SIOG CRC Guidelines

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SIOG 2014
Special SIOG Guidelines Session
Lisbon
October 25th
Outline

• Background
• Surgery in older adults
• Adjuvant therapy
  - Single agent 5FU-based therapy
  - Combination chemotherapy
• Metastatic disease
• Rectal cancer
• Conclusions
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How Japan Stood Up to Old Age

Twenty-five per cent of Japanese are over 65. What can they teach us about ageing?

David Pilling reports
Doctor wants to deny elderly cancer drugs

Sarah-Kate Templeton, Health Editor
Published: 4 May 2014

Comment (137)    Print
SIOG Expert Recommendations in 2009 already....

- It is important to establish an overall treatment plan for the management of elderly CRC patients.
- Older patients should receive screening and earlier diagnosis.
- Older patients should be exposed to more aggressive management than they are currently receiving, closer to that currently received by younger patients.

SIOG Expert Recommendations in 2009 already….

- Patients should receive the most intensive and appropriate treatment thought to be safe and effective according to their biological age and comorbidities.

- The aim should be to maximize OS while minimizing toxicity to achieve the greatest patient benefit.

- There is a need to identify the right patient for the right treatment:
  - Pharmacogenetics, pharmacogenomics, etc.

Why is it that Survival Gains are Limited to Younger CRC Patients?

Survival of patients with synchronous mCRC by age and time period.
(A) <60 years; (B) 61-70 years; (C) 71-75 years; (D) 76-80 years; (E) >80 years

Older Patients with CRC: Key Issues

- Limited life expectancy
- Physiological heterogeneity
  - Chronologic age $\neq$ biologic age
- Reduced treatment tolerance (frailty)
- Different treatment goals (frailty)
- Limited evidence
  - Under-representation in clinical trials

SIOG Expert Recommendations: 2014 Update

- Surgery in older patients
- Adjuvant chemotherapy
- Palliative chemotherapy
- Rectal cancer

Adapted from Papamichael et al. Ann Oncol. 2014 July 11 pii mdu 253 (Epub ahead of print)
the idea behind this slide is that these are the 5 major issues addressed in the new guidelines, and this presentation will cover only 3 of them due to time limitations. If we get rid of the surgery section, then remove the red circle around "Surgery in older patients"

Claire Gilmore; 24.06.2014
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- Rectal cancer
- Conclusions
Challenges to Using GA in Older Patients with CRC

- GA and surgery – studies not limited to cancer surgery
- GA and cancer - studies include all cancer types, but no subgroup analyses by site
- Variable tools
- Variable outcomes
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- Background
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Recommendations for patients undergoing surgery

- A protocol should be devised to identify those patients for whom a geriatrician needs to be involved and for whom co-morbidity and frailty are a hazard.
- A formal GA should be considered and if this is not feasible, rapid screening tools for frailty should be used.
- A prehabilitation program should be considered, where necessary, which should include correction of malnutrition, and optimization of cardiovascular and pulmonary co-morbidities as well as medication use.
- For patients requiring prehabilitation, major resection should be postponed and emergency surgery avoided.
- Emergency surgery should be kept to a minimum, and, in the case of obstructive disease alternative procedures such as the construction of a diverting stoma or stenting, if cure is not the aim, must be considered.
- Careful consideration should also be given to the consequences of the construction and siting of the stoma.
- The combination of an emergency procedure with a major resection or multimodality treatment within too short a time frame should be avoided.
- Patients (especially high-risk patients) and their families need to be informed about the risks, possible functional impairment and oncological outcome before consenting to a treatment plan.
- High-risk patients should be offered alternative options, ranging from no tumor-controlling treatment at all, to palliative treatment, through to full treatment. Ideally, the preferences of patients if serious complications occur should be discussed.
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Life Expectancy

Women have a life expectancy of more than 20 years at 60, 15 years at 70 and 10 years at 80
Men of 20 years at 60, 12 years at 70 and 8 years at 80

Most recurrences of Stage III and high-risk Stage II colon cancer occur in the 3 years after surgery…Adjuvant chemotherapy should be considered

Adjuvant Setting: Initial Pooled Analysis: 5-FU/LV vs Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCTG</td>
<td>5-FU/Lev</td>
<td>271</td>
</tr>
<tr>
<td>ECOG</td>
<td>5-FU/LV</td>
<td>415</td>
</tr>
<tr>
<td>SWOG</td>
<td>5-FU/Lev</td>
<td>936</td>
</tr>
<tr>
<td>NCIC</td>
<td>5-FU/LV</td>
<td>364</td>
</tr>
<tr>
<td>FFCD</td>
<td>5-FU/LV</td>
<td>259</td>
</tr>
<tr>
<td>Siena</td>
<td>5-FU/LV</td>
<td>239</td>
</tr>
<tr>
<td>GIVIO</td>
<td>5-FU/LV</td>
<td>867</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>3351</strong></td>
</tr>
</tbody>
</table>

Sargent et al, NEJM 2001
Deaths without cancer

- As patients aged, the probability of death without cancer increased

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>Deaths w/o cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50</td>
<td>564</td>
<td>1%</td>
</tr>
<tr>
<td>51-60</td>
<td>1012</td>
<td>4%</td>
</tr>
<tr>
<td>61-70</td>
<td>1269</td>
<td>7%</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>506</td>
<td>13%</td>
</tr>
<tr>
<td>Overall</td>
<td>3351</td>
<td>6%</td>
</tr>
</tbody>
</table>

Sargent et al, NEJM 2001
### ACCENT update 2008: 6 trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrual Period</th>
<th># pts</th>
<th>% pts ≥70 yrs</th>
<th>Experimental treatment arm†</th>
<th>% stage III‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC</td>
<td>1998-01</td>
<td>2246</td>
<td>14</td>
<td>FOLFOX4</td>
<td>60</td>
</tr>
<tr>
<td>NSABP C-07</td>
<td>2000-02</td>
<td>2434</td>
<td>16</td>
<td>FLOX</td>
<td>71</td>
</tr>
<tr>
<td>C89803</td>
<td>1999-01</td>
<td>1263</td>
<td>24</td>
<td>IFL</td>
<td>98</td>
</tr>
<tr>
<td>PETACC-3</td>
<td>2000-02</td>
<td>3186</td>
<td>13</td>
<td>FOLFIRI</td>
<td>71</td>
</tr>
<tr>
<td>NSABP C-06</td>
<td>1997-99</td>
<td>1557</td>
<td>23</td>
<td>Uracil/tegafur</td>
<td>53</td>
</tr>
<tr>
<td>X-ACT</td>
<td>1998-01</td>
<td>1983</td>
<td>20</td>
<td>Capecitabine</td>
<td>100</td>
</tr>
</tbody>
</table>

† Compared to control arm of intravenous 5-flourouracil (IV 5-FU) and leucovorin (LV)
‡ Remaining patients were stage II or unknown
### Efficacy – All 7 trials (addition of XELOXA data)

<table>
<thead>
<tr>
<th>Age</th>
<th>Experimental v Control IV 5-FU/LV</th>
<th>Deaths within 6 mo Exp v Control % (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DFS*</td>
<td>OS*</td>
</tr>
<tr>
<td>&lt;70 n = 11,953</td>
<td>0.85 (0.80-0.90)</td>
<td>0.87 (0.81-0.93)</td>
</tr>
<tr>
<td>≥ 70 n = 2575</td>
<td>1.05 (0.94,1.19)</td>
<td>1.08 (0.95,1.23)</td>
</tr>
<tr>
<td>Interaction of age by treatment p-value</td>
<td>0.001</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* * Values < 1 favor experimental arm

N Jackson-McLeary et al J Clin Oncol 2013;31:2600-2607
# Efficacy – oxaliplatin-based therapy (3 Trials)

<table>
<thead>
<tr>
<th>Age</th>
<th>Experimental HR (95% CI)</th>
<th>Deaths within 6 mo Exp v Control % (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endpoint</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DFS*</td>
<td>OS*</td>
</tr>
<tr>
<td>&lt;70 n = 5,420</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.78 (0.71,0.86)</td>
<td>0.83 (0.74,0.92)</td>
</tr>
<tr>
<td>≥ 70 n = 1,119</td>
<td>0.94 (0.78,1.13)</td>
<td>1.04 (0.85,1.27)</td>
</tr>
<tr>
<td>Interaction of age by treatment p-value</td>
<td>0.09</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Values < 1 favor experimental arm

N Jackson-McLeary et al J Clin Oncol 2013;31:2600-2607
Interpretation pitfalls

• No information for:
  - Toxicity data
  - Dose-intensity
  - Comorbidity

This may confound interaction between age & newer adjuvant chemotherapy regimens

(- Small population)
(- Different FP regimens)
IDEA: International Duration Evaluation in Adjuvant colon cancer

- Worldwide effort to address duration question of oxaliplatin (3 v 6 mo)
- 6 trials: TOSCA, SCOT, CALGB/SWOG, GERCOR/PRODIGE, HORG, ACHIEVE

Current accrual: 8500 patients. Goal 10,500
Recommendations on adjuvant therapy

- XELOX and FOLFOX are considered to be standard treatment options for the adjuvant management of stage III colon cancer, but their use is of uncertain benefit in patients aged >70 years.

- In view of the potential for increased serious adverse events (AEs) associated with combination chemotherapy regimens, the choice of whether to treat older patients with oxaliplatin-containing combination therapy or fluoropyrimidine monotherapy should depend on the treating physician's clinical judgment and the individual patient's risk of recurrence. The gains from the addition of oxaliplatin are modest and most of the benefit is still conferred by the fluoropyrimidine.

- The use of fluoropyrimidine monotherapy, either 5-FU/LV or capecitabine, is an appropriate adjuvant treatment option for many patients ≥70 years.

- The benefit of adjuvant chemotherapy in the management of stage II colon cancer remains controversial for patients of all ages.
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Clinical Trials and the Elderly?

I just heard there's a drug in trials that might stop my cancer!!

Of course not...why would I do that?

Great! Are you going to volunteer to participate for the trial?

I wouldn't either. Sure hope they get some results soon...
MRC FOCUS2

Chemotherapy choices and doses
in frail and elderly patients
with advanced colorectal cancer

Matt Seymour, Tim Maughan, Harpreet Wasan, Alison Brewster, Steve Shepherd,
Sinead O’Mahoney, Beth May, Lindsay Thompson, Angela Meade and Ruth Langley,
on behalf of
The UK NCRI Colorectal Clinical Studies Group and FOCUS2 Investigators
Trial Design: 2x2 Factorial

- FU
- OxFU
- Cap
- OxCap

Seymour et al The Lancet 2011;377:1749-1759
### Toxicity by regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>FU</th>
<th>OxFU</th>
<th>Cap</th>
<th>OxCap</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>109</td>
<td>109</td>
<td>112</td>
<td>109</td>
</tr>
</tbody>
</table>

**Factorial Toxicity**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no oxaliplatin vs oxaliplatin</td>
<td></td>
</tr>
<tr>
<td>[FU + Cap] vs [OxFU + OxCap]</td>
<td></td>
</tr>
</tbody>
</table>
| worse with oxaliplatin:  
diarrhoea (6% vs 12%)  
sens. neuro (0% vs 2%)   | 0.042   |
| worse with no oxaliplatin:  
hand/foot derm (5% vs 0.5%) | 0.004   |
| FU vs capecitabine |         |
| [FU = OxFU] vs [Cap + OxCap]   |         |
| worse with capecitabine:  
any grade >3 tox (27% vs 39%) | 0.006   |
| nausea (1% vs 5%)          | 0.032   |
| diarrhoea (5% vs 13%)      | 0.003   |
| lethargy (8% vs 14%)        | 0.037   |
| hand/foot derm. (0% vs 5%) | <0.001  |

Seymour et al The Lancet 2011;377:1749-1759
## Overall Survival

![Graph of Overall Survival](image)

### Factorial Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no oxaliplatin vs oxaliplatin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[FU + Cap] vs [OxFU + OxCap]</td>
<td>0.99 (0.81, 1.18)</td>
<td>p=0.91</td>
</tr>
<tr>
<td><strong>FU vs capecitabine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[FU = OxFU] vs [Cap + OxCap]</td>
<td>0.96 (0.79, 1.17)</td>
<td>p=0.71</td>
</tr>
</tbody>
</table>

### Events Total

<table>
<thead>
<tr>
<th></th>
<th>115</th>
<th>115</th>
<th>115</th>
<th>114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>94</td>
<td>102</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>At risk</td>
<td>81</td>
<td>82</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>FU</td>
<td>60</td>
<td>62</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>OxFU</td>
<td>38</td>
<td>43</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td>Cap</td>
<td>29</td>
<td>30</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>OxCap</td>
<td>15</td>
<td>20</td>
<td>23</td>
<td>16</td>
</tr>
</tbody>
</table>

RANDOMIZED PHASE III IN ELDERLY PATIENTS COMPARING LV5FU2 WITH OR WITHOUT IRINOTECAN FOR 1ST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (FFCD 2001-02)

E. Mitry¹, L. Venat-Bouvet², J.-M. Phelip³, E. Maillard⁴, J.-L. Jouve⁴, X. Adhoute⁵, D. Gargot⁶, M. Gasmi⁷, L. Bedenne⁴, T. Aparicio⁸

¹ Paris/FR, 2 Limoges/FR, 3 St-Etienne/FR, 4 Dijon/FR, 5 Pessac/FR, 6 Blois/FR, 7 Marseille/FR, 8 Avicenne/FR
**Stratification criteria:**

- Center
- Charlson index (0 vs 1-2 vs 3+)
- Karnofsky index (100 vs 90-80 vs 70-60)
- Previous adjuvant CT
- Sex
- Age (< 80 vs ≥ 80 yrs)
- Alkaline phosphatase (≤ 2ULN vs > 2ULN)
FFCD 2001-02: Progression-Free Survival

Median PFS (months [95%CI])
- FU: 5.2 [3.9;6.1]
- IRI: 7.3 [6.5;8.6]

HR=0.84 (95%CI: 0.66;1.07) p=0.15

FFCD 2001-02:
Overall Survival

Median OS (months [95%CI])
FU: 14.2 [9.5;19.0]
IRI: 13.3 [11.2;17.9]

HR=0.96 (95%CI: 0.75;1.24)
p=0.77

# FFCD 2001-02: Predictors of Toxicity

<table>
<thead>
<tr>
<th>Predictive Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.53</td>
<td>0.50 to 4.71</td>
<td>.454</td>
</tr>
<tr>
<td>Primary tumor not resected</td>
<td>1.20</td>
<td>0.34 to 4.21</td>
<td>.779</td>
</tr>
<tr>
<td>No previous adjuvant chemotherapy</td>
<td>3.85</td>
<td>0.67 to 22.03</td>
<td>.130</td>
</tr>
<tr>
<td>Irinotecan arm</td>
<td>5.03</td>
<td>1.61 to 15.77</td>
<td>.006</td>
</tr>
<tr>
<td>Impaired cognitive function (MMSE ≤ 27/30)</td>
<td>3.84</td>
<td>1.24 to 11.84</td>
<td>.019</td>
</tr>
<tr>
<td>Impaired autonomy (IADL)</td>
<td>4.67</td>
<td>1.42 to 15.32</td>
<td>.011</td>
</tr>
<tr>
<td>Better mood</td>
<td>0.41</td>
<td>0.12 to 1.36</td>
<td>.145</td>
</tr>
</tbody>
</table>

Abbreviations: IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; OR, odds ratio.

AVEX Trial: A prospective trial in elderly patients

Previously untreated mCRC, age ≥70 years N=280

Randomize 1:1

Stratification factors:
- ECOG PS (0–1 vs 2)
- Geographic region

Capecitabine 1000 mg/m² b.i.d. days 1–14, q21d
+ Bevacizumab 7.5 mg/kg day 1, q21d

Key inclusion criteria
- ECOG PS 0–2
- Prior adjuvant chemotherapy allowed if completed >6 month before inclusion
- Not optimal candidates for a combination chemotherapy with irinotecan or oxaliplatin

Key exclusion criteria
- Prior chemotherapy for mCRC or prior adjuvant anti-VEGF treatment
- Clinically significant cardiovascular disease
- Current or recent use of aspirin (>325 mg/day) or other NSAID
- Use of full-dose anticoagulants or thrombolytic agents
Progression-free survival

HR=0.53 (95% CI: 0.41–0.69)  
\( P<0.001 \)

ITT population. 113 PFS events in the Cape + BEV arm; 127 PFS events in the Cape arm. CI = confidence interval; PFS = progression-free survival

Overall survival

Cape + BEV (n=140)
Cape (n=140)

HR=0.79 (95% CI: 0.57–1.09)
P=0.182

ITT population. 75 OS events in each treatment arm.

## Analysis of Bevacizumab in Older Patients with mCRC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age (yrs)</th>
<th>Median PFS, mos (HR, P value)</th>
<th>Median OS, mos (HR, P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AVEX</strong>&lt;br&gt;Cape+BV vs Cape (N=280)</td>
<td>≥70</td>
<td>9.1 vs. 5.1 (0.53, P&lt;0.001)</td>
<td>20.7 vs. 16.8 (0.79, P=0.182)</td>
</tr>
<tr>
<td><strong>AGITG MAX</strong>&lt;br&gt;Cape+BV vs Cape (N=99)</td>
<td>≥75</td>
<td>8.8 vs 5.6 (0.52, P=0.01)</td>
<td>15.7 vs 13.4 (0.80, P=0.41)</td>
</tr>
<tr>
<td><strong>Pooled analysis</strong>&lt;br&gt;(AVF2107&amp;2192)&lt;br&gt;CT+BV vs CT (N=439)</td>
<td>≥65</td>
<td>9.2 vs 6.2 (0.52, P&lt;0.001)</td>
<td>19.3 vs 14.3 (0.70, P=0.006)</td>
</tr>
<tr>
<td><strong>Pooled analysis</strong>&lt;br&gt;(NO16966/AVF2107&amp;2192/E3200)&lt;br&gt;CT+BV vs CT (N=712)</td>
<td>≥70</td>
<td>9.2 vs. 6.4 (0.54, P&lt;0.05)</td>
<td>17.4 vs 14.1 (0.79, P&lt;0.05)</td>
</tr>
<tr>
<td><strong>BRITE</strong>&lt;br&gt;CT+BV (N=363)</td>
<td>≥75</td>
<td>10.0</td>
<td>20.3</td>
</tr>
<tr>
<td><strong>ARIES</strong>&lt;br&gt;CT+BV (N=424)</td>
<td>≥70</td>
<td>9.9</td>
<td>19.6</td>
</tr>
</tbody>
</table>

**KEY:** Cape – capecitabine; BV – bevacizumab; PFS – progression-free survival; mos – months; HR – hazard ratio; OS – overall survival; CT - chemotherapy

Adapted from Papamichael et al. *Ann Oncol.* 2014 July 11 pii mdu 253 (Epub ahead of print)
Anti-EGFR therapy in elderly patients with metastatic CRC

TTD 04/01: Cetuximab first-line in patients ≥ 70 years
(Sastre et al. Crit Rev Oncol/Hematol 2011)

TTD 06/01: Cetuximab plus capecitabine in patients ≥ 70 years
(Sastre et al. The Oncologist 2012)

Pooled analysis of Crystal and Opus according to age
(Folprecht et al. ESMO 2010)

NCIC CTG CO.17: Subgroup analysis according to age.
(Asmis et al Ann Oncol 2011)
Recommendations on metastatic disease and systemic therapy

- Fit older patients can benefit from systemic cytotoxic combination therapy.
- Age alone should not be an exclusion criterion for the use of newer targeted agents in the treatment of patients with mCRC.
- Those fit older patients selected for inclusion in clinical trials appear to derive a similar benefit to younger patients in terms of RR and PFS from the use of bevacizumab or anti-EGFRs plus full-dose combination chemotherapy. However, the data are lacking as to whether this leads to significant patient-relevant gains such as improved survival with an acceptable QoL.
- For those older patients for whom such therapy would be inappropriate, less intensive regimens such as reduced-dose oxaliplatin + 5-FU or “low-dose” capecitabine + bevacizumab may be used.
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Rectal cancer: preoperative and palliative radiotherapy in older patients

- RT (5 x 5 Gy) and immediate surgery (2–3 days) or long-course CRT with an interval of 6–8 weeks prior to surgery for cancers with no MRI-predicted threat to the mesorectal fascia (MRF) (<1mm), based on three-dimensional imaging reconstructions.

- Preoperative long-course RT alone although less effective for local control than long-course CRT, can be used as an alternative if there are concerns over the safety of chemotherapy.

- In locally inextirpable tumors, or where MRI predicts a threat to the MRF, long-course CRT is the treatment of choice in older patients who are fit enough for this therapy.

- If shrinkage of the tumor away from the MRF is required following CRT, a sufficient interval is required to allow an adequate response. Although the optimum interval has not been determined, most consider a delay of 6 -12 weeks reasonable.

- Treatment with 5 x 5 Gy with a delay of 6–8 weeks (or longer) prior to surgery is an alternative option in very old and/or frail patients.

- HDR-brachytherapy or contact therapy are promising techniques for older patients with rectal cancer but should not be used in the anal canal.
Overall conclusions - recommendations

- Embracing the concept of individualized treatment is an absolute requirement for further improvements in the management of these patients.
- MDTs are the key to individualized treatment in older patients.
- The treatment challenges presented by older patients with CRC make it important to use some form of comprehensive GA to inform our clinical decision making.
- Guidelines are urgently needed to support surgeons, medical and radiation oncologists in the treatment of older patients including formal assessments of the benefit/risk ratios of the various treatment interventions.
- The potential for morbidities and the choices if serious complications do occur or treatments fail, should be discussed in advance.
- Investigators should be encouraged to design not only trials using low-toxicity treatments that maintain most of the efficacy of full-dose treatments but patient-centered assessments to expand the evidence base in the treatment of older patients with CRC.
THANK YOU