Gynecologic Oncology 184 (2024) 150–159

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Impact of different follow-up regimens on health-related quality of life and costs in endometrial cancer patients: Results from the TOTEM randomized trial

Rosalba Rosato [a,b,*], Annamaria Ferrero [c], Paola Mosconi [d], Giovannino Ciccone [b], Daniela Di Cuonzo [b], Andrea Evangelista [b], Luca Fuso [c], Elisa Piovano [e], Eva Pagano [b], Maria Elena Laudani [f], Luca Pace [c], Paolo Zola [f] TOTEM Collaborative Group [1]

[a] Department of Psychology, University of Turin, Italy
[b] Epidemiologia Clinica e Valutativa, AOU Città della Salute e della Scienza di Torino e CPO, Piemonte, Torino, Italy
[c] SCDU Ginecologia e Ostetricia, AO Ordine Mauriziano Torino, Dipartimento di Scienze Chirurgiche, Università degli studi di Torino, Torino, Italy
[d] Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy
[e] SCDU Ginecologia e Ostetricia 2U, Ospedale Sant'Anna, AOU Città della Salute e della Scienza di Torino, Torino, Italy
[f] Dipartimento di Scienze Chirurgiche, Università degli studi di Torino, Torino, Italy

HIGHLIGHTS

- Quality of life and healthcare costs of intensive follow up for endometrial cancer were assessed in the TOTEM trial.
- Intensive follow up, proved to have no benefit on survival, does not impact quality of life.
- Minimalist follow up is cost saving compared to an intensive regimen.
- A minimalist regimen for endometrial cancer follow up is the best choice for patients and the health care system.

ARTICLE INFO

Article history:
Received 4 September 2023
Received in revised form 16 January 2024
Accepted 29 January 2024
Available online xxxx

Keywords:
Health related quality of life
Healthcare costs
Patient reported outcomes
Endometrial cancer
Follow-up regimen

ABSTRACT

Purpose. To investigate whether intensive follow-up (INT) after surgery for endometrial cancer impact health-related quality of life (HRQoL) and healthcare costs compared to minimalist follow-up (MIN), in the absence of evidence supporting any benefit on 5-year overall survival.

Methods. In the TOTEM trial, HRQoL was assessed using the SF-12 and the Psychological General Well-Being (PGWB) questionnaires at baseline, after 6 and 12 months and then annually up to 5 years of follow-up. Costs were analyzed after 4 years of follow-up from a National Health Service perspective, stratified by risk level. The probability of missing data was analyzed for both endpoints.

Results. 1847 patients were included in the analyses. The probability of missing data was not influenced by the study arms (MIN vs INT OR: 0.97 95%CI: 0.87–1.08). Longitudinal changes in HRQoL scores did not differ between the two follow-up regimens (MIN vs INT SF-12 PCS: -0.573, CI95%: −1.31; 0.16; SF-12 MCS: -0.243, CI95%: −1.08; 0.59; PGWB: -0.057, CI95%: −0,88; 0,77). The mean cost difference between the intensive and minimalist arm was €531 for low-risk patients and €683 for high-risk patients.

Conclusion. In the follow-up of endometrial cancer after surgery, a minimalist treatment regimen did not affect quality of life and was cost-saving in both low-risk and high-risk recurrence patients. As previous results showed no survival benefit, a minimalist approach is justified. The relevant proportion of missing data on secondary outcomes of interest could be a critical point that deserves special attention.

* Corresponding author at: Department of Psychology, University of Turin, Italy.
E-mail address: rosalba.rosato@unito.it (R. Rosato).
Social media:

[1] Membership of the TOTEM collaborative group is provided at the end of the manuscript.

https://doi.org/10.1016/j.ygyno.2024.01.050

1. Introduction

Follow-up is an important aspect of cancer care, both for monitoring the disease and treatment and for addressing qualitative aspects such as quality of life, information, and the doctor-patient relationship [1]. However, follow-up practice is still very uneven. The recent Europe's Beating Cancer Plan sets out a series of strategic flagship initiatives that put the patient at the centre and aim to maximise the potential of new technologies and evidence to promote treatment equity, follow-up, and quality of life [2].

Endometrial cancer is the most common gynaecological cancer in Europe and the incidence is increasing, with approximately two-thirds of women still alive five years after diagnosis [3,4]. Different approaches to endometrial cancer follow-up have been investigated, e.g. patient-initiated or hospital-based [5–7], oncologist-led or general practitioner-led [8], intensive or minimalist [9], with varying duration and impact on women's lives. As reported in the ESGO/ESTRO/ESP guidelines, a survivorship care plan is needed to help patients cope with the long-term physical and psychosocial side effects of the disease and treatment and maintain their quality of life. All patients should be offered information on lifestyle, prevention and contact with support groups [10].

In addition to these controversial issues, previous reviews [11–13] found a lack of evidence on the cost and cost-effectiveness of cancer follow-up interventions and strategies.

As follow-up is so complex, patient opinion and the impact on quality of life and cost need to be carefully assessed to complement clinical outcomes. TOTEM (Follow-Up Regimen on Survival in Patients with Endometrial Cancer), a large, pragmatic, randomized controlled trial comparing an intensive versus a minimalist follow-up regimen in endometrial cancer, failed to demonstrate an improvement in 5-year overall survival with an intensive follow-up regimen [14]. According to the study protocol, health-related quality of life (HRQoL) and healthcare costs during follow-up were analyzed, primarily to assess whether an intensive protocol has an advantage in patient-reported outcomes and economic impact.

2. Methods

2.1. Study design and patients

The TOTEM study was conducted in 42 hospitals (in Italy and France) and involved patients who had undergone surgery for FIGO stage I-IV endometrial cancer and were in complete clinical remission. Patients were enrolled in the study between November 2008 and July 2018. After stratification by center and recurrence risk (low [LR] or high [HR]), patients were randomly assigned to an intensive [INT] or minimalist [MIN] hospital-based follow-up regimens. The primary outcome of the study was overall survival after 5 years of follow-up. HRQoL and healthcare costs were included as secondary outcomes in the study protocol.

2.2. QoL measures

Health-Related Quality of Life (HRQoL) was assessed at the beginning of the study, after 6 months, after 12 months and then annually up to the 5-year follow-up mark. For this assessment, the SF-12 (Short Form 12) questionnaire [15,16], was used, which consists of 12 questions leading to two summarized scores: the Physical Composite Score (PCS) and the Mental Composite Score (MCS), each ranging from 0 to 100. These scores were standardized to a population mean of 50 and a standard deviation of 10, with higher scores indicating better functioning.

Psychological well-being was measured using the short version of the Psychological General Well-Being Scale (PGWB) questionnaire [17,18]. This instrument provides an overview of self-perceived psychological well-being and provides a summary score on a scale from 0 (for the lowest well-being) to 110 (for the highest achievable well-being). All patients who completed at least one quality of life questionnaire during the follow-up period were included in the analyses. Both questionnaires were translated in Italian and validated [16,18].

2.3. Healthcare costs

A within-trial cost analysis with the perspective of the National Health Service (NHS) was performed including the costs of follow-up visits and diagnostic tests. Healthcare resource use data were derived from the case report form at the patient level. The assessment of resource costs was based on the NHS tariffs rewarded to providers as standard costs. Costs per patient were collected throughout the study period, but data in the fifth year of follow-up were affected by high censoring (>50%), so costs were only analyzed at four years [19,20] and were reported as total (four years) and per year of follow-up. Patients who did not have a visit or test during the follow-up period were excluded from the analyses.

2.4. Statistical analysis

Descriptive data were reported as number of patients and percentage by study arm, overall and by study outcome (HRQoL and cost). Given the missing data, we attempted to profile patients who did not complete the HRQOL questionnaires and patients who had no visits during follow-up. The level of completion of HRQoL questionnaires was described at different time points during follow-up and by centers.

The probability of missing data for each of the HRQoL questionnaires was modelled using a random-effects logistic regression model to account for repeated observations of patients over time and center of enrollment, including age (divided into ten-year classes), follow-up regimen, surgical technique, risk of relapse (splitting HR into those who received adjuvant chemotherapy or not) and follow-up time. A logistic model with the same set of covariates was estimated to assess the probability of missing cost data.

HRQoL analyses were performed according to the intention-to-treat principle. The change in SF-12 PCS, SF-12 MCS and PGWB scores during follow-up was reported as a comparison of means +/− 95%CI, overall and stratified by the combination of risk level and treatment supplied.

Using mixed random effects models, with a subject-related random effect to account for patients' repeated measurements and a random effect related to the participating center, longitudinal changes in HRQoL scores were compared between MIN and INT follow-up regimens, adjusting for age, follow-up time and clinical characteristics.

As centers had significantly different rates of HRQoL questionnaire completion, the potential impact of missing data on results was assessed in the tercile of centers with higher compliance as a sensitivity analysis.

Costs were analyzed by intention to treat and stratified by risk level. Patients who relapsed or died were included with full follow-up costs, as were patients who were followed for all 4 years. Patients with less than four years of follow-up were analyzed as censored and weighted by the inverse of the probability of not being censored (IPW) [21]. The weights were estimated using a non-parametric estimator, which is a version of the Kaplan-Meier estimator where censoring is treated as death. Costs were described as the average cost per patient at 4 years of follow-up and per single year. Costs were also described by type of healthcare resource (visits and diagnostic tests). The cost difference between the two study arms was calculated using ordinary least squares regression on weighted costs. The confidence interval around the mean cost difference between the two study arms was calculated using a bootstrap percentile method with 1000 resampling of the regression [22].

Finally, the observed costs were also compared with the expected ones based on the scheduling of visits and examinations (standard

costs) to account for the difference between the follow-up planned in the protocol and the follow-up actually performed.

3. Results

Between 2008 and 2018, 1884 patients were randomized and 1847 patients were available for analysis, of whom 1549 completed at least one HRQOL questionnaire (83.7%) and 1698 (92%) had at least one follow-up visit allowing for cost analysis (Fig. 1). French centers did not participate in the HRQoL data collection.

The characteristics of the populations analyzed, overall and by HRQoL and cost analyses, are shown in Table 1.

The completion rate of HRQoL questionnaires varied over time, ranging from 46.4% at baseline to 27.8% at five-year follow-up (see Appendix Fig. 1). We assessed the completion rate of the HRQoL during follow-up in the participating centers (Appendix, Fig. 2). This showed a considerable heterogeneity between centers and a positive correlation with the number of patients included ($r = 0.57$, $p = 0.00007$).

Missing HRQoL data were influenced by duration of follow-up, patient age and risk treatment groups, but were very similar between study arms. The likelihood of missing data increased with time (e.g. the risk of missing a data item is about 2 times higher at 24 months than at baseline and about 3 times higher at 60 months) and with increasing age (8% per decade, Appendix Table 1). The probability of missing data on follow-up costs was not associated with the study arm and showed the same pattern of associations observed in the HRQoL data (Appendix Table 2).

Figure 2 shows the mean and 95% CI of Physical, Mental and PGWB scores during the 5 years of follow-up, by study arm and risk treatment groups. Overall, both study arms showed consistent patterns in all three HRQoL scales within all strata, with a slight increase in scores over time.

Multivariable regression showed slightly lower mean HRQoL scores for the MIN versus the INT arm, although this effect was negligible and <1 point in all dimensions analyzed (SF-12 PCS: −0.573, 95%CI: −1.31; 0.16; SF-12 MCS: −0.243, 95%CI: −1.08; 0.59; PGWB: −0.057, 95%CI: −0,88; 0,77). The physical and psychological well-being index scores decreased with age. There was no significant effect of risk/treatment groups for either HRQoL measure, but physical composite scores were higher in those who underwent laparoscopic surgery. Finally, HRQoL increased during follow-up (Table 2), with a non-linear trend and most of the increase in the first 6 months.

In a sensitivity analysis, HRQoL changes were estimated only for patients enrolled in centers with higher compliance. This analysis confirmed the results obtained for the total sample (Appendix Table 3).

Table 3 describes the weighted costs and the cost difference between the two study arms after four years. For both risk levels, the MIN arm was cost-saving (cost difference: €531 for LR and €683 for HR). Table 4 in the appendix shows the contribution of the various items to the total costs, broken down by follow-up schedule. The TC scan was the main cost driver, accounting for most of the difference between the study arms in both risk levels. For HR patients, transvaginal ultrasound was also a relevant cost driver for the INT arm compared to the MIN arm. When analyzing cost accumulation during the 4 years of follow-up (Fig. 3), LR-INT and HR-MIN showed a very similar pattern, with a sharp decrease after the second year and costs close to LR-MIN in the fourth year. Only HR-INT had costs above €300/year during the entire follow-up period.

Compared to the standard costs expected according to the protocol (Appendix Fig. 3), the costs in LR-INT were much lower in the first two years of follow-up. After the second year, no differences were observed between the observed and expected costs in LR-INT and during the entire follow-up period in LR-MIN. In the HR strata, the observed costs in the INT arm were lower than expected throughout the follow-up period, while this pattern occurred in the MIN arm only in the first and second year.

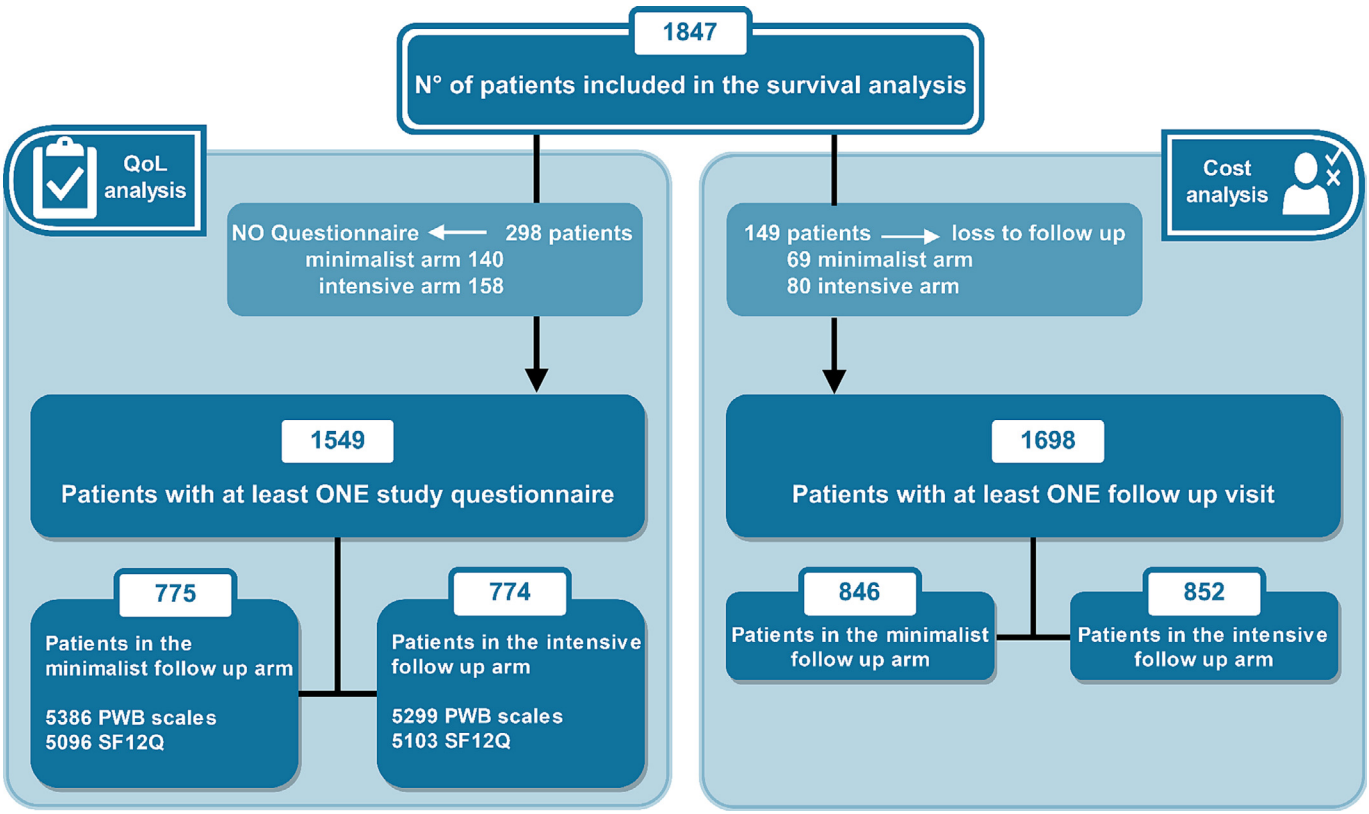


Fig. 1. Flow chart of the study.

Table 1
Descriptive characteristics of patients with at least one HRQoL questionnaire and cost data by follow-up strategies ($N = 1847$).

	HRQoL $N = 1549$				Cost $N = 1698$				Total N = 1847			
	Follow up protocol				Follow up protocol				Follow up protocol			
	Intensive		Minimalist		Intensive		Minimalist		Intensive		Minimalist	
	N	%	N	%	N	%	N	%	N	%	N	%
Age												
<55	133	17.2	156	20.1	143	16.8	162	19.1	153	16.4	171	18.7
55–64	289	37.3	276	35.6	312	36.6	306	36.2	334	35.8	324	35.4
65–74	249	32.2	227	29.3	279	32.7	253	29.9	306	32.8	279	30.5
75+	103	13.3	116	15.0	118	13.8	125	14.8	139	14.9	141	15.4
Type of surgery												
Laparoscopy	399	51.6	392	50.6	439	51.5	418	49.4	472	50.6	454	49.6
Open	375	48.4	383	49.4	413	48.5	428	50.6	460	49.4	461	50.4
Risk class												
Low Risk	493	63.7	485	62.6	532	62.4	516	61.0	562	60.3	549	60.0
High Risk	281	36.3	290	37.4	320	37.6	330	39.0	370	39.7	366	40.0
Type of therapy												
Surgery alone	542	70.0	540	69.7	584	68.5	575	68.0	621	66.6	609	66.6
Surgery & Adjuvant therapy	232	30.0	235	30.3	268	31.5	271	32.0	311	33.4	306	33.4
Risk-treatment groups												
Low Risk	493	63.7	485	62.6	532	62.4	516	61.0	562	60.3	549	60.0
High Risk without Adjuvant therapy	82	10.6	82	10.6	88	10.3	89	10.5	96	10.3	94	10.3
High Risk with Adjuvant therapy	199	25.7	208	26.8	232	27.2	241	28.5	274	29.4	272	29.7
Total	774	100.0	775	100.0	852	100.0	846	100.0	932	100.0	915	100.0

4. Discussion

4.1. Principal findings

The TOTEM trial showed no difference in survival among patients with MIN and INT follow-up at low and high risk of recurrence [14]. In the present study, results on the impact on HRQoL of a MIN versus an INT follow-up show no difference between the two study arms in HRQoL measures, with consistent results across the different scales analyzed and for both risk levels.

In terms of healthcare resource utilization, the MIN arm was cost-saving in both risk levels, although in the INT arms costs were lower than expected in the protocol, as fewer visits and examinations took place than planned. In addition, costs in the first 2 years of follow-up were much lower than expected in the LR-INT group. The physician adherence to INT schedules suggests that intensive monitoring was perceived as unnecessary or inconvenient in clinical practice. In MIN follow-up the procedure with the greatest impact on cost reduction was the CT scan. A reduction in routine CT scans during follow-up would help to reduce unnecessary radiation exposure and shorten waiting lists in favour of more appropriate indications.

Overall, these findings, together with the clinical results, confirm that a MIN approach is the preferred clinical care option. It can have a major impact on routine practice by avoiding unnecessary medicalization of women and reducing the waist of healthcare resources. In daily practice, these results may support clinicians in presenting and prescribing the minimalist follow-up option to patients, fostering acceptance and compliance.

4.2. Comparison with existing literature

Follow-up of oncological diseases is a tricky issue with implications for healthcare systems, clinical practice, and psychological and social aspects on patients' lives. In recommending oncological follow-up regimens, health-related quality of life is an important outcome that needs to be considered, along with survival, to ensure the best possible treatment. Still, besides quality of life, relational and emotional aspects, any follow-up program should also consider its financial cost [23]. A previous clinical trial of women with low-risk endometrial cancer showed that patients' fear of cancer recurrence was greater with self-managed follow-up than with hospital-based follow-up [5], but with cost benefits with self-management strategy for both patients and the healthcare system [6,7]. For ovarian cancer only few randomized trials comparing follow-up strategies are available, with limited evidence on HRQOL, psychological effects, and cost [24]. For breast cancer, several studies, between 1994 and 2020 [25–31], measured quality of life during follow up. These studies did not demonstrate superiority of an intensive model in terms of clinical outcomes, and women's quality of life. Anyway, the selection of low-risk patients and some methodological problems of available literature do not support strong conclusions and easy transferability to clinical practice. A review of the existing literature suggested that intensive follow-up of women with breast cancer was not likely to be cost-effective [12]. In non-metastatic colorectal cancer, a 2019 Cochrane review [32] pointed out that intensive follow-up led to little or no difference in overall survival. Still, no difference in the domains of quality of life, anxiety, or depression was evidenced for intensive follow up. Results were consistent even if the studies were carried out in different settings (general practitioner-led, nurse-led, or surgeon-led). The limited data on costs suggested that the cost of more intensive follow-up may be increased.

Available evidence on follow-up in patients with cancer is therefore variable, so it is quite difficult to compare different experiences. The results of the TOTEM study are in trend with results of the literature reported: intensive follow-up did not lead to improvements in survival, and the patients' quality of life was also not affected.

4.3. Strengths and limitations

Randomized clinical trials comparing follow-up regimens are very complex and long to conduct and do not have the same appeal as drug studies. As reported in the literature, these studies are limited in number and often with methodological fallacies. Not all studies accurately measure patients' quality of life or satisfaction. The TOTEM study, evaluating both survival and quality of life, adds a new piece to the knowledge of follow-up.

The low response rate in HRQOL data collection frequently affects longitudinal studies [33,34]. For example, in the PORTEC clinical trial [35] on endometrial cancer treatment, enrolling 660 eligible patients in 103 centers between 2006 and 2013, the completion rate at baseline for HRQoL questionnaires was 87% and it fell to 63% after 5 years of

A: SF12-PCS

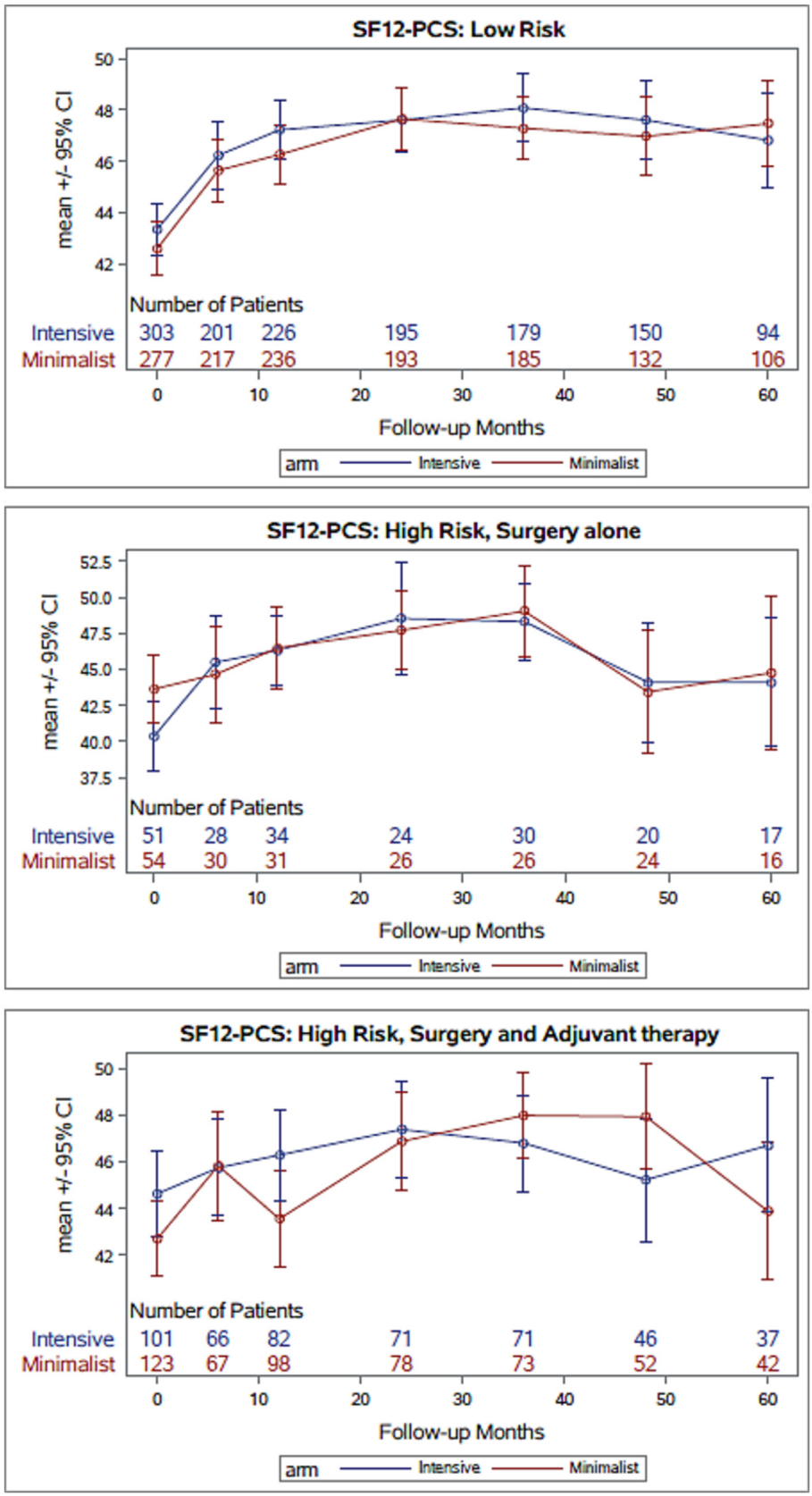
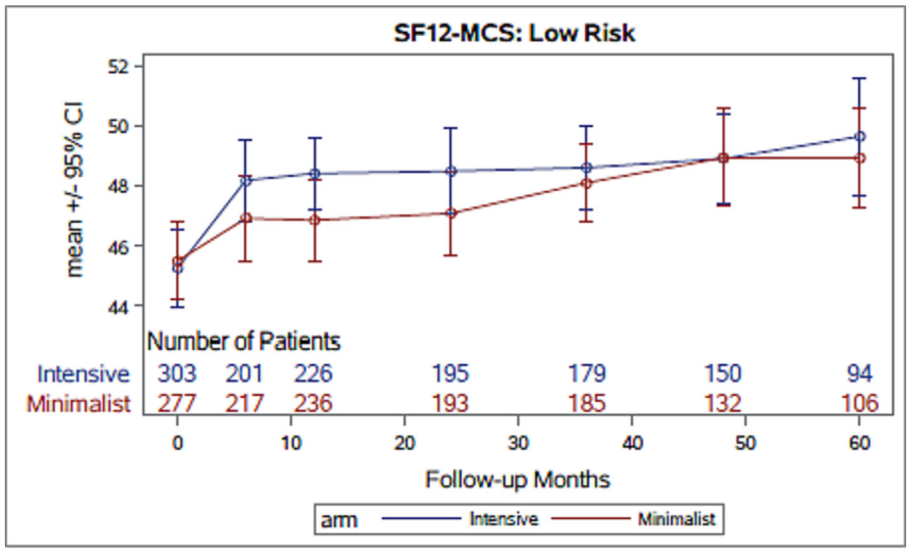
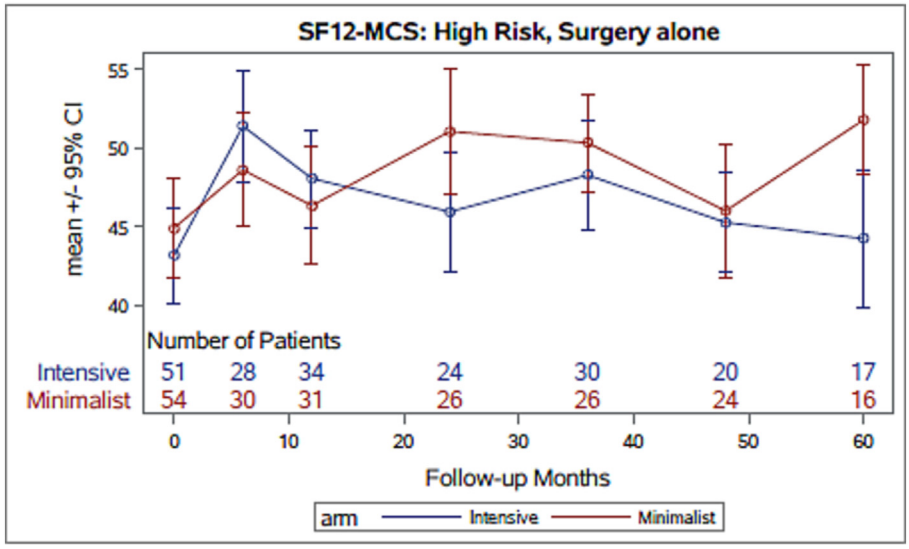


Fig. 2. Mean and 95%CI for physical (Fig. 2A: SF12-PCS), mental (Fig. 2B: SF12-MCS), and psychological wellbeing (Fig. 2C: PGWB) scores by treatment arms and stratified by risk-treatment groups (low risk; high risk without adjuvant therapies; high risk with adjuvant therapies).

B: SF12-MCS





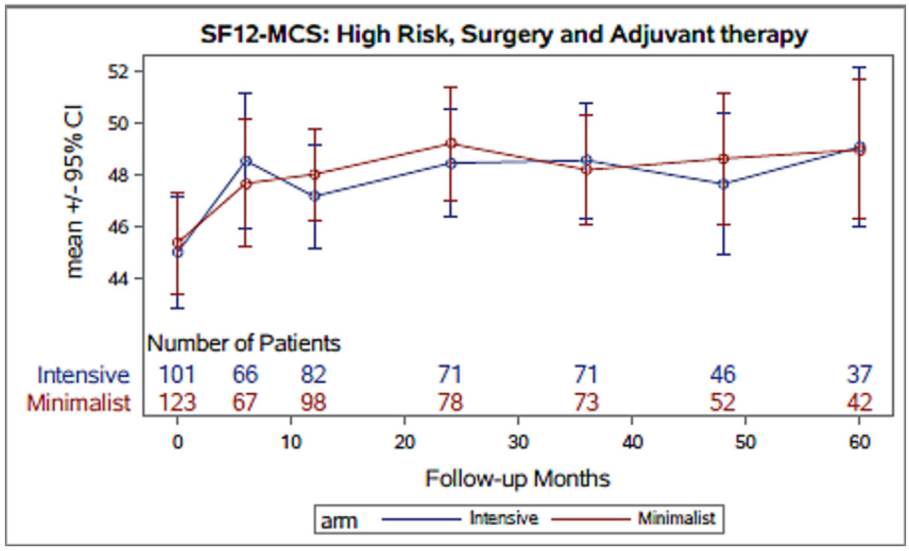
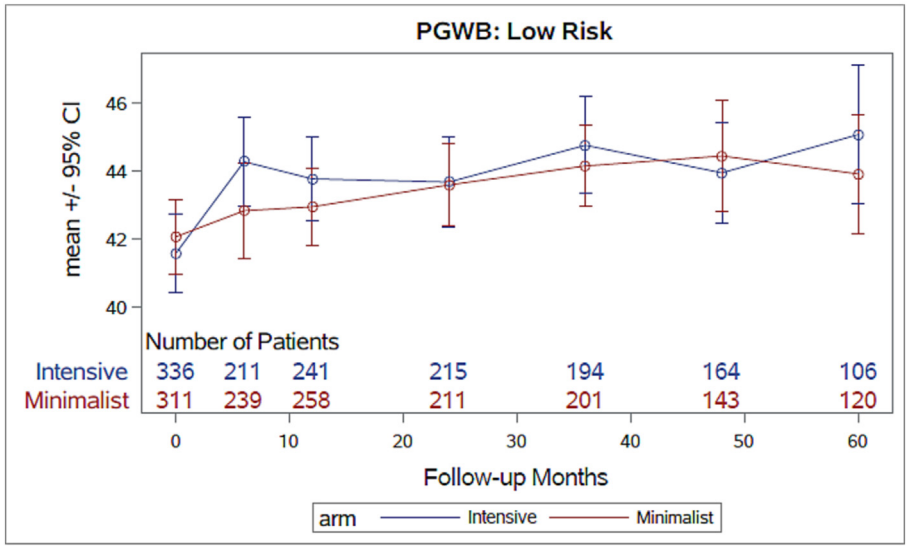
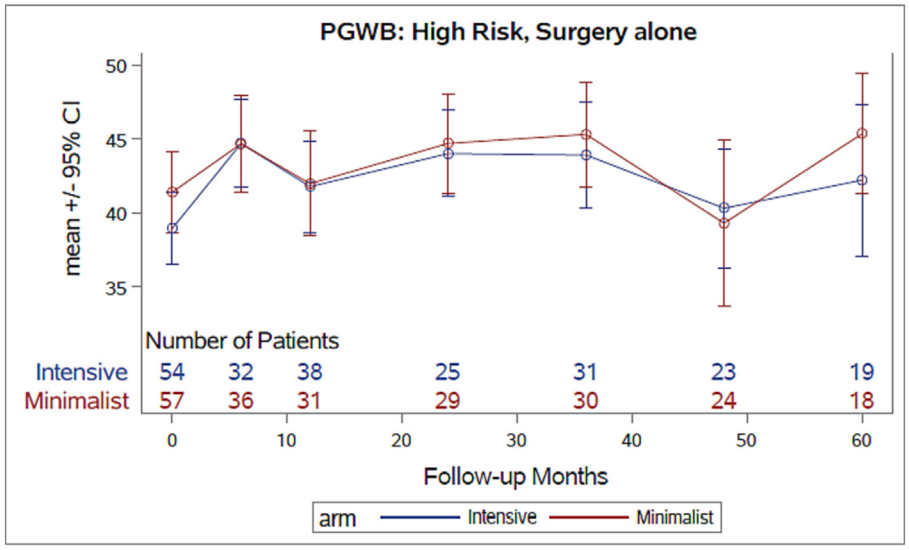


Fig. 2 (*continued*).

C: PGWB





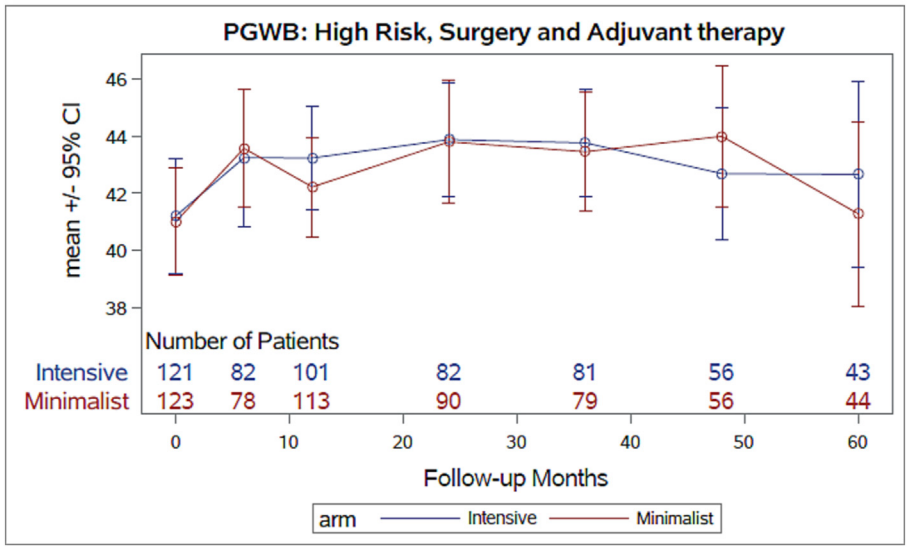


Fig. 2 (*continued*).

Table 2
Adjusted mixed-effects model estimates for follow-up regimen and patient characteristics on HRQoL: physical (SF -12 Physical Composite Score), mental (SF -12 Mental Composite Score), and psychological well-being (PGWB) scores.

	SF-12 Physical Composite Score			SF-12 Mental Composite Score			PGWB score		
	b	95CI%	p	b	95CI%	p	b	CI95%	p
Intercept	45,800	44,34; 47,26	<0,001	44,496	42,77; 46,22	<0,001	42,468	40,72; 44,21	<0,001
Age: 10 yrs	−0,796	−0,99; −0,60	<0,001	0,005	−0,17; 0,27	0,658	−0,290	−0,51; −0,07	0,009
Arm:									
Minimalist vs Intensive regimen	−0,573	−1,31; 0,16	0,1267	−0,243	−1,08; 0,59	0,5676	−0,057	−0,88; 0,77	0,891
Risk-treatment groups:									
High Risk without adjuvant therapies vs low risk	−0,402	−1,68; 0,87	0,5358	−0,820	−2,27; 0,63	0,2668	−1009	−2,44; 0,42	0,167
High Risk, with adiuv ther. vs low risk	0,053	−0,87; 0,98	0,9112	0,293	−0,76; 1,35	0,5821	0,044	−1,0; 1,09	0,934
Laparoscopy vs laparothomy	1308	0,49; 2,12	0,0017	0,109	−0,82; 1,04	0,8195	0,429	−0,50; 1,36	0,364
Follow up: baseline									
6	3073	2,33; 3,82	<0,001	2788	1,95; 3,62	<0,001	2058	1,34; 2,78	<0,001
12	3590	2,88; 4,30	<0,001	2635	1,84; 3,43	<0,001	1696	1,00; 2,39	<0,001
24	4577	3,82; 5,33	<0,001	2956	2,11; 3,80	<0,001	2024	1,29; 2,76	<0,001
36	4583	3,82; 5,34	<0,001	3268	2,41; 4,12	<0,001	2788	2,05; 3,53	<0,001
48	3899	3,06; 4,74	<0,001	3280	2,33; 4,23	<0,001	1754	0,93; 2,57	<0,001
60	4358	3,38; 5,32	<0,001	4904	3,81; 5,99	<0,001	3189	2,25; 4,12	<0,001

follow-up. The pragmatic TOTEM trial scheduled seven data collection points over 5 years, via self-administered questionnaires supplied by professionals during follow-up visits. A total of 1549 patients completed at least one questionnaire during the study (83.9%), with a response rate of nearly 50% at baseline and declining to 30% after 60 months. This trend demonstrates the difficulties of conducting such no-profit, pragmatic, long-term studies, with limited resources and the inclusion of centers usually excluded from other trials. The wide variability between centers and physicians indicates varying levels of interest and commitment to patient-reported outcomes, with low overall completeness of data collection and a decline over time. In the future, different strategies should be adopted to improve centers' involvement and to encourage patient participation, like using different data collection systems, i.e., the electronic ones. Greater involvement of nurses would also be recommended. Finally, local patient associations could be involved to identify the best approach for patient engagement. Nevertheless, the data set collected remains very interesting and represents a richness gathered thanks to the willingness of the women who completed the questionnaires and shared their experiences, and the clinicians who organized the distribution of the questionnaires and motivated the women to complete them. Analyzing studies with a relevant proportion of missing data on the patients' reported outcomes is a critical issue [36]. In our study, the interpretation of the results should consider the characteristics of the population included in the analysis, younger and less clinically impaired, likely to be more interested in quality of life and more confident in completing questionnaires. However, as this selection affected both arms of the study similarly, the biased effect on the results should be negligible.

We used two validated questionnaires, such as the SF12 and the Psychological Well-being Questionnaire to assess the physical, mental and psychological status of patients. They are short and well-known HRQoL questionnaires commonly used in clinical practice, especially during long follow-ups. Due to the 5 years' longitudinal nature of the study, we favored generic questionnaire to facilitate acceptance from patients and clinicians. We recognize this as a potential limitation of the study, as we did not use specific questionnaires assessing, for example, worries or fears related to disease recurrence.

Completely missing cost data were not imputed even if suggested in the literature [37]. This decision was supported by the results of the analysis of factors influencing the likelihood of missing data, in which no influence of the study arm could be demonstrated. Nevertheless, the large sample size allowed sufficient power for the analysis, even after excluding completely missing data.

The presence of patients with administrative censoring probably leads to a biased, lower estimate of actual costs and could be a limitation of the study. This problem is known in the literature for studies with a long enrollment period and a long follow-up [38]. However, the decision to include only four years of follow-up and to use the inverse probability weighting method limited this potential source of bias.

Table 3
Four years follow up costs (€) by risk level and study arm and cost difference between the two study arms.

Follow up costs (€)		N	Weighted costs		Cost difference between study arms	
			Mean	SD	Estimate	95%CI
Low Risk	Intensive	532	868.00	436.59	531	492–557
	Minimalist	516	337.18	235.03		
High Risk	Intensive	320	1529.05	651.10	683	599–769
	Minimalist	330	845.83	467.50		

5. Conclusions and implications

In summary, this large pragmatic multicenter study, after excluding any meaningful survival benefit of an intensive follow-up regimen, found no differences in HRQoL outcomes and confirmed potential cost savings, supporting the choice of a minimalist approach to endometrial cancer follow-up after completion of treatment and confirming that sometimes “less represents progress”, as stated in the editorial of the TOTEM trial by Beavis and Fader [39]. These results, together with clinical outcomes, can have a major impact on routine practice by limiting the burden that intensive follow-up can place on women and saving resources. This positive outcome of minimalist follow-up is fueling the debate about the possibility of organizing a routine follow-up by primary care physicians [9]. In light of the lessons from the COVID−19 pandemic, less intensive follow-up could also be organized remotely using computer platforms, the benefits of which are increasingly being demonstrated in terms of time savings, energy savings and effectiveness [40–42].

5.1. TOTEM collaborative group (alphabetical order)

Roberto Angioli (UO di Ginecologia Oncologica, Università Campus Bio-Medico, Roma, Italy), Roberto Berretta (UOC Ginecologia e Ostetricia, Azienda Ospedaliero Universitaria di Parma, Parma, Italy), Gloria Borra (SCDU Oncologia, AOU Maggiore della Carità, Novara, Italy), Enrico Busato (UOC Ginecologia e Ostetricia, Ospedale di Treviso, Treviso, Italy), Chiara Cassani (Dipartimento di Ostetricia e Ginecologia,

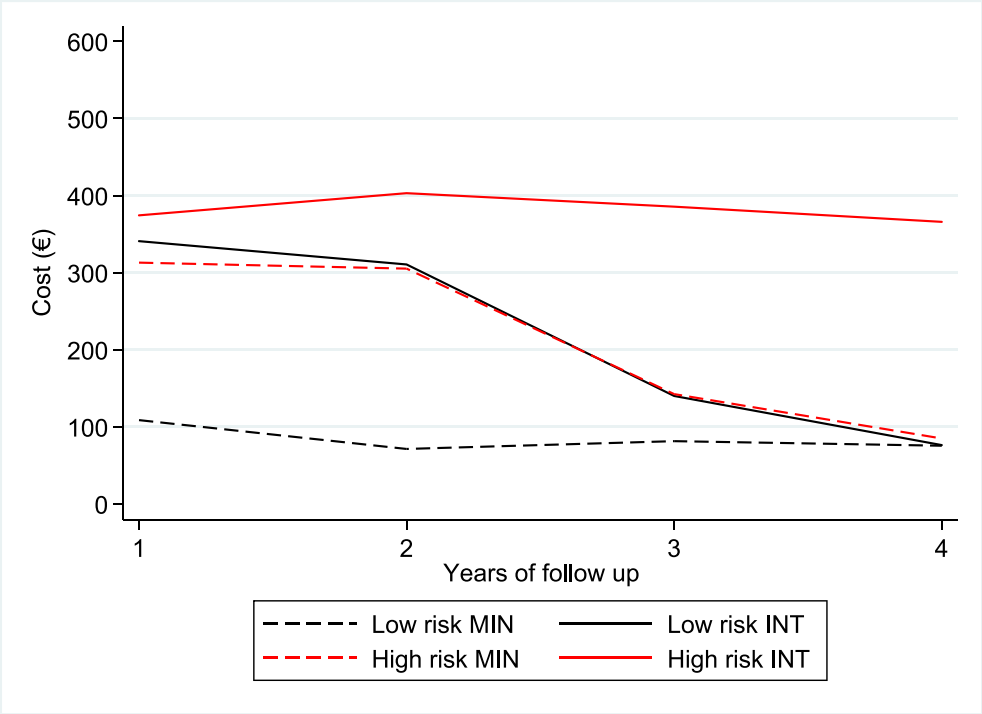


Fig. 3. Observed follow up costs (€) for year of follow-up, by risk level and study arm.

Fondazione IRCCS Policlinico San Matteo - Dipartimento di Scienze Clinico-Chirurgiche, Diagnostiche e Pediatriche, Università degli Studi Pavia, Pavia, Italy), Francesca Chiudinelli (Ginecologia e Ostetricia, Ospedale di Manerbio ASST del Garda, Manerbio, Italy), Giuseppe Comerci (UOC di Ostetricia e Ginecologia, Ospedale Santa Maria delle Croci, Ravenna, Italy), Vincenzo Distratis (SC Ostetricia e Ginecologia, Ospedale Martini, ASL "Città di Torino", Torino, Italy), Massimiliano Fambrini (Unità di Ginecologia e Ostetricia, Università degli Studi di Firenze - AOU Careggi, Firenze, Italy), Giorgio Giorda (SOC Chirurgia Oncologica Ginecologica, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy), Fabio Landoni (Clinica Ginecologica UNIMIB, Ospedale San Gerardo, Monza, Italy), Lucia Longo (Oncologia Area Sud AUSL Modena, Ospedale di Sassuolo, Modena, Italy), Vincenzo Dario Mandato (Unità di Ginecologia e Ostetricia, AO Arcispedale *S. Maria* Nuova, Reggio Emilia, Italy), Marco Marinaccio (Dipartimento di Ginecologia Ostetricia e Neonatologia (DIGON) AOU Consorziale - Policlinico, Bari, Italy), Mario Valenzano Menada (Clinica Ostetrica e Ginecologica, Dipartimento DINOGMI, Università di Genova, Genova, Italy), Anna Myriam Perrone (IRCCS Azienda Ospedaliero-Universitaria di Bologna, Dipartimento di Scienze Mediche e Chirurgiche DIMEC, Università di Bologna, Bologna, Italy), Francesca Piccione (Unità di Ginecologia Oncologica, Ex Fondazione per la Ricerca e la Cura dei Tumori Tommaso Campanella - Università Magna Graecia di Catanzaro, Catanzaro, Italy), Francesco Raspagliesi (SC Chirurgia Ginecologica, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy), Fabio Saccona (Epidemiologia Clinica e Valutativa, AOU Città della Salute e della Scienza di Torino e CPO Piemonte, Torino, Italy), Enrico Sartori (Divisione di Ostetricia e Ginecologia 1 e 2, Università di Brescia, ASST Spedali Civili di Brescia, Brescia, Italy), Cono Scaffa (Unità di Ginecologia Oncologica, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS Fondazione G. Pascale, Napoli, Italy), Giovanni Scambia (UOC di Ginecologia Oncologica, Policlinico Universitario Agostino Gemelli - Università Cattolica del Sacro Cuore, Roma, Italy), Eugenio Volpi (SC Ginecologia e Ostetricia, ASO S. Croce e Carle, Cuneo, Italy), Laura Zavallone (UOA Oncologia Medica, Ospedale degli Infermi, Biella, Italy).

Funding

The trial was funded by the Regional Oncology Network of Piemonte e Valle d'Aosta.

The study was registered with Clinicalrial.gov, NCT00916708.

CRediT authorship contribution statement

Rosalba Rosato: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Annamaria Ferrero:** Conceptualization, Data curation, Project administration, Writing – original draft, Writing – review & editing. **Paola Mosconi:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Giovannino Ciccone:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Daniela Di Cuonzo:** Formal analysis, Writing – review & editing. **Andrea Evangelista:** Formal analysis. **Luca Fuso:** Conceptualization, Project administration, Writing – review & editing. **Elisa Piovano:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing. **Eva Pagano:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Maria Elena Laudani:** Project administration, Writing – review & editing. **Luca Pace:** Project administration, Writing – review & editing. **Paolo Zola:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The trial was funded by the Regional Oncology Network of Piemonte e Valle d'Aosta.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.01.050.

References

[1] L.A. Jacobs, L.N. Shulman, Follow-up care of cancer survivors: challenges and solutions, Lancet Oncol. 18 (2017) e19–e29.
[2] European Commission, Europe's Beating Cancer Plan [Internet], [Cited 2023 May 11] Available from: https://ec.europa.eu/health/system/files/2022-02/eu_cancer-plan_en_0.pdf 2022.
[3] A. Oaknin, T.J. Bosse, C.L. Creutzberg, et al., Endometrial cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up, Ann Oncol Off J Eur Soc Med Oncol 33 (2022) 860–877.
[4] H. Sung, J. Ferlay, R.L. Siegel, et al., Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249.
[5] M. Jeppesen, P. Jensen, D. Hansen, et al., Patient-initiated follow up affects fear of recurrence and healthcare use: a randomised trial in early-stage endometrial cancer, BJOG 125 (2018) 1705–1714.
[6] S. Coleridge, J. Morrison, Patient-initiated follow-up after treatment for low risk endometrial cancer: a prospective audit of outcomes and cost benefits, Int. J. Gynecol. Cancer 30 (2020) 1177–1182.
[7] I. Luqman, R. Wickham-Joseph, N. Cooper, et al., Patient-initiated follow-up for low-risk endometrial cancer: a cost-analysis evaluation, Int. J. Gynecol. Cancer 30 (2020) 1000–1004.
[8] H.L. Fidjeland, M. Brekke, I. Vistad, General practitioners' attitudes toward follow-up after cancer treatment: a cross-sectional questionnaire study, Scand. J. Prim. Health Care 33 (2015) 223–232.
[9] L. Wullaert, K.R. Voigt, C. Verhoef, et al., Oncological surgery follow-up and quality of life: meta-analysis, Br. J. Surg. znad022 (2023).
[10] N. Concin, X. Matias-Guiu, I. Vergote, et al., ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma, Int. J. Gynecol. Cancer 31 (2021) 12–39.
[11] E. Pagano, S. Sobrero, C. Cavallero, et al., Economic considerations on the follow-up practice in gynecologic cancers: few lights and many shadows from a literature review, Int. J. Gynecol. Cancer 25 (2015) 1144–1150.
[12] M. Barbieri, G. Richardson, S. Paisley, The cost-effectiveness of follow-up strategies after cancer treatment: a systematic literature review, Br. Med. Bull. 126 (2018) 85–100.
[13] B.L. Høeg, P.E. Bidstrup, R.V. Karlsen, et al., Follow-up strategies following completion of primary cancer treatment in adult cancer survivors, Cochrane Database Syst. Rev. 11 (2019) 35.
[14] P. Zola, G. Ciccone, E. Piovano, et al., Effectiveness of intensive versus minimalist follow-up regimen on survival in patients with endometrial cancer (TOTEM study): a randomized, pragmatic, parallel group, multicenter trial, J Clin Oncol 40 (2022) 3817–3827.
[15] J.E. Ware, M. Kosinski, S.D. Keller, A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity, Med. Care 34 (1996) 220–233.
[16] B. Gandek, J.E. Ware, N.K. Aaronson, et al., Cross-validation of item selection and scoring for the SF—12 health survey in nine countries: results from the IQOLA project, J. Clin. Epidemiol. 51 (1998) 1171–1178.
[17] H. Dupuy, The Psychological general Well-Being (PGWB) Index, in Assessment of Quality of Life in clinical trials of cardiovascular therapies, Le Jacq Publishing, 1984 170–183.
[18] E. Grossi, N. Groth, P. Mosconi, et al., Development and validation of the short version of the psychological general well-being index (PGWB-S), Health Qual. Life Outcomes 4 (2006) 88.
[19] M. Raikou, A. McGuire, Estimating medical care costs under conditions of censoring, J. Health Econ. 23 (2004) 443–470.
[20] H.C. Wijeysundera, X. Wang, G. Tomlinson, et al., Techniques for estimating health care costs with censored data: an overview for the health services researcher, Clin Outcomes Res 4 (2012) 145–155.
[21] D.Y. Lin, Linear regression analysis of censored medical costs, Biostatistics 1 (2000) 35–47.
[22] D. Polsky, H.A. Glick, R. Willke, et al., Confidence intervals for cost–effectiveness ratios: a comparison of four methods, Health Econ. 6 (1997) 243–252.
[23] B.N. Fahy, Follow-up after curative cancer surgery: understanding costs and benefits, Ann. Surg. Oncol. 21 (2014) 731–732.
[24] G. Zachou, F. El-Khouly, J. Dilley, Evaluation of follow-up strategies for women with epithelial ovarian cancer following completion of primary treatment [internet], Cochrane Database Syst. Rev. (2023), Available from: https://doi.org/10.1002/14651858.CD006119.pub4. 2023[cited 2024 Jan 15].
[25] P. Ghezzi, Impact of follow-up testing on survival and health-related quality of life in breast Cancer patients: a multicenter randomized controlled trial, JAMA 271 (1994) 1587.
[26] E. Grunfeld, D. Mant, P. Yudkin, et al., Routine follow up of breast cancer in primary care: randomised trial, BMJ 313 (1996) 665–669.
[27] L. Brown, S. Payne, G. Royle, Patient initiated follow up of breast cancer, Psychooncology 11 (2002) 346–355.
[28] E. Grunfeld, M.N. Levine, J.A. Julian, et al., Randomized trial of long-term follow-up for early-stage breast cancer: a comparison of family physician versus specialist care, J. Clin. Oncol. 24 (2006) 848–855.
[29] M.L. Kimman, C.D. Dirksen, A.C. Voogd, et al., Nurse-led telephone follow-up and an educational group programme after breast cancer treatment: results of a 2×2 randomised controlled trial, Eur. J. Cancer 47 (2011) 1027–1036.
[30] M.N. Kirshbaum, J. Dent, J. Stephenson, et al., Open access follow-up care for early breast cancer: a randomised controlled quality of life analysis, Eur J Cancer Care (Engl) 26 (2017), e12577.
[31] C.L. Riis, P.T. Jensen, T. Bechmann, et al., Satisfaction with care and adherence to treatment when using patient reported outcomes to individualize follow-up care for women with early breast cancer – a pilot randomized controlled trial, Acta Oncol. 59 (2020) 444–452.
[32] M. Jeffery, B.E. Hickey, Hider PN: follow-up strategies for patients treated for non-metastatic colorectal cancer [internet], Cochrane Database Syst. Rev. (2019), Available from: https://doi.org/10.1002/14651858.CD002200.pub4. 2019[cited 2024 Jan 15].
[33] P. Mosconi, V. Torri, S. Cifani, et al., The multi-Centre assessment of quality of life: the interdisciplinary Group for Cancer Care Evaluation (GIVIO) experience in Italy, Stat. Med. 17 (1998) 577–585.
[34] S. Fielding, A. Ogbuagu, S. Sivasubramaniam, et al., Reporting and dealing with missing quality of life data in RCTs: has the picture changed in the last decade? Qual. Life Res. 25 (2016) 2977–2983.
[35] C.C.B. Post, S.M. de Boer, M.E. Powell, et al., Long-term toxicity and health-related quality of life after adjuvant chemoradiation therapy or radiation therapy alone for high-risk endometrial cancer in the randomized PORTEC-3 trial, Int J Radiat Oncol 109 (2021) 975–986.
[36] R. Mercieca-Bebber, M.J. Palmer, M. Brundage, et al., Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: a systematic review, BMJ Open 6 (2016), e010938.
[37] A. Gabrio, A.J. Mason, G. Baio, Handling missing data in within-trial cost-effectiveness analysis: a review with future recommendations, Pharm. Econ. - Open 1 (2017) 79–97.
[38] H.A. Glick, J.A. Doshi, S.S. Sonnad, et al., Analyzing Censored Cost, in Economic Evaluation in Clinical Trials, Second edition OUP Oxford, 2015.
[39] A.L. Beavis, A.N. Fader, Surveillance strategies in endometrial cancer care: why less represents Progress, J. Clin. Oncol. 40 (2022) 3790–3795.
[40] A.D. Falchook, G. Tracton, L. Stravers, et al., Use of mobile device technology to continuously collect patient-reported symptoms during radiation therapy for head and neck cancer: a prospective feasibility study, Adv. Radiat. Oncol. 1 (2016) 115–121.
[41] E. Furlong, A. Darley, P. Fox, et al., Adaptation and implementation of a mobile phone–based remote symptom monitoring system for people with cancer in Europe, JMIR Cancer 5 (2019), e10813.
[42] E. Basch, D. Schrag, S. Henson, et al., Effect of electronic symptom monitoring on patient-reported outcomes among patients with metastatic Cancer: a randomized clinical trial, JAMA 327 (2022) 2413–2422.