XVIII ASSEMBLEA MANGO

Ricerca Clinica e Traslazionale in Ginecologia Oncologica

MILANO, 2-3 LUGLIO 2021

Con il Patrocinio di:
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
TOTEM trial

History and development 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
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.

<table>
<thead>
<tr>
<th>Guidelines Endometrial cancer</th>
<th>Pap test</th>
<th>Chest x-ray</th>
<th>US abdomen-pelvi</th>
<th>CT scan abdomen-pelvi</th>
<th>Ca 125</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN 2013</td>
<td>Controversial</td>
<td>Every year</td>
<td>No</td>
<td>No</td>
<td>Optional</td>
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<tr>
<td>ACOG 2005 reaffirmed 2009</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>AGO 2009</td>
<td>No</td>
<td>No</td>
<td>3 mos till the third year</td>
<td>No</td>
<td>No</td>
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<td>CCO 2006</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>ESMO 2011</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SGO 2011</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
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.
The Value of Gynecologic Cancer Follow-Up
Evidence-Based Ignorance?

Hourik Lajer, PhD,* Mette B. Jensen, PhD,† Annie Kilsmark, Candi, Oeocon., † Jens Albaek, PhD, † Danny Svané, PhD, † Manoosor R. Mirza, MD, * Paul F. Goertsen, PhD, † Diana Riemann, MSc, † Kåre Hansen, MSc, † Maya C. Miller, MSc, † and Ole Magensen, DSc, †

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, †

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. Nicolajie a,b, † Nicole P.M. Ezendam a, b, † M. Caroline Vos a, b, † Dorry Boll a, b, † Johanna M.A. Pijnenborg a,d, † Roy F.P.M. Kruitwagen a, b, † Marnix L.M. Lybeert a, † Loncke V. van de Poll-Franse a, b, †

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

Simon Leeson, 1 Nick Stuart, 2 Yvonne Sylvestre, 3 Liz Hall, 3 Rhianne Whitaker 3

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

INGVILD VISTAD, 1,BIRGIT W MOY, 1, HELGA B SALVESEN 1,2, & ASTRID H LIVAAG 1

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

- 19% Doubtful usefulness of FU
- 13% FU is useful
- 68% No comment

G. Favalli unpublished data 2000
Follow-up of gynecological cancer patients after treatment –
the views of European experts in gynecologic oncology

INGVILD VISTAD¹, MILADA CVANCAROVA² & HELGA B. SALVESEN³,⁴

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

<table>
<thead>
<tr>
<th>Routine tests</th>
<th>TVU</th>
<th>CA125</th>
<th>Other blood tests</th>
<th>CT</th>
<th>MRI</th>
<th>Cyt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
<td>59</td>
<td>76</td>
<td>17</td>
<td>15</td>
<td>4</td>
<td>13</td>
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<tr>
<td>Endometrial cancer</td>
<td>56</td>
<td>20</td>
<td>18</td>
<td>12</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>49</td>
<td>4</td>
<td>23</td>
<td>13</td>
<td>9</td>
<td>56</td>
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<tr>
<td>Vulvar cancer</td>
<td>20</td>
<td>7</td>
<td>19</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

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 variability 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)**

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

**RESULTS**

<table>
<thead>
<tr>
<th>Center</th>
<th>Visit</th>
<th>Papsmear</th>
<th>US</th>
<th>TC</th>
<th>ChX</th>
<th>Ca125</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3m</td>
<td>1y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3m</td>
<td>3m</td>
<td>2y</td>
<td>1y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>6m</td>
<td>6m</td>
<td>6m</td>
<td>6m</td>
<td>6m</td>
<td>6m</td>
</tr>
<tr>
<td>D</td>
<td>4m</td>
<td>6m</td>
<td></td>
<td>6m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>6m</td>
<td>6m</td>
<td>6m</td>
<td>6m</td>
<td>1y</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>3m</td>
<td>colpo3m</td>
<td>3m</td>
<td>1y</td>
<td>3m</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>3m</td>
<td>3m</td>
<td>3m</td>
<td>1y</td>
<td>6m</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>3m</td>
<td>colpo3m</td>
<td>1y</td>
<td>1y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Minimalist FU
- Intensive FU

![Graph showing visit types and associated tests](chart.png)

Ch X: 1
US: 15
TC: 40
RM: 5
PAP: 10
Visit: 50
Most of recurrences were found in asymptomatic patients

**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
Heterogeneity in schedule of exams in Piemonte-Valle d’Aosta

Endometrial Cancer - Visit

Endometrial cancer – Pap smear

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

Endometrial cancer

- Low (LoR) risk of recurrence
  IA, G1-2

- High (HiR) risk of recurrence
  IA G3, or >= IB

- INT
- MIN
TOTEM trial design

Endometrial cancer

Low (LoR) risk of recurrence IA, G1-2

High (HiR) risk of recurrence IA G3, or >= IB

R

INT

MIN

R

INT

MIN

<table>
<thead>
<tr>
<th>PROCEDURES</th>
<th>Months since randomization</th>
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</thead>
<tbody>
<tr>
<td>Clinical Examination</td>
<td>0  4  6  8  12  16  18</td>
</tr>
<tr>
<td>Pap Smear</td>
<td>X  X  X  X  X  X  X  X  X  X  X</td>
</tr>
<tr>
<td>CT chest, abdomen, pelvis</td>
<td>X  X  X  X  X  X  X  X  X  X  X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROCEDURES</th>
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<tr>
<td>Pap Smear</td>
<td>X  X  X  X  X  X  X  X  X  X  X</td>
</tr>
<tr>
<td>CT chest, abdomen, pelvis</td>
<td>X  X  X  X  X  X  X  X  X  X  X</td>
</tr>
</tbody>
</table>
TOTEM trial design

Endometrial cancer

Low (LoR) risk of recurrence IA, G1-2

High (HiR) risk of recurrence IA G3, or >= IB

R

INT

MIN

R

INT

MIN

| 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  | 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  | X  |    |    |    |    |    |    |    |    |    |
| Pap Smear                | X |   |   |   | X  | X  | X  | X  | X  | X  |    |    |    |    |    |    |    |    |
| CT chest, abdomen, pelvis| X |   |   |   |    | X  | X  | X  | X  | X  |    |    |    |    |    |    |    |

| 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  | X  | X  | X  | X  |
| CT chest, abdomen, pelvis|   |   |   |   | X  | X  | X  | 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

1884 Enrolled patients
1866 Eligible patients
1847 Eligible patients for final analysis

18 screening failure
19 early withdrawal

1111 LoR (60.1%)
549 MIN 49.4%
562 INT 50.6%

736 HiR (39.9%)
366 MIN 49.7%
370 INT 50.3%
Setting

✓ 39 Italian centers, 3 French centers
✓ 2008-2018
TOTEM trial: results
Patients’ features

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>25th quartile</th>
<th>Median</th>
<th>75th quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>942</td>
<td>57</td>
<td>64</td>
<td>71</td>
</tr>
<tr>
<td>Minimalist</td>
<td>924</td>
<td>57</td>
<td>63</td>
<td>71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>% INT</th>
<th>% MIN</th>
<th>N</th>
<th>% TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid, Stage IA, G1-G2</td>
<td>59.0</td>
<td>58.9</td>
<td>1100</td>
<td>58.9</td>
</tr>
<tr>
<td>Endometrioid, Stage IA G3</td>
<td>5.2</td>
<td>6.4</td>
<td>108</td>
<td>5.8</td>
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<tr>
<td>Endometrioid, Stage IB, any G</td>
<td>19.6</td>
<td>18.4</td>
<td>355</td>
<td>19.0</td>
</tr>
<tr>
<td>Endometrioid, Stage II</td>
<td>3.4</td>
<td>3.2</td>
<td>62</td>
<td>3.3</td>
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<tr>
<td>Endometrioid, Stage III-IV</td>
<td>4.7</td>
<td>4.5</td>
<td>86</td>
<td>4.6</td>
</tr>
<tr>
<td>Non endometrioid, any stage</td>
<td>7.7</td>
<td>8.5</td>
<td>152</td>
<td>8.1</td>
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<tr>
<td>NA</td>
<td>0.3</td>
<td>0</td>
<td>3</td>
<td>0.2</td>
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</table>
## Patients’ features

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>% INT</th>
<th>% MIN</th>
<th>N</th>
<th>% TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopy</td>
<td>50.4</td>
<td>49.5</td>
<td>932</td>
<td>49.9</td>
</tr>
<tr>
<td>Total hysterectomy and BSO</td>
<td>83.9</td>
<td>84.1</td>
<td>1567</td>
<td>83.9</td>
</tr>
<tr>
<td>Radical hysterectomy and BSO</td>
<td>15.6</td>
<td>15.4</td>
<td>289</td>
<td>15.5</td>
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<tr>
<td>NA</td>
<td>0.5</td>
<td>0.5</td>
<td>10</td>
<td>0.5</td>
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</table>

<table>
<thead>
<tr>
<th>Adjuvant therapy</th>
<th>% INT</th>
<th>% MIN</th>
<th>N</th>
<th>% TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>66.7</td>
<td>66.3</td>
<td>1241</td>
<td>66.5</td>
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<tr>
<td>S + RT</td>
<td>20.7</td>
<td>19.3</td>
<td>373</td>
<td>20.0</td>
</tr>
<tr>
<td>S + CT</td>
<td>4.6</td>
<td>4.7</td>
<td>86</td>
<td>4.6</td>
</tr>
<tr>
<td>S + CT + RT</td>
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<td>6.8</td>
<td>111</td>
<td>5.9</td>
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<tr>
<td>S + Adjuvant therapy (not specified)</td>
<td>3.0</td>
<td>2.9</td>
<td>55</td>
<td>2.9</td>
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</table>
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

<table>
<thead>
<tr>
<th>Time from randomization (months)</th>
<th>Minimalist</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>915</td>
<td>932</td>
</tr>
<tr>
<td>6</td>
<td>889</td>
<td>899</td>
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<tr>
<td>12</td>
<td>847</td>
<td>856</td>
</tr>
<tr>
<td>18</td>
<td>741</td>
<td>742</td>
</tr>
<tr>
<td>24</td>
<td>631</td>
<td>620</td>
</tr>
<tr>
<td>30</td>
<td>516</td>
<td>518</td>
</tr>
<tr>
<td>36</td>
<td>439</td>
<td>431</td>
</tr>
</tbody>
</table>

HR (Int vs Min) = 1.12
(95% CI: 0.85 – 1.48, p=0.424)
Overall survival, by risk

Low risk

HR (Int vs Min) = 1.48
(95% CI: 0.92 – 2.37, p=0.104)

High risk

HR (Int vs Min) = 0.96
(95% CI: 0.68 – 1.36, p=0.814)
Relapse Free Survival, by risk

**Low risk**

HR (Int vs Min)=**1.45**
(95%CI: 0.95 – 2.22, p=0.085)

**High risk**

HR (Int vs Min)=**1.00**
(95%CI: 0.72 – 1.39, p=0.997)

---

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Minimalist</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>549</td>
<td>562</td>
</tr>
<tr>
<td></td>
<td>532</td>
<td>533</td>
</tr>
<tr>
<td></td>
<td>505</td>
<td>505</td>
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<tr>
<td></td>
<td>448</td>
<td>430</td>
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<td>377</td>
<td>365</td>
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<td>293</td>
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<td>258</td>
<td>252</td>
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</tbody>
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**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Minimalist</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>366</td>
<td>370</td>
</tr>
<tr>
<td></td>
<td>315</td>
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<tr>
<td></td>
<td>286</td>
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</table>

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**HR (Int vs Min)=1.45**
(95%CI: 0.95 – 2.22, p=0.085)

**HR (Int vs Min)=1.00**
(95%CI: 0.72 – 1.39, p=0.997)
Relapses

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

Relapse rate: 12.3%
HRQL: SF12-Physical Component Summary, by risk

**Low risk**

Mean difference (Int-Min)=**0.51**
(95%CI: -0.47; 1.48, p=0.308)

**High risk**

Mean difference (Int-Min)=**0.33**
(95%CI: -1.05; 1.70, p=0.641)
HRQL: SF12-Mental Component Summary, by risk

Low risk

Mean difference (Int-Min)=0.55
(95%CI: -0.58; 1.67, p=0.341)

High risk

Mean difference (Int-Min)=-0.23
(95%CI: -1.74; 1.28, p=0.765)
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 LVI
✓ 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