Oncologic impact of micrometastases or isolated tumor cells in sentinel lymph nodes of patients with endometrial cancer: a meta-analysis

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Abstract

Purpose—There is a gap in knowledge regarding the impact of micrometastases (MIC) and isolated tumor cells (ITCs) found in the sentinel lymph nodes of patients with endometrial cancer. Here, we present a meta-analysis of the published literature on the rate of MIC and ITCs after lymphatic mapping and determine trends in postoperative management.

Methods—Literature search of Medline and PubMed was done using the terms: micrometastases, isolated tumor cells, endometrial cancer, and sentinel lymph node. Inclusion criteria were: English-language manuscripts, retrospectives, or prospective studies published between January 1999 and June 2019. We removed manuscripts on sentinel node mapping that did not specify information on micrometastases or isolated tumor cells, non-English-language articles, no data about oncologic outcomes, and articles limited to ten cases or less.

Results—A total of 45 manuscripts were reviewed, and 8 studies met inclusion criteria. We found that the total number of patients with MIC/ITCs was 286 (187 and 99, respectively). The 72% of patients detected with MIC/ITCs in sentinel nodes received adjuvant therapies. The MIC/

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ITCs group has a higher relative risk of recurrence of 1.34 (1.07, 1.67) than the negative group, even if the adjuvant therapy was given.

Conclusion—We noted that there is an increased relative risk of recurrence in patients with low-volume metastases, even after receiving adjuvant therapy. Whether adjuvant therapy is indicated remains a topic of debate because there are other uterine factors implicated in the prognosis. Multi-institutional tumor registries may help shed light on this important question.

Keywords

Micrometastases; Isolated tumor cells; Endometrial cancer; Sentinel lymph node

Introduction

Endometrial carcinoma is the most common gynecologic cancer in developed countries. In 2019, an estimated 61,880 new cases and 12,160 deaths from uterine cancer were diagnosed in the USA [1]. The standard management of patients diagnosed with endometrial cancer has changed in the last few years, the current recommendation is total hysterectomy and bilateral salpingo-oophorectomy along with sentinel lymph node mapping alone, to avoid full lymphadenectomy.

Sentinel nodes are considered positive for disease if they contain macrometastases (MAC > 2 mm), micrometastases (MIC 0.2–2 mm), or isolated tumor cells (ITC 0.2 mm) [2, 3]. The relationship between MIC or ITCs and increased risk of recurrence, as well as prognosis, has been demonstrated in a number of cancers such as breast cancer [4, 5], vulvar cancer [6–8], gastric cancer [9], esophageal cancer [10], colon cancer [11, 12], prostate cancer [13], and cervical cancer [14, 15].

In endometrial carcinoma, the clinical impact of low-volume metastasis remains unknown. Cibula et al. [16] published a study on the impact of MIC and ITCs in the sentinel lymph nodes (SLNs) and non-SLNs of cervical cancer patients. The patients selected for that study (17 patients in total) had cervical cancer and were at high risk of lymph node (LN) positivity (stage IB–IIA, biggest diameter 3 cm). A total of 573 pelvic LNs were examined through ultrastaging protocol (5762 slides). Metastatic involvement was detected in SLNs of eight patients (1 × MAC; 4 × MIC; 3 × ITCs) and in non-SLNs in two patients (2 × MIC). The authors found that using pathologic ultrastaging, there were no false-negative cases of positive non-SLN (MAC or MIC) and negative SLN. The presence of MAC and MIC was associated with a decrease in overall survival, but no difference in survival was found between patients with negative LN and ITCs.

It is hypothesized that MIC represents a truly small metastatic involvement, while ITC can be a different entity with a limited potential for the development of distant disease spread. Furthermore, there is a gap in knowledge regarding the prognosis impact and the ideal management of patients with endometrial cancer who have MIC or ITCs in the sentinel lymph nodes. The aim of this review is to explore the clinical significance of MIC or ITC in endometrial cancer and summarize the reported literature on the impact on postoperative management in patients with such findings.

Methods

Search strategy and selection criteria

Keywords including "micrometastases", "isolated tumor cells", "endometrial cancer", and "sentinel lymph node" were used for literature searches in MEDLINE and PubMed. The search spanned from January 1999 to June 2019 and included all articles that contained information regarding "endometrial cancer" and "micrometastases and isolated tumor cells" in the titles and abstracts.

Articles had to meet the following inclusion criteria: English-language manuscripts limited to endometrial cancer, patients who had micrometastases and/or isolated tumor cells in the sentinel lymph nodes, studies that report oncologic outcomes, articles including   10 patients, patients who underwent open, laparoscopic or robotic surgery, and studies that did not present duplicated data. We included all retrospective and prospective studies. Two authors (NRGH and BN) reviewed the titles and abstracts of publications and excluded all unrelated articles (Fig. 1).

We collected information on study design, year of publication, time period of study accrual, number of patients included, median age of patients, histological type, myometrial invasion (MI), lymphovascular invasion (LVI), grade, MIC/ITCs detection rate, and technique of detection (Table 1). We report the articles that compared the recurrences among patients with micrometastases, isolated tumor cells, and negative patients and studies that provided information on adjuvant therapy (Table 2).

Statistical analysis

From each study, a number of cases and recurrences for each group of patients were extracted to calculate recurrence incidence. Relative risk and 95% confidence interval were calculated for each group number of cases. A random-effects meta-analysis was carried out for each comparison. Using the data, we created tables and forest plot was drawn. For each comparison, combined relative risk, given more weight for those studies with more cases, was calculated using DerSimonian–Laird random-effects mode, which accounts for both intra- and inter-study variability. All analyses were carried out with Stata 15.1

Results

We collected a total of 45 manuscripts, and 8 studies met our inclusion criteria (Fig. 1). Study characteristics are shown in Table 1. Studies totaled 2873 patients (range 41–508) among patients with MAC, negative lymph nodes, and MIC or ITCs. The median age was 62 years (range 54–69). Most of the patients (88%) reported an endometrioid histology on the final pathology, but 61% of total patients had more than 50% of myometrial invasion, 19% presented positive lymphovascular invasion, and Grade 3 was reported in the 20% of total patients. The median detection rate for MIC/ITCs was 17% (range 3–56). The ultrastaging technique was used in all the included studies.

Among all the studies which report data about oncologic outcomes, the total number of negative patients for MIC and ITCs was 2415, and the total number of patients with MIC/ITCs was 286 (187 and 99, respectively) (Table 2).

A total of 284 negative patients and 28 patients with either MIC or ITCs recurred. Table 3 shows the relative risk of recurrence between negative and MIC/ITCs patients.

Considering only studies with clear data about the administration of adjuvant therapy (Tables 4 and 5), in the MIC/ITCs patients who did not receive adjuvant therapy, compared to negative patients and to MIC/ITCs patients who did receive adjuvant therapy, the relative risk of recurrence was similar in both groups not depending on adjuvant therapy.

Discussion

Our findings suggest that there is a higher relative risk of recurrence in patients with low-volume metastases, even after receiving adjuvant therapy.

As previously noted, the incidence of MIC can differ according to the histological and biological technique used. Several studies proved that CK 20 is more sensitive than traditional histopathologic method with H&E (sensitivity was 94.5 and 91%, respectively) [17, 18]. Table 1 shows different ultrastaging techniques used in all the studies. Moreover, the SLN mapping with pathologic ultrastaging identified MIC or ITCs in 4.5% patients with endometrial cancer in whom no metastatic disease would have otherwise been detected by conventional pathologic processing [19, 20].

In terms of oncologic outcomes, the findings of low-volume metastases might have a negative impact on prognosis. Erlanki et al. [21] found that 2/7 (28%) of patients with micrometastases recurred and died of disease: both were of high risk—one had no adjuvant therapy, and the other one had both chemotherapy and radiotherapy. They reported a 36-month recurrence-free survival of 100% in patients who did not have micrometastases. Furthermore, Clair et al. [22] described a recurrence-free survival (RFS) of 86% for both MIC and ITCs patients. They observed that adjuvant therapy improves the survival rates in patients with low-volume metastasis compared to patients with macrometastasis. On the other hand, Todo et al. [23] reported that 28.6% of patients with ITC or MIC who received adjuvant therapy recurred ($p = 0.17$). Moreover, they found a higher rate of deep myometrial invasion in the ITCs or MIC patients than in node-negative patients ($p = 0.028$). However, this study presents some limitations: the majority of the patients had an early-stage carcinoma, received adjuvant therapy, or were patients with high-risk factors. In fact, histological grade, stage, and high-risk status are all important prognostic factors predicting disease recurrence. In addition, although we found that the 88% of the patients had an endometrioid histology on the final pathology, 61% of patients had more than 50% of myometrial invasion and 19% presented positive lymphovascular invasion.

Interestingly, Plante et al. [24] published a study on ITCs in patients with endometrial cancer, including 519 patients with a median follow-up of 29 months (range 0–67), and the progression-free survival (PFS) at 3 years for the ITC patients was 95.5%, similar to node-negative (87.6%) and micrometastasis patients (85.5%), but statistically better than patients

with macrometastasis (58.5%) ($p = 0.0012$). Moreover, the latest prospective study to assess the association between treatment and recurrence-free survival in stage I–II endometrioid endometrial cancer patients with ITCs was published by Backes et al. [25]. They found that in a total of 175 patients with ITCs, 49% had stage IA, 39% stage IB, and 12% stage II disease (all with ITCs). Fifty-one percent underwent SLN assessment only, and the remainder underwent SLN and lymphadenectomy. A total of 76 (43%) received either no adjuvant therapy or vaginal brachytherapy only; 21 (12%) had external beam radiation; and 78 (45%) received chemotherapy $+/-$ radiation. Patients who received chemotherapy more often had tumors with deep myometrial invasion, LVI, and higher grade. Nine (5.1%) patients recurred: 5 distant, 3 retroperitoneal, and 1 vaginal. After controlling for stage, LVI, and grade, chemotherapy was not associated with recurrence (HR = 0.63, 95% CI 0.11–3.52, $P = 0.39$). They concluded that the risk of retroperitoneal and/or distant recurrence is low (4.6%) for patients with stage I–II endometrioid EC and ITCs in SLNs regardless of adjuvant treatment or observation. The preliminary data suggest that adjuvant therapy does not appear to affect RFS.

The most recent publication is a multicenter, retrospective registry-based study of 2392 patients with endometrial cancer with and without MIC [26]. Without adjuvant therapy, the disease-free survival in the cohort of patients with MIC was reduced as compared with disease-free survival in the node-negative cohort, even after adjustment for age at diagnosis, myometrial invasion, histological grade and type, and performance status.

Although most of the studies recommended that the presence of isolated tumor cells should not drive the need for adjuvant treatments, the 72% of MIC/ITCs patients received some kind of adjuvant therapies. We could conclude that the benefit by giving additional treatments to ITCs patients depends on the presence of other high-risk uterine factors.

However, we recognize several important limitations. First, the number of the studies is small, given to the analysis a small power to make any conclusion. Second, in some studies, there were ITCs patients who received adjuvant therapy (chemotherapy or radiation) because of high-risk uterine factors or more advanced disease, and probably the prognosis could change. Lastly, given the favorable prognosis of endometrial cancer, our study is underpowered to detect small differences in survival.

In summary, when considering the association of MIC and ITCs with recurrence, we noted that patients with low-volume metastases had an increase relative risk of recurrence compared to negative patients, even if the adjuvant therapy was given. Further studies are needed in order to determine whether adjuvant therapy is indicated for both MIC and ITCs or only for those patients with MIC and to elucidate the specifics uterine factors that could change the indication of adjuvant therapy.

Conclusion

The current data show a higher sensibility and specificity of ultrastaging technique to detect MIC and ITCs; however, when we find these low-volume metastases, the clinical implications on adjuvant therapy remain a controversy. Currently, whether adjuvant therapy

(chemotherapy or radiation) should be recommended in patients, at least, with MIC in regional LNs remains a topic of debate. In the near future, with the growing incorporation of SLN mapping and the initiatives of multi-institutional tumor registries, more data will elucidate the true clinical impact of MIC and ITCs on prognosis.
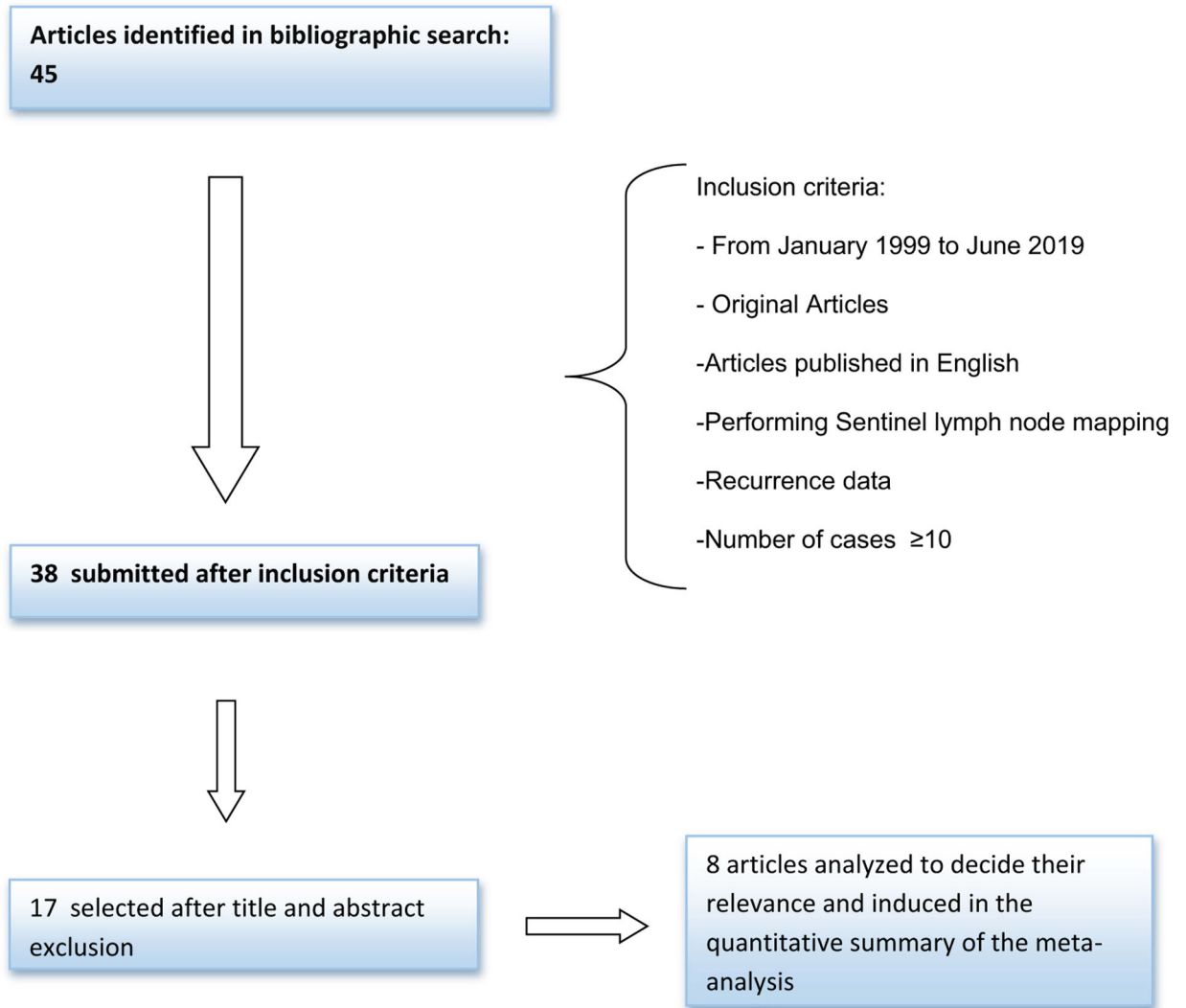
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Articles identified in bibliographic search:
45

Inclusion criteria:

- From January 1999 to June 2019

- Original Articles

-Articles published in English

-Performing Sentinel lymph node mapping

-Recurrence data

-Number of cases ≥10

38 submitted after inclusion criteria

17 selected after title and abstract exclusion

8 articles analyzed to decide their relevance and induced in the quantitative summary of the meta-analysis

Fig. 1.
Flowchart of studies retrieved and finally included in the meta-analysis

Table 1

Baseline characteristics of the included studies in the meta-analysis

Authors	Design	Year	Study period	Number of patients	Median age	Endometrioid histology	Non endometrioid	MI	LVI	Grade 1	Grade 2	Grade 3	Total MIC/ITCs patients	MIC/ITC (%)	Technique
Kim et al. [19]	Prospective cohort	2013	2005–2011	425	58	415	10	None: 241; < 50%: 184	Yes: 58; no: 367	302	108	15	12 (9 ITCs) (3 MIC)	3	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Kim et al. [20]	Retrospective cohort	2013	2005–2011	508	61	413	Serous: 62; clear cell: 12; carcinosarcoma: 21	None: 242; < 50%: 198; 50%:68	Yes: 132; no: 376	261	116	131	23 (19 ITCs) (4 MIC)	5	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Erlanki et al. [21]	Retrospective cohort	2010	2003–2006	47	60	37	Adenosquamous: 7; serous papillary: 2; clear cell: 1	None: 9; < 50%: 19; > 50%: 19	Yes: 4; no: 40; no data: 3	15	21	8	7(MIC)	15	Ultrastaging (H&E + IHC: Standard ABC + Anticytokeratin AE1/AE3)
Clair et al. [22]	Retrospective cohort	2015	2005–2013	844	61	724	Serous: 104; clear cell: 16	None: 422; < 50%: 310; 50%:1 12	Yes: 201; no: 618; no data: 25	479	177	188	44 (23 ITCs) (21 MIC)	5	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Todo et al. [23]	Retrospective cohort	2016	1997–2014	61	57	52	9	< 50%: 29; 50%:3 2	Yes: 15; no: 46	28	7	17	9 (6 ITCs) (3 MIC)	15	Ultrastaging (H&E + IHC: AE1/AE3 monoclonal antibody staining using an automated immunostainer)
Plante et al. [24]	Prospective cohort	2017	2010–2015	519	64	448	Serous: 36; carcinosarcoma: 25; clear cell: 7; other: 3	None: 125; < 50%: 234; 50%:1 60	Yes: 142; no: 362; no data: 15	260	150	109	42 (31 ITCs) (11 MIC)	8	Ultrastaging (H&E + IHC: Cytokeratin AE1/AE3)
Piedimonte et al. [27]	Retrospective case–control	2018	2012–2018	41	64	41	0	> 50%:1 6	17	No data	No data	No data	23 (11 ITCs)	56	Ultrastaging (H&E + IHC:

Authors	Design	Year	Study period	Number of patients	Median age	Endometrioid histology	Non endometrioid	MI	LVI	Grade 1	Grade 2	Grade 3	Total MIC/ITCs patients	MIC/ITC (%)	Technique
													(12 MIC)		Cytokeratin-based)
Ignatov et al. [26]	Prospective cohort	2019	2000–2017	428	69	399	26	> 50%: 152; < 50%: 240	No data	145	174	100	126 (MIC)	29	Ultrastaging
Summary	Meta-analysis			2873	62	2529				1490	753	568		17	

SLN sentinel lymph node, *MM* micrometastases, *ITCs* isolated tumor cells, *RT-PCR* reverse transcription polymerase chain reaction, *H&E* hematoxylin and eosin; *IHC* immunohistochemistry, *MI* myometrial invasion, *LVI* lymphovascular space invasion, *ABC* avidin–biotin–peroxidase complex
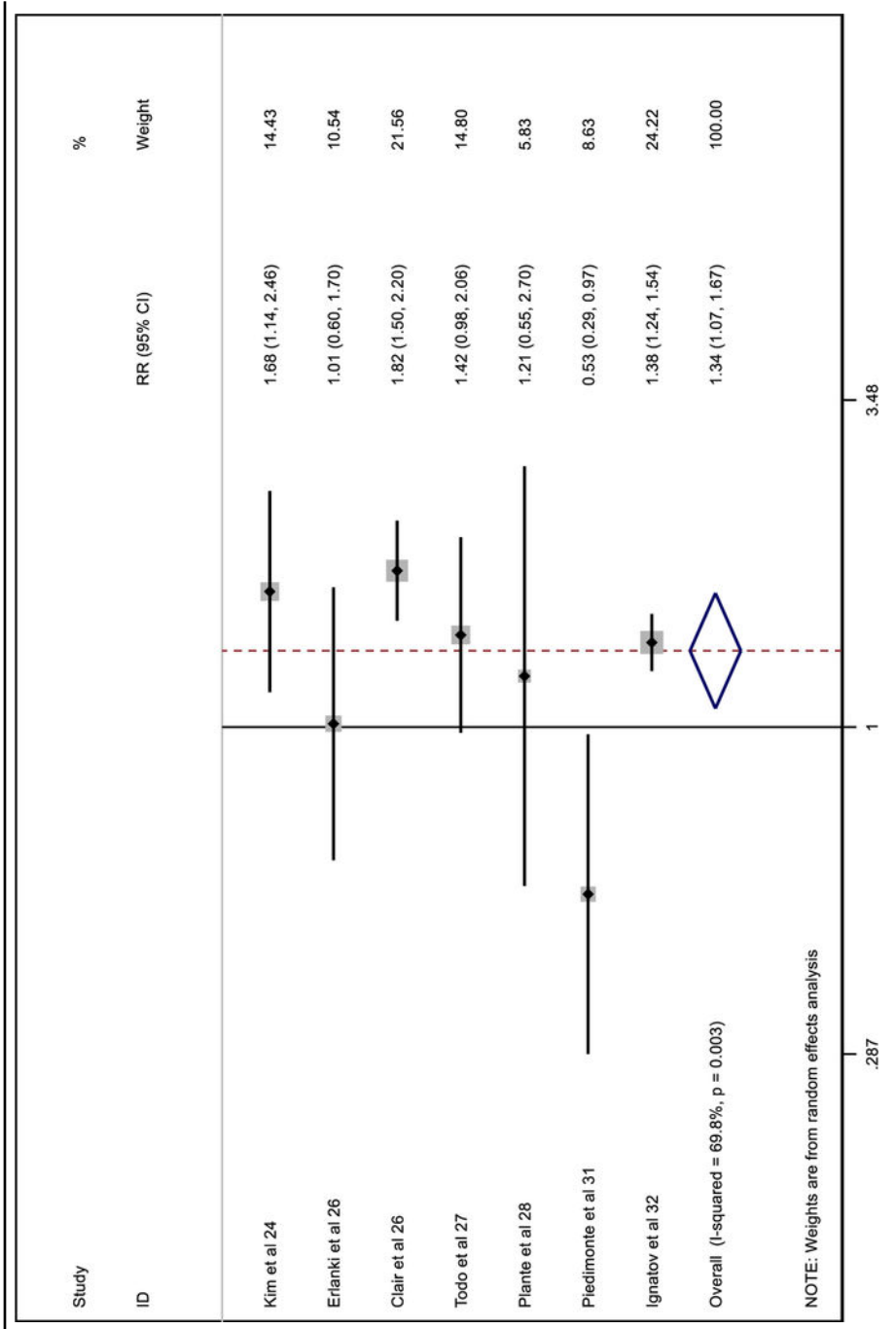
Table 2

Number of patients with adjuvant therapy and recurrences

	Total patients	Total negative patients		Total MIC/ITCs patients	Adjuvant therapy	No adjuvant therapy
		Adjuvant therapy	No adjuvant therapy			
Total patients						
Kim et al. [19]	425	400	94	306	12 (9 ITCs) (3 MIC)	9	3
Kim et al. [20]	413	355	No data	No data	23 (19 ITCs) (4 MIC)	No data	No data
Erlanki et al. [21]	47	40	12	28	7 (MIC)	5	2
Clair et al. [22]	844	753	No data	No data	44 (23 ITCs) (21 MIC)	40	4
Todo et al. [23]	61	52	34	18	9 (6 ITCs) (3 MIC)	2	1
Plante et al. [24]	519	434	No data	No data	42 (31 ITCs) (11 MIC)	39	3
Piedimonte et al. [27]	41	18	3	15	23 (11 ITCs) (12 MIC)	16	2
Ignatov et al. [26]	428	302	0	302	126 (MIC)	95	31
Summary	2778	2354	143	669	286	206	46
Recurrences						
Kim et al. [19]	11	8	3	5	3 (2 ITCs). (1 MIC)	2(TCs)	1(MIC)
Kim et al. [20]	2	No data	No data	0	2 (ITCs)	2 (ITCs)	0
Erlanki et al. [21]	2	0	0	0	2 (MIC)	1(MIC)	1(MIC)
Clair et al. [22]	51	47	No data	No data	4 (2 ITCs) (2 MIC)	4 (2 ITCs) (2 MIC)	0
Todo et al. [23]	12	8	No data	0	4 (ITCs/MIC)*	2(ITCs/MIC)*	2(ITCs/MIC)*
Plante et al. [24]	1	0	No data	No data	1 (ITCs)	1 (ITCs)	0
Piedimonte et al. [27]	2	0	0	0	2	2 (MIC)	0
Ignatov et al. [26]	231	221	No data	No data	10 (MIC)	No data	No data
Summary	312	284	3	5	28	15	4

*
There is no difference between MIC and ITCS reported in the study

Table 3

Comparative recurrences between negative patients and MIC/ITC patients

Study		
ID	RR (95% CI)	% Weight
Kim et al 24	1.68 (1.14, 2.46)	14.43
Erlanki et al 26	1.01 (0.60, 1.70)	10.54
Clair et al 26	1.82 (1.50, 2.20)	21.56
Todo et al 27	1.42 (0.98, 2.06)	14.80
Plante et al 28	1.21 (0.55, 2.70)	5.83
Piedimonte et al 31	0.53 (0.29, 0.97)	8.63
Ignatov et al 32	1.38 (1.24, 1.54)	24.22
Overall (I-squared = 69.8%, p = 0.003)	1.34 (1.07, 1.67)	100.00

NOTE: Weights are from random effects analysis

.287   1   3.48

Table 4

Comparative recurrences between non-adjuvant negative patients and MIC/ITC non-adjuvant patients

Study ID	RR (95% CI)	% Weight
Kim et al 24	1.19 (0.83, 1.70)	51.67
Erlanki et al 26	3.68 (0.33, 40.65)	24.86
Todo et al 27	5.55 (0.44, 69.91)	23.47
Piedimonte et al 31	(Excluded)	0.00
Overall (I-squared = 62.0%, p = 0.072)	2.26 (0.44, 11.70)	100.00

NOTE: Weights are from random effects analysis
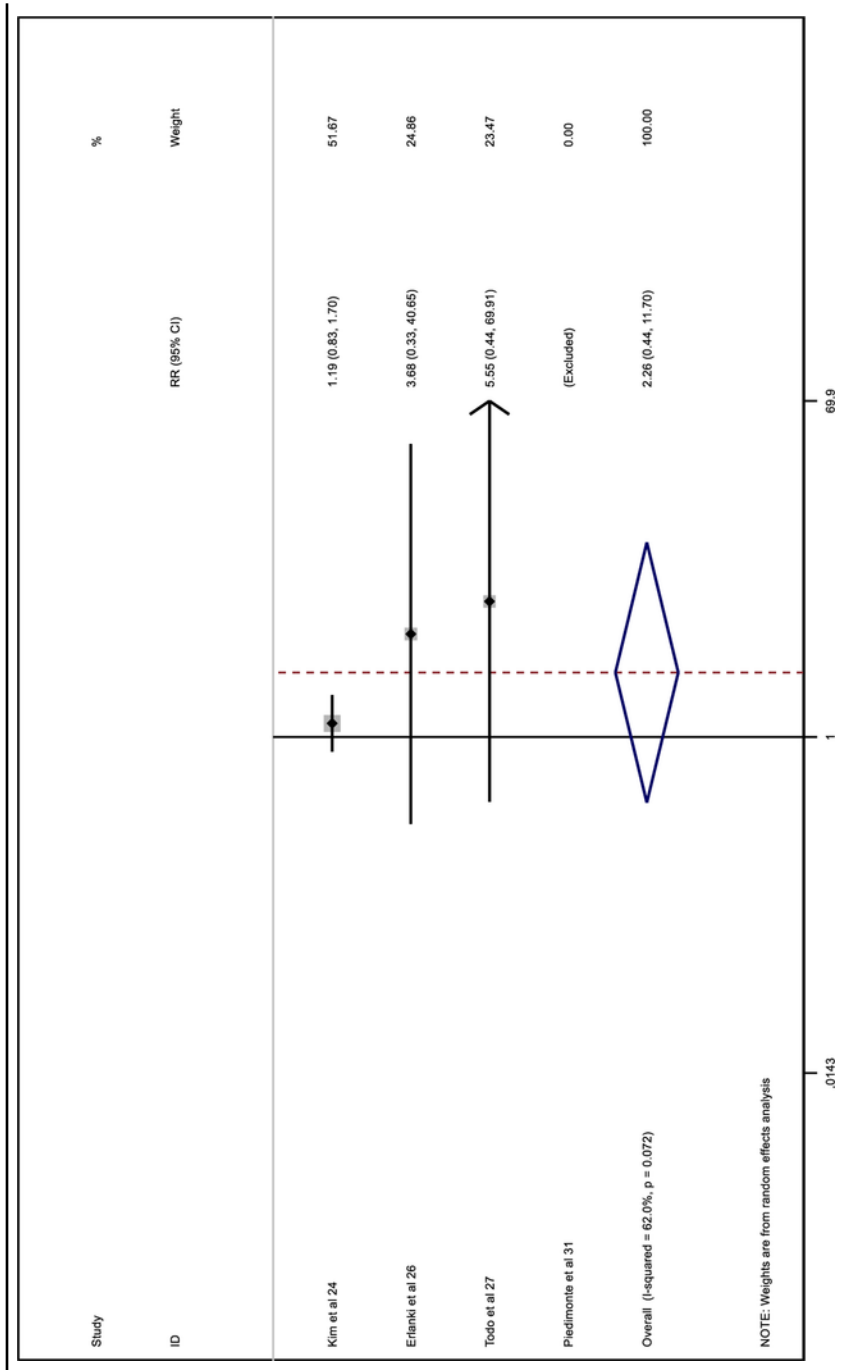
Table 5

Comparative recurrences between MIC/ITC patients with adjuvant therapy and MIC/ITC non-adjuvant patients

Study		
ID	RR (95% CI)	% Weight
Kim et al 24	1.13 (0.47, 2.67)	7.44
Erlanki et al 26	1.43 (0.33, 6.17)	2.60
Clair et al 26	1.00 (0.73, 1.36)	58.56
Todo et al 27	1.33 (0.38, 4.72)	3.47
Plante et al 28	1.22 (0.55, 2.74)	8.57
Piedimonte et al 31	1.04 (0.61, 1.78)	19.37
Overall (I-squared = 0.0%, p = 0.979)	1.05 (0.83, 1.34)	100.00

NOTE: Weights are from random effects analysis

.162   1   6.17