UPDATE ON COLORECTAL CANCER

Peter Gibbs MBBS, FRACP, MD

Overview - 1

- Epidemiology
- BioGrid
  - What is it?
  - How does it work?
  - Examples of research output
- Update on treatment of colorectal cancer
- TRACC data
  - Treatment of metastatic colorectal cancer in Australia

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Overview -2

- Adjuvant therapies
- Review of first line therapy
- Review of second line therapy
- Review later
- Choice of Rx – prognostic factors, biomarkers, ECOG, previous adjuvant therapy
- Increase in resection of liver and lung mets
- Supportive measures
- BioGrid and the Australian context of how avastin is used in clinical practice

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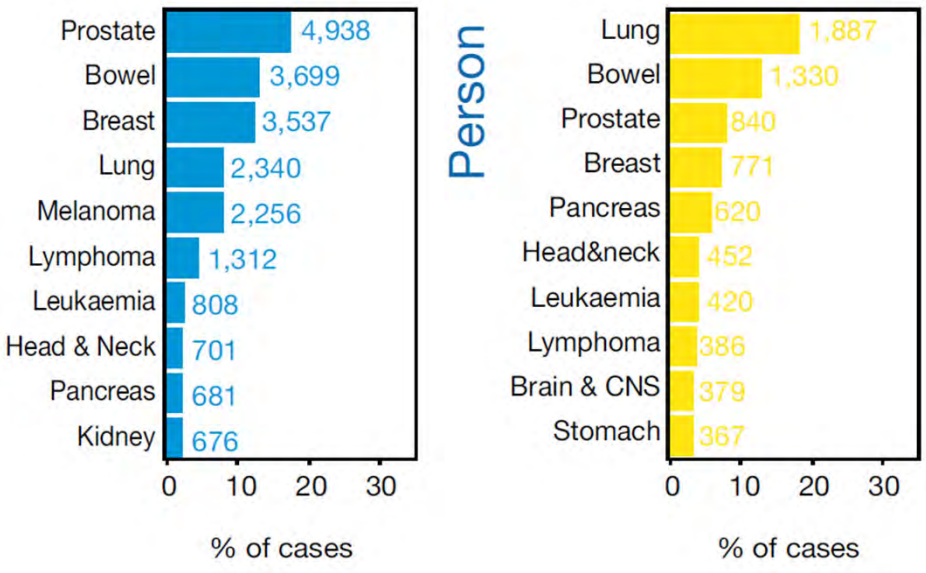
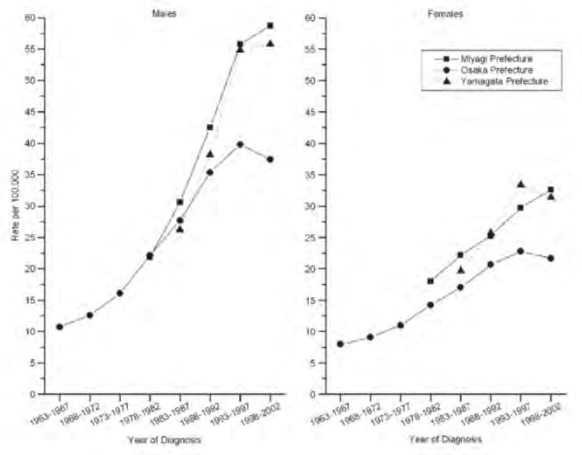


Epidemiology

- We know a lot, we have a lot to learn
- The rise of colorectal cancer
  - Asia – Diet & lifestyle
- The fall of colorectal cancer
  - US - Screening
- Diet & Lifestyle factors
  - Red meat
  - Obesity & exercise
- Chemoprevention

The Rise Of Colorectal Cancer (Asia)

- Rapidly increasing incidence in Asia countries
  - ?Adoption of Western lifestyle
  - Japanese data



Japanese Migrating To Hawaii

- Reliable cancer incidence data in both countries
- Cancer incidence
  - (Previously) low incidence in Japan
  - Japanese born in Japan and move to US have an increased risk
  - Japanese born in Hawaii have a similar CRC risk to US population

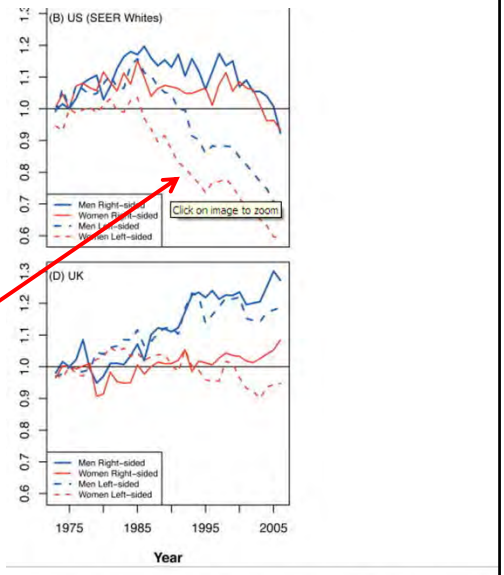
Flood DM, *Cancer Causes Control*, 2000. Sakamoto K, *Dis Col Rect* 2006

The Fall Of Colorectal Cancer

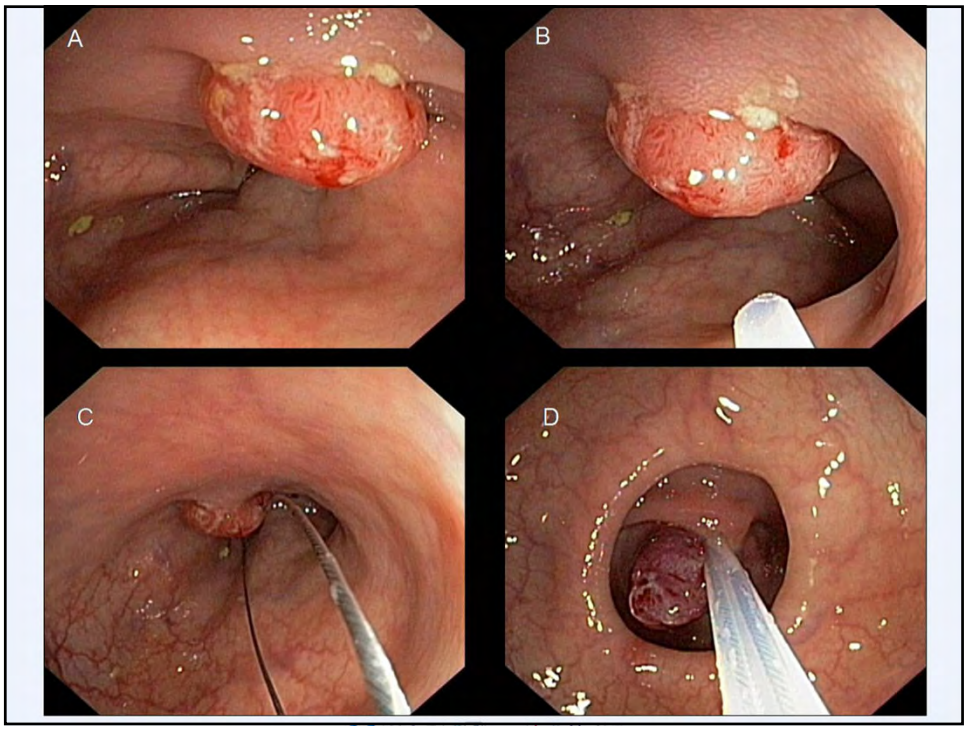
- Declining incidence of CRC in the US
  - Likely due to increased screening
  - (& despite increasing obesity)

The Fall Of Colorectal Cancer?

- ↓ incidence in US
- ↑Rising incidence in UK
  - particularly males
- US - ↓ left cancers
- Screening ↓ left cancers



US 2000 population by sex and subsite. Right. Estimated calendar-year effec



Colorectal screening		Men and women ≥ 50 years
	Flexible sigmoidoscopy	Every 5 years*, or
	Colonoscopy	Every 10 years, or
	CT colonography (virtual colonoscopy)	Every 5 years*
	Double-contrast barium enema	Every 5 years*
	Fecal occult blood test (gFOBT)	Annually*, or
	Fecal immunochemical test (iFOBT/FIT)	Annually*, or
	Stool DNA test (sDNA)	Interval uncertain (possibly 3–5 years)*

- 17% increase in screening over last decade
- 54% of over 50s had had a bowel cancer screening test
- Declines in screening rates for all other cancers.

Clark T, *Frontiers Oncology*, 2013

Other Countries Not Doing So Well…….

- Australian Data
  - National Bowel Cancer Screening Program
    - FOBT based offer at 50,55, 60 & 65
    - ~ 40% participation rate
    - ?2/3 with a positive FOBT do not have a colonoscopy
  - 77% of over 50 y.o. have never had CRC screening
- Low rates of take up of colonoscopy when offered
  - Australians = 22%
  - Dutch = 22%
  - Germans = 1%

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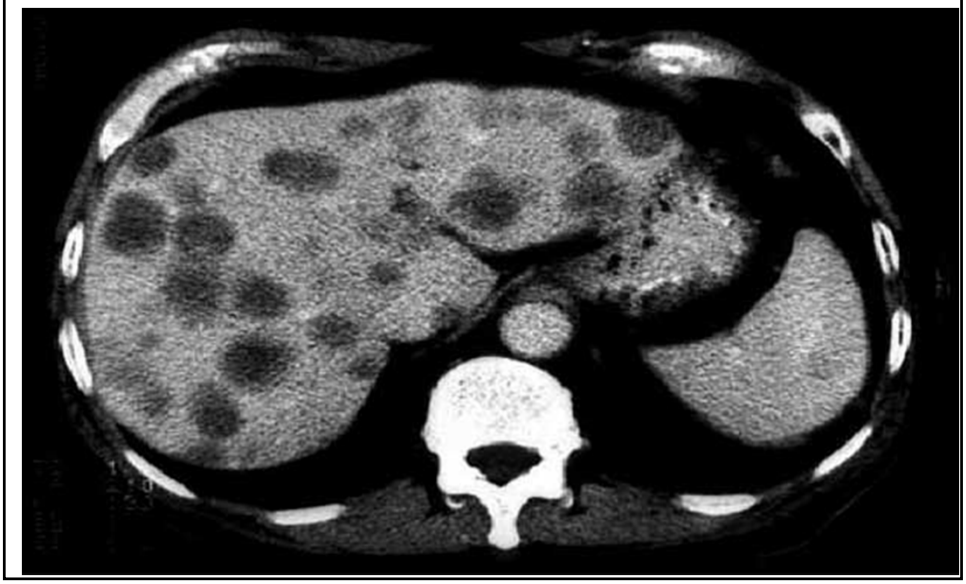
About 20% present with incurable disease



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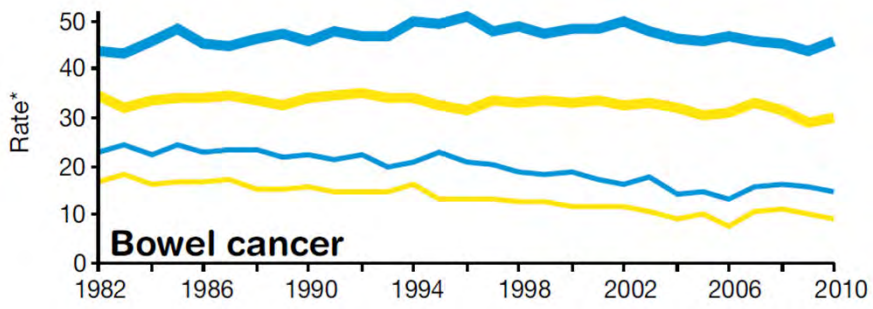
Australian Incidence & Survival

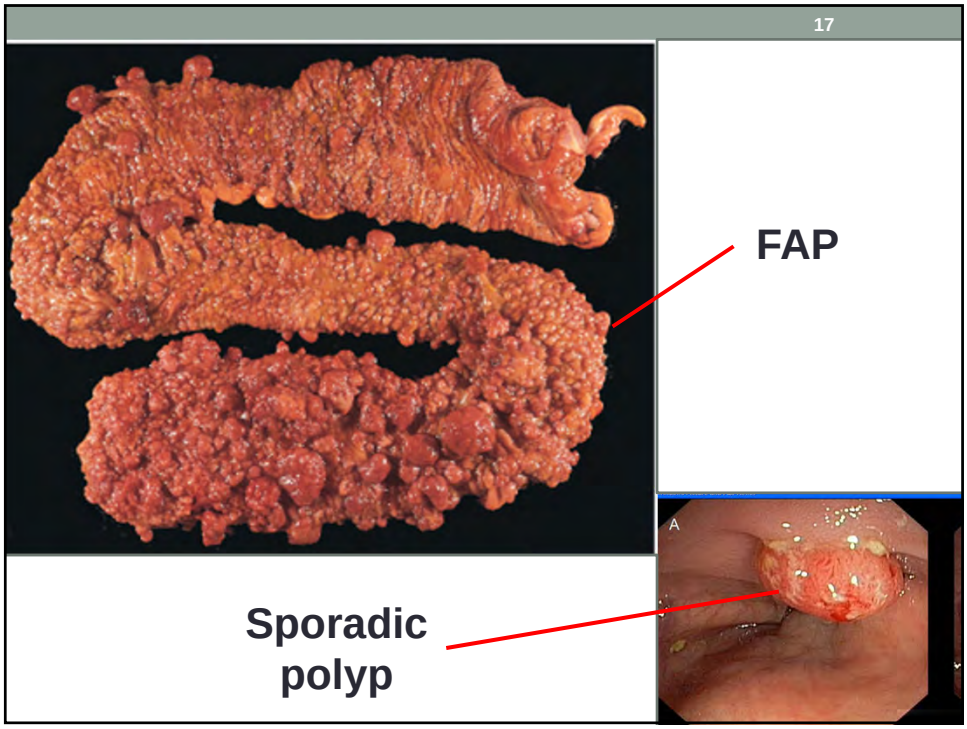


Colorectal Cancer Risk –Genetic

- 25% of patients have a family history
- Defined genetic syndromes
  - 1% Familial Adenomatous Polyposis
  - 2-3% HNPCC
- Genetic testing available
  - Low attendance rates (50% in Australia)
  - Poor compliance with screening advice

Defining Genetic Risk – Counselling And Screening Family Members

- Familial cancer clinics
  - Low attendance rates (50% in Australia)
- Poor compliance with screening advice



Colorectal Cancer Risk – Non Genetic

- Increased risk
  1. Age
  2. Diet / obesity / exercise
  3. Smoking and alcohol
- Decreased risk
  1. Aspirin

Lack Of Physical Activity

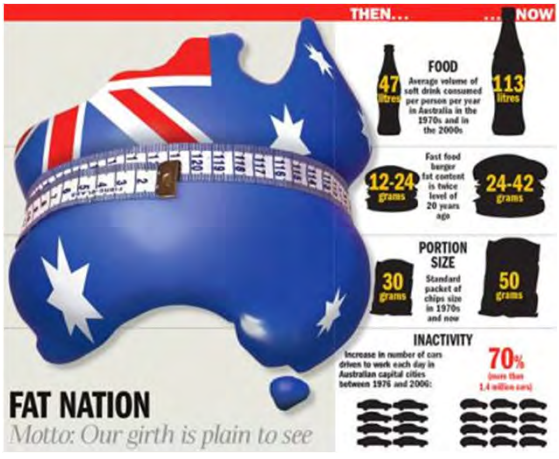
- Excess of colorectal, breast, and endometrial cancers
- Accounts for 12% of colorectal cancer?

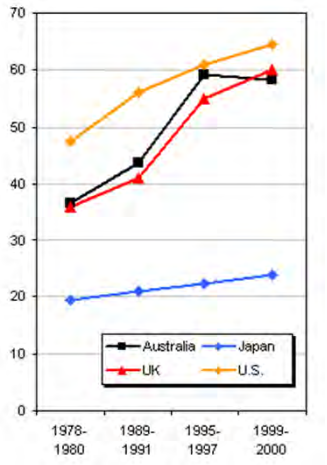
Obesity

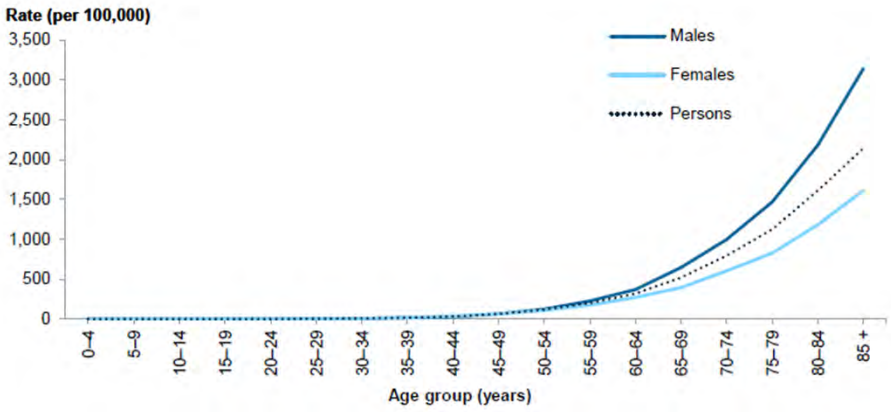
- 40% increased risk if BMI > 30 kg/m^2

Parkin D, BJC, 2011

Overweight/obese patients







Notes

1. Mortality data for 2010 are preliminary and are subject to further revision.
2. Data pertain to cancers coded in ICD-10 as C00–C97, D45, D46, D47.1 and D47.3.
3. Data for this figure are in online Table D3.1.

Source: AIHW National Mortality Database.

Figure 3.1: Mortality from all cancers combined by age at death, Australia, 2010

Age and Lifestyle – Impact Is Unpredictable….

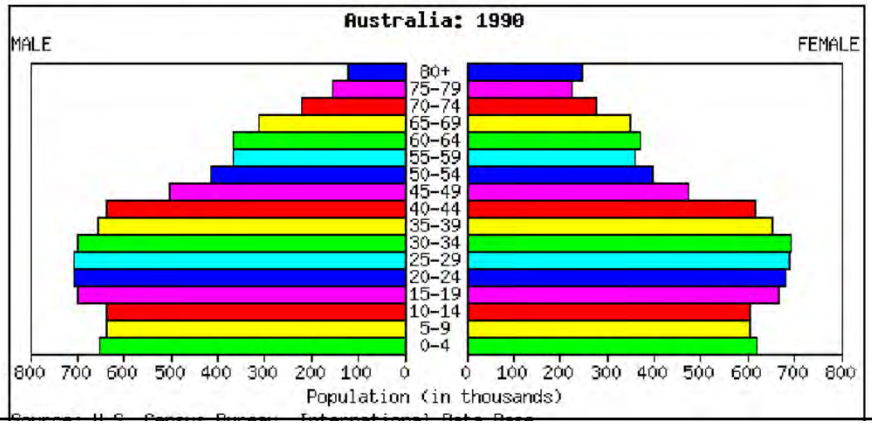
In the UK:

- Isolated
  - Half of all people aged 75 and over live alone
  - 1 in 10 < monthly contact with friends, family and neighbours.
- Limited mobility
  - 1 in 5 aged 75 and over find it very difficult to get to hospital.
- Poor
  - 16% of pensioners live below the poverty line.
- Malnourished
  - 22% of people aged over 60 report they skip meals to cut costs
- Childcare responsibilities
  - 1 in 3 families where mother works rely on grandparents for child care.

Age Distribution

Australia Population Pyramid for 1990

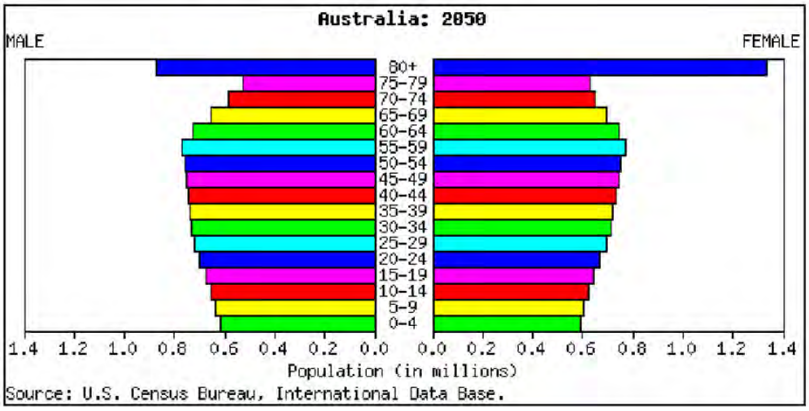
Age and sex distribution for the year 1990:



Age Distribution

Australia Population Pyramid for 2050

Predicted age and sex distribution for the year 2050:



COLORECTAL CANCER PREVENTION

1. Aspirin
2. (COX-2 inhibitors)
3. (NSAIDs)

Aspirin

- 1988 – Kune et al.
  - CRC HR 0.53 for chronic aspirin users
- 19 case control studied – 20% risk reduction
- ?working as an anti-inflammatory

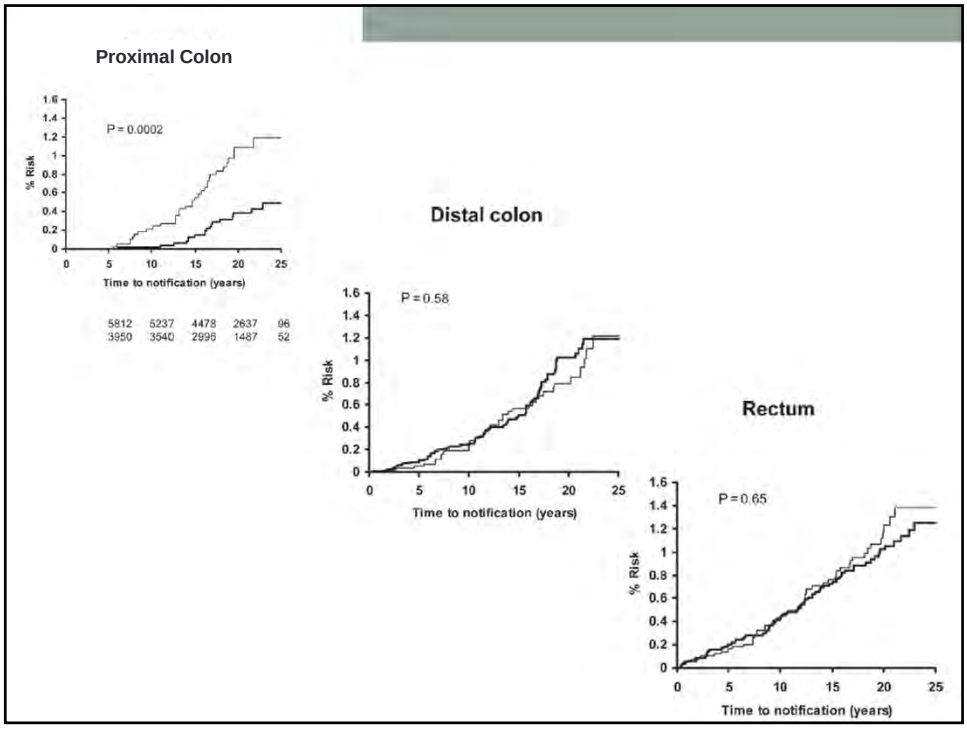
Table 1: Results of colorectal cancer and adenoma incidence in aspirin trials.

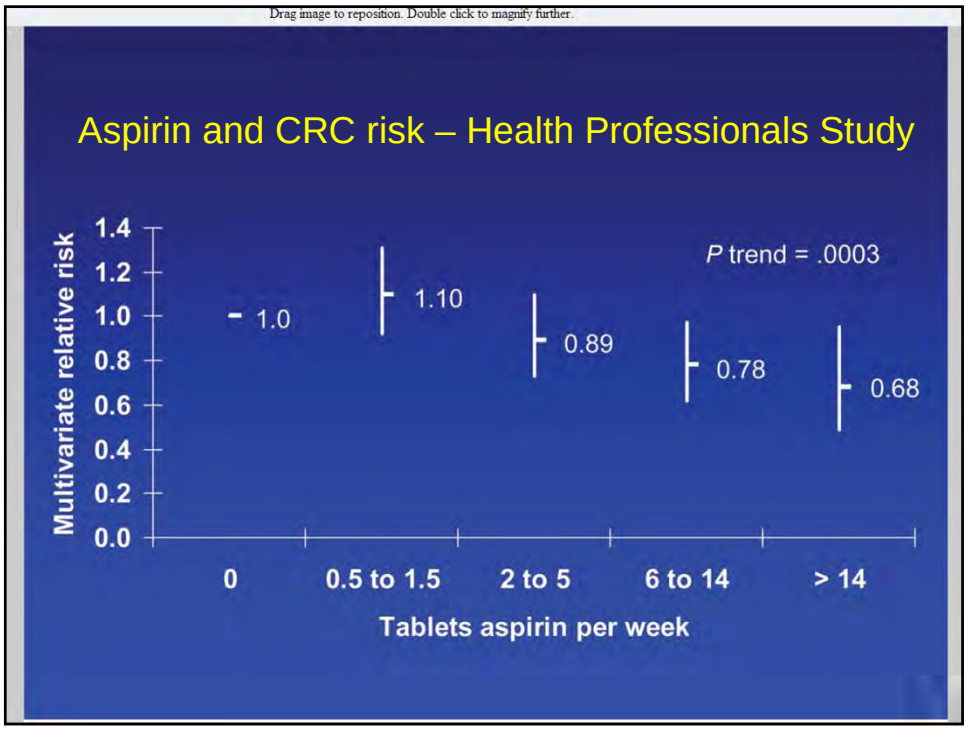
Study	Year	Cohort	N° cases	Intervention	End Point	RR
PHS (Gann)	1993	Healthy	22071	325 mg every other day versus placebo	CCR incidence	1.15 0.80–1.65
PHS (Stürmer)	1998	Healthy	22071	325 mg every other day versus placebo	CCR incidence	1.03 0.83–1.28
Cook et al.	2004	Healthy	39876	100 mg every other day	CCR incidence	0.97 0.77–1.24
Baron et al.	2003	Prior adenoma	1121	81 mg versus 325 mg daily versus placebo	Adenomas incidence	0.81* 0.69–0.96
Sandler et al.	2003	Prior CCR	635	325 mg daily versus placebo	Adenomas incidence	0.65 0.46–0.91
APPAC	2003	Prior adenoma	272	160 mg versus 325 mg versus placebo**	Adenomas incidence	0.73 0.52–1.04

* Positive for 81 mg arm. ** Negative for both arms.

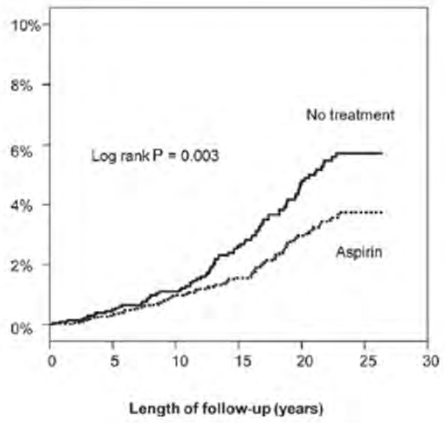
Inconsistent results because
- Site specific?
- Optimal dose?
- Optimal duration?
- Other?

Manzano et al. Scientific World Journal 2012


Proximal Colon
P = 0.0002
% Risk
Time to notification (years)
5812 5237 4478 2637 96
3950 3540 2996 1487 52
Distal colon
P = 0.58
% Risk
Time to notification (years)
Rectum
P = 0.65
% Risk
Time to notification (years)


Drag image to reposition. Double click to magnify further.
Aspirin and CRC risk – Health Professionals Study
Multivariate relative risk
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.0
1.10
0.89
0.78
0.68
P trend = .0003
0
0.5 to 1.5
2 to 5
6 to 14
> 14
Tablets aspirin per week

ITT



Pooled analysis of the effect of low-dose (75–300 mg) aspirin (thick line) versus control (thin line) on subsequent incidence and mortality due to colorectal cancer in TPT, SALT and UK-TIA.

Aspirin as adjuvant Rx

- Chan AT, *JAMA* 2009
  - 1279 with stage I-III CRC
    - Aspirin use associated with a HR of CRC mortality of 0.71, and OS 0.79
    - Greatest benefit in COX-2 + tumours
- Fuchs C, *JCO* 2005 (CALGB 89803)
  - Consistent aspirin or COX2 - HR of 0.46 for DFS and 0.49 for OS
- Current studies
  1. CALGB/SWOG 80702
     - Randomised to celcoxib vs placebo and FOLFOX 3 vs 6 months
  2. ASCOLT

- 19,000 healthy people to be recruited
- ≥ 70 years old
- Randomised to 100mg aspirin vs placebo for 5 years
- Primary endpoint is cardiovascular health
- Secondary endpoints include CRC incidence & outcome cancers

COX2 Inhibitors

Table 2: Results in adenoma incidence in COXIB trials.

Study	Year	Cohort	N° cases	Intervention	End point	RR
APPROVe	2006	Prior adenoma	2587	25 mg rofecoxib versus placebo	Adenoma incidence	0.76 0.69–0.83
APC	2006	Prior adenoma	2035	200 mg bid versus 400 mg bid versus placebo*	Adenoma incidence	0.67 0.55
PreSAP	2006	Prior adenoma	1561	400 mg once versus placebo	Adenoma incidence	0.64 0.56–0.75

* Positive for both arms.

•Meta-analysis – RR 0.72 (0.68 – 0.77)

•However, adverse events (predominantly cardiovascular) limit their use

Manzano et al. *Scientific World Journal* 2012

NSAID`s

- Observational, cohort and case-control studies
- Meta-analysis (Rostom)
  - 30-40% reduction in CRC
  - GI toxicity ~ ulcer complication rate of 1.5% per year
  - Cardiovascular toxicity profile, comparable to COXIBs?

- No direct comparison - NSAIDs, aspirin and COX2

DATA COLLECTION IN ROUTINE PRACTICE

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Value of Data Collection

- Audit
  - How well are we doing?
- Research
  - What determines high quality outputs?
  - How do we improve outcomes?
- Validation of standards established in clinical trials
  - Select patient entry and strict protocols
    - ?Relevance to routine clinical practice

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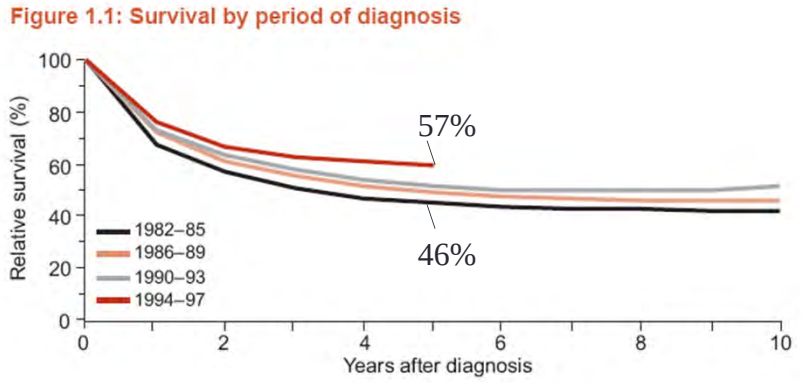
Data Collection

- Ideally
  - Large numbers of patients
  - Representative data
    - Specialist vs generalist
    - Metropolitan vs regional
    - Public vs private
- Challenges
  - Supporting installation of databases and data linkage
  - Supporting data collection

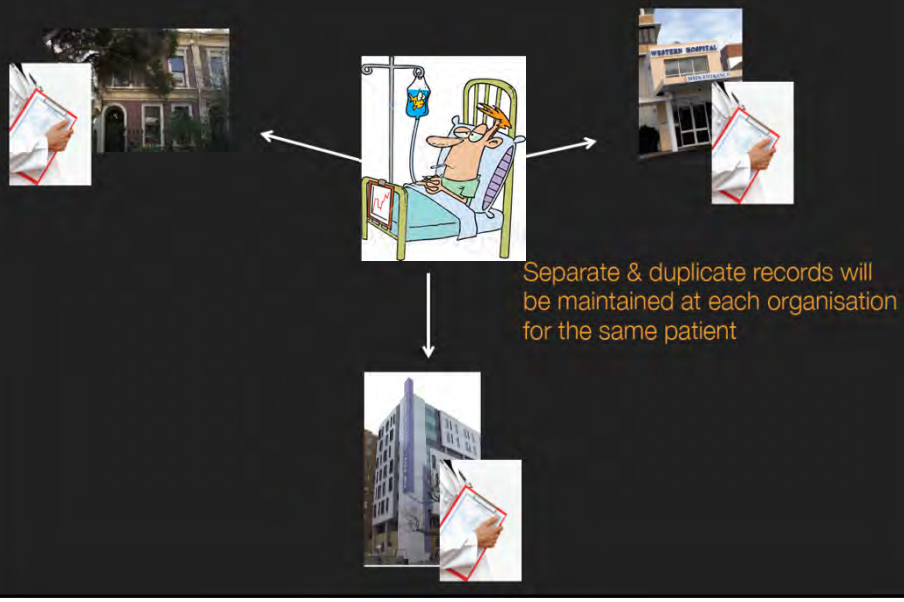
Cancer Registry



- No stage, treatment or cause of death data
- Why are we doing better? How do we improve further?

- **Traditional method**
  - **Try to identify the patients of interest**
- **Try to find their records**
- **Try to extract the data required**

The Modern Patient Journey……



The Ever Increasing Amount Of Data

- More molecular and imaging data
  - Molecular markers
    - Tumour - Single mutations e.g., KRAS <===> whole genome
    - Imaging – CT, MRI, PET
- More treatment
  - Lines of therapy +/- biological therapy
  - Intermittent therapy, blurring of “lines” of therapy
  - Salvage surgery
  - Regional therapies – SIRT, DC Beads
- Longer survival
  - Better palliative treatment
  - More “cured” patients on long term follow-up
- Multi-disciplinary and multi-institutional care

A single patients medical record on paper …..

1. Designing smarter, faster clinical trials

2. **Harnessing information technology**
   - Ensure that every patients experience can inform research & improve care

3. A new approach to therapeutic development

4. Focus on areas of most importance

ASCO Aspirational Goals

1. Consensus dataset for all patients x
2. Secure systems for using data for research x
3. Patient notification of trial availability x
4. Patient entered information x
5. Biospecimen data linked to clinical data x

Australian (BioGrid) Achievements

1. Consensus dataset for all patients
2. Secure systems for using data for research
3. Patient notification of trial availability
4. Patient entered information
5. Biospecimen data linked to clinical data

Data Quality?

- Complete data
  - Relevant events at initial diagnosis
  - Outcome – further Rx, recurrence & survival data
- Accurate data
  - Recording what happened
  - Not recording what didn't happen

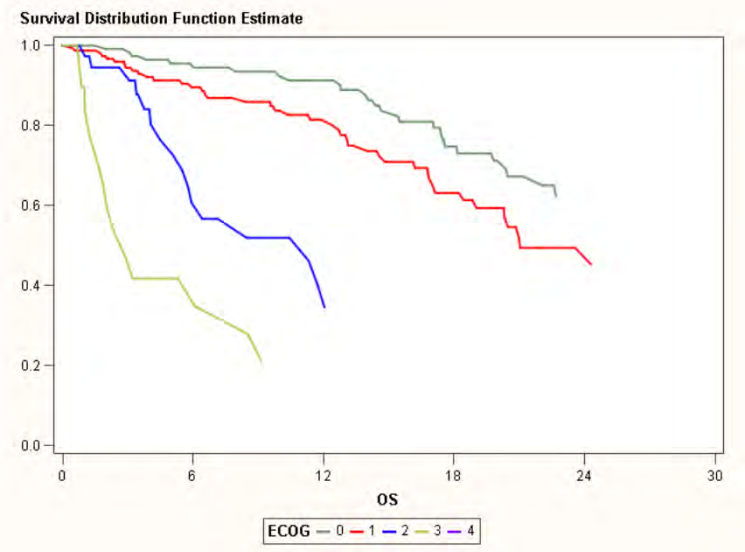
Complete Data – An Ongoing Challenge

- Abernethy AP. Poor documentation prevents adequate assessment of quality metrics in colorectal cancer. JOP 5;167-74:2009
  - Trained abstractors
  - Specific dataset for CRC
  - 13 sites in the US

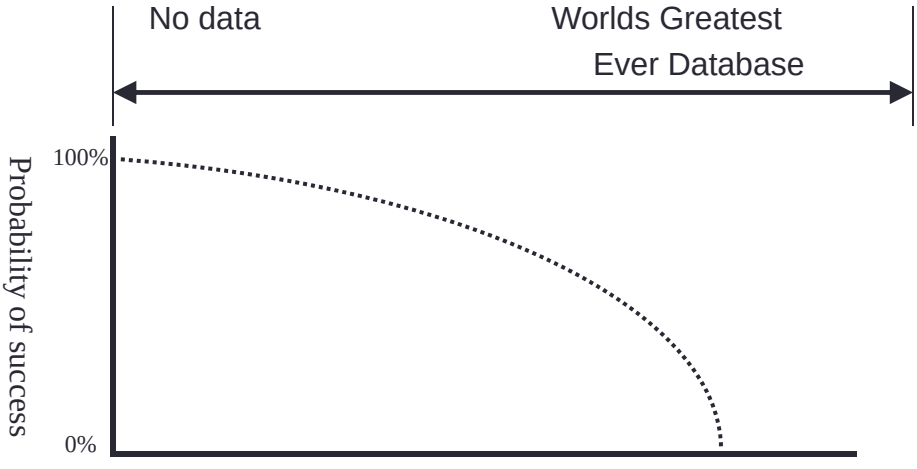
Table 2. Patient Demographics and Clinical Characteristics

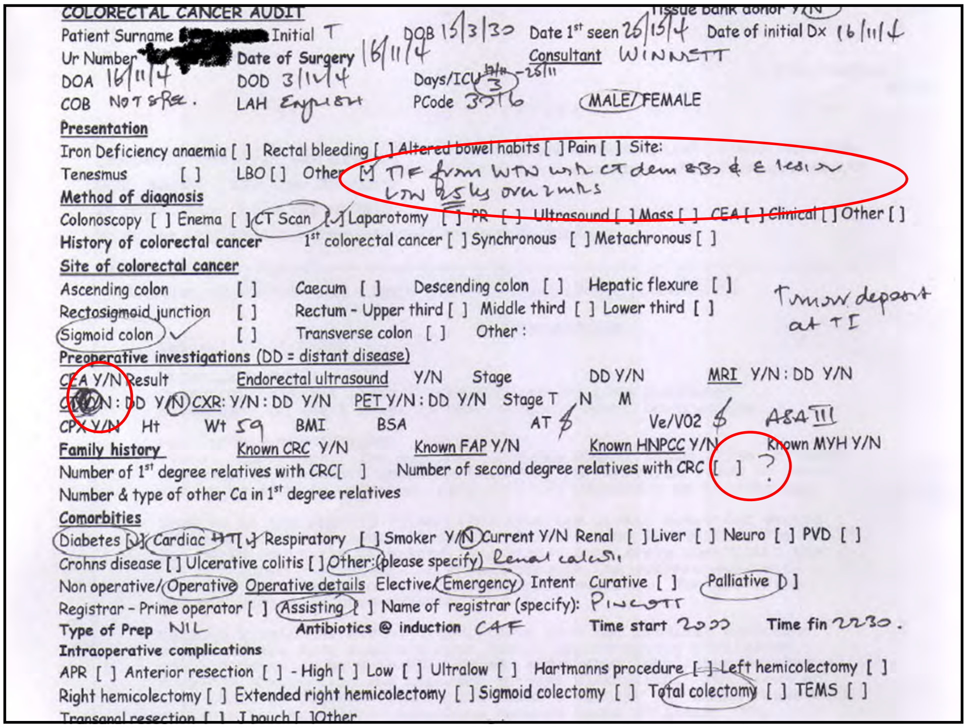
Demographic or Characteristic	Total Population of Patients (N = 499)		Final Study Sample (n = 61)	
	No.	%	No.	%
Diagnosis				
Colon cancer	321	64	48	79
Rectal cancer	106	21	13	21
Missing or unknown	72	14	—	—
Stage				
I	4	1	—	—
II	19	4	11	18
III	65	13	50	82
IV	278	56	—	—
Missing or unknown	133	27	—	—
Sex				
Female	216	43	31	51
Male	199	40	30	49
Missing or unknown	84	17		

Impact Of ECOG On Patient Survival (p<0.0001)



Defining The Data To Collect




COLORECTAL CANCER AUDIT

Tissue bank donor Y/N

Patient Surname [redacted] Initial T DOB 15/3/30 Date 1st seen 26/10/14 Date of initial Dx 16/11/14

Ur Number [redacted] Date of Surgery 16/11/14 Consultant WINNETT

DOA 16/11/14 DOD 3/11/14 Days/ICU 3

COB NOT SPEC. LAH English PCode 3016 MALE/FEMALE

Presentation

Iron Deficiency anaemia [ ] Rectal bleeding [ ] Altered bowel habits [ ] Pain [ ] Site:

Tenesmus [ ] LBO [ ] Other [✓] T/F from WTN with CT dem SBO & lesion, LTW 25kg over 2mths

Method of diagnosis

Colonoscopy [ ] Enema [ ] CT Scan [✓] Laparotomy [ ] PR [ ] Ultrasound [ ] Mass [ ] CEA [ ] Clinical [ ] Other [ ]

History of colorectal cancer 1st colorectal cancer [ ] Synchronous [ ] Metachronous [ ]

Site of colorectal cancer

Ascending colon [ ] Caecum [ ] Descending colon [ ] Hepatic flexure [ ]

Rectosigmoid junction [ ] Rectum - Upper third [ ] Middle third [ ] Lower third [ ]

Sigmoid colon ✓ [ ] Transverse colon [ ] Other :

Tumour deposit at TI

Preoperative investigations (DD = distant disease)

CEA Y/N Result Endorectal ultrasound Y/N Stage DD Y/N MRI Y/N : DD Y/N

CT Y/N : DD Y/N CXR: Y/N : DD Y/N PET Y/N : DD Y/N Stage T N M

CPX Y/N Ht Wt 59 BMI BSA AT Ve/VO2 ASA III

Family history Known CRC Y/N Known FAP Y/N Known HNPCC Y/N Known MYH Y/N

Number of 1st degree relatives with CRC[ ] Number of second degree relatives with CRC [ ] ?

Number & type of other Ca in 1st degree relatives

Comorbities

Diabetes [N] Cardiac HT [✓] Respiratory [ ] Smoker Y/N Current Y/N Renal [ ] Liver [ ] Neuro [ ] PVD [ ]

Crohns disease [ ] Ulcerative colitis [ ] Other:(please specify) Renal calculi

Non operative/Operative Operative details Elective/Emergency Intent Curative [ ] Palliative [✓]

Registrar - Prime operator [ ] Assisting [✓] Name of registrar (specify): PINCOTT

Type of Prep NIL Antibiotics @ induction CAF Time start 2022 Time fin 2230.

Intraoperative complications

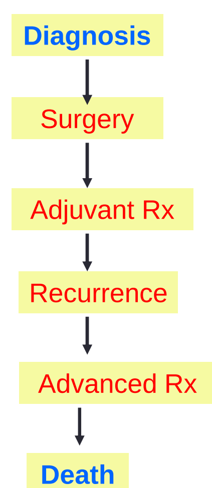
APR [ ] Anterior resection [ ] - High [ ] Low [ ] Ultralow [ ] Hartmanns procedure [ ] Left hemicolectomy [ ]

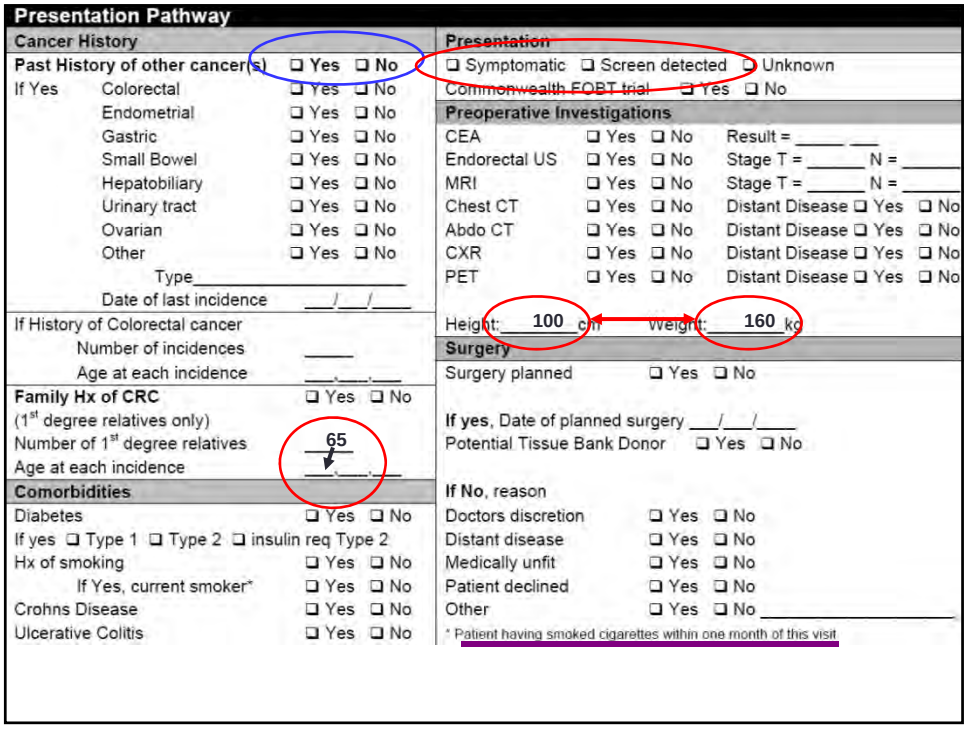
Right hemicolectomy [ ] Extended right hemicolectomy [ ] Sigmoid colectomy [ ] Total colectomy [ ] TEMS [ ]

Transanal resection [ ] J pouch [ ] Other

BioGrid 2003 -

1. Consensus datasets (databases)
   - Multi-disciplinary datasets for each disease type
     - **Minimum** dataset => comprehensive dataset
   - Cancer and other diseases (epilepsy, diabetes)
2. Ability to link data across multiple sites





Presentation Pathway

Cancer History

Past History of other cancer(s) ❑ Yes ❑ No

If Yes
- Colorectal ❑ Yes ❑ No
- Endometrial ❑ Yes ❑ No
- Gastric ❑ Yes ❑ No
- Small Bowel ❑ Yes ❑ No
- Hepatobiliary ❑ Yes ❑ No
- Urinary tract ❑ Yes ❑ No
- Ovarian ❑ Yes ❑ No
- Other ❑ Yes ❑ No
  - Type_____
  - Date of last incidence ___/___/____

If History of Colorectal cancer
- Number of incidences _____
- Age at each incidence ___,___,___

Family Hx of CRC ❑ Yes ❑ No

(1st degree relatives only)

Number of 1st degree relatives 65

Age at each incidence ___,___,___

Comorbidities

Diabetes ❑ Yes ❑ No

If yes ❑ Type 1 ❑ Type 2 ❑ insulin req Type 2

Hx of smoking ❑ Yes ❑ No

If Yes, current smoker* ❑ Yes ❑ No

Crohns Disease ❑ Yes ❑ No

Ulcerative Colitis ❑ Yes ❑ No

Presentation

❑ Symptomatic ❑ Screen detected ❑ Unknown

Commonwealth FOBT trial ❑ Yes ❑ No

Preoperative Investigations

CEA	❑ Yes	❑ No	Result = _____ ___
Endorectal US	❑ Yes	❑ No	Stage T = _____ N = _____
MRI	❑ Yes	❑ No	Stage T = _____ N = _____
Chest CT	❑ Yes	❑ No	Distant Disease ❑ Yes ❑ No
Abdo CT	❑ Yes	❑ No	Distant Disease ❑ Yes ❑ No
CXR	❑ Yes	❑ No	Distant Disease ❑ Yes ❑ No
PET	❑ Yes	❑ No	Distant Disease ❑ Yes ❑ No

Height: 100 cm Weight: 160 kg

Surgery

Surgery planned ❑ Yes ❑ No

If yes, Date of planned surgery ___/___/____

Potential Tissue Bank Donor ❑ Yes ❑ No

If No, reason
- Doctors discretion ❑ Yes ❑ No
- Distant disease ❑ Yes ❑ No
- Medically unfit ❑ Yes ❑ No
- Patient declined ❑ Yes ❑ No
- Other ❑ Yes ❑ No _____

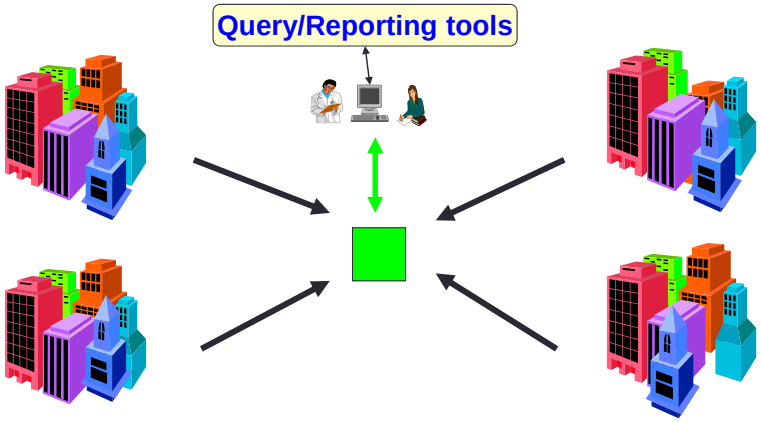
* Patient having smoked cigarettes within one month of this visit

BioGrid Planning 2003

Must address the following

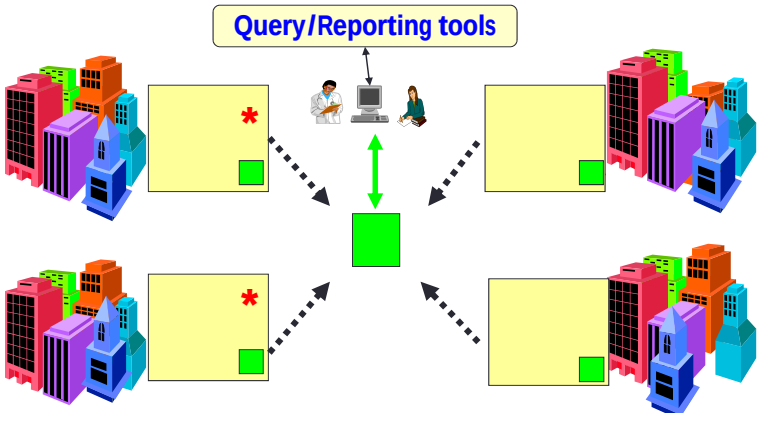
- Data security
- Data ownership
- Authorship, IP
- Simplified ethics
- Assistance with data linkage and analysis

Traditional Model For Multi-Site Data Collection



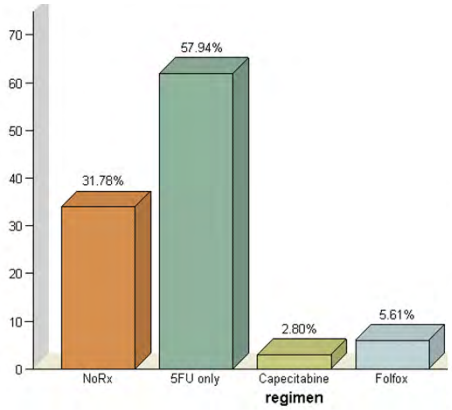
- Who owns and controls the data? Is the data secure?
  - One off, stand alone projects

BioGrid Model

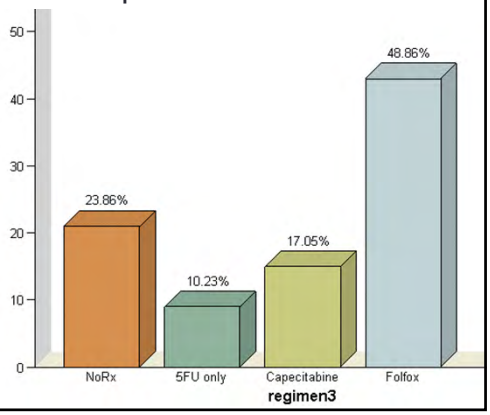


1. Data owned and controlled by local clinicians
2. Data de-identified before linkage (can be re-identified)
3. The same patient * can be identified by USI across databases
4. Only data required for a specific project is linked
5. Broad ethics approval to use de-identified data for research

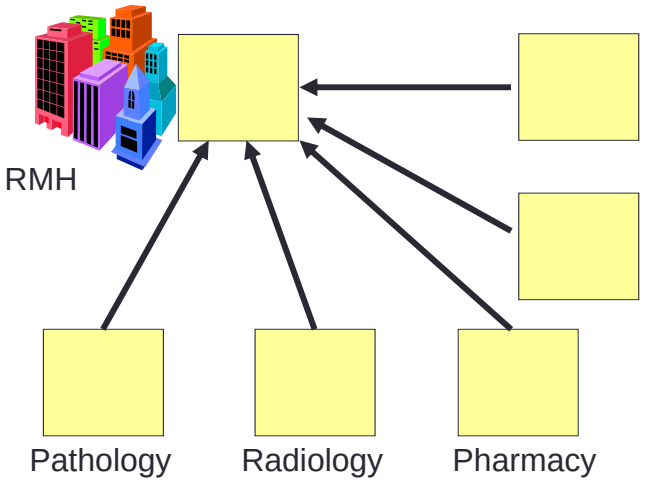
Jan 2003 – August 2005



April 2006 – Feb 2008



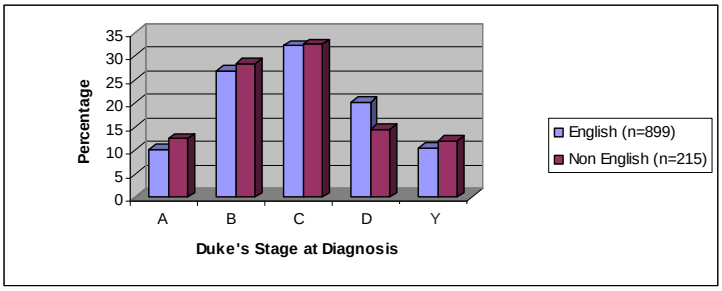
Links With "Internal" Data



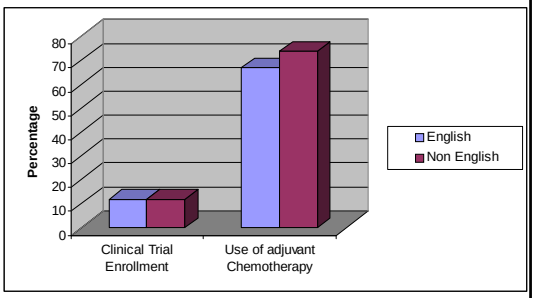
Other…..

- Familial cancer
- Other Cancer
- Other diseases

Administration



Rodrigues J, et al.
ANZ J Surg 76;671-2:2006



Links With "External" Data

RMH

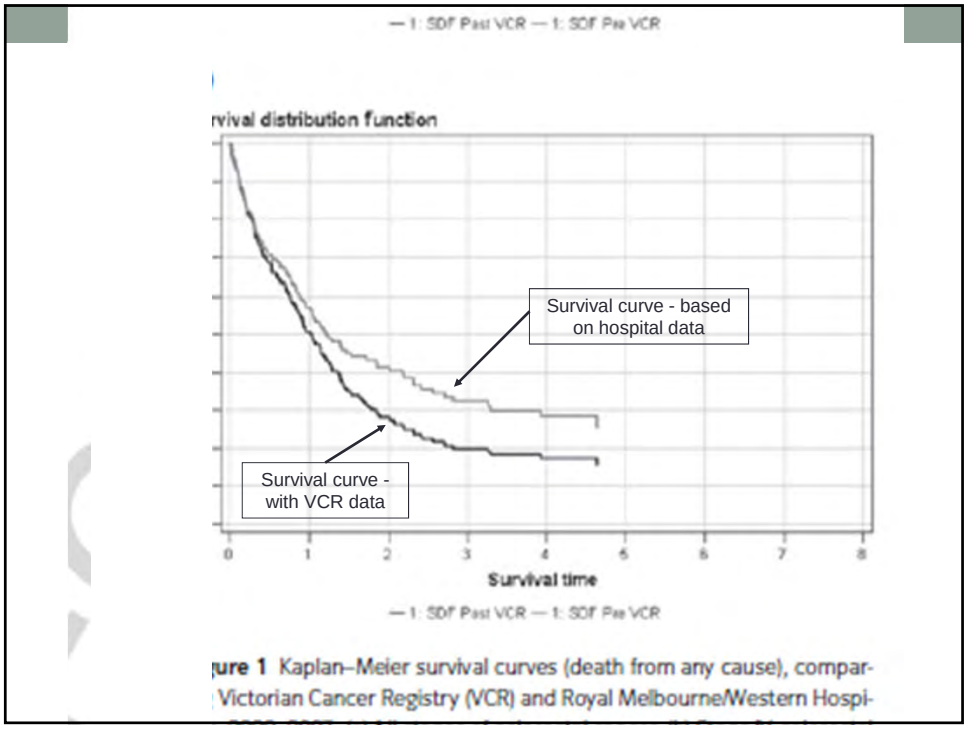
CRC

Cancer Registry

State Gov Data

Federal Gov Data

1. Death data AIHW
   - Date and cause
2. Prescriptions (PBS)
3. Procedures (MBS)



ure 1 Kaplan–Meier survival curves (death from any cause), compar-
Victorian Cancer Registry (VCR) and Royal Melbourne/Western Hospi-

Quality Of Care - Combined Data

- Excellent outcomes on every measure
  - Operative mortality
    - 2% vs 5-6% (UK data)
  - Median lymph node yield
    - 14 vs 6 - 12
  - Local recurrence rate for rectal cancer
    - 2% vs ≥ 7%
  - Median survival for stage IV CRC
    - 15 months vs 9 months (US data)

ENCOURAGING DATA COLLECTION (& IMPROVING ACCURACY)

Integrating data collection into routine care

VA Midwest Health Care Network – ECP Impact

- Review of chemotherapy orders pre ECP
- Many errors, mostly physicians, most frequently
  1. Omissions
     - Most frequent error
     - Includes leaving out pre-Rx anti-emetics, hydration, discharge medications, etc,.
  2. Dose miscalculation
  3. Incorrect chemotherapy timing
     - Start dates
     - Treatment frequency
  4. Patient identification

Impact on Providers Corrections To Orders

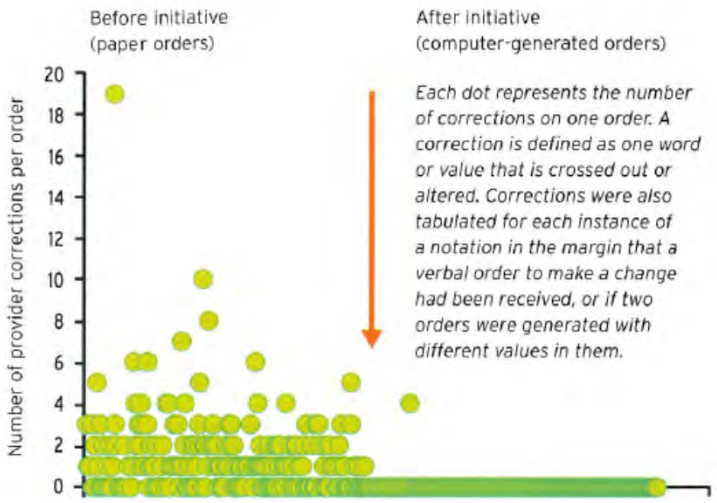


Figure 1: Impact of Software on Providers' Corrections to Chemotherapy Orders

Impact on Time Taken to Order Chemotherapy

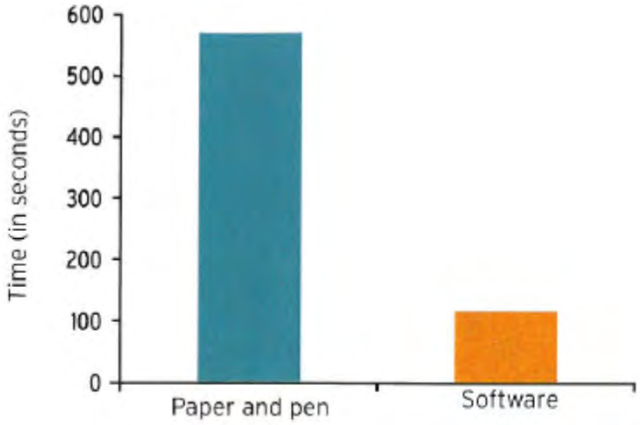
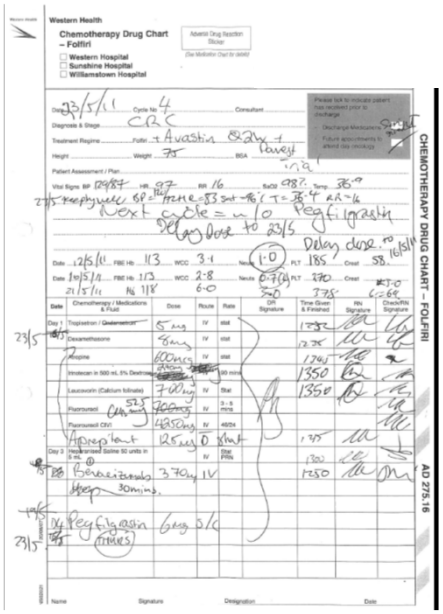


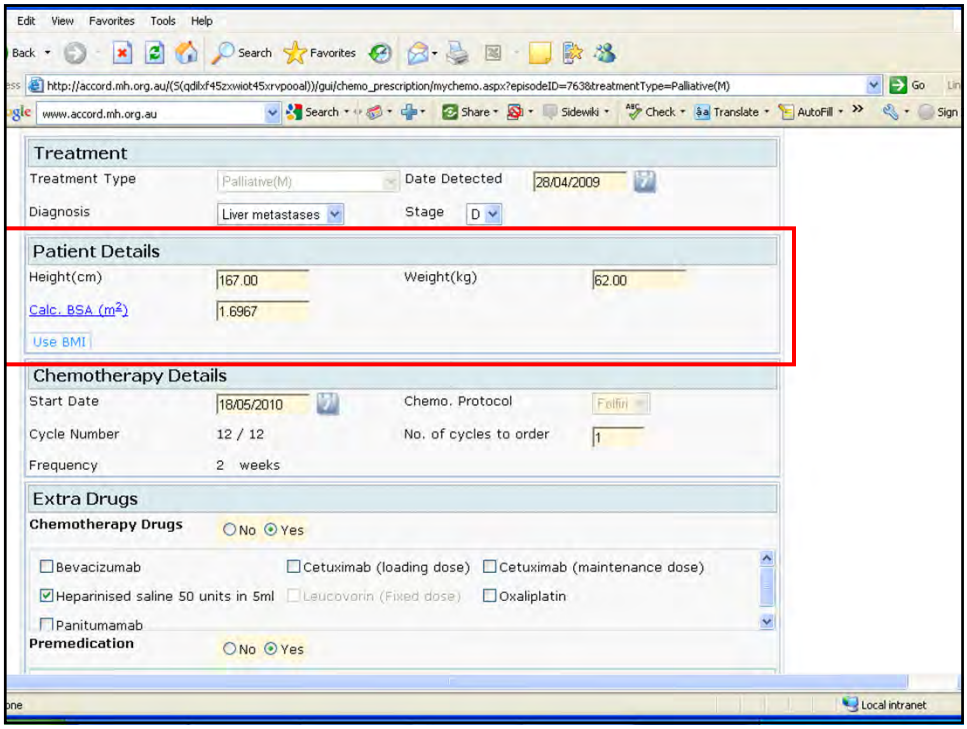
Figure 2: Time Needed for Providers to Write Chemotherapy Orders

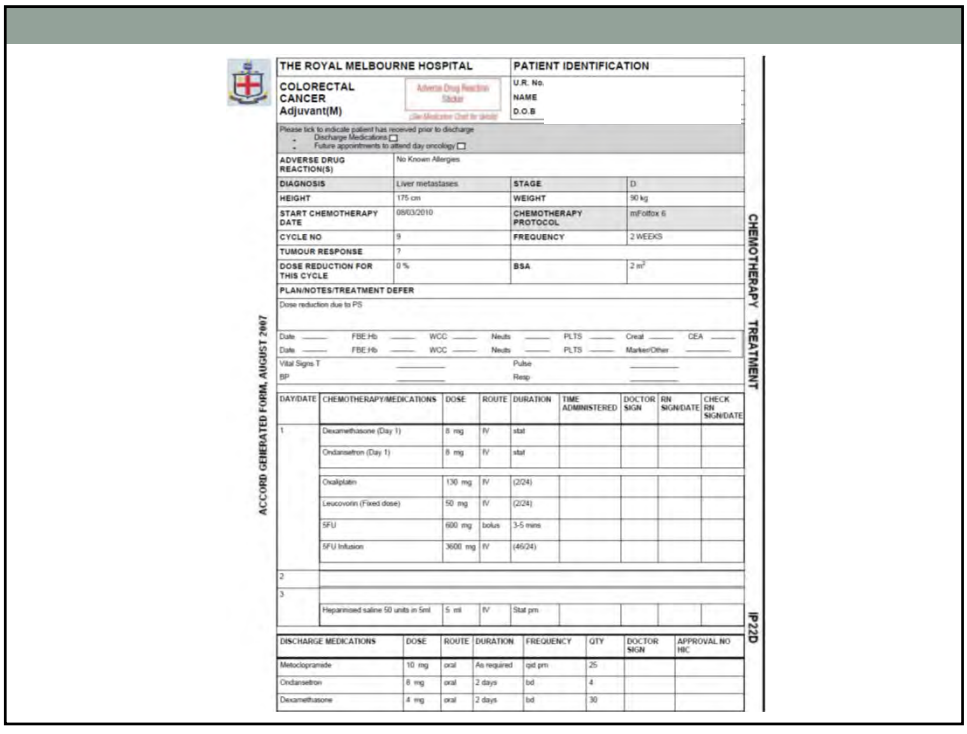


Data entered into database

Why should BioGrid develop an Electronic Chemotherapy Prescribing tool?

1. Defined standards – regimen, BSA based dose
2. Designed with the intent of extracting data
3. Built in safety
   - Dose calculation
4. Built in link with EviQ
   - Auto-population of accepted regimens
   - Education / information


Edit View Favorites Tools Help
Back Search Favorites
http://accord.mh.org.au/(S(qdllxf45zxwiot45xrvpooal))/gui/chemo_prescription/mychemo.aspx?episodeID=7638treatmentType=Palliative(M)
www.accord.mh.org.au
Treatment
Treatment Type
Palliative(M)
Date Detected
28/04/2009
Diagnosis
Liver metastases
Stage
D
Patient Details
Height(cm)
167.00
Weight(kg)
62.00
Calc. BSA (m2)
1.6967
Use BMI
Chemotherapy Details
Start Date
18/05/2010
Chemo. Protocol
Folfiri
Cycle Number
12 / 12
No. of cycles to order
1
Frequency
2 weeks
Extra Drugs
Chemotherapy Drugs
No Yes
Bevacizumab
Cetuximab (loading dose)
Cetuximab (maintenance dose)
Heparinised saline 50 units in 5ml
Leucovorin (Fixed dose)
Oxaliplatin
Panitumamab
Premedication
No Yes
Local intranet


THE ROYAL MELBOURNE HOSPITAL
PATIENT IDENTIFICATION
COLORECTAL CANCER Adjuvant(M)
U.R. No.
NAME
D.O.B
ADVERSE DRUG REACTION(S)
No Known Allergies
DIAGNOSIS
Liver metastases
STAGE
D
HEIGHT
175 cm
WEIGHT
90 kg
START CHEMOTHERAPY DATE
08/03/2010
CHEMOTHERAPY PROTOCOL
mFolfox 6
CYCLE NO
9
FREQUENCY
2 WEEKS
TUMOUR RESPONSE
?
DOSE REDUCTION FOR THIS CYCLE
0 %
BSA
2 m2
PLAN/NOTES/TREATMENT DEFER
Dose reduction due to PS
DAY/DATE
CHEMOTHERAPY/MEDICATIONS
DOSE
ROUTE
DURATION
TIME ADMINISTERED
DOCTOR SIGN
RN SIGN/DATE
CHECK RN SIGN/DATE
Dexamethasone (Day 1)
8 mg
IV
stat
Ondansetron (Day 1)
8 mg
IV
stat
Oxaliplatin
130 mg
IV
(2/24)
Leucovorin (Fixed dose)
50 mg
IV
(2/24)
5FU
600 mg
bolus
3-5 mins
5FU Infusion
3600 mg
IV
(46/24)
Heparinised saline 50 units in 5ml
5 ml
IV
Stat prn
DISCHARGE MEDICATIONS
DOSE
ROUTE
DURATION
FREQUENCY
QTY
DOCTOR SIGN
APPROVAL NO HIC
Metoclopramide
10 mg
oral
As required
qid prn
25
Ondansetron
8 mg
oral
2 days
bd
4
Dexamethasone
4 mg
oral
2 days
bd
30
ACCORD GENERATED FORM, AUGUST 2007
CHEMOTHERAPY TREATMENT
IP22D

Additional Value Of Electronic Chemotherapy Prescribing

1. Defined standards
   - Ideally only one protocol for FOLFOX etc.,
   - Standard dosing (justify variations)
2. Built in link with EviQ
   - Auto-population of accepted regimens
   - Education / information
3. Designed with the intent of extracting data
4. Built in safety
   - Dose calculation
   - Minimising transcription and interpretation errors

Improving Treatments & Outcomes

- Clinical trials remain the gold standard but…..
  - Becoming more expensive and time consuming

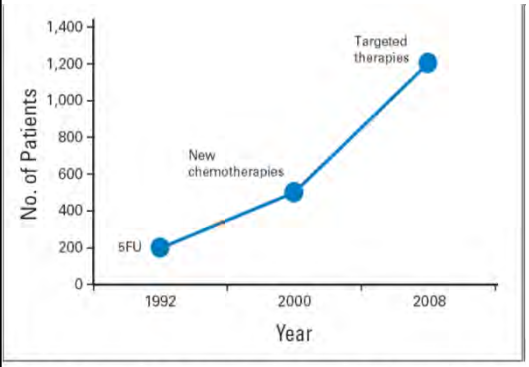


Fig 1. Median number of patients in advanced colorectal cancer trials (A. de Gramont, unpublished results).

- **$1 – 2 billion dollars to bring a new drug to market**
- **~ $26,000 / patient entered**
- **Increasing regulatory requirements**

Stewart JD, et al.

JCO 28;2925-35:2010

Improving Treatments & Outcomes

- Clinical trials remain the gold standard but…..

Australia

- PBS spending growing 10-15% per year (> $300M)
- Surgical equipment / prosthesis
- Imaging – MRI for rectal cancer staging, PET for ?resectable disease
- Molecular testing – eg., KRAS mutation testing

US

- Insurance for a family of four – $15,000 (+ co-payments)
- Nearly 1 million families suffered medical bankruptcy in 2011
- 25% of all funds are spent in the last year of life and 9% ($50 billion) in the last month of life

The Price Of Progress – Cost vs Stage At Presentation

	1999 Cost	2009 cost	Change
Stage A	**17,100**	**23,100**	**135%**
Stage B	**33,400**	**63,500**	**190%**
Stage C	**25,800**	**80,000**	**310%**
Stage D	**6,300**	**97,300**	**1544%**

"Clinical Trial Land"

Bowel and Uterine Cancers

Gene changes and the risk of Bowel & Uterine Cancer

Approximately 1 in 21 people will develop bowel cancer during their lifetime. It is uncommon before the age of 40, and is slightly more common among men than women.

Bowel Cancer

When your medical practitioner talks about bowel cancer (also known as colorectal cancer) they are referring to cancer of the colon or rectum.

Patients look like this

Doctors look like this

How Selective Are Clinical Trials?

ECOG 4599 – NSCLC, 1st line Rx, Carbo/Taxol +/- Bev

- Fox Chase Cancer Centre - Review of 116 pts at, no prior chemotherapy, initially seen while the study was open
- Excluded = 71%, due to
  - ECOG ≥ 2 26%
  - CNS metastases 24%
  - Other exclusions 26%
- Enrolled = 5% (6 of 116)
  - 6 of 34 "eligible" patients enrolled

Elderly Patients With Stage III Colon Cancer

40% of colorectal cancer patients are 75 +

- Subset analysis of clinical trials (65yrs+, 70yrs+)

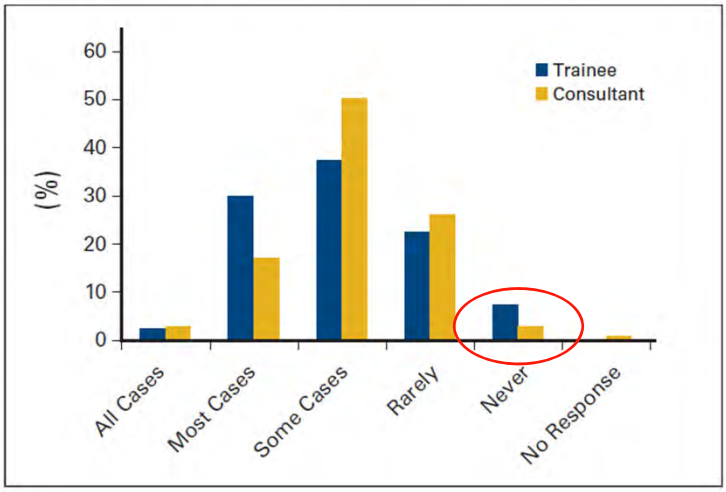
Should a fit elderly patients with stage III colon cancer receive adjuvant chemotherapy, and at what dose?

1. Yes, fit elderly patients benefit from adjuvant chemotherapy for stage III colon cancer
2. Fit elderly patients should be treated at standard doses

Chemotherapy Dosing Strategies in the Obese, Elderly, and Thin Patient: Results of a Nationwide Survey

By Kathryn M. Field, MD, Suzanne Kosmider, MD, Michael Jefford, PhD, MBBS, MPH, Michael Michael, MBBS, Ross Jennens, MD, Michael Green, MD, and Peter Gibbs, MD, MBBS

Figure 4. Dose reduction frequency in fit elderly patients.



Age Specific Rx Stage III Colon Cancer

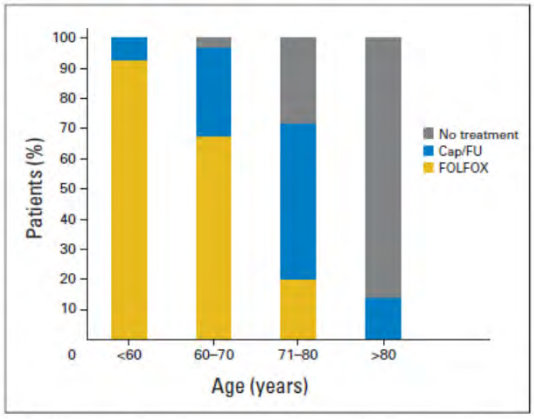


Fig 1. Choice of chemotherapy regimen for stage III colon cancer (n = 125) stratified by age group. Data are from September 2005, when oxaliplatin became routinely available. No treatment = no adjuvant therapy. Cap/FU, capecitabine or fluorouracil; FOLFOX, fluorouracil, leucovorin, and oxaliplatin.

Ananda S, et al. *J Clin Oncol.* 26;4516-7:2008

One Interpretation - Getting Oncologists To Follow Protocols Is A Bit Like ……

Value Of Chemotherapy For Very Elderly Stage III Colon Cancer?

	Number of cases	Median Survival	5 Year Survival	Death without cancer recurrence
Stage III colon cancer ≥80 y.o.	84	2.94 yrs	26.9%	27 (58.7%)

- 2613 patients at 4 hospitals over 7 years

= 84 cases of stage III colon cancer in patients ≥ 80 years

- ?limited / no benefit from adjuvant chemotherapy

Field K, et al. The cost of cancer care – considering the value of caring for the elderly. *NEJM*. 365;675:2011

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METASTATIC COLORECTAL CANCER

In The Last 15 Years

THERAPIES

- 5-fluorouracil

- 3 additional cytotoxics – capecitabine, oxaliplatin, irinotecan
- 4 new biologics - bevacizumab, cetuximab, aflibercept, regorafenib,

NCCN National Comprehensive Cancer Network®

NCCN Guidelines™
Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

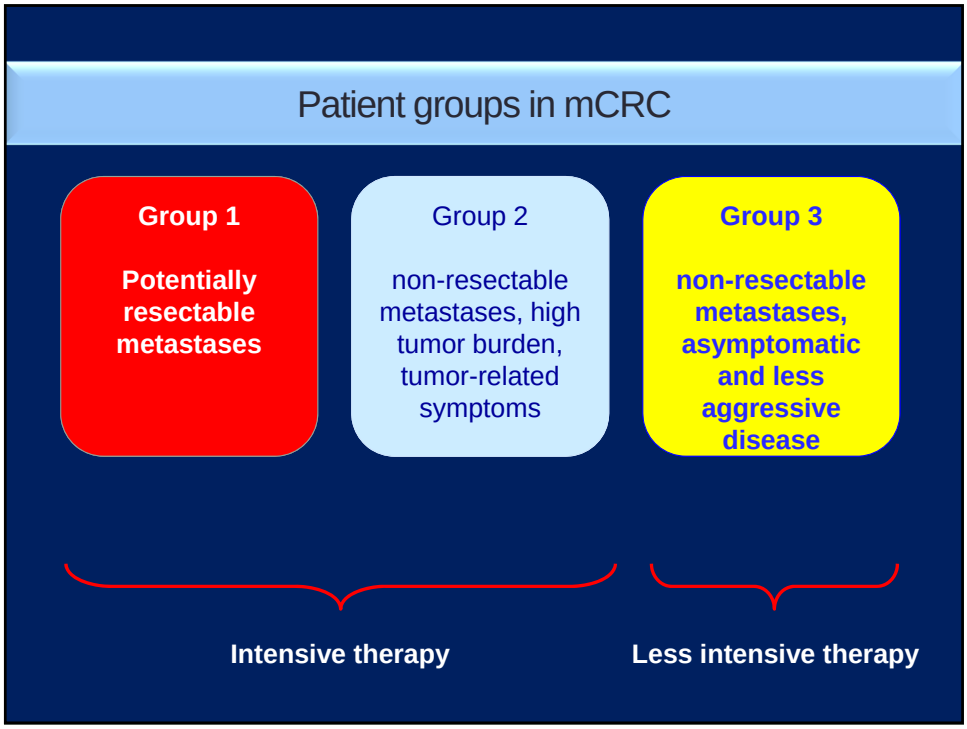
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 6)

Initial therapy | Therapy after First Progression

Patient appropriate for intensive therapy[2]

5-FU/leucovorin → Clinical trial or best supportive care[19]

Note: All recommendations are category 2A unless otherwise indicated.

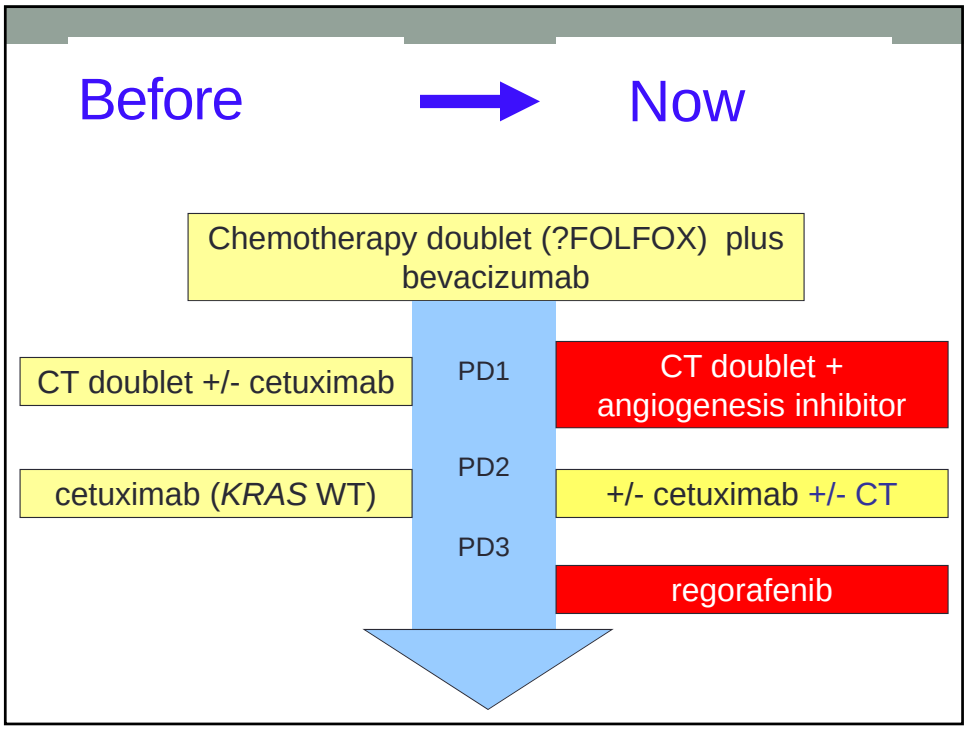


Controversy In Defining Optimal Rx

- Contradictory study results
- Multiple ways to interpret studies
- Anecdotes versus clinical trials
- Clinical judgment (the art of medicine) vs the data
- Not possible to predict study results

Therapies for Patient groups in mCRC

K-ras	Regimen	Group 1 Potentially resectable metastases<	Group 2 Non-resectable metastases, high tumor burden, tumor-related symptoms	Group 3 Non-resectable metastases, asymptomatic and less aggressive disease
wt	1st Choice	FOLFIRI or FOLFOX + Cmab	FOLFIRI or FOLFOX + Cmab	FOLFIRI or FOLFOX + Cmab
	2nd Choice	FOLFIRI or FOLFOX or FOLFOXIRI	(FOLFOXIRI)	FOLFIRI or FOLFOX
mut	1st Choice	FOLFOXIRI	FOLFIRI or FOLFOX	Fluoropyrimidine + Bevacizumab
	2nd Choice	FOLFIRI or FOLFOX	(FOLFOXIRI)	FOLFIRI or FOLFOX



EGFR antibodies – 1st line k-ras wt only

1st Line mCRC				
Trial	**Therapy**	**ORR**	**PFS (mo)**	**OS (mo)**
CRYSTAL *(n=666) **	*FOLFIRI +/- Cetux**	✓ 40% vs. 57%	✓ 8,4 vs. 9,9 HR = 0,696	✓ 20.0 vs.23,5 HR = 0,796
PRIME *(n=656) **	*FOLFOX +/- Pani**	✓ 48% vs. 57%	✓ 10,0 vs.8,6 HR = 0,80	(✓) 19,7 vs. 23,9 HR = 0.88
OPUS *(n=197) **	*FOLFOX +/- Cetux**	✓ 34% vs. 57%	✓ 7,2 vs.8,3 HR = 0,567	(✓) 18,5 vs.22,8 HR = 0,855
COIN *(n=729) **	*XELOX/ FOLFOX +/- Cetux**	✓ 57% vs. 64%	– 8,6 vs.8,6 HR = 0,959	– 17,9 vs.17,0 HR = 1,038
NORDIC *(n=194)*	*FLOX +/- Cetux*	– 47 vs. 46%	– 8,7 vs. 7,9 HR = 1.07	– 22,0 vs. 21,0 HR = 1.14

✓ sig. diff; (✓) clinically relevant not statist. Sig; – no sig. diff * KRAS wt population

NO16966: FOLFOX vs XELOX +/- BV

Recruitment
June 2003 – May 2004

XELOX N=317

FOLFOX4 N=317

Initial 2-arm
open-label study (N=634)

Recruitment
Feb 2004 – Feb 2005

XELOX + placebo N=350	**XELOX + bevacizumab N=350**
FOLFOX4 + placebo N=351	**FOLFOX4 + bevacizumab N=350**

Protocol amended to 2x2 placebo-controlled design after bevacizumab phase III data became available (N=1401)

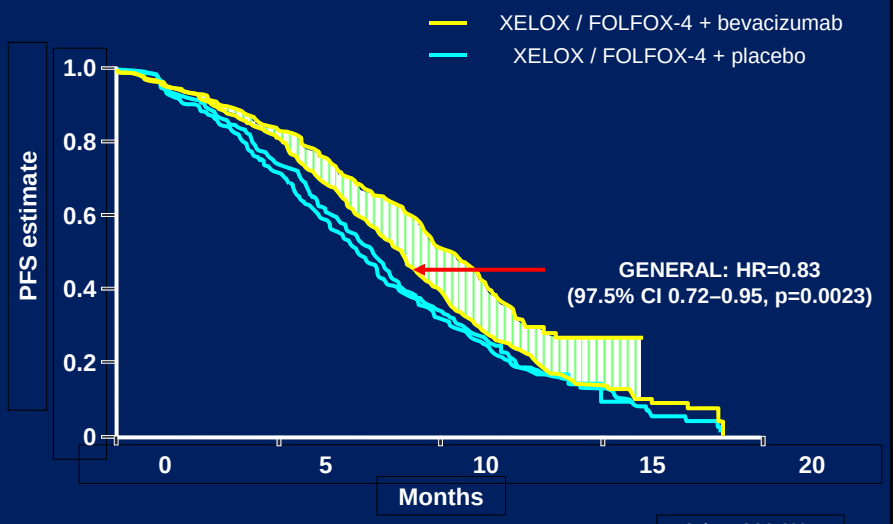
Primary Endpoint: PFS

Non-inferiority of XELOX vs FOLFOX

Superiority of Bevacizumab vs Placebo

J Cassidy ESMO 2006

NO16966: FOLFOX vs XELOX +/- BV PFS

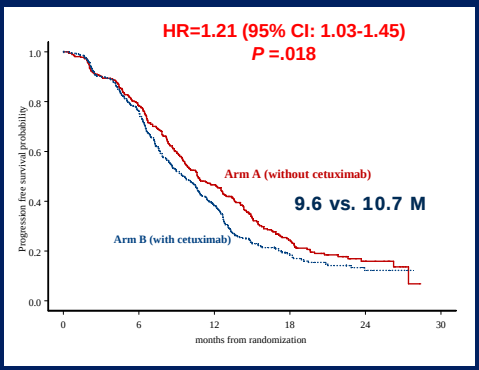


Saltz ASCO 2007

Phase III Trials of Combined Biologic Therapy with Negative Impact on PFS

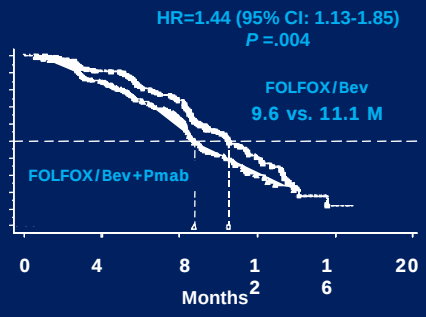
CAIRO2

CapeOx / Bev + / - Cetux



PACCE

FOLFOX / Bev + / - Pan



Hecht et al; World GI Cancer, Barcelona, 2007

Multi-Site Data Collection

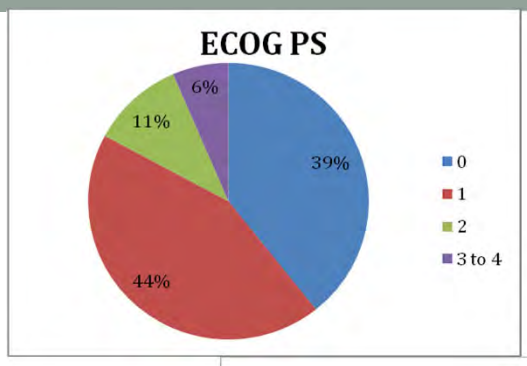
- 1 hospital = 100 patients per year
- 10 hospitals = 1000 patients per year
- 100 hospitals = 10,000 patients per year

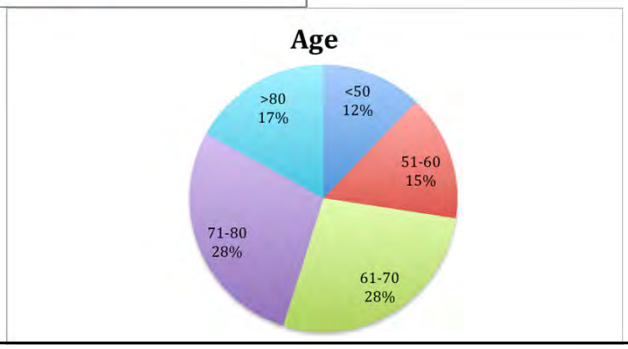
Registries

- Consensus datasets for all cancer types
- Comprehensive dataset
  - Screening, co-morbidity, surgery, pathology,
  - adjuvant Rx, recurrence, further Rx
- Resource intensive, limited participation
- Prospective (limited) data collection
  - One scenario = metastatic CRC
  - One discipline = medical oncology
  - Industry support for data collection

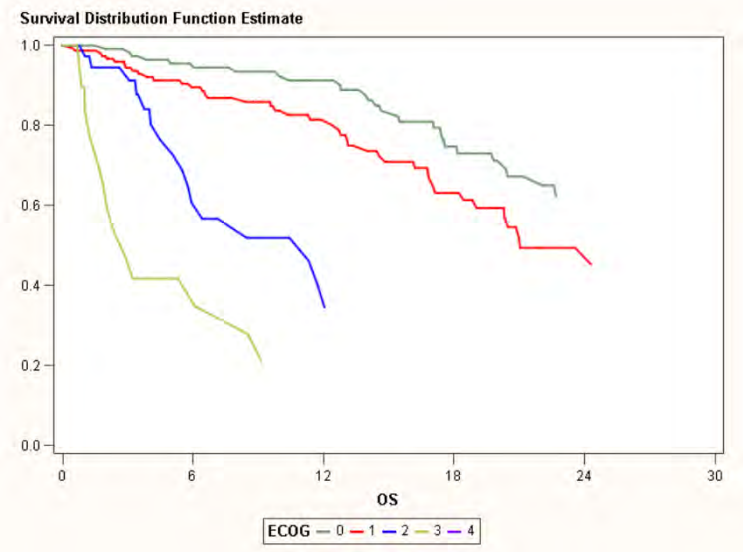
TRACC Database - Treatment Recurrent and Advanced Colorectal Cancer

- July 2009, Roche sponsored, data entry support
- Rx and outcomes of mCRC in Australia
  - Agreed dataset on all patients
- Particular focus on bevacizumab
  - Bevacizumab duration of use
  - Reasons bevacizumab not given
  - Major adverse events
- 1000 patients over 15 sites by end 2012

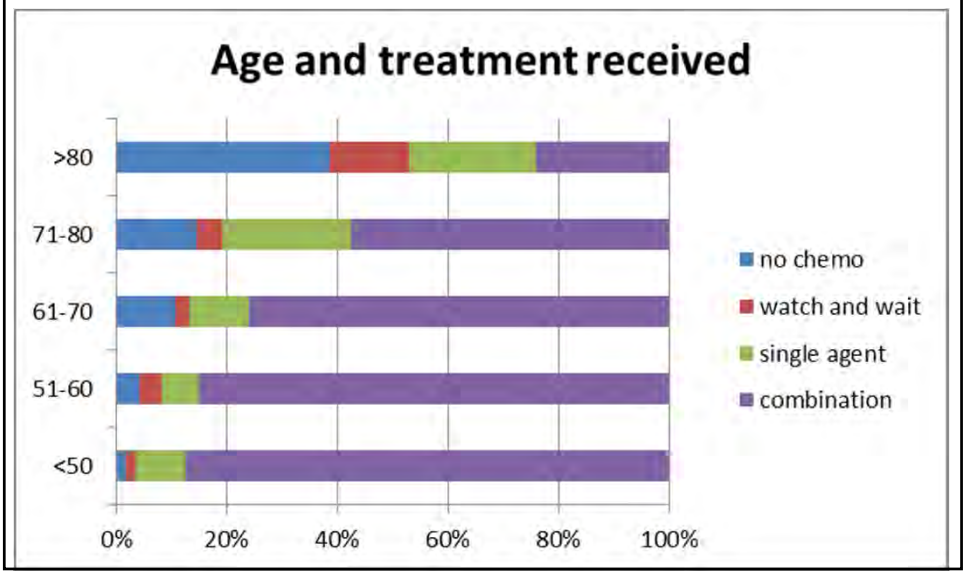




Impact Of ECOG On Patient Survival (p<0.0001)



Patient Age & Rx In Routine Practice



TRACC vs BRITE vs BEAT

	TRACC (AUS)	BRITE (US)	BEAT (Europe)
FOLFOX	**66%**	**56%**	29%
FOLFIRI	8%	14%	**26%**
XELOX	5%	5%	**18%**
Other	21%	25%	25%
No treatment	(20%)	0%	0%

100

With The Introduction Of Any New Therapy Into Routine Clinical Practice

1. Is the expected efficacy being observed?
2. Are there any unexpected adverse events?
3. Is the treatment being appropriately used?
   - How many patients are receiving treatment?
   - When is it being used?

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What Is The Optimal Timing Of Cetuximab? (In Australia)

	Yes	No
First Line	- ↑ Response rates - (↑ Resection rates) - ↑ Survival (+)	- Not funded - Competes with bevacizumab – funded & maximal benefit in 1st line
Second Line	- Funded - ↑ Likelihood of receiving cetuximab	- No OS benefit - (Competes with OS benefit from anti-VEGF Rx)
Third Line	- Funded - ↑ (+++) survival	- Too many patients miss out on Rx

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PATTERNS OF CHEMOTHERAPY USE IN A U.S.-WIDE POPULATION-BASED COHORT OF PATIENTS WITH METASTATIC COLORECTAL CANCER

Thomas A. Abrams[1], Gary Meyer[2], Julie Moloney[2], Jeffrey A Meyerhardt[1], Deborah Schrag[1], Charles S. Fuchs[1]
[1]Dana-Farber Cancer Institute, Boston, MA, [2]IntrinsiQ, LLC an AmerisourceBergen Specialty Group Company, Burlington, MA

We studied 4,877 consecutive mCRC patients (pts) who started chemotherapy (Jan. 2004 – Mar. 2011) in U.S. academic, private or community hospital-based practices that employed a chemotherapy (CT) computerized order entry (COE) system to capture pt and physician characteristics, disease information and treatment data

USE OF SUBSEQUENT LINES OF THERAPY AMONG 4,877 mCRC PTS WHO RECEIVED 1ST LINE CT

CT line	No. pts/line	% pts/line
1st line	4877	100%
2nd line	2575	53%
3rd line	1373	23%
4th line	640	13%

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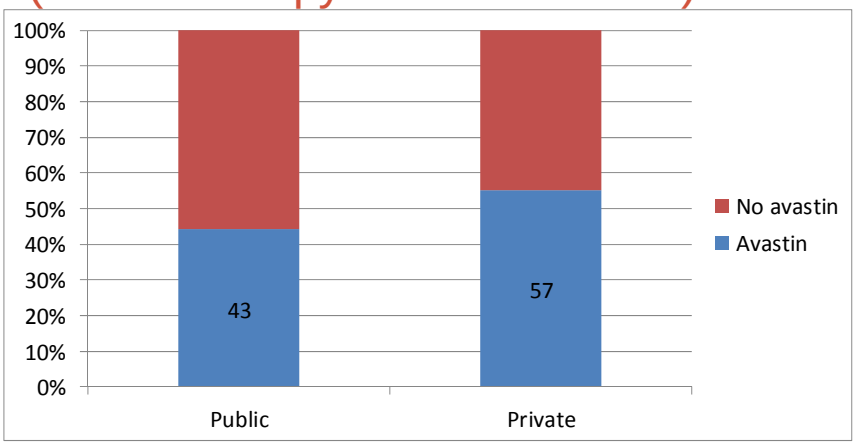
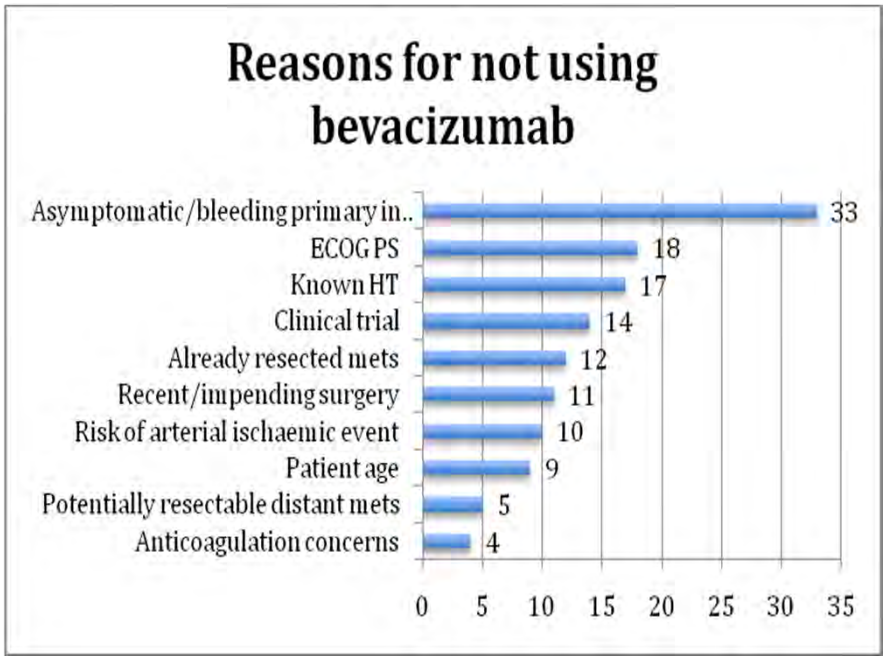
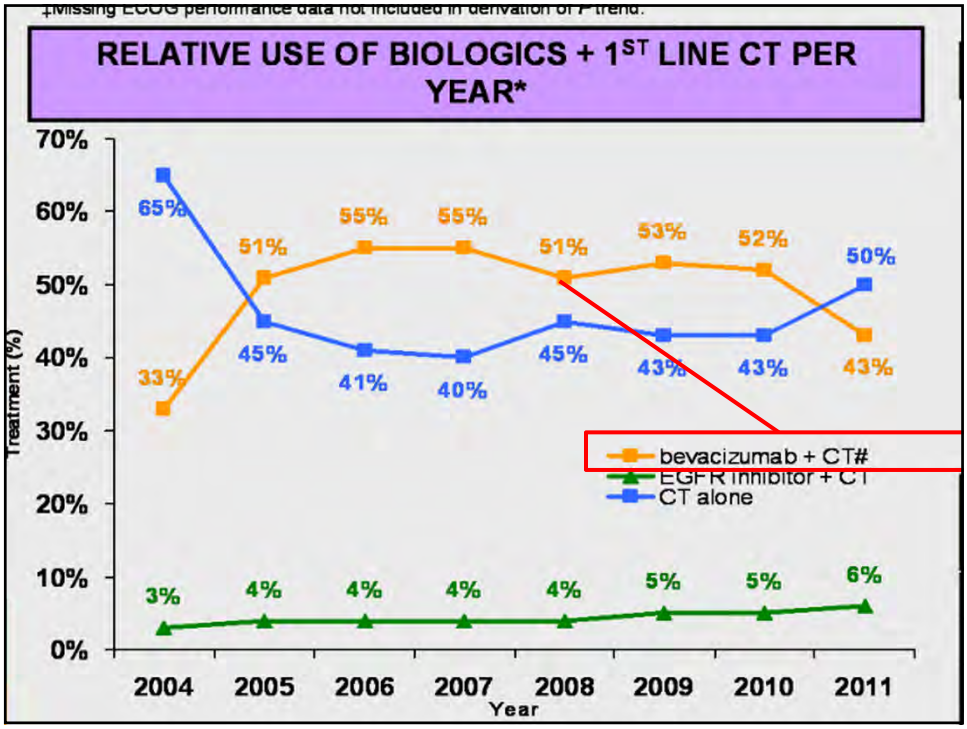
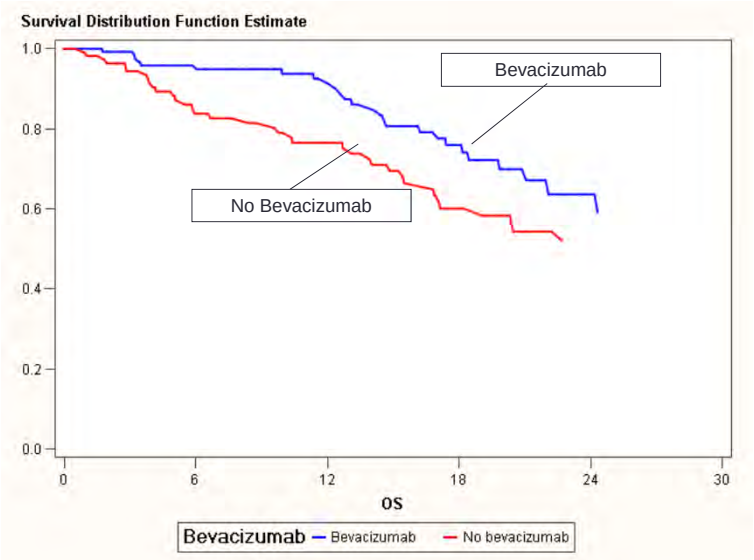
Bevacizumab Use In Australia (Chemotherapy Treated Patients)







Chemo Plus Bev vs CT Alone (p=0.034)



TRACC DATA

- Public and private data, 15 centres
- July 2009 – January 2013
- n = 885
- Median age 68.7 years

TRACC Cetuximab Data

	Patients	Chemotherapy (%)	Cetuximab (% of all)	Cetuximab (% of treated)
First line	885	694 (78%)	4 (0.4%)	4(0.6%)

TRACC Cetuximab Data

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3 were clinical trial patients

TRACC Cetuximab Data

	Pts	Treatment (%)	Cetuximab (% of all)	Cetuximab (% of treated)
2nd line	417	276 (66%)	20 (4.8%)	20 (7.2%)

111

TRACC Cetuximab Data

	Pts	Treatment (%)	Cetuximab (% of all)	Cetuximab (% of treated)
2nd line	417	276 (40%)	20 (4.8%)	20 (7.2%)

	Patients (%)
Combination	13 (65)
Single agent	7 (35)

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TRACC Cetuximab Data

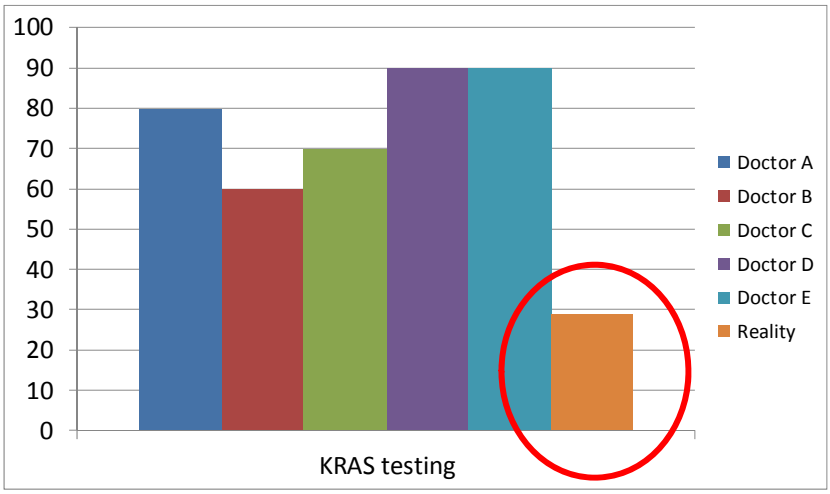
	Pts	Treatment (%)	Cetuximab (% of all)	Cetuximab (% of treated)
2nd line	417	276 (40%)	20 (4.8%)	20 (7.2%)

NO THIRD LINE DATA BEING COLLECTED

Combination	13 (65)
Single agent	7 (35)

How Many Patients Get KRAS tested?

Diagnosed from 1/2009, still alive at 7/2011
(508 of 631 alive at 2/2013)



Cetuximab Use In Australia

- Almost no first line use
  - Clinicians not convinced of the value?
  - Clinicians not comfortable asking patients to pay?
  - Patients not willing to pay?
- Practice will continue to evolve
  - 2nd line bevacizumab or aflibercept - ↓cetuximab
  - Effective salvage therapies e.g., regorafenib - ↑cetuximab
- How many patients should receive cetuximab?
  - Does keeping cetuximab till 3rd line mean many miss out?
  - Future studies need to explore how to optimise delivery of all active agents to our patients

PUBLIC VS PRIVATE PRACTICE IN AUSTRALIA

1. What are the differences?
2. What can we learn?

Conflicts of Interest - 1

- I work in a Private hospital

Conflicts of Interest - 2

- I work in a Public hospital

Private vs Public

Public hospital often perceived as

- “centres of excellence”,
- where optimal Rx choices => best outcome

- Multi-disciplinary care
- Sub-specialty management
- Evidence based medicine
- Peer review/audit
- Access to latest imaging modalities – e.g., MRI, PET
- Access to clinical trials

Private vs Public

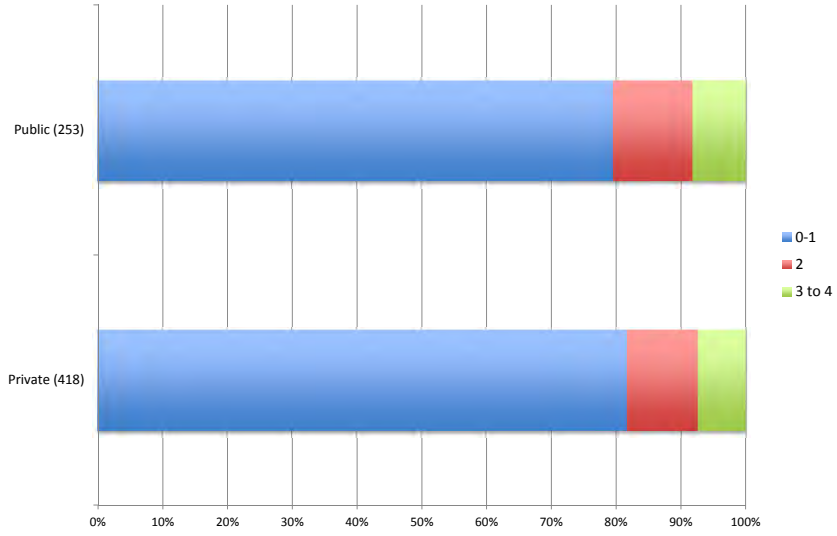
Advantages of the private system

- Continuity of care : An identifiable “Captain”
- Consultant management
- Ease and speed of investigations
- Ease and speed of treatment

TRACC priv v public: evaluable pts (n=677)

	Private	Public
n	420 (62%)	257 (38%)
Age - median	68.9 years	66.1 years
Age > 75 yrs	37 %	27 % (p=.0071)

TRACC priv v public: ECOG

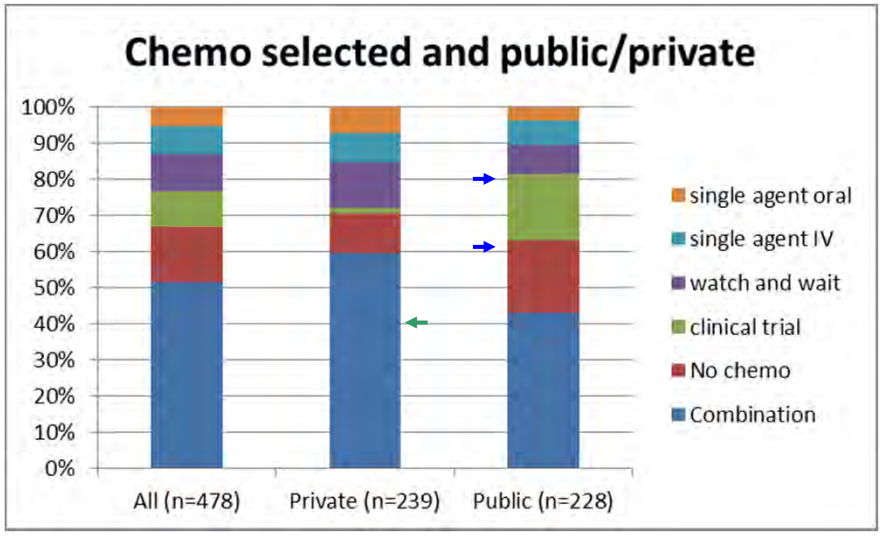


priv v public: PS 0-1: 82% v 80%, p=0.55

TRACC: no difference in Charlson co-morbidity scores

Charlson Score (age-unadjusted)	Private	Public	p value
0 (no comorbidity)	246 (59%)	156 (61%)	p=0.55
1 or more	174 (41%)	101 (39%)	p=0.63

Treatment – Private vs Public



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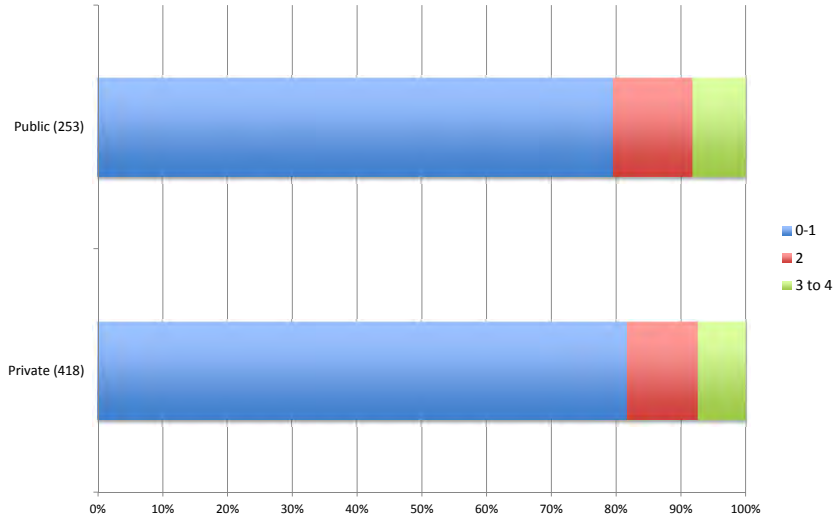

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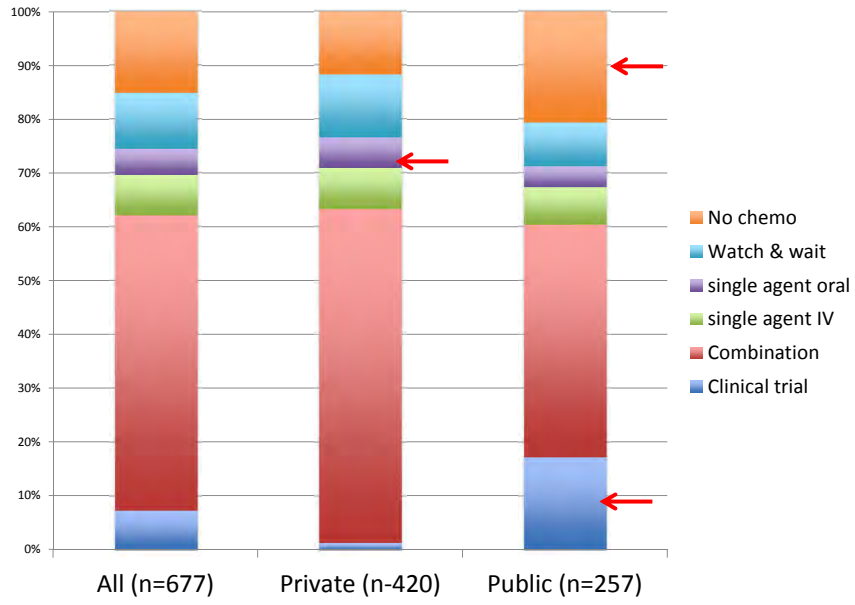
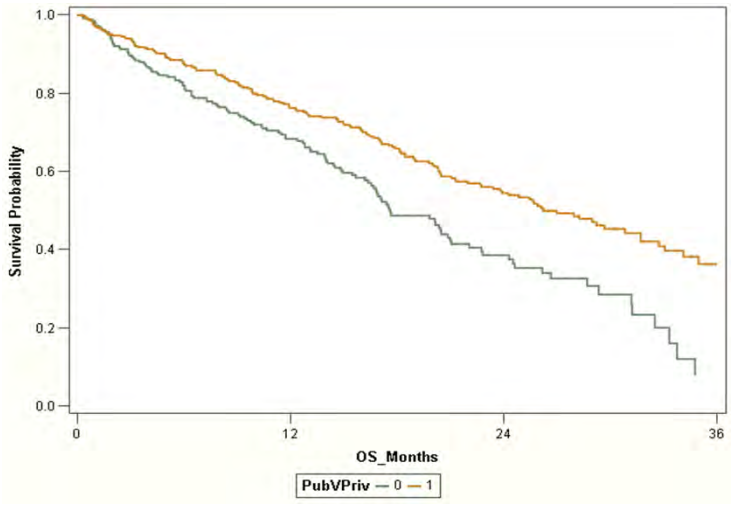
1st line choice of chemotherapy

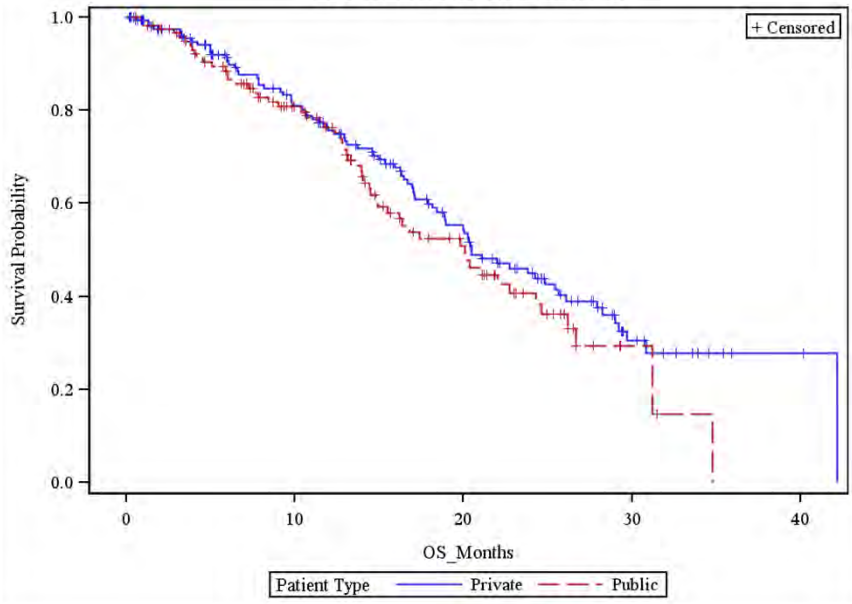


TRACC overall survival data



Med OS private v public pts
(26.2 v 17.6 months, HR 0.611 p<0.001)

Treatment With Combination Chemotherapy



Differing Patient Attitudes & Motivation?

Table 2. Cancer Diagnosis, Presentation, and Treatment

Characteristic	Private (n = 362) No.	%	Public (n = 1,568) No.	%	*P*
Adjuvant chemotherapy (stage II and III)					
Recommended	141	63	482	54	.003
Accepted	134	95	430	89	.007
Dose reduction	47	35	132	31	.521
Completed	122	91	347	81	.002
Unknown†	19	8	54	6	

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TRACC Database - Treatment Recurrent and Advanced Colorectal Cancer

- Funding for ongoing data collection recently confirmed
- A further 1500 patients
- 2013-2015
- Additional sites
- Additional data being collected

Summary

1. Epidemiology
2. Treatment of metastatic colorectal cancer
3. BioGrid
   - Value of comprehensive data collection
   - Value of linkage – internal, external
4. TRACC database
   - Public vs private
   - Chemotherapy use
   - Bevacizumab
   - Cetuximab

The end!