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Long-Term Quality of Life after Adjuvant Sequential Chemotherapy and/or Radiotherapy in Endometrial Cancer Survivors

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Abstract

Background: Multimodal treatments for high-risk endometrial cancer (EC) combining surgery followed by chemotherapy (CT) and radiotherapy (RT) (either concomitant RTCT or sequential CT followed by RT) have numerous side-effects that can negatively impact EC survivor's quality of life (QoL).

Objective: We aimed to evaluate the long-term impact on QoL of sequential adjuvant radio-chemotherapy (RTCT) for women treated for localized EC.

Methods: A retrospective study was conducted among patients with FIGO stage II or III endometrial cancer treated with surgery followed by sequential carboplatin-paclitaxel based chemotherapy and radiotherapy (RTCT), or by radiotherapy alone (RT), without recurrence within 5 years after surgery. Concomitant chemotherapy was not allowed. Quality of life was evaluated at least 2 years after the end of treatment by EORTC QLQ-C30, EN24, CIPN20 and HADS questionnaires.

Results: Of 97 eligible patients, 69 (71%) accepted to participate and 51 (53%) fulfilled the questionnaires. 50 patients were finally included, with 20 RTCT patients and 30 RT patients. Mean age was 67.9 years old, median time between the end of treatment and inclusion was 46.8 months [range: 30.47-55.7. Quality of life was significantly deteriorated in RTCT group (global QOL score 61.7 for RTCT vs 71.1 for RT, p=0.019). Scores of fatigue (38.9 vs 22.7; p=0.023), lymphedema (36.7 vs 19.1; p=0.051) and sensitive chemotherapy induced neuropathy (20.04 vs 6.86; p<0.001) were significantly higher in RTCT group. No difference in depression and anxiety rates was observed. RTCT and sensory neuropathy were associated with deteriorated quality-of-life in univariate analysis.

Conclusions: RTCT durably deteriorates quality of life more than 2 years after the end of treatment with persistent fatigue, chemo-induced neuropathy and lymphedema.

Keywords: Endometrial cancer; Quality of life; Adjuvant chemotherapy; Radiotherapy; Chemotherapy induced neuropathy.

Key Messages:

- Compared with RT alone, sequential RTCT has a significant impact on long-term quality of life of EC patients
- Long-term fatigue, lymphedema and peripheral neuropathy were higher

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for patients treated with RTCT in comparison with RT alone

- Impact of chemotherapy on quality of life of HREC patients should be measured and balanced with the expected benefits

Introduction

Endometrial cancer (EC) is the most prevalent gynecological cancer in developed nations, predominanatly affecting affects postmenopausal women with a mean age at diagnosis of 69 years old [1]. Women with EC often have comorbidities such as cardiovascular diseases, diabetes and obesity [2]. Therapeutic decisions for endometrial cancer (EC) involve risk stratification based on factors such as FIGO stage, histological type, grade (for endometrioid type), lymphovascular space invasion (LVSI), and molecular profile (MMR status, TP53 mutation, POLE mutation) [3]. Molecular classification, established by TCGA [4] includes POLE ultramutated (favorable prognosis), MMRd hypermutated (intermediate prognosis), TP53 mutated (unfavorable prognosis), and non-specific molecular profile (NSMP). Adjuvant treatment decisions for EC now consider molecular classification alongside clinical and pathological factors [5, 6]. About 15% of all women with localized EC are diagnosed with high-risk endometrial cancer (HREC) which comprises: (i) endometrioid endometrial cancer (EEC) stage I-II with TP53 mutation or stage III-IVA with MMRd or NSMP profiles; (ii) non-EEC stage I-IVA with MMRd or NSMP profiles. Hysterectomy with bilateral salpingo-oophorectomy and nodal staging is the primary HREC treatment. ESGO/ESTRO/ESP guidelines recommend radiotherapy with concurrent or sequential chemotherapy for HREC [3]. Pelvic radiotherapy (RT) is the primary adjuvant care for HREC, demonstrating similar recurrence and survival rates to chemotherapy but with fewer local relapses [7, 8]. The addition of chemotherapy to HREC treatment lacks standardized schemes. Concomitant radio-chemotherapy (RTCT), including radiochemotherapy with cisplatin followed by four cycles of carboplatin-paclitaxel , was analyzed in two phase III trial using radiotherapy alone for control group in the PORTEC3 trial [9]; and chemotherapy alone in the GOG-258 trial [10] . These phase III trials revealed improved overall survival in PORTEC3 (5% benefit at 5 years; HR =0.70 (95% CI 0.51–0.97); p adjusted=0.034) but mixed results in GOG-258 (HR 0.90 (90% CI, 0.74–1.10; p=0.20). Significant toxicity was observed with RTCT: in PORTEC3 trial, serious adverse events were 60% for RTCT (vs 12% with RT alone), with increasingly late toxicity events after 5-years (40% vs 28%) [11]. In the GOG-258 trial, patient reported outcome and quality of life (QoL) analysis indicated that, at the end of treatments, the RTCT group experienced worse QoL and gastro-intestinal toxicity. Both groups reported chemo-induced neuropathy (CIPN) which did not recover after 1 year [12]. The GOG-249 trial showed no significant benefit with vaginal cuff brachytherapy and chemotherapy compared to pelvic radiotherapy [13]. Retrospective studies reported a survival benefit in HREC patients treated with a combination of radiotherapy and chemotherapy (either sequential or sandwich method), compared with radiotherapy alone or chemotherapy alone [14-18]. The Mango-Iliade trial [19], though improving recurrence-free survival with sequential chemotherapy and radiotherapy (HR =0.63), didn't impact overall survival (as previous trials [20, 21]. Most patients received doxorubicin/epirubicin + cisplatin, with carboplatin-paclitaxel emerging as the first-line treatment for advanced endometrial cancer [22]. Acute toxicities, were higher with RTCT [23, 10], but long-term side effects and their impact on QoL in EC survivors are poorly documented [24-27]. The specific impact of sequential RTCT on long-term quality of life (QoL) remains poorly understood in real-life conditions. Thereby, we performed a study to evaluate the long-term impact of sequential RTCT after surgery among women with localized HREC.

Methods

Patients' selection

This multicenter case-control study enrolled women aged 18 or older with surgical stage II or III endometrial carcinoma, following FIGO 2009 criteria, who were relapse-free with a minimum 5-year follow-up post-treatment. All underwent hysterectomy and bilateral salpingo-oophorectomy with no residual tumor mass. Pelvic radiotherapy was administered to all; lombo-aortic radiotherapy was given to those with IIIC2 Figo stage, and brachytherapy was optional. Case patients had sequential carboplatin AUC5 -paclitaxel 175 mg/m2 J1=J21, excluding concomitant chemotherapy with radiotherapy, while control patients received only surgery and radiotherapy.

Trial design and endpoints

The primary objective was to compare long-term QoL between patients treated with adjuvant RTCT and those treated with RT alone, more than two years post-treatment. Secondary objectives included measuring persistent symptoms (chemo-induced neuropathy, depression, and anxiety) and analyzing the impact of confounding factors like age, BMI, and comorbidities.

Quality of life measurements

The EORTC EN24 questionnaire targets disease and treatment-specific aspects of QoL for endometrial cancer patients [28]. To evaluate chemo-induced peripheral neuropathy, the EORTC CIPN20 questionnaire includes sensory, motor, and autonomy scales, each converted to a 0–100 linear scale [29]. Higher scores indicate better functioning for the global health scale or functioning scales,

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while higher symptom scores reflect increased symptom severity. Depression and anxiety were measured using the HADS scale.

Statistical analysis

The study's sample size was determined to detect a 10-point difference in global EORTC-QLQC30 scores between RTCT and RT groups, with a 1:2 ratio and an alpha risk of 5%. A minimum of 39 patients (13 RTCT, 26 RT) was required for an 80% statistical power. Quantitative scores from QoL, physical activity, anxiety, and depression scales (EORTC QLQ-C30, EN-24, CIPN20, HADS) were described using means and standard deviations. Group comparisons utilized the Student t-Test (or Wilcoxon test for non-Gaussian data), and linear regression adjusted for lombo-aortic radiotherapy and FIGO stage compared QLQ-C30 and EN-24 scores. A logistic regression, considering a normative data threshold of 70 points for global quality health score from Nolte et al. (2019), identified risk factors associated with altered scores. Treatment and patient characteristics were analyzed in a multivariable model. Statistical analyses used R software version 4.0.2. The trial adhered to regulatory requirements and the Declaration of Helsinki. Central institutional review board and ethics committee approvals were obtained (CPP Sud-Est ID-RCB: 2017-A02809-44 / CPP 17/080). Patients provided written non-opposition consent before enrollment. The study is registered on Clinicaltrials.gov (NCT03466788).

Results

Between 2011 and 2015, 97 patients were eligible: 37 (38%) for the RTCT group and 60 (62%) for RT group. As shown in patient's flow chart, 20 patients (54% of eligible patients) were analyzed for the RTCT group and 30 (50% of eligible patients) for the RT group (Figure 1).

Patients' characteristics are summarized in Table 1. Median age at inclusion was 66.5 years in RTCT group and 70 in RT group. Characteristics were well balanced between the two groups except FIGO stage with more stage III in the RTCT group (90 % vs 34%, p<0.001). RTCT group tends to have more non endometrioid subtypes (35% vs 16%, p=0.1), and more patients with a history of depression (15% vs 0, p=0.058). Concerning adjuvant treatments, all patients received pelvic RT and 35 % of RTCT group received lombo-aortic RT vs 3% in RT group (p= 0.0046). A majority of patients received brachytherapy (85% for

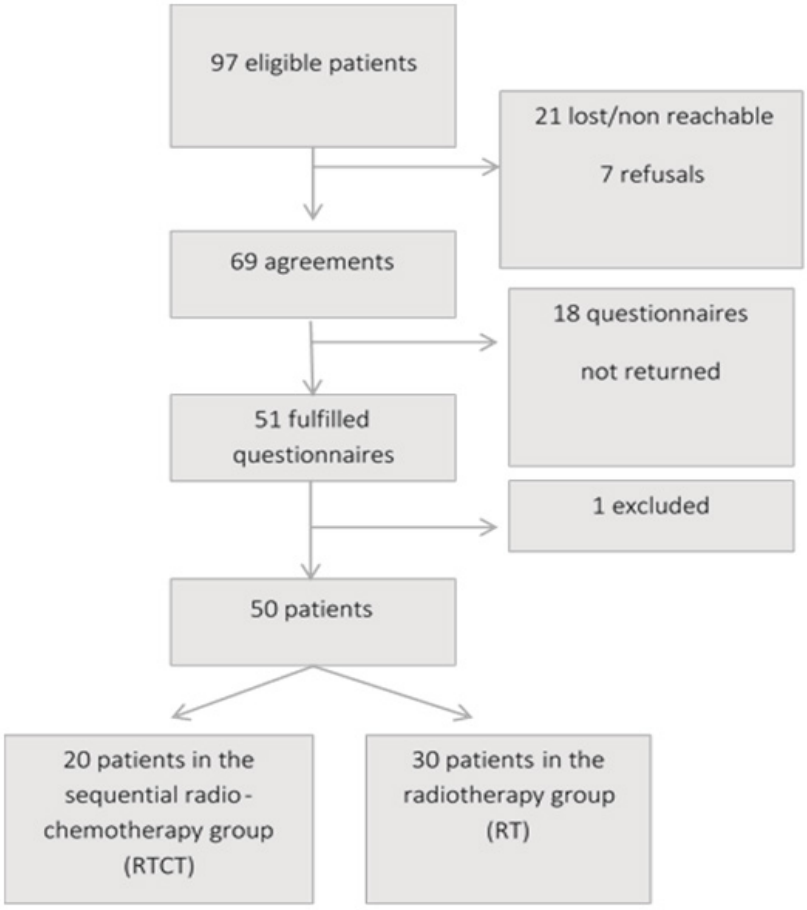

Figure 1: Flow chart of patient population

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RTCT, 97% for RT; p=0.29). For the RTCT group, all patients received carboplatin -paclitaxel with a median of 4 cycles. Chemotherapy was mainly delivered before radiotherapy (80%), 3 patients received chemotherapy after radiotherapy (15%) and 1 patient received 3 cycles before and 3 cycles after radiotherapy (5%). Only one patient interrupted prematurely paclitaxel at cycle 3 because of grade III neuropathy. No premature stop was observed for carboplatin.

Table 1: Clinical and pathological characteristics and treatment details

	RTCT N= 20	RT N=30	P VALUE
Age at inclusion (year)			0.11
Median [min-max]	66.5 [42-80]	70 [47-88]	
WHO performance score			0.6
0	16 (80%)	24 (80%)	
1	2 (10%)	2 (7%)	
2	1 (5%)	0 (0%)	
Unknown	1 (5%)	4 (13%)	
Comorbidity			
Diabetes	3 (15%)	6 (20%)	0.7
Hypertension	5 (25%)	11 (37%)	0.58
Cardiovascular	4 (20%)	5 (17%)	1
Depression	3 (15%)	0 (0%)	0.058
Median BMI (kg/m^2) [min-max]	29.9 [18.3-56.8]	27.1 [19.9-46.4]	0.33
Marital status			
In couple	13 (65%)	16 (55%)	0.69
Single	7 (35%)	13 (45%)	
FIGO 2009 stage			**0.00025**
II	2 (10%)	19 (66%)	
IIIA	4 (20%)	4 (14%)	
IIIB	0 (0%)	0 (0 %)	
IIIC1	8 (40%)	5 (17%)	
IIIC2	6 (30%)	1 (3%)	
Histological type			0.1
Endometrioid carcinoma	13 (65%)	25(84%)	
Serous carcinoma	5 (25%)	1 (3%)	
Clear cell carcinoma	2 (10%)	3 (10%)	
Mucinous carcinoma	0 (0%)	1 (3%)	
Surgery			
Total abdominal hysterectomy and bilateral salpingo-oopherectomy	12 (60%)	18 (60%)	1
Total laparoscopic hysterectomy and bilateral salpingo-oopherectomy	8 (40%)	11 (37%)	1
Pelvic node dissection	18 (90%)	21 (70%)	0.16
Lombo-aortic node dissection	13 (65%)	13 (43%)	0.16
Revision surgery	8 (40%)	7 (23%)	0.34
Radiotherapy			
Pelvic radiotherapy	20 (100%)	30 (100%)	1
Lombo-aortic radiotherapy	7 (35%)	1 (3%)	**0.0046**
Brachytherapy	17 (85%)	29 (97%)	0.29
Chemotherapy			
Before radiotherapy	17 (85%)	-	
After radiotherapy	4 (20%)	-	
Number of cycles: Median [min-max]	4 [3-6]	-	

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Median delay between surgery and questionnaires completion was 40.6 months [min 23.9; max 93.0], without difference between groups (p=0.39). In RTCT group, 15% were depressed and 47.4% suffered from anxiety versus 10.3% and 37.9% in RT group, respectively (p=0.68 and p=0.73). QoL and symptoms issued from EORTC QLQ-C30 and EN24 questionnaires are reported in Tables 2 and 3. Patients treated by RTCT had significantly lower global QoL score than patients treated by RT alone (61.7 vs 71.1 respectively, adjusted p=0.049). No significant difference between groups was observed on functioning scale (physical, role, emotional, cognitive and social scales) of the QLQ-C30 and EN24 (sexual scales). Sexual interest and activity were low in both groups. Data about sexual enjoyment were irrelevant due to 68 % of missing data. RTCT patients complained most frequently of fatigue (38.8 vs 22.7, adjusted p=0.01) and lymphedema (36.6 vs 19.1, adjusted p=0.03). After adjustment on lombo-aortic radiotherapy and FIGO stage, poor body image score did not differ between groups (23.7 vs 8.1, adjusted p=0.13).

All subscales responses were converted to 0 to 100 scales (according to the EORTC guidelines). Higher scores for functioning items and global quality of life scale represent a

Table 2: Quality of life and symptoms using the EORTC QLQ-C30 at least 2 years after the end of the treatment

	RTCT N= 20	RT N=30	P	ADJUSTED BETA	Adjusted P
Global health status/quality of life	61.7± 13.3	71.1 ± 18.9	**0.019**	**-11.7 [-23.4; -0.02]**	**0.049**
QLQ-C30 functioning scales					
Physical	75.3 ± 19	76.8 ± 23	0.49	-2.4 [-18.1;13.4]	0.76
Role	77.2 ± 24.3	80.7 ± 27	0.39	-2.6 [-21.9;16.7]	0.79
Emotional	67.1 ± 27	79.5 ± 24.6	0.088	-11.3 [-30.3;7.6]	0.23
Cognitive	76.7 ± 21.9	81 ± 24.3	0.38	-4.8 [-21.4;11.8]	0.56
Social	75.4± 30.6	84.6 ± 24.9	0.32	-11.1 [-31.3;9.2]	0.28
QLQ-C30 symptom scales					
Fatigue	38.8 ± 23.8	22.7 ± 17.7	**0.023**	**20.2 [5.3;35.1]**	**0.01**
Nausea and vomiting	5.8± 16.5	8.9 ± 24.6	0.85	-4.5 [-20.0;10.9]	0.56
Pain	31.6 ± 33.7	25.0 ± 25.5	0.67	7.6 [-13.1;28.2]	0.46
Dyspnea	22.8 ± 25	16 ± 23.3	0.32	2.1 [-15.2;19.4]	0.81
Insomnia	36.8 ± 31.2	32.2± 24.4	0.76	3.1 [-17.2;23.3]	0.76
Loss of appetite	15 ± 27.5	7.1 ± 16.6	0.3	2.6 [-12.5;17.7]	0.73
Financial difficulties	18.3 ± 33.3	6 ± 15.9	0.16	16[-1.9;33.8]	0.08

All subscales responses were converted to 0 to 100 scales (according to the EORTC guidelines). Higher scores for functioning items and global quality of life scale represent a better level of functioning. For the symptom scales, a higher score reflects a higher level of symptoms. Beta parameters of linear regression are adjusted on lombo-aortic radiotherapy and FIGO stage.

Table 3: Quality of life and symptoms using the EORTC QLQ-EN24 dedicated to specific aspects of endometrial cancer at least 2 years after the end of the treatments

	RTCT N= 20	RT N=30	P	ADJUSTED BETA	ADJUSTED P
EN24 functioning scales					
Sexual interest	8.8 ± 15.1	9.9 ± 22.3	0.82	-5.7 [-20;8.6]	0.43
Sexual activity	8.3 ± 14.8	11.1 ± 20.7	0.84	-6.1 [-19.4;7.1]	0.36
Sexual enjoyment*	33.3 ± 29.8	30 ± 33.1	0.86	2.4 [-38.8;43.5]	0.9
EN24 symptom scales					
Lymphedema	36.6± 31.3	19.1± 20.0	0.051	**20.3 [2.2;38.3]**	**0.03**
Urological symptoms	23.7 ± 25	25± 26.5	0.82	5.6 [-12.3;23.5]	0.53
Gastrointestinal symptoms	23.5 ± 19.2	20.2 ± 22	0.4	2.7 [-12.5;17.9]	0.72
Body image problems	23.7 ± 25.7	8.1 ± 17	**0.028**	11.7 [-3.5;27]	0.13
Sexual/vaginal problems*	27.8 ± 32.8	44.4 ± 37.8	0.32	-38.1 [-79.7;3.5]	0.07
Back/pelvic pain	48.1 ± 32.8	35.6 ± 30.8	0.21	13.4 [-9.7;36.5]	0.25
Muscular/joint pain	38.6± 33.8	33.3 ± 28.2	0.65	8.1 [-13.9;30.1]	0.46
Hair loss	26.6 ± 44.1	13.8 ± 24.4	0.7	15.5 [-8.0;39.1]	0.19
Taste change	8.8 ± 26.9	3.6 ± 10.5	0.94	4.7 [-8.5;18.0]	0.47

All subscales responses were converted to 0 to 100 scales (according to the EORT guidelines). Higher scores for functioning items and global quality of life scale represent a better level of functioning. For the symptom scales, a higher score reflects a higher level of symptoms. Beta parameters of linear regression are adjusted on lombo-aortic radiotherapy and FIGO stage. *34 missing values.

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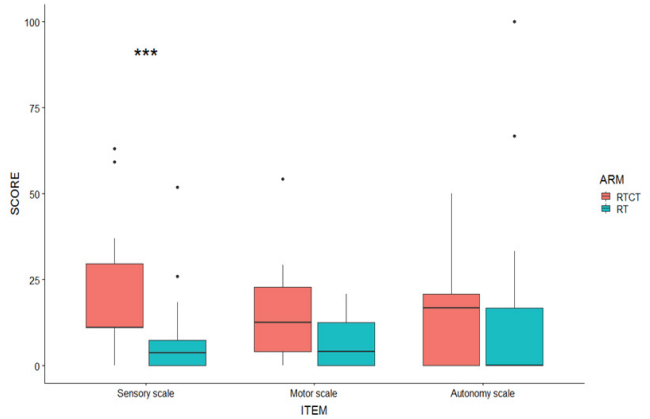
Patients of the RTCT group had persistent peripheric neuropathy with significantly higher sensory score (20.04 vs 6.86, adjusted p<0.001) (Figure 2). The most frequent neurologic symptom reported was severe tingling in the hands in 21.1% patients in the RTCT group versus 3.4 % in the RT group (p=0.001). No difference was observed for motricity and autonomy. RTCT, sensory neuropathy and comorbidities were shown to be associated with an altered QLQ-C30 global score (score<70), with OR of 7.41, 1.15 and 2.43 respectively in univariate logistic regression. In multivariable model adjusted on age, obesity and lombo-aortic radiotherapy, only RTCT remained associated with altered QoL (OR 25.1 [2.06-1191.98], Figure 3).

Discussion

Summary of Main Results

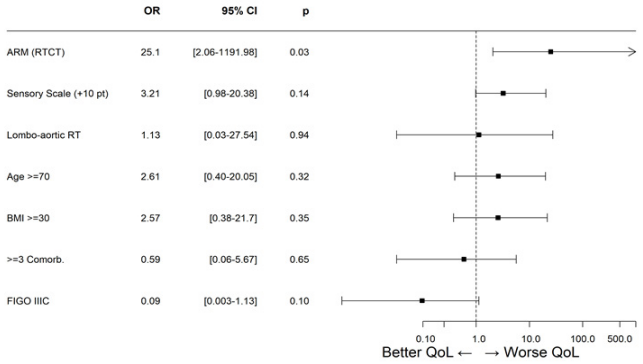
This case-control study is one of the firsts to describe the long-term impact of adjuvant sequential radio-chemotherapy on QoL in real-life conditions for patients with EC. Sequential RTCT durably deteriorate global QoL of women treated for localized HREC with more fatigue, lymphedema and persistent CIPN, compared with RT patients, more than two years after treatments.

Figure 2: Self-reported neurological symptoms using CIPN20 subscales.



A higher score indicates a higher level of symptoms. ***significant difference with p value < 0.05 adjusted on lombo-aortic radiotherapy and FIGO stage.

Figure 3: Multivariate analysis on factors influencing long term global quality of life by logistic regression.



Global health quality of life scores under 70 points were considered altered.

Results in the Context of Published Literature

Few studies have assessed the impact of this sequential schedule on long-term QoL [24-26]. In our study, most patients received 4 cycles of carboplatin-paclitaxel followed by radiation, aiming for reduced acute toxicity compared to concomitant chemoradiation. Patients in the RTCT group showed lower global QoL scores than those in the RT group, with more fatigue and lymphedema. In a cohort of 35 EC patients, Mustea et al [26] conducted a study with longitudinal assessment of QoL during sequential RTCT in real life conditions. Median age was 65 years and median BMI 27 kg/m2. Global QLQ C30 score at the end of treatment was particularly poor (score of 50), which is similar to our results. A SEER database analysis in women ≥65 years with stage III uterine cancer showed lower early toxicity with RT compared to chemoradiotherapy, while CT and RTCT had equivalent risks [27]. Late toxicity was comparable for CT, RT and RTCT. Arden et al. reported benefits in overall chronic toxicity with sandwich therapy, but lacked QoL analysis [18]. Datta et al. studied sexual health and QoL in 132 EC patients at 6 months and 1 year post-treatment, revealing lower QoL scores for those who underwent surgery, chemotherapy, and radiation, but the study lacked focus on treatment type and sequence, and long-term evaluation [24].

Two major studies (PORTEC3 and GOG258) investigated the impact of concomitant RTCT on EC patients QoL. Control groups were different: PORTEC3 employed radiotherapy alone and GOG258 used chemotherapy alone (6 cycles of carboplatin-paclitaxel). Comparisons between these studies and ours are notable for differences in patient demographics, comorbidities, follow-up durations, and evaluation tools. In GOG258 trial, follow-up was shorter than in our study (median follow-up 1.3 years vs 3.3 years, respectively), and patients were younger with fewer comorbidities (median age 60 versus 66.5 years in our RTCT group). PORTEC3 trial also included younger patients (median age of 62 vs 66.5

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years old in our RTCT group) and less comorbidities (7.5% of cardiovascular disease vs 20% in our RTCT group for example). GOG258 reported a lower Trial Outcome Index for concomitant RTCT patients, but this difference wasn't considered clinically significant. PORTEC3 suggested that despite higher toxicity in the RTCT group, global QoL recovered to match the RT group at 5 years. Notably, QoL scores in PORTEC3 at 2 years were higher than our study, potentially due to population differences. PORTEC3 did not detail factors like BMI, depression, or marital status, and its baseline QoL was notably higher than age-matched normative values (EORTC manuel [30]). This may stem from trial selection bias favoring women likely to recover from late toxicities and maintain a high QoL.

Our study revealed a high neuropathy score in the RTCT group. However, we did not find a clear correlation between persistent CIPN and diminished QoL, potentially due to a small sample size. CIPN is a recognized influencer of cancer survivor QoL, particularly affecting EC patients who are at higher risk due to a prevalent diabetes background [31, 32]. In the GOG258 trial, both groups reported a high level of neuropathy that did not impact global QoL 16 months post-treatment. In PORTEC 3, grade 2 neuropathy rates were higher in the RTCT arm at 2, 3, and 5 years post-treatment compared to the RT arm [33]. After adjusting for FIGO stage and lombo-aortic radiotherapy, we found that RTCT patients reported more lymphedema. Despite no statistical difference, there was a tendency for RTCT patients to undergo more pelvic and lombo-aortic node dissection. Forsse et al. and a retrospective study linked chemotherapy (carboplatin-paclitaxel and docetaxel, respectively) to lymphedema [34, 38], but further investigations are needed on lower limb lymphedema and taxanes.

In a longitudinal study within the MoMaTEC2 trial, Forsse et al [34] evaluated the impact of lymphadenectomy and adjuvant chemotherapy on EC patients' symptoms, function, and quality of life. Comparable to our population in age and BMI, baseline QoL matched an age-weighted reference cohort. Two years post-treatment, the adjuvant chemotherapy group experienced greater reductions in physical functioning, increased lymphedema, and more neuropathy compared to the surgery-only group, with associations noted for fatigue, lymphedema, and neuropathy. In our study, RTCT patients had higher fatigue than RT patients (38.8 vs 22.7). While fatigue is commonly reported in EC patients, specific data on chemo-induced fatigue is lacking. PORTEC3 showed equivalent fatigue scores at 2 years. Long-term impact in our "real-life" population might be worsened by age and comorbidities. Various studies have attempted lifestyle interventions with some success, but they are particularly challenging in EC patients who often have correctable risk factors but may be less receptive due to age, sedentary lifestyle, and comorbidities [35-37].

Strengths and Weaknesses

This study has several limits. The number of patients is quite low, partly due to the competing PORTEC3 trial that was opened at the same time in all the centres. Only 52 % of eligible patients responded to questionnaires, this proportion of responders was equivalent in the two groups. However, 50% response rate is expected in this type of study [39]. Patients treated with RTCT were not matched with controls (RT) resulting in a slight difference between the two groups characteristics with more advanced FIGO stage and more lombo-aortic radiation in the RTCT group. This difference is explained by selection bias, as advanced FIGO stage III EC patients are recommended to receive adjuvant chemotherapy. However, even after adjustment on FIGO stage and lombo-aortic radiation, global score of QoL and fatigue remained significantly worse in the RTCT group.

Implications for Practice and Future Research

Expected benefit of RTCT must be balanced with acute and long-term toxicity. Benefit of chemotherapy is limited and probably not efficient for all the clinicopathological subgroups. A retrospective study of PORTEC3 trial [40], exploring the impact of the molecular classification, showed that POLE hypermutated had an excellent prognosis in both arms (5 years RFS >96%), and that MMRd did not seem to benefit from chemotherapy (5 years RFS 75.6% for RT vs 72.4% for RTCT; p= 0.687). Only p53 mutant had significant improvement of RFS with chemotherapy (37.2 vs 61.1, HR 0.50, p=0.017). Molecular classification has already been integrated in adjuvant treatment decisions guidelines [6], as the ESGO-ESTRO-ESP guidelines encouraged the determination of the molecular subtype, and classification of all EC patients [3]. Patients with early POLE mutated EC are recommended to be treated as low-risk, while TP53 mutated patients (except stage IA) are considered at high-risk and receive extended adjuvant treatment. For the MMRd and NSMP groups, the determination of other features such as LVSI and grading is employed to decide the individual patients' risk and need for treatment. In order to avoid unnecessary adjuvant treatments, these data need to be confirmed in prospective trials such as the ongoing PORTEC 4 trial [41] aiming to compare women with high-intermediate risk endometrial cancer, treated after surgery with molecular-integrated risk profile-based recommendations (for either observation, vaginal brachytherapy or external pelvic beam radiotherapy) versus standard adjuvant vaginal brachytherapy.

Conclusions

Overall, real-life EC survivors experienced long-term toxicity of sequential RTCT. Benefit of sequential RTCT must be balanced with late toxicity. Consideration is needed to limit the impact of chemotherapy related-toxicity in these elderly and comorbid women. New systemic treatments

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with a lower toxicity profile are warranted. Also, a better selection of patients who could benefit of RTCT is necessary to avoid useless treatments and limit long term impact on EC survivors.

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