Société Internationale d'Oncologie Gériatrique

ΟΓΚΟΛΟΓΙΚΟ ΚΕΝΤΡΟ
Τράπεζας Κύπρου

Treatment of the elderly metastatic colorectal cancer patient: SIOG Recommendations

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On behalf of the SIOG CRC in the Elderly Task Force

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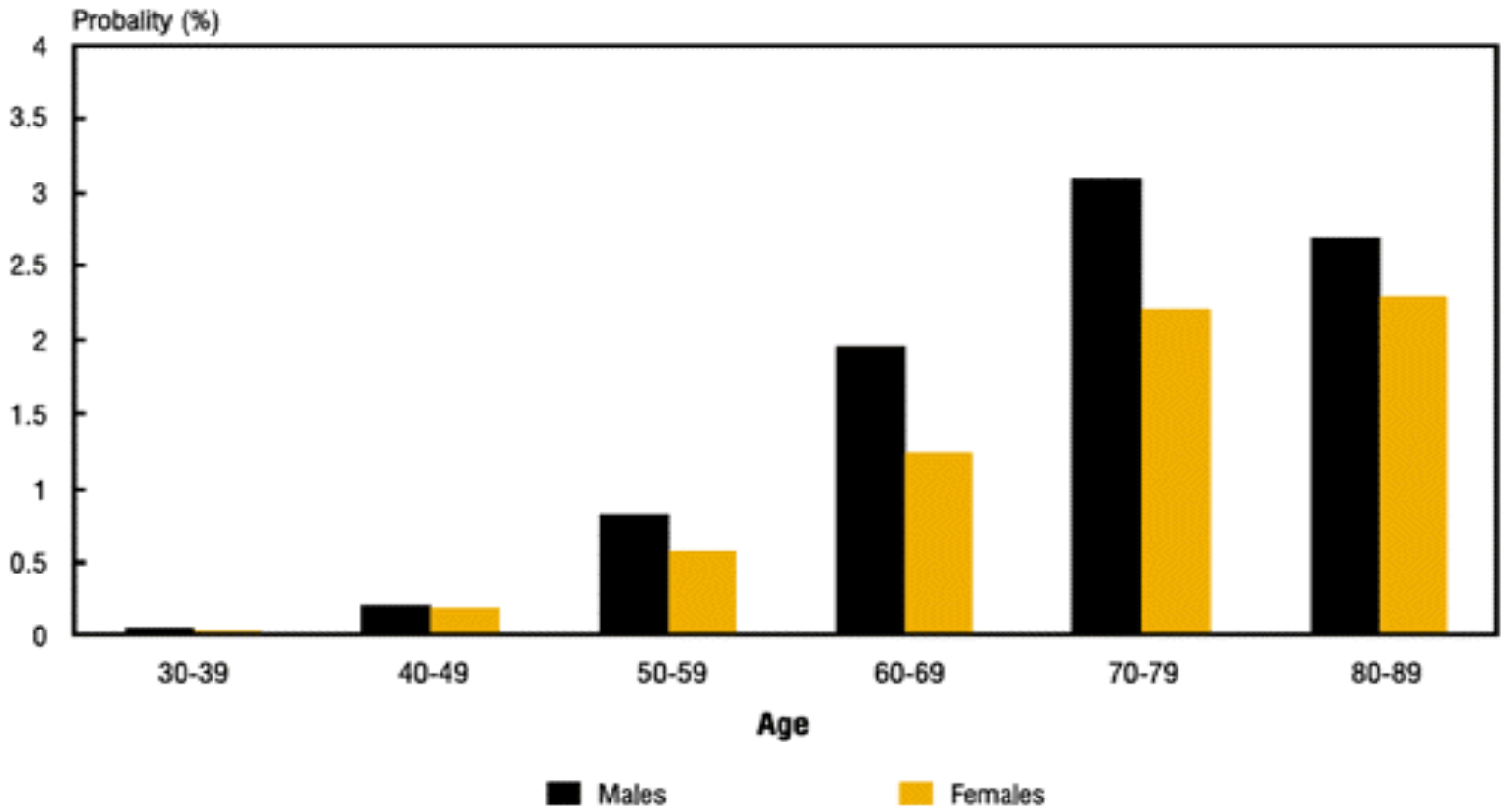
Background

- 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

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



NCIC, Canadian Cancer Statistics 2002.

Key areas for discussion

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

Targeted therapies

Palliative vs curative therapy

/

Metastasectomy

Palliative chemotherapy - options

- 5FU/LV (bolus – infusion)
- Capecitabine / UFT
- Irinotecan
- Oxaliplatin

- (Biologics – bevacizumab / cetuximab)

CTx in the elderly randomized trial
Median age 75 years [range 70 - 85]

	N Pat	RR	Tox* 3º	Survival Median
"BSC"	83	-	-	5.5 mo
CTx weekly ℓ-FA 300mg/m² FU 500mg/m²	80	12%	16%	7.5 mo
p-value				*<0.002*

* no grade 4 occurred

Beretta et al. ASCO 1997

Age dependent efficacy of 5-FU

•**age**	**< 70 y**	**> 70 y**	***70-74***	***75-79***	***>=80***
•*n*	*3,196*	*629*	*484*	*125*	*20*
•OS	11.3	10.8	*10.9*	*9.4*	*13.4*
•	(5.1-5.5)	(5.2-5.8)			
•	p = 0.31				
•PFS	5.3	5.5	*5.5*	*5.5*	*6.4*
•	(5.1-5.5)	(5.2-5.8)			
•	p = 0.01				
•CR/PR	21.1%	23.9%	*24%*	*26%*	*(11%)*
•	p = 0.14				

Folprecht …. Köhne et al. Ann Oncol 2004

Efficacy and 5-FU administration

age	**< 70 y.**		**> 70 y.**	
•5-FU	Bolus	infus.	Bolus	infus.
n	*2072*	*1124*	*456*	*173*
•OS	10.7	12.3	11.3	11.9
	p < 0.0001		p = 0.014	
•PFS	4.8	5.9	5.2	5.8
	p < 0.0001		p = 0.0002	
•CR/PR	18.5%	26.2%	21.3%	31.2%
	p < 0.0001		p = 0.014	

Folprecht …. Köhne et al. Ann Oncol 2004

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

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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

Studies Included

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

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

Efficacy, toxicity, dose intensity

- No difference in:
  - DFS, OS in 1st line
  - OS 2nd line
  - Adverse events
  - Dose intensity

for <70 vs >70

Conclusions (Dr Goldberg's)

- Among patients entered onto clinical trials
  - Younger and older patients accrue the same benefit from FOLFOX4
  - Elderly patients do not experience clinically meaningful increased toxicity
- Age alone should not exclude an otherwise healthy elderly patient from receiving FOLFOX4 chemotherapy

Caution

- Conclusions only apply to patients deemed fit for entry into clinical trials
- 3 of 4 trials limited eligibility to patients $\leq$ 75 years
- Care must be used in extrapolating to the entire population of elderly patients

Irinotecan/5-FU/FA (I-FU) or 5-FU/FA (FU) first-line therapy in older and younger patients with metastatic colorectal cancer: Combined analysis of 2,691 patients in randomized controlled trials.

G. Folprecht, M. T. Seymour, L. Saltz, J. Y. Douillard, R. J. Stephens, E. Van Cutsem, P. Rougier, T. S. Maughan, C. H. Köhne, Irinotecan Meta-analysis Group

Proceedings ASCO 2007

Efficacy and Main Toxicity

	I-FU, < 70y N= 777	FU, < 70y N=1315	I-FU, >=70y N= 220	FU, >=70y N=379	*p* Comparing age groups
CR/PR p comp. I-FU vs. FU	46.6% N=745 p<0.0001	29.0% N= 1218	50.5% N=208 p<0.0001	30.3% N=346	FU: p=0.3 IFU: p=0.6
median PFS (95% CI) p comp. I-FU vs. FU	8.2 (7.7- 8.7) N=776 p<0.0001	6.3 (5.9-6.7) N=1308	9.2 (8.5-9.9) N=220 p<0.0026	7.0 (6.2-7.9) N=376	FU: p=0.22 IFU: p=0.04
median OS (95% CI) p comp. I-FU vs. FU	17.1 (15.9-18.3) N=765 p=0.0003	14.7 (13.9-15.6) N=1308	17.6 (15.5-19.7) N=219 p=0.15	14.2 (12.7-15.7) N=375	FU: p=0.6 IFU: p=0.3
Toxicity gr. >=3					
Neutropenia	28.5% *	16.1%	29.7% *	19.9%	FU: p=0.10 IFU: p=0.8
Diarrhea	20.5% *	11.4%	23.5% *	12.6%	FU: p=0.5 FU: p=0.5
Nausea	11.3% *	5.8%	10.8%*	3.7%	FU: p=0.18 IFU: p=1.0
Vomiting	9.6% *	5.3%	9.7% *	2.5%	FU:p=0.053 IFU: p=1.0
Stomatitis	2.5%	2.6%	4.0%	3.6%	FU: p=0.4 IFU: p=0.4

* significant difference to FU in the same age group

Conclusion

- Patients over 70 yrs who are selected for inclusion in phase III trials derive similar benefits from irinotecan-containing chemotherapy, and with similar risks of toxicity, compared with younger patients.

Folprecht…Köhne et al, ASCO 2007, abstract 4071

Combination chemotherapy in the elderly

•Regimen	FU_{48h}/Iri	UFT/FA/l-OHP	Cape/Ox	
•Age years	>70	>72	<65	>65
•N Pat	85	45	52	44
•RR	35%	51%	58%	52%
•TTP	8.0	8.0	similiar	
•OS	15.3	14.1	similiar	
•Author	***Sastre***	***Rosati***	***Twelves***	
	JCO 2005	***Oncology 2005***	***Clin Col Can 2005***	

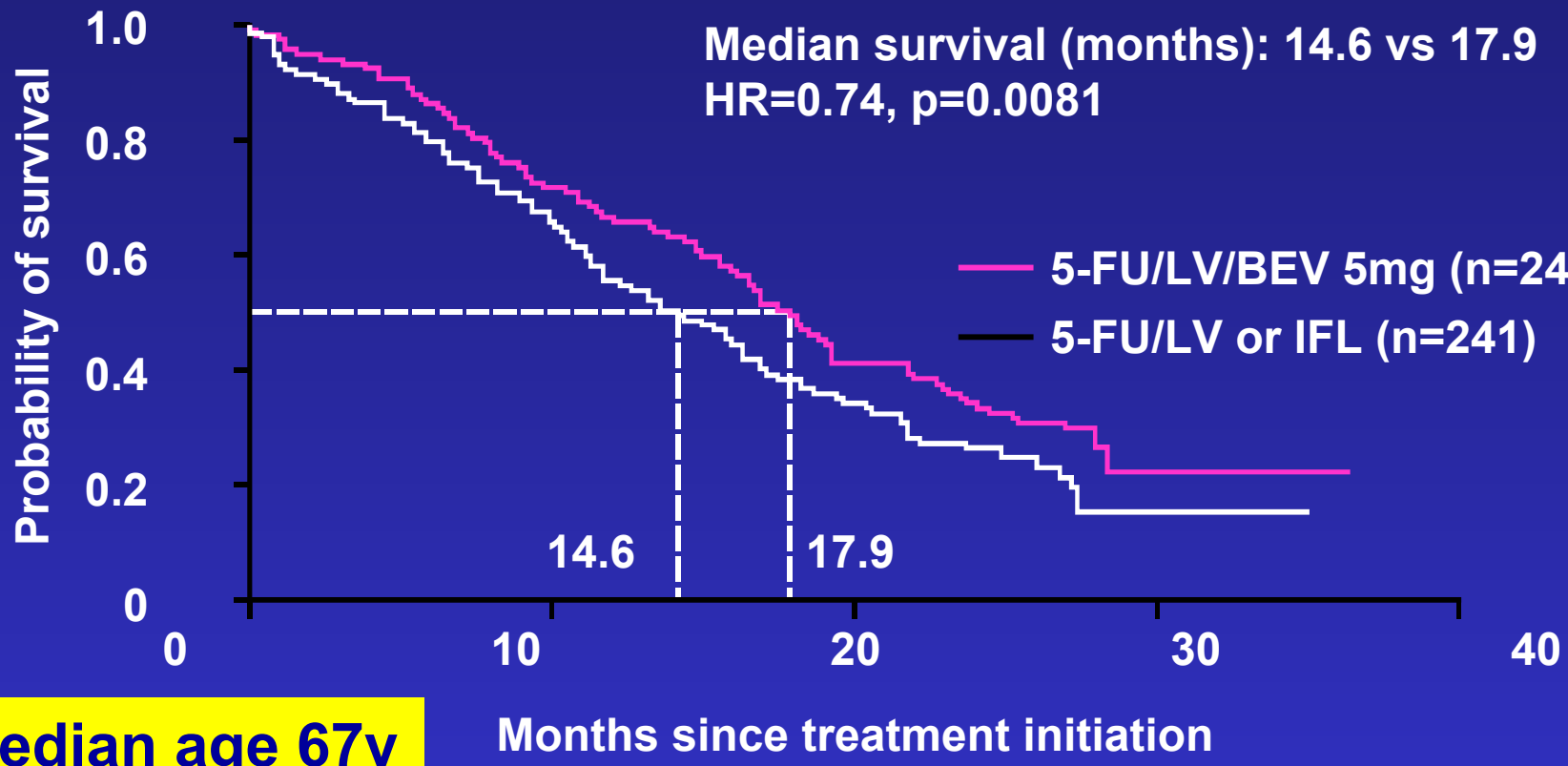
Palliative therapy in elderly CRC patients

- Fit elderly patients do benefit from systemic chemotherapy
- 5FU continuous infusion is more effective and less toxic than bolus 5FU
- Combination chemotherapy for good PS patients - treatment of choice
- For capecitabine, dose reduction according to clearance is necessary

Incorporation of targeted therapies to the elderly with MCRC: Rationale

- Two monoclonal antibodies have recently been registered for advanced colorectal cancer patients: cetuximab and bevacizumab
- Is there enough information about activity and toxicity of these drugs in the elderly population to recommend its use routinely?

Bevacizumab in combination with 5 FU/LV improves survival in patients with metastatic CRC: a combined analysis (cont'd)



Median age 67y

Range 23 – 90y

Kabbinavar et al. J Clin Oncol 2005

Bevacizumab-related adverse events in clinical trials

Hypertension (the most frequent)

Proteinuria

Thromboembolic events

Wound healing complications

Bleeding

Bowel perforation

Kabbinavar FF, et al. J Clin Oncol 2003;21:60–5
Hurwitz H, et al. N Engl J Med 2004;350:2335–42
Giantonio BJ, et al. Presented at: 2005 Gastrointestinal Cancers Symposium; 27–29 January 2005; Hollywood, Fl. Abstract 169a. Available at: http://www.asco.org. Accessed 15 February 2005.
Kabbinavar FF, et al. J Clin Oncol 2005.

CRC = colorectal cancer
GI = gastrointestinal

Physician-identified putative risk factors in patients with GI perforations (BRiTE)

1.7% of patients (34/1968) had GI perforation

Putative risk factor	Nº of patients with GI perforation (% of 34)
Any	23 (67.6%)
Acute diverticulitis	2
Intra-abdominal abscess	3
GI obstruction	7
Tumor at site of perforation	9
Peritoneal carcinomatosis	4
Prior abdomino/pelvic radiation	9
No associated findings	11 (32.4)
Data unavailablle	0

Bevacizumab in the elderly patients with ACRC

- Elderly patients with history of myocardial infarction, stroke or any other arterial thrombotic event should be excluded for receiving bevacizumab (higher incidence of ATEs for over 65s).
- Bevacizumab should not be initiated in patients with uncontrolled hypertension. Blood pressure should be monitored frequently and if it becomes uncontrolled in spite of adequate antihypertensive treatment, bevacizumab discontinuation is mandatory.
- Elderly patients with primary tumour not removed, peritoneal carcinomatosis, prior abdomino-pelvic radiation, diverticulitis or abdominal abscess should be carefully monitored. If symptoms or signs of abdominal inflammation appear, bevacizumab should be discontinued.

Single-agent Cetuximab in the elderly with ACRC

Author	Indication	% elderly	ORR (%)	% G ¾ Skin toxicity	% G-3 Allergic reactions
Saltz	Irinotecan-refractory	?	9	18	3.5
Cunningham	Irinotecan-refractory	29 ≥ 65 y	10.8 15	5.2	3.5
Lenz	Irinotecan-oxaliplatin refractory	?	12	5	0.8
Pessino	Chemo-naïve	?	10.2	10	5
Sastre	Chemo-naïve	100	15.4	10	0

Cetuximab vs BSC in previously treated mCRC patients

NCIC CTG and AGITG CO.17 trial

- 572 pts with EGFR +ve tumours
- Randomised to cetuximab + BSC (287) vs BSC (285)
- Endpoints: OS (primary), TTP, RR, toxicity, QOL
- Median age: 65 (upto 88 yrs old)

- Results:

  median OS - 6.1mo vs 4.6mo (p=0.005),

  improvement in risk of PD, HR=0.68 for TTP (P=0.0001)

  overall RR (CR+PR) = 6.6%

H.Au et al Proceedings ASCO 2007

Cetuximab/irinotecan combination in irinotecan-refractory ACRC patients

Author	pts	% elderly	ORR (%)	TTP (m)
Saltz	57	?	17	1.4
Cunningham	218	29	22.9	4.1
Smith*	41	?	20	4.3

* FOLFIRI/CETUXIMAB

Cetuximab does not increase the incidence or severity of irinotecan-induced toxicity

Cetuximab in the elderly with advanced CRC: Conclusions

- Cetuximab is safe and active in fit elderly patients with ACRC and might be an option for those patients not candidates for chemotherapy.
- It should be employed preferentially with irinotecan in irinotecan-refractory tumors.
- Toxicity is mild and does not increase irinotecan-induced toxicity.
- Toxicity should be evaluated weekly and dose adjustment is mandatory in case of grade 3 skin rash.
- At the moment, there are not enough data to recommend cetuximab plus chemotherapy in first-line.

Resection of metastases in the elderly

- Small experience in the elderly
- Factors influencing decision
  - Life expantancy: age, concomitant illnesses
  - Operative risk: morbidity vs mortality:
    - cardiovascular, renal, pulmonary,…
  - Oncological outcome/prognosis: e.g. resection of liver metastases: 5 year survival: 25 – 30 %
  - Desire of patient / family

Potentially resectable LM

- Elderly patients
  - Chemotherapy + biologics
  - Tolerance of triplet CT?
    - Probably more active than doublets
    - Certainly more toxic
  - Increased morbidity of surgery after CT ?
    (e.g. steatosis)

Recommendations for chemoherapy in metastatic disease

- Fit elderly patients do benefit from systemic chemotherapy
- 5-FU continuous infusion is more effective and less toxic than at least some bolus 5-FU schedules.
- Combination chemotherapy should be the treatment of choice with or without bevacizumab (beaware of ATEs)
- For capecitabine dose reduction according to creatinine clearance is necessary
- Cetuximab should be used within the context of its licensed indication (although data for the use of cetuximab in the treatment of elderly patients are lacking, it is unlikely that cetuximab has a different tolerance in elderly compared to younger patients)

Overall conclusions and recommendations

- It is important to establish an overall treatment plan for the management of elderly CRC patients
- Elderly patients should receive screening and earlier diagnosis.
- Some elderly patients should be exposed to more aggressive management than they are currently receiving which is closer to that currently received by younger patients
- Patients should receive the most intensive and appropriate treatment thought to be safe and effective according to their biological age and co-morbidities
- The aim should be to maximize overall survival whilst minimizing toxicity to achieve the greatest patient benefit
- There is, as in younger patients, a need to identify the right patient for the right treatment (pharmacogenetics, pharmacogenomics etc.)

Clinical Trials and the Elderly

“Your pulse may be too weak to be eligible for my study”

Aknowledgements

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