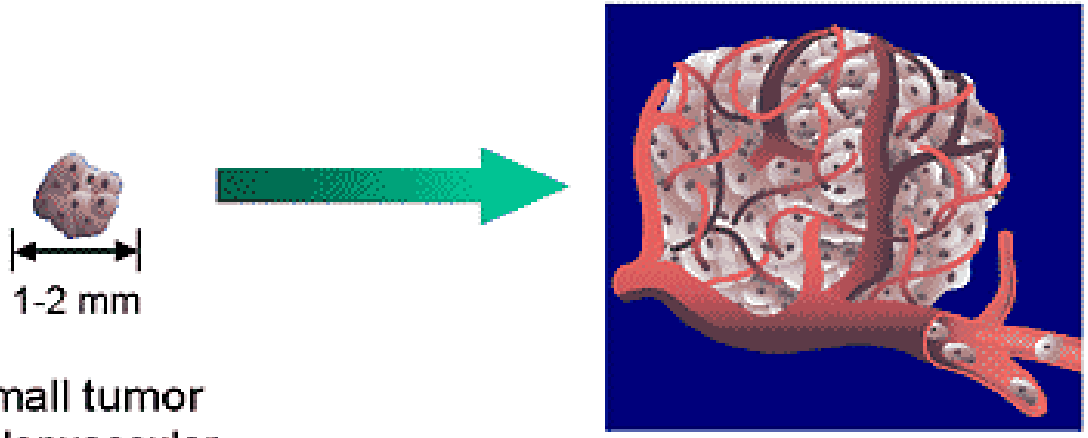
Evidence for Docetaxel				
SCOTROC Vasel et al 2003	1077	Stage 1c to IV	Paclitaxel 175mg/m2 over 3 hrs+ carboplatin (AUC 5) vs Docetaxel 75mg/m2 over 1hr + carobplatin (AUC 5)	No difference in PFS Greater myelosuppression (neutropenia, need GCSF) Less sensory neuropathy, arthralgia, myalgia, alopecia.



- Can be used as an alternative to Paclitaxel to minimise neurotoxicity.
- Evidence implies at least equivalence (N.B. Study powered for superiority)

VEGF Blockade?

The Angiogenic Switch



Small tumor
- Nonvascular
- "Dormant"

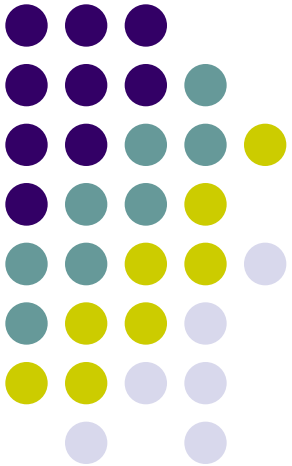
Larger tumor
- Vascular
- Metastatic potential

Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study.

Author(s): R. A. Burger, M. F. Brady, M. A. Bookman, J. L. Walker, H. D. Homesley, J. Fowler, B. J. Monk, B. E. Greer, M. Boente, S. X. Liang; Fox Chase Cancer Center, Philadelphia, PA; Gynecologic Oncology Group, Buffalo, NY; Arizona Cancer Center, Tucson, AZ; University of Oklahoma Health Sciences Center, Oklahoma City, OK; The Brody School of Medcine, Greenville, NC; James Cancer Hospital, The Ohio State University, Hilliard, OH; University of California, Irvine Medical Center, Orange, CA; Seattle Cancer Care Alliance, Seattle, WA; Minnesota Oncology and Hematology, Minneapolis, MN; Stony Brook University, Stony Brook, NY

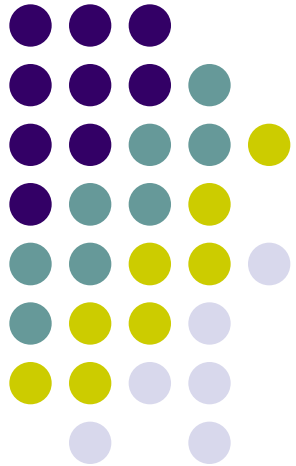
Background: BEV, a humanized anti-VEGF monoclonal antibody, has demonstrated single-agent activity in patients with recurrent EOC, or PPC. The therapeutic impact of concurrent ± maintenance BEV with standard chemotherapy (CT) was evaluated in an international, double-blind, placebo-controlled phase III trial.

Methods: Eligible patients had newly diagnosed, previously untreated EOC, PPC or FTC following abdominal surgery for staging and maximal effort at tumor debulking; stage III (macroscopic residual disease) or stage IV disease. The randomly allocated regimens were (1) CT (IV paclitaxel 175 mg/m2 + carboplatin AUC 6 cycles 1-6) + placebo cycles (C)2-22 (R1) (2) CT + concurrent BEV (15 mg/kg) C2-6 + placebo C7-22 (R2) (3) CT + concurrent BEV C2-6 + maintenance BEV C7-22 (R3) Infusions were administered d1 of a 21d cycle. The primary endpoint is progression-free survival (PFS) (radiographic, CA125, clinical criteria or death); secondary endpoints include overall survival, safety, and QoL.



GOG
VEGF blockade - Avastin

		PFS
1873 Adv Ovarian Cancer →	Pac/Carbo x 6	10.3 mths
	Pac/Carbo/Avastin x 6	11.2 mths
	Pac/Carbo/Avastin + Avastin Maintenance*	14.1 mths

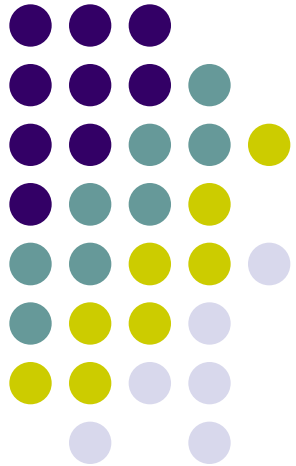


*Estim cost > SGD 100 000

Results:

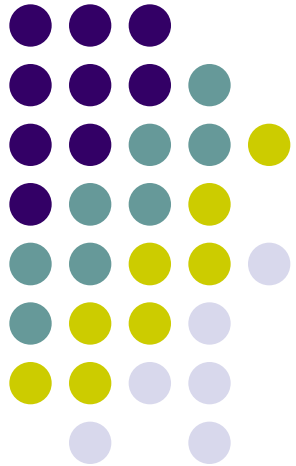
- 1,873 patients, median age 60, were enrolled from 9/05 - 6/09. Stage III optimally debulked (34%), stage III sub-optimally debulked (40%), and stage IV (26%) patients were similarly distributed in each treatment group.
- Grade 3 - 4 hypertension was reported in 1.6% (R1), 5.4% (R2), and 10.0% (R3). Grade = 3 GI perforation, hemorrhage or fistula occurred in 0.8% (R1), 2.6% (R2) and 2.3% (R3).
- Relative to R1, the hazard of first progression or death for R2 was 0.908 (95% CI: 0.795 - 1.04, p=0.16) and for R3 was 0.717 (95% CI: 0.625 - 0.824, p<0.0001).

Conclusions: This study demonstrates that front-line treatment of EOC, PPC, and FTC patients with CT plus concurrent and maintenance BEV prolongs PFS. This is the first anti-angiogenic agent to demonstrate benefit in this population.

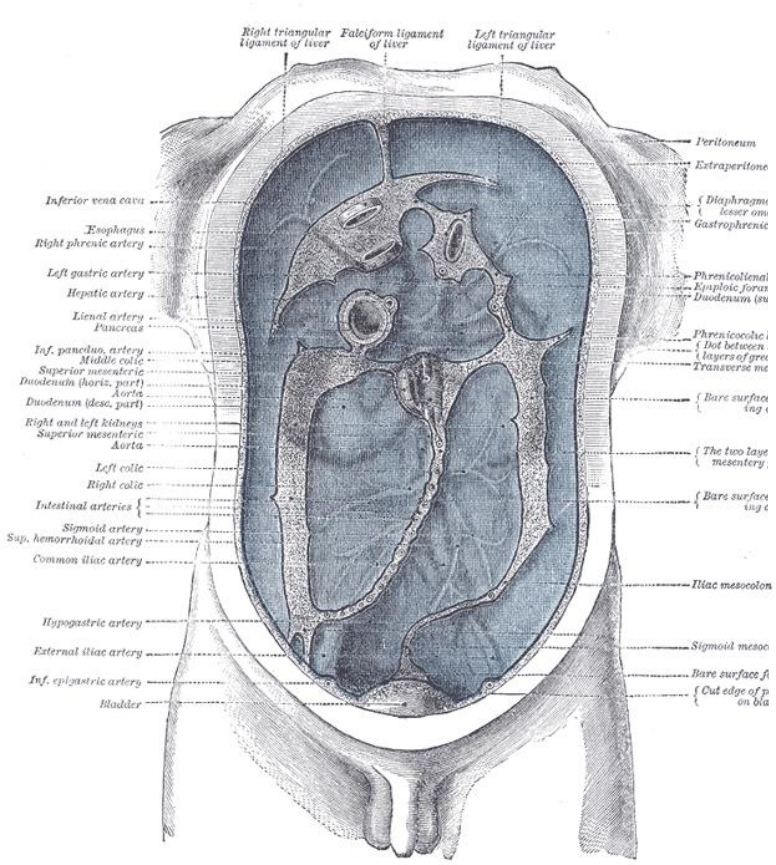


Schedule and Route

(Taxol/Platinum)



Peritoneal Compartment



[CANCER RESEARCH 44, 3584–3592, August 1984]

Mechanisms of Human Tumor Metastasis Studied in Patients with Peritoneovenous Shunts[1]

David Tarin,[2] Janet E. Price, Michael G. W. Kettlewell,[3] Robin G. Souter, Alan C. R. Vass, and Beryl Crossley

Nuffield Departments of Pathology [D. T., J. E. P., B. C.] and Surgery [M. G. W. K., R. G. S.], (University of Oxford) John Radcliffe Hospital, Oxford, OX3 9DU, and Department of Obstetrics and Gynaecology [A. C. R. V.], Wycombe General Hospital, High Wycombe, Buckinghamshire HP11 2TT, England

ABSTRACT

The technique of peritoneovenous shunting for the alleviation of abdominal pain and distension in malignant ascites due to inoperable cancer, returns the fluid to the circulation via a one-way, valved, anastomosis between the peritoneum and the jugular vein. Surprisingly, although the patients treated with this technique receive direct infusions of malignant tumor cells into the blood, this study of 29 patients, 15 of whom came to autopsy, shows that they did not all develop metastases, some being completely free of such lesions despite long survival. Even when metastases do form, they are small and clinically asymptomatic, and the technique is therefore not hazardous. In some patients, inert tumor cells identifiable by natural markers were recognized

laboratory studies on 29 patients treated with this technique and pathological findings in 15 of them who were subsequently autopsied. Although several reports (1, 7, 8, 13, 18, 19, 23, 26) have been published on the efficacy of this procedure for relief of symptoms, there has been no evaluation of the scientific implications of the observations which can be made. The findings must be interpreted with caution, because the sample of patients that can be studied thoroughly, even by laboratories with adequate resources and appropriate clinical associations, is small, and there are unavoidable differences in length of survival and in diagnosis between individual patients.

However, it is already clear that the findings in humans corroborate and extend those in other species and that patients

Summary of clinical details and pathological findings

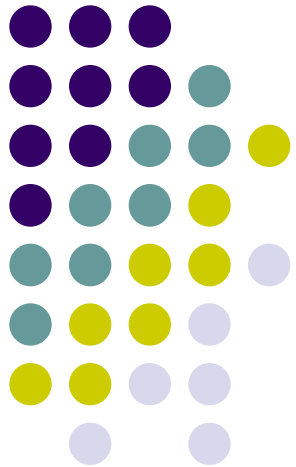
Patient	Sex	Age	Site of primary tumor	Survival time after shunting (mo)	Distribution of metastases
Group 1: no hematogenous metastases					
D. G.	F	53	Ovary	27#	None
E. H.	F	66	Ovary	2	None
R. H.	F	68	Stomach	1	None
D. J.	M	60	Unknown	2.5	None
A. R.	F	57	Ovary and breast	7	None
H. M.	F	48	Ovary	2	None
J. B.	F	76	Ovary	4	None
B. B.	F	46	Ovary	1	None

David Tarin et al , Cancer Res 1984

Evidence for IP Chemotherapy

Studies in IP chemotherapy

Albert et al1996 GOG 104/SWOG	546	Stage IIC - IV	IV cisplatin 100mg/m2 + IV cyclophosphamide 600mg/m2 vs IP cisplatin 100mg/m2 q 3wks x 6 cycles	PFS not reported OS 41 vs 49 mths p=0.02
Markman et al 2001 GOG 114/SWOG	462	Stage III, < or = 1cm RD	IV cisplatin 75mg/m2 + IV paclitaxel 135 mg/m2 over 24 hrs q 3wks x 6cycles vs IV carboplatin (AUC 9) q 28 days x 2cycles + IV cisplatin 100mg/m2 + IV paclitaxel 135 mg/m2 over 24 hrs q3 wks x 6 cycles	PFS 22 vs 28 p=0.01 OS 52 vs 63 mths p=0.05
Armstrong et al GOG 172	415	Stage III, < or = 1cm RD	IV cisplatin 75mg/m2 + IV paclitaxel 135 mg/m2 over 24 hrs q 3wks x 6cycles vs IV paclitaxel 135mg/m2 over 24 hrs D1 + IP cisplatin 100mg/m2 D2 + IP paclitaxel 60mg/m2 D8 q3 wks x 6 cycles	PFS 18 vs 24 mths p=0.05 OS 50 vs 66 mths p=0.03



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

Deborah K. Armstrong, M.D., Brian Bundy, Ph.D., Lari Wenzel, Ph.D., Helen Q. Huang, M.S., Rebecca Baergen, M.D., Shashikant Lele, M.D., Larry J. Copeland, M.D., Joan L. Walker, M.D., and Robert A. Burger, M.D., for the Gynecologic Oncology Group*

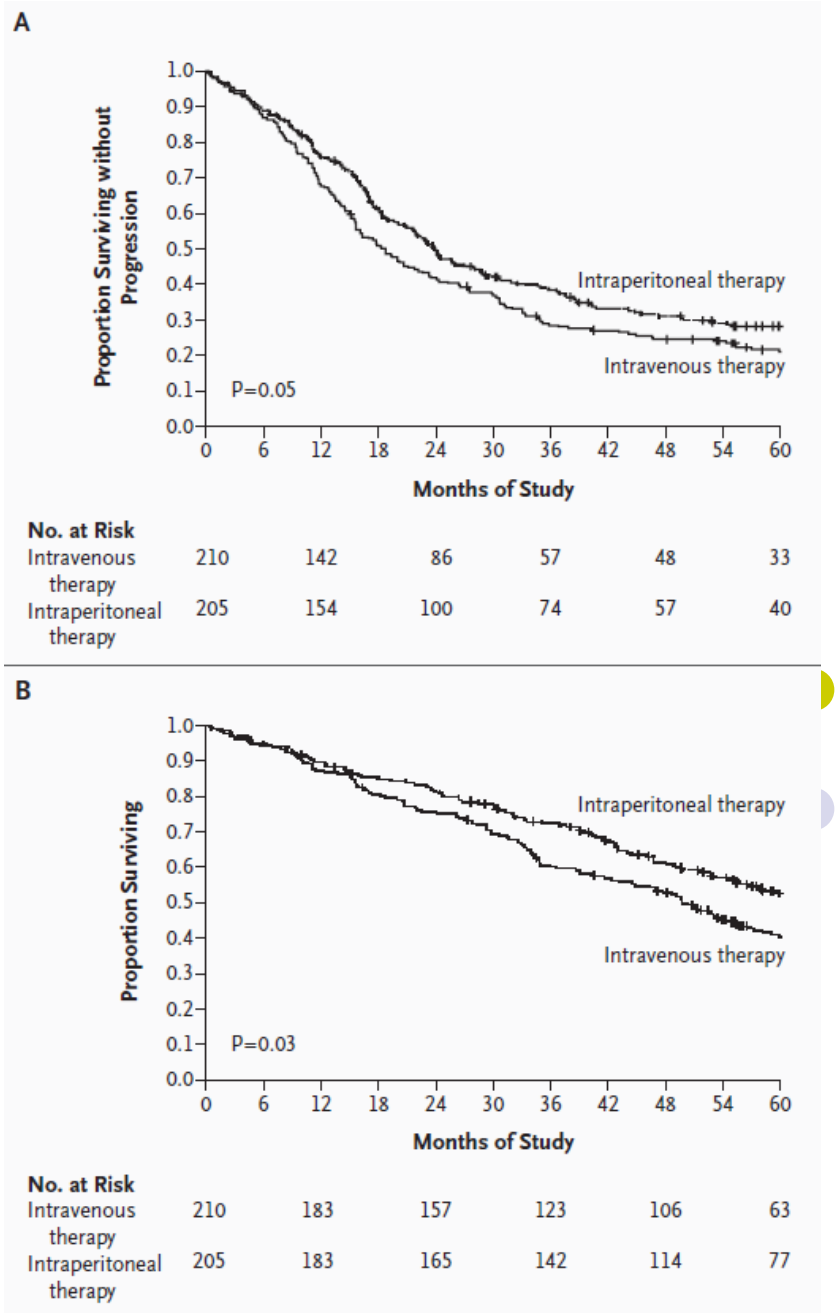
ABSTRACT

BACKGROUND

Standard chemotherapy for newly diagnosed ovarian cancer is a platinum–taxane combination. The Gynecologic Oncology Group conducted a randomized, phase 3 trial that compared intravenous paclitaxel plus cisplatin with intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel in patients with stage III ovarian cancer.

METHODS

We randomly assigned patients with stage III ovarian carcinoma or primary peritoneal carcinoma with no residual mass greater than 1.0 cm to receive 135 mg of intravenous paclitaxel per square meter of body-surface area over a 24-hour period followed by either 75 mg of intravenous cisplatin per square meter on day 2 (intravenous-therapy group) or 100 mg of intraperitoneal cisplatin per square meter on day 2 and 60 mg of intraperitoneal paclitaxel per square meter on day 8 (intraperitoneal-therapy group). Treatment was given every three weeks for six cycles. Quality of life was assessed.



Armstrong et al. NEJM 2006

Results

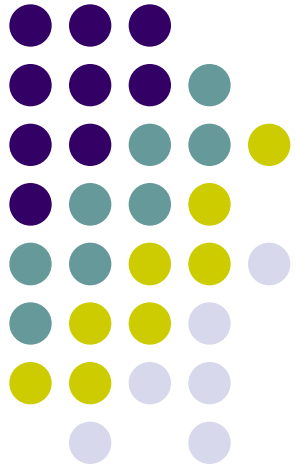
•Of 429 patients who underwent randomization, 415 were eligible.

•Grade 3 and 4 pain, fatigue, and hematologic, gastrointestinal, metabolic, and neurologic toxic effects were more common in the intraperitoneal-therapy group than in the intravenous-therapy group (P ≤ 0.001).

•***Only 42 percent of the patients*** in the intraperitoneal therapy group completed six cycles of the assigned therapy, ***but the median duration of progression-free survival in the intravenous-therapy and intraperitoneal-therapy groups was 18.3 and 23.8 months, respectively (P = 0.05 by the log-rank test).***

•***The median duration of overall survival in the intravenous-therapy and intraperitoneal therapy groups was 49.7 and 65.6 months, respectively (P = 0.03 by the log-rank test).***

•Quality of life was significantly worse in the intraperitoneal-therapy group before cycle 4 and three to six weeks after treatment but not one year after treatment.



Conclusions

As compared with intravenous paclitaxel plus cisplatin, intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival in patients with optimally debulked stage III ovarian cancer.

Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial

*Noriyuki Katsumata, Makoto Yasuda, Fumiaki Takahashi, Seiji Isonishi, Toshiko Jobo, Daisuke Aoki, Hiroshi Tsuda, Toru Sugiyama, Shoji Kodama, Eizo Kimura, Kazunori Ochiai, Kiichiro Noda, for the Japanese Gynecologic Oncology Group**

Summary

Background Paclitaxel and carboplatin given every 3 weeks is standard treatment for advanced ovarian carcinoma. Attempts to improve patient survival by including other drugs have yielded disappointing results. We compared a conventional regimen of paclitaxel and carboplatin with a dose-dense weekly regimen in women with advanced ovarian cancer.

Methods Patients with stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer were eligible for enrolment in this phase 3, open-label, randomised controlled trial at 85 centres in Japan. Patients were randomly assigned by computer-generated randomisation sequence to receive six cycles of either paclitaxel (180 mg/m^2; 3-h intravenous infusion) plus carboplatin (area under the curve [AUC] 6 mg/mL per min), given on day 1 of a 21-day cycle (conventional regimen; n=320), or dose-dense paclitaxel (80 mg/m^2; 1-h intravenous infusion) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle (dose-dense regimen; n=317). The primary endpoint was progression-free survival. Analysis was by intention to treat (ITT). This trial is registered with ClinicalTrials.gov, number NCT00226915.

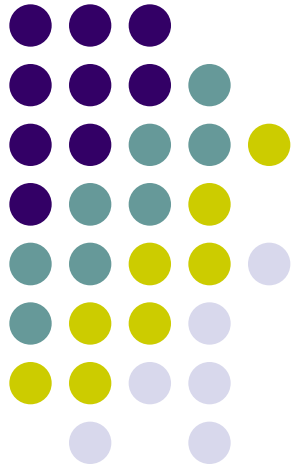
Lancet 2009

Findings

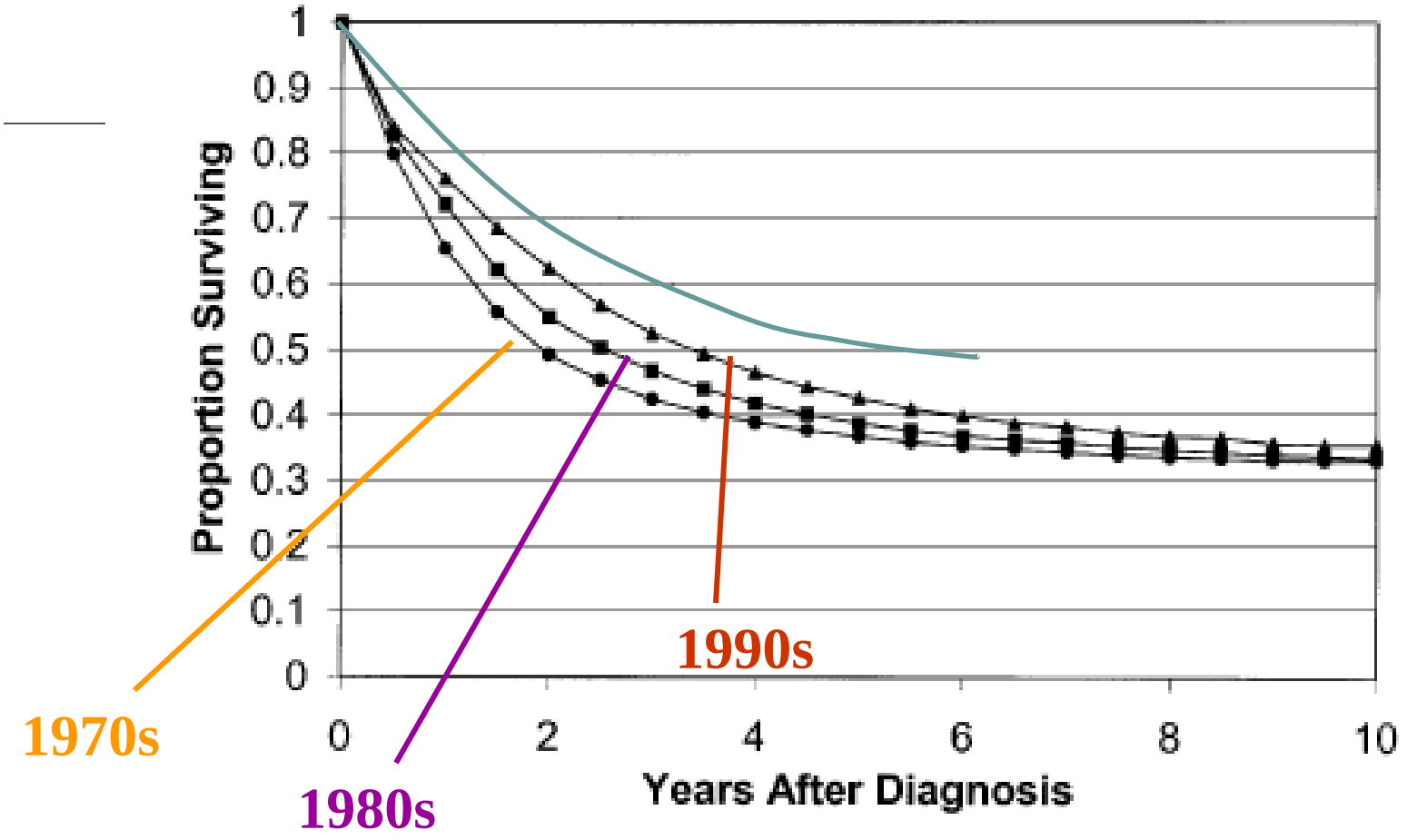
- **631 of the 637 enrolled patients were eligible for treatment and were included in the ITT population (dosedense regimen, n=312; conventional regimen, n=319).**
- **Median progression-free survival was longer in the dosedensetreatment group (28·0 months, 95% CI 22·3–35·4) than in the conventional treatment group (17·2 months,15·7–21·1; hazard ratio [HR] 0·71; 95% CI 0·58–0·88; p=0·0015).**
- **Overall survival at 3 years was higher in the dosedenseregimen group (72·1%) than in the conventional treatment group (65·1%; HR 0·75, 0·57–0·98; p=0·03).**
- **165 patients assigned to the dose-dense regimen and 117 assigned to the conventional regimen discontinued treatment early. Reasons for participant dropout were balanced between the groups, apart from withdrawal because of toxicity, which was higher in the dose-dense regimen group than in the conventional regimen group (n=113 *vs* n=69).**
- **The most common adverse event was neutropenia (dose-dense regimen, 286 [92%] of 312; conventional regimen, 276 [88%] of 314). The frequency of grade 3 and 4 anaemia was higher in the dose-dense treatment group (214 [69%]) than in the conventional treatment group (137 [44%]; p<0·0001). The frequencies of other toxic effects were similar between groups.**

Interpretation

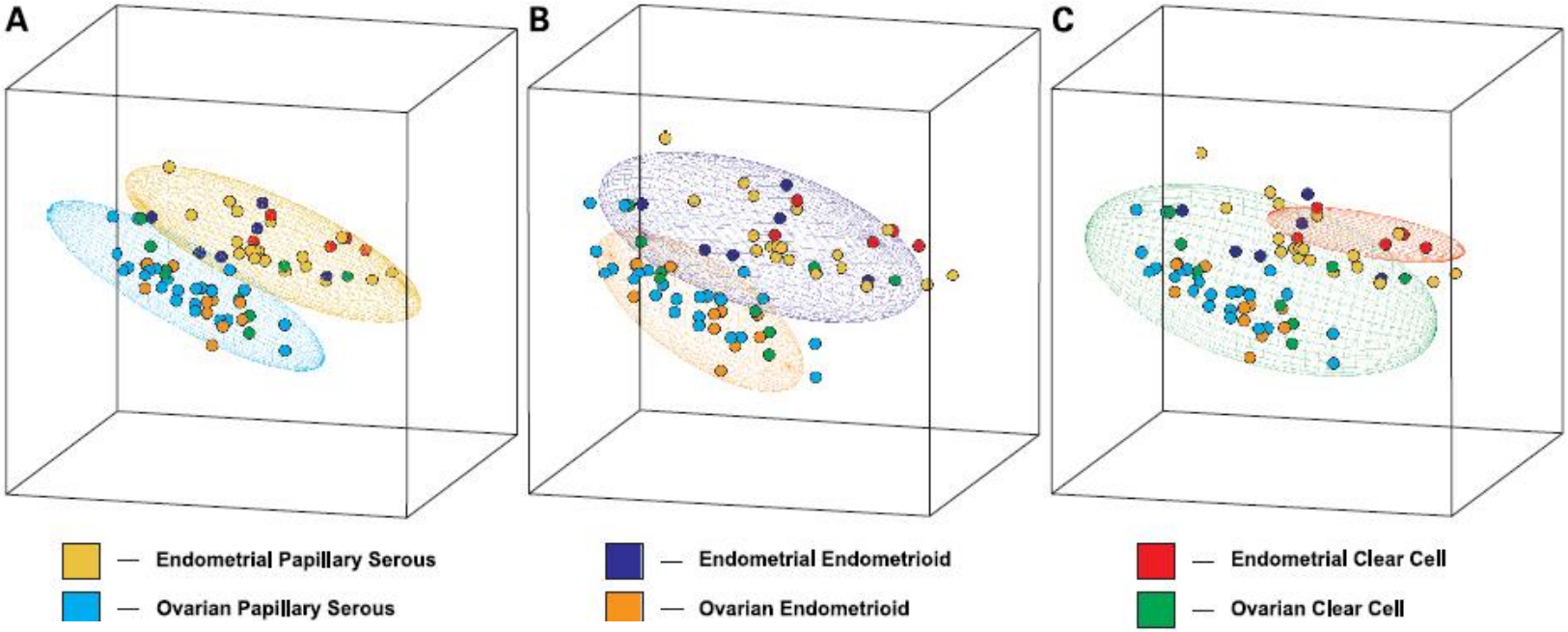
Dose-dense weekly paclitaxel plus carboplatin improved survival compared with the conventional regimen and represents a new treatment option in women with advanced epithelial ovarian cancer.

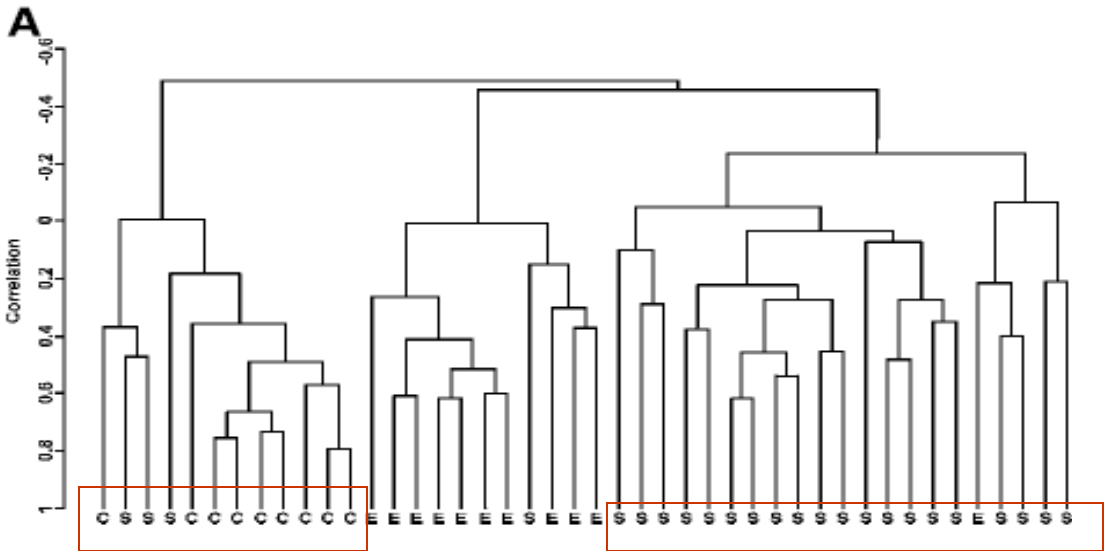


Ovarian Cancer Survival –
across 30 years



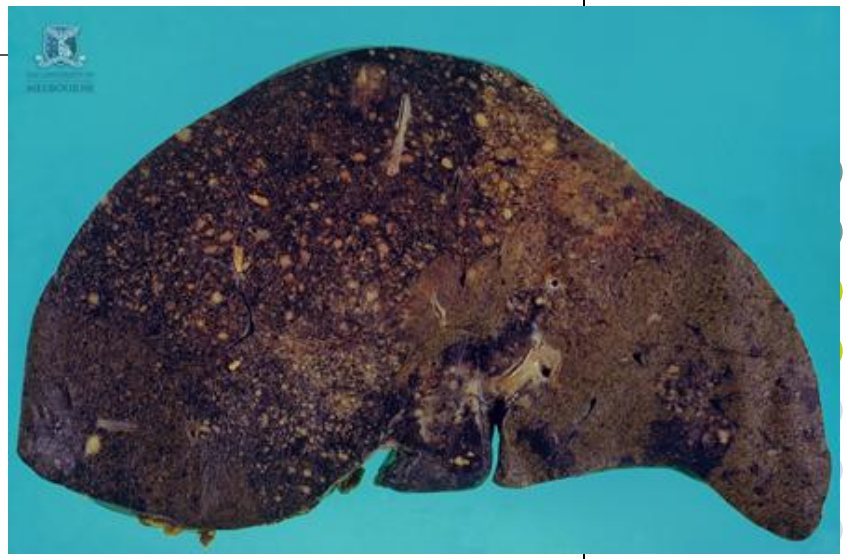
Ovarian Cancer is not one disease



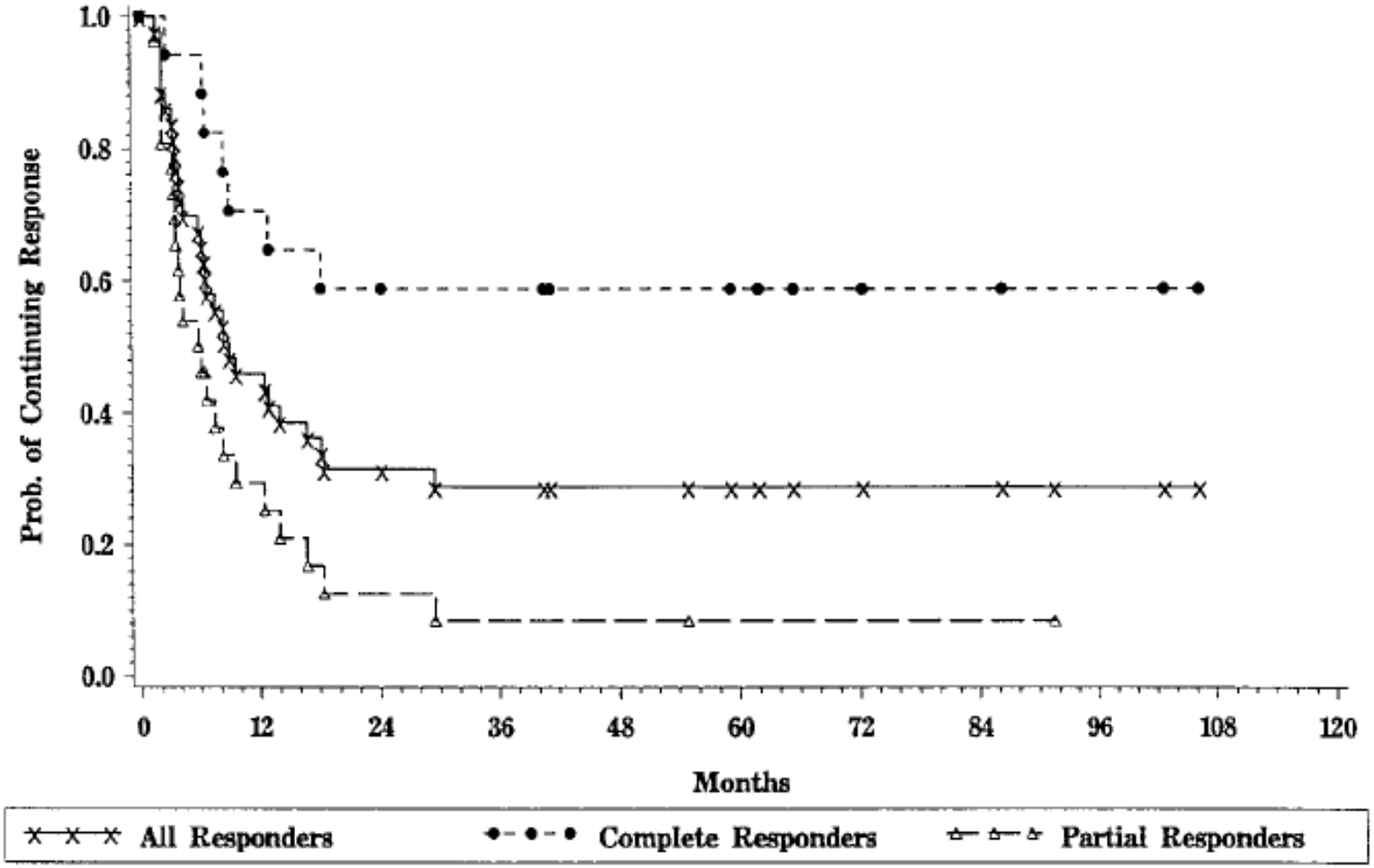


Kristin et al. CCR 2005

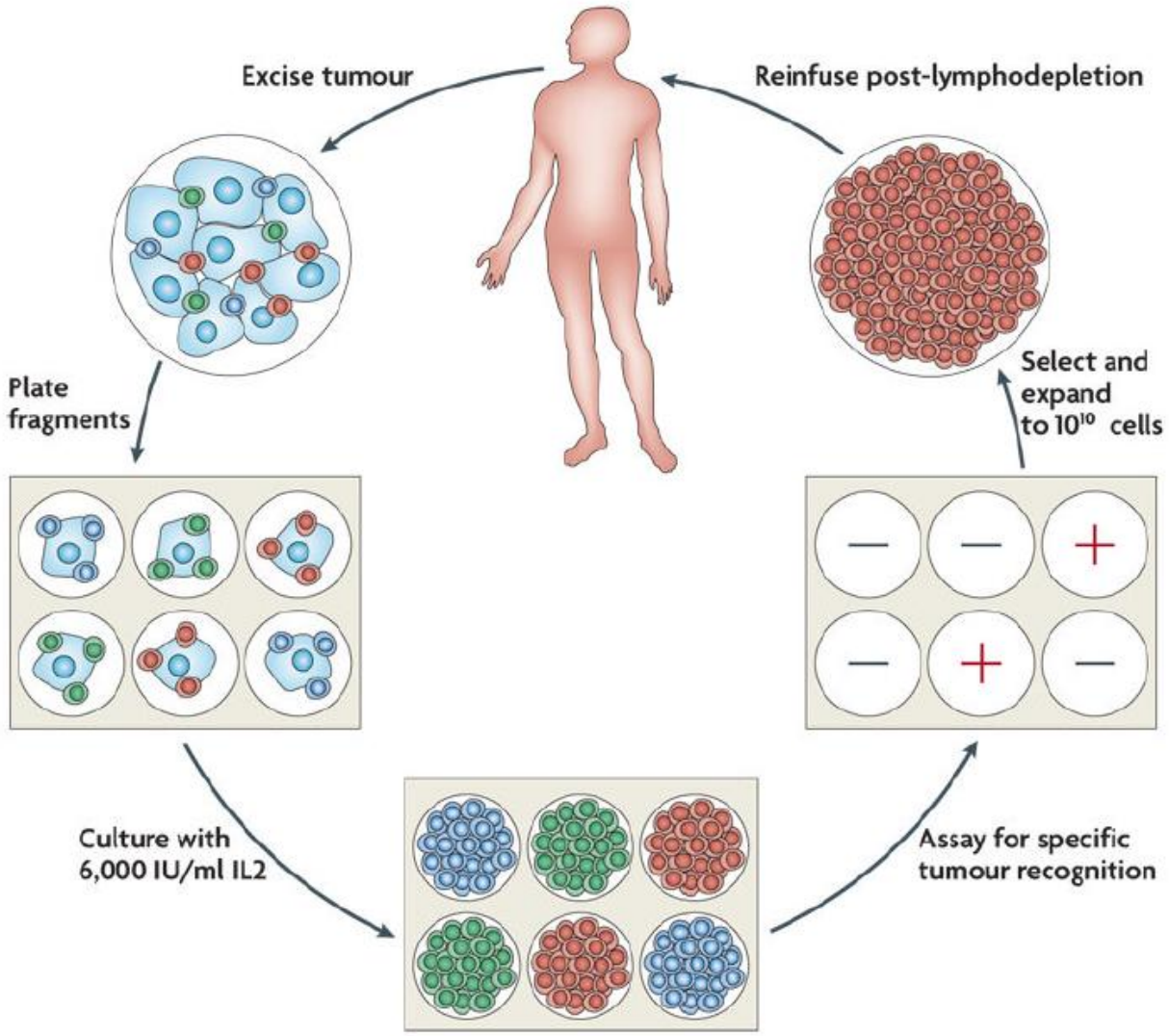
The Immune System is necessary for controlling Cancer



High dose IL-2 cures 8% of Stage IV disease



Adoptive T cell therapy



Results – Adoptive T cell therapy

A

Day of treatment	-7	-6	-5	-4	-3	-2	-1	0	1	2	3
Non-myeloablative	Cy	Cy	Flu	Flu	Flu	Flu	Flu	TIL	IL-2	IL-2	IL-2
Ablative (200cGy)		Cy Flu	Cy Flu	Flu	Flu	Flu	TBI	TIL	IL-2	IL-2 CD34+	IL-2
Ablative (1,200cGy)	Cy Flu	Cy Flu	Flu	Flu	Flu TBI	TBI	TBI	TIL	IL-2 CD34+	IL-2	IL-2

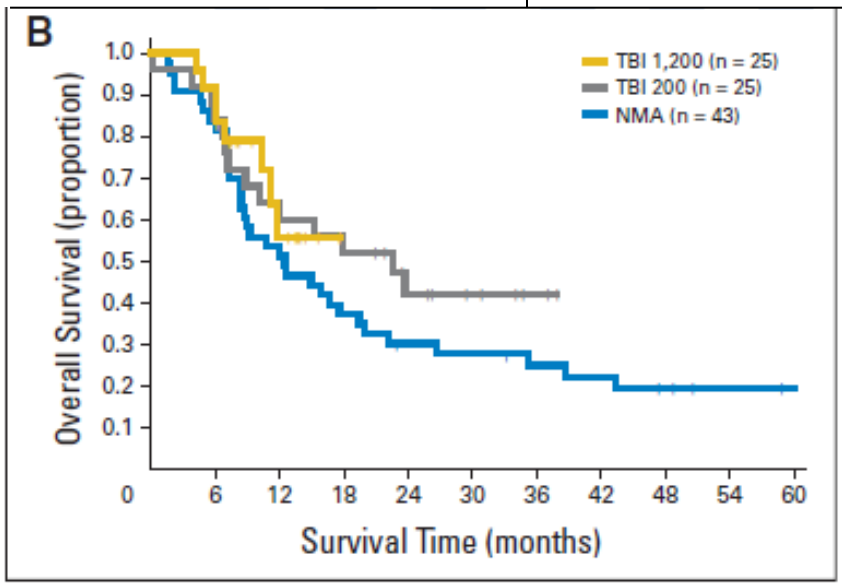
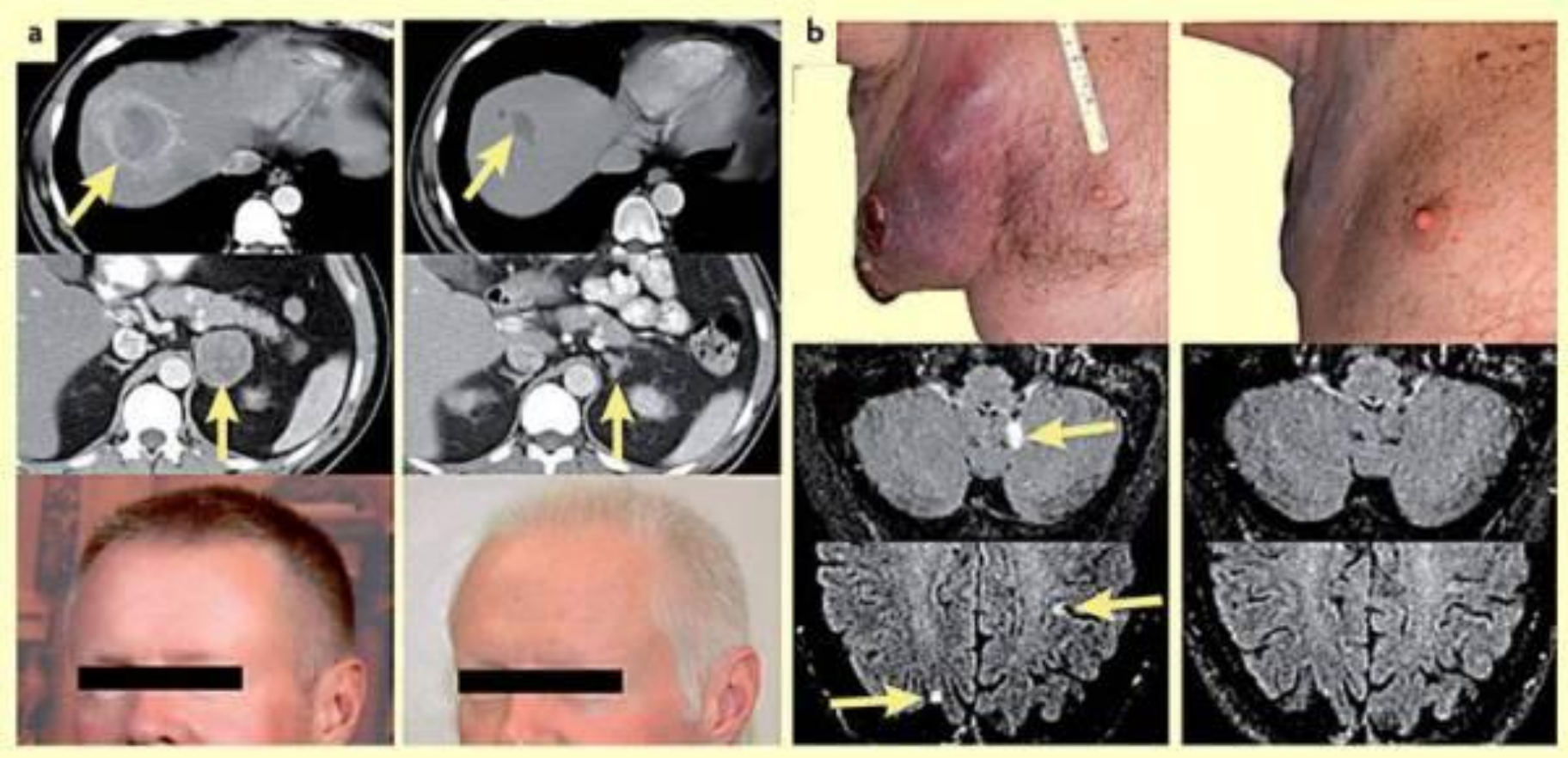


Table 2. Frequency and Duration of Objective Responses

TBI	Total No. of Patients	PR			CR			OR	
		No.	%	Duration (months)	No.	%	Duration (months)	No.	%
None*	43	17	39.5	64+, 32+, 20+, 29, 28, 14, 13, 11, 8, 8, 7, 4, 3, 3, 2, 2, 2	4	9.3	63+, 58+, 48+, 47+	21	48.8
2 Gy	25	11	44.0	33+, 29+, 23+, 14, 10, 6, 5, 5, 4, 3, 3	2	8.0	37+, 25+	13	52.0
12 Gy	25	14	56.0	14+, 13+, 10+, 7+, 7+, 7+, 6+, 6+, 4+, 7, 6, 6, 4, 3	4	16.0	17+, 15+, 13+, 8+	18	72.0

NOTE. All patients received cyclophosphamide 60 mg/kg × 2 days + fludarabine 25 mg/m^2 × 5 days.
Abbreviations: TBI, total-body irradiation; PR, partial response; CR, complete response; OR, objective response; TIL, tumor-infiltrating lymphocytes.

Adoptive T cell therapy

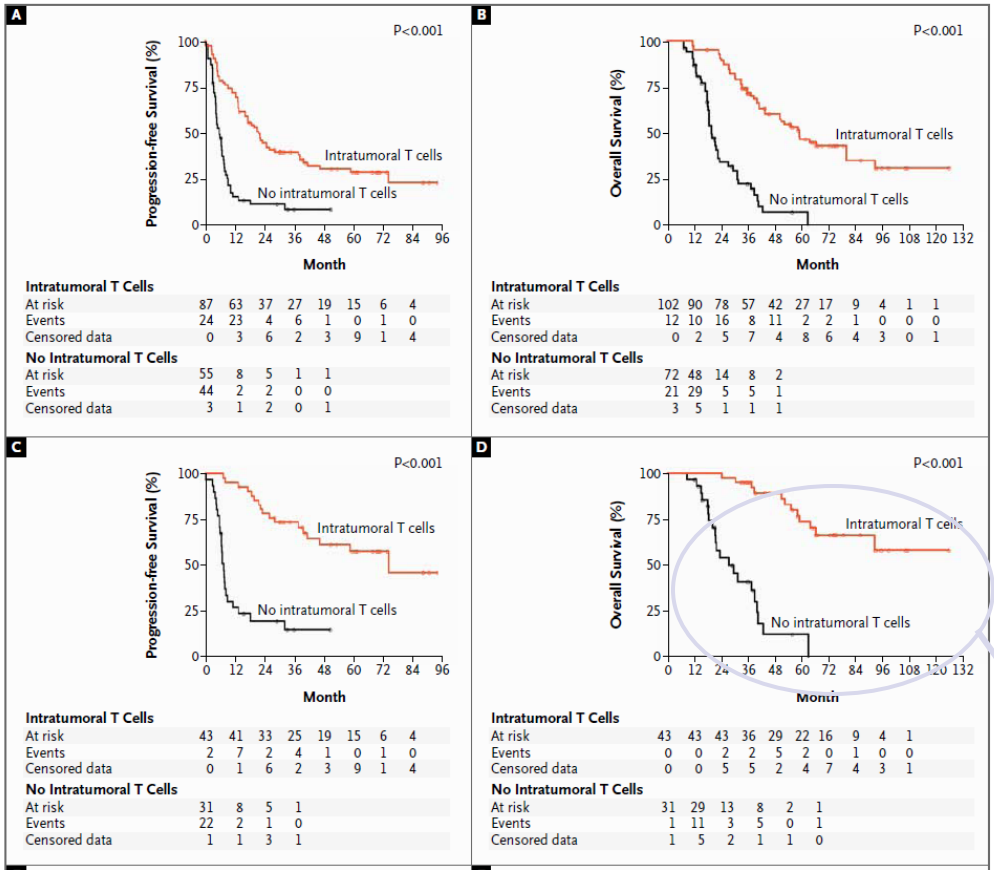


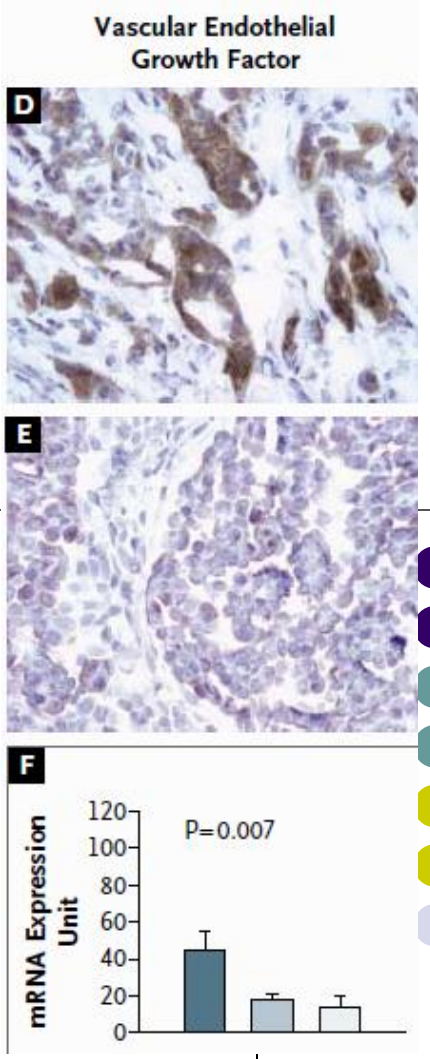
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D., and George Coukos, M.D., Ph.D.



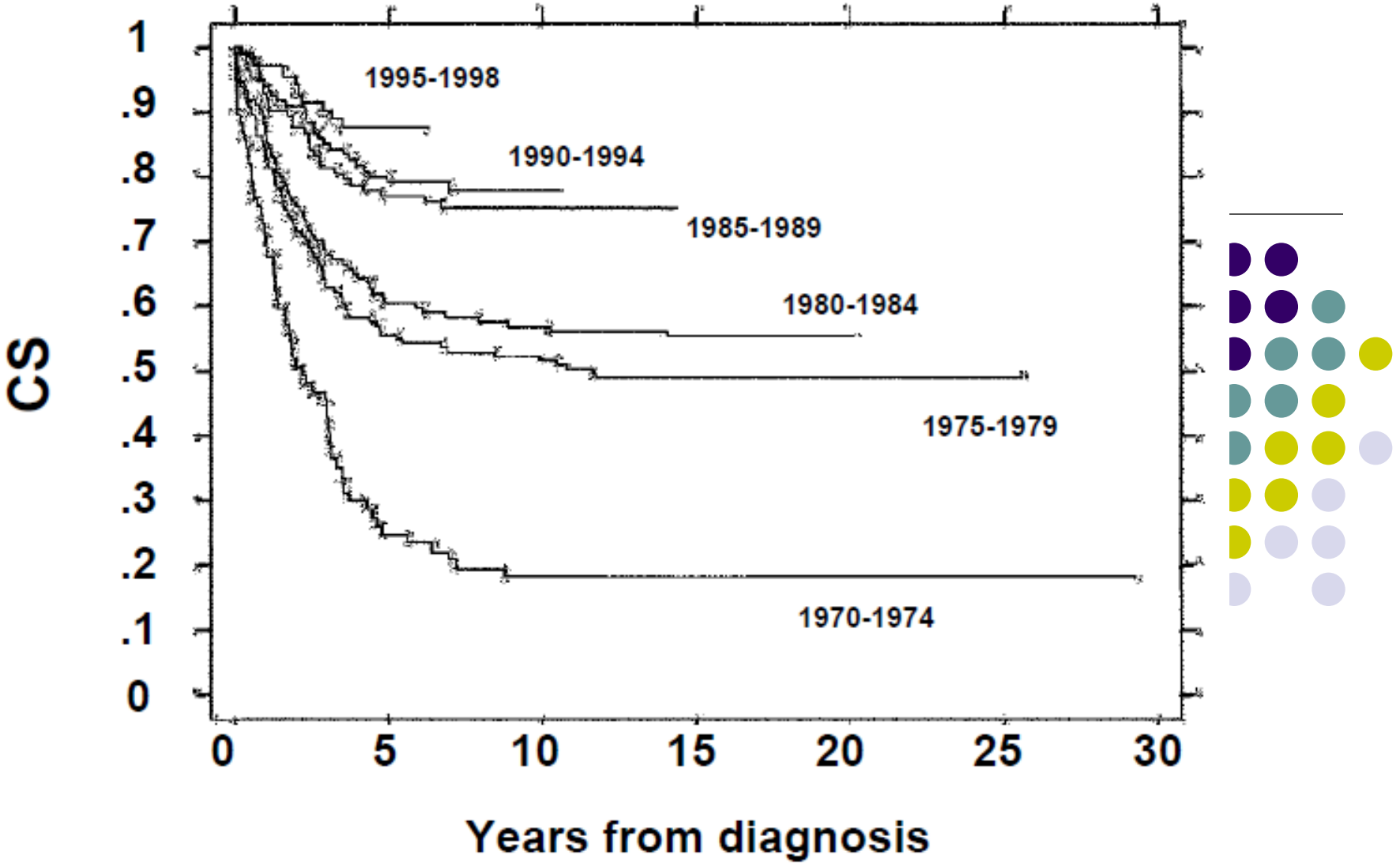


No intratumoral T cells
Intratumoral T cells; progression-free survival, <6 months
Intratumoral T cells; progression-free survival, >30 months

73% vs 11% 5yr OS

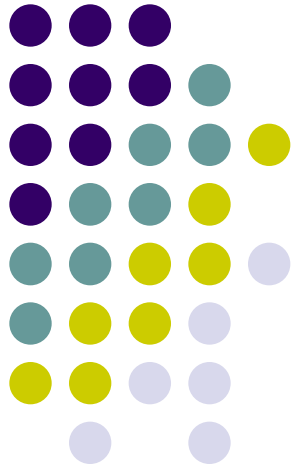
NEJM 2003

Acute lymphocytic leukemia



Conclusions

- EOC is Highly Chemosensitive.
- Trends towards Dose Dense Chemotherapy and IP chemotherapy.
- EOC is VEGF sensitive: ? new paradigm shift to include VEGF in treatment regimen
- Paradigm for immRx & immunosuppression
  - T-regs
  - TILs
  - Cytokines



Thank You