Effectiveness of Intensive Versus Minimalist Follow-Up Regimen on Survival in Patients With Endometrial Cancer (TOTEM Study): A Randomized, Pragmatic, Parallel Group, Multicenter Trial.

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Effectiveness of Intensive Versus Minimalist Follow-Up Regimen on Survival in Patients With Endometrial Cancer (TOTEM Study): A Randomized, Pragmatic, Parallel Group, Multicenter Trial

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Abstract

PURPOSE

In the absence of clear evidence from randomized trials, the intensity of follow-up regimens after surgical treatment of endometrial cancer is highly variable in clinical practice. To reduce this uncertainty, we conducted a randomized trial to test whether an intensive (INT) versus a minimalist (MIN) follow-up regimen improves overall survival (OS) in patients undergoing operation for endometrial cancer.

METHODS

The TOTEM study was a large, pragmatic randomized trial, conducted in 42 hospitals (in Italy and France) including patients surgically treated for endometrial cancer, in complete clinical remission, International Federation of Gynecology and Obstetrics stage I-IV. After stratification by center and risk of relapse (low or high), patients were randomly assigned (1:1) to INT or MIN hospital-based follow-up regimens. The study was powered to demonstrate an absolute improvement of 5% of the 5-year OS with the INT regimen.

RESULTS

In total, 1,871 patients were randomly assigned between November 2008 and July 2018, and 1,847 patients (98.7%) were available for the final analysis (60% low risk). After a median follow-up of 69 months, the 5-year OS was 90.6% in the INT and 91.9% in the MIN arms (hazard ratio, 1.13, 95% CI, 0.86 to 1.50, P = .380). No differences in OS were found in subgroup analyses considering age, cancer treatment, risk of relapse, and degree of adherence of the center to the scheduled follow-up. The probability of detecting a relapse was slightly higher in the INT arm (hazard ratio, 1.17; 95% CI, 0.92 to 1.48; P = .194).

CONCLUSION

An INT follow-up in endometrial cancer–treated patients does not improve OS, even in high-risk patients. According to available evidence, there is no need to routinely add vaginal cytology, laboratory, or imaging investigations to the MIN regimens used in this trial.

INTRODUCTION

Endometrial carcinoma is the most common gynecological cancer in Europe with approximately 130,000 new cases and 30,000 deaths in Europe in 2020. The population 5-year relative survival is 76%,

and the early diagnosis explains this relatively high survival rate. According to current guidelines, after treatment, patients are followed for 5 years with hospital visits every 3-4 months in the first 2 years and every 6-12 months for up to 5 years.

CONTEXT

Key Objective

To test in a randomized pragmatic trial whether an intensive follow-up regimen improves overall survival in patients operated for endometrial cancer.

Knowledge Generated

An intensive follow-up in patients treated for endometrial cancer does not improve overall survival, even in patients at high risk of relapse.

Relevance

With a high level of confidence and transferability to clinical practice, there is no reason to systematically add vaginal cytology, laboratory, or imaging investigations to the minimalist follow-up used in this trial. These results add robust evidence to reinforce the existing trend in guideline recommendations to encourage a minimalist follow-up, including scheduled clinical visits and chest, abdomen, and pelvis computed tomography in the first two years in high-risk patients.

The follow-up requires a considerable investment of clinical resources

, although there is a surprisingly scarcity of evidence supporting the effectiveness of follow-up in either improving survival or quality of life in patients with cancer and low agreement among guidelines. Moreover, adherence to guidelines is low, barely 50%, and intensive (INT) follow-up regimens, with multiple scheduled visits and examinations, are widely adopted at least in Southern Europe,,,

maybe because of a supposed utility and for medicolegal issues.

A few randomized controlled trials (RCTs) have been published in this setting in the recent years, dealing with the reduction of the number of the scheduled visits

and with the setting of the follow-up (hospital v nurse-led telephone follow-up),

but never investigating the impact of routine serum, cytological or imaging investigations in improving overall survival (OS), or quality of life.

To test whether INT follow-up improves survival or quality of life, we conducted a large, pragmatic randomized trial in patients operated for endometrial cancer.

METHODS

Study Design

The TOTEM study is a randomized, pragmatic, parallel group, multicenter trial planned to compare INT versus minimalist (MIN) 5-year hospital-based follow-up regimens in patients with endometrial cancer conducted in 42 National Health Service hospitals in Italy and France.

All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki. The study was approved by the ethics committees of all the participating centers.

Data were entered by local data managers into a web-based database. A remote, centralized data monitoring was conducted by the coordinating center. The recruitment was supported by periodic newsletters and updates during Italian and international meetings that helped to keep the interest active for a prolonged period.

An independent data monitoring committee (IDMC) has been appointed to provide trial oversight and to review the results of interim analyses. The study Protocol (online only) and related documents are available at EPICLIN.

Patients

Included patients were surgically treated for endometrial cancer, in complete clinical remission confirmed by imaging (chest x-ray or computed tomography [CT scan] and abdomen and pelvis CT scan or magnetic resonance imaging) at the end of treatment (including adjuvant therapy), age older than 18 years, and with International Federation of Gynecology and Obstetrics (FIGO) stage I-IV.

Exclusion criteria were prior or concomitant malignancy (except for carcinoma in situ of the cervix and cutaneous basalioma), Lynch syndrome, inclusion in other studies with potential interference with proposed follow-up regimens, and living conditions that are a clear barrier to regular follow-up adherence, including geographic distance from the treating hospital or other access difficulties.

Random Assignment and Masking

After enrollment, baseline data were entered into a web-based database

to stratify participants by center and risk of relapse in low risk (LoR; FIGO 2009 stage IA, grade 1-2) or high risk (HiR; FIGO 2009 stage IA grade 3, or ≥ IB).

Patients who underwent surgery before 2009, classified as IAG3 according to previous FIGO classification, were shifted to HiR after this update, and their follow-up program was updated consequently. After completion of primary (surgical and possibly adjuvant) treatment, patients were randomly allocated in a 1:1 ratio, within each stratum, to INT or MIN follow-up regimens using a web-based system with a computer-generated sequence of permuted blocks of different sizes (completely concealed to all researchers). After the random assignment, a 5-year follow-up program was automatically generated, with planned dates for scheduled visits and examinations according to the risk and assigned arm. To prevent

potential biases during treatment, the random assignment result was made available to treating physicians and patients only at the end of primary treatment (surgery or adjuvant treatment) and after imaging confirmation of no evidence of disease. A printed copy of the follow-up program was then given to the patients.

Procedures

For LoR patients, the MIN follow-up regimen scheduled only 11 physical examinations (general and gynecological examinations, hereinafter referred to as visit), without serological, vaginal cytological, or imaging tests while the INT follow-up regimen had 13 visits, annual vaginal-cytology, and, in the first 2 years, annual chest, abdomen, and pelvis CT scan.

For HiR patients, the MIN follow-up regimen included 13 visits and annual CT scan in the first 2 years; the INT follow-up 14 visits with serum cancer antigen 125 (CA-125) dosage at every visit, abdomen and pelvis ultrasound examinations twice a year for 3 years, and then yearly, annual vaginal cytology and annual CT scan (Appendix Table A1, online only). In case of clinical suspicion or abnormal test results, further unscheduled examinations were allowed independently from the assigned follow-up regimen.

Outcomes

The primary outcome is OS, defined as the time from random assignment to death or last verification of vital status. During the first 5 months of 2021, a systematic check was carried out at the local municipality registries, with verification of the life status with 96% of completeness.

Secondary outcomes are relapse-free survival, defined as the time from random assignment to endometrial cancer relapse or death from any cause, proportion of asymptomatic patients with diagnosis of relapse, the health-related quality of life assessed at baseline, at 6 and 12 months, and then yearly (with the SF-12 Physical and Mental Health-Summary Scale),

the compliance to the follow-up program, and costs.

We herein report on the trial findings relating to clinical outcomes and compliance; health-related quality of life and costs will be discussed in a separate report.

Statistical Analysis

The study sample size was calculated to evaluate a 5-year OS increase of 5%, approximately from 75% to 80%, corresponding to a hazard ratio (HR) of 0.78, with a power = 0.80 and a two-tail alpha error of .05. Assuming a 5% dropout rate, a sample size of 2,300 patients was estimated (1,150 for each arm).

An interim analysis was planned when one third of the events were expected (with a threshold value of P of log-rank test of .0006, calculated with the Fleming and O'Brien design). Another unplanned interim analysis was proposed by the IDMC in 2018, after 10 years of recruitment. Considering a slower than expected accrual, an observed OS (around 90%) that was much better than assumed in the protocol (on the basis of population survival data), evidence that the risk of recurrence was concentrated in the first 2-3 years of follow-up, and that prolonging the accrual would not add many more events (deaths), the IDMC recommended that study

enrollment be closed with 1,871 randomly assigned patients and that final analyses be performed after an additional 3 years of follow-up, thus ensuring adequate statistical power (> 85%) to demonstrate a 5% absolute increase in survival.

After exclusion of few randomly assigned patients for early withdrawal of consent, all others were analyzed by intention to treat. The baseline clinical and demographic characteristics were summarized by means (with standard deviations, SD) or medians (with interquartile ranges) for continuous variables and by frequency for categorical variables. The survival functions were estimated by the Kaplan-Meier method, and differences between the follow-up arms were evaluated by the stratified log-rank test. A secondary analysis was carried out with a Cox proportional hazard model, to estimate adjusted HRs and 95% CI for some potential confounders and considering centers as random effects. Adherence to scheduled follow-up visits and examinations was measured as the difference between those scheduled and those performed, after excluding unplanned examinations performed in patients with suspicion of a relapse and considering the actual duration of each patient's follow-up.

Patients with an absolute difference ≤ 2 visits during the entire follow-up were considered adherent. The comparisons between the follow-up regimens for the proportion of the adherent patients and of those with asymptomatic relapses were expressed in terms of odds ratios (ORs) and estimated with logistic regression models with random effects (centers and risk of relapse).

Subgroup analyses on OS with Cox models (stratified by center and risk of relapse) were performed to explore the potential modification of the effect of the intensity of follow-up programs, according to the risk of relapse (stratification variable, planned), age class (younger than 64 years, 65-74 years, and older than 75 years), surgical technique (laparoscopic/robotic-assisted or open), adjuvant therapy (yes/no), and level of adherence of the center according to the mean absolute difference between expected and performed visits (high ≤ 2; medium 2.01-4; and low > 4). The trial is registered at ClinicalTrials.gov (identifier: NCT00916708).

Role of the Funding Source

The trial was funded by the Regional Oncology Network of Piemonte e Valle d’Aosta. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors are fully responsible for accuracy, completeness of data, adherence of the statistical analyses to the study protocol, and decision for publication.

RESULTS

A total of 1,871 patients were assessed for eligibility in 39 centers in Italy (between November 1, 2008, and July 31, 2018) and in three centers in France (between March 1, 2017, and July 31, 2018; participating centers are listed in the Data Supplement, online only).

After the exclusion of five patients because of screening failure and 19 patients with early withdrawal of consent, analyses were performed by intention to treat in 1,847 of 1,866 randomly assigned patients (99.0%; Fig 1). The baseline characteristics of the analyzed population are summarized in Table 1. The two arms were well balanced with respect to

baseline characteristics, including stage, grade, or histologic subtype. The mean age of the patients was 63.7 years. Most patients (59.3%) had endometrioid, stage IA, and grade 1-2 endometrial cancer. The surgical treatment alone was performed in 1,230 patients (66.6%) while 617 (33.4%) received surgery and adjuvant treatment. Vaginal hysterectomy was performed in 120 (6.5%) patients while 926 (50.1%) underwent minimally invasive surgery (by laparoscopy or robotic-assisted). Minimally invasive surgery was performed in 56.6% of LoR patients and 40.5% of HiR patients. Hysterectomy, bilateral oophorectomy, and lymphadenectomy were performed according to national and European guidelines,

, but detailed data collection on lymphadenectomy was not planned. Among 617 patients submitted to adjuvant treatment, 371 (60.1%) received radiotherapy (RT), 86 (13.9%) received chemotherapy (CHT), and 108 (17.5%) received both RT and CHT, according to national and European guidelines.21,22.

Patients had a median length of study follow-up of 69 months. Overall, 198 patients died (5-year OS, 91.3%): 72 of 1,111 in LoR (5-year OS, 95.5%) and 126 of 736 (5-year OS, 85.0%) in HiR groups. The 5-year OS was 90.6% (95% CI, 88.4 to 92.4) in the INT arm and 91.9% (95% CI, 89.9 to 93.6) in the MIN arm (HR, 1.13; 95% CI, 0.86 to 1.50; P = .380; Fig 2A and Table 2).

In the LoR group, the estimated 5-year OS of INT versus MIN arm were 94.1% and 96.8% (HR, 1.45; 95% CI, 0.91 to 2.33; P = .121) and corresponding figures in the HiR group were 85.3% and 84.7% (HR, 0.99; 95% CI, 0.69 to 1.40; P = .936; Figs 2C and 2E and Table 2), respectively.

Most recurrences were diagnosed during the first 2 years of follow-up, with a median time from random assignment to diagnosis of the relapse of 14 months, 23 months in the LoR, and 12 months in the HiR. The 5-year relapse-free survival was 90.7% (131 of 932; 95% CI, 87.7 to 93.0) in the INT arm and 93.7% (108 of 915; 95% CI, 91.1 to 95.5) in the MIN arm (HR, 1.17; 95% CI, 0.92 to 1.48; P = .194; Fig 2B and Table 2). The HRs were 1.35 (95% CI, 0.91 to 1.99) and 1.07 (95% CI, 0.80 to 1.44) in the LoR and HiR groups, respectively (Figs 2D and 2F and Table 2).

With regards to the relapses (n = 175), 171 occurred during the first 5 years of follow-up. About half of relapses were asymptomatic (91 of 171, 53.2%), with a tendency of higher proportions in the INT than in the MIN arm, both in the LoR group (59.3% v 40.0%, OR, 2.18; P = .195) and in the HiR one (56.3% v 51.7%, OR, 1.17; P = .701). The other four relapses occurred after the first 5 years of follow-up.

Fifty-eight of 175 women (33.1%) had a single site of relapse, 62.3% had multiple sites of relapse, and in 8 of 175 (4.6%) the site of relapse was unavailable. Only 19 of 109 multiple site relapses were in LoR women. More than one third of recurrences in the LoR group occurred in the vaginal vault or pelvis (19 of 51, 37.3%), but 25 of 51 women (49%) developed a distant site relapse (Appendix Table A2, online only). In the HiR group, 93 of 124 (75%) relapses were in a distant site. A total of 89 deaths occurred after cancer recurrence (89 of 175, 51%): 18 of 51 (35.3%) in the LoR group and 71 of 124 (57.3%) in the HiR group.

At the time of the relapse diagnosis, 58 of 175 patients (33%) performed an unscheduled follow-up visit: 42 because of symptoms and 16 because of a suspicion of relapse on a

scheduled procedure carried out (eg, a new lesion on a CT scan or a rise of CA-125), without symptoms.

Most of the relapses (129 of 175, 73.7%) were detected by the visit, alone (10.8%) or by visit and CT scan (50.8%) or by visit and other examinations (12%) and 10.9% by other single examinations while for 15.3% the diagnostic method was not available (Appendix Table A2).

Patients diagnosed with a relapse were submitted to surgery (10%), RT (15%), CHT (30%), hormone therapy (3%), or a combination of these therapies (21%). For 37 of 175 relapsed patients (21%), no details on further therapies were available (Appendix Table A2).

Patient adherence to the follow-up scheduled visits was slightly lower in the INT arm (65.5%) than in the MIN arm (69.5%; OR for adherence, 0.80; 95% CI, 0.64 to 1.00; P = .048), with similar differences in LoR and HiR groups. As expected, the mean number of recorded examinations per patient (laboratory or imaging) was markedly higher in the INT than in the MIN arms (9.7 v 2.9; P < .0001).

Focusing on the compliance with the examinations during the whole follow-up schedule, in the LoR group, the mean difference of performed versus expected examinations per patient was minimal in both arms (Figs 3A and 3B) while in the HiR group, the INT arm performed fewer examinations than expected, although the difference between arms remained wide (Figs 3C and 3D).

The results of subgroup analyses for OS are displayed with a forest plot (Fig 4). In none of the subgroups analyzed (by age, surgical technique, adjuvant therapy, risk of relapse, and center adherence), the regimen of follow-up showed a meaningful interaction. Interestingly, no differences were observed stratifying centers according to their average adherence to the scheduled follow-up.

DISCUSSION

The results of the TOTEM trial did not show any improvement in OS and in early detection of relapses for patients treated for endometrial cancer and followed with a 5-year INT regimen of follow-up, independently from their risk of relapse. More recent guidelines have moved toward less INT follow-up regimens,

but in the early 2000s, recommendations on follow-up in patients with endometrial cancer were contradictory, and the follow-up schemes adopted by the centers were heterogeneous,, being the existing evidence derived from small retrospective/historical cohort studies. Because the follow-up represents a high time and resource consuming activity and the urgent need for a large and well-designed RCT was highlighted,

the TOTEM study was set up in 2008 as a large, pragmatic, randomized trial to test whether a more INT regimen of follow-up could improve the OS in patients treated for endometrial cancer.

In women surveilled with the INT regimen, the detection of relapses, especially of those asymptomatic, was slightly higher, but this earlier detection did not translate in OS improvements.

No benefit of the INT regimen was detected in the planned subgroup analysis for the risk of relapse and in other explorative analyses by age and treatment modality of endometrial cancer.

The suboptimal adherence to the protocol could have diluted possible differences in clinical outcomes between the two regimens. In particular, women in the MIN arm were occasionally submitted to unplanned vaginal cytology, CA-125, and abdominal pelvic ultrasonography, probably considered not invasive examinations and useful to complete the visit, while women in the INT arm, omitted some of the scheduled examinations, suggesting a limited acceptability of this regimen. However, the actual differences in type and frequency of performed examinations remained large and subgroup analyses did not show any advantage of the INT regimen, even in the group of centers with the highest level of adherence.

A few other RCTs were set up in the last years, and some of them are ongoing. They deal with the reduction of the number of the scheduled visits, as in the ENSURE trial,

with the setting of the follow-up (hospital versus nurse-led telephone follow-up; ENDCAT-NEMO-TOPCAT-G trials) or with the comparison between scheduled versus patient-initiated follow-up (OPAL trial). The published trials,,

showed that nurse-led telephone follow-up can replace doctor-led follow-up in routine surveillance of patients with stage I endometrial cancer, in terms of patients' satisfaction, psychological morbidity, and cost-effectiveness. However, hospital-based follow up alleviates fear of cancer recurrence significantly more than patient-initiated follow up. However, these trials were not powered to compare OS and included only low-to-intermediate–risk patients.

The major strengths of the TOTEM study are its large sample size with a long follow-up, the inclusion of several different centers that enrolled patients representing the real-life population, and the strict verification of the life status run on the whole cohort. The very long study duration could have reduced the quality of data collection during the follow-up, but it was irrelevant to survival, which was the primary end point of the study. The TOTEM study can safely be interpreted as true negative because, in addition to the very similar OS probability, the lower limit of the 95% CI of the HR for OS (0.85) excludes the hypothesized benefit of the INT regimen (0.78) with a wide margin.

Suboptimal patient adherence to scheduled visits and examinations of the INT arm during the 5-year follow-up is not only a limitation of the study but also an indicator of poor acceptability and feasibility of these INT regimens. The lack of data on the lymphovascular space invasion (LVSI) at diagnosis prevents the possibility to explore also this variable in subgroup analyses, but at the time TOTEM was set up, LVSI was not yet recognized as a relevant prognostic factor in endometrial cancer.

An important feature of a pragmatic trial is its representativeness of the real population. This aspect was carefully considered during the design and conduct of the study, defining few, simple inclusion criteria and promoting the involvement of a large number of centers (in

different regions and with various workloads). However, the contribution of all centers was not uniform during the study for several reasons (delayed participation and reduced enrollment because of concurrent protocols) leading to the need of extending the accrual period with increasing risk of patient selection. During these 10 years, a certain degree of underrepresentation of nonendometrioid histology and misclassification of the risk of relapse cannot be excluded, especially for the possible inclusion in the low-risk group of some patients with mutated p53, an unfavorable prognostic factor not known when the TOTEM study was conceived.

In conclusion, the TOTEM trial clearly showed that an INT follow-up in patients treated for endometrial cancer does not improve OS, even in HiR patients. These results, on the basis of a large, pragmatic, multicenter trial, have a high degree of statistical robustness and transferability to clinical practice. According to available evidence, there is no reason to routinely add vaginal cytology, laboratory, or imaging investigations to the MIN regimens used in this trial.

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DISCLAIMER

The views expressed in this publication are those of the authors and not necessarily those of the Regional Oncology Network of Piemonte e Valle d'Aosta.

PRIOR PRESENTATION

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

Data sharing requests will be considered by the management group upon written request to the corresponding author. Deidentified participant data or other prespecified data will be available subject to a written proposal and a signed data sharing agreement.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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This article is dedicated to the memory of Dott. Alessandro Liberati for his valuable contribution to the ideation of the trial.

Membership of the TOTEM collaborative group is provided in Appendix 1

REFERENCES

1. World Health Organization: GLOBOCAN 2020: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2020. http://gco.iarc.fr/today/data/

factsheets/cancers/24- Corpus-uteri-fact-sheet.pdf

2. Sant M, Chirlaque Lopez MD, Agresti R, et al: Survival of women with cancers of breast and genital organs in Europe 1999-2007: Results of the EUROCARE-5

study. Eur J Cancer 51:2191-2205, 2015

3. Colombo N, Preti E, Landoni F, et al: Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 24:vi33-vi38,

2013 (suppl 6)

4. NCCN Guidelines, Uterine Neoplasms, version 4.2021. 2021. https://www.nccn.org/guidelines/category_1

5. Salani R, Khanna N, Frimer M, et al: An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of

Gynecologic Oncology (SGO) recommendations. Gynecol Oncol 146:3-10, 2017

6. Carrara L, Gadducci A, Landoni F, et al: Could different follow-up modalities play a role in the diagnosis of asymptomatic endometrial cancer relapses? An Italian

multicentric retrospective analysis. Int J Gynecol Cancer 22:1013-1019, 2012

7. Zola P, Fuso L, Mazzola S, et al: Follow-up strategies in gynecological oncology: Searching appropriateness. Int J Gynecol Cancer 17:1186-1193, 2007

8. Giglio V, Schneider P, Madden K, et al: Published randomized controlled trials of surveillance in cancer patients - a systematic review. Oncol Rev 15:522, 2021

9. Merkow RP, Korenstein D, Yeahia R, et al: Quality of cancer surveillance clinical practice guidelines: Specificity and consistency of recommendations. JAMA

Intern Med 177:701-709, 2017

10. Phelippeau J, Rouzier R, Koskas M: Adherence to guidelines during follow-up of endometrial cancer: Analysis of French health insurance database. Anticancer

Res 38:2977-2982, 2018

11. Nicolaije KA, Ezendam NP, Vos MC, et al: Follow-up practice in endometrial cancer and the association with patient and hospital characteristics: A study from

the population-based PROFILES registry. Gynecol Oncol 129:324-331, 2013

12. Favalli G: About the Follow Up in Endometrial Cancer. Proceedings of the National Academy of Medicine Meeting “The Uterine Malignancies: From the EBM to

Pathways,” Santa Margherita Ligure, Italy, November 21-23, 2002

13. Fuso L, Evangelista A, Pagano E, et al: Variation in gynecological oncology follow-up practice: Attributable to cancer centers or to patient characteristics? A

Piedmont Regional Oncology Network Study. Tumori 97:551-558, 2011

14. Ezendam NPM, de Rooij BH, Kruitwagen RFPM, et al: ENdometrial cancer SURvivors’ follow-up carE (ENSURE): Less is more? Evaluating patient satisfaction

and cost-effectiveness of a reduced follow-up schedule: Study protocol of a randomized controlled trial. Trials 19:227, 2018

15. Beaver K, Williamson S, Sutton C, et al: Comparing hospital and telephone follow-up for patients treated for stage-I endometrial cancer (ENDCAT trial): A

randomised, multicentre, non-inferiority trial. BJOG 124:150-160, 2017

16. An Individualised and Patient-Centred Follow-Up Program for Women With Gynaecological Cancer (NEMO Trial). https://clinicaltrials.gov/ct2/show/

NCT03838861?cond5endometrial1cancer%2C1follow1up&draw52&rank51

17. Morrison V, Spencer LH, Totton N, et al: Trial of optimal personalised care after treatment-gynaecological cancer (TOPCAT-G): A randomized feasibility trial. Int

J Gynecol Cancer 28:401-411, 2018

18. EPICLIN: Studio TOTEM: Documents. https://www.epiclin.it/totem/documents

19. EPICLIN: Studio TOTEM. https://www.epiclin.it/totem

20. Ware J, Kosinski M, Keller S: SF-12: How to score the SF-12 Physical and Mental Health Summary Scales (ed 2). New Boston, MA, England Medical Center, The

Health Institute, 1995

21. Linee Guida AIOM neoplasia dell’utero: endometrio e cervice – linee guida 2018. https://www.aiom.it/wp content/uploads/2018/11/2018_LG_AIOM_Utero.pdf

22. Colombo N, Creutzberg C, Amant F, et al: ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. Ann Oncol

27:16-41, 2016

23. Vistad I, Moy BW, Salvesen HB, et al: Follow-up routines in gynecological cancer—Time for a change? Acta Obstet Gynecol Scand 90:707-718, 2011

24. Menczer J: Endometrial carcinoma. Is routine intensive periodic follow-up of value? Eur J Gynaecol Oncol 21:461-465, 2000

25. Lajer H, Jensen MB, Kilsmark J, et al: The value of gynecologic cancer follow-up: Evidence-based ignorance? Int J Gynecol Cancer 20:1307-1320, 2010

26. Salvesen HB: Rutinekontroller etter gynekologisk cancerbehandling [Routine follow up after treatment for gynecological cancer]. Tidsskr Nor Laegeforen 121:

1253-1255, 2001

27. Vistad I, Cvancarova M, Salvesen HB: Follow-up of gynecological cancer patients after treatment—The views of European experts in gynecologic oncology. Acta

Obstet Gynecol Scand 91:1286-1292, 2012

28. Sartori E, Pasinetti B, Chiudinelli F, et al: Surveillance procedures for patients treated for endometrial cancer: A review of the literature. Int J Gynecol Cancer 20:

985-992, 2010

29. Fung-Kee-Fung M, Dodge J, Elit L, et al: Follow-up after primary therapy for endometrial cancer: A systematic review. Gynecol Oncol 101:520-529, 2006

30. Jeppesen MM, Jensen PT, Hansen DG, et al: Patient-initiated follow up affects fear of recurrence and healthcare use: A randomized trial in early-stage

endometrial cancer. BJOG 125:1705-1714, 2018

31. Dixon P, Beaver K, Williamson S, et al: Cost-consequence analysis alongside a randomised controlled trial of hospital versus telephone follow-up after treatment

for endometrial cancer. Appl Health Econ Health Policy 16:415-427, 2018

32. Concin N, Matias-Guiu X, Vergote I, et al: ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 31:

12-39, 2021

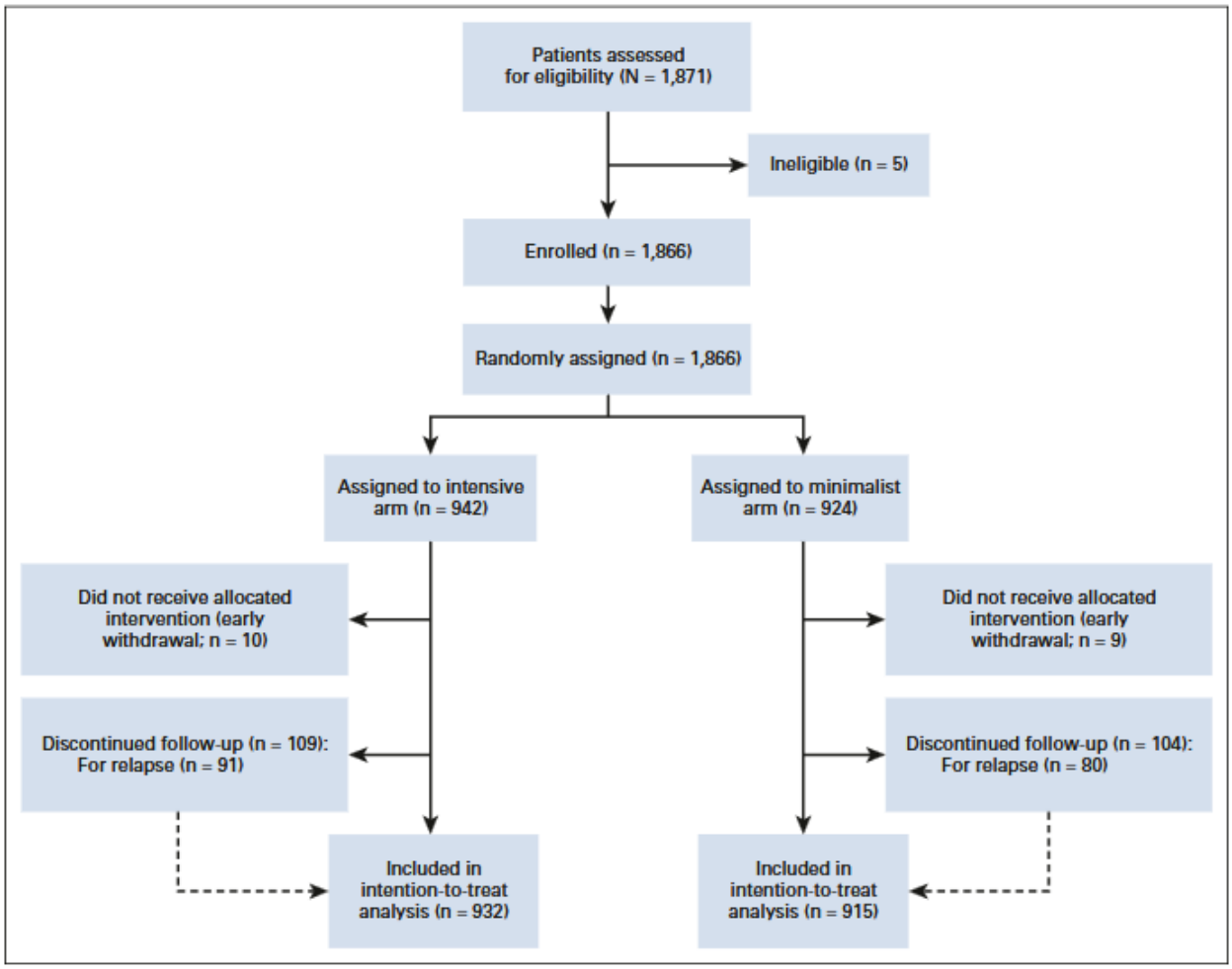

FIG 1. CONSORT diagram

TABLE A1. Follow-Up Visits and Examinations by Risk of Relapse (LoR, A; HiR, B) and Follow-Up Regimen

A. LoR Follow-Up Regimen and Procedures	Months Since Random Assignment														
	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
MIN															
Clinical examination	X		X		X		X		X	X	X	X	X	X	X
INT															
Clinical examination	X	X		X	X	X		X	X	X	X	X	X	X	X
Vaginal cytology					X				X		X		X		X
CT scan of the chest, abdomen, and pelvis					X				X						

B. HiR Follow-Up Regimen and Procedures	Months Since Random Assignment																
	0	4	6	8	12	16	18	20	24	28	30	32	36	42	48	54	60
MIN																	
Clinical examination	X	X		X	X	X		X	X		X		X	X	X	X	X
CT scan of the chest, abdomen, and pelvis					X				X								
INT																	
Clinical examination	X	X		X	X	X		X	X	X		X	X	X	X	X	X
CA-125		X		X	X	X		X	X	X		X	X	X	X	X	X
Abdomen and TV US		X		X		X		X		X		X		X		X	
Vaginal cytology					X				X				X		X		X
CT scan of the chest, abdomen, and pelvis					X				X				X		X		X

NOTE. Clinical examination includes the gynecologic examination.

Abbreviations: CA-125, cancer antigen 125; CT, computed tomography; HiR, high risk; INT, intensive; LoR, low risk; MIN, minimalist; TV, transvaginal; US, ultrasonography.

TABLE A2. Characteristics of Endometrial Cancer Relapses by Risk and Follow-Up Regimen

	LoR		HiR		
Characteristic	**INT (n = 28), No. (%)**	**MIN (n = 23), No. (%)**	**INT (n = 64), No. (%)**	**INT (n = 60), No. (%)**	**Total (N = 175[a]), No. (%)**
Relapse site					
Vaginal vault	8 (28.6)	11 (47.8)	6 (9.4)	4 (6.7)	29 (16.6)
Pelvis	1 (3.6)	1 (4.4)	7 (10.9)	11 (18.3)	20 (11.4)
Distant site	17 (60.7)	8 (34.8)	49 (76.6)	44 (73.3)	118 (67.4)
Not specified	2 (7.1)	3 (13.0)	2 (3.1)	1 (1.7)	8 (4.6)
Diagnostic examination of the relapse					
Visit only	5 (17.9)	5 (21.7)	5 (7.8)	4 (6.7)	19 (10.9)
Visit plus CT scan (plus any other examination)	13 (46.4)	10 (43.5)	29 (45.3)	37 (61.6)	89 (50.9)
Visit plus other examinations	3 (10.7)	5 (21.7)	9 (14.1)	4 (6.7)	21 (12.0)
CT scan only		1 (4.4)	2 (3.1)	7 (11.6)	10 (5.7)
Ultrasonography only			3 (4.7)	1 (1.7)	4 (2.3)
Vaginal cytology only	1 (3.6)				1 (0.6)
CA-125 only			1 (1.6)		1 (0.6)
Other combinations			2 (3.1)	1 (1.7)	3 (1.7)
Not specified	6 (21.4)	2 (8.7)	13 (20.3)	6 (10.0)	27 (15.3)
Therapy of recurrences					
Surgery alone	4 (14.2)	9 (14.1)	1 (4.3)	4 (6.7)	18 (10.3)
RT alone	5 (17.8)	6 (9.4)	9 (39.2)	7 (11.6)	27 (15.5)
CHT alone	8 (28.6)	20 (31.2)	2 (8.8)	23 (38.3)	53 (30.3)
HT alone	1 (3.6)	2 (3.1)	1 (4.3)	2 (3.3)	6 (3.4)
Surgery plus RT	2 (7.1)	2 (3.1)	1 (4.3)	2 (3.3)	7 (4.0)
Surgery plus CHT		4 (6.3)	1 (4.3)	3 (5.0)	8 (4.6)
Surgery plus CHT plus RT	1 (3.6)	2 (3.1)	1 (4.3)	1 (1.7)	5 (2.9)
Surgery plus HT	1 (3.6)			1 (1.7)	2 (1.1)
CHT plus RT	1 (3.6)	2 (3.1)		3 (5.0)	6 (3.4)
CHT plus HT				1 (1.7)	1 (0.6)
RT plus HT		2 (3.1)			2 (1.1)
CHT plus RT plus HT	1 (3.6)	1 (1.6)		1 (1.7)	3 (1.7)
No therapy	4 (14.3)	14 (21.9)	7 (30.5)	12 (20.0)	37 (21.1)

Abbreviations: CA-125, cancer antigen 125; CHT, chemotherapy; CT, computed tomography; HiR, high risk; HT, hormone therapy; INT, intensive; LoR, low risk; MIN, minimalist; RT, radiotherapy (external beam radiotherapy with or without brachytherapy); visit, physical examination (general and gynecological examinations).

[a]One hundred seventy-one relapses during the first 60 months and 4 afterward.

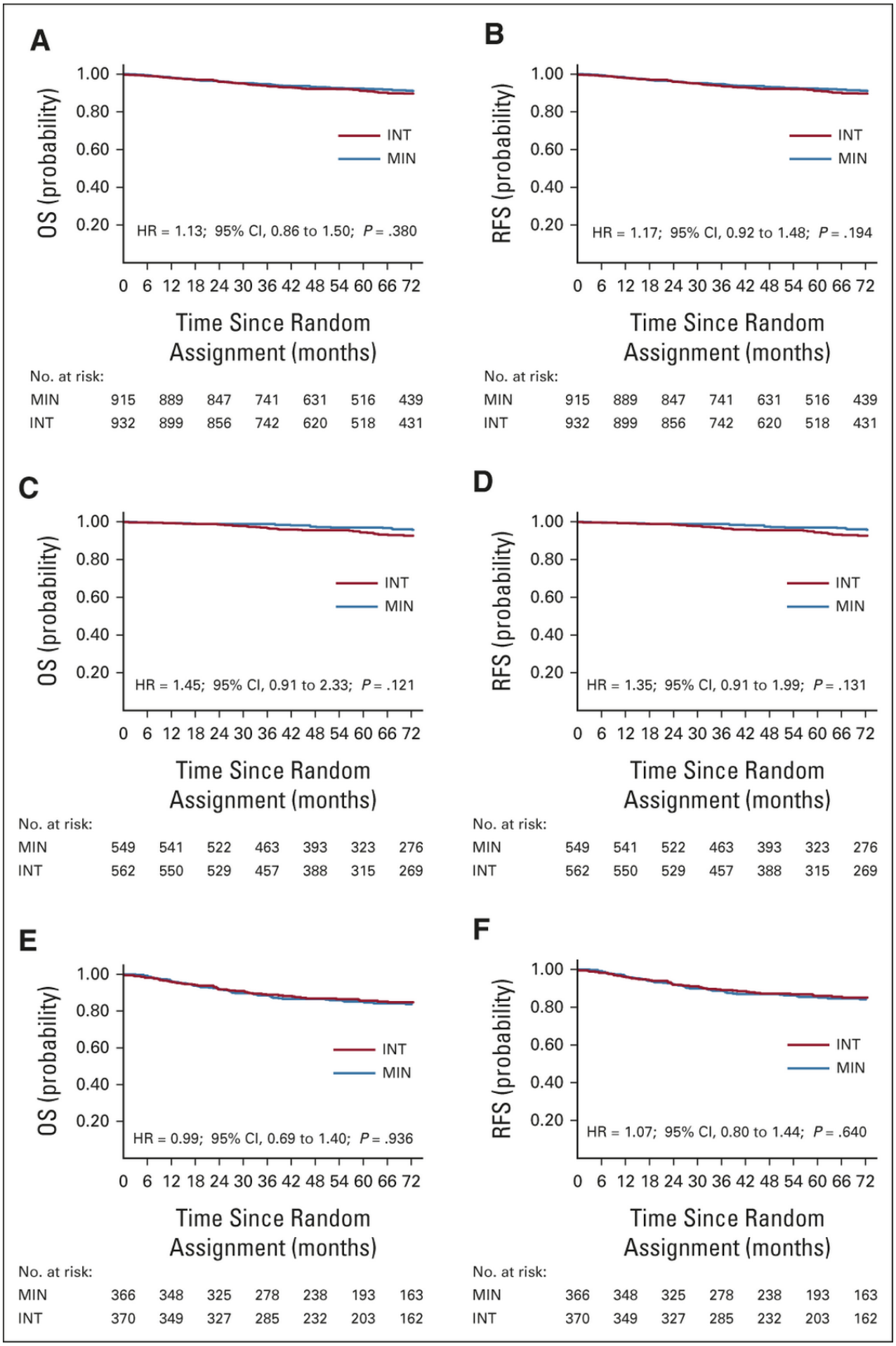
A
OS (probability)
1.00
0.80
0.60
0.40
0.20
INT
MIN
HR = 1.13; 95% CI, 0.86 to 1.50; P = .380
0 6 12 18 24 30 36 42 48 54 60 66 72
Time Since Random Assignment (months)
No. at risk:
MIN 915 889 847 741 631 516 439
INT 932 899 856 742 620 518 431
B
RFS (probability)
1.00
0.80
0.60
0.40
0.20
INT
MIN
HR = 1.17; 95% CI, 0.92 to 1.48; P = .194
0 6 12 18 24 30 36 42 48 54 60 66 72
Time Since Random Assignment (months)
No. at risk:
MIN 915 889 847 741 631 516 439
INT 932 899 856 742 620 518 431
C
OS (probability)
1.00
0.80
0.60
0.40
0.20
INT
MIN
HR = 1.45; 95% CI, 0.91 to 2.33; P = .121
0 6 12 18 24 30 36 42 48 54 60 66 72
Time Since Random Assignment (months)
No. at risk:
MIN 549 541 522 463 393 323 276
INT 562 550 529 457 388 315 269
D
RFS (probability)
1.00
0.80
0.60
0.40
0.20
INT
MIN
HR = 1.35; 95% CI, 0.91 to 1.99; P = .131
0 6 12 18 24 30 36 42 48 54 60 66 72
Time Since Random Assignment (months)
No. at risk:
MIN 549 541 522 463 393 323 276
INT 562 550 529 457 388 315 269
E
OS (probability)
1.00
0.80
0.60
0.40
0.20
INT
MIN
HR = 0.99; 95% CI, 0.69 to 1.40; P = .936
0 6 12 18 24 30 36 42 48 54 60 66 72
Time Since Random Assignment (months)
No. at risk:
MIN 366 348 325 278 238 193 163
INT 370 349 327 285 232 203 162
F
RFS (probability)
1.00
0.80
0.60
0.40
0.20
INT
MIN
HR = 1.07; 95% CI, 0.80 to 1.44; P = .640
0 6 12 18 24 30 36 42 48 54 60 66 72
Time Since Random Assignment (months)
No. at risk:
MIN 366 348 325 278 238 193 163
INT 370 349 327 285 232 203 162

FIG 2.

OS and RFS in the overall population (A, B), in low-risk patients (C, D), and in high-risk patients (E, F), by follow-up regimen. HR, hazard ratio; INT, intensive; MIN, minimalist; OS, overall survival; RFS, relapse-free survival.

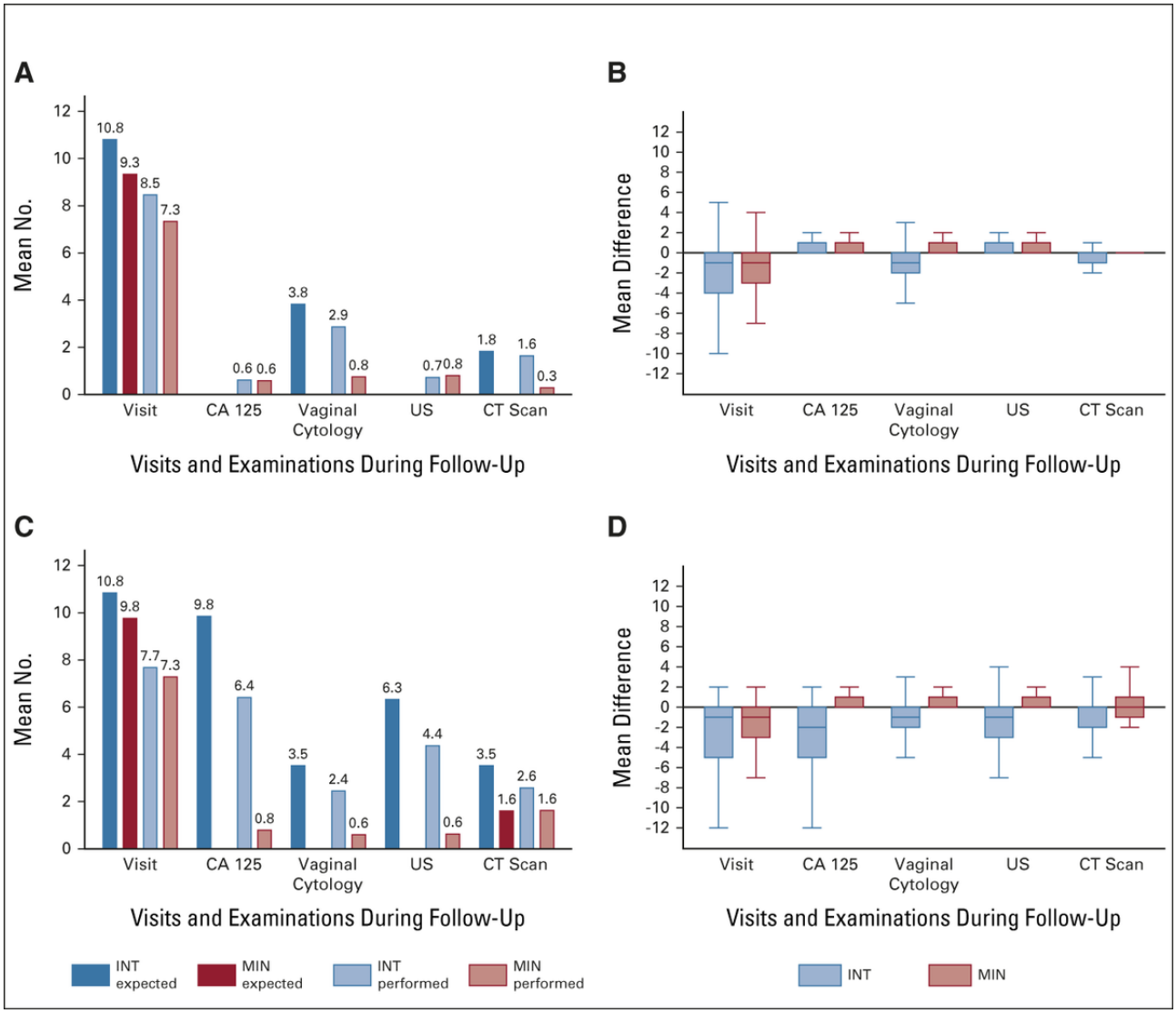

FIG 3.

(A, C) Mean number and (B, D) mean difference of performed minus expected visits and examinations per patient during follow-up, by risk of relapse (A, B: low-risk; C, D: high-risk). CA-125, cancer antigen 125; CT, computed tomography; INT, intensive; MIN, minimalist; US, ultrasound.

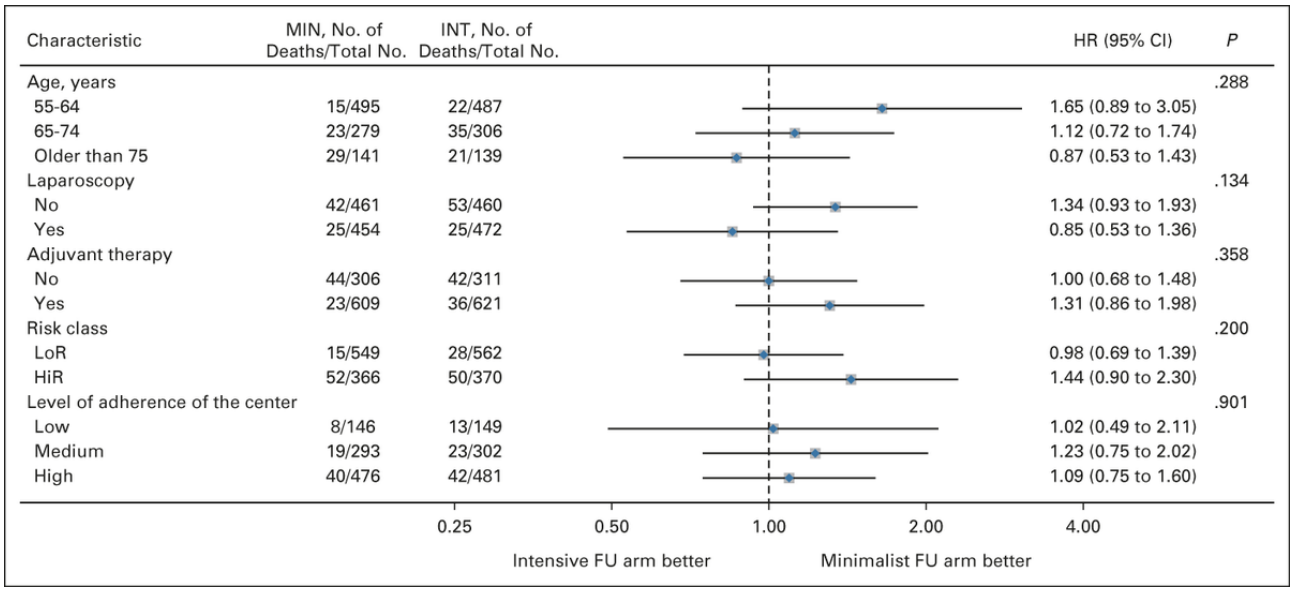

FIG 4.

Subgroup analysis of OS. P values are based on the interaction test. FU, follow-up; HiR, high risk; HR, hazard ratio; INT, intensive; LoR, low risk; MIN, minimalist; OS, overall survival.

TABLE A1. Follow-Up Visits and Examinations by Risk of Relapse (LoR, A; HiR, B) and Follow-Up Regimen

A. LoR Follow-Up Regimen and Procedures	Months Since Random Assignment														
	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
MIN															
Clinical examination	X		X		X		X		X	X	X	X	X	X	X
INT															
Clinical examination	X	X		X	X	X		X	X	X	X	X	X	X	X
Vaginal cytology					X				X		X		X		X
CT scan of the chest, abdomen, and pelvis					X				X						

B. HiR Follow-Up Regimen and Procedures	Months Since Random Assignment																
	0	4	6	8	12	16	18	20	24	28	30	32	36	42	48	54	60
MIN																	
Clinical examination	X	X		X	X	X		X	X		X		X	X	X	X	X
CT scan of the chest, abdomen, and pelvis					X				X								
INT																	
Clinical examination	X	X		X	X	X		X	X	X		X	X	X	X	X	X
CA-125		X		X	X	X		X	X	X		X	X	X	X	X	X
Abdomen and TV US		X		X		X		X		X		X		X		X	
Vaginal cytology					X				X				X		X		X
CT scan of the chest, abdomen, and pelvis					X				X				X		X		X

NOTE. Clinical examination includes the gynecologic examination.

Abbreviations: CA-125, cancer antigen 125; CT, computed tomography; HiR, high risk; INT, intensive; LoR, low risk; MIN, minimalist; TV, transvaginal; US, ultrasonography.

TABLE A1.

Follow-Up Visits and Examinations by Risk of Relapse (LoR, A; HiR, B) and Follow-Up Regimen

TABLE A2. Characteristics of Endometrial Cancer Relapses by Risk and Follow-Up Regimen

	LoR		HiR		
Characteristic	**INT (n = 28), No. (%)**	**MIN (n = 23), No. (%)**	**INT (n = 64), No. (%)**	**INT (n = 60), No. (%)**	**Total (N = 175[a]), No. (%)**
Relapse site					
Vaginal vault	8 (28.6)	11 (47.8)	6 (9.4)	4 (6.7)	29 (16.6)
Pelvis	1 (3.6)	1 (4.4)	7 (10.9)	11 (18.3)	20 (11.4)
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Not specified	2 (7.1)	3 (13.0)	2 (3.1)	1 (1.7)	8 (4.6)
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Visit plus other examinations	3 (10.7)	5 (21.7)	9 (14.1)	4 (6.7)	21 (12.0)
CT scan only		1 (4.4)	2 (3.1)	7 (11.6)	10 (5.7)
Ultrasonography only			3 (4.7)	1 (1.7)	4 (2.3)
Vaginal cytology only	1 (3.6)				1 (0.6)
CA-125 only			1 (1.6)		1 (0.6)
Other combinations			2 (3.1)	1 (1.7)	3 (1.7)
Not specified	6 (21.4)	2 (8.7)	13 (20.3)	6 (10.0)	27 (15.3)
Therapy of recurrences					
Surgery alone	4 (14.2)	9 (14.1)	1 (4.3)	4 (6.7)	18 (10.3)
RT alone	5 (17.8)	6 (9.4)	9 (39.2)	7 (11.6)	27 (15.5)
CHT alone	8 (28.6)	20 (31.2)	2 (8.8)	23 (38.3)	53 (30.3)
HT alone	1 (3.6)	2 (3.1)	1 (4.3)	2 (3.3)	6 (3.4)
Surgery plus RT	2 (7.1)	2 (3.1)	1 (4.3)	2 (3.3)	7 (4.0)
Surgery plus CHT		4 (6.3)	1 (4.3)	3 (5.0)	8 (4.6)
Surgery plus CHT plus RT	1 (3.6)	2 (3.1)	1 (4.3)	1 (1.7)	5 (2.9)
Surgery plus HT	1 (3.6)			1 (1.7)	2 (1.1)
CHT plus RT	1 (3.6)	2 (3.1)		3 (5.0)	6 (3.4)
CHT plus HT				1 (1.7)	1 (0.6)
RT plus HT		2 (3.1)			2 (1.1)
CHT plus RT plus HT	1 (3.6)	1 (1.6)		1 (1.7)	3 (1.7)
No therapy	4 (14.3)	14 (21.9)	7 (30.5)	12 (20.0)	37 (21.1)

Abbreviations: CA-125, cancer antigen 125; CHT, chemotherapy; CT, computed tomography; HiR, high risk; HT, hormone therapy; INT, intensive; LoR, low risk; MIN, minimalist; RT, radiotherapy (external beam radiotherapy with or without brachytherapy); visit, physical examination (general and gynecological examinations).

[a]One hundred seventy-one relapses during the first 60 months and 4 afterward.

TABLE A2.

Characteristics of Endometrial Cancer Relapses by Risk and Follow-Up Regimen