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Impact of a Province-wide Endometrial Cancer Guideline on Daily Practice

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Abstract. *Background/Aim: Most women are managed by a general gynaecologist rather than being centralized in an oncogynaecology unit, resulting in different clinical management. In 2006, a hub & spoke model was introduced in the Provincial Healthcare System of Reggio Emilia, and shared guidelines were written. We aimed to verify the adherence to guidelines and the consequent improvements in quality care. Patients and Methods: All patients who underwent a hysterectomy for endometrial cancer in the Reggio Emilia Province hospitals from 2000 to 2016 were included in the study. Clinical and pathological data were carefully recorded for each patient included. Results: This study included 132 and 277 patients in the periods before and after the implementation of the guideline, respectively. In the post-guideline period, the use of hysteroscopy, magnetic resonance, laparoscopy and adjuvant treatment significantly increased. Conclusion: Common shared guidelines and a clinical audit can help in improving centralization, resulting in an increased quality of care.*

Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries; 319605 new cancer cases and 76160 cancer deaths were recorded worldwide in 2012 (1). Most patients with EC are diagnosed after the menopause, with the highest incidence occurring around the seventh decade of life (2). The early onset of symptoms explains why 70% of the patients present an early-stage disease at the time of diagnosis, resulting in a favourable prognosis with a 77% 5-year overall survival (OS) rate. In contrast, women with advanced or recurrent disease present low response rates to conventional chemotherapy and extremely poor outcomes (3).

Traditionally, EC is classified into two types according to the clinical-pathological features (4). Type 1 ECs are endometrioid cancers associated with hyperoestrogenism that is typically preceded by endometrial hyperplasia. These tumours are often diagnosed at an early stage and have a good prognosis. Type 2 EC includes non-endometrioid cancers, such as serous, clear cell, mixed cell, undifferentiated and carcinosarcoma tumours. These neoplasms are not correlated with oestrogens levels, frequently occur in the atrophic endometrium and have a poor prognosis. The 5-year OS rate of patients with type 1 EC ranges from 75% to 86% compared to 50% to 60% for patients with type 2 EC. Well-known prognostic factors include the patient's age, International Federation of Gynaecology and Obstetrics (FIGO) stage, depth of myometrial invasion, tumour differentiation grade (G), tumour type and lymphovascular space invasion (LVSI) (5-7). New prognostic factors have been investigated (8-11) to identify tumours with poor outcomes. EC has traditionally been regarded as easy to treat, although 25% of women die of recurrence within 5 years of the diagnosis (12). Most women are managed by a general gynaecologist, resulting in differences and discrepancies in the clinical management (13). Several audits have investigated the best approaches to guarantee a uniform high standard of care. Audits have frequently reported inadequate standards and complete basic staging procedures are only performed on one-third of patients (14). Deficiencies in staging and variations in the use of adjuvant radiotherapy are predictors of worse outcomes (15). This audit concluded that although the centralization of women with EC produced accurate staging information, the potential effect of this accurate staging on patient outcomes remains

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Key Words: Endometrial cancer, diagnostic hysteroscopy, clinical audit, hub & spoke, centralization, mini-invasive surgery.

Table I. *Distribution of the characteristics of and clinical approaches used in the total population of patients with EC.*

Total patients	N=409 (%)
Age [mean±sd, (range)]	64.5±10.4 (32-93)
BMI [mean±sd, (range)]	30.2±8.8 (15.6-90)
Parity	1.68±1.4 (0-8)
Fever*	
No	314 (94.9)
Yes	17 (5.1)
ASA score*	
1-2	226 (67.7)
3-4	108 (32.3)
Symptoms	
No	40 (9.8)
Yes	369 (90.2)
Hypertension*	
No	182 (46.9)
Yes	206 (53.1)
Diabetes*	
No	313 (81.1)
Yes	73 (18.9)
Diagnostic procedure*	
Biopsy	1 (0.3)
DH	208 (79.1)
DH+D&C	37 (10.4)
D&C	36 (10.2)
Radiodiagnostic procedure*	
Ultrasound	1 (0.2)
MR	142 (38.3)
MR+CT	7 (1.9)
CT	221 (59.6)
Transfusions	
No	367 (89.7)
Yes	42 (10.3)
Hemoglobin variation (24h) (mean±sd, (range))	–1.8±1.2 (–7.6-3.4)
Surgical approach	
Vaginal	30 (7.3)
LPS	101 (24.7)
LPT	278 (68.0)
Pelvic lymphadenectomy	
No	166 (40.6)
Yes	243 (59.4)
Lomboaortic lymphadenectomy	
No	380 (92.9)
Yes	29 (7.1)
Number of pelvic lymph nodes (mean±sd)	20.9±9.9
Number of pelvic and lomboaortic lymph nodes (mean±sd)	26.9±10.2
Omentectomy	
No	351 (85.8)
Yes	58 (14.2)

Total patients	N=409 (%)
Peritoneal washing*	
No	28 (7)
Yes	374 (93)
Peritoneal biopsy*	
No	292 (72.8)
Yes	109 (27.2)
FIGO-stage	
IA	234 (57.3)
IB	100 (24.4)
II	23 (5.6)
III	45 (11)
IV	7 (1.7)
Histology	
Type 1	346 (84.6)
Type 2	63 (15.4)
Grading type 1 (342)	
G1	145 (41.9)
G2	141 (40.8)
G3	60 (17.3)
Hospitals	
Spokes	61 (14.9)
Hub	348 (85.1)
Adjuvant therapy	
None	237 (58.1)
Radiotherapy	113 (27.7)
Chemotherapy/Chemo+radiotherapy	59 (14.2)
Lost at follow up at 2 years from diagnosis	36 (8.8)
Recurrence at 2 years from diagnosis	17 (4.2)
Death at 2 years from diagnosis	19 (4.6)
Lost at follow up at 5 years from diagnosis	129 (31.5)
Recurrence at 5 years from diagnosis	25 (6.1)
Death at 5 years from diagnosis	46 (11.2)
Lost at follow up at 10 years from diagnosis	316 (77.3)
Recurrence at 10 years from diagnosis	33 (8.1)
Death at 10 years from diagnosis	61 (14.9)

BMI: Body mass index; DH: diagnostic hysteroscopy; D&C: dilatation and curettage; LPS: laparoscopy; LPT: laparotomy: MR: magnetic resonance; CT: computed tomography. *missing data.

unclear (16, 17). A recent study showed that centralization of care may have unwanted consequences. The number of surgeons and hospitals caring for EC women decreased, whereas the distance that patients travel to receive care increased over time (18). Unfortunately, a longer travel distance increases the chance of fragmented care, which may decrease survival (18).

A hub & spoke model was introduced in the Provincial Healthcare System of Reggio Emilia to offer better quality care associated with more acceptable costs. The hub & spoke model assumes that certain situations and complex diseases requiring rare and expensive skills must be concentrated in highly specialized regional centres (hub) where patients are sent from a peripheral hospital (spoke). Cancers that require more complex surgery or a more specialized multidisciplinary approach, such as ovarian cancer or advanced EC, or patients at increased anaesthesiologic risk, are treated by gynaecological oncologists at the main

Table II. *Distribution of the characteristics and clinical approaches used in patients with EC who were treated before and after the introduction of the guidelines.*

	Up to 2006	Since 2007	*p*-Value
N	132	277	
Age			0.813
	64.3±10.7	64.4±10.4	
BMI			0.220
	29.4±7.6	30.6±9.3	
Parity			0.210
	1.57±1.17	1.74±1.4	
Symptoms			**<0.001**
No	2 (1.5)	38 (13.7)	
Yes	130 (98.5)	239 (86.3)	
Fever*			0.059
No	94 (91.3)	220 (96.5)	
Yes	9 (8.7)	8 (3.5)	
ASA score*			0.312
1-2	74 (71.8)	152 (65.8)	
3-4	29 (28.2)	79 (34.2)	
Hypertension*			**0.013**
No	72 (56.3)	110 (42.3)	
Yes	56 (43.7)	150 (57.7)	
Diabetes*			0.272
No	108 (84.4)	205 (79.5)	
Yes	20 (15.6)	53 (20.5)	
Diagnostic procedure*			0.05
Biopsy	0 (0)	1 (0.4)	
DH	73 (70.9)	207 (82.4)	
DH+D&C	14 (13.6)	23 (9.2)	
D&C	16 (15.5)	20 (8.0)	
Radiodiagnostic procedure*			**<0.001**
Ultrasound	0 (0)	1 (0.4)	
MR	14 (13.1)	128 (48.5)	
MR+CT	2 (1.9)	5 (1.9)	
CT	91 (85.0)	130 (49.2)	
Transfusions			0.863
No	118 (89.4)	249 (89.9)	
Yes	14 (10.6)	28 (10.1)	
Hemoglobin variation (24 h)			0.107
	–2±1.4	–1.8±1.1	
Surgical approach			**<0.001**
Vaginal	14 (10.6)	16 (5.8)	
LPS	6 (4.5)	95 (34.3)	
LPT	112 (84.8)	166 (59.9)	
Pelvic lymphadenectomy			0.748
No	52 (39.4)	114 (41.2)	
Yes	80 (60.6)	165 (58.8)	
Lomboaortic lymphadenectomy			0.217
No	126 (95.5)	254 (91.7)	
Yes	6 (4.5)	23 (8.3)	
Number of pelvic lymph nodes			**0.005**
	23.5±10.8	19.5±9.1	
Number of pelvic and lomboaortic lymph nodes	30±11.9	26±9.9	0.407
Omentectomy			1
No	113 (85.6)	238 (85.9)	
Yes	19 (14.4)	39 (14.1)	
Peritoneal washing*			0.140
No	5 (4)	23 (8.3)	
Yes	121 (96)	253 (91.7)	
Peritoneal biopsy*			0.397
No	95 (76)	197 (71.4)	
Yes	30 (24)	79 (28.6)	
FIGO_stage			1
IA	69 (52.3)	165 (59.6)	
IB	35 (26.5)	65 (23.5)	
II	10 (7.6)	13 (4.7)	
III	16 (12.1)	29 (10.4)	
IV	2 (1.5)	5 (1.8)	
Histology			1
Type 1	112 (84.8)	234 (84.5)	
Type 2	20 (15.2)	43 (15.5)	
Grading _type 1 (346)	112	234	0.654
G1	51 (45.5)	94 (40.2)	
G2	43 (38.4)	98 (41.9)	
G3	18 (16.1)	42 (17.9)	
Hospitals			0.074
Spokes	26 (19.7)	35 (12.6)	
Hub	106 (80.3)	242 (87.4)	
Adjuvant therapy			**0.002**
No	91 (68.9)	146 (52.7)	
Yes	41 (31.1)	131 (47.3)	
Adjuvant therapy approach			**0.003**
None	91 (68.9)	146 (52.7)	
Radiotherapy	23 (17.5)	90 (32.5)	
Chemotherapy/ Chemo+radiotherapy	18 (13.6)	41 (14.8)	

BMI: Body mass index; DH: diagnostic hysteroscopy; D&C: dilatation and curettage; LPS: laparoscopy; LPT: laparotomy: MR: magnetic resonance; CT: computed tomography. *missing data. Bold value denotes statistical significance.

hospital (hub). Hence, because early EC has a better prognosis, it can be treated in peripheral low volume hospitals (spoke) by general gynaecologists. A multidisciplinary inter-hospital group was trained in clinical audits, identified quality indicators and devised shared provincial guidelines (GL) to guarantee a standardized EC management in the various hospitals located in Reggio Emilia Province (19). Quality and standard indicators were identified in the diagnostic and therapeutic strategy of EC: diagnostic hysteroscopy (DH) use, dilatation & curettage (D&C) use, total abdomen and pelvis computed tomography (CT) use and diagnostic accuracy, lower abdomen and pelvis magnetic resonance imaging (MRI) use and diagnostic accuracy, surgical approach, lymphadenectomy (LND) adequacy, early surgical complications, and radiotherapy use. Then, the multidisciplinary inter-hospital group evaluated the

Table III. *Distribution of the characteristics and clinical approaches used in patients with EC who were treated before the introduction of the guidelines (up to 2006), in the years immediately following the introduction of the guidelines (2007-2008) and since 2009. p-Values were calculated for the total distribution (Fisher's exact test for discrete variables and linear regression analysis for continuous variables) and for comparisons of each period (Kruskal-Wallis test followed by Dunn's test with false discovery rate adjustment for continuous variables and pairwise Fisher's test with false discovery rate adjustment for discrete variables).*

	Up to 2006	2007-2008	Since 2009	*p*-Value	"Since 2009" *vs.* "2007-2008"	"Since 2009" *vs.* "up to 2006"	"2007-2008" *vs.* "up to 2006"
N	132	79	198				
Age				0.916	1	1	0.765
	64.3±10.7	64.2±10.6	64.7±10.3				
BMI				0.247	0.884	1	0.799
	29.4±7.6	31.6±12.1	30.2± 7.9				
Parity				0.690	0.737	0.38	0.738
	1.57±1.2	1.63±1.3	1.67±1.2				
Fever*				0.111	0.540	0.140	0.540
No	94 (91.3)	56 (94.9)	164 (97.0)				
Yes	9 (8.7)	3 (5.1)	5 (3)				
ASA score*				0.540	1	0.730	0.730
1-2	74 (71.8)	40 (66.7)	112 (65.5)				
3-4	29 (28.2)	20 (33.3)	59 (34.5)				
Hypertension*				**0.036**	0.891	**0.064**	**0.066**
No	72 (56.3)	32 (41.0)	78 (42.9)				
Yes	56 (43.7)	46 (59.0)	104 (57.1)				
Diabetes*				0.491	0.870	0.850	0.850
No	108 (84.4)	62 (80.5)	143 (79.0)				
Yes	20 (15.6)	15 (19.5)	38 (21.0)				
Diagnostic procedure*				0.215	0.920	0.150	0.150
Biopsy	0 (0)	0 (0)	1 (0.5)				
ISC	73 (70.9)	61 (84.7)	146 (81.6)				
ISC+RASCH	14 (13.6)	6 (8.3)	17 (9.5)				
RASCH	16 (15.5)	5 (7.0)	15 (8.4)				
Radiodiagnostic procedure*				**<0.001**	0.160	**<0.001**	**<0.001**
Ultrasound	0 (0)	1 (1.4)	0 (0)				
MR	14 (13.1)	39 (53.4)	89 (46.6)				
MR+CT	2 (1.9)	0 (0)	5 (2.6)				
CT	91 (85.0)	33 (45.2)	97 (50.8)				
Transfusions				0.953	1	1	1
No	118 (89.4)	72 (91.1)	177 (89.4)				
Yes	14 (10.6)	7 (8.9)	21 (10.6)				
Hemoglobin variation (24 h)				0.916	0.678	0.356	0.569
	–2±1.4	–1.8±1.1	–1.8±1.1				
Surgical procedure				**<0.001**	**0.004**	**<0.001**	**0.002**
Vaginal	14 (10.6)	4 (5.1)	12 (6.1)				
LPS	6 (4.5)	16 (20.2)	79 (39.9)				
LPT	112 (84.9)	59 (74.7)	107 (54.0)				
Pelvic lymphadenectomy				**0.003**	**0.002**	0.175	0.076
No	52 (39.4)	20 (25.3)	94 (47.5)				
Yes	80 (60.6)	59 (74.7)	104 (52.5)				
Lomboaortic lymphadenectomy				0.089	0.22	0.48	0.17
No	126 (95.5)	69 (87.3)	185 (93.4)				
Yes	6 (4.5)	10 (12.7)	13 (6.6)				
Number of pelvic Lymph nodes				0.015	0.443	**0.03**	0.280
	23.5±10.8	20.4±9.4	19±9				
Number of pelvic and lomboaortic lymph nodes	30±11.9	28.2±9.0	24.2±10.6	0.475	1	0.732	0.915
Omentectomy				**0.001**	**0.001**	0.155	0.067
No	113 (85.6)	58 (73.4)	180 (90.9)				
Yes	19 (14.4)	21 (26.6)	18 (9.1)				
Peritoneal washing*				0.122	0.33	0.33	0.14
No	5 (4)	9 (11.5)	14 (7.1)				
Yes	121 (96)	69 (88.5)	184 (92.9)				

Table III. *Continued*

Table III. *Continued*

	Up to 2006	2007-2008	Since 2009	*p*-Value	"Since 2009" *vs*. "2007-2008"	"Since 2009" *vs*. "up to 2006"	"2007-2008" *vs*. "up to 2006"
Peritoneal biopsy*				0.067	0.11	0.20	0.49
No	95 (76)	63 (80.8)	134 (67.7)				
Yes	30 (24)	15 (19.2)	64 (32.3)				
FIGO_stage				0.114	0.11	0.31	0.63
I	104 (78.8)	59 (74.7)	172 (86.9)				
II	10 (7.6)	5 (6.3)	8 (4)				
III	16 (12.1)	12 (15.2)	17 (8.6)				
IV	2 (1.5)	3 (3.8)	1 (0.5)				
Histology				0.214	0.29	0.63	0.40
Type 1	112 (86.9)	62 (78.5)	172 (84.8)				
Type 2	20 (13.1)	17 (21.5)	26 (15.2)				
Grading type 1	112	62	172	0.655	0.73	0.73	0.73
G1	51 (38.9)	27 (43.5)	67 (45.5)				
G2	43 (44.2)	22 (35.5)	76 (38.4)				
G3	18 (16.9)	13 (21)	29 (16.1)				
Hospitals				0.133	0.46	0.17	0.46
Spokes	26 (19.7)	12 (15.2)	23 (11.6)				
Hub	106 (80.3)	67 (84.1)	175 (88.4)				
Adjuvant therapy				**0.002**	0.144	**0.024**	**0.004**
No	91 (68.9)	36 (45.6)	110 (55.6)				
Yes	41 (31.1)	43 (54.4)	88 (44.4)				
Adjuvant therapy approach				**0.005**	0.249	**0.022**	**0.007**
None	91 (68.9)	36 (45.6)	110 (55.6)				
Radiotherapy	23 (17.4)	28 (35.4)	62 (31.3)				
Chemotherapy/ Chemo+radiotherapy	18 (13.6)	15 (19.0)	26 (13.1)				

BMI: Body mass index; DH: diagnostic hysteroscopy; D&C: dilatation and curettage; LPS: laparoscopy; LPT: laparotomy: MR: magnetic resonance; CT: computed tomography. *missing data. Bold value denotes statistical significance.

process indicators before and after GL introduction to identify the site of improvement and verify that standards were achieved (20). In this paper, we aimed to verify if the improvements that were initially reported (20) after GL introduction were maintained and if adherence to GL and centralization were associated with a higher quality of care.

Patients and Methods

In 2006, a province-wide audit on EC treatment was performed (20) and common and shared guidelines (GL) were written (19). Quality and standard indicators for improvements were identified after a careful review of the literature and the GL of principal gynaecological societies. When these indicators were not identified in the literature, they were defined by consensus of an oncology group based on their current practice. Quality and standard indicators were identified in the diagnostic and therapeutic strategies for EC, and complications were also recorded (20). We compared data obtained from patients with EC who were treated before the introduction of the GL with data obtained from patients with EC who were consecutively treated in the period from 2007 to 2016 (ten years after the introduction of the GL). The aims were to verify adherence to GL (19), to record changes observed after the introduction of the GL, and to verify standard achievement. Moreover, we aimed to verify if centralization affected standard achievement and the quality of care.

Patients. After Regional ethical committee approval (number: 2018/0125649), all patients who underwent a hysterectomy for EC in the Reggio Emilia Province hospitals from 2000 to 2016 were included in the study. Patients were identified by record linkage between data retrieved from hospital records, the pathological database and oncological and gynaecological ambulatory follow-up visits. Clinical and pathological data were carefully recorded for each patient included. Patients' characteristics, including age, parity, body mass index (BMI), American Society of Anaesthesiologists (ASA) classification system score, symptoms and comorbidities such as diabetes and hypertension, were recorded. As described in our previous study (20), quality indicators such as the use of DH, D&C, total abdomen and pelvis CT, lower abdomen and pelvis MRI, surgical approach, LND adequacy, staging procedures adequacy and adjuvant therapy use were reported. Complications such as postoperative fever, a decrease in the haemoglobin level, and a requirement for blood transfusions were also reported (Table I). All cases were revised and classified according to the 2009 International FIGO staging system (21).

Table IV. *Distribution of the characteristics and clinical approaches used in patients with EC who were treated at the Hub centre and at Spoke centres.*

N=409	Spoke centers	Hub center	*p*-Value
	61	348	
Age			0.887
	64.7±8.8	64.4±10.7	
BMI			**0.019**
	32.7±11.1	29.8±8.3	
Parity			**0.526**
	1.71±0.93	1.62±1.25	
ASA score*			1
1-2	1 (100)	225 (67.6)	
3-4	0 (0)	108 (32.4)	
Hypertension*			0.887
No	28 (48.3)	154 (46.7)	
Yes	30 (51.7)	176 (53.3)	
Diabetes*			0.072
No	42 (72.4)	271 (82.6)	
Yes	16 (27.6)	57 (17.4)	
Diagnostic procedure*			**0.002**
Biopsy	0 (0)	1 (0.3)	
DH	18 (54.5)	262 (81.6)	
DH+D&C	7 (21.2)	30 (9.3)	
D&C	8 (24.3)	28 (8.7)	
Radiodiagnostic procedure*			**0.018**
Ultrasound	1 (2.6)	0 (0)	
MR	17 (44.7)	125 (37.5)	
MR+CT	2 (5.3)	5 (1.5)	
CT	18 (47.4)	203 (61)	
Transfusions			0.172
No	58 (95.1)	309 (88.8)	
Yes	3 (4.9)	39 (11.2)	
Hemoglobin variation (24h)			**0.032**
	–2.2±1	–1.8±1.2	
Surgical procedure			**<0.001**
Vaginal	5 (8.2)	25 (7.2)	
LPS	0 (0)	101 (29.0)	
LPT	56 (91.8)	222 (63.8)	
Pelvic lymphadenectomy			0.204
No	20 (32.8)	146 (42)	
Yes	41 (67.2)	202 (58)	
Lomboaortic lymphadenectomy			**0.013**
No	61 (100)	319 (91.7)	
Yes	0 (0)	29 (8.3)	
Number of pelvic lymph nodes			0.716
	21.4±8	20.8±10.3	
Number of pelvic and lomboaortic lymph nodes			
	-		
	-	26.9±10.2	
Omentectomy			0.425
No	55 (90.2)	296 (85.1)	
Yes	6 (9.8)	52 (14.9)	
Peritoneal washing*			**0.022**
No	0 (0)	28 (8.2)	
Yes	59 (100)	315 (91.8)	
Peritoneal biopsy*			**<0.001**
No	32 (54.2)	260 (76)	
Yes	27 (45.8)	82 (24)	
FIGO stage			**0.003**
IA	24 (39.3)	210 (60.3)	
IB	27 (44.3)	73 (21.0)	
II	4 (6.6)	19 (5.5)	
III	6 (9.8)	39 (11.2)	
IV	0 (0)	7 (2.0)	
Histology			1
Type 1	52 (85.2)	294 (84.5)	
Type 2	9 (14.8)	54 (15.5)	
Grading_type 1	52	296	0.428
G1	19 (36.5)	126 (42.9)	
G2	21 (40.4)	120 (40.8)	
G3	12 (23.1)	48 (16.3)	
Adjuvant therapy			**<0.001**
No	20 (32.8)	217 (62.4)	
Yes	41 (67.2)	131 (37.6)	
Adjuvant therapy			**<0.001**
None	20 (32.8)	217 (62.4)	
Radiotherapy	30 (49.2)	83 (23.9)	
Chemotherapy/ Chemo+radiotherapy	11 (18.0)	48 (13.8)	

BMI: Body mass index; DH: diagnostic hysteroscopy; D&C: dilatation and curettage; LPS: laparoscopy; LPT: laparotomy: MR: magnetic resonance; CT: computed tomography. *missing data. Bold value denotes statistical significance.

Statistical analysis. R software version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis. Differences in population characteristics were investigated using a linear regression analysis and Fisher's exact test. Pairwise comparisons of more than two groups were performed using the Kruskal-Wallis test followed by Dunn's test for continuous variables and using the pairwise Fisher test for categorical variables. In both cases, the false discovery rate adjustment was applied. Continuous variables are reported as the means±standard deviations, while categorical variables are presented as numbers of patients and relative frequencies or percentages. Recurrence-free survival (RFS) and overall survival (OS) were computed as the interval from the date of surgery to the date of relapse or death, respectively. When no events occurred, the date of the last follow up visit was recorded. Differences in survival were evaluated using the Cox model and presented in Kaplan-Meier survival curves. Significant differences were considered when *p*-values were less than 0.05.

Results

Four hundred nine patients who received an operation for EC were included in this study (Table I): 132 patients were diagnosed before 2000-2006 and 277 were diagnosed after

Table V. *Risk classification for adjuvant therapy decisions in hub and spoke centres.*

	Spoke centers	Hub center	*p*-Value
N	55	97	
Risk			<0.001
Low	12 (19.7)	167 (48.0)	
Intermediate	25 (41.0)	81 (23.3)	
High	24 (39.3)	100 (28.7)	

Table VI. *Adjuvant therapy application to different risk patients in hub and spoke centers.*

	Spoke centers	Hub center	*p*-Value
Low risk	12	167	
Adjuvant therapy			0.390
None	11 (91.7)	161 (96.4)	
Chemo or chemo+radio	0 (0.0)	0 (0.0)	
Radio	1 (8.3)	6 (3.6)	
Intermediate risk			
Adjuvant therapy	25	81	0.154
None	5 (20.0)	32 (39.5)	
Chemo or chemo+radio	1 (4.0)	3 (3.7)	
Radio	19 (76.0)	46 (56.8)	
High risk			
Adjuvant therapy	24	100	0.590
None	4 (16.6)	24 (45.0)	
Chemo or chemo+radio	10 (41.7)	45 (24.0)	
Radio	10 (41.7)	31 (31.0)	

the introduction of the GL from 2007-2016 (Tables II and III). Sixty-one of the 409 patients (14.9%) were treated in provincial spoke centres, while 348/409 (85.1%) were treated in the high centre (hub) of Reggio Emilia (Table IV). Overall comparisons between patients who underwent surgery before and after the introduction of the GL showed increases in the numbers of patients with asymptomatic EC and patients with hypertension. Significant differences were observed in the diagnostic methods, surgical approaches and adjuvant treatment. In particular, DH use increased after GL introduction (82.4% after GL *vs*. 70.9% before GL, $p=0.05$) compared to the uses of D&C and the DH-D&C combination, which were slightly reduced. After GL introduction, an increase in the use of MRI (48.5% after GL *vs*. 13.1% before GL, $p<0.01$) and a laparoscopic surgical approach (34.4% after GL *vs*. 4.5% before GL, $p<0.001$) was observed. The mean number of lymph-nodes analysed during a pelvic lymphadenectomy was significantly reduced after GL introduction (19.5±9.1 after GL *vs*. 23.5±10.8 before GL, $p=0.005$) (Table II). A significant reduction in fever incidence was observed but was not associated with the surgical approach (Table II). The postoperative decrease in haemoglobin levels did not change before and after GL introduction (Table II).

We further subdivided patients into three periods of time based on the surgery date to obtain a better understanding of the number of years that elapsed after the introduction of the GL before significant changes in clinical practice were recorded. One hundred thirty-two patients were surgically treated up to 2006 (GL introduction year), 79 in the two years after the GL introduction (2007-2008) and 198 were treated after 2008. Laparoscopic surgery was continuously improving during the period, showing significant differences in all periods compared in the present study. Patients subjected to surgery using a vaginal approach presented a higher ASA score [13/25 (52%)] compared with patients who underwent a laparotomy [74/210 (35.2%)] and laparoscopy [20/97 (20.6%)]. Patients subjected to surgery using a vaginal approach presented a higher BMI and older age than patients subjected to laparoscopy (mean BMI 32.2±8.2 SD and 27.1±6.4 SD, $p=0.008$; mean age: 68.7±10.7 SD and 60.8±9.5 SD years, $p=0.0003$). Patients subjected to laparoscopic and vaginal approaches required fewer transfusions than patients subjected to laparotomy [7/128 (5.5%) and 35/275 (12.7%), respectively, $p=0.034$]. The use of MRI as the preferred radiodiagnostic procedure significantly increased in the first few years after GL introduction and a slight, but not significant, reduction was observed after 2008. Pelvic lymphadenectomy and omentectomy registered a statistically significant increase two years after GL introduction, but decreased again after 2008 (Table III).

We compared patients treated in peripheral hospitals with patients treated at the Reggio Emilia Hospital to investigate how GL were implemented by hub and spoke centres. Considering all patients included in this study, spoke centres preferentially performed a laparotomy in 91.8% of patients and no laparoscopy was performed, while 29% of patients were treated with laparoscopy ($p<0.001$) at the hub centre. Moreover, lombo-aortic lymphadenectomy was not performed in spoke centres, while higher percentages of peritoneal washing (100% *vs*. 91%, $p=0.022$) and peritoneal biopsy (45.8 *vs*. 24%, $p<0.001$) were recorded compared to the hub centre. Spoke centres registered a significantly higher percentage of stage IB EC (44.3% *vs*. 21%), while approximately 60% of tumours treated at the hub centre were stage IA EC ($p=0.003$). Intermediate- and high-risk patients treated at spoke centres did not receive a comprehensive surgical staging and a higher percentage received adjuvant treatment (Table V). The same criteria were used to select patients who received adjuvant treatment in spoke and hub centres (Table VI). However, considering all patients, a

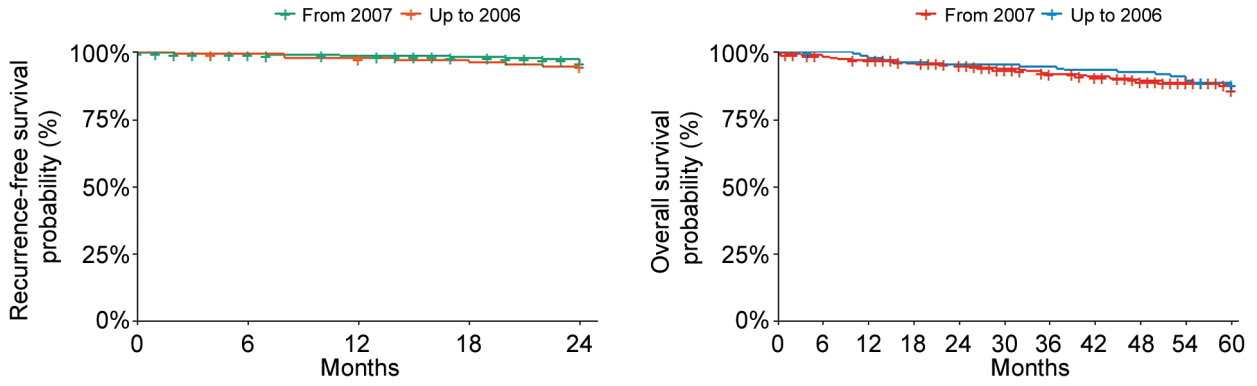

Figure 1. *Effects of guideline adherence on recurrence-free and overall survival.*

Table VII. *Adjuvant therapy application to different risk patients in different years before and after GL introduction.*

	Up to 2006	2007-2008	Since 2009	*p*-Value	"Since 2009" *vs.* "2007-2008"	"Since 2009" *vs.* "up to 2006"	"2007-2008" *vs.* "up to 2006"
Low risk	55	27	97				
Adjuvant therapy				0.123	0.65	0.24	0.24
None	55 (100)	25 (92.6)	92 (94.8)				
Chemo or chemo+radio	0 (0)	0 (0.0)	0 (0.0)				
Radio	0 (0)	2 (7.4)	5 (5.2)				
Intermediate risk							
Adjuvant therapy	36	21	49	**<0.001**	0.884	**<0.001**	**0.011**
None	23 (63.9)	5 (23.8)	9 (18.4)				
Chemo or chemo+radio	1 (2.8)	1 (4.8)	2 (4.1)				
Radio	12 (33.3)	15 (71.4)	38 (77.6)				
High risk							
Adjuvant therapy	41	31	52	0.558	1	0.78	0.78
None	13 (31.7)	6 (19.4)	9 (17.3)				
Chemo or chemo+radio	17 (41.5)	14 (45.2)	24 (46.2)				
Radio	11 (26.8)	11 (35.5)	19 (36.5)				

Bold value denotes statistical significance.

significant increase in the treatment of patients with intermediate risk was observed after GL introduction, with a reduction in the number of untreated patients and a continuous increase in the use of radiotherapy (from 33.3% before GL introduction to 77.6% since 2009) (Table VII). Finally, we performed an RFS and OS analysis to evaluate the effect of GL introduction on patients' prognoses, but no differences were observed (Figure 1).

Discussion

This study of changes in the quality of care before and after GL implementation showed that the adherence to GL has been preserved over time and changed EC management. Quality indicators confirmed the performance registered at the first assessment (21) and subsequent continuous improvements. The use of DH was maintained throughout the period analysed, whereas the use of D&C was reduced. In particular, the use of DH was significantly increased in women treated at the Hub centre. DH is considered the gold standard investigation to study the uterine cavity (22-24), although some scientific societies continue to emphasize the diagnostic and therapeutic value of D&C (25). Usually, D&C is used in women with severe bleeding when DH is not available to study the uterine cavity and when haemostasis must be achieved. In our population, the number of asymptomatic women with an occasional diagnosis of EC increased during the period analysed. In these women, the

percentage of use of D&C was similar to women with bleeding, probably with the aim of sampling as much endometrial tissue as possible. Our GL was established according to international GLs (22, 24-26) and considers MRI the best tool for a preoperative assessment of the myometrial infiltration depth and cervical involvement (4, 8, 17, 22, 24-26). In the last few years, transvaginal ultrasound was considered an alternative to MRI in the evaluation of local infiltration at referral centres, and thus the patient may receive complete preoperative staging with a CT scan (27). This strategy will be employed in the next few months at the Hub centre, where clinicians have gained sufficient experience over the study period.

The use of laparoscopy increased approximately ten times during the study period at the hub centre. In contrast, a decrease of approximately 30% in the use of laparotomy and a decrease of approximately 50% in the use of the vaginal approach were recorded. The use of pelvic lymphadenectomy increased significantly in low-risk patients with EC in the first two years after GL implementation, and then significantly decreased to the percentage observed prior to the introduction of the GL. Minimally invasive surgery (MIS) is the preferred approach when it is feasible (25). In our study, the use of laparoscopy increased approximately ten times during the analysed period, but only at the hub centre. The laparoscopic approach was significantly more frequently adopted in the high case-volume centres (28) and by gynaecologic oncologists who have an important role in the implementation of MIS (29, 30). Although laparoscopy should be used for EC treatment in patients with type II EC (31, 32), the laparotomic approach is usually mandatory in patients with tumours presenting a serous or clear cell histology (28, 33). Laparoscopy is associated with decreased bleeding, fever, pain, wound infection and hospital stay. In our population, a significant reduction in fever incidence was observed, but it was not associated with the surgical approach. The postoperative decrease in haemoglobin levels did not change before and after GL introduction. However, patients subjected to MIS required less transfusion than patients who received a laparotomy. Vaginal hysterectomy was preferentially performed in women with a higher ASA, higher BMI and older age and in patients with a vaginal prolapse. Regarding staging procedures, the use of pelvic and lombo-aortic lymphadenectomy significantly increased in the first two years after GL introduction and then subsequently decreased to the rate observed prior to the introduction of the GL. In particular, the use of pelvic lymphadenectomy increased significantly in low-risk patients with EC in the first two years after GL introduction and then significantly decreased to the rate observed prior to the introduction of the GL. This change might be attributed to trials that stated that lymphadenectomy is unnecessary in low-risk patients with EC (34, 35). Thus, the use of unnecessary pelvic lymphadenectomy should be further reduced. In contrast, no differences in the rates of pelvic lymphadenectomy were observed in intermediate- and high-risk patients with EC between the three study periods. Lymphadenectomy use should be increased in high-risk patients with EC to tailor adjuvant therapy (22, 36). Patients probably did not undergo staging procedures because they presented comorbidities that increased the surgical risk or because they were improperly treated at spoke centres. Lymph node counts are used to measure the adequacy of an LND, and more than 10 nodes should be removed (37, 38). According to retrospective reviews, survival improves when at least 10-12 lymph nodes are removed during LND (39, 40). In our study, the median number of pelvic lymph nodes removed was significantly decreased during the study period, but remained adequate to obtain a correct stage (23.5±10.8 *vs*. 19.5±9.1). In contrast, no difference in the median number of pelvic and lombo-aortic lymph nodes removed was observed during the study period. The use of omentectomy, peritoneal biopsies and peritoneal cytology after GL implementation was not different compared with the pre-GL period, although peritoneal cytology is no longer considered mandatory in an apparent early stage (22). As reported in the literature (41), EC treatment by a gynaecoloncologist is associated with an increased use of adjuvant therapy. After centralization, a significant increase in radiotherapy use from 17.5% before GL implementation to 32.5% after GL introduction was observed. Adjuvant therapy use was increased, particularly in intermediate-risk patients with EC. Interestingly, most intermediate-risk patients with EC were treated in spoke centres rather than at the hub centre. Adjuvant therapy use mainly increased in patients treated in spoke centres, probably because intermediate-risk patients did not undergo adequate surgical staging (22, 42). Incomplete surgical staging could be due to the unavailability of the frozen section in the spokes. Particularly, frozen section remains a useful tool to tailor surgery in EC patients, avoiding secondary surgery to complete staging particularly in patients with low and intermediate risk EC (42).

During the study period, the number of low-risk patients treated at the hub centre increased and the number of intermediate-risk patients treated at spoke centres increased. The increased use of DH at the hub centre might have improved the diagnosis of early EC. However, the selection of patients with EC to centralize should be improved to avoid the treatment of intermediate/high-risk patients at spoke centres and to avoid the useless centralization of low-risk patients.

Although previous studies included a large sample of patients, they lacked data on tumour characteristics, such as the stage and histology, which influenced treatment planning and outcomes. Moreover, long-term outcomes were not reported (30). Our study reports complete data for the histology, surgery, adjuvant treatment and follow up. Additionally, our hub and spoke model ensured uniform histological classification, adjuvant treatment and follow up procedures. However, we

were unable to show that centralization and adherence to the guidelines increased RFS and OS because of the small sample size. Other potential limitations include an inaccurate centralization of patients or an insufficient improvement in treatment. Generally, EC is not an aggressive cancer; thus, the potential positive effect of centralization on EC might be more difficult to confirm (43). An analysis of 441,863 patients with EC from the National Cancer Database showed that the risk of death decreased from 1% to 2% per 20-patients-per-year increase in the mean annual EC hospital volume. Independent of the stage and histotype, an increased hospital volume was associated with an increase in the OS of patients with EC (44). According to a previous study (45), the hospital volume has little independent effect on outcomes, whereas high-volume surgeons were associated with an approximately 40% lower rate of perioperative surgical complications, medical complications and intensive care unit stay (41). In a recent study, medium-volume hospitals and surgeons presented an increased risk of adverse outcomes, but surgeons and centres with the highest volumes of treatment presented the lowest complication rates (30), along with decreased resource utilization and hospital charges (30, 46, 47).

Wide variations exist in patterns of treatment for patients with EC across centres, likely due to the significant controversy regarding the appropriate treatment, despite the relatively high incidence of EC. Although researchers have not yet determined whether the centralization of EC treatment improves survival, centralization is recommended for patients with complex conditions or patients requiring complex surgery. Centralization improves MIS, staging procedures and adjuvant therapy use. Common shared guidelines and a clinical audit can help improve centralization over time and result in an increased quality of care. Better patient selection procedures should favour a two-way centralization of patients in which low-risk patients will receive operations at spoke centres and intermediate-high-risk patients will undergo surgery at the hub centre. Finally, this study presents a common and shared guideline that may produce improvements in daily practice.

Conflicts of Interest

The Authors declare that they have no competing interests. All Authors deny any financial or personal relationships with other people or organizations/companies that could inappropriately influence their work.

Authors' Contributions

VDM conceived of the manuscript, performed operations, collected data, and wrote the manuscript. FT performed statistical analysis and wrote the manuscript. VM collected data and wrote the manuscript. DP performed operations and follow up, collected patients written consent and wrote the manuscript. GA performed operations and follow up, collected patients written consent wrote the manuscript. GC performed operations and follow up, collected patients written consent and wrote the manuscript. GD performed follow up and revised the manuscript. EDB collected data and wrote the manuscript. LA performed operations and wrote the manuscript.

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