Adjuvant therapy for Endometrial Cancer

- Simon Pledge, Weston Park [1997-to the future and beyond]
  - Nothing to disclose
  - No financial connections

I hear and I forget.

I see and I remember.

I do and I understand.

Confucius

To understand the public, your patients

- "What do you understand so far?"
  - "Nothing"
  - "You're going to mop up any remaining cancer cells"
  - "Your going to blast any remaining cancer cells"
- Nobody has said I might kill or maim them…

BGCS Uterine Cancer Guidelines: Recommendations for Practice

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The remit of this guideline is to collate and propose evidence based guidelines for the diagnosis and management of uterine cancer. This document covers all uterine cancers of any histological type.

Hierarchy of evidence
Recommendations are graded as per the Royal College of Obstetricians and Gynaecologists document. Clinical Governance Advice No. 1: Guidance for the Development of RCOG Green-top Guidelines (available on the RCOG website at https://www.rcog.org.uk/globalassets/documents/guidelines/clinical-governance-advice/clinical-governance-advice-1c.pdf

See appendix for more details.

What is the risk?

Chi et al GOG. 2008

Only endometrioid and "adequately staged"

Retrospective over 12 years of FIGO stage 1 cases

1036 operations, 349 eligible. Recurrence rates:

	No invasion	Inner half	Outer half
Grade 1 (n=80)	0%	0%	0%
Grade 2 (n=182)	4%	7%	10%
Grade 3 (n=87)	0%	7%	28%

The simple bit

- Low risk, stage 1a grade 1-2
- ***Do nothing***
- Low risk of recurrence, less than 10%
- Hence over 9/10 patients can only be harmed…
- Less than 1/10 MIGHT (but may not) benefit

So you need the nodes to stage?…

- But in stage 1 disease that worsens outcomes…
  - ASTEC pre publication meeting…
- Possibly sentinel node as less morbid…in the future
- In advanced disease the evidence is poor
  - Fit patients more likely to have more done, so might they fare better because they were fitter?

So what *shall* we do?

- Hormones (Progesterone) can shrink some advanced endometrial cancers…
  - But 7 RCTs show no benefit in adjuvant context
  - Increases mortality due to cardiovascular toxicity

Radiotherapy

- Meta-analysis 3628 trial cases – no OS benefit
- Delays recurrence, alters pattern of recurrence
- suggested 10% DFS advantage 1cG3

Late Effects

- Portec 2 (compared EBRT v brachytherapy)
- Use of incontinence products 43% vs 15%
- Poorer QoL scores

- But could IMRT be less toxic?
- c.2015 £25 million (of £1.3billion – 2%)

- https://youtu.be/msX1ypCjkK4

What if you just follow up?

- Vaginal recurrence most common
- Portec 1: 39/714 had isolated vaginal recurrence
  - 35 treated with curative intent, 31 complete remission
  - 24 long term survivors, 5 had distant relapse
  - 5 year survival from relapse 65%

So, intermediate risk disease…

- Stage 1b G2, 1a G3 NO LVSI
- Remember recurrences not common!
- Brachytherapy
  - reduces recurrence,
  - rare seriously toxic

High-Intermediate risk

- 1A G3, G1/2 with LVSI
  - Nodes unknown – EBRT or brachy
  - Nodes negative - brachy or followup
- Do not forget NO overall survival advantage

High risk

- 1b G3
  - Radiotherapy vs Brachytherapy ?? Chemotherapy…

So what about chemotherapy?

- The adjuvant trials are “messy”
- Absolute benefit may be in range 1-8%
- Many real patients have comorbidities
- Drugs often toxic (platinum and anthracycline)
- BGCS “lack of significant long term toxicity”
- Grade 2 neuropathy 25% vs 6% in PORTEC 3

PORTEC 3

- Phase 3 RCT
  - Stage 1b/1a with LVSI, G3
  - Stage 2-3 endometriod
  - Stage 1-3 clear cell/serous
- Radiotherapy vs Radiotherapy and chemo
- 686 subjects, 660 eligible

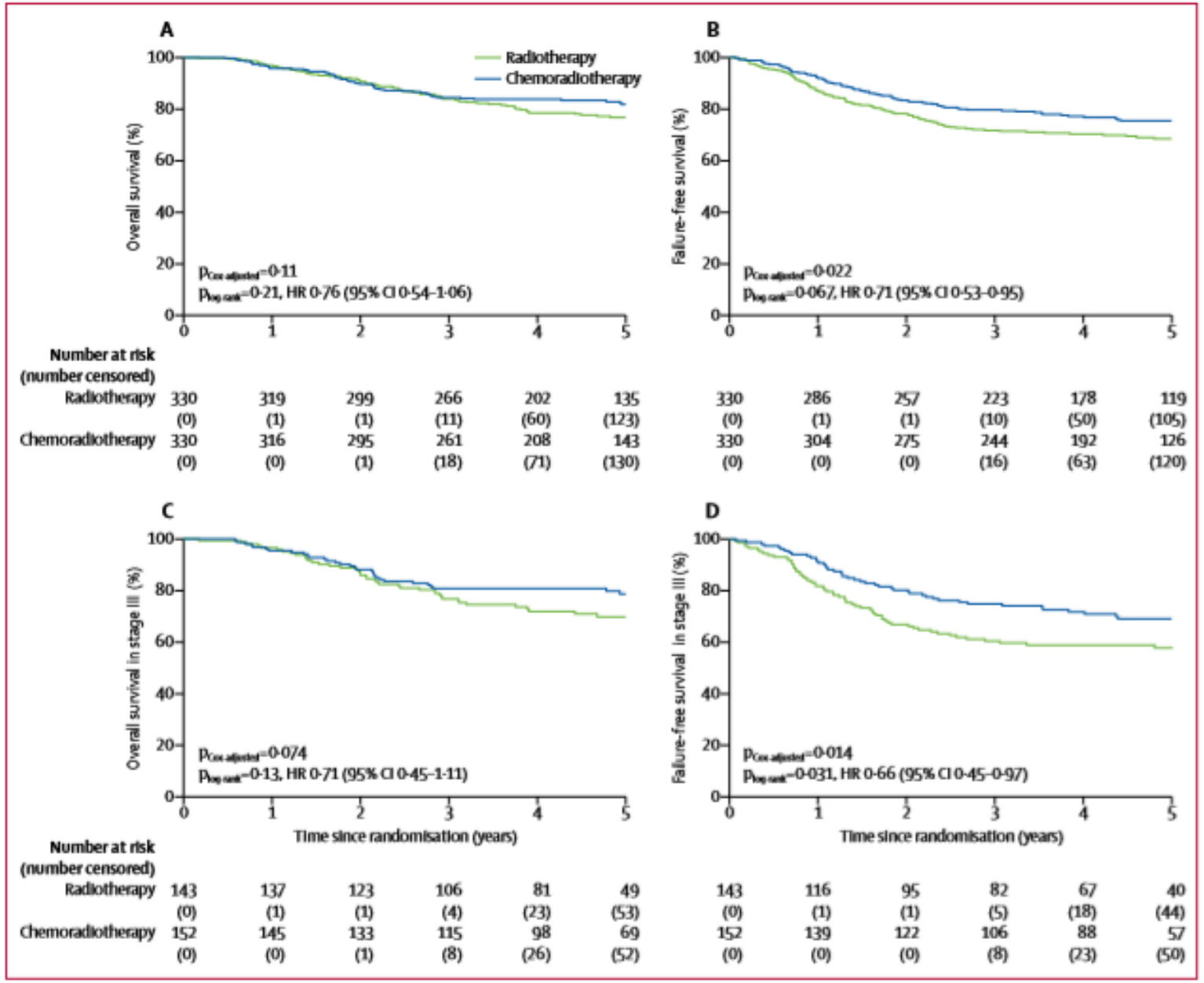

Figure 2: **Overall survival and failure-free survival**

Kaplan–Meier survival curves for overall survival (A) and failure-free survival (B) in all patients, and for overall survival (C) and failure-free survival (D) of patients with stage III endometrial cancer. $P_{log\ rank}$=unadjusted log-rank p value. $P_{Cox\ adjusted}$=p value adjusted for stratification factors. HR=hazard ratio.

	Grade 2			Grade 3–4		
	Chemoradiotherapy	Radiotherapy	p value*	Chemoradiotherapy	Radiotherapy	p value†
Any	110 (33%)	103 (31%)	<0·0001	198 (60%)	41 (12%)	<0·0001
Any grade 3	NA	NA	..	148 (45%)	41 (12%)	..
Any grade 4	NA	NA	..	50 (15%)	0	..
Auditory or hearing	14 (4%)	3 (1%)	0·011	1 (<1%)	1 (<1%)	1·00
Allergy	23 (7%)	1 (<1%)	<0·0001	5 (2%)	0	0·062
Fatigue	69 (21%)	7 (2%)	<0·0001	10 (3%)	0	0·0018
Hypertension	19 (6%)	12 (4%)	0·14	6 (2%)	3 (1%)	0·50
Alopecia	187 (57%)	1 (<1%)	<0·0001	NA	NA	..
Dermatitis	18 (5%)	5 (2%)	0·013	1 (<1%)	1 (<1%)	1·0
Any gastrointestinal	145 (44%)	79 (24%)	<0·0001	47 (14%)	18 (5%)	<0·0001
Diarrhoea	104 (32%)	69 (21%)	<0·0001	35 (11%)	14 (4%)	0·0027
Nausea	68 (21%)	24 (7%)	0·0010	9 (3%)	2 (1%)	0·06
Vomiting	31 (9%)	9 (3%)	<0·0001	5 (2%)	0	0·06
Anorexia	30 (9%)	9 (3%)	0·0033	3 (1%)	4 (1%)	1·00
Constipation	32 (10%)	6 (2%)	<0·0001	1 (<1%)	0	1·00
Genito-urinary: frequency or urgency	24 (7%)	10 (3%)	0·020	2 (1%)	2 (1%)	1·00
Any haematological	100 (30%)	19 (6%)	<0·0001	149 (45%)	18 (5%)	<0·0001
Febrile neutropenia	NA	NA	..	9 (3%)	1 (<1%)	0·021
Infection with neutropenia	3 (1%)	0	0·0018	7 (2%)	0	0·015
Infection without	21 (6%)	1 (<1%)	<0·0001	12 (4%)	1 (<1%)	<0·0001

Combination chemo

- Something vs nothing ? benefit
- Something vs Something else ? Side effects
- Single most active drug – platinum
- Balance toxicity and efficacy

What about the non-endometriod

- Smaller numbers usually mean less evidence
- Uterine serous 10% (39% of deaths uterine Ca)
- Limited invasion still associated with spread
- *Retrospective* studies show more surgery=better
- Radiotherapy no OS/DFS benefit
- Chemotherapy no benefit in 1a

What about the non-endometriod

- Smaller numbers usually mean less evidence
- Clear cell 5% (8% of deaths uterine Ca)
- Slower, not too bad if early so no adjuvant Rx
- Often poor response to treatment in recurrence
- BGCS guidance quotes grade C evidence only

What about the non-endometriod

- Smaller numbers usually mean less evidence
- Carcinosarcoma 8% - not really sarcomas
- Behave like grade 3 carcinoma
- Can respond well but relapse quickly
- BGCS guidance quotes grade C/D evidence only

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Confucius

To understand the problem…

- The disease types, stages, risks of recurrence
- The reactions of individuals and families told of recurrence
- The burden of the treatments, the chance of benefit
- The late effects, the failure to prevent

To understand the (healthcare) system…

- Both your responsibilities to the patient
- And to use resources wisely
- Recognise not all who speak have the same system
- Recognise Publication bias
- Why do we get free lunches?