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Clinical Significance of Low Volume Lymph Node Metastasis in Early Stage Cervical Cancer: A Single Centre Case Series

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background and Objectives: Lymph node involvement is uncommon in early-stage cervical cancer (7-20%), with low volume nodal disease (micrometastasis and isolated tumour cells) representing a further small subset (2-23%) of this small population. Fewer data are available on the impact of low volume metastasis in cervical cancer. The current consensus is to treat this group of patients in the same way as for nodal macrometastasis although the prognostic significance of low volume lymph node metastasis still remains contested. The purpose of this study was to

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retrospectively analyze a cohort of patients who underwent primary surgery for early-stage cervical cancer and where the post operative histopathology report demonstrated low volume lymph node metastasis. The aim was to determine the frequency of recurrence and progression free survival in groups with isolated tumor cells (<0.2 mm), micrometastasis (0.2 – 2 mm) and macrometastasis (>2 mm).

Methods: Retrospective review had identified 18 patients who underwent primary surgery in single Gynaecology Cancer Centre between 2007 and 2018 for cervical cancer with subsequent histologically demonstrated lymph node metastasis. Progression free survival curves were generated for each patient group based on their histological type of lymph node metastasis. Log rank, chi squared test statistic was calculated to test for statistically significant difference in survival between groups.

Results: A total of 18 patients were identified as having isolated tumor cells (n=7), micrometastasis (n=5) or macrometastasis (n=6) on post operative lymph node histopathology. Follow up data demonstrated a total of 6 recurrences overall, with the highest number in the “macrometasitasis“ group (66.7%), followed by “isolated tumor cells” group (28.6%). No recurrence was observed in the “micrometastasis” group. The difference in progression-free survival between groups was not statistically significant at alpha = 0.05 (p=0.0685).

Conclusion: Further research and larger studies are required to evaluate the prognostic significance and the overall outcome in patients with isolated tumor cell lymph node metastasis in early stage cervical cancer.

Keywords: Clinical significance; cervical cancer; low volume lymph node; metastasis.

1. INTRODUCTION

Lymph node involvement is thought to be present in 7-20% of early-stage cervical cancer cases [1,2,3]. It represents a significant negative prognostic factor for early-stage disease, directing the most appropriate adjuvant treatment [1,4,5,6,7,8,9,10,11]. During pathological examination, specifically ultrastaging, low volume lymph node metastasis is categorized into isolated tumor cells (<0.2 mm), micrometastases (0.2mm–2 mm) and macrometastasis (>2mm) [12]. This classification is based on the American Joint Committee on Cancer (AJCC) for breast cancer staging and although it has not been specifically validated for cervical cancer, it is routinely employed in histopathological evaluation and reporting of cervical cancer [13,14,6]. Micrometastasis represents 2%-23% of cases of nodal disease which upstages the disease significantly [1]. The updated 2018 FIGO staging criteria for cervical cancer classifies lymph node macrometastasis and micrometastasis as stage 3 disease and the latest update to ESGO cervical cancer guidelines recommends that micrometastases are treated as equivalent to macrometastatic disease [15,7].

Whilst the clinical impact of large volume lymph node metastatic disease has been well evaluated, fewer data are available on the impact of low volume metastasis (isolated tumor cells and micrometastasis) [1]. In the last 20 years, several studies have reported on overall survival and progression free survival in low volume lymph node metastatic disease, but since nodal disease and specifically low volume nodal metastasis represents a small fraction of affected patients, cases are infrequent. A relatively low number of cases have been reported, particularly in relation to isolated tumor cells, making it difficult to detect statistically significant differences in outcomes. In a recent meta-analysis which included 11 studies, Guani et al. [16] have proposed that the presence of micrometastasis is associated with a negative impact on disease free and overall survival, however analysis of the specific subgroup of isolated tumor cells alone was not possible [13,16]. On the other hand, an earlier systematic review by Delomenie et al in 2019 concluded that there was inadequate evidence to assess the prognostic effect of lymph node micrometastasis and isolated tumor cells in women with cervical cancer [17]. It is apparent that despite the documented literature, the prognostic significance of low volume lymph node metastasis in cervical cancer still remains open to debate, however the current consensus is to treat this group of patients in the same way as for macrometastasis in lymph nodes [7,17].

The aim of this study was to retrospectively analyse data from a cohort of patients who underwent primary surgery for early-stage cervical cancer in a gynaecology oncology

centre, and to assess the frequency of recurrence, indications for adjuvant treatment and progression free survival in patients with low volume lymph node metastasis.

2. METHODS

We conducted a retrospective review of cases at the West Kent Gynaecology Cancer Centre in the United Kingdom over a period of 11 years between 2007 and 2018. Patients who underwent primary surgery for cervical cancer were identified and those with histologically confirmed lymph node metastasis were selected. 20 patients were identified with lymph node metastasis consisting of isolated tumor cells (n=7), micrometastasis (n=7) or macrometastasis (n=6). One patient died from an unrelated cause and another patient was lost to follow up; both were therefore excluded from analysis. Surgical staging assessment consisted of sentinel node identification using a combination of blue dye and Tc99, and where this was unsuccessful, a full pelvic lymph node dissection was performed.

Histological evaluation was performed by an experienced gynaecological pathologist.

All sentinel nodes were fixed in 10% buffered formalin, dissected into 3mm slices, processed in their entirety and embedded in paraffin wax. A standard 3µm haematoxylin and eosin (H and E) stained section was prepared from each paraffin block, with minimal trimming, in the first instance. Sentinel nodes showing metastatic carcinoma in this initial section were not examined with further sections. Sentinel nodes which showed a benign initial section were further examined ('ultrastaged') by preparing multiple additional sections stained with H and E and cytokeratin immunohistochemistry. The ultrastaging protocol was changed twice over the period under study. From 2007 to 2013 the method of Terada et al [18] was followed whereby three serial sections were cut at 400µm intervals through the full thickness of each paraffin block of sentinel node. One of the sections was stained with H and E, one with immunohistochemistry for the pancytokeratin MNF116 and one unstained section retained as a spare. For the immunohistochemistry, each 3µm section was deparaffinised, rehydrated and then submitted to antigen retrieval. The antigen retrieval was performed in antigen retrieval solution (Vector H3300) in a Dako Pascal pressurised heating chamber for 1 minute 50 seconds at 125˚C, 15lb/in^2. The sections were incubated for 30 minutes in 1:200 MNF116 mouse monoclonal antibody (Dako) using a Dako autostainer with a Dako 'Real' kit system (K5001). The latter incorporated secondary and tertiary amplification steps with endogenous peroxidase blocking and yielded a permanent DAB visualisation product. From 2013 to 2015 the ultrastaging method was altered slightly such that sections for H and E and MNF116 staining were cut at intervals of 330µm rather than 400µm. From 2015 to 2018 the ultrastaging method was altered again to parallel the GROINSVI protocol [8] for inguinal node ultrastaging and sections were cut at 500µm intervals through the paraffin blocks of sentinel node for staining with H and E and the cytokeratin AE1/AE3. For the immunohistochemistry, antigen retrieval was performed with protease (Roche RTU Pronase) for 8 minutes. The sections were incubated for 32 minutes in 1:100 AE1/AE3 mouse

monoclonal antibody (Leica NCL-L-AE1/AE3) using a Roche/Ventana autostainer (multimer based technology) and with a Roche Ultraview kit system. Following examination of the sections produced from ultrastaging by light microscopy, any metastatic disease detected was classified according to UICC TNM criteria as macrometastatic (>2mm in diameter), micrometastatic (0.2 – 2mm) or isolated tumour cells (<0.2mm). Patients were followed up using a standardized protocol for a minimum of 60 months. Recurrence was confirmed radiologically and/or histologically by the multidisciplinary team. Results were analysed using the MS Excel package. Kaplan-Meier Survival Curves were generated and calculations were performed for log rank, chi squared test statistic to determine if the survival curves were statistically significantly different. As the data was obtained from retrospective surgical outcomes audit, no specific ethical approval was required to conduct this retrospective review.

3. RESULTS

A total of 18 patients with follow up were included in the study and identified as having lymph node metastasis. This group included lymph nodes with isolated tumor cells (n=7), micrometastasis (n=5) or macrometastasis (n=6). Group characteristics are recorded in Table 1 and are comparable across the 3 groups. The average patient age at diagnosis in the three groups was comparable: 37.6 years in ITC group, 41.8 in the micrometastatic (MIC) group and 39.2 in the macrometastatic (MAC) group. The majority of

Table 1. Primary data table

	PFS (months)	Age at surgery	FIGO Stage	HPV associated	Histological type	Grade (1/2/3)	Max Tumour Size (mm)	LVSI	Lap/Open	Total Bilateral PLND	Procedure	Adjuvant Radiotherapy	Adjuvant Chemotherapy	Recurrence	Site of Recurrence
ITC	114	55	Ib1	+	squamous carcinoma	2	15x5	+	lap	no	Radical hysterectomy BSO	+	-	-	
	8	24	Ib1	+	adenosquamous carcinoma	3	13x4	+	lap	no	Radical vaginal Trachelectomy lap SLND only	- (declined)	-	+	Vagina
	70	42	Ib2	+	endocervical adenocarcinoma	2	48x22	-	lap	no	TLH, BSO, RIGHT SLNB, LEFT NON-SLNB	+	+	+	Vagina
	72	28	Ib1	unknown	squamous carcinoma	3	>20	-	open	yes	Wertheim's (ovarian conservation), BPLND	-	-	-	
	72	31	Ib1	+	adenosquamous carcinoma	3	20	+	lap	yes	Laparoscopic Wertheim's BSO BPLND	+	+	-	
	66	38	Ib1	+	squamous carcinoma	3	20x13	-	lap	no	Radical hysterectomy bilateral salpingectomy	+	-	-	
	66	45	Ib1	+	endocervical adenocarcinoma	2	21x13	+	lap	no	Laparoscopic radical hysterectomy , BSO	+	+	-	
MIC	96	34	Ib1	+	squamous carcinoma	3	25x11	+	lap	no	Trachelectomy SLND only	+	+	-	
	72	39	Ib1	+	endocervical adenocarcinoma	2	24x5	-	lap	no	Laparoscopic radical hysterectomy BSO SLND only	+	+	-	
	150	59	IIa	+	squamous carcinoma	3	15	+	open	yes	Wertheims BPLND	+	+	-	
	140	41	Ib1	+	squamous carcinoma	2	40	+	open	yes	Wertheims BPLND	-(declined)	-	-	
	92	36	Ib1	+	endocervical adenocarcinoma	2	15	-	lap	yes	Laparoscopic Wertheim BSO BPLND	+	+	-	
MAC	50	31	Ib1	+	endocervical adenocarcinoma	3	13	+	lap	yes	Schauta BSO BPLND sentinel node	+	+	+	Pulmonary
	96	25	Ib1	+	squamous carcinoma	2	26	+	lap	yes	Radical trachelectomy, BPLND, Sentinel	+	+	-	

	PFS (months)	Age at surgery	FIGO Stage	HPV associated	Histological type	Grade (1/2/3)	Max Tumour Size (mm)	LVSI	Lap/Open	Total Bilateral PLND	Procedure	Adjuvant Radiotherapy	Adjuvant Chemotherapy	Recurrence	Site of Recurrence
											node				
	23	72	Ib2	+	endocervical adenocarcinoma	3	42x26	+	open	Yes	Open Wertheims BSO SLND and BPLND	+	+	+	Pulmonary
	18	52	Ib1	+	squamous carcinoma	2	30x19	+	open	Yes	Open Wertheims BSO left SLN biopsy, BPLND	+	+	+	Vagina
	84	30	Ib1	+	squamous carcinoma	3	27x7	+	lap	Yes	Radical Trachelectomy SLND and BPLND	+	+	-	
	10	25	Ib1	+	endocervical adenocarcinoma	3	30x10	+	lap	yes (sampling)	Laparoscopic Wertheims SND and BPLND ovarian conservation	- (declined)	-	+	Died of disease

ITC = Isolated Tumour Cells, MIC = Micrometastasis, MAC = Macrometastasis, PFS = Progression free survival, LVSI = Lymphovascular space invasion, PLND = Pelvic lymph node dissection, Lap = Laparoscopic, FIGO stage = Figo 2008 staging for cervical cancer, BSO = Bilateral Salpingo-Ophorectomy, SLND = Sentinel Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy, BPLND = Bilateral Pelvic Lymph Node Dissection, SLN = Sentinel Lymph Node, SND = Sentinel Node Dissection

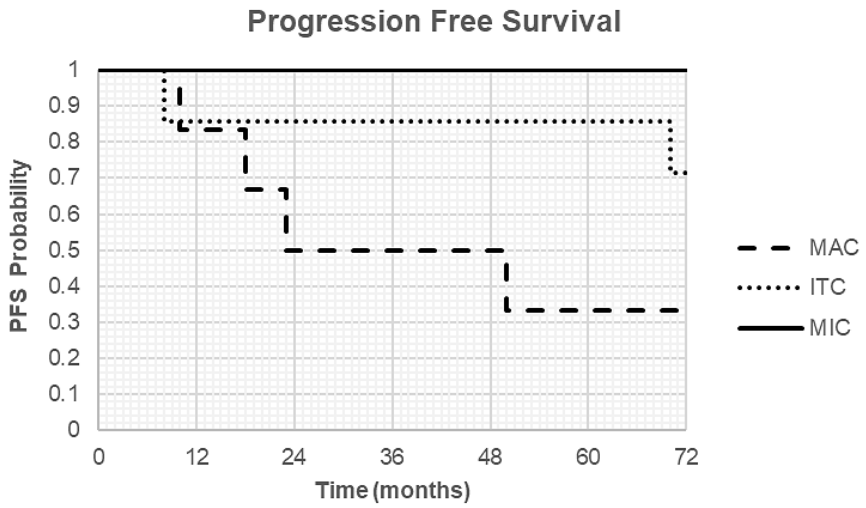

Fig. 1. Kaplan meier graph for progression free survival (PFS) in macrometastasis (MAC), micrometastasis and isolated tumour cells (ITC)

Table 2. comparison of group characteristics

	ITC (n=7)	MIC (n=5)	MAC (n=6)
Average age	37.6	41.8	39.2
Figo stage			
IB1	6	4	5
IB2	1	N/A	1
IIa	N/A	1	N/A
Histology			
squamous cell carcinoma	3	3	3
endocervical adenocarcinoma	2	2	3
adenosquamous carcinoma	2	N/A	N/A
Grade			
2	3	3	2
3	4	2	4
LVSI positivity	4	3	6
Laparoscopic vs Laparotomy			
Laparotomy	1	2	2
Laparoscopic	6	3	4
Adjuvant treatment	5	4	6
Recurrence	2	0	4

cases were FIGO stage 1B1 (pre-2018: 85.7% in ITC group, 80% in MIC group, 83.3% in MAC group). Squamous cell carcinoma histological type was present in 42.8% of ITC cases, 60% of MIC cases and 50% of MAC cases. Almost all of the cases (17/18) demonstrated HPV association. LVSI positivity was noted in 57.2% of cases with ITC, 60% of cases with MIC and 100% of cases with MAC. There were a total of 6 recurrences over 72 months with the highest number observed in the MAC group (66.7%). In addition, there were 2 recurrences in the ITC group (28.6%) but no recurrence was observed in the MIC group. Despite this, and due to low case numbers, the difference in progression-free survival (Fig. 1 between groups was not statistically significant at alpha = 0.05 (p=0.0685). In our series there were 2 recurrences in the ITC group, with one early recurrence at 8 months and one late recurrence at 70 months. Both patients were offered adjuvant chemoradiotherapy following surgery, however one patient undergoing fertility sparing surgery had declined this and unfortunately a vaginal recurrence was diagnosed later at 8 months. An additional adverse prognostic factor in that case was the presence of LVSI. The second recurrence in the ITC group was late in the course of follow-up at 70 months and this patient did undergo adjuvant chemoradiotherapy post surgery. Although there was no LVSI, the tumor was bulky (4.8cm) and this likely increased

the risk of recurrence in this instance. There were no recurrences in the MIC group. All of the patients in the MAC group exhibited LVSI and almost all (5 of 6) had received adjuvant chemoradiation with the exception of one patient who declined further treatment.

4. DISCUSSION

Although our case series did not have sufficient statistical power to demonstrate a significant difference in progression free survival among the three groups, it could suggest that ITC may be a significant risk factor for disease recurrence. Further collective research, including meta-analyses would be required to detect a statistically significant difference in such a rare event as ITC. Whilst there are other factors which influence prognosis and risk such as LVSI, tumor resection margins and bulk, we must interpret the presence of isolated tumor cells with caution. In our gynaecology cancer centre, patients with isolated tumor cells would go on to have a discussion regarding the benefits of adjuvant radiotherapy (RT) alone while those with micrometastasis would be offered concurrent chemoradiation (CCRT). On the other hand, for patients with macrometastasis the combination of treatment would be determined by additional risk factors such as LVSI, tumor size and histological features.

It is known that MIC is associated with a negative impact on both disease-free survival and overall survival [16], but despite previous meta-analysis of the literature, there does not appear to be enough data regarding the impact of isolated tumor cells alone. It could be inferred that this is due to the rarity of low volume nodal metastasis, as can be seen in our case series which identified only 20 cases over the course of 11 years in a large cancer centre.

It is worth noting that there are limitations to the ultrastaging technique such that it cannot be performed intraoperatively as it is too cumbersome and time-consuming. Moreover, the frozen section accuracy for the detection of MIC is low.

Another important issue in pathological analysis relates to the lack of studies specific to cervical cancer to define the size criteria of low volume metastasis for this tumor site. The current system uses the classification of the American Joint Committee on Cancer (AJCC) for staging of breast cancer to classify MICs and ITCs in relation to their size [19,20-22].

The large meta-analysis of Guani et al. on the clinical impact of low volume metastasis did not show a significant effect in the ITC group due to the low number of events [16]. Prospective studies therefore do not appear appropriate in studying these rare outcomes, which would explain why only three prospective studies with small numbers of patients and events were identified in the meta-analysis by Guani et.al [16]. A multicentre approach with large cohorts of patients and events might have the required statistical power to identify significant differences in outcomes. For now, clinicians must exercise caution when treating cervical cancer patients with isolated tumor cells metastatic to lymph nodes [23-26].

5. CONCLUSION

Despite the uncertain clinical significance of isolated tumor cell lymph node metastasis, we observed that recurrence is not uncommon in this small cohort of patients. In our case series there was a 28.6% recurrence rate in patients with ITC nodal metastasis, however due to low statistical power there was no statistically significant difference in progression-free survival between ITC, MIC and MAC groups. It is therefore important that clinicians consider the benefits of adjuvant treatment in patients with ITC, as recurrence in this group has been demonstrated. Further research and larger studies are required to evaluate the prognostic significance and the overall outcome in patients with isolated tumor cell lymph node metastasis in early stage cervical cancer.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image

generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests, non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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