Are we radical enough in fully staged intermediate risk endometrial cancer patients?

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Some definitions

Risk group	GOG-99 criteria*	Simplified criteria†
Low-risk	IA	IA
Intermediate-risk	IB, IC, II	IB, II
LIR group	Age ≤50 yr +≤2 pathologic risk factors‡ Age 50–69 yr +≤1 pathologic risk factor Age ≥70 yr +no pathologic risk factors	No pathologic risk factors§
HIR group	Any age +3 pathologic risk factors‡ Age 50–69 yr +≥2 pathologic risk factors Age ≥70 yr +≥1 pathologic risk factor	Any age +≥1 pathologic risk factor§
High-risk	III, IV	

GOG, Gynecologic Oncology Group; HIR, high-intermediate risk; LIR, low-intermediate risk.

*Based on 1988 International Federation of Gynecology and Obstetrics (FIGO) staging system. †Based on 2009 FIGO staging system. ‡(1) Grade 2 or 3 histology; (2) positive lymphovascular space invasion; (3) myometrial invasion to outer 1/3. §(1) Grade 2 or 3 histology; (2) positive lymphovascular space invasion.

ESMO Stage 1 Risk Groups

Low risk:	Stage IA (G1 and G2) with endometrioid type
Intermediate risk:	Stage IA G3 with endometrioid type
	Stage IB (G1 and G2) with endometrioid type
High risk:	Stage IB G3 with endometrioid type
	all stages with non-endometrioid type

Why is this even a question?

CANCER RESEARCH UK

Estimated number of new cases of u

2,963 females

Estimated % of all new female cases

4.7%

Estimated number of deaths from ut

466 females

Estimated % of all female deaths fro

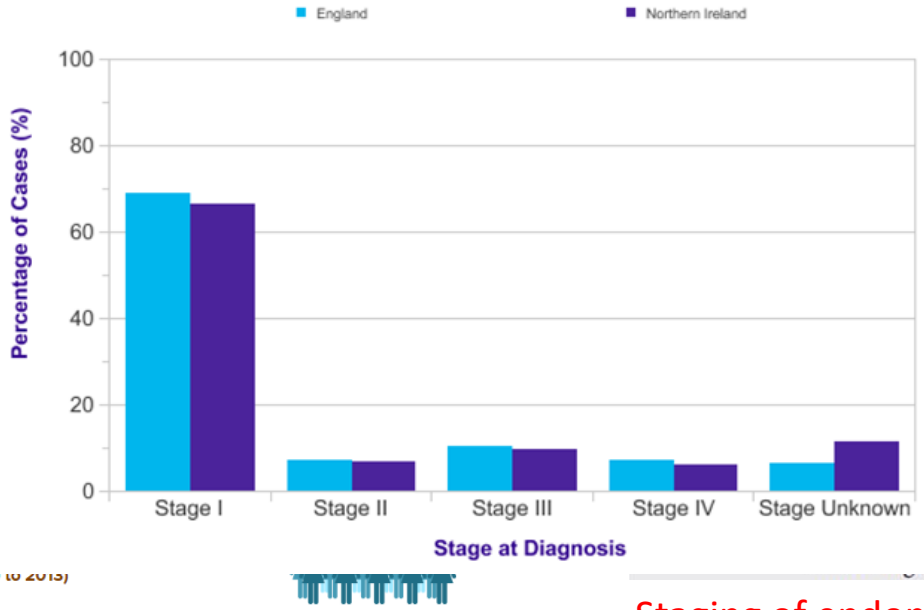
2.2%

Chance of surviving at least 5 years

83%

Females living with uterine cancer a
(diagnosed in the 5 year period 2009 to 2013)

10,036



the corpus uteri
myometrial invasion
more than half of the myometrium
ical stroma, but does not extend beyond

l spread of the tumour
serosa of the corpus uteri and/or

netrial involvement
nd/or para-aortic lymph nodes

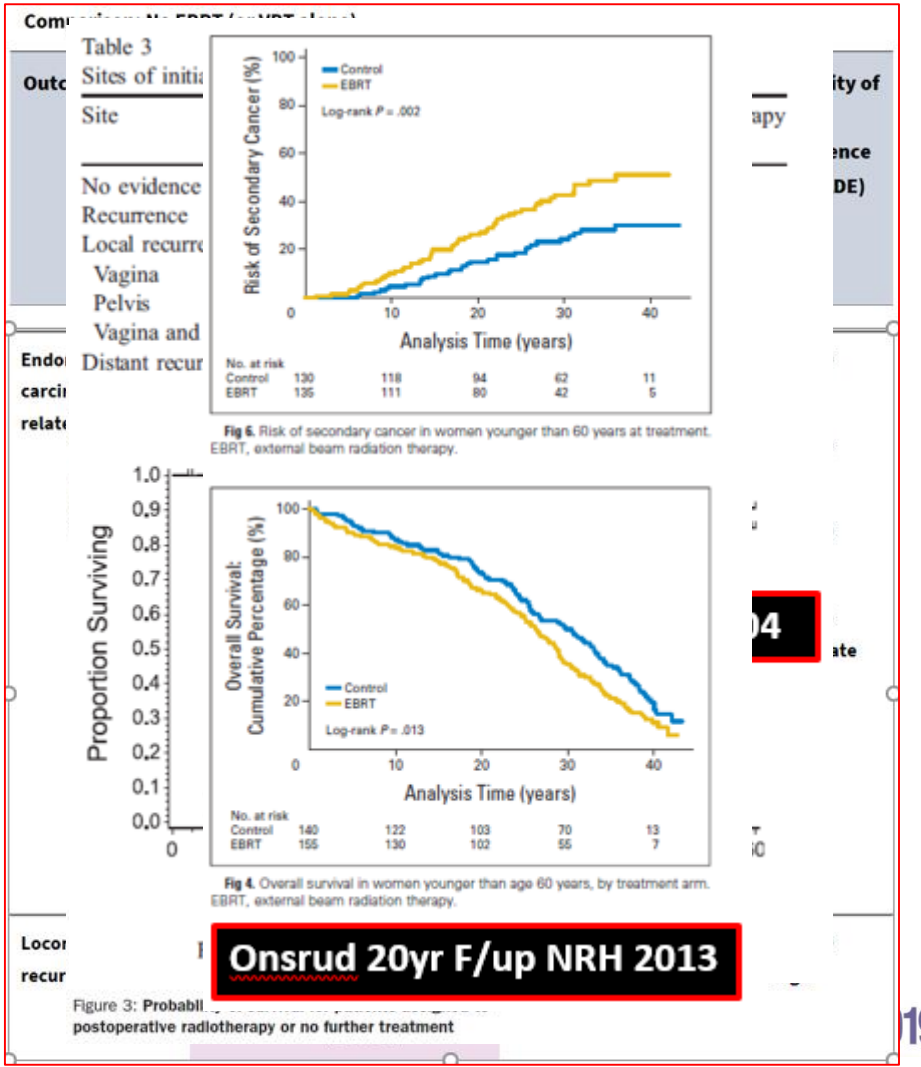
ymph nodes with or without positive
s
lder and/or bowel mucosa, and/or

bladder and/or bowel mucosa
ncluding intra-abdominal metastases
mph nodes

Staging of endometrial cancer (FIGO 2009)

We have learnt…

1. Randomised trials adjuvant radiation therapy in early stage endometrial cancer;
   - Improved loco-regional control, relapse-free survival
   - No significant impact on cancer-related deaths or overall survival
   - Associated with morbidity and negative impact on QOL
     - Increased second cancers
     - Possible reduced survival
2. Meta-analyses (Cochrane 2012)
   - Confirms and strengthens



Local control matters

- Surveillance with regular pelvic examinations and vaginal vault smears associated with anxiety (for patients and healthcare workers)
  - Even with surveillance 40-80% recurrences are associated with symptoms
- Vaginal recurrence associated with bleeding and pelvic mass effects
- Pelvic recurrence associated with pain, lower limb oedema, visceral obstruction

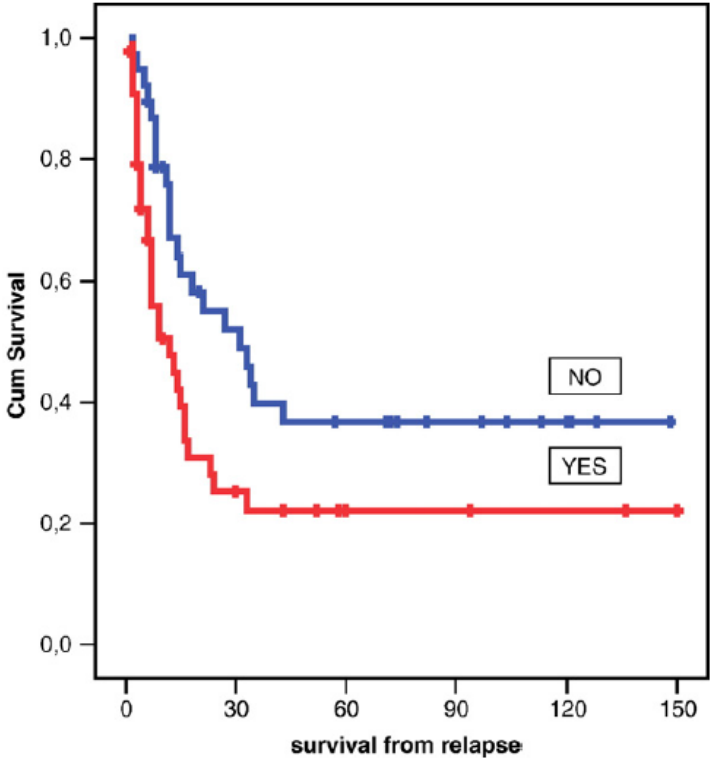


Fig. 2. Overall survival from relapse (OSFR) by symptoms at recurrence in endometrial cancer patients.

And salvage is not simple

Categories

1. Recurrence with no previous RT
   - Isolated vaginal vault recurrence
   - Isolated pelvic recurrence
   - Other recurrence
     - Isolated para-aortic
     - Distant
2. Recurrence with previous RT

Management

EBRT +/- brachytherapy
- Reasonable local control
- 5 yr OS 50-90%
- Large volumes, large doses, significant treatment morbidity

EBRT +/- brachytherapy
- Outcomes substantially worse

- Post op … e best lim … aginal risk loc… RT >15%
- In those … nferior) stage 1 … vaginal with th… ry for early (and hig… high … uced

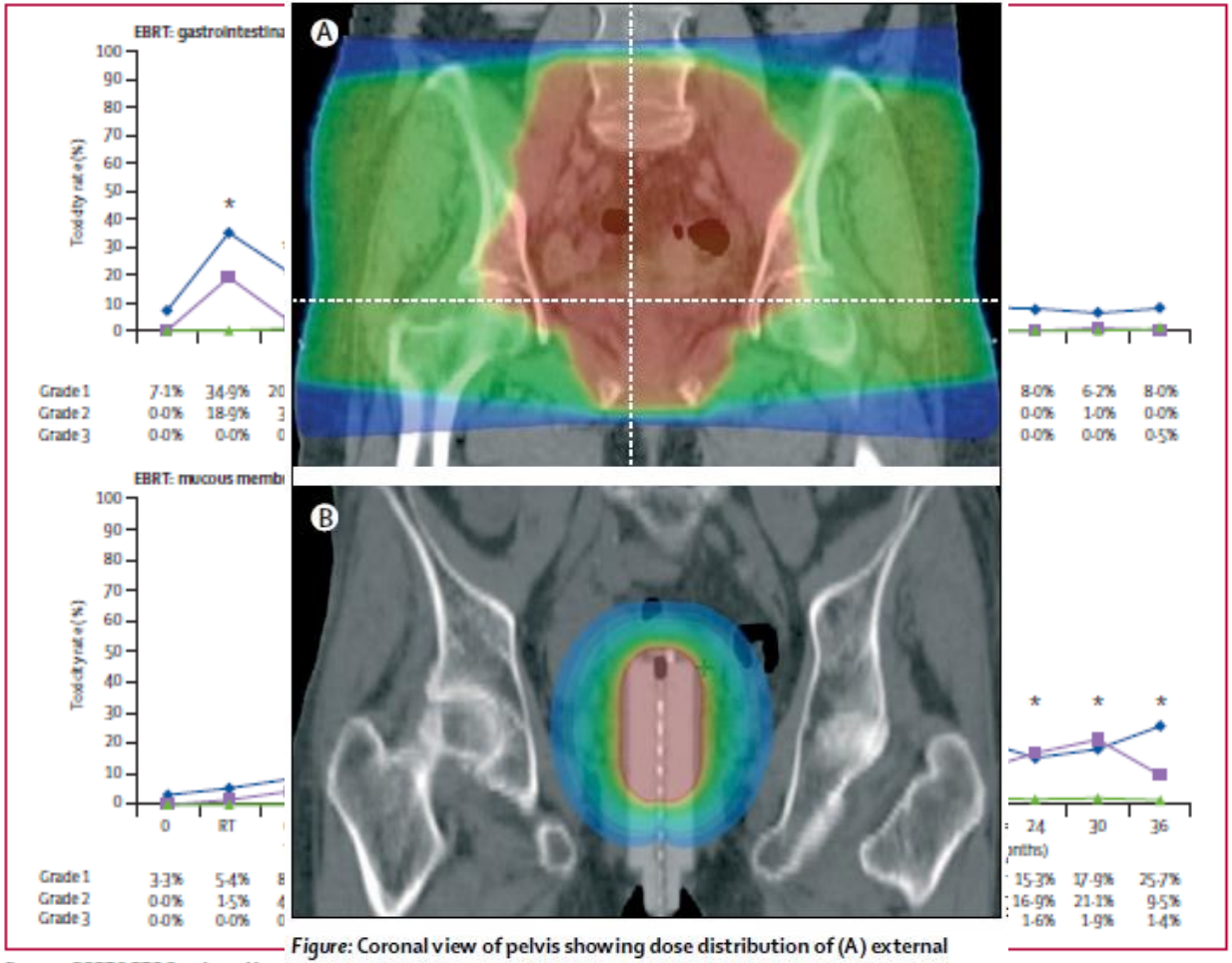


Figure 3: EORTC-RTOG early and late

Figure: Coronal view of pelvis showing dose distribution of (A) external beam radiotherapy and (B) vaginal brachytherapy
Red=high dose. Blue=low dose.

Table 2. Acute and late vaginal toxicity after adjuvant high dose rate (HDR) vaginal brachytherapy (21 Gy delivered in three fractions)

Grading	Acute toxicity			
	G1	G2	G3	Any G
Vaginal inflammation	14	4	0	18 (14.3%)
Dyspareunia	6	1	0	7 (5.5%)
Hemorrhage	0	1	0	1 (0.8%)
All	20 (15.8%)	6 (4.8%)	0 (0%)	26 (20.6%)
Grading	**Late Toxicity**			
	G1	G2	G3	Any G
Dryness	4	2	0	6 (4.8%)
Telangiectasias	6	1	0	7 (5.5%)
Fibrosis	13	1	0	14 (11.1%)
Stenosis	2	0	0	2 (1.6%)
All	25 (19.9%)	4 (3.1%)	0	29 (23.0%)

- Acute endovaginal toxicity occurred in less than 20.6%

Review Papers

Review paper

Vaginal toxicity after high-dose-rate endovaginal brachytherapy: 20 years of results

Durim Delishaj, MD[1], Amelia Barcellini, MD[2], Romerai D'Amico, MD[1], Stefano Ursino, PhD[3], Francesco Pasqualetti, PhD[3], Ilaria Costanza Fumagalli, MD[1], Carlo Pietro Soatti, MD[1]

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itching, bleeding, fibrosis, telangiectasias, stenosis, short or narrow vagina, and dyspareunia.

Table 2. Summary of acute and late vaginal toxicities after high-dose-rate endovaginal brachytherapy in patients with low/intermediate-risk endometrial cancer

Author (year)	Acute vaginal toxicity			Late vaginal toxicity			Score used
	G1-G2 (%)	G3-G4 (%)	Type of toxicities	G1-G2 (%)	G3-G4 (%)	Type of toxicities	
Laliscia *et al.* [56] (2016)	20.6	0	Vaginal inflammation Dyspareunia	23	0	Fibrosis Telangiectasias Dryness Stenosis	CTCAE v. 4.2
(2014)						Stenosis Dryness	
Rovirosa *et al.* [38] (2012)	10.9	0	–	24.9	0.09	Stenosis	RTOG/EORTC
Nout *et al.* [6] (2010)	25.2	0	–	–	2	Atrophy Stenosis Shortening or narrowing	EORTC-RTOG

RTOG – Radiation Therapy Oncology Group; NCI – National Cancer Institute; CTCAE – common terminology criteria for adverse events; EORTC – European Organization for Research and Treatment of Cancer; LENT – late effects normal tissue task force; SOMA – subjective, objective, management, analytic scale

ESMO Surgical & Adjuvant treatment Stage 1

Surgery

Stage I	I A G1–G2	Hysterectomy with bilateral salpingo-oophorectomy
	I A G3	Hysterectomy with bilateral salpingo-oophorectomy ± bilateral pelvic-para-aortic lymphadenectomy
	I B G1 G2 G3	Hysterectomy with bilateral salpingo-oophorectomy ± bilateral pelvic-para-aortic lymphadenectomy

Radiation Therapy

Stage I	I A G1–G2	Observation
	IA G3	Observation or vaginal BT - If negative prognostic factor pelvic RT and/or adjunctive chemotherapy could be considered
	I B G1 G2	Observation or vaginal BT - If negative prognostic factor pelvic RT and/or adjunctive chemotherapy could be considered
	IB G3	Pelvic RT - If negative prognostic factor: combination of radiation and chemotherapy could be considered

Are we radical enough in fully staged intermediate risk endometrial cancer patients?

- Considering knowledge of the natural history of disease, and the impact of treatment options available,
  - Does current treatment meet aim of maximal benefit and minimal harm?
- **I think it does – so we appear to be RADICAL ENOUGH**
- The risk of isolated distant failure remains a problem - for high grade deeply invasive stage 1 patients

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Faculty Disclosure

X	No, nothing to disclose
	Yes, please specify:

	Honoraria/ Expenses	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership / Equity Position*	*Employee*	*Other (please specify)*

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