



Société
Internationale
d'Oncologie
Gériatrique



ΟΓΚΟΛΟΓΙΚΟ ΚΕΝΤΡΟ
Τραπεζας Αθήνας

Adjuvant therapy for colon cancer: not forgetting the elderly patient

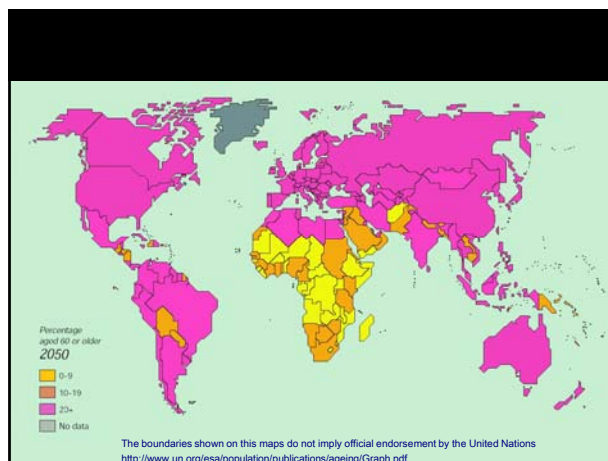
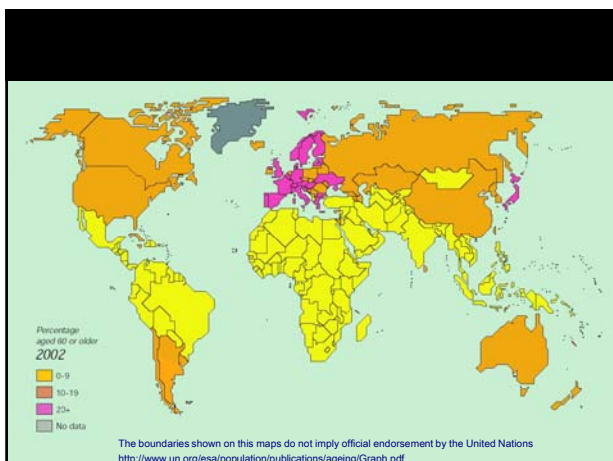
D Papamichael MB BS FRCP

EORT-GI Winter Meeting on
Gastrointestinal Cancer

February 28-29 2009
Nice, FRANCE

Background

- Fastest growing section of population in Western countries is that of over 65s
- Approximately half the incidence of colorectal cancer occurs in the over 70s
- Evidence that elderly patients with colorectal cancer are:
 - under-staged
 - under-treated
 - under-represented in clinical trials



Baseline life expectancy-women

Age (years)	Life expectancy		
	Healthy	Average	Sick
65	20	18.5	9.7
70	15.8	14.8	8.6
75	12.1	11.5	7.3
80	8.8	8.4	5.9
85	6.1	5.9	4.5

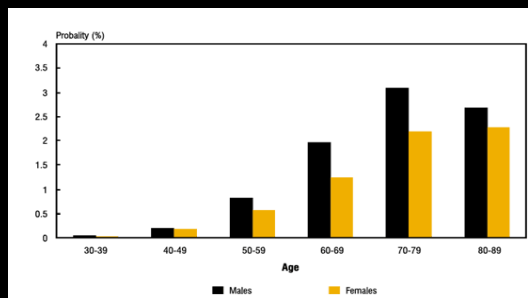
Baseline life expectancy-men

Age (years)	Life expectancy		
	Healthy	Average	Sick
65	15.9	14.9	8.5
70	12.5	11.8	7.4
75	9.5	9.1	6.2
80	7.0	6.8	4.5
85	5.0	4.9	3.8

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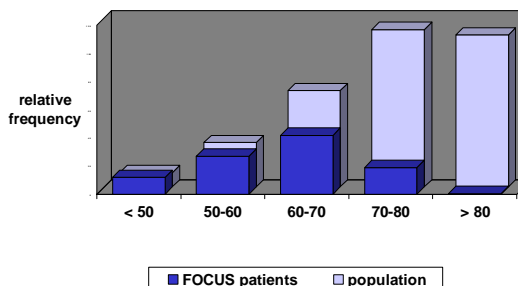
Probability (%) of Developing Colorectal Cancer in the Next 10 Years by Age



NCIC, Canadian Cancer Statistics 2002

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FOCUS: Lancet 370:143-52, 2007

Cancer Registry data

Key areas

- **Diagnosis, staging and patient assessment**
- Surgical management
- Radiotherapy in rectal cancer
- Chemotherapy
 - a. Adjuvant
 - b. Metastatic
 - Palliative
 - Targeted therapies
 - Palliative vs curative therapy

Key areas

- Diagnosis, staging and patient assessment
- **Surgical management**
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- Diagnosis, staging and patient assessment
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- **Chemotherapy**
 - a. Adjuvant
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 - Targeted therapies
 - Liver resection/metastasectomy

Questions in adjuvant therapy

- Toxicity - are elderly patients more prone to it?
- Efficacy - is adjuvant therapy less likely to work in the elderly?
 - Biological considerations
 - Co-morbidities etc.

How is cancer treatment studied

- Primarily middle-aged patients; minimal inclusion of older patients
- Minimal comorbidity; patients with other medical problems excluded
- Caucasian
- Cancer Centre based

The evidence

- Individual clinical trials; pooled analysis of clinical trials. Retrospective subset analyses – older patients make up only a fraction
- Retrospective reviews from institutions
 - Bias
- Population based studies
 - More “real life” (but non-randomised)

Colon Cancer: Burden of Comorbidity

Disorder Predictors of early mortality with colon cancer

	<u>RR</u>
Heart disease	1.31
COPD	1.51
Renal failure	1.73
Liver disease	2.54

Yancik et al Cancer 1998;82:2123-34

Colon cancer and diabetes

- Review of patients with stage II/III colon cancer receiving adjuvant therapy
- Patients with diabetes mellitus:
 - Decreased DFS, OS, RFS
 - Median survival 6 vs 11.3 yrs
 - 42% increased risk of death from any cause
 - 21% increased risk of recurrence
 - Increased diarrhoea

Myerhardt et al JCO 2003;21:433-40

Adjuvant therapy—treatment options

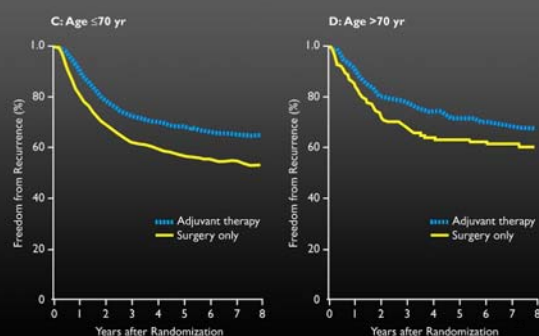
- Roswell Park (bolus)
Mayo, weekly - modulated by LV (bolus)
weekly 5FU/LV - QUASAR (bolus)
Lokich – PVI-5FU (infusion)
“de Gramont” (bolus + infusion)
- Oral 5FU analogues: Capecitabine, UFT
- Combination chemotherapy: FOLFOX/FUFOX

Pooled analysis – NSABP trials

- 5FU (+LV or LEV) vs observation – stage II/III disease
- Individual patient data
- Total of 3351 patients / 7 studies
- Endpoints
 - OS / TTR
 - Toxicity
 - Deaths (with/without recurrence)

Sargent et al NEJM 2001;345: 10091-7

Elderly vs Younger patients DFS



Pooled analysis - NSABP

- Similar TTR and OS across all age groups
 - Consistent benefit
 - No significantly increased toxicity
- Death without cancer:
 - 13% > 70 yrs
 - 7% in 61-70 yrs
 - 4% in 51-60
 - 1% < 50

Sargent et al NEJM 2001;345: 10091-7

Population based studies - 1

- 4768 stage III pts 65 or older 1992-1996 (SEER)
- Half received adjuvant therapy
- HR for death: 0.66 (95% CI 0.60-0.73) for 5FU based tx; i.e. 5FU based adjuvant therapy significantly associated with reduced mortality in older patients

Sundararajan et al Ann Int Med 2002;136: 349-57

Population based studies - 2

- 85934 pts, stage III, NCBDB 1990-2002
- Lower use of adjuvant tx in elderly
 - 80% in <70
 - 70% in 70-79
 - 40% in >80
- Adjuvant chemotherapy increases survival in elderly as it does in younger patients

Jessup et al JAMA 2005;294:2703-11

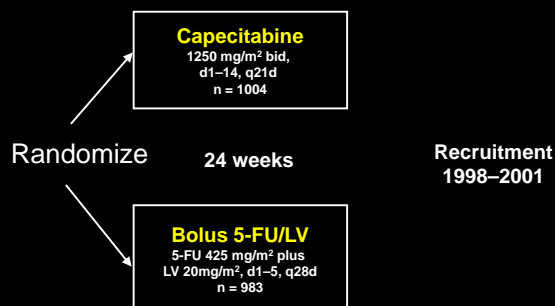
Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 yrs or older

Retrospective review – Royal Marsden Data

- 310/1387 CRC pts were 70 yrs or older
 - **More frequent severe mucositis in the 5FU bolus (vs PVI) adjuvant tx but no other differences in toxicities (72 bolus : 49 PVI)**
 - In the palliative setting:
 - similar responses and FFS,
 - as well as 1 yr survival.
 - Slightly less OS (p=.04)

Popescu et al JCO 1999;17: 2412-18

X-ACT Dukes' C colon



Scheithauer et al Ann Oncol 2003;14: 1735-43

X-ACT - safety

- Effect of age on capecitabine toxicity
 - upper age limit 75 (but pts up to 82 yrs old included!)
 - safety profile analyzed for pts under and over 65 receiving capecitabine
 - Result: no major differences
 - (capecitabine vs infusional 5FU?)

Scheithauer et al Ann Oncol 2003;14: 1735-43

X-ACT: 5-year efficacy update at ASCO GI 2008

Age was a significant factor on multivariate analysis for overall survival

Twelves et al Proceedings ASCO GI 2008 abstract 274

CAPECITABINE Renal impairment guidelines

Renal impairment	Calculated creatinine clearance (mL/min)	Starting dose (mg/m ² twice daily)
None	>80	1,250
Mild	51-80	1,250 ¹
Moderate	30-50	950 ¹
Severe	<30	Contra-indicated

¹With careful monitoring throughout treatment
PK = pharmacokinetic

¹In patients with and without renal impairment

Poole C et al. *Cancer Chemother Pharmacol* 2002;49:225-34

A Pooled Safety And Efficacy Analysis Of FOLFOX4 In Elderly Compared To Younger Patients With Colorectal Cancer

R M Goldberg, D Sargent, H Bleiberg, A de Gramont, C Tournigand, T Andre, ML Rothenberg, E Green, L Mounedji-Boudiaf, I Tabah-Fisch

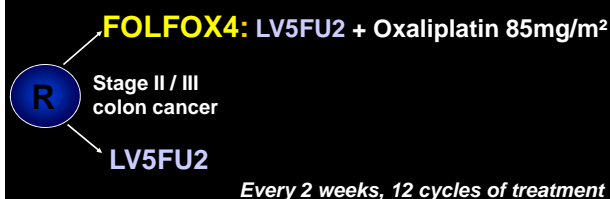
J Clin Oncol 2006; 24:4085-4091

Studies Included

Study	Comparator regimen	Setting	N
MOSAIC ¹	5-FU/LV	Adjuvant	2246
N9741 ²	IFL	1 st Line	546
de Gramont ³	5-FU/LV	1 st Line	420
Rothenberg ⁴	5-FU/LV	2 nd Line	531
Total			3743

¹Andre et al, *NEJM* 2004; ²Goldberg et al, *JCO* 2004; ³de Gramont et al, *JCO* 2000; ⁴Rothenberg et al, *JCO* 2003

MOSAIC: study design



Primary end-point: disease-free survival
Secondary end-points: safety, overall survival
Upper age limit: 75

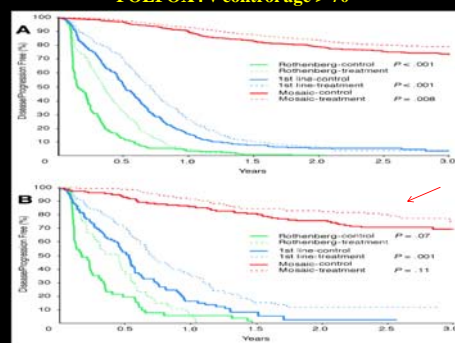
MOSAIC adverse events grade >3

- < 70 vs > 70
- any
- non-heme
- Deaths in 60 days

No significant difference

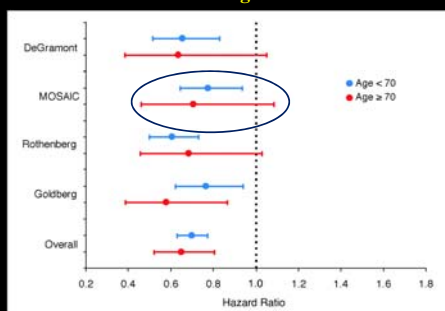
Goldberg, R. M. et al. *J Clin Oncol*; 24:4085-4091 2006

Kaplan-Meier plots of progression or disease-free survival for oxaliplatin plus fluorouracil/leucovorin administered bimonthly (FOLFOX4) v control by study and age group: (A) FOLFOX4 v control age < 70; (B) FOLFOX4 v control age > 70



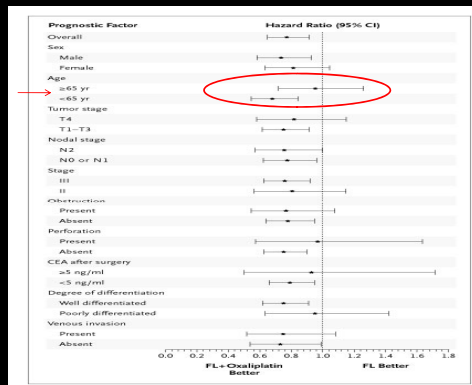
Goldberg, R. M. et al. *J Clin Oncol* 2006; 24:4085-4091

Forest plot of progression or disease-free survival by study for oxaliplatin plus fluorouracil/leucovorin administered bimonthly v control by age. de Gramont et al; MOSAIC.; Rothenberg et al; Goldberg et al



Goldberg, R. M. et al. J Clin Oncol 2006; 24: 4085-4091

Hazard Ratios and 95 Percent Confidence Intervals for Recurrence



Andre et al NEJM 2004;350:2343-51

Conclusions

- Younger and older patients receive the same benefit from FOLFOX4
- Elderly patients do not experience clinically meaningful increased toxicity from this regimen
- Age alone should not exclude an otherwise healthy elderly patient from receiving combination chemotherapy

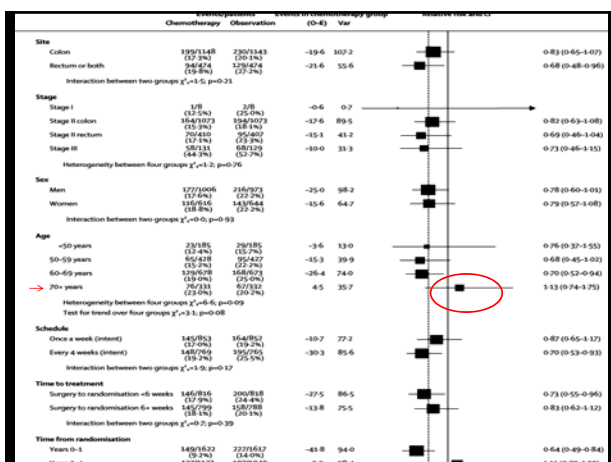
Limitations

- Selected patients fit for trial inclusion – small numbers
- MOSAIC eligibility – up to 75
- Care when extrapolating ...
- No population studies as yet

What about stage II disease?

Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised Study

The Lancet, Volume 370, Issue 9604, Pages 2020 - 2029, 15 December 2007



Case 1

- Mrs SJ – 83 year old retired librarian presented with increasing tiredness – found to be anaemic.
- Colonoscopy revealed a fungating mass in the caecum.
- Bx – adenocarcinoma. CT staging – no metastasis; CEA 2.1
- Right hemicolectomy performed without complications – no evidence of metastasis at exploration.
- Histology: pT3,N2 (7/16), Mx GII, adenocarcinoma, lymphovascular invasion present

Case 1 – continued

- She lives alone in a ground floor flat, with her daughter living nearby
- She takes medication for hypertension and hypercholesterolaemia. She had a cholecystectomy and hysterectomy in the past

You see her in outpatients and recommend:

www.adjuvantonline.com

- 31.2% alive at 5 years
- 14.3% alive due to chemotherapy
- 26% die due to cancer
- 28.5% die due to other causes

With FOLFOX

Case 2

- Mr AB, 80 year old retired accountant who noted blood in the toilet recently.
- Colonoscopy revealed a tumour at 35 cm; biopsy is positive for adenocarcinoma
- CT staging is unremarkable; CEA 1.1
- He undergoes a sigmoid colectomy without any complications.
- Histology: pT3, N0 (0/7), Mx, GIII adenocarcinoma, with lymphovascular invasion

Case 2 – continued

- He had a myocardial infarction 10 years ago and underwent CABGx3. He has NIDDM, ECOG PS 0.
- He lives with his wife and they will be celebrating their 60th wedding anniversary in 4 months

You see him in outpatients and recommend:

www.adjuvantonline.com

- 50.8% alive at 5 years
- 2.8% alive due to chemotherapy
- 12.1% die due to cancer
- 34.3% die due to other causes

With FOLFOX...

On-line tools

- Do not take into account all risk factors for recurrence
- Do not take into account nuances of co-morbidities best appreciated in clinic
- Cognitive status, polydrug use, psychosocial factors also important in decision making

General considerations for adjuvant therapy

- Toxicity probably not a major issue for “fit” elderly. Age related PK changes with age unlikely to be significant. Co-morbidities, functional status, PS, physiologic changes with age more relevant
- Gain may be inversely proportional to age due to increased deaths from other causes
- Duration of tx may be important for survival among the elderly (*Neugut et al JCO 2006*)
- Multiple regimens to consider/decision making process

General considerations for adjuvant therapy (cont.)

- Therapeutic decisions as regards adjuvant therapy should be reached jointly by patient and physician on an individual basis
- Need to understand further the characteristics that place certain older adults at risk for complications
- A shift in clinical colorectal cancer research is desirable, so as to represent the actual patient population of the disease treated