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Review Article

Low-volume disease in endometrial cancer: The role of micrometastasis and isolated tumor cells

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HIGHLIGHTS

- Sentinel node mapping improves detection of stage IIIC endometrial cancer.
- Patients at low risk of lymphatic spread are more likely to be diagnosed with low volume disease.
- Patients with micrometastasis in sentinel nodes should be receive adjuvant treatment.
- Patients with isolated tumor cells in sentinel nodes deserve to be treated on the basis of uterine factors.

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ABSTRACT

Nodal assessment represents an integral part of staging procedure for endometrial cancer. The widespread diffusion of sentinel node mapping determinates a phenomenon of migration from stage I to stage III disease, especially for low-risk endometrial cancer patients. The adoption of sentinel node mapping and pathological ultrastaging increase the detection of low volume disease (i.e., micrometastasis and isolated tumor cells), being low volume disease detected in >30% of patients with positive nodes. The prognostic role of low volume disease is discussed as well as the possible adjuvant strategies for patients diagnosed with micrometastasis and isolated tumor cells. The role of further prospective treatments in endometrial cancer, including molecular and genetic profiling, is critically reviewed.

Contents

1. Introduction . . . 670
2. Pathological ultrastaging . . . 671
3. The prevalence of low volume disease in endometrial cancer . . . 671
4. Sentinel node mapping improves detection of stage IIIC disease in endometrial cancer . . . 671
5. The role of adjuvant therapy in low volume disease in endometrial cancer . . . 673
6. Future perspective . . . 673
7. Conclusions . . . 674
Conflicts of interest . . . 674
Author contribution . . . 674
References . . . 674

1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries, with >55,000 new cases diagnosed every year in the United States (U.S.) [1,2]. EC incidence is increasing: in the U.S. its incidence has increased of >20,000/year cases from 2007

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to 2017 [1–3], and the Centers for Disease Control and Prevention (CDC) estimates that uterine cancer death rates increased approximately 1.1% per year in the U.S. [4].

Surgery represents the main step of the treatment for EC [4,5]. Hysterectomy (with or without salpingo-oophorectomy) allows tumor removal and can be useful to tailor adjuvant treatments. The role of retroperitoneal staging is still debated [4,5]. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) introduced the concept of surgical staging for EC [6]. In 2005, the American College of Obstetricians and Gynecologists (ACOG) recommended surgical staging as an important part of EC management [7]. In 2015, the last practice bulletin published by the committee ACOG in association with Society of Gynecologic Oncology (SGO) recommended the importance of retroperitoneal staging, reporting that "the initial management of endometrial cancer should include comprehensive surgical staging" [8]. However, randomized controlled trials failed to demonstrate the therapeutic role of lymphadenectomy in EC [9,10]. The cumulative results of these trials showed that the execution of lymphadenectomy increases the risk of developing postoperative morbidity (including lymphoceles, lymphoedema and lymphorrhagia) without significant impacts on oncologic outcomes [9,10]. In the recent years several publications showed that sentinel node mapping is an effective method to identify disease harboring in the lymph nodes, which may allow us to avoid the performance of lymphadenectomy [11–20].

The most recent guidelines published by the National Comprehensive Cancer Network (NCCN introduced), with a level IIB evidence, acknowledge the concept of sentinel node mapping, stating that "The role of sentinel node mapping in endometrial carcinoma is under evaluation, sentinel node mapping can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extra-uterine disease at exploration" [21]. To date, several retrospective experiences underline that sentinel node mapping upholds oncologic results of standard lymphadenectomy, minimizing surgery-related morbidity [11–20]. Furthermore, pathological ultrastaging of sentinel nodes result in a more sensitive and accurate identification of lymphatic disease in comparison to standard lymphadenectomy [22–24]. In fact, the adoption of sentinel node mapping allows to identify low volume disease (i.e., micrometastasis and isolated tumor cells) not detectable via conventional examinations. However, the prognostic value and therapeutic implications related of the detection of low volume disease in EC is still controversial [25–27]. Here, we sought to review the current evidence regarding the importance of pathological ultrastaging, and the role of micrometastasis and isolated tumor cells in EC. Further perspective in EC managements are discussed as well.

2. Pathological ultrastaging

Lymphadenectomy represents the most important staging procedure for the management of endometrial cancer. Nodes' examination allows to identify extra-uterine diffusion, thus permitting to tailor appropriate adjuvant treatments [4,5]. With the increasing adoption of the sentinel node technique, the number of nodes evaluated at pathological examination decreases dramatically. The harvesting of fewer nodes, and the increased importance of accurate assessment to minimize false-negative findings, have resulted in more intensive pathological examination of sentinel nodes yielded. Pathological ultrastaging is an integral part of the sentinel node mapping [22–28]. According with protocols translated from breast cancer literature, sentinel nodes are initially examined by routine hematoxylin and eosin (H&E) staining, and subsequent ultrastaging is performed if the initial H&E assessment is negative. As of today, there is not a recognized and widely accepted technique for ultrastaging. In most studies (including the FIRES trial, that is the largest trial on sentinel node mapping in EC [19]), ultrastaging is performed by cutting two adjacent 5-μm sections at each of two levels, 50-μm apart, from each paraffin block lacking metastatic carcinoma [12,29]. At each level, one slide is stained with H&E and with IHC using the anti-cytokeratin AE1:AE3. This kind of examination allows to identify low-volume disease, not detectable by conventional H&E examination. In fact, as described in breast cancer medical literature by the American Joint Committee on Cancer (AJCC), sentinel node mapping carries the diagnosis of low volume disease: micrometastasis and isolated tumor cells [29]. According to the classification of the AJCC, micrometastases are classified as microscopic clusters and single neoplastic cells measuring >0.2 mm to ≤2 mm; isolated tumor cells are classified as microscopic clusters and single neoplastic cells measuring ≤0.2 mm [29] (Fig. 1). The presence of low volume lymphatic disease ranges from 25% to 62% across various studies on this issue [11–20]. The adoption of sentinel node mapping increases 'stage migration' due to increased detection of low volume disease, the clinical significance of which is still controversial.

3. The prevalence of low volume disease in endometrial cancer

Accumulating data indicate that the detection of micrometastasis and isolated tumor cells is common in patients undergoing sentinel node mapping [22–25]. In 2013, Kim et al., evaluated data 635 patients undergoing sentinel node mapping (with blue dye) for EC. Among those, 508 (80%) had at least one sentinel node detected during surgery [23]. Routine H&E examination showed metastatic disease in about 7% of patients (35 out of 508). Pathological ultrastaging detected an additional 4.5% (23 out of 508) of patients with low volume disease. They included 4 (0.7%) micrometastases and 19 (3.7%) isolated tumor cells. Additionally, ultrastaging detected 10 (1.9%) patients with isolated cytokeratin-positive cells (considered as negative nodes) [23]. These data are confirmed in another paper of the Memorial Sloan Kettering Cancer Centre (MSKCC) study group [22]. Focusing on 425 low-risk patients, they observed about 6% of patients with lymphatic disease. Macrometastases, micrometastases and isolated tumor cells were identified in 2.6%, 0.7% and 2.1% of cases. In addition, 0.5% of patients were found to have metastatic disease in non-sentinel nodes (removed in case of non-adequate mapping) [22]. Desai et al., reported outcomes of a series of patients undergoing robotic-assisted surgery and sentinel node mapping using blue dye [30]. The authors reported that positive nodes were identified in 10 patients out of 120 (8%) [30]. Of those with positive sentinel nodes, 5 out of 10 (50%) were detected by ultrastaging alone [30]. More recently, Clinton LK et al., reported outcomes of a series of 350 robotic assisted procedures for EC staging (utilizing near-infrared technology and indocyanine green (IGC)), including 187 (53%) patients undergoing sentinel node mapping [25]. Twenty-four patients were diagnosed with metastatic sentinel nodes: macrometastasis, micrometastasis and isolated tumor cells were identified in 12 (50%), 3 (13%) and 9 (38%), of cases [25]. Prospective experience, with the embrace of minimally invasive surgery and IGC, corroborated these results, thus suggesting than >30% of patients stage IIIC EC would be missed without ultrastaging [19,20]. The FIRES and the FILM trials, reported that low volume disease in sentinel nodes (detected by ultrastaging) was 54% and 62%, respectively [19,20]. In particular, the FILM trial reported data of 16 out of 176 patients (9%) with disease harboring in 21 sentinel lymph nodes. Macrometastatic disease was found in 8 (38%) of 21 sentinel nodes, micrometastatic disease in five (24%), and isolated tumor cells in 8 (38%) [20]. Table 1 reports the prevalence of macrometastasis, micrometastasis and isolate tumor cells among large cohorts (>300 individuals) of patients undergoing surgery for EC. These data highlight that despite the type of surgery and the type of tracer utilized, low volume disease represents a non uncommon entity.

4. Sentinel node mapping improves detection of stage IIIC disease in endometrial cancer

The widespread diffusion of sentinel mapping provides a trend in stage migration from stage I to stage IIIC EC. Consistently with data

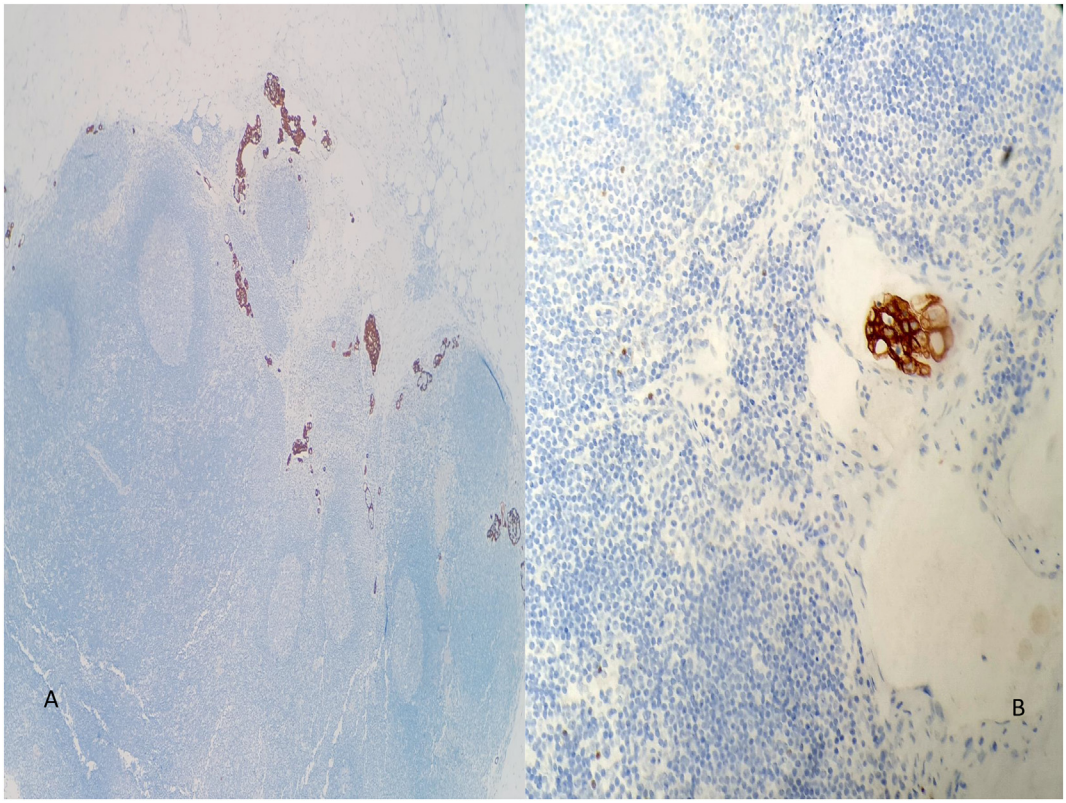

Fig. 1. Microscopic features of micrometastasis and isolated tumor cells.

reporting an increased number of patients with low-volume disease in their lymph nodes, we are observing a growing number of patients upstaged at surgery. Retrospective studies comparing two different methods of nodal assessment (sentinel node mapping vs. lymphadenectomy) highlighted this trend [11–14]. A recent study performed in two referral centers in the US (the Mayo Clinic (Rochester, MN) and the MSKCC (NY)) evaluated outcomes of patients affected by low risk EC (those with endometrioid histology and limited myometrial involvement). At MSKCC, a sentinel lymph node mapping algorithm was used per institutional protocol [12]. At Mayo Clinic, full pelvic and paraaortic lymphadenectomy was performed in cases deemed at risk for nodal metastasis (FIGO grade 3 and/or primary tumor diameter > 2 cm). Details regarding these two approaches are presented elsewhere [12]. Interestingly, metastases (including micrometastasis and isolated tumor cells) to pelvic nodes were detected in 5.1% and 2.6% of patients respectively ($p = 0.03$), thus highlighting that sentinel node mapping improves detection of extra-uterine disease in comparison to conventional lymphadenectomy [12]. Buda et al., performed a similar investigation among low-risk EC, reporting a rate of 4.1% and 1.5% of positive lymph nodes after sentinel node mapping and lymphadenectomy, respectively [13]. Another paper from Mayo and MSKCC groups, comparing sentinel node mapping with lymphadenectomy in

Table 1
Prevalence of macrometastasis, micrometastasis and isolated tumor cells in patients undergoing sentinel nodes mapping.

Authors	Year of publication	Principal institution(s) involved	Study design	Study period	Number of patients included	Macrometastasis	Micrometastasis	Isolated tumor cells
Kim CH [23]	2013	Memorial Sloan Kettering Cancer Center, NY, USA	Retrospective	2005–2011	508	35 (6.9%)	4 (0.7%)	19 (3.7%)
Clinton LK [25]	2017	Burns School of Medicine, University of Hawaii	Retrospective	2012–2015	350*	12 (3.4%)	3 (0.8%)	9 (2.6%)
Zahl Eriksson AG [12]	2017	Memorial Sloan Kettering Cancer Center, NY, USA; Mayo Clinic, Rochester, MN, USA	Retrospective	2006–2013	642	11 (3.2%)	2 (0.3%)	23 (3.6%)
Rossi EC [19]	2017	University of North Carolina, Chapel Hill, NC, USA Las Vegas Institute for Robotic Surgery at Mountain View Hospital, NV, USA University of South Alabama Mitchell Cancer Institute, Mobile, AL, USA. University of Virginia, Charlottesville, VA, USA. TriHealth Tristate Gynecologic Oncology, Cincinnati, OH, USA. Department of Women's Health, Division of Gynecologic Oncology, Henry Ford Health System, Detroit, MI, USA. Indiana University, Indianapolis, IN, USA	Prospective	2012–2015	385	16 (4.5%)	9 (2.3%)	10 (2.6%)

The table included the studies reporting >300 patients undergoing surgery including sentinel node mapping, * 187 had sentinel node mapping;

intermediate/high-risk EC showed that these two techniques provide similar results in term of metastatic node detection [14]. In the "intermediate-risk" cases nodal metastasis were identified in 35.4% and 28% of patients after sentinel node mapping and lymphadenectomy respectively ($p = 0.28$). In high-risk cases nodal metastasis were identified in 21.7% and 19.4% of patients after sentinel node mapping and lymphadenectomy respectively ($p = 0.68$). Clinton et al., investigating 24 patients with positive sentinel nodes, observed that patients with low-volume disease are more likely to have FIGO grade 1 (58% vs. 14%), endometrioid EC (100% vs. 46%), with myometrial invasion confined in the inner half (67% vs. 4%) in comparison to patients with micrometastasis [14]. These data show that sentinel node mapping provides a more accurate evaluation of stage distribution among EC patients, especially in the low-risk population. Although it is clear that sentinel node mapping improves the detection of extra-uterine disease in EC, the prognostic role of low-volume disease is still unclear. Several studies investigated the prognostic role of low-volume disease presenting interesting findings. Todo et al. reported outcomes of 63 patients affected by intermediate-risk endometrial cancer (stage I and II with negative nodes). Ultrastaging was performed on nodes that had been classified as "negative" for metastases to assess the presence of low-volume disease [28]. Nine (14.8%) patients with low volume disease were identified (micrometastasis and isolated tumor cells were observed in three and six cases, respectively) [28]. The Authors reported that low-volume disease correlates with an increased risk for extra-pelvic recurrence (3/52 (5.7%) patients with negative ultrastaging vs. 4/9 (44.4%) patients with positive ultrastaging; $p = 0.007$) [28]. Moreover, although it did not reach statistical significance due to the small sample size of the study population, low-volume disease correlated with worse recurrence-free (55.6% vs. 84.0%; $p = 0.066$) and overall (71.4% vs. 91.9%; $p = 0.074$) survivals. [28]. St. Clair et al., reported a series of 44 stage IIIC EC with low-volume disease [24]. All those patients received adjuvant therapy [24]. Recurrence rate was 6.2%, 8.7%, 9.5% and 34.8% in patients with negative nodes ($n = 753$), isolated tumor cells ($n = 23$), micrometastasis ($n = 21$), and macrometastasis ($n = 46$), respectively [24]. The adoption of adjuvant treatment in the majority of patients with low volume disease does not allow us to evaluate natural history of those patients. Plante et al. reported a series of 519 patients undergoing surgery including sentinel node mapping followed by lymphadenectomy for EC [26]. Overall, 85 (16.4%) patients were found to have metastatic sentinel nodes (including 11 (31%) micrometastasis and 31 (36%) isolated tumor cells) [26]. Although patients having low volume disease were more likely to have adjuvant treatment in comparison with node negative patients, the authors observed that there was no difference in survival outcomes between patients with low volume disease and patients with negative nodes. Moreover, it is important to stress that albeit literature data are scant, patients in whom isolated tumor cells are detected would be treated in the basis of tumor characteristics. In fact, accumulating data suggest that low risk endometrial cancer patients in whom isolated tumor cells are identified are at low risk of developing recurrent disease. Patients with micrometastasis should be treated regardless tumor characteristics [24–28]. Owing to the low presence of low volume disease, further collaborative prospective studies are warranted to assess the prognostic value of low volume disease in EC.

5. The role of adjuvant therapy in low volume disease in endometrial cancer

The presence of low volume disease is of uncertain significance in EC. Although medical literature regarding the adoption of technique and tracers for sentinel node mapping is growing sharply, few data regarding treatment options for patients with low volume disease are available. To date, no specific guidelines describe an optimal management of patients with low volume lymphatic disease. The MSKCC group reported a series of 44 stage IIIC EC with low-volume disease [24]. All these patients were considered as node positive and had adjuvant treatments, with very encouraging results. In the study published by St. Clair et al., patients with micrometastasis and isolated tumor cells had adjuvant therapy in about 85% and 95% of cases, respectively [24]. Nodal and distant recurrence occurred in 4.7% and 4.7% of patients with micrometastasis. Nodal and distant recurrence occurred in 0% and 8.7% of patients with isolated tumor cells [24].

In another experience reporting data on low volume disease, Plante et al. observed that 3-year progression-free survival of patients with isolated tumor cells (95.5%) was similar to node negative patients (87.6%) and patients with micrometastasis (85.5%), but it was statistically different in comparison to patients with macrometastasis (58.5%) [26]. The authors concluded that patients with isolated tumor cells should not have adjuvant treatment based on nodal status only, but the choice to have adjuvant treatments should be tailored to uterine factors (e.g., histology, myometrial invasion) [26]. Table 2 reports details about various treatment modalities and oncologic outcomes of patients detected with isolated tumor cells. We have to point out that difference in adjuvant treatments may have influenced the results achieved by the Authors in various experiences, thus advocating the need of further prospective trials on this issue. Given the lack of reliable data on the role of low-volume lymphatic disease, more high-level evidence is needed.

6. Future perspective

Changing our surgical practice from lymphadenectomy to sentinel node mapping represents an intermediate step. In fact, molecular classification would offer even more accurate risk stratification. Surgical-pathologic staging is the current standard for assessing the need of post-operative treatments but growing data show that molecular characterization offers more precise prognostic data in comparison with conventional histology and other prognostic features currently available [31–32]. The Cancer Genome Atlas (TCGA) studied molecular ad genomic profiling based on whole exome sequencing, microsatellite instability (MSI) analysis, and assessment of copy number alterations across the entire genome [33,34]. The TCGA identified four molecular types: copy number high (serous-like), copy number low (endometrioid-like), presence of POLE exonuclease domain hotspot mutation (ultra-mutated), and MSI (hyper-mutated) [33,34]. TGCA data reveal that molecular classification is more accurate than histological one. However, the extensive genomic characterization undertaken by TCGA is not easy to be translated into clinical practice. Few Authors proposed various clinically applicable classifications [35,36].

The NRG Oncology/GOG study evaluated >1000 endometrial cancers included in the NRG/GOG Study#210, "A Molecular Staging of Endometrial Cancer NCT00340808" [35]. Tumors were classified in four classes: copy number altered (CNA), copy number stable (CNS), POLE mutant, and mismatch repair deficient (MMRd). Cancer-specific mortality occurred in 5% of patients with CNS tumors, 2.6% with POLE tumors, 7.6% with MMRd tumors and 19% with CNA tumors. The CNA group had worse survival outcomes than other groups. The POLE group had better (but not statistically significant) outcomes. CNA class is associated with p53 abnormality (p53abn) [35]. Recently, Bosse T et al., evaluated whether molecular classification might be helpful in estimating prognosis of FIGO grade 3 endometrioid endometrial cancer. Patients characterized by POLE mutation had better prognosis than patients with no specific molecular profile (NSMP); similarly, patients with MMRd tumors experienced more acceptable/satisfying outcomes than NSMP tumors. While patients with tumors characterized by p53 abnormality experienced a worse prognosis in comparison to NSMP, the authors reported an estimated 5-year overall survival of 89%, 75%, 69% and 47% for POLE, MMRd, NSMP and p53abn group, respectively ($p < 0.001$) [36]. The innovative data regarding the prognostic role of molecular/genetic profiling in endometrial cancer are promising. Molecular/genetic profiling might be helpful in driving the choice of the most appropriate treatment modality and to avoid unnecessary treatments in

Table 2
Treatment modalities and oncologic outcomes of endometrial cancer patients detected with isolated tumor cells in sentinel nodes.

Authors	Year of publication	Principal institution(s) involved	Study design	Study period	Number of patients with ITCs	Treatment modalities	Oncologic outcomes
Todo Y [28]	2016	National Hospital Organization, Hokkaido Cancer Center, Sapporo, Japan	Retrospective	1997–2004	6	Chemotherapy alone: 4 (66.7%) ERT: 1 (16.6%)	Recurrences: 4/6 (66.7%) * Local: 0 Nodal: 3 (50%) – para-aortic area Distant: 2 (33.3%)
St Clair CM [24]	2016	Memorial Sloan Kettering Cancer Center, NY, USA	Retrospective	2005–2013	23	Chemotherapy alone: 1 (4.3%) Chemotherapy + IVRT: 12 (52.2%) Chemotherapy + IMRT: 7 (30.5%) ERT: 2 (8.7%) No adjuvant therapy: 1 (4.3%)	Recurrences: 2/23 (8.7%) Local: 1 (4.3%) Nodal: 0 Distant: 1 (4.3%)
Plante M [26]	2017	L'Hôtel-Dieu de Québec, Centre Hospitalier Universitaire de Québec, Laval University	Retrospective	2010–2015	31	Chemotherapy ± ERT: 11 (35.5%) ERT ± IVRT: 10 (32.2%) None or IVB: 10 (32.2%)	Recurrence: 1/31 (3.2%) Local: 0 Nodal: 1 (3.2%) – para-aortic area Distant: 0

Abbreviation: ITCs, isolated tumor cells; IVRT intravaginal radiation therapy, IMRT intensity-modulated radiation therapy, ERT, external radiation therapy: * one patient had both nodal and distant recurrence.

low risk patients with low volume lymphatic disease. Further prospective studies addressing the clinical impact of the adoption of molecular/genomic profiling are warranted. In particular it would be interesting to combine results achieved by pathological ultrastaging and molecular/genetic classification. In fact, it is possible than patients with low volume disease and favorable molecular profile do not need adjutant treatment.

7. Conclusions

With the adoption of sentinel node mapping, detection of low-volume disease represents a common occurrence. Prospective studies shows that low-volume disease accounts for >30% of positive nodes in EC patients. The role of low-volume disease is particularly important for patients affected by low-risk endometrial cancer, in which adjuvant treatments are generally omitted. Moreover, micrometastasis and isolated tumor cells are more likely to be diagnosed in the low-risk than in the high-risk group. Patients with low volume disease undergoing adjuvant treatment seem to experience similar long-term oncologic results to patients with negative nodes. Although prospective evidence is essential in order to assess the role of micrometastasis and isolated tumor cells, current evidence seems to support the use of adjuvant treatments for patients in which micrometastases are detected; while, it seems that the choice to have adjuvant treatments in patients with isolated tumor cells could be tailored on uterine-factors only. Further data are needed to clarify these points. Moreover, molecular and genetic profiling would be helpful for improving knowledge and identifying appropriate treatment modalities for endometrial cancer diagnosed with low-volume disease.

Conflicts of interest

The Authors declare no conflicts of interest. No funding sources supported this investigation.

Author contribution

Conceptualization: GB., Methodology: All authors.; Project administration: FR.; Supervision: AM; FR.; writing - original draft: GB, AD, BP, writing - review & editing: all authors.

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