CLINICAL TRIAL

The impact of isolated tumor cells on loco-regional recurrence in breast cancer patients treated with breast-conserving treatment or mastectomy without post-mastectomy radiation therapy

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Abstract To compare the outcome of patients with invasive breast cancer, who had isolated tumor cells (ITC) in sentinel lymph nodes, pN0(i+), to patients with histologically negative nodes, pN0. We retrospectively studied 1,273 patients diagnosed with T1–T3 breast cancer from 1999 to 2009. Patients were divided into 2 populations: 807 patients treated with breast-conserving surgery (BCS) and radiotherapy (RT), 85(10.5 %) with pN0(i+) and 722(89.5 %) with pN0. And the other population had 466 patients treated with mastectomy without post-mastectomy radiation therapy (PMRT), 80(17.2 %) with pN0(i+),and 386(82.8 %)with pN0. All patients underwent sentinel node biopsy, and the presence of ITC was determined. Patients with axillary dissection only or neoadjuvant chemotherapy were excluded. Among the 1,273 patients studied; 87.3 % received adjuvant systemic therapy. Kaplan–Meier, Cox regression, and log-rank statistical tests were used. Median patient age was 55.7 years. Median follow-up was 69.5 months. The 5- and 10-year cumulative incidence of Loco-regional recurrence (LRR) for patients treated with BCS and RT was 1.6 and 3.5 % for 85 pN0(i+) patients, and 2.4 and 5 % for 722 pN0 patients, respectively. For patients treated with mastectomy without PMRT, 5- and 10-year LRR rates were 2.8 and 2.8 % for 80 pN0(i+) patients, and 1.8 and 3 % for 386 pN0 patients, respectively. There were no statistically significant differences in LRR ($p = 0.9$), distant recurrence ($p = 0.3$) ,and overall survival ($p = 0.5$) among all groups. On multivariate analysis, ITC were not associated with increased risk of LRR, distant recurrence and overall survival. Grade ($p = 0.003$) and systemic therapy ($p = 0.02$) were statistically significantly associated with risk of LRR. Sentinel node ITC have no significant impact on LRR, distant recurrence and overall survival in breast cancer patients. Additional treatments such as axillary dissection, chemotherapy, or regional radiation should not be given solely based on the presence of sentinel node ITC.

Keywords Isolated tumor cells (ITC) · Breast cancer · Outcome

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Introduction

Axillary nodal status is one of the most important prognostic factors in patients with breast cancer [1]. Axillary staging via sentinel lymph node (SLN) biopsy reduces the need for axillary lymph node dissection (ALND) and associated complications [2, 3] including lymphedema [4]. Enhanced pathologic evaluation of sentinel lymph nodes

led to increased detection of isolated tumor cells (ITC) often includes use of immunohistochemistry staining (IHC) in addition to conventional hematoxylin and eosin (H&E) [5, 6]. The definition of ITC was updated in the American Joint Committee on Cancer (AJCC) staging manual, seventh edition [7], to be included in the pN0(i+) which was defined as malignant cells in regional lymph node(s) not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histological cross-section (detected by H&E or IHC). Nodes containing only ITC are excluded from the total positive node count for purposes of nodal staging but are included in the total number of nodes evaluated [7]. The impact of ITC on loco-regional recurrence (LRR) and survival outcomes has not been well established [8–16].

The goal of this study is to compare the clinical outcomes [loco-regional recurrence (LRR), distant recurrence, and overall survival (OS)] of invasive breast cancer (BC) patients with and without sentinel node ITC following treatment with lumpectomy and radiation therapy, or mastectomy without post-mastectomy radiation (PMRT).

Materials/methods

Patient selection

We retrospectively identified 1,273 women with pT1–T3, pN0–N0(i+), M0 invasive carcinoma of the breast diagnosed between 1999 and 2009. Patients included in this study were treated with either BCS and RT 807 patients (63.4 %) or mastectomy with no PMRT 466 patients (36.6 %) at Massachusetts General Hospital (MGH). Exclusion criteria were as follows: male sex, pure ductal carcinoma in situ (DCIS), locally advanced breast cancer (T4), any N1–N3 node positive breast cancer, distant metastasis (M1), ALND without sentinel node biopsy, and neoadjuvant chemotherapy. This investigation was approved by the Partners and MGH institutional review board (IRB).

Patient classification

The cohort (1273 pts) was divided into 2 populations: the first included 807 patients (63.4 %) treated with BCS and RT, among them 85 patients (10.5 %) presented with pN0(i+) (Group 1) and 722 patients (89.5 %) with pN0 (Group 2). and the second included 466 patients (36.6 %) treated with mastectomy with no PMRT, among them 80 patients (17.1 %) with pN0(i+) (Group 3) and 386 patients (82.9 %) with pN0 (Group 4).

Table 1 Patient's characteristics and percentage of the population studied

Characteristics	N.	%
T stage	1273	100
T1mic	80	6.28
T1a	174	13.67
T1b	336	26.39
T1c	502	39.43
T1 (1mic + 1a + 1b + 1c)	1,092	85.79
T2	177	13.90
T3	4	0.31
N stage		
BCS and RT	807	63.4
pN0(i+) (Group 1)	85	10.53
pN0 (Group 2)	722	89.47
Mastectomy with no PMRT	466	63.6
pN0(i+) (Group 3)	80	17.17
pN0 (Group 4)	386	82.83
Pathological grading		
Grade 1	347	27.26
Grade 2	548	43.05
Grade 3	338	26.55
Unknown	40	3.14
ER		
Positive	1,065	83.67
Negative	156	12.25
Unknown	52	4.08
PR		
Positive	998	78.40
Negative	214	16.81
Unknown	61	4.79
Her2		
Positive	164	12.88
Negative	1,000	78.55
Unknown	109	8.56
Final surgical margins:		
Positive (tumor on ink)	22	1.72
Close (<0.2 cm but no tumor on ink)	138	10.84
Negative (≥0.2 cm)	1,110	87.20
Unknown	3	0.24
LVI present	191	15.00
EIC present	160	12.57
Menopausal status		
Premenopausal	411	32.29
Perimenopausal	75	5.89
Postmenopausal	787	61.82
Systemic therapy		
Yes	1,111	87.27
Chemotherapy only	107	8.40
Hormonal therapy only	682	53.57
Both chemotherapy and hormonal	322	25.29

Table 1 continued

Characteristics	N.	%
Herceptin based chemotherapy	47	3.69
No	162	12.72

ER estrogen receptor, *PR* progesterone receptor, *LVI* lymphovascular invasion, *EIC* extensive intraductal carcinoma

All patients had sentinel node biopsy evaluation with serial sectioning and H&E staining. The majority also had IHC assessment with cytokeratin stains.

Treatment characteristics

Majority of patients who were treated with breast-conserving surgery received whole breast radiation. The median dose was 50 Gy (range between 45 and 50.4 Gy), using 1.8- to 2.0-Gy daily fractions. The tumor bed received a boost to a total cumulative dose of 60–61 Gy. Patients who were treated with partial breast irradiation (PBI) received 4 Gy per fraction in a b.i.d. fashion, with 6 h between treatments to a total dose of 32 Gy, or 36 Gy, or 40 Gy in a dose-escalation study.

Adjuvant systemic therapy was given to 1,111 patients (87.3 %). 682 patients (53.6 %) received adjuvant hormonal therapy alone, 107 (8.4 %) received adjuvant chemotherapy alone, 322 (25.3 %) received both adjuvant hormonal and chemotherapy, and 47 (3.7 %) received Trastuzumab-based chemotherapy. Patients' demographic, clinical, and pathological characteristics are shown in Table 1.

Follow-up, endpoint, and statistical analysis

Patients were evaluated 4–6 weeks after either RT completion for patients treated with BCS and RT, or mastectomy for patients who had been treated with mastectomy without PMRT and followed up every 6 months, thereafter, with a physical examination and annual breast imaging. Follow-up time was defined as the date of diagnosis until the date of last follow-up visit or first recurrence of cancer within the breast or regional lymph nodes, including the ipsilateral supraclavicular, axillary, or internal mammary lymph nodes, without evidence of distant recurrence.

The primary endpoint was defined as the time to invasive or noninvasive cancer recurrence within the ipsilateral breast or nodal region without evidence of distant recurrence within the first 4 months [17]. Patients diagnosed with distant recurrence within 4 months of LRR were considered to have a simultaneous local and distant recurrence and were not considered to have reached the primary endpoint. The cumulative incidence of LRR was analyzed using univariate and multivariable analysis (MVA) Cox regression. Five-year LRR recurrence, distant recurrence, and overall survival
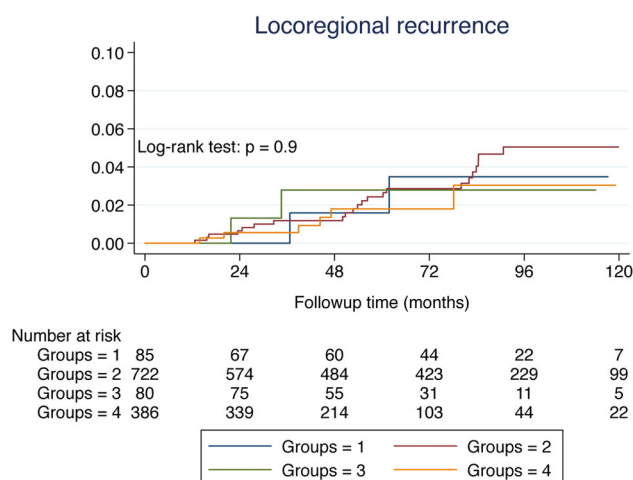
Fig. 1 Cumulative incidence of local–regional recurrence at 5 and 10 years, with 95 % confidence intervals. (Group 1) 85 patients (10.5 %) with pN0(i+) treated with BCS and RT. (Group 2) 722 patients (89.5 %) with pN0 treated with BCS and RT. (Group 3) 80 patients (17.1 %) with pN0(i+) treated with mastectomy with no PMRT. (Group 3) 386 patients (82.9 %) with pN0 treated with mastectomy with no PMRT
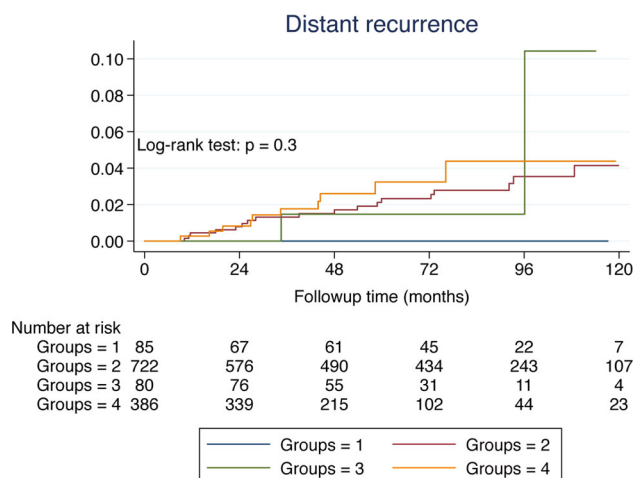
Fig. 2 Cumulative incidence of distant recurrence rate at 5 and 10 years, with 95 % confidence intervals

were computed by Kaplan–Meier (KM) methods and compared using loge-rank tests. The threshold for statistical significance was set at 0.05. Analyses were performed using Stata (StataCorp, 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.).

Results

Local recurrence

Median follow-up was 69.5 months. Median age was 55.7 years. Among patients treated with BCS and RT, the

5- and 10-year cumulative incidence of LRR was 1.6 % (95 % CI 0.2–10.7 %) and 3.5 % (95 % CI 0.8–13.2 %), respectively, for the 85 pN0(i+) patients and 2.4 % (95 % CI 1.4–4.1 %) and 5 % (95 % CI 3.3–7.6 %), respectively, for the 722 pN0 patients. For patients treated with mastectomy without PMRT, the 5- and 10-year cumulative incidence of LRR was 2.8 % (95 % CI 0.7–10.7 %) and 2.8 %(95 % CI 0.7–10.7 %), respectively, for the 80 pN0(i+) patients and 1.8 % (95 % CI 0.7–4.3 %) and 3 % (95 % CI 1.1–7.8 %), respectively, for the 386 pN0 patients. There was no statistically significant difference between all groups ($p = 0.9$). (Figure 1).

Distant recurrence

The 5- and 10-year cumulative incidence of distant recurrence in the 722 pN0 BCS and RT patients was 2.3 % (95 % CI 1.4–4.0 %) and 4.1 % (95 % CI 2.5–6.8 %).
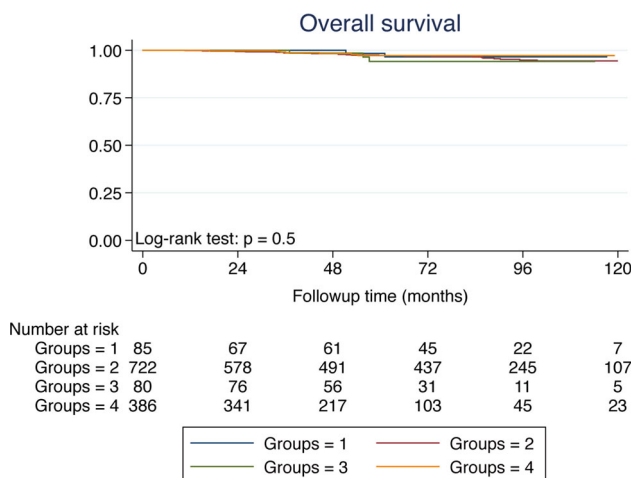
Fig. 3 Overall survival at 5 and 10 years, with 95 % confidence intervals

There were no distant recurrences among the 85 BCS and RT patients with pN0(i+). For patients treated with mastectomy without PMRT, The 5- and 10-year cumulative incidence of distant recurrence was 3.2 % (95 % CI 1.6–6.3 %) and 4.4 % (95 % CI 2.2–8.8 %), respectively, for the 386 pN0 patients. And 1.5 % (95 % CI 0.2–9.9 %) and 10.4 % (95 % CI 2.0–45.8 %), respectively, for the 80 pN0(i+) patients There was no statistically significant difference between groups ($p = 0.3$). (Figure 2).

Overall survival

The 5- and 10-year overall survival for patients treated with BCS and RT was 98.3 % (95 % CI 88.8–99.8 %) and 96.6 % (95 % CI 86.9–99.1 %), respectively, for the 85 pN0(i+) patients, and 97.2 % (95 % CI 95.4–98.3 %) and 94.4 % (95 % CI 91.6–96.3 %), respectively, for the 722 pN0 patients. For patients treated with mastectomy without PMRT, the 5- and 10-year overall survival was 94.1 % (95 % CI 82.6–98.1 %) and 94.1 % (95 % CI 82.6–98.1 %), respectively, for the 80 pN0(i+) patients, and 97.2 % (95 % CI 94.2–98.8 %) and 97.2 % (95 % CI 94.2–98.8 %), respectively, for the 386 pN0 patients. There was no statistically significant difference between groups ($p = 0.5$). (Figure 3).

On multivariate analysis adjusted for systemic therapy, grade, and mastectomy, ITC were not associated with increased risk of LRR (HR = 1.1, 95 % CI 0.4–3.3, $p = 0.8$). Similar results were found for distant recurrence and overall survival. Multivariate Cox regression for the whole population for the ITC as a risk factor is demonstrated in Table 2. Higher grade was statistically significantly associated with increased risk of LRR (HR = 2.9, 95 % CI 1.4–5.8) ($p = 0.003$) and use of systemic therapy statistically significantly associated with decreased risk of LRR (HR = 0.38 95 % CI 0.17–0.86 $p = 0.02$).

Table 2 Multivariate Cox regression for the whole population for the ITC as a risk factor (1,273 patients):

Variable	Risk group	Hazard ratio	95 % Confidence interval	P value
Loco-regional recurrence for pN0(i+) versus pN0	Breast conservation surgery and radiation therapy	0.9	0.2–3.9	0.9
	Mastectomy without post-mastectomy radiation therapy	1.6	0.3–8.2	0.6
Distant recurrence for pN0(i+) versus pN0	Breast conservation surgery and radiation therapy	N/A	N/A	1.0
	Mastectomy without post-mastectomy radiation therapy	0.8	0.2–3.5	0.8
Overall survival for pN0(i+) versus pN0	Breast conservation surgery and radiation therapy	0.7	0.2–2.9	0.6
	Mastectomy without post-mastectomy radiation therapy	2.4	0.7–8.2	0.2

Discussion

The presence of metastatic tumor in the axillary lymph nodes remains one of the most important prognostic factors in women with breast cancer and is an indicator for adjuvant treatment. [18]. Enhanced histological examination of sentinel lymph nodes with serial sections and/or IHC staining now identifies small areas of metastatic tumor previously missed by conventional techniques. [15]. However, there is no consensus on the prognostic significance of ITC as well as the impact of sentinel node ITC on loco-regional recurrence and overall survival has not been established. [10, 14–16, 19, 20]. The present study addresses this issue by evaluating LRR, distant recurrence, and survival outcomes in breast conservation and mastectomy patients with and without sentinel node ITC. Our analysis revealed that the presence of sentinel node ITC does not increase risk of LRR, distant recurrence, or decrease the overall survival.

The impact of the presence of ITC on clinical outcome and the need for further surgery, chemo- or radiation treatment has been controversial. Despite a lack of evidence-based guidelines to define optimal management for pN0(i+) disease, several studies did report use of additional adjuvant systemic therapy and regional RT in patients with pN0(i+) compared with pN0 disease [16, 19].

Karam et al. [16] studied 5,999 patients with invasive breast cancer pT1–3, pN0–N1a, M0 diagnosed between 2003 and 2006 and divided according to nodal status; 72 % with pN0, 2 % with pN0(i+), 6 % with pNmic, and 20 % with pN1a. They performed a case-matched analysis to examine the outcomes in patients with pN0(i+) compared to patients with pN0. Although, adjuvant systemic therapy use and nodal radiation increased with nodal stage, the multivariate analysis and case-matched analysis found that the presence of ITC did not affect overall survival or loco-regional control.

Reed et al. [14] evaluated prospectively the axillary node status and distant metastasis outcome between patients with ITC and micrometastasis. They examined 1,259 patients by SLN biopsy at multiple levels followed by ALND, they didn't find any more involvement; they concluded that ITC were not associated with additional positive nodes or with increased risk of distant recurrence and unlikely to need more aggressive therapy as ALND.

Calhoun et al. [20] examined 634 breast cancer patients with SLN biopsy and evaluated for the presence of ITC. Sixty one out of 78 patients with positive ITC agreed to underwent ALND. The authors found that there is no axillary failure in patients with pN0(i+), and the study failed to support the routine use of ALND for SLN with positive ITC.

On the contrary, Tan et al. [15] re-evaluated 368 patients with axillary node negative invasive BC, treated between 1976 and 1978 by mastectomy, ALND, and no systemic therapy. They examined the axillary tissue blocks after 17.6 years follow-up using their recent pathologic protocol for SLN which includes getting two adjacent sections at 2 levels 50 μm apart. At each level, one slide was stained with H&E and the other with IHC, using the anticytokeratin AE1:AE3. The authors found 83 patients with tumor cells in the lymph nodes, 61 of them (73 %) presented with occult lymph node with involvement with ≤0.2 mm in size (pN0i+). In the setting of not receiving systemic therapy, this study showed that Disease-free survival was lower in node negative pN0 versus pN0i+ versus pNmic ($p < 0.001$)**.

Leidenius et al. [19] evaluated 63 patients with pN0(i+) and compared them with 868 patients with pN0 disease. Although 5-year LRR rates were 3 % in both pN0(i+) and pN0 cohorts, patients with pN0(i+) had lower 5-year breast cancer-specific survival (95.2 versus 98.4 %; $p = 0.035$) and higher rates of distant recurrence (8.1 versus 1.9 %; $p = 0.001$) than those with pN0 cancer. This was despite higher rates of systemic therapy and loco-regional RT use in patients with pN0(i+).

Weaver et al. [21] in the NSABP-B32 trial of the 3,887 patients 11.1 % of them with ITC; the adjusted hazard ratios of pN0(i+) versus pN0 were 1.27 (95 % CI, 1.04–1.54) for death and 1.19 (95 % CI, 1.00–1.41) for distant recurrence. The magnitude of the difference in 5-year Kaplan–Meier calculated for BC-related death was small for detection of ITC versus no detection (0.6 percentage points).

It has been advocated that ITC can possibly originate from the primary tumor, but these cells do not necessarily signify a capability of surviving and metastasizing to distant locations. Those are likely temporary cells that are intended to perish and continue to be clinically irrelevant [22]. Therefore, in our cohort, the decision to pursue more aggressive treatment in form of radiation, chemotherapy or ALND for patients with occult ITC, was predominantly based on prognostic characteristics of the primary tumor and not on the nodal status. Our analysis suggested that all patients with ITC treated with either lumpectomy and radiation or mastectomy with no PMRT share similar outcome with no significant difference between any group versus another in the LRR rate, DM rate, and overall survival.

Conclusion

Our data suggest that there is no significant difference in rates of loco-regional recurrence, distant recurrence, or

overall survival between breast cancer patients who received either lumpectomy with radiation or mastectomy without radiation with sentinel node isolated tumor cells and patients with negative sentinel nodes. Decisions regarding axillary dissection, chemotherapy, or regional radiation should not be made solely on the presence of ITC.

Conflicts of interest No conflict of interest to disclose for all authors.

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