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Review article

The clinical implication of lymph nodes micrometastases and isolated tumor cells in patients with cervical cancer: A systematic review

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ABSTRACT

Lymph node macroscopic involvement in cervical cancer is a well-known prognostic factor, allows the gynecologic-oncologist to identify women at increased risk for recurrence. Since the development of sentinel node biopsy, micrometastases (MMs) and Isolated Tumor Cells (ICTs) have been increasingly identified in cervical cancer, however their prognostic value and treatment are still controversial. We reviewed the literature (MEDLINE and EMBASE database analysis) from inception up to January 2019, concerning the incidence of lymph nodes MMs and ITCs in cervical cancer, their controversial histologic and molecular biology definition, their anatomic distribution, the role of frozen section and the prognostic value and treatment options for women diagnosed with lymph nodes MMs/ITCs.

Contents

Introduction

Cervical cancer ranks fourth for both incidence and mortality in women, contributing 6.9% of the total number of new cases diagnosed in 2018 [1]. Unfortunately, the incidence and death rates are different in developing countries and particularly in Africa and in Central America. Cervical cancer remains the leading cause of cancer-related mortality among women in these continents [2].

Cervical cancer may spread to the pelvic or paraortic lymph nodes (LNs), as well as more distant nodes. LNs involvement is the most important prognostic factor in early stage cervical carcinoma and impacts therapeutic decisions including treatment modality and radiation fields [3,4]. Traditionally, surgery with lymphadenectomy was essential for the evaluation of LNs metastases. Currently, options for evaluating for LNs involvement include LNs dissection, imaging studies, or both. Diagnostic value

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of Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) warrant any use for treatment decision making with a sensitivity for MRI and CT of 56 and 58 percent in one meta-analysis, respectively [5]. The advantage of Positron Emission Tomography scan (PET) to other imaging modalities was illustrated in this meta-analysis of 72 studies that found a sensitivity of 75 percent and specificity of 98 percent for the detection of LNs metastases in cervical cancer with this modality [5]. As a result, pelvic lymphadenectomy remains the gold standard for evaluating LNs involvement in cervical cancer. Sentinel lymph node (SLN) technique is proposed for over 15 years as an alternative to lymph nodes dissection. According to the sentinel lymph node hypothesis, tumor cells migrating from a primary tumor metastasize to one or a few lymph nodes (LNs) before involving other LNs. Injection of blue dye and/or radiolabeled colloid into the uterine cervix permits identification of one or more SLNs in the majority of patients. The status of the SLNs accurately predicts the status of the remaining pelvic and paraaortic LNs [6,7].

Rob et al. in a review of 1811 patients who underwent lymphatic mapping and SLN detection as part of their cervical cancer treatment reported a sensitivity for metastatic disease of 93 percent and a sensitivity of 100 percent in tumors limited to ≤2 cm in size [8]. Other studies emphasized the importance of bilateral detection [7–10]. Forty-seven studies (4130 patients) were analyzed in the Tax's review. Pooled data of diagnostic accuracy on ultrastaging (18 studies; 1275 patients) showed a sensitivity of 94% (95% CI 80–99%) and negative predictive values ranging

between 91 and 100%. After ultrastaging, 19 false negative results remained. Prerequisites such as early FIGO stage (IA2, IB1, IIA primary tumor size b40 mm), no suspicious pre-, and per-operative lymph nodes, and bilateral negative SLNs after ultra-staging resulted in 1 remaining false negative result among 1257 patients (0.08%) [11].

Standard LNs assessment involves sectioning the node once along the longitudinal axis and staining it with hematoxylin and eosin (H&E) to determine if it contains metastatic tumor cells. For SLNs, enhanced pathologic assessment is performed if the initial H&E stain is negative. Ultrastaging involves additional sectioning and staining of the SLN with H&E and immunohistochemistry (IHC) in order to examine the SLN for low-volume metastatic disease. Low-volume metastatic disease, as defined in the breast cancer literature, includes micrometastases (MMs) and isolated tumor cells (ITCs) [12]. Macrometastases are defined as metastatic tumor cells measuring >2 mm, MMs are defined as a focus of metastatic tumor cells measuring >0.2 mm and ≤2 mm, whereas ITCs are defined as microscopic clusters and single cells measuring ≤0.2 mm.

Originally, MMs were distinguished from ITCs morphologically not only by their size, but also by contact with vessel or lymph sinus wall, extravasation, extravascular (extrasinusoidal) stromal reaction and tumor cells proliferations [13].

Pathology evaluation with ultrastaging is typically used for sentinel nodes, and this may result in increased identification of metastatic lymph nodes [14].

While there is a wide consensus regarding the clinical importance and therapeutic implications of positive LNs macro-metastases (MACs) in cervical cancer, the significance of MMs and ITCs needs to be assessed and discussed.

Incidence

In patients with FIGO stages IA2-IB2 cervical cancer (FIGO 2009), although with a lack of consensual definition, MMs were detected between 9% [15] and 15% (19 of 132 patients; 95% confidence interval _CI_ 9%, 22%) [16], while MACs were detected in 14.7% of patient in a large retrospective multicenter cohort of 645 patients [6]. This study showed over 30% LNs involvement in early stage cervical cancer, when all types of spread are considered. In the SENTICOL study, 139 patients were included. All macro-metastases were identified in standard analysis. After ultrastaging, 8 SLN were positive for isolated tumor cells [17]. The incidence rate of SLNs with MMs/ITCs depends on the pathological technique that is being used. Pathological ultrastaging, as described above, may result in increased identification of metastatic lymph nodes [14]. Pathological techniques, which include serial sections, IHC and H&E reveal MMs in 5.1–8.1% of nodes considered normal by conventional techniques [18,19]. **In the older studies we don't have information for ITCs.** The incidence of MMs/ITCs differs according to the technique used for their identification: H&E staining on a few slides, the number of sections and their thickness, IHC with or without an anti-cytokeratin antibody cocktail, reverse-transcriptase PCR (RT-PCR) detection of cytokeratin 19 (CK 19) mRNA, or HPV-16 and -18 DNA detection by PCR. The rates of MMs in apparently negative nodes in several studies using molecular biology methods are listed in Table 1. Unfortunately, except from the study of Van Trappen et al. [20] a description of the histological slides thickness could not be found in any of the other studies mentioned in Table 1 [21–23,2], neither data on the median size of LNs metastases diagnosed histologically. Several studies, using various molecular biology methods for LNs evaluation have reported positive MMs in up to 44% of the apparently negative LNs for MMs by conventional histology as demonstrated by Van Trappen et al. using RT-PCR for CK 19 in 32 patients [22]. Consequently, CK19 is probably not a suitable marker due to its low specificity and relative higher baseline expression in normal nodes [24]. Recently, Okomoto et al. used one-step nucleic acid amplification (OSNA) method to detect sentinel lymph node metastases in cervical cancer by assessment of KRT19 mRNA in 32 patients [25]. The concordance between the two-mm interval histopathological examination and the OSNA assay was 96.2%, with sensitivity and specificity of 50% and 98.4%, respectively [25]. Pappa et al. compared the detection rates of LNs MMs in cervical, endometrial and vulvar cancers using histology versus CK 19 and carbonic anhydrase 9 (CA9) levels and qRT-PCR for CK19 and CA9 expression [26]. In this study, 11 positive and 71 negative histologically nodes were examined by IHC and genetically. There weren't negative histologically nodes that were positive by IHC or

Table 1
Rate of micrometastases in apparently negative nodes in studies using molecular biology methods.

Study	N	Method of analysis	Positive hist nodes (%)	MMs in apparently neg nodes (%)	Association with recurrence/ survival
Lee [2]	57	HPV16/18	19.3	71.7	+
Guani [17]	139	AE1-AE3	17.3	7	–
Van Trappen [20]	32	CK19	18.7	44	+
Yuan [21]	36	SSAg	13.9	6.7	+
Czeglédy [22]	91	HPV16	35.5	60	–
Lukaszuk [23]	116	HPV16/18/31/33	52.6	36.4	+
Colturato [41]	83	AE1-AE3	NA	7	+

qRT-PCR. The author suggested that qRT-PCR exhibits a better diagnostic accuracy compared to IHC, while CK19 displays a consistent pattern of detection compared to CA9 [26].

Approximately 80% of cervical cancer cases are squamous cell (SCC) carcinomas. SCC-Ag is the serum tumor marker most commonly used for clinical monitoring of SCC cervical cancer [27,28] and elevated pre-treatment SCC-Ag levels correlate with nodal involvement [29,24]. Yuen et al. concluded that molecular SLNs metastasis based on elevated SCC-Ag mRNA level is the best predictor of recurrence in a study where 178 samples were assessed by quantitative reverse transcription-PCR assay. High-risk types of HPV are etiological factors in cervical cancer. Yet, the impact of positive HPV DNA on prognosis and survival in histopathologically negative lymph nodes remains uncertain. In one of the first studies regarding HPV DNA positive LNs in cervical cancer patients, Czeglédy et al. Using polymerase chain reaction (PCR) found positive HPV DNA lymph nodes in 91% (10/11) of patients with histologically detectable metastasis at surgery and in 60% (12/20) of patients without metastasis [22]. HPV 16 DNA was detected in extirpated lymph nodes in 75% (6/8) of patients with recurrence and in 70% (16/23) of recurrence-free patients. The author concluded that the presence of HPV DNA in extirpated lymph nodes at cervical cancer operation does not appear to be predictive of tumor recurrence.

In another study HPV DNA was detected in 69.8% of the LNs dissected intraoperatively and the presence of HPV DNA in LNs was independent parameter correlating with survival and mortality risk [23]. In a study that investigated the correlation between the SLNs HPV status and pelvic lymph node metastasis in patients with cervical cancer with a 3 years follow up, the combination of SLNs histology and HPV typing showed a negative predictive value of 100% in predicting non-metastasis of LNs and no recurrence of disease [2].

Dürst in a prospective, multi-center prognostic study, analyzed 189 patients free of lymph node metastases by conventional histopathology

All patients underwent complete lymphadenectomy. Of each sentinel node (SLN) a biopsy was taken for the detection of HPV-E6-E7-mRNA.

HPV-mRNA could be detected in SLN of 52 patients (27.5%). Recurrence was observed in 22 patients. Recurrence-free-survival was significantly longer for patients with HPV-negative SLN (log rank $p = 0.002$). By Cox regression analysis the hazard ratio (95%CI) for disease-recurrence was 3.8 (1.5–9.3, $p = 0.004$) for HPV-mRNA-positive compared to HPV-mRNA-negative patients [30].

Topographic distribution of LNs MMs

There was no significant difference between the distribution of the lymph node metastases depending from their size (micro- versus macrometastases) in a study aimed to investigate the topographic distribution and prognostic impact of nodal MMs in patients with cervical carcinoma. The most frequent sites of pelvic lymph node involvement were the obturator and internal iliac nodes, without any differences within the right and the left sides [31]. This study is consistent with the results of other studies dealing with the mapping of sentinel lymph nodes in cervical cancer [32–34].

Role of frozen section in detection LNs MMs

The diagnosis of lymph node metastases in women undergoing surgical management for cervical cancer is an indication to abort the surgery. Hence, frozen section evaluation of sentinel lymph nodes has been used for these patients. However, several studies have found significantly reduced sensitivity of intraoperative frozen section in detection of MMs and small MACs in cervical cancer [35,36]. In our multi-center study of 139 patients with stage IA1 and lymphovascular space involvement to IB1 cervical cancer, we noted the overall sensitivity of frozen section per node was only 20.7%. In this study we failed in the intraoperative diagnosis of the all nodes that finally were diagnosed with MMs and ICTs: 4 nodes with MMs and 9 nodes with ICTs [36].

In another study of 225 patients, Slama et al. noted the overall sensitivity of frozen section to be 56% for detecting LNs metastases and only 8% for the detection of MMs [36].

Prognostic value and treatment options for women diagnosed with LNs MMs

Prognostic value

The prognostic value of LNs ITCs and MMs is controversial and most of the studies are limited due to their small sample size, short follow up period and different methodology detecting MMs. Some data are taken from sentinel node series, in which patients with positive LNs for MMs/ITCs treated as with MACs. In the largest retrospective series to date which included 645 patients, Cibula and his colleagues observed the same prognosis in patients with positive LNs for MMs and MACs in terms of overall survival. In this study the overall survival was significantly reduced in patients with MACs and MMs; the hazard ratio for overall survival reached 6.85 (95% CI, 2.59–18.05) and 6.86 (95% CI, 2.09–22.61) respectively [6,37].

This result was supported by other series [38], especially for IB and IIA FIGO stages; lymph node involvement was illustrated as the most important prognostic factor and LNs MMs was an independent prognostic factor in multivariate analysis of 894 patients [31]. Other authors reported an increased risk of recurrence in cases of LNs MMs, whether detected by pathological or molecular biology techniques such as quantitative reverse transcription-PCR assay for detecting SCC-Ag in LNs [21,39]. A retrospective review of the medical records of 62 patients who underwent radical hysterectomy and lymphadenectomy for FIGO stage IA2-IB2 cervical cancer showed a recurrence rate of 50% (2/4 patients) among patients who were diagnosed with LNs MMs compared with 6.7% (3/45 patients) in patients without MMs in a mean follow up time of 39.4 months [19]. Marchiolé et al. performed a retrospective histological analysis of 2 groups: 26 cases who recurred in a median time of 36.8 months and the second series were 26 cases matched for age, histological sub-type, surgico-pathological stage and maximal tumor diameter, who did not recur after a median follow-up of 122 months. The relative risk of recurrence was shown to be 2.44 (1.58–3.78, $P < 0.01$) in the in the presence of LNs MMs [40].

The retrospective study by Colturado et al. has reviewed patients with stage IB1, IB2, and IIA cervical cancer who were surgically treated (radical hysterectomy) with no lymph nodes metastases after standard pathological examination, without adjuvant treatment and with a minimum of 5 years of follow-up [41]. Every tumor sections were reviewed and lymph nodes were analyzed with pathological ultrastaging. 6 patients/ 83 (7%) were found to have pelvic lymph node micrometastases. Multivariate regression analysis results showed significant associations between recurrence and the presence of lymph node micrometastases: patients with micrometastases had an 11.73-times higher risk of recurrence than did those without micrometastase [41] (Table 2).

Contrarily, 2 studies found no impact of micrometastasis in sentinel lymph nodes on disease-free survival.

The Stany et al. retrospective review of 129 patients with early-stage cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy, found retrospectively LNs MMs in 26 patients

Table 2
Prognosis of women diagnosed with early stage cervical cancer LNs MACs/MMs/ITCs compared with patients without LNs involvement (N0).

Study	N	Detected nodes (% patients)			Overall survival			Recurrence		
Juretzka [19]	62							Recurrence in a mean follow up of 39.4 months (%)		
2004		MACs	MMs	ITCs				MACs	MMs	N0
		20.1	6.5	MD				MD	50.0 [a]	6.7
Horn [31]	894				Overall survival HR in relation to N0			5-years recurrent free survival (%)		
2008		MACsMMs	MMs	ITCs	MACs	MMs		MACs	MMs	N0
		23.1	6.6	MD	3.4 [a]	2.5 [a]		62.0 [a]	68.9 [a]	91.4
Yuan [21]	36							Recurrence in a mean follow up of 29 months (%)		
2008		MACs	MMs	ITCs				MACs	MMs	N0
		19.4	5.6	MD				57.1 [a]	50.0 [a]	3.7
Cibula [6]	645				Overall survival HR in relation to N0			Relapse-free survival (RFS) HR in relation to N0		
2012		MACs	MMs	ITCs	MACs	MMs	ITCs	MACs	MMs	ITCs
		21.1	7.1	3.9	6.85[a]	6.86 [a]	MD	3.15 [a]	3.15	MD
Colturato [41]	83				Overall survival HR in relation to N0			Recurrence in a mean follow up of 60 months (%)		
2016		MACsMMs	MMs	ITCs	MACs	MMs		MACs	MMs	N0
		MD	7	MD	MD	11.73		MD	66.6 [a]	14
Guani [17]	139				DFS in a mean follow up of 36 months (%)			Recurrence in a mean follow up of 36 months (n)		
2019		MACsMMs	MMs	ITCs	N+	N0		MACs	MMs	ITCs
		7.2	5.8	5.8	91.66	90.43		1	1	0

NS- Non Significant. MD- Missing Data. a. $P < 0.01$. b. MACs and MMs detection by histology and Squamous Cell Carcinoma Antigen mRNA, respectively. DFS- Disease-free survival.

(20%) diagnosed with negative nodes before [42]. LNs MMs were not associated with any other high-risk clinical or pathologic variables and survival data analysis did not demonstrate an association between the presence of MMs and recurrence or overall survival in an average follow-up of 70 months [42]. The author did not explain why patients with MMs were more likely to have received adjuvant radiation and chemotherapy.

Secondly, the recent follow-up results after 3 years of the prospective study SENTICOL (Ganglion Sentinelle dans le Cancer du Col) reported 13 recurrences. The study included patients with cervical carcinoma FIGO (International Federation of Gynecology and Obstetrics) stage IA1 with lymphovascular space invasion, stage IA2 and IB1, who participated in the prospective SENTICOL study. Among patients with sentinel lymph nodes positive for micrometastasis, only one had a recurrence [17].

Two recurrences in patients with positive sentinel lymph nodes (one macrometastasis and one micrometastasis) and 11 recurrences in patients with negative lymph nodes (sentinel lymph nodes and non-sentinel lymph nodes) were found. There was no statistically significant difference in disease-free survival in terms of prognostic factors in the cohort, except patient age: a significant decrease in disease-free survival was found in patients >50 years old ($p = 0.01$). In the study the discovery of micrometastasis did not change oncological management, therefore these patients did not receive additional adjuvant therapy. These data were obtained after ultrastaging of the sentinel lymph nodes and non-sentinel lymph nodes several months after the surgery, when the adjuvant therapy had been defined.

Unlike previous retrospective studies, this prospective study of 139 patients showed no impact of micrometastasis in sentinel lymph nodes on disease- free survival. However, due to the relatively short follow-up, the authors concluded that some late recurrences may have been missed [17].

The precise prognosis of ITCs and MMs need further evaluation. The main limitation of must studies is the small size of the cohorts. Well conducted prospective series with long term follow-up are necessary. This is mandatory to indicate the appropriate adjuvant treatment in case of low volume nodal disease if these lesions have an impact. This specific issue will be studied in the ongoing SENTICOL III trial [17]. On the other hand, very small deposits could have no prognosis impact, making their diagnosis unnecessary.

Treatment options

LNs involvement with MACs is considered a major prognostic factor and a decision criterion for adjuvant therapy. This approach is based primarily on a trial in which 243 patients that were diagnosed with cervical cancer, FIGO stage Ia2-IIa, after radical hysterectomy and lymphadenectomy with positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium, were randomly divided into 2 group: 127 patients who received radiotherapy (RT) and chemotherapy (CT) (Cisplatin based) and 116 patients who received RT only. The progression-free survival at 4 years was 63% with RT and 80% with RT/CT. The overall survival rate at 4 years was 71% with RT and 81% with RT/CT. The author concluded that addition of cisplatin- based CT to RT significantly improves progression-free and overall survival for high-risk, early-stage patients [43]. The current different treatment protocols in the presence of MMs or ITCs in women with cervical cancer are based mainly on retrospective data. The incidence of MMs observed in previous studies (Table 1 and Table 2) and the presented incidence of recurrence in apparent negative lymph node patients might argue in favor of aggressive treatment of these patients.

In 2005, the prognostic value of MMs was evaluated in a retrospective case control study including 52 patients (26 with and 26 without recurrence) [44]. An association between lymphovascular space involvement and the presence of MMs in SLNs was illustrated.

In a multi-centered retrospective study of 645 patients with an early stage cervical cancer, 85.3% of patients with macrometastasis, 82.6% with MMs, 52% with ITCs and 10.5% with negative pelvic nodes received adjuvant therapy (RT + CT) [6]. The two groups of patients with macrometastasis and MMs could not be statistically distinguished in the effect on overall survival rate ($p = 0.886$). Both these groups were significantly different from the group of patients with negative lymph node status ($p = 0.001$) [6]. Finally, Zaal et al. recently published a retrospective analysis of the same data of women who underwent SLNs biopsy followed by pelvic LNs dissection. Interestingly, among the patients diagnosed with MMs in the sentinel node, the overall survival was significantly better if more than 16 non-SNs were removed. This result could not be observed among women with macrometastases or women without SLN disease [44]. This study, despite his retrospective and multicenter nature limitations, identifies a subgroup of

patients with MMs LNs who might be treated differently from women without nodal disease or women with LNs macrometastases. Despite the lack of data, most teams offer adjuvant radiotherapy. These results should be further validated, preferably by randomized controlled studies in this specific population.

Prognostic value and treatment options for women diagnosed with LNs ITCs

We have little data for ITCS. We said before for MMS, than Cibula observed the same prognosis in patients with positive LNs for MMs and MACs in terms of overall survival. Any prognostic significance for positive nodes with ITCs was found [37].

In addition, Marchiolé et al. found that the relative risk of recurrence in women with SLN MMs and ITCs was 2.30 (CI 1.65, 3.20, $p < 0.01$) and 2.22 (CI 1.30,3.80, $p = 0.09$), respectively. Using bivariate model analysis, MMs were the only independent risk factor for recurrence [40].

The prospective SENTICOL study of 139 patients, unlike previous retrospective studies, showed no impact of isolated tumor cells in sentinel lymph nodes on disease- free survival.

The discovery of isolated tumor cells did not change oncological management, therefore these patients did not receive additional adjuvant therapy [17].

Summary

In general we have much more data for MMs than for ITCs. The available knowledge in the literature is inadequate to assess the prognostic effect of LNs MMs and ITCs in women with cervical cancer. Unfortunately, there is a scarce data to conclude whether the diagnosis of MMs or ITCs should influence the treatment decisions as occurs in LNs MACs. Despite the insufficient data that exists regarding treatment options for women diagnosed with LNs MMs/ITCs, whether detected by pathological or molecular biology techniques, it is unlikely that a large trial, in which patients with small nodal disease would be randomly assigned to treatment versus observation, will be feasible. We are forced to await long-term follow up from further prospective cohort studies. In the meantime, with the limitations of the current evidence regarding MMs/ITCs presented here, we and other groups continue diagnosing women with small nodal disease by using ultrastaging technique and prefer to treat them as an high risk group.

Author contribution

- Study conception and design: MD, FL
- Acquisition of data: MD
- Analysis and interpretation of data: MD, FL
- Drafting of manuscript: MD
- Critical revision: MD, HBK, ASB,CNG,VB, HTNX, MK, PM, FL
- Final approval of the version to be submitted and any revised version: MD, HBK, -ASB,CNG,VB, HTNX, MK, PM, FL

Declaration of Competing Interest

All authors disclose no financial and personal relationships with other people or organizations that could inappropriately bias their work.

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