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Impact of Extent of Lymphadenectomy on Survival in Patients With Endometrial Cancer: A Matched Cohort Study

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Abstract. *Background/Aim: This study aimed to determine whether a pelvic and para-aortic lymphadenectomy (PPAL) improves survival compared with a pelvic lymphadenectomy (PL) in patients with endometrial cancer. Patients and Methods: Data from all women operated for endometrial cancer between 1998 and 2013 were extracted from the Surveillance, Epidemiology and End Results database. Women treated with PL were matched with those treated with PPAL according to age and risk of recurrence. The primary endpoint was disease-specific survival (DSS). Results: A total of 1015 patients who underwent PL were matched with 1015 patients who underwent PPAL. The 3-year DSS probabilities for patients at intermediate- and high-risk (IHR) of recurrence were similar in the PPAL group and the PL group. Multivariate analysis of prognostic factors indicated that in patients with an IHR of recurrence, PPAL did not reduce the risk of death compared with PL. Conclusion: For patients with an IHR of recurrence, the extent of lymphadenectomy does not impact DSS.*

Endometrial cancer (EC) is the most common gynecological cancer among women in western Europe and North America (1). The European Society for Medical Oncology (ESMO) divided EC into three categories based on the recurrence risk: low, intermediate, and high (2). The surgical assessment of lymph nodes for staging remains one of the most varied practices worldwide, and controversies remain regarding the need for and the extent of para-aortic lymph node dissection in all patients (3). Surgical staging is associated with risks of complications, including lymphedema, infections, and nerve damage, and sentinel node assessment has been proposed as a safe alternative for surgical staging. However, the ESMO guidelines have not decided on the use of the sentinel lymph node, and they recommend a pelvic and para-aortic lymphadenectomy (PPAL) up to the level of the renal veins for patients with intermediate- and high-risk EC (4). The findings of two independent randomized trials that evaluated the role of pelvic lymph node dissection in early-stage EC failed to demonstrate any therapeutic benefits for disease-free or overall survival (5, 6). Nevertheless, these findings must be tempered because of several pitfalls in both studies, namely, the short duration of follow-up and the large proportion of low-risk women. Two cohorts of patients receiving either a pelvic lymphadenectomy (PL) or a combined PPAL were subsequently compared in the Survival Effect of Para-aortic Lymphadenectomy (SEPAL) study (7), and the results suggested that in patients with an intermediate- or high-risk of recurrence, a PPAL reduced the risk of death compared with a PL.

In view of the increasing use of the sentinel node, the prognostic and therapeutic value of an extensive lymphadenectomy for patients with an intermediate- or high-risk EC is questionable. We aimed to compare two cohorts of patients operated on for EC, receiving either a PL or a combined PPAL, to evaluate the impact of an extended lymphadenectomy on survival.

Patients and Methods

Study population. Data from all patients operated on for EC between January 1998 and December 2013 were extracted from the Surveillance, Epidemiology, and End Results database. The SEER program of the National Cancer Institute comprises a population-based program with a database that contains information on women diagnosed with cancer; these data are representative of approximately 14% of the US population and are reported from 12 population-based registries (8). Clinical and pathological variables included the patient's age, race, contract health service delivery areas (CHSDAs), primary surgery, lymphadenectomy, adjuvant radiotherapy-included beam radiation and radioactive implants.

We identified patients with histologically proven EC and case listings were generated using codes specific for both clinical and tumor characteristics. We included women who underwent primary surgery for EC with at least a hysterectomy and a PPL or a

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combined PPAL. Patients were excluded if they had a uterine sarcoma, had a carcinosarcoma, or had not undergone a hysterectomy and lymphadenectomy.

We selected patients with more than 15 pelvic nodes and more than 10 para-aortic lymph nodes removed according to the results of a large retrospective study that demonstrated that the number of lymph nodes removed is determined by the efficiency of the surgical staging and that a more extensive lymph node resection is associated with improved 5-year disease-specific survival (9). Moreover, to avoid management bias related to age, patients younger than 25 and over 70 years were excluded. Surgical management and adjuvant therapy may be different for elderly woman with less surgical staging and less adjuvant chemotherapy or radiotherapy (10).

Data on the women in the case group were extracted from the SEER database using the previously described inclusion criteria, and patients with EC who underwent surgical treatment with a PPAL were selected. The control group data were extracted from the SEER database, and patients who underwent a PL were included. One-to-one matching was performed according to patient age and risk of recurrence.

Recurrence risk was defined according to the depth of myometrial invasion, histological subtype, and tumor grade in accordance with ESMO's latest stratification risk (2). Patients with 2009 FIGO stage IA and grade 1-2 endometrioid adenocarcinoma were classified as low risk, while patients with 2009 FIGO stages III and IV were classified as high-risk, and the others were classified as intermediate risk.

The primary outcome was disease-specific survival, which was defined as the time from surgery to death from EC. The secondary outcome was overall survival, which was defined as the time from surgery to death (any cause). Patients known to be alive or lost to follow-up at the time of analysis were censored at their last follow-up.

Statistical analysis. The categorical and numerical variables were analyzed using the chi-squared *t*-test and Student's *t*-test, respectively. Furthermore, the cancer-related survival in each group was calculated using Kaplan–Meier analysis and compared based on the extent of a lymphadenectomy. We used the Kaplan–Meier method, log-rank test, and Cox regression analysis for final analysis. Differences were considered to be significant at a level of 0.05, and statistical analyses were performed with the R Statistical Software.

Results

Patients accrual. In total, data on 176,317 patients with EC managed between January 1998 and December 2013 were extracted from the SEER database. Of these, 4162 who met the inclusion criteria were identified.

One-to-one matching was performed according to age and risk of recurrence. This enabled a comparison of the outcome of 1,015 patients who underwent a PL and 1,015 patients who received a PPAL. Checking the quality of matching, we determined that the two groups were comparable with regard to race, age, CHSDA region, FIGO surgical stage, and risk of recurrence (Figure 1).

Patient characteristics. After matching, patients' characteristics and their tumors were well balanced (Table I). However, patients who underwent a PPAL had a higher tumor grade (p=0.001) and had serous adenocarcinoma and clear-cell adenocarcinoma more frequently. The distribution of other important prognostic factors did not differ significantly between the two groups, and no difference was recorded between the two groups regarding the adjuvant therapy (p=0.87), the adnexal metastasis (p=0.40), and the lymph node metastasis (p=0.07).

Surgical procedures. A median number of 20 (IQR=17-24) lymph nodes were removed from patients in the PL arm, and a median number of 23 (IQR=18-30) pelvic nodes were removed from patients in the PPAL group.

Adjuvant therapy. Details of the adjuvant therapy are presented in Table I. Most women in both arms did not receive adjuvant radiotherapy (60.4% in the PL group and 58.3% in the PPAL group). When primary surgery was followed by radiotherapy, beam radiation was most frequently administered. Finally, no significant differences were recorded in the distribution of adjuvant radiotherapy between the two groups (p=0.87).

Overall and disease-specific survivals. At a median follow-up of 20 months (interquartile range=10-33), 42 deaths were observed in the PL group, and at a median follow-up of 22 months (interquartile range=10-33), 62 deaths were observed in the PPAL group. The 3-year disease-specific survival probability was 92.4% in the PL group and 89.5% in the PPAL group (p=0.15). in addition, the 3-year overall survival probability was 91.2% in the PL group and 86.4% in the PPAL group (p=0.07) (Table II).

In the analyses of the subgroups, focusing on low-risk and intermediate- or high-risk of recurrence, no significant statistical differences were found between the two groups in the disease-specific survival of patients (Figure 2).

In multivariate analysis in patients who were at intermediate- or high-risk, age, lymph node metastasis, and tumor type were independently related to survival (HR for death from any cause=3.92, 95%CI=2.39-6.44, p<0.0001) when grade-3 endometrioid adenocarcinoma and non-endometrioid carcinoma were compared with grade 1-2 endometrioid carcinoma, whereas the extent of a lymphadenectomy was not (Table III).

The prognostic value of the type of extent of lymphadenectomy was evaluated in all intermediate- and high-risk patients (740 patients in each group). In these patients, the extent of lymphadenectomy was not associated with survival (HR=1.08, 95%CI=0.69-1.69, p=0.74) when patients with a PL were compared with patients with a PPAL (Table III).

Discussion

To better assess the impact of a para-aortic lymphadenectomy on the survival of EC patients, we compared the survival of patients who underwent a PL and those who underwent a

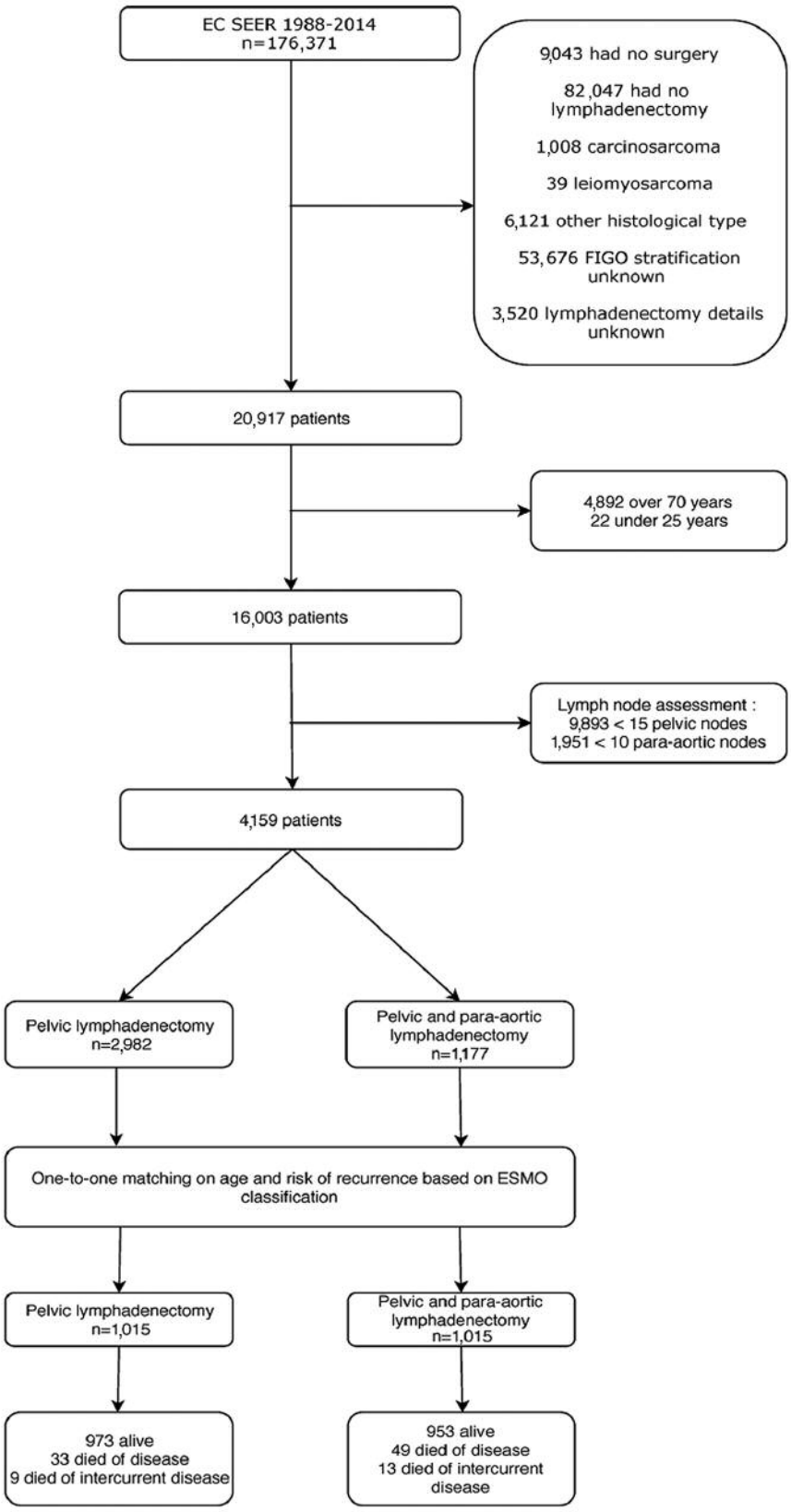

Figure 1. *Flow-chart*.

Table I. *Clinical and pathological characteristics of patients with endometrial cancer.*

	PL n=1015	PPAL n=1015	*p*-Value
Age (years)	60 (54.5-64)	59 (53.5-64)	0.43
	58.1 (7.9)	57.8 (8.1)	
ESMO risk group for recurrence			
Low risk			
IA Grade 1-2	275	275	
Intermediate risk	414	414	
IA Grade 3	120	120	
IB	222	222	
II	72	72	
High risk	326	326	
III	291	291	
IV	35	35	
FIGO surgical stage 2009			0.29
IA	449 (44.23%)	424 (41.77%)	
IB	234 (23.05%)	233 (22.95%)	
II	77 (7.58%)	82 (8.07%)	
IIIA	43 (4.23%)	48 (4.72%)	
IIIB	14 (1.37%)	6 (0.59%)	
IIIC1	156 (15.36%)	73 (7.19%)	
IIIC2	7 (0.68%)	114 (11.23%)	
IVA	6 (0.59%)	3 (0.29%)	
IVB	29 (2.85%)	32 (3.15%)	
Tumour type			0.001
Grade 1 endometrioid adenocarcinoma	394 (38.81%)	268 (26.4%)	
Grade 2 endometrioid adenocarcinoma	252 (24.84%)	304 (29.95%)	
Grade 3 endometrioid adenocarcinoma	163 (16.05%)	204 (20.09%)	
Serous adenocarcinoma	66 (6.5%)	102 (10.04%)	
Clear cell adenocarcinoma	9 (0.88%)	19 (1.87%)	
Lymph nodes removed			<0.001
Pelvic nodes	20 (17-24)	23 (18-30)	
Para-aortic nodes	0	14 (11-18)	
Adnexal metastasis			0.40
Negative	938 (92.41%)	913 (89.95%)	
Positive	77 (7.58%)	102 (10.04%)	
Lymph node metastasis			0.07
Yes	179 (17.63%)	212 (20.88%)	
No	836 (82.36%)	803 (79.11%)	
Adjuvant therapy			0.87
None	613 (60.39%)	592 (58.32%)	
Beam radiation	123 (12.11%)	118 (11.62%)	
Radioactive implants	177 (17.43%)	195 (19.21%)	
Combination of beam radiation with implants or isotopes	60 (5.9%)	67 (6.60%)	
Unknown	40 (3.94%)	42 (4.13%)	
Follow-up			0.96
	20 (10-33)	22 (9.5-33)	

PL: Pelvic lymphadenectomy; PPAL: pelvic and para-aortic lymphadenectomy; ESMO: European Society of Medical Oncology; FIGO: International Federation of Gynecology and Obstetrics.

PPAL. The present study suggests that for patients who are at intermediate- and high-risk of recurrence, the extent of the lymphadenectomy does not impact overall and disease-specific survival. Despite the FIGO recommendations, the surgical assessment of lymph nodes for staging at primary surgery remains one of the most varied practices worldwide, including no surgical staging, sentinel lymph node, and extensive lymphadenectomy up to the renal vessels (3). The therapeutic role of extensive surgical staging was previously only found to be correlated with the number of lymph nodes removed, without distinction between pelvic or para-aortic nodes, and the benefit of a para-aortic lymphadenectomy associated with a PL for patients who are at intermediate- or high-risk of recurrence for overall and disease-free survival remains unclear (9).

Table II. *Overall and disease-specific survival of patients with endometrial cancer with intermediate- or high-risk of recurrence according to type of lymphadenectomy.*

Survival	PL	PPAL
Overall survival		
Died	42 (4.13%)	62 (6.10%)
6 months	99.3%	98.6%
12 months	97.3%	96.7%
24 months	94.4%	90.3%
36 months	91.2%	86.4% p=0.07
Disease-specific survival		
Died	33 (3.25%)	49 (4.82%)
6 months	98.9%	99.1%
12 months	98.2%	97.5%
24 months	95.7%	92.3%
36 months	92.4%	89.5% p=0.15

PL: Pelvic lymphadenectomy; PPAL: pelvic and para-aortic lymphadenectomy.

Two randomized studies evaluating the impact of PL did not reveal any significant benefit of a PL in comparison with no lymphadenectomy, even in intermediate- or high-risk patients (6, 11). In response, the SEPAL study compared the survival effect of a para-aortic lymphadenectomy. This retrospective study found that overall survival was higher in the PPAL group than in the pelvic group for patients who are at intermediate- or high-risk (7). Furthermore, a meta-analysis by Guo *et al*. focused on the survival benefits of a PL *versus* a PPAL for EC patients (12). It suggested that a PPAL is associated with a favorable outcome in relation to overall survival, specifically for patients who are at intermediate- or high-risk of recurrence (HR=0.52; 95%CI=0.39-0.69, p<0.001), but found no significant difference in regard to progression-free survival and no enhanced disease-free survival in patients who underwent a PPAL. In terms of disease-related survival, a benefit was found only if the para-aortic lymphadenectomy extended up to the renal vein (12).

This is the first meta-analysis focused on this comparison; however, the studies selected are retrospective studies with some hidden selection biases, which can affect the analysis. Patients who are selected for a PPAL may have a better performance status and/or less obesity than patients who undergo only a PL. Moreover, the extension of a lymphadenectomy up to the renal vein can more likely concern patients treated in tertiary medical centers with more experienced surgical oncologists. All these differences might have finally translated into a better overall survival and bias the analysis. The extent of a lymphadenectomy in EC can be conceived more as having a prognostic rather than a therapeutic value. The identification of patients with nodal metastases is important for providing guidance on prognosis and adjuvant therapy (9). The major risk of a PL without a para-aortic lymphadenectomy lies in the risk of skip metastasis. In a prospective study, Altay *et al*. reported lymph node metastasis in 21.9% of patients with intermediate- or high-risk EC (pelvic in 17.9% and para-aortic in 15% of patients). Lymph node involvement was observed in both pelvic and para-aortic areas in 10.9% and isolated para-aortic in only 4% of patients (13). Concerning the complication rate of a PPAL, Agar *et al*. demonstrated that morbidity increases with the number of lymph nodes removed and their positivity and that the para-aortic lymphadenectomy is primarily responsible for complications, especially lymphedema and nerve injury (14). An enlarged lymphadenectomy is a source of morbidity, which should not be neglected because of the risk involved in increasing the delay before possible adjuvant treatment.

The results of the present study provide another comparison of PLs and PPALs after conventional surgery in patients with EC since the SEPAL study in 2010. However, findings from this study have indicated that a para-aortic lymphadenectomy has no survival benefits for patients who are at intermediate- or high-risk of recurrence. Furthermore, the SEPAL study is not a randomized controlled trial and remains a retrospective study with some hidden bias. The present population-based study was extracted from the gynecological tumors registries of two tertiary centers in Japan, while the patient population was drawn from general practices throughout only tertiary centers in Japan, and some results could be related to the clustering effect of surgeries. There is also a lack of uniformity concerning adjuvant treatments, specifically regarding the heterogeneous nature of adjuvant therapy (only chemotherapy is offered in the Hokkaido University Hospital, whereas in the Hokkaido Cancer Centre, patients could have radiotherapy or chemotherapy) (7). As with the SEPAL study, we used a categorization of the risk of recurrence, which led to a lack of uniformity with more grade-3 endometrioid and serous adenocarcinomas in the pelvic and para-aortic group, which can be a hidden bias and may explain, in part, the lack of significance.

The SEER database does not provide information concerning adjuvant chemotherapy. However, the survival effect of chemotherapy was not demonstrated in high-risk patients. In addition, in 2006, Maggi *et al*. did not find any improvement in the survival of patients treated with chemotherapy in comparison to radiotherapy (15). More recently, the PORTEC-3 trial suggested that for women with high-risk EC, adjuvant chemotherapy does not improve 5-year overall survival in comparison with pelvic radiotherapy alone (81.8% *versus* 76.7% respectively; p=0.11) (16).

The present study highlights the absence of a therapeutic effect of an extensive lymphadenectomy, even for intermediate- and high-risk EC; the benefit of a lymphadenectomy seems to be in staging and allows for a better adaptation to adjuvant therapy, although skip metastasis is rare in this subset

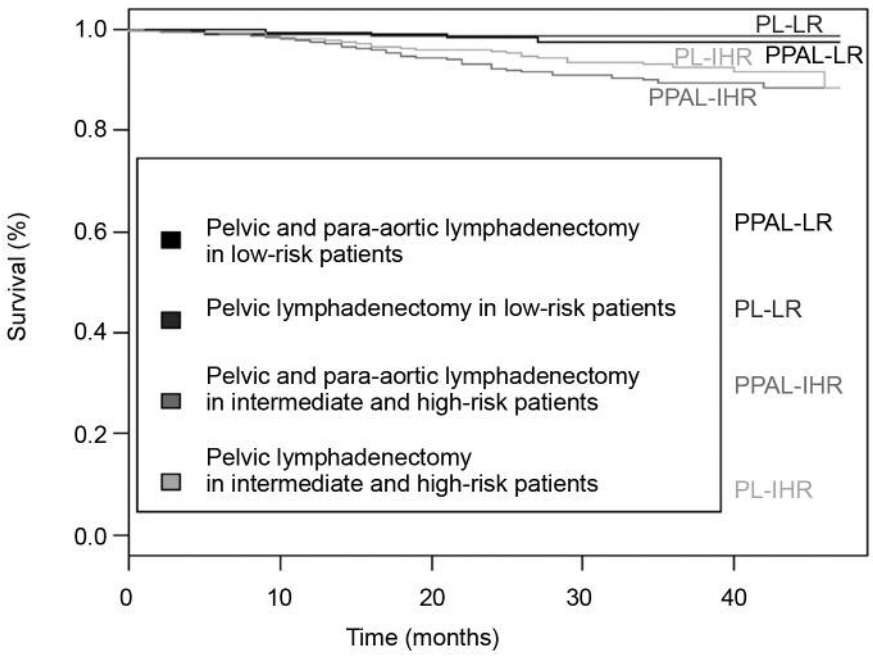

Figure 2. *Kaplan–Meier Analysis of disease-specific survival for patients with endometrial cancer according to type of lymphadenectomy and risk of recurrence*.

Table III. *Multivariate analysis of prognostic factors of overall survival for patients with endometrial carcinoma at intermediate- or high-risk of recurrence*

	Hazard ratio (95%CI)	*p*-Value
Age-group (years)		
<59	1.00	
>59	1.22 (0.77-1.94)	0.39
Tumour type		
Grade 1-2 endometrioid adenocarcinoma	1.00	
Grade 3 endometrioid adenocarcinoma and non-endometrioid carcinoma	3.92 (2.39-6.44)	<0.0001
Lymph node metastasis		
Negative	1.00	
Positive	4.96 (3.17-7.75)	<0.00001
Type of lymphadenectomy		
Pelvic	1.00	
Pelvic and para-aortic	1.08 (0.69-1.69)	0.74
Radiotherapy		
None	1.00	
Adjuvant radiotherapy	0.43 (0.21-0.68)	0.00012

population of patients with EC (13). The STATEC trial will explore this theory even for high-risk patients with a randomized trial of non-selective *versus* selective adjuvant therapy in high-risk apparent stage-1 EC (17). The benefit of the sentinel lymph node for high-risk patients remains unclear. The low number of high-risk patients in the FIRES trial does not allow us to draw conclusions for these patients (18).

Conclusion

The present matched-cohort study indicates that EC patients with intermediate- and high-risk of recurrence who underwent a PL do not have a worse prognosis than those who underwent a PPAL. This finding is a relevant conclusion because a para-aortic lymphadenectomy is associated with

more postoperative complications and with a benefit that remains unclear and therefore, requires additional randomized clinical studies. We look forward to the results of the SEPAL-P3 trial, a phase III trial that aims to confirm the superiority of a PPAL over a PL alone for EC (19).

Funding

None.

Conflicts of Interest

The Authors have no conflict of interests regarding this study.

Authors' Contributions

Léa Pauly contributed to study design, data interpretation and writing the manuscript, Louise Benoit contributed to data analysis and Martin Koskas contributed to study design and final approval.

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