MAEDICA – a Journal of Clinical Medicine
2025; 20(2): 353-357
https://doi.org/10.26574/maedica.2025.20.2.353

MÆDICA - a Journal of Clinical Medicine

REVIEW

Clinical Significance of Micrometastases and Isolated Tumor Cells in Breast Cancer

Christos AMPATZIS[a], Stefanos ZERVOUDIS[b, c], Panagiotis ESKITZIS[d], Panagiotis TSIKOURAS[e], Anthi PAPAKONSTANTINOU[f], Georgios IATRAKIS[b, c]

[a]Rural doctor, G. H. Krestena, Ilia, Greece

[b]Rea Maternity Hospital: Breast Unit, Athens, Greece

[c]University of West Attica, Athens, Greece

[d]Department of Obstetrics, University of Western Macedonia, Kozani, Greece

[e]University Hospital of Alexandroupolis, Greece

[f]"St Andrews" General Hospital of Patras, Patras, Greece

ABSTRACT

We decided to do a literature search for information about the clinical significance of micrometastases (pN1mi) and isolated tumor cells (ITCs). A detailed search was conducted in the existing bibliography. We found that pN1mi and ITCs had differences in prognosis and were handled in a different way. However, some researchers do not accept this difference. Many studies have shown no differences in their prognosis and the distinction of these terms is questioned. This fact is attributed to different definitions, diagnostic approaches that have been used and not well organised research. For their diagnosis, single hematoxylin and eosin (H&E) stain slide section, and not routine immunohistochemical (IHC) stain, is recommended, despite a lot of institutions perform multiple level sections and IHC stains for each block of sentinel lymph nodes (SLNs). Once the limits within pN1mi and ITCs were defined, they have been based in small data, and here is an area where we should focus and build evidence based definitions that have proven differences and importance in clinical management. As for their therapy, in ITCs cases, axillary lymph node dissection (ALND) is omitted, but a large amount of data questions the safety of this omission. In pN1mi cases, ALND is performed.

Keywords: breast cancer, isolated tumor cells, ITC, micrometastases.

Address for correspondence:
Christos Ampatzis, MD, MSc
Tel.: 6948225454; email: chrisabatzis@gmail.com

Article received on the 14th of April 2025 and accepted for publication on the 4th of June 2025

INTRODUCTION

The management of breast tumors has considerably changed through the years. In 1804, the Japanese surgeon Seishu Hanaoka performed the first mastectomy under general anesthesia. In 1894, Halsted described a procedure called radical mastectomy, which included the removal of the breast tissue, muscles and axillary lymph nodes (1). Pierre Denoix developed the tumour, node, and metastase (TNM) system in France between 1943 and 1952 (2). In 1994, Giuliano *et al* described the sentinel node biopsy (SLN biopsy) (3). In the fifth edition of AJCC (American Joint Committee on Cancer), a definition of the term micrometastases was given.

Micromestases were defined as lesions no larger than 2 mm. They were classified as pN1. So, the limit that separated the terms micrometastases and macrometastases was defined, which was based on only two studies (4, 5). The sixth edition of AJCC established the lower limit for micrometastases, which was 0.2 mm. Single cells or cell deposits no larger than 0.2 mm were defined as isolated tumor cells (ITCs), which were classified as pN0, with this definition being based solely on one study (6). Their clinical significance is questioned by numerous researchers.

Concerns about definitions and diagnostic approach

This separation of the lower and upper limits for ITC and micrometastases was based on the above-mentioned studies, which did not take into account differences in overall survival and factors such as size of the tumor and type of therapy. Also, the immunohistochemical (IHC) stain is far more sensitive than H&E stain. It can convert 12-29% of negative SLN into positive SLN and has the capability to find one cell in SLN, which is not clinically significant. It is obvious that all data based on H&E stain about ITC prognosis would be different with IHC. Isolated tumor cells were introduced to prevent overtreatment because of the concern about tumor cells being transported to SLN before the procedure, mainly due to fine needle aspiration (FNA) and breast massage, without having true lymph node metastases, but their clinical significance has been not elucidated yet.

In the seventh AJCC edition, one more thing was added. The definition of a positive node was a metastasis no smaller than 0.2 mm or greater than 200 counted tumor cells. If the diameter of the metastasis is smaller than 0.2 mm or has fewer than 200 counted tumor cells, then it is defined as ITC. This cutoff of 200 cells was arbitrary, but has helped in greater reproducibility and agreement between pathologists. But in this point, we saw that one more point was added which was not based on clinical trials.

In 2000, the College of American Pathologists (CAP) recommended single H&E stain slide section, and not routine IHC, because a trial that tested the five-year disease-free survival found no difference between groups with negative nodes by H&E alone and by H&E and IHC, and those with positive findings on IHC (7-9).

However, many institutions perform multiple level sections and IHC stains for each block of SLN. There is no consensus on this point and the correct method is a matter of debate.

Despite these directions of seventh AJCC edition, some reports stated that, in 24% of cases, there was no consensus no consensus in those with low volume metastasis of nodes such ITC and micrometastasis (10). This discrepancy has led the pathologists to ask for more precise definitions and TNM changes. The above-mentioned percent of 24% is one in four cases, and if pathologists do not agree on this rate, the conversation about differences in treatment between ITC and micrometastasis is held on a wrong basis. Additionally, there are many aspects to clarify in this area. For example, when there are multiple foci of metastatic carcinoma but with less than 2 mm in diameter, this situation is defined as micrometastasis. Should not the number of micrometastases be upgraded to macrometastasis or lead to the modification of the case management? (11)

Treatment

The clinical question in cancer treatment has always to do with the type of treatment that leads to cancer eradication. This outcome should come with the fewer side effects. When it comes to breast procedures, hematomas, lymphedema and swelling can take place and this probability raises with the extent of the procedure. So, the breast surgeon should think wisely when an axillary lymph node dissection (ALND) should be

performed. In breast cancer, the dilemma is the evaluation of SLN and whether to perform ALND, axillary irradiation, with or without irradiation of the regional nodes or observation. In order to take these decisions, some facts must be taken into account. According to the current guidelines, ALND is omitted in ITC cases, but many data questions the safety of this omission. In pN1mi cases, the current guidelines state that ALND is performed. The questioning of these guidelines is explained with the following data.

A study reported that, among patients undergoing ALND, nodal metastases were found in 48.3% of cases with a positive SLN by H&E stain (12). Also, during ALND in non-sentinel nodes, metastases were found in 9-15% of patients with ITC in SLN and in 15-35% of those with micrometastasis in SLN. Complete ALND was commonly performed for SLN with micrometastasis and macrometastasis, but not ITC. What happens with the 9-15% of patients with ITC who have metastasis when ALND was performed?

In patients whose tumour size allows the SLN biopsy procedure, about 1/3 of them have lymph node involvement. Also, 25-46% of positive SLNs present micrometastases. Also, the risk of having positive NSLNs in patients with micrometastases or ITCs in the SLN is higher than in patients with negative SLNs and lower than in those with macrometastases in the SLNs (13). Although there is evidence that micrometastases or ITCs in the SLN are associated with worse outcomes, the therapeutic approach of these cases remains controversial.

So, here comes the question if a complementary axillary treatment (cALND) is mandatory and when. In cases when complementary axillary treatment is performed in the involved SLNs, axillary recurrence (AR) is low (0-2%) but it may be attributed to the radiation and the systemic treatments such as chemotherapy, hormonal therapy and targeted therapy followed by the patient. The ACOSOG Z0011 trial randomised patients with positive SLNs, half of whom had ITCs or pN1mi. Some of them received only SLND and irradiation of the whole breast and some subjects underwent ALND and whole breast irradiation. Most of participants were given an adjuvant systemic treatment. No significant difference in treatment groups was found. Also, there was no difference between conservative surgery or mastectomy in the groups. Pepels *et al* compared patients with pN1mi in the SLN who received cALND and those with pN1mi in the SLN who did not receive cALND. Those who omitted cALND had a higher five-year AR (5.6% *versus* 2.3%, respectively) (14).

So, it seems that, if adjuvant treatments are omitted in cases with minimal nodal involvement, the prognosis is poorer. When adjuvant treatments are performed, AR is rare.

Data about survival rates on pN0(I+), pN1mi and pN1 are mixed, which may be explained by different definitions of ITC and micrometastases in the literature and different ways of detection. An analysis of 209,720 cases using the surveillance, epidemiology and end results (SEER) database concluded that micrometastases were a significant prognosis factor. In this review, 10-year survival was 78% for pN0(I+), 77% for pN1mi and 73% for pN1 (15). De Boer *et al* found a reduced disease-free survival in patients with ITC or micrometastases who did not receive adjuvant chemotherapy, when compared to those who received chemotherapy (16). But multiple further studies and the NSABP B-32 randomised controlled phase 3 trial concluded that there was no difference in overall survival among pN0, pN0(I+) and pN1mi. Also, the ACOSOG Z0011 trial 2 concluded that, in patients receiving whole breast radiation, it was not necessary to perform ALND in T1 and T2 stages. The disease-free survival and recurrence rates did not differ between patients undergoing ALND and those who received SLN biopsy only and had up to two positive SLNs. It seems safe to omit ALND in these cases. Importantly, it looks likely that, in patients with positive SLNs, axillary irradiation is equivalent to cALND but with less lymphedema risk (17).

As for chemotherapy, it seems that it reduces the locoregional recurrences (LRR) in axilla. In a study conducted by Mamounas *et al* (18), patients treated with placebo presented 14.9% LRR and those who received tamoxifen had 7.7% LRR. Addition of trastuzumab lead to further reduction of LRR.

Furthermore, Imo *et al* (19) noted that, when using immunohistochemical staining, ITCs had no impact on the relapse-free survival (RFS). The data is controversial and the significance of ITCs and pN1mi is a non-elucidated topic. They have been related with poor survival and increased recurrence risk. So, here comes the question if the

molecular subtypes of ITCs and pN1mi play a role. There is no available data on this topic, but it could be a good area for further research. This could be a difference that we do not take into account but finally could explain the wide spectrum of the literature outcomes.

Based on these facts, here comes the question whether it is necessary to separate pN0(I+) and pN1mi and why should the N-stage in breast cancer be different from the N-stage in other organs.

It seems that data provided by the research of Shiping Lou *et al* (20) lead not only in separation of the stages of pN0(I+) and pN1mi, but pN1mi needs further categorisation. In this interesting research, the authors designed a study to compare the differences of N1mi breast cancer cases with different number of micrometastatic lymph nodes. Thus, 27,032 cases with breast cancer with T1-2N1miM0 were divided into three groups comprising patients with one involved lymph node (group 1), two involved lymph nodes (group 2) and three or more involved lymph nodes (group 3). There was a significant difference in the prognosis of these groups. In particular, for patients twho had two involved lymph nodes, the overall death risk was increased by 1.145 times compared to those with one involved lymph node ($p=0.003$) and for patients with at least three involved lymph nodes, the overall death risk was increased by 1,697 times ($p<0.001$). The remaining prognostic factors were adjusted. We conclude that there is significantly different prognosis in patients with the same stage (pN1mi) when they have different numbers of involved lymph nodes. Also, their treatment should be individualized, and not generalised. It seems that local radiotherapy and avoidance of ALND is the option that better combines improved outcomes with less complications. If an increasing number of lymph nodes are involved, ALND should be considered, because in these cases it provides significant survival benefit. In the ALND group there were no differences between approaches with or without radiotherapy. ❑

RESULTS

A considerable number of researchers refuse to acknowledge that pN1mi and ITCs have differences in their prognosis. However, patients with pN1mi and ITC should receive treatment, because they are a significant prognostic factor and, if left untreated, they lead to worse outcomes than patients without pN1mi or ITCs. When the number of lymph nodes with pN1mi or ITCs is increasing, the prognosis worsens. It seems that the right diagnostic approach of pN1mi and ITCs is a single H&E stain slide section, and not the routine IHC.

Local radiotherapy is likely to be the most effective treatment and with less side effects. When the number of involved lymph nodes is increasing, ALND should be considered by experts. Treatment should be individualised.

Further and better research needs to be conducted in order to have evidence based guidelines in pN1mi and ITCs management. ❑

DISCUSSION AND CONCLUSION

The literature search that we conducted does not give us too many answers about the clinical significance of pN1mi and ITCs and their differences. Their arbitrary definitions and not well organised research on this topic raises numerous questions, which can be a field for improvement in organised research.

The research should start from the basis of this topic. Should we establish new definitions, and not separate pN1mi and ITCs? It is not proven that they differ. It is believed that, when they are managed with cALND or irradiation, there is no difference in survival and recurrence rates.

Should we manage pN1mi and ITCs when they affect multiple nodes in a different way? Is there any other factor that causes this controversy in this topic and we ignore it? There were no available data about molecular subtypes of pN1mi and ITCs in the literature. However, they could change their clinical significance and prognosis.

It seems that further research needs to be done in order to answer these questions and the future ones when a clinician has to deal with these cases. ❑

Conflicts of interest: none declared.
Financial support: none declared.

References

1. The evolution of mastectomy surgical technique: from mutilation to medicine – PMC [Internet]. [cited 2024 Aug 21]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6006018/
2. **Sobin LH, Gospodarowicz MK, Wittekind C.** TNM Classification of Malignant Tumours.
3. **Giuliano AE, Kirgan DM, Guenther JM, Morton DL.** Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;220:391-398; discussion 398-401.
4. **Huvos AG, Hutter RV, Berg JW.** Significance of axillary macrometastases and micrometastases in mammary cancer. *Ann Surg* 1971;173:44-46.
5. **Fisher ER, Palekar A, Rockette H, et al.** Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol No. 4). V. Significance of axillary nodal micro- and macrometastases. *Cancer* 1978;42:2032-2038.
6. **Nasser IA, Lee AK, Bosari S, et al.** Occult axillary lymph node metastases in "node-negative" breast carcinoma. *Hum Pathol* 1993;24:950-957.
7. **Fitzgibbons PL, Page DL, Weaver D, et al.** Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 2000;124:966-978.
8. **Hansen NM, Grube BJ, Giuliano AE.** The time has come to change the algorithm for the surgical management of early breast cancer. *Arch Surg* 2002;137:1131-1135.
9. **Singletary SE, Connolly JL.** Breast cancer staging: working with the sixth edition of the AJCC Cancer Staging Manual. *CA Cancer J Clin* 2006;56:37-47; quiz 50-1.
10. Variations in sentinel node isolated tumour cells/micrometastasis and non-sentinel node involvement rates according to different interpretations of the TNM definitions - PubMed [Internet]. [cited 2024 Aug 21]. Available from: https://pubmed.ncbi.nlm.nih.gov/18691877/
11. **Apple SK.** Sentinel Lymph Node in Breast Cancer: Review Article from a Pathologist's Point of View. *J Pathol Transl Med* 2016;50:83-95.
12. **Kim T, Giuliano AE, Lyman GH.** Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer* 2006;106:4-16.
13. **Tallet A, Lambaudie E, Cohen M, et al.** Locoregional treatment of early breast cancer with isolated tumor cells or micrometastases on sentinel lymph node biopsy. *World J Clin Oncol* 2016;7:243-252.
14. **Pepels MJ, de Boer M, Bult P, et al.** Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. *Ann Surg* 2012;255:116-121.
15. **Chen SL, Hoehne FM, Giuliano AE.** The prognostic significance of micrometastases in breast cancer: a SEER population-based analysis. *Ann Surg Oncol* 2007;14:3378-3384.
16. **de Boer M, van Deurzen CHM, van Dijck JAAM, et al.** Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med* 2009;361:653-663.
17. **Donker M, van Tienhoven G, Straver ME, et al.** Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:1303-1310.
18. **Mamounas EP, Tang G, Fisher B, et al.** Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol* 2010;28:1677-1683.
19. **Imoto S, Ochiai A, Okumura C, et al.** Impact of isolated tumor cells in sentinel lymph nodes detected by immunohistochemical staining. *Eur J Surg Oncol* 2006;32:1175-1179.
20. **Luo S, Fu W, Lin J, et al.** Prognosis and local treatment strategies of breast cancer patients with different numbers of micrometastatic lymph nodes. *World Journal of Surgical Oncology* [Internet]. 2023 [cited 2024 Sep 10];21. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10332040/