Excerpta Medica

The American Journal of Surgery

The American Journal of Surgery 189 (2005) 606–609
Scientific paper

The association of cytokeratin-only–positive sentinel lymph nodes and subsequent metastases in breast cancer

Philip S. Mullenix, M.D.[a], Tommy A. Brown, M.D., F.A.C.S.[a,*], Micheal O. Meyers, M.D.[b], Lydia R. Giles, R.N., B.S.N.[b], Elin R. Sigurdson, M.D., F.A.C.S.[b], Marcia C. Boraas, M.D., F.A.C.S.[b], John P. Hoffman, M.D., F.A.C.S.[b], Burton L. Eisenberg, M.D., F.A.C.S.[b], Michael H. Torosian, M.D., F.A.C.S.[b]

[a]*Department of Surgery, Madigan Army Medical Center, 9040A Reid Street, Tacoma, WA 98431, USA*
[b]*Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA*

Manuscript received December 23, 2004; revised manuscript January 27, 2005

Presented at the 91st Annual Meeting of the North Pacific Surgical Association, Tacoma, Washington, November 12–13, 2004

Abstract

Introduction: The purpose of this study was to better characterize the clinical significance of cytokeratin immunohistochemistry (IHC)-only–positive lymph node metastases among patients with breast cancer.
Methods: We performed a retrospective review of 334 patients who underwent sentinel lymph node (SLN) biopsy from 1 February 1997 through 31 July 2001. SLN biopsies were evaluated using standard hematoxylin and eosin (H&E) techniques. If H&E was negative, cytokeratin IHC was performed. We then evaluated the incidence of subsequent regional and distant metastatic disease.
Results: Cytokeratin IHC was performed on 183 sentinel node biopsies from 180 patients comprising a total of 427 sentinel lymph nodes. The procedures included lumpectomy and SLN biopsy (n = 83), mastectomy with SLN biopsy (n = 7), lumpectomy with SLN biopsy and completion axillary dissection (n = 80), and modified radical mastectomy with SLN biopsy and completion axillary dissection (n = 13). Cytokeratin IHC was negative in 175 axillary specimens and positive in 8 (4.4%) from 8 different patients. In these eight specimens, deeper sections with subsequent H&E staining additionally identified micrometastasis in four patients. Three of these 8 patients (37.5%) developed distant metastatic disease compared with 1 of the 172 patients (0.6%) with negative cytokeratin IHC ($P < .001$). Additionally, one of the cytokeratin-positive patients developed regional nodal metastasis compared with none of the 172 cytokeratin-negative patients.
Conclusions: Cytokeratin IHC provides a clinically relevant adjunct to H&E staining for evaluating sentinel lymph nodes in breast cancer. These data suggest that patients with cytokeratin-positive sentinel nodes are at increased risk for development of regional and distant metastatic disease.

Keywords: Immunohistochemistry; Cytokeratin; Sentinel lymph node; Adenocarcinoma; Micrometastasis; Breast; Cancer

Sentinel lymph node (SLN) mapping and biopsy is being used with increasing frequency to stage patients with breast cancer. This technique allows for comprehensive evaluation of the sentinel node by step cutting and application of both routine histopathology and immunohistochemistry. Through selective pathologic examination of the SLN, microscopic foci of tumor cells are being found that would not have been seen using traditional methodology. In addition, immunohistochemistry (IHC) for cytokeratin can identify micrometastases not detected on traditional hematoxylin and eosin (H&E) staining. This retrospective analysis was performed to determine the incidence and clinical significance of cytokeratin staining of SLNs in patients with breast cancer.

Methods

Between February 1997 and July 2001, 334 breast cancer patients underwent sentinel lymph node biopsy (S.L.N.B.), performed by 5 surgeons (E.S., M.B., J.H., B.E., M.T.) at Fox Chase Cancer Center, Philadelphia, PA. Early in the

* Corresponding author. Tel. +1-253-968-2200; fax: +1-253-968-0232.
E-mail address: tommy.brown@nw.amedd.army.mil

0002-9610/05/$ – see front matter
doi:10.1016/j.amjsurg.2005.01.031

series (until each surgeon had completed 20 SLNB procedures), a completion axillary dissection (CAD) was performed to confirm the accuracy of the SLNB procedure. After this initial period, CAD was performed only if the SLN was positive. A combination of blue dye and sulfur colloid intraparenchymal injections was used in a standard fashion for identification of the SLNs. Preoperative lymphoscintigrams were completed, and a handheld gamma probe was used intraoperatively for localization of the SLN. Each SLN was evaluated by using H&E stain on 5 cut levels; each separated by 50 μm. If the H&E stain detected no metastatic disease, IHC was used to detect the presence of cytokeratin using CAM 5.2 antibodies. IHC is performed on a 5-μm section taken between levels one and two. IHC is currently performed on all SLNs that stain negative by H&E; however, early in our series, during the initial development of this test in our surgical pathology laboratory, IHC was used on an intermittent trial basis. If metastatic disease was found by IHC only, the decision to proceed with CAD was at the discretion of the operating surgeon in discussion with the patient. Statistical analysis and level of significance were determined by a two-sided Fisher exact test.

Results

Over a 53-month period, 334 individual patients with breast cancer underwent SLNB. IHC for cytokeratin was performed on 183 specimens from 180 patients with SLNs negative for metastasis by H&E staining. An average of 2.4 sentinel nodes was removed per patient. The surgical procedures included lumpectomy and SLNB (n = 83), mastectomy with SLNB (n = 7), lumpectomy with SLNB and CAD (n = 80), and modified radical mastectomy with SLNB and CAD (n = 13). In total, 90 SLNBs without CAD and 93 SLNBs with CAD were performed in 180 patients.

IHC was negative for cytokeratin in 175 specimens (95.6%) from 172 patients and positive in 8 (4.4%) specimens from 8 separate patients. Of the 175 specimens with negative IHC, 88 (50.3%) had CAD. Metastasis was found on further analysis of the CAD specimens in 3 of the 88 patients (3.4%). These three patients had histologically negative SLNs by both H&E and IHC staining. With a median follow-up of 15 months, 2 of the 172 (1.2%) IHC-negative patients have documented recurrent disease. Of these two patients, one developed distant disease in the form of brain metastasis and one presented with a second primary cancer in a separate quadrant of the ipsilateral breast.

Cytokeratin-positive SLNs were detected in 8 patients. Deeper sections with subsequent H&E staining identified micrometastasis in four of the eight specimens. Six of these patients underwent CAD. No further evidence of cancer was found in the axillary lymph nodes removed from these six patients. However, 3 of the 8 (37.5%) patients with IHC-positive SLNs developed distant metastasis with a medium follow-up of 25 months compared with 1 of the 172 (0.6%) IHC-negative patients ($P = .00023$). Our point estimate of the recurrence rate is three of eight or 37.5%. A lower one-sided 95% confidence bound on this rate is 11%. Our estimate of the rate is 1 of 172 or 0.6%. An upper one-sided 95% confidence bound on this rate is 2.7%. Subsequent H&E stain of the SLN was negative on the three patients who developed distant metastasis. Of the three IHC-positive patients with metastatic disease, one did not have CAD and subsequently developed bulky nodal metastasis and distant disease. The other two patients had CAD and later developed distant disease. All three patients received adjuvant chemotherapy and tamoxifen after their initial definitive breast cancer surgery.

Comments

The clinical significance and optimal surgical treatment of breast cancer patients with micrometastatic regional lymph node metastasis of the breast is controversial [1]. Because microscopic nests of tumor cells are not easily detected using routine H&E staining, the potential for enhanced pathologic investigation of the SLN with resultant upstaging of breast cancer patients exists and is estimated to occur in 7% to 14% of patient series [2–4].

In our study, 4.4% of patients were upstaged by IHC. Various practitioners do not consider patients with only IHC-positive staining as being upstaged [1,2]. Cytokeratin positivity in the absence of H&E documented metastasis is thought by some to represent intransit tumor cells disrupted at surgery or portions of epithelial cell membranes and not actually metastatic deposits [5]. Before our review, it has not been an institutional policy here to recommend CAD for patients with positive sentinel nodes only shown by cytokeratin staining. Five of the eight patients with positive IHC in our study had CAD only as part of our learning curve in performing SLNB. In only one IHC-positive patient was CAD recommended based on IHC results.

IHC-positive cells are a part of the spectrum of micrometastatic disease. In 1990, the International (Ludwig) Breast Cancer Study Group reported the results of a prospective study in stage I breast cancer, defining the prognostic significance of micrometastatic disease [6]. The 5-year disease-free survival was 58% in patients with micrometastases compared with 74% in those with negative nodes ($P = .003$). The overall survival was 79% versus 88%, respectively ($P = .002$). However, in a more recent study, authors found micrometastases in 15 of 226 (6.7%) patients [7]. Eleven of the 15 patients underwent CAD. The 15 patients showed no evidence of local or regional/distant recurrence with a median follow-up of 13.5 months. The authors suggest that CAD may not be necessary. In the aforementioned studies, micrometastatic disease was detected by detailed serial sectioning with H&E stain and defined as a metastatic deposit not detected by routine H&E evaluation or a metastatic deposit less than or equal to 2 mm