MaNGO
Mario Negri Gynecologic Oncology

XVIII ASSEMBLEA MANGO

Ricerca Clinica e Traslazionale in Ginecologia Oncologica

MILANO, 2-3 LUGLIO 2021

Con il Patrocinio di:

AIOM Associazione Italiana di Oncologia Medica

FICOG | Federation of Italian Cooperative Oncology Groups

SOCIETA' ITALIANA DI CANCEROLOGIA

SIGO SOCIETA' ITALIANA DI GINECOLOGIA E OSTETRICIA

ACTO ALLEANZA CONTRO IL TUMORE OVARICO

Intensive versus minimalist follow-up in patients treated for endometrial cancer: A multicentric randomized controlled trial ***The TOTEM study*** - NCT00916708

Paolo Zola

Gynecologic Oncology Unit, Dep. Surgical Sciences, University Of Turin, Italy

MaNGO Multicentric Network Gynecologic Oncology

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TOTEM trial

History and developement of a prospective randomized clinical trial

Background

- Endometrial cancer recurs in less than 20% of cases
- Most recurrences (70–95%) occur within three years from initial treatment
- Recurrence is often symptomatic (40-91%)

Follow-up

- Group of pre-defined procedures scheduled to monitoring patients after primary treatment
- Match point where the needs of physician, patient and Health Care System meet and generate expectations

Background

1. The guidelines focusing on follow-up, available in the early 2000s, were contradictory and the follow-up schemes adopted by the centers were heterogeneous

Guidelines Endometrial cancer		Pap test	Chest x-ray	US abdomen-pelvi	CT scan abdomen-pelvi	Ca 125
NCCN *2013*		**Controversial**	**Every year**	No	No	**Optional**
ACOG *2005 reaffirmed 2009*		No	No	No	No	No
AGO *2009*		No	No	**3 mos till the third year**	No	No
CCO *2006*		No	No	No	No	No
ESMO *2011*		No	No	No	No	No
SGO *2011*		No	No	No	No	No

Background

1. The guidelines focusing on follow-up, available in the early 2000s were contradictory and the follow-up schemes adopted by the centers were heterogeneous
2. Only retrospective trials were available, no RCT

International Journal of Gynecological Cancer • Volume 20, Number 6, August 2010

ORIGINAL ARTICLE

The Value of Gynecologic Cancer Follow-Up

Evidence-Based Ignorance?

Henrik Lajer, PhD, Mette B. Jensen, PhD,† Jannie Kilsmark, Cand. Oecon.,† Jens Albæk, PhD,† Danny Svane, PhD,* Mansoor R. Mirza, MD,* Poul F. Geertsen, PhD,‡ Diana Reerman, MSc,§ Kåre Hansen, MSc,§ Maya C. Milter, MSc,§ and Ole Mogensen, DSc¶*

Gynecologic Oncology 129 (2013) 324–331

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Follow-up practice in endometrial cancer and the association with patient and hospital characteristics: A study from the population-based PROFILES registry

Kim A.H. Nicolaije [a,b,*], Nicole P.M. Ezendam [a,b], M. Caroline Vos [c], Dorry Boll [d], Johanna M.A. Pijnenborg [d], Roy F.P.M. Kruitwagen [e], Marnix L.M. Lybeert [f], Lonneke V. van de Poll-Franse [a,b]

[a] CoRPS — Center of Research on Psychology in Somatic Diseases, Department of Medical and Clinical Psychology, Tilburg University, The Netherlands
[b] Eindhoven Cancer Registry, Comprehensive Cancer Center South (CCCS), The Netherlands

AOGS ACTA Obstetricia et Gynecologica Scandinavica

ACTA REVIEW

Follow-up routines in gynecological cancer – time for a change?

INGVILD VISTAD[1], BIRGIT W MOY[1], HELGA B SALVESEN[2,3] & ASTRID H LIAVAAG[4]

[1]Department of Obstetrics and Gynecology, Sorlandet Hospital HF, Kristiansand, [2]Institute of Clinical Medicine, University of Bergen, [3]Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, and [4]Department of Obstetrics and Gynecology, Sorlandet Hospital HF, Arendal, Norway

REVIEW ARTICLE

Surveillance Procedures for Patients Treated for Endometrial Cancer

A Review of the Literature

Enrico Sartori, MD, Brunella Pasinetti, MD,* Francesca Chiudinelli, MD,* Angiolo Gadducci, MD,† Fabio Landoni, MD,‡ Tiziano Maggino, MD,§ Elisa Piovano, MD,|| and Paolo Zola, MD||*

BMJ open

Gynaecological cancer follow-up: national survey of current practice in the UK

Simon Leeson,[1] Nick Stuart,[2] Yvonne Sylvestre,[3] Liz Hall,[1] Rhiannon Whitaker[3]

To cite: Leeson S, Stuart N, Sylvestre Y, *et al*. Gynaecological cancer follow-up: national survey of current practice in the UK. *BMJ Open* 2013;**3**:e002859. doi:10.1136/bmjopen-2013-002859

ABSTRACT

Objective: To establish a baseline of national practice for follow-up after treatment for gynaecological cancer.
Design: Questionnaire survey.
Setting: Gynaecological cancer centres and units.
Geographical location: UK.
Participants: Members of the British Gynaecological

ARTICLE SUMMARY

Article focus

- Follow-up after treatment for cancer is a resource-intense area of clinical practice which does not have clear benefits for patients.
- Doctors and nurses involved in care for women

AOGS MAIN RESEARCH ARTICLE

Follow-up of gynecological cancer patients after treatment – the views of European experts in gynecologic oncology

INGVILD VISTAD[1], MILADA CVANCAROVA[2] & HELGA B. SALVESEN[3,4]

[1]Department of Obstetrics and Gynecology, Sorlandet Hospital HF, Kristiansand, [2]National Resource Center for Late Effects, Department of Oncology, Oslo University Hospital and University of Oslo, Oslo, [3]Institute of Clinical Medicine, University of Bergen, Bergen, and [4]Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway

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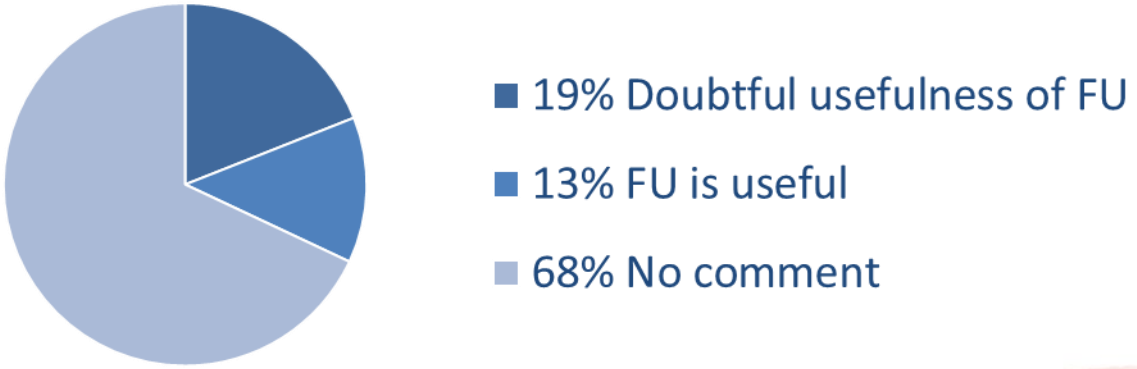
Background

1. The guidelines focusing on follow-up, available in the early 2000s were contradictory and the follow-up schemes adopted by the centers were heterogeneous
2. Only retrospective trials were available, no RCT
3. Gynecologists' attitude



G.Favalli unpublished data 2000

AOGS MAIN RESEARCH ARTICLE

Follow-up of gynecological cancer patients after treatment – the views of European experts in gynecologic oncology

INGVILD VISTAD[1], MILADA CVANCAROVA[2] & HELGA B. SALVESEN[3,4]

[1]*Department of Obstetrics and Gynecology, Sorlandet Hospital HF, Kristiansand,* [2]*National Resource Center for Late Effects, Department of Oncology, Oslo University Hospital and University of Oslo, Oslo,* [3]*Institute of Clinical Medicine, University of Bergen, Bergen, and* [4]*Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway*

Table 3. Surveillance tests applied routinely at follow-up examinations according to cancer type. All values are given as percentages.

Routine tests	TVU	CA125	Other blood tests	CT	MRI	Cyt
Ovarian cancer	59	76	17	15	4	13
Endometrial cancer	56	20	18	12	4	37
Cervical cancer	49	4	23	13	9	56
Vulvar cancer	20	7	19	8	4	2

CA125, cancer antigen 125; CT, computer tomography; Cyt, cytological examination of smear; MRI, magnetic resonance imaging; TVU, transvaginal ultrasound.

Background

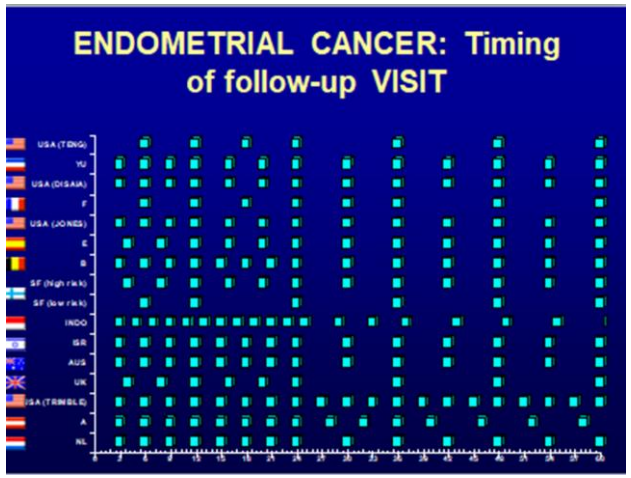
1. The guidelines focusing on follow-up, available in the early 2000s were contradictory and the follow-up schemes adopted by the centers were heterogeneous
2. Only retrospective trials were available, no RCT
3. Gynecologists' attitude
4. International survey by G. Favalli

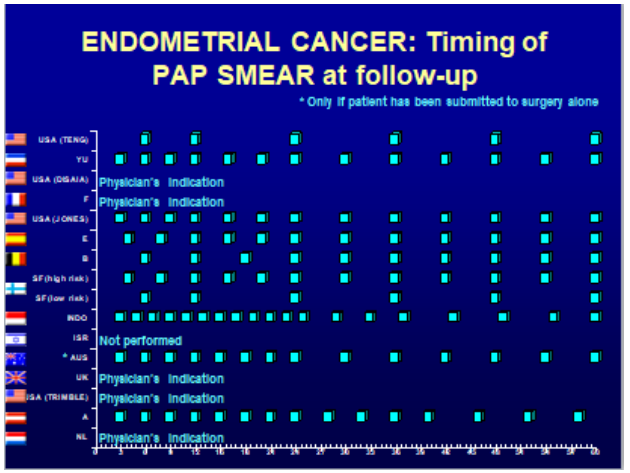
Follow-up

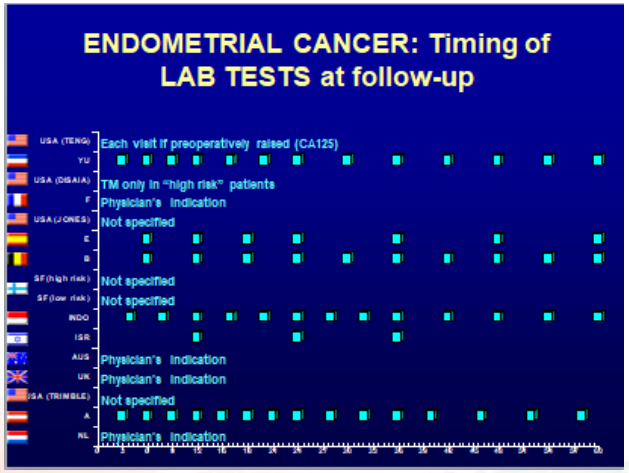
- G. Favalli performed an international survey in the early 2000s to evaluate follow-up variability

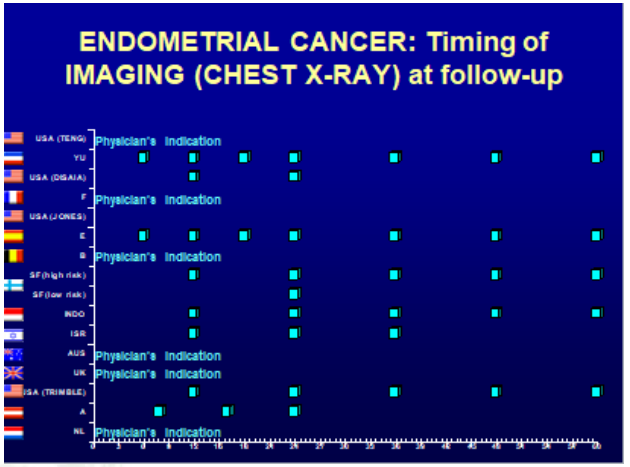
G. Kenter, Leiden (NL)
R. Winter, Graz (A)
E. Trimble, Bethesda (USA)
R. Gordon, London (UK)
N. Hacker, Sidney (AUS)
G. Ben-Baruch, Tel Ashomer (Israel)
F. Sahil, Medan (Indonesia)
J. Puolakka, Jyvaskyla, (SF)
I. Vergote, Leuven (B)
M. Jurado, Pamplona (E)
H. Jones III, Nashville (USA)
A. Floquet, Bordeaux (F)
P. DiSaia, Orange (USA)
V. Kesic, Beograd (YU)
N. Teng, Stanford (USA)

International survey by G. Favalli









Strong international variability!

Follow-up today

A problem of public health

WISHED PRACTICE

- Standardized
- Reproducible among different institutions
- Effective surveillance

≠

THE PRACTICE

International Variability

Does this varibility exist among Italian Institutions?

Retrospective multicentric italian CTF study: RESULTS

POPULATION

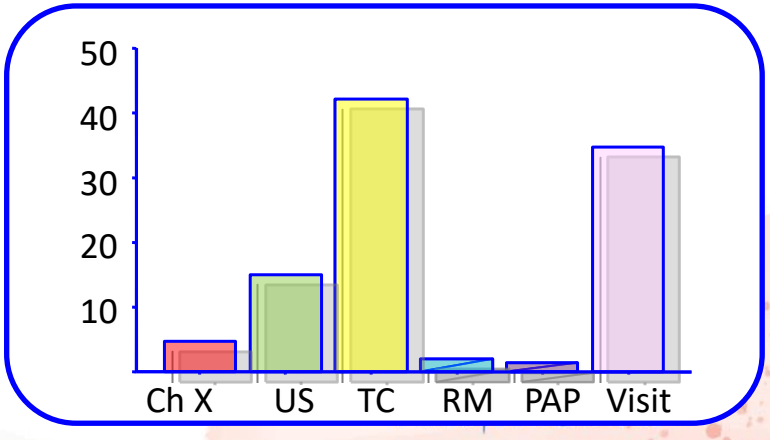
TOT: 1120 patients

- Endometrium: 282
- Cervix: 327
- TMEO: 419
- Vulva: 92

Institutions follow up protocols for Endometrial cancer (First 2 years of surveillance)

center	visit	Papsmear	US	TC	ChX	Ca125	
A	3m	1y					→ Minimalist FU
B	3m	3m		2y	1y		→ Intensive FU
C	6m	6m	6m	6m		6m	→ Intensive FU
D	4m	6m			6m		→ Intensive FU
E	6m	6m	6m		1y		→ Intensive FU
F	3m	+ colpo3m	3m	1y		3m	→ Intensive FU
G	3m	3m	3m	1y	6m		→ Intensive FU
H	3m	+colpo3m		1y	1y		→ Intensive FU

- Asymptomatic: 52.1 %
- Symptomatic + anticipate scheduled visit of follow-up: 13.1%
- Symptomatic: 32.9%



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Most of recurrences were found in asymptomatic patients

ENDOMETRIUM

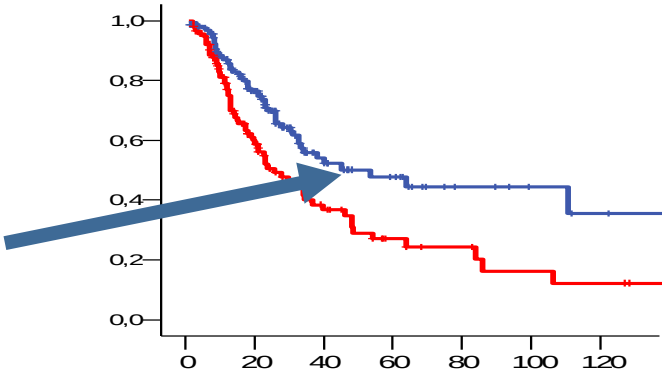
CERVIX

OVARY

VULVA

Endometrial & Cervical Cancer :

- Asymptomatic patients gain in survival



Ovarian & Vulvar Cancer :

- No difference in terms of survival in being Asymptomatic or Symptomatic at time of relapse

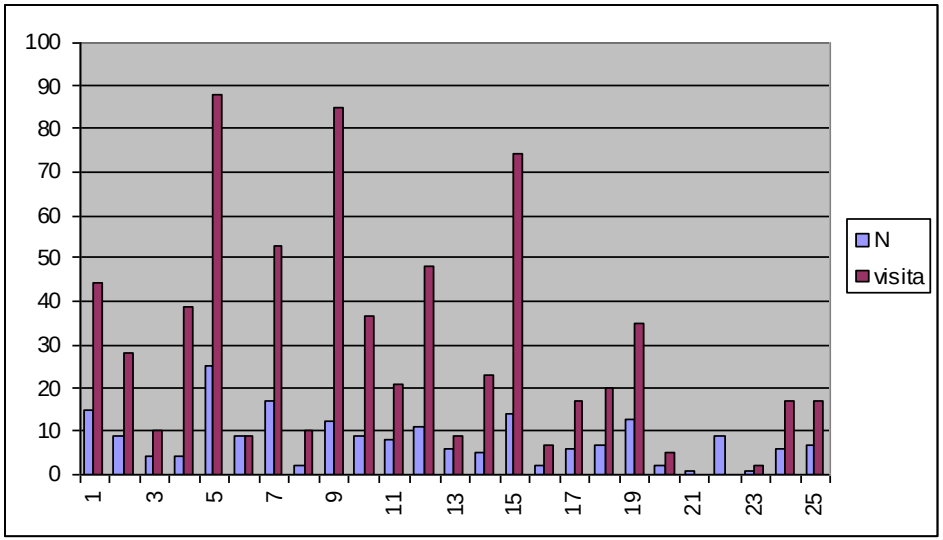
- In case of ovarian cancer VISIT, TC and Ca 125 started diagnostic pathway in most of recurrences

Variability was observed on an internazional level by G.Favalli and on a nazional level by CTF study:

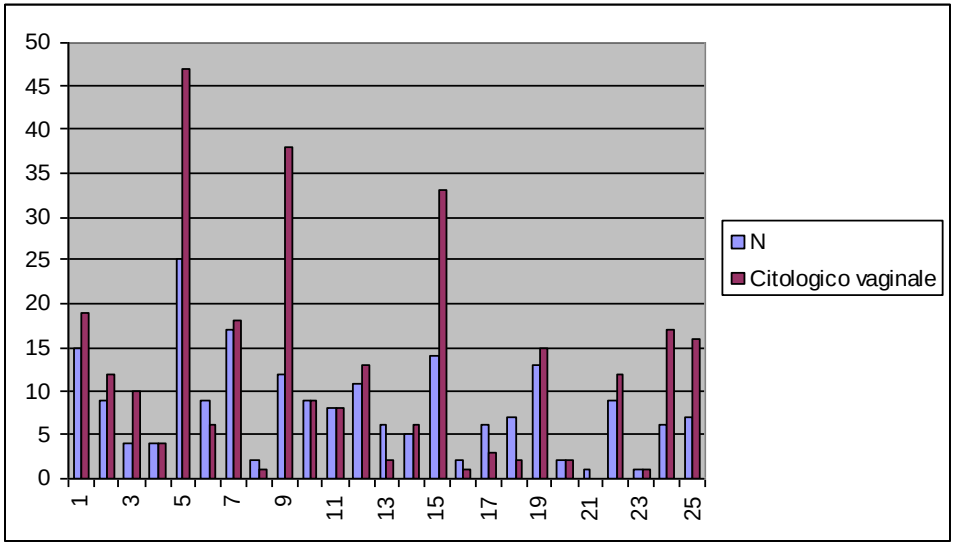
Does it exist on a regional level too?

Oncologic Network Piemonte-Valle d'Aosta study

Endometrial Cancer - Visit

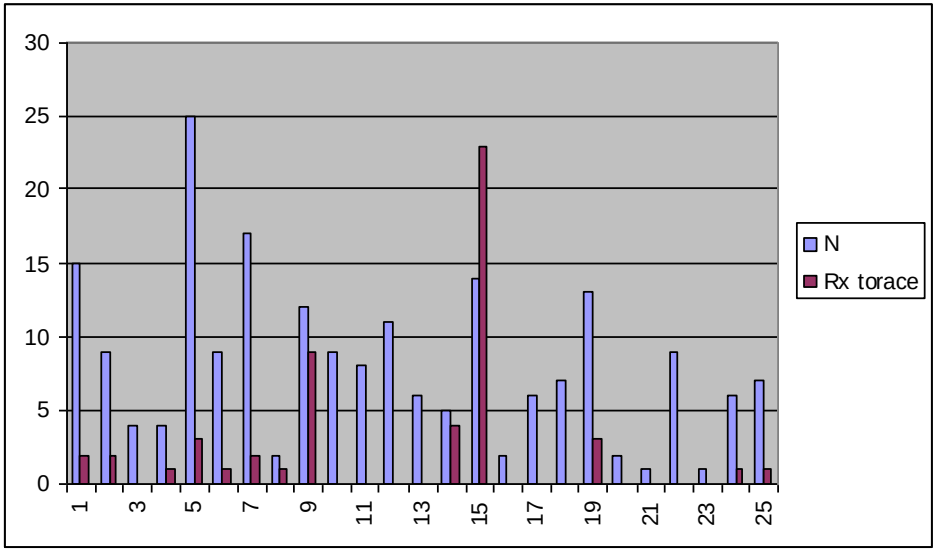


Endometrial cancer – Pap smear

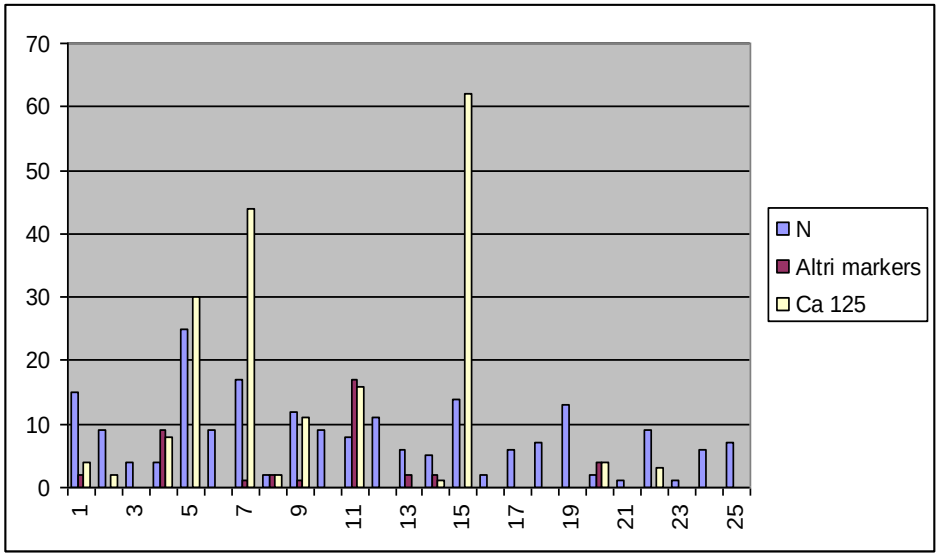


Heterogeneity in schedule of exams in Piemonte-Valle d'Aosta

Endometrial cancer – Chest Rx



Endometrial cancer – Ca125 & other markers



Pathway to TOTEM

International Survey by G.Favalli (unpublished data 2000)

↓

Retrospective multicentric Italian CTF study

↓

Oncologic network Piemonte - Valle d'Aosta study

↓

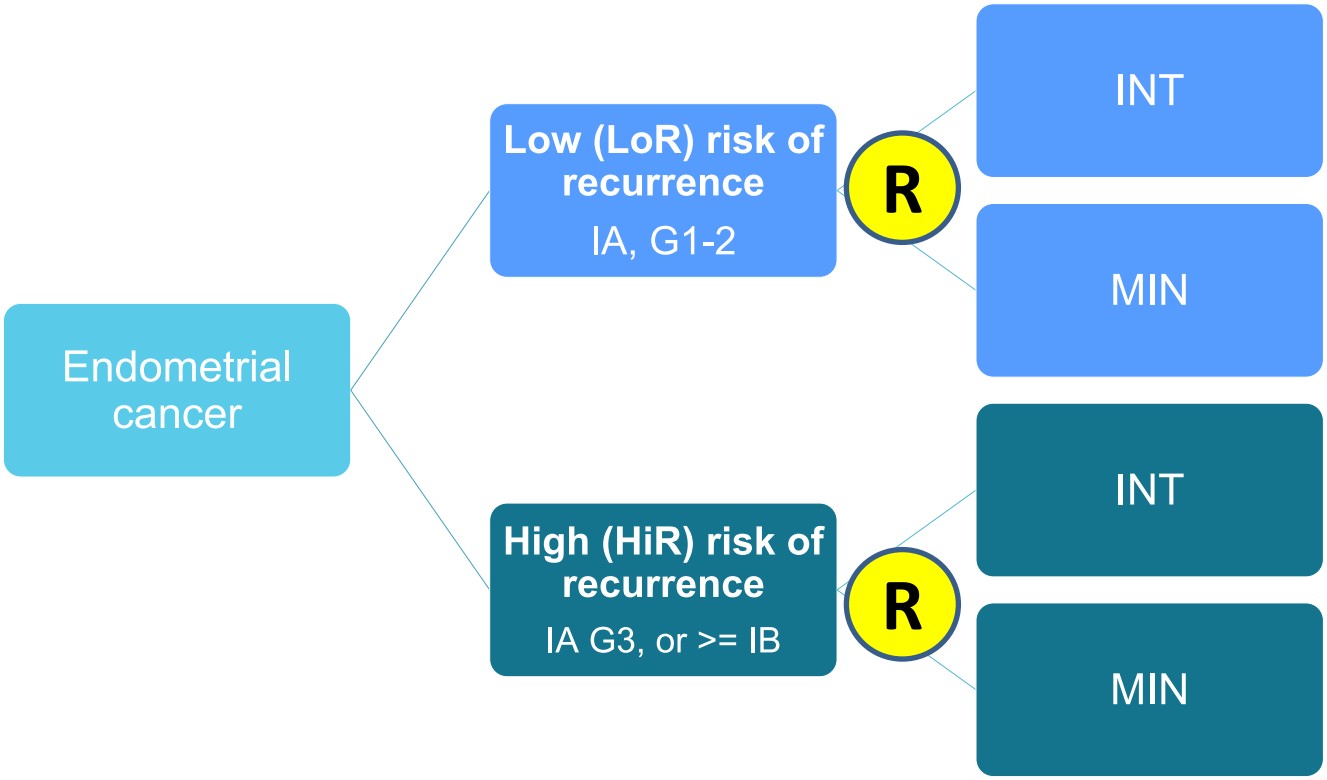
TOTEM Study

TOTEM trial

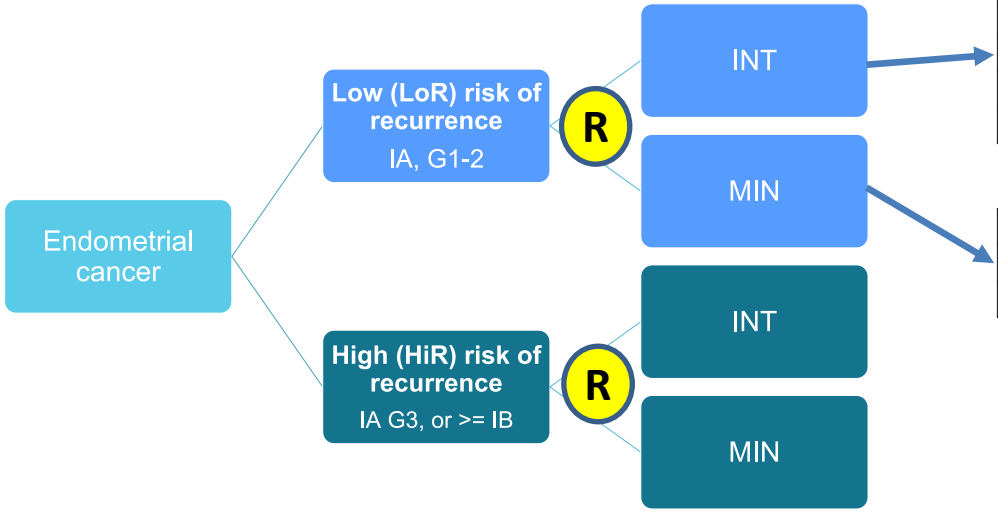
TOTEM trial: aims

To compare with a randomized trial an intensive (INT) vs minimalist (MIN) 5-year follow-up regimen in endometrial cancer patients in terms of overall survival (OS)

TOTEM trial design



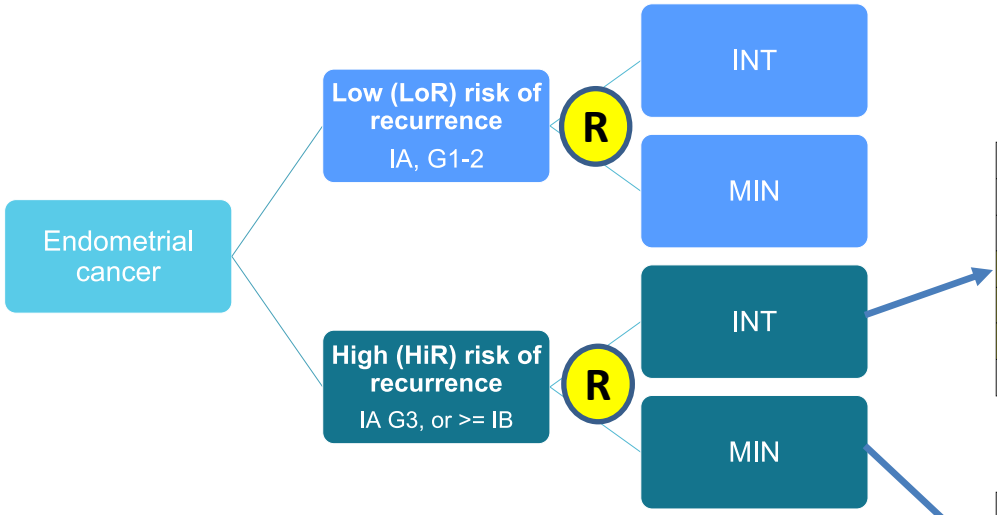
TOTEM trial design



	Months since randomization														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X	X	X	X	X	X	X
Pap Smear					X				X		X		X		X
CT chest, abdomen, pelvis					X				X						

	Months since randomization														
PROCEDURES	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
Clinical Examination	X		X		X		X		X	X	X	X	X	X	X

TOTEM trial design



	Months since randomization																
PROCEDURES	0	4	6	8	12	16	18	20	24	28	30	32	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X	X		X	X	X	X	X	X
Ca125		X		X	X	X		X	X	X		X	X	X	X	X	X
Abdomen & TV US		X		X		X		X		X		X		X		X	
Pap Smear					X				X				X		X		X
CT chest, abdomen, pelvis					X				X				X		X		X

	Months since randomization																
PROCEDURES	0	4	6	8	12	16	18	20	24	28	30	32	36	42	48	54	60
Clinical Examination	X	X		X	X	X		X	X		X		X	X	X	X	X
CT chest, abdomen, pelvis					X				X								

Inclusion criteria

- Age > 18 years
- Endometrial carcinoma all stages histologically confirmed
- No residual macroscopic tumour after surgery
- No previous or concomitant second neoplasms, no hereditary syndrome
- Informed consent

Endpoints

Primary endpoint:

- ✓ Overall survival (OS): time from randomization to death or last verification of vital status

The vital status was checked at the local registries for all Italian patients

Secondary endpoints:

- ✓ Relapse free survival (RFS): time from randomization to endometrial cancer relapse or death from any cause
- ✓ Health-related quality of life (HRQL): SF-12, PGWBI
- ✓ Compliance to the follow-up program
- ✓ Costs

Statistical methods

Sample size calculations:

- ✓ 5-year OS from 75% to 80% (expected HR = 0.78) with the INT regimen
- ✓ Power=80%, alpha error=5% (two tails), recruitment=4 years, F-UP=3 years
- ✓ Recruitment target: 2300

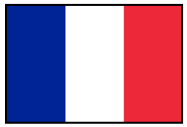
  Interim Analysis by independent panel of experts: after 10 years of recruitment the panel recommended closure of the study with 1884 randomized patients having achieved sufficient statistical power (85%)

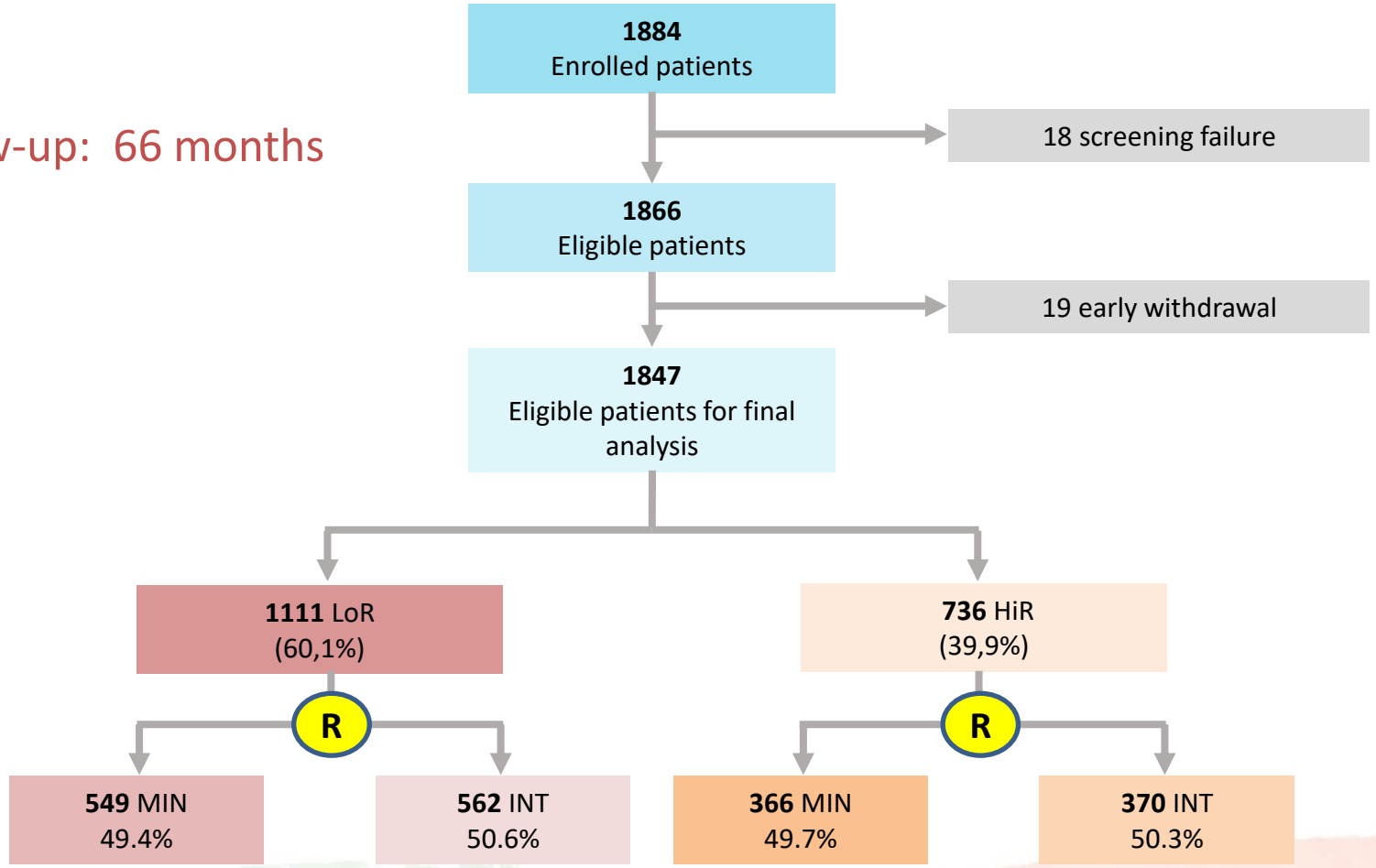
Analyses:

- ✓ OS, RFS: Kaplan Meier (with stratified Log Rank test), adjusted Cox regression model (Hazard Ratio, HR; 95% Confidence Interval, 95%CI)
- ✓ HRQL: SF-12: two level linear models (for repeated measures) stratified for baseline risk of recurrence

Patients' study flow

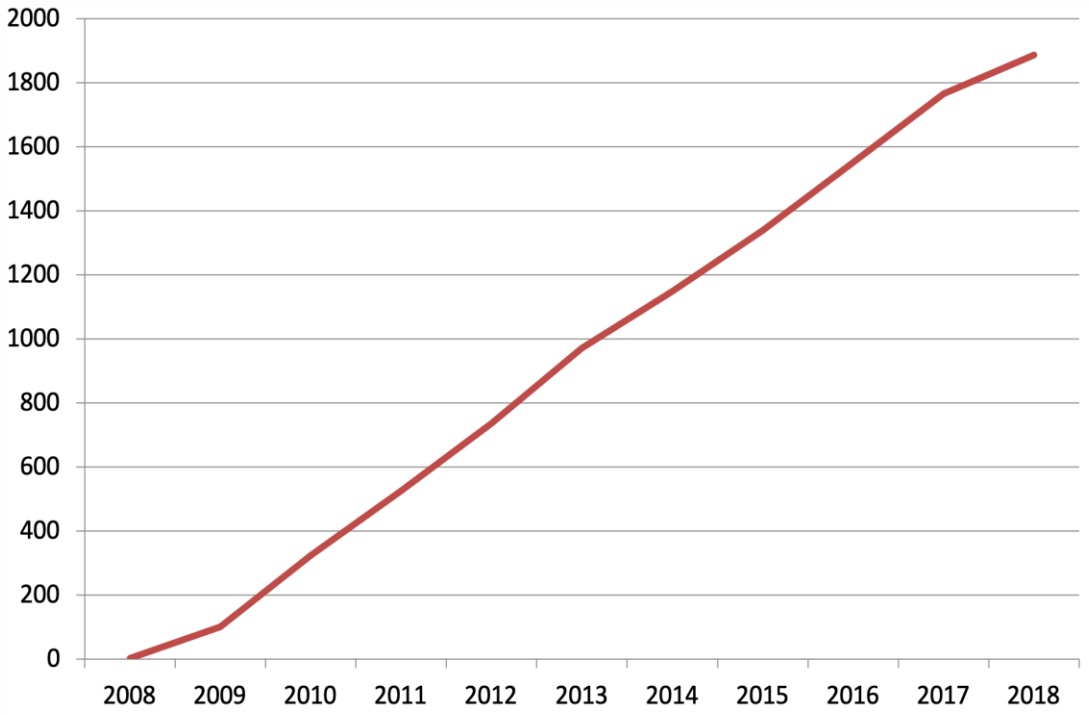
Median follow-up: 66 months





Setting

- ✓ 39 Italian centers, 3 French cente
- ✓ 2008-2018



TOTEM trial: results

Patients' features

Age	N	25th quartile	Median	75th quartile
Intensive	942	57	64	71
Minimalist	924	57	63	71

Histology	% INT	% MIN	N	% TOT
Endometrioid, Stage IA, G1-G2	59.0	58.9	1100	58.9
Endometrioid, Stage IA G3	5.2	6.4	108	5.8
Endometrioid, Stage IB, any G	19.6	18.4	355	19.0
Endometrioid, Stage II	3.4	3.2	62	3.3
Endometrioid, Stage III-IV	4.7	4.5	86	4.6
Non endometrioid, any stage	7.7	8.5	152	8.1
NA	0.3	0	3	0.2

Patients' features

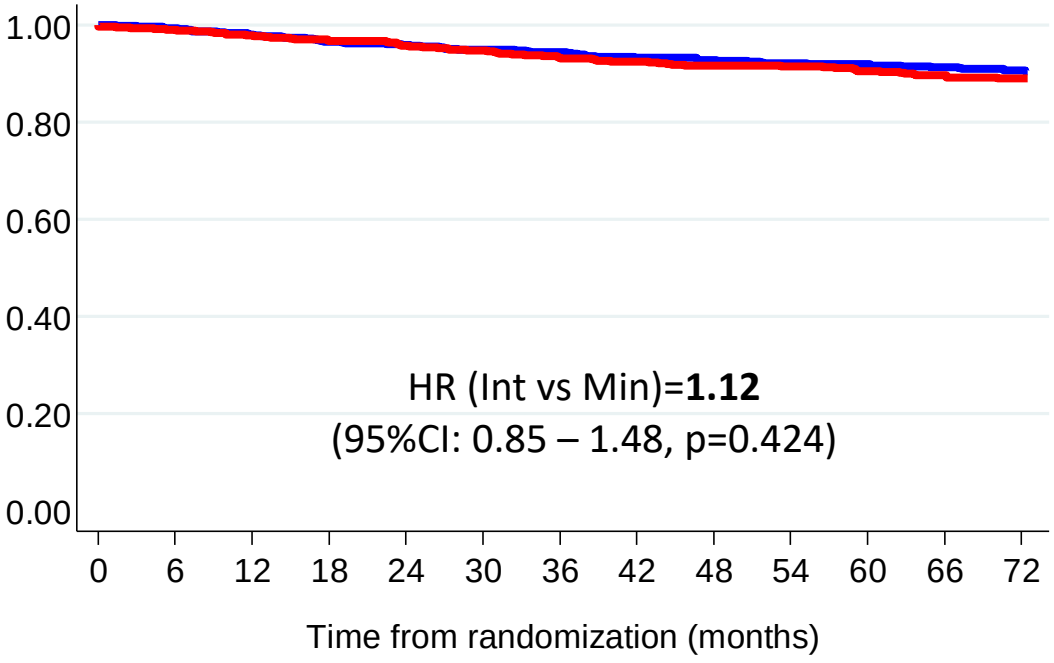
Type of surgery	% INT	% MIN	N	% TOT
Laparoscopy	50.4	49.5	932	49.9
Total hysterectomy and BSO	83.9	84.1	1567	83,9
Radical hysterectomy and BSO	15.6	15.4	289	15.5
NA	0.5	0.5	10	0.5

Adjuvant therapy	% INT	% MIN	N	% TOT
Surgery alone	66.7	66.3	1241	66.5
S + RT	20.7	19.3	373	20.0
S + CT	4.6	4.7	86	4.6
S + CT + RT	5.1	6.8	111	5.9
S + Adjuvant therapy (not specified)	3.0	2.9	55	2.9

Compliance

- ✓ Compliance with the follow-up scheduled procedures: 75.3% similar between INT (74.7%) and MIN (75.9%)
- ✓ As expected, the mean number of recorded exams was markedly higher in the INT than in the MIN arms (9.7 vs 2.9, $p < 0.0001$)
- ✓ Some additional, unplanned examinations were carried out in both arms

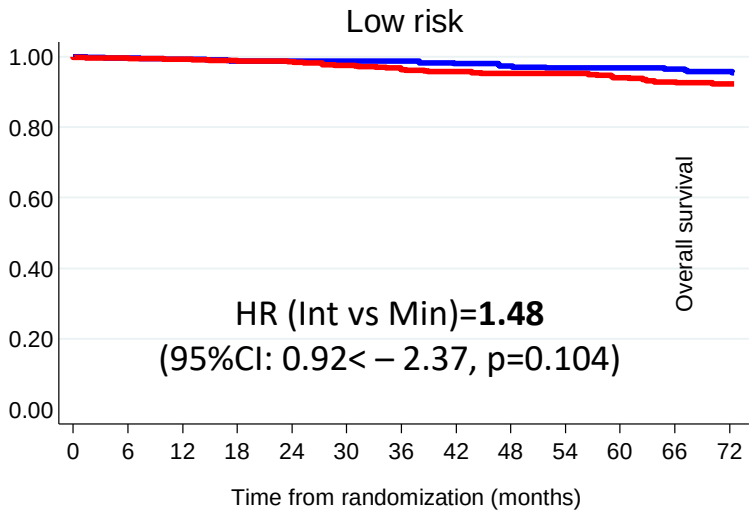
Overall survival

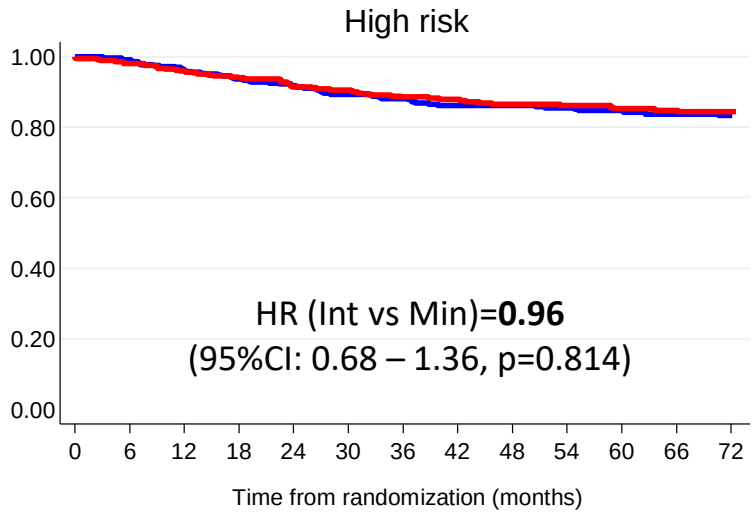


Number at risk							
Minimalist	915	889	847	741	631	516	439
Intensive	932	899	856	742	620	518	431

Minimalist Intensive

Overall survival, by risk





Number at risk

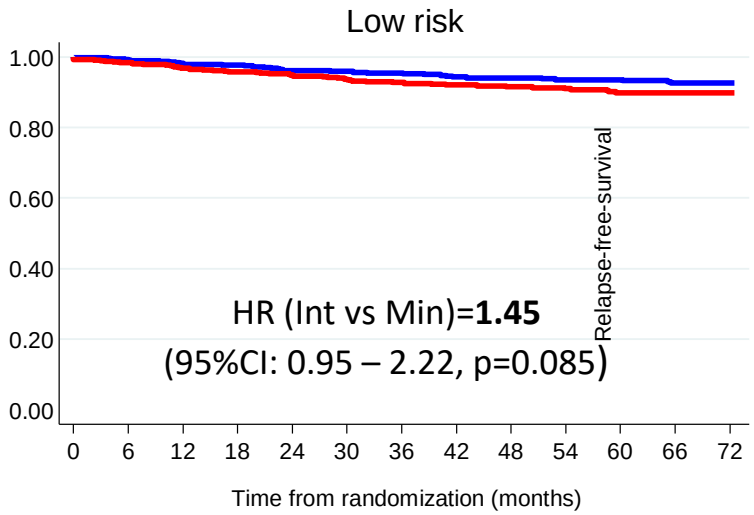
Minimalist	549	541	522	463	393	323	276
Intensive	562	550	529	457	388	315	269

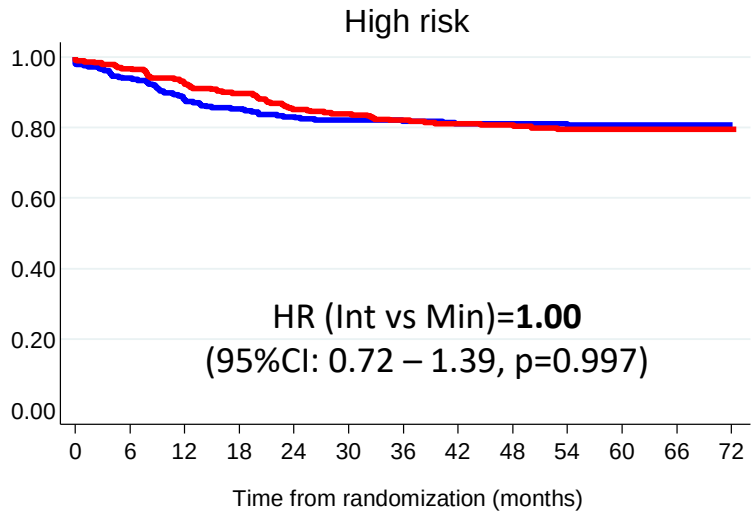
Number at risk

Minimalist	366	348	325	278	238	193	163
Intensive	370	349	327	285	232	203	162

Minimalist Intensive

Relapse Free Survival, by risk





Number at risk							
Minimalist	549	532	505	448	377	307	258
Intensive	562	533	505	430	365	293	252

Number at risk							
Minimalist	366	315	286	247	216	177	150
Intensive	370	329	293	255	209	181	145

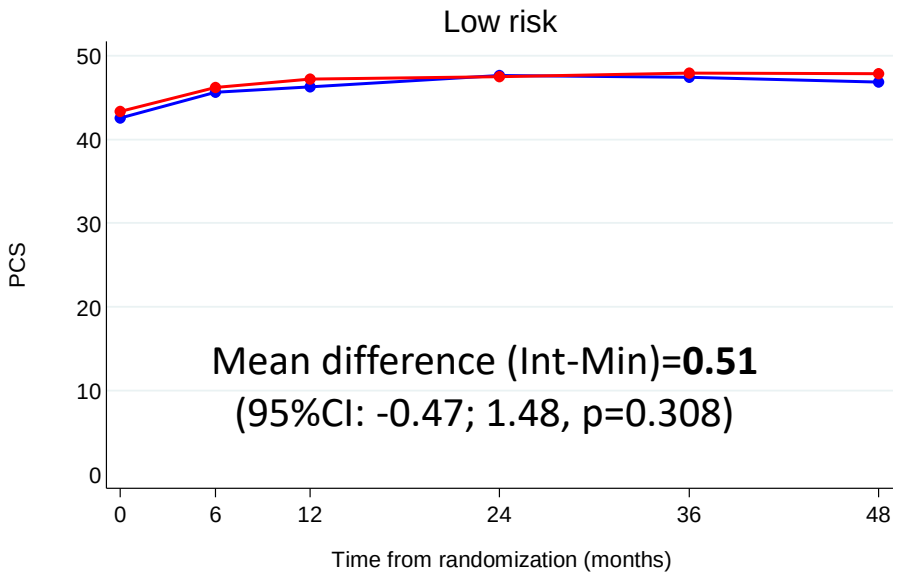
Minimalist Intensive

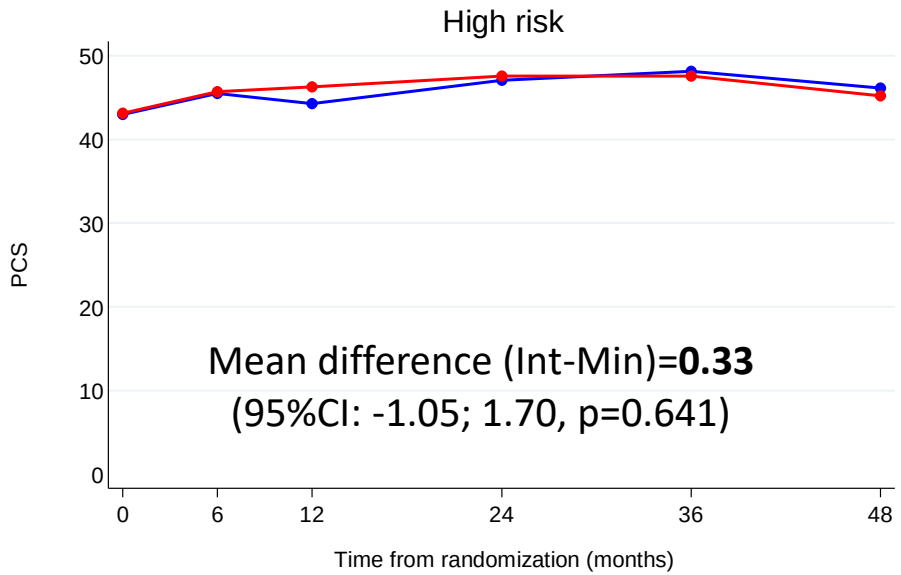
Relapses

Pattern of recurrence	N INT	% INT	N MIN	% MIN	N TOT	% TOT
Vaginal vault	**13**	10.6 %	**14**	13.3 %	**27**	11.8 %
Pelvis	**8**	6.5 %	**12**	11.4 %	**20**	8.8 %
Distant	**62**	50.4 %	**49**	46.7 %	**111**	48.7 %
Not specified	**40**	32.5 %	**30**	28.6 %	**70**	30.7 %
TOTAL	**123**	100 %	**105**	100 %	**228**	100 %

Relapse rate: 12.3%

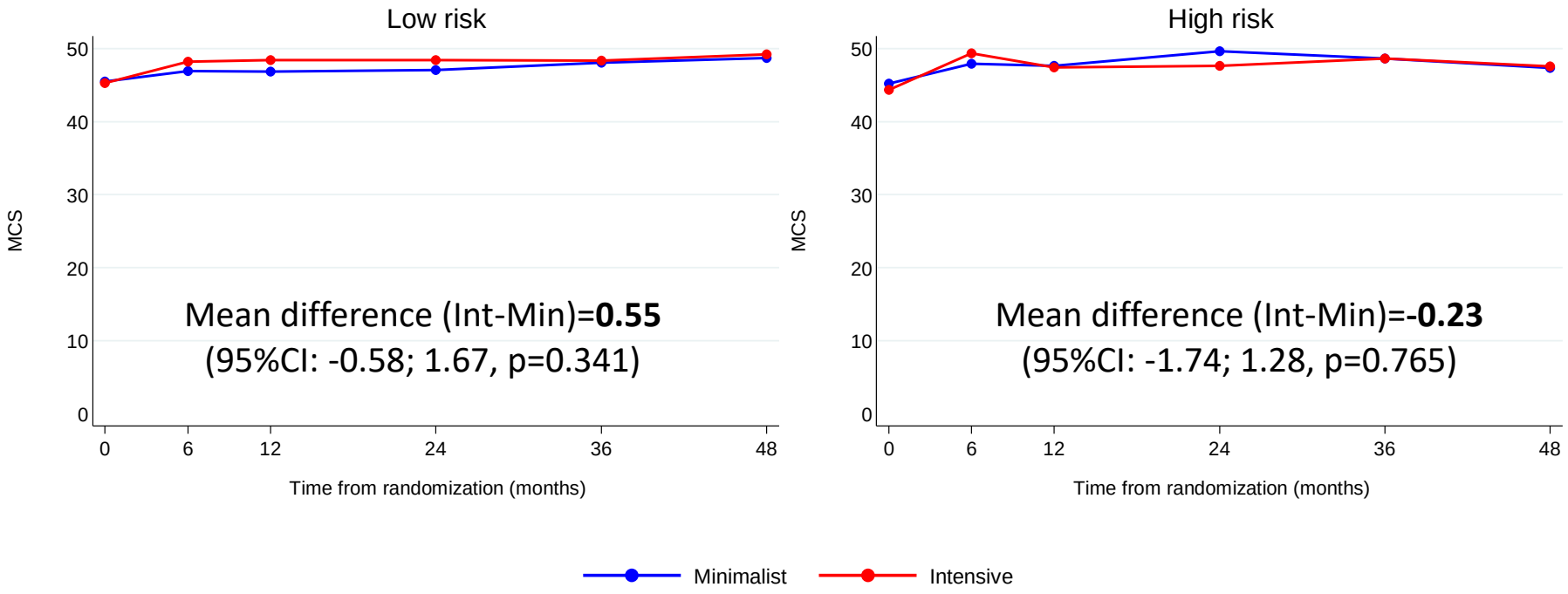
HRQL: SF12-Physical Component Summary, by risk





Minimalist Intensive

HRQL: SF12-Mental Component Summary, by risk



Strengths

- ✓ Large trial with long follow-up (median=66 months)
- ✓ Representativeness of the real-life population
- ✓ Strict verification of the life status in August 2020 on the whole cohort
- ✓ The lower limit of 95%CI of the HR for OS (0.85) excludes the hypothesized benefit of the Intensive regimen (0.78) with high certainty

Weaknesses

- ✓ Stratification of the risk of recurrence did not take into account LVSI
- ✓ Only remote monitoring (incidence of relapses may be underestimated)
- ✓ The performance of some additional exams could have reduced the differences between study arms
- ✓ The HRQL evaluation was made in about 50% of the sample only

Conclusions

- ✓Intensive follow-up in endometrial cancer treated patients does not improve OS, even in HiR patients
- ✓The HRQL, in our study, is not influenced by different regimens of follow-up
- ✓According to our data there is no need to routinely add vaginal citology, laboratory or imaging investigations to the minimalist regimens used in this trial

Thank you for your attention