



Is intraoperative touch imprint cytology indicated in the surgical treatment of early breast cancers?

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Accepted 10 January 2017
Available online 18 January 2017

Abstract

Introduction: Intraoperative touch imprint cytology (TIC) of the sentinel lymph node(s) (SLN(s)) in the treatment of breast cancer has significantly reduced the number of axillary block dissections (ABD) required during second surgeries. Based on recent studies, ABD was not considered necessary if the presence of tumor cells/micrometastasis was confirmed in the SLN(s) or in the case of macrometastases in a patient group meeting the inclusion criteria for the ACOSOG Z0011 study. Our aim was to determine the sensitivity and usefulness of TIC with regard to these results.

Methods: TICs of the SLN(s) were examined in 1168 patients operated on for breast cancer. The method was also analyzed retrospectively based on the guidelines for the Z0011 study. During TIC, new samples were cut every 250 μm; impression smears were evaluated after being stained with hematoxylin eosin.

Results: TIC confirmed metastasis in 202 cases (202/1168, 17.29%). Metastasis was confirmed in SLN(s) in 149 additional cases during a final histological examination. The sensitivity of TIC was found to be 57.18%, and its specificity was 99.63%. An analysis was then performed except for cases that met the inclusion criteria for the Z0011 study and with metastasis smaller than 2 mm (micrometastasis/isolated tumor cells) considered to be positive during intraoperative cytology. The sensitivity of the method decreased to 34.23%, while its specificity was still high at 99.76%.

Conclusions: Based on the new guidelines for ABD, imprint cytology cannot be considered a beneficial and cost-effective intervention in the surgical treatment of early breast cancer.

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Keywords: Axillary block dissection; Breast cancer; Intraoperative imprint cytology; Sentinel lymph node biopsy

Introduction

The introduction of sentinel lymph node biopsy (SLNB) in the treatment of early breast cancer 20 years ago significantly reduced the number of radical surgical interventions

and the number of axillary block dissections (ABD).^{1,2} Intraoperative analysis of the sentinel lymph node(s) has been used increasingly, as surgeries performed in two sessions can be avoided with this method in most cases.^{1,3}

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Intraoperative histological examinations include imprint cytology, frozen section histology and a nucleic acid amplification study. The specificity and sensitivity of these examinations are similar. The sensitivity of the nucleic acid amplification study is 76.9–98.2%, and that of frozen section histology and imprint cytology varies between 68.49 and 98.81%. The specificity of all three methods is considered almost 100%.^{4–7}

Surgical treatment of the axilla has changed significantly, particularly with regard to the indication for supplementary ABD. Based on the results of several prospective studies, ABD is not indicated for positive sentinel lymph nodes containing isolated tumor cells (ITC, <0.2 mm) and micrometastases (<2 mm), adjuvant therapy being sufficient.^{8–10} The results were also described in several international guidelines.^{9,11} Axillary block dissection is not necessarily required for patients with wide excision and sentinel lymph node biopsy for stage T₁ or T₂ breast cancer with sentinel lymph nodes containing no more than 1–2 macrometastases, according to the ACOSOG Z0011 study published in 2011 (neoadjuvant therapy is an exclusion criterion as well), as additional surgical treatment neither increases survival significantly nor reduces the incidence of axillary recurring tumors.⁸ In these cases, adjuvant systemic treatment and complete irradiation of the breast are sufficient.^{8,11–17} According to the ACOSOG Z0011 study criteria, a consensus conference held in St. Gallen in 2013, the Guidelines of the American Association of Oncology (NCCN) and axillary block dissection may be omitted.^{8,13,14}

According to several studies, ABD is an equivalent therapeutic alternative to targeted axillary radiation.^{15–17} Knowledge of treatment alternatives and participation in treatment selection represent a growing demand among patients. However, in the case of axillary block dissection performed for positive imprint cytology, patients cannot participate in the therapeutic decision.

In conclusion, the routine use of imprint cytology should be reconsidered. In our study, imprint cytology results were examined and analyzed retrospectively based on new national guidelines on the treatment of the axilla. Moreover, we analyzed the cost and time of breast surgery taking into account the necessity of imprint cytology.

Patients and methods

Between 2008 and 2014, a total of 1673 patients underwent surgery in our institution for invasive breast cancer and other breast malignancies. In this period, 1168 patients who were suffering from consecutive early invasive breast carcinoma and whose preoperative axillary US + FNA did not show axillary lymph node metastasis were examined with imprint cytology of the SLN(s).

Sentinel lymph nodes were removed with the double tracer method published by Albertini in 1996.¹⁸ On the day before the surgery (but at least four hours before the surgery), human colloidal albumin was administered with isotope (99mTc) tracing under ultrasound or X-ray guidance near the lesion. A lymphoscintigraphic (static) examination was then performed to determine the projection of SLN(s) and lymphatic drainage. The patent blue dye was periareolarly. The SLN(s) were identified with a manual gamma camera.

The technique for touch imprint cytology (TIC) was as follows: the cut surface of the fresh sample prepared from a lymph node (250 µm slices) was pressed on a slide, and then an impression smear was prepared. The resulting imprint cut surfaces were fixed in 95% ethanol for 5–6 s, and the samples were evaluated after hematoxylin eosin staining. Every SLN underwent a standard histological examination later.

We allocated the sensitivity and specificity of TIC based on the intraoperative and final histological result. Based on the final histological examination of the sentinel lymph node(s), we selected patients in whose cases performing an ABD is no longer justified according to the new international recommendations (ITC, micro- and macrometastases, which meet the criteria for ACOSOG Z0011) and thus there is no need for intraoperative lymph node analysis either. Based on these data, the imprint cytology results were re-evaluated and compared with non-modified data.

Statistics

We studied the sensitivity and specificity of imprint cytology with the scheme below:

$$\text{sensitivity} = \frac{\text{realpositivecases}}{\text{realpositivecases} + \text{falsenegativecases}}$$

$$\text{specificity} = \frac{\text{realnegativecases}}{\text{realnegativecases} + \text{falsepositivecases}}$$

We used the SPSS (Statistical Package for the Social Sciences) programme for comparing the operating time. We analyzed the data two-sample T-test. The study has been approved by the local Ethics Committee.

Results

In our Department, TIC was performed for invasive breast tumor in 1168 cases during the period under examination. The average age of the patients was 58.63 (25–88) years. TIC was positive in 202 cases in 17.29% (202/1168) of the cases. A total of 2101 lymph nodes were sent for imprint cytology, which is an average of 1.8 (1–6) lymph nodes per patient.

During a final histological examination of the samples, metastasis was found in 149 additional previously (intraoperatively) negative sentinel lymph nodes (false negative cases: 149/1168 [12.75%]), and metastasis was not confirmed in three cases found to be positive with imprint cytology (false positive cases: 3/149 [0.25%]). The sensitivity of the imprint cytology was 57.18%, with a specificity of 99.63% (Table 1).

A total of 202 axillary block dissections were performed in one session, and then 80 block dissections were performed on a separate occasion. In 64 cases, an ABD was not performed, as the patient had not given his consent for the intervention, the patient had chosen adjuvant chemotherapy, or the oncoteam had not recommended additional surgery due to the presence of micrometastasis.

At that point, patients meeting the inclusion criteria for the Z0011 study ($n = 117$) and seven patients not meeting the criteria for Z0011 but with micrometastasis ($n = 7$) were excluded from the positive cases by intraoperative examination (Tables 1 and 2), and then the sensitivity and specificity of the method were recalculated.

After screening, 78 positive (number of positive cases = 202 minus number of patients meeting criteria

Table 2

Patients meeting the criteria for the Z0011 study and with a positive imprint cytology.

	Total	%
Number of patients	117	100
Imprint cytology results		
Positive	116	99.15
Negative	1	0.85
False negative	0	
False positive	1	0.85
Number of final, positive histological examinations	116	
Type of surgery		
Excision	117	100
Mastectomy	0	0
Average tumor size (mm)	20.56286	
Average number of SLNBs	1.97	
ABDs		
Performed in one session	111	94.87
Supplementary	2	1.71
Not performed ^a	4	3.42

^a Axillary block dissection was not performed in four cases when a patient made a request in advance to that effect or in the presence of micrometastases.

for Z0011 [$n = 117$] and number of patients not meeting criteria for Z0011 but with micrometastasis [$n = 7$]), two false positive, 149 false negative and 966 negative cases were found in the repeated imprint cytology group. Sensitivity fell to 34.23%, and specificity remained 99.76% (Table 3).

As can be seen on Table 4, axillary block dissection was performed in 284 cases, but, based on the new guidelines, only 105 cases were indicated. 179 cases, that is, 15.32% of the cases, were performed unnecessarily.

As the results were processed, the average size of the metastases and the distribution of micro- and macrometastases in false negative and positive cases were examined as well (Table 5). In positive cases, the average size of the micrometastases was 1.52 mm, while that of the macrometastases was 8.33 mm. The average size of the micrometastases was 1.1 mm, while that of the macrometastases was 4.79 mm in the false negative group. Therefore, it can be concluded that imprint cytology cannot be considered a sensitive intervention for surgeries on smaller metastases.

The costs of ABDs performed with imprint cytology and with supplementary imprint cytology were compared in financial terms. (The costs of SLNBs and ABDs performed during surgery are similar.) During imprint cytology, an average of five cut surfaces is prepared of the lymph node. A cut surface costs €32.50. The average price of histology performed during surgery is therefore $1.8 \times €32.50$, that is, €58.52. An ABD costs €431.17. Based on the results, the 1168 imprint cytologies cost €68,359.23, while the 76 supplementary ABDs cost €32,768.49. Therefore, the difference is €35,586.73. Patient hospital stay after ABD is longer (about one day) and more out-patient visits are required, thus further increasing the difference in expenses. This represents an extra charge of about €100

Table 1

Imprint cytology results (1 May 2008–31 Dec 2014).

	Total	%
Number of patients	1168	100
Imprint cytology results		
Intraoperative (positive)	202	17.3
Intraoperative (negative)	966	82.7
False negative	149	12.76
False positive	3	0.25
Number of positive final histological examinations	348	29.79
Number of negative final histological examinations	820	70.21
Type of surgery		
Excision	883	75.6
Mastectomy	285	24.4
Average tumor size (mm)	19.61	
Average number of SLNBs	1.8	
ABDs	284	24.32
In one session	204	17.47
Supplementary	80	6.85

Table 3
Results modified in accordance with the criteria.

	Imprint (all cases)	Cases meeting Z0011 criteria	Cases not meeting Z0011 criteria but involving micrometastasis	Results recalculated
Number of patients	1168	117	7	1168
Imprint				
Positive	202	117	7	78
Negative	966	0	0	966
Final histology				
Positive	348	116	7	225
False positive	3	1	0	2
False negative	149	0	0	149

Table 4
Distribution of axillary block dissections.

		Total number of ABDs
Imprint	Supplementary ABDs	80
	ABDs performed in one session	204
Positive cases according to Z0011 criteria	Supplementary ABDs	2
	ABDs performed in one session	112
False negative cases according to Z0011 criteria	Supplementary ABDs	56
	ABDs performed in one session	2
Cases not meeting Z0011 criteria but involving micrometastasis	Supplementary ABDs	0
	ABD performed in one session	7
Total	Supplementary ABDs	22
	ABDs performed in one session	83

per patient (based on Hungarian expenses). We have examined the average duration of breast surgery with and without imprint cytology. Surgeries were longer by approximately 1.6–5 min when cytology was used, and the difference was non-significant (data not shown).

Discussion

The introduction of SLNB has been a milestone in the treatment of early breast cancer, as it has significantly reduced the number of axillary block dissections and similarly improved staging and oncology/complex treatment of breast cancers. Simultaneously, intraoperative examination of the sentinel lymph node(s) has been introduced, and, as a result, the number of surgeries performed in two stages and, consequently, both the burden on the patients and surgical costs have decreased.

According to recent studies and guidelines, in cases meeting certain criteria, such as isolated tumor cells,

sentinel lymph nodes with micrometastasis and no more than two macrometastases, ABD may be omitted, as it does not increase the risk of overall mortality and locally recurring cancer.^{8,9,11} Similarly, the indication for ABD is reduced by clinical studies supporting the fact that axillary radiation is an alternative treatment option to surgery, but it is associated with lower morbidity.^{15–17} Axillary radiotherapy does not pose an increased risk to survival and locally recurring cancer, and the incidence of lymphedema, which is primarily responsible for morbidity, is significantly decreased as well. Another important factor is the fact that in the case of axillary block dissection performed for positive imprint cytology, the patient is unable to participate in the therapeutic decision and choose from among therapeutic options.

These factors suggest a reconsideration of the routine use of imprint cytology. Based on our results, the sensitivity of imprint cytology is 57.18%, its specificity is 99.63%, and these values are consistent with international data. (The

Table 5
Lymph node metastases in false negative and false positive cases.

	Sizes of metastases (mm)	Number of metastases	Distribution in % of all metastases	Distribution in % of all micro-metastases	Distribution in % of all macro-metastases
Positive cases					
Micrometastases	1.52	13	3.73	15.85	
Macrometastases	8.33	187	53.58		70.3
False negative cases					
Micrometastases	1.10	69	19.77	84.15	
Macrometastases	4.79	80	22.92		29.7

sensitivity of imprint cytology varies between 68.49 and 98.81%, with a specificity of approximately 100%).^{5,19–21} With regard to metastasis sizes and distribution, imprint cytology is less suited to detecting metastases of 2 mm or smaller, with 84.15% of micrometastases remaining undetected, but 70.3% of macrometastases can be detected with this method.

However, according to the latest guidelines, the sensitivity of imprint cytology (based on cases with therapeutic consequences) is only 34.23% (with unchanged specificity). This sensitivity value is so low that the usability of this method is questionable. ABD was only indicated in 9% of the patients in the period under examination (105/1168). However, based on the new guidelines, supplementary lymph node dissection was performed “unnecessarily” in 15.32% of the patients (179/1168).

It is not insignificant that imprint cytology increased surgical costs and the duration of surgery unnecessarily in a large percentage of the patients (91%). Imprint cytology and surgical costs are significantly higher in Western Europe and the United States; differences in costs (cost effectiveness) are therefore more significant in those regions (due to the operational cost of the surgery and the surgeon’s fee, these interventions cost at least €32–100 per surgery, totaling €37,376–116,800 for 1168 patients.²²)

The price of imprint cytology of a lymph node in the United States in 2010 was (the dollar equivalent of) €57.²³ Based on this data, in our case, the total cost would be €119,832. If we use the latest intraoperative histological diagnostic method, nucleic acid amplification, it costs €172.50 to examine a lymph node, based on data from a French survey.²⁴ The cost for the total patient population was €362,664. Intraoperative histological examinations are less effective^{4,6} and significantly increase treatment costs for patients operated on for early breast cancer.

Our study shows that axillary block dissection is only necessary in the treatment of the axillary region in an increasingly smaller group of patients (9%), and this percentage will further decrease with more extensive use of alternative axillary radiotherapy.

Based on our results, imprint cytology of the sentinel lymph node(s) in patients operated on for malignant breast cancer has no confirmed benefits based on the current guidelines, and its routine use is not indicated. According to the latest international guidelines, intraoperative examination of the sentinel lymph node(s) may be indicated in the case of mastectomy (when postoperative radiotherapy is not planned) and after neoadjuvant therapy, as ABD is still indicated in these cases.

Conflict of interest statement

The authors have no conflict of interest or financial disclosure.

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