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The current role of touch imprint cytology in sentinel lymph node intra-operatory examination

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One of the strongest prognostic factors of long-term survival is the regional lymph node status. Sentinel lymph node (SLN) biopsy is the standard of care for axillary staging in clinically node-negative breast cancer. The most common methods to intraoperatively detect SLN metastases include frozen section (FS), touch imprint intraoperative cytology (TIIC), and one-step nucleic acid amplification (OSNA).

The aim of the study was to evaluate TIIC effectiveness in detecting clinically relevant sentinel lymph node metastases.

This is a retrospective cohort analysis conducted on prospectively recorded data from the data base of the Breast Unit of Trieste Academic Hospital, Italy, that includes all patients with node-negative invasive breast cancer who underwent SLN assessment using TIIC between January 2011 and December 2017.

A lymphoscintigraphy was performed to identify SLNs. The radioactive SLN was intraoperatively localized using a gamma-ray detecting probe. SLNs were immediately sent fresh to pathology laboratory and analyzed using TIIC.

The SLN was cut in short axis in slices of 2-3 mm. To obtain cellular material, some of the cut surfaces were scraped, the others pressed on a slide, then smeared using another slide, rapidly dehydrated with alcohol solution (50%-100%), stained with a rapid hematoxylin and eosin method, and microscopically examined. The SLN was formalin-fixed and paraffin-embedded: Paraffin blocks were sectioned at 250-micron intervals. Morphologic examination was integrated with immunohistochemical analysis.

Axillary lymph node dissection (ALND) was performed at the time of breast surgery (when TIIC was positive) or at supplementary session (when TIIC was negative but definitive pathology was positive). ALND was carried out until 2014 in micro- and macro-metastatic disease, after only in macro-metastatic disease.

Statistical analyses were performed using R software (version 3.0.3). We evaluated TIIC's performance computing sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with confidence interval at 95%. We considered the rate of ALNDs performed per year. *P*-values <.05 were considered statistically significant.

Between January 2011 and December 2017, 1069 clinically node-negative invasive breast cancers underwent SLN TIIC.

TIIC was able to correctly predict the status of 935 SLNs: The true negative SLNs were 790, and the true positives, 145. Eighty-five/130 false negatives (65%) resulted in pN1mi, likewise 15/145 true positives (10%).

TIIC sensitivity in detecting metastases was 52.7% [49.7-55.8], and its specificity was 99.5% [98.8-99.8]. PPV and NPV were 97.3% [96.1-98.2] and 85.9% [83.6-87.9]. If we considered pN1mi as clinically not relevant for ALND, the sensitivity arises to 87.4% [85.2-89.3], showing a significant increase ($P > .001$); these performance indicators (Table 1) were evaluated per year, showing an improvement from 2012 on.

To evaluate TIIC impact, we analyzed the trend of ALDN performed in a supplementary session: It showed a progressive significant decrease ($P < .001$) through the years (Table 2).

The median time required by the pathologist to receive the specimen and communicate the result was 20 (15-45) minutes. The overall cost was 30€ (33.52$) per analysis.

The results of our study are comparable to the literature, where we find sensitivities ranging between 69% and 99%[1]: TIIC showed

TABLE 1 Performance indicators per year (pN1mi considered as clinically negative)

Year (N° cases)	Sensitivity	Specificity	Predictive positive value	Predictive negative value
2011 (97)	60% [26-88]	97% [90-99]	67% [30-93]	96% [89-99]
2012 (121)	69% [48-86]	99% [94-100]	95% [74-100]	92% [85-97]
2013 (146)	76% [57-90]	99% [95-100]	96% [78-100]	94% [89-98]
2014 (145)	77% [58-90]	99% [95-100]	96% [79-100]	94% [88-98]
2015 (148)	67% [41-87]	97% [92-99]	75% [48-93]	96% [90-98]
2016 (203)	83% [63-95]	97% [93-99]	77% [56-91]	98% [94-99]
2017 (209)	82% [66-92]	98% [95-99]	91% [76-98]	96% [92-98]

TABLE 2 Trend of ALND in supplementary session

Year	ALND in supplementary session
2011	14/96 (14.6%)
2012	10/118 (8.5%)
2013	8/143 (5.6%)
2014	7/140 (5.0%)
2015	4/143 (2.8%)
2016	5/199 (2.5%)
2017	5/202 (2.5%)

optimal specificity, PPV, and good sensitivity, that increases if we consider that 65% of false negatives are pN1mi, confirming that this technique is less sensitive in detecting micrometastasis. In fact, we showed a lowering rate of ALND in a supplementary session from 2014, when we ceased performing ALND for micrometastases.

The indication to ALND has been challenged by various studies, leading the 2011 St. Gallen Consensus Conference to state that micrometastasis in a single SLN should not represent an indication for ALND.[2,3] Besides, the importance itself of intraoperative examination of the SLN is decreasing. Recently, the NCCN guidelines stated that T1-2 tumors undergoing conservative surgery with postoperative whole-breast radiation planned, not submitted to preoperative chemotherapy, do not require ALDN even when 1-2 SLNs are macro-metastatic.[4]

The most common techniques to intraoperatively detect SLN metastases are TIIC, FS, and OSNA.

Many studies have proven that FS's high specificity does not match with high sensitivity. FS is expensive, time-consuming, and operator dependent, and it causes an irreversible tissue loss. It is three times more expensive than TIIC: Evaluating two SLNs using TIIC costs 131$ vs 356$ for FS.[5]

OSNA seemed promising to guarantee standardized evaluation of the sample. It showed higher sensitivity in detecting micrometastases, but similar to FS and TIIC in macro-metastases. OSNA causes an irreversible tissue loss and prevents the chance to analyze the extra-capsular invasion, a predictor of non-SLN involvement, related to poor prognosis. Besides, it is burdened by longer preparing time (33-45 minutes) and higher costs (180.000$ per year).[6-8]

In our opinion, these factors suggest a reconsideration of the use of TIIC in selected cases—neo-adjuvant setting, mastectomies, IORT, and more than 2 SLNs—or as a complement to OSNA, since it remains an easy, safe, and fast technique, necessary to maintain a morphological document. TIIC is extremely accurate when only macro-metastases are considered, and these data are confirmed by our study.

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