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The role of lymphatic and blood vessel invasion in predicting survival and methods of detection in patients with primary operable breast cancer

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Abstract

Lymphovascular invasion (LBVI) has long been recognized as an essential step of metastases in patients with cancer. However, the process of invasion into lymphatic and blood vessels is still not well defined in breast cancer. To examine the evidence for LBVI, lymphatic vessel invasion (LVI) and blood vessel invasion (BVI) in predicting survival in patients with primary operable breast cancer, and to evaluate the detection methods of vessel invasion. A systematic review of data published from 1964 to 2012 was undertaken according to a pre-defined protocol. There is robust evidence that general LBVI and LVI are independent prognostic factors of poorer survival. The prognostic role of BVI remains unclear. Most studies detected LBVI using H&E stained sections. The overall weighted average of the LBVI rate using immunostaining was higher (35%) than H&E (24%). The LBVI rate using H&E was variable (9–50%) and less variable using immunostaining (32–41%). The overall weighted average of the LVI rate was similar using H&E and immunostaining (33% vs. 25%). The LVI rate using H&E was variable (10–49%) and less variable using immunostaining (21–42%). The overall weighted average of the BVI rate was similar using H&E and/or classical staining and immunostaining (16% vs. 10%). The BVI rates using H&E and/or classical staining approach (4–46%) and immunostaining (1–29%) were both variable. The LBVI and LVI are powerful

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prognostic factors in primary operable breast cancer. However, BVI was rarely specifically examined and its role in predicting survival is not clear. Further work is required using reliable specific staining to establish the routine use of LVI and BVI in the prediction of outcome in patients with primary operable breast cancer.

Keywords: Breast cancer; Lymphatic and blood vessel invasion; Detection methods; Survival

1. Introduction

Breast cancer is the commonest female malignancy and a leading cause of cancer death in western world. More than a million women are diagnosed with breast cancer each year, accounting for approximately tenth of all new cancers and a quarter of all female cancer cases [1]. However, during the last decade despite increasing incidence, there has been a decrease in disease mortality, indicating an improvement in patient management [2].

The process by which breast cancer kills patients is primarily through progression, in particular metastatic disease. One of the very early steps of metastatic spread is penetration of tumor cells into lymph and/or blood vessels in and around the primary tumor.

In breast cancer lymphovascular invasion (LBVI) including both lymphatic vessel invasion (LVI) and blood vessel invasion (BVI), has been defined as presence of tumor cells within an endothelial-lined space in the area surrounding the invasive carcinoma [3]. The prognostic significance of LBVI in breast cancer was described more than four decades ago [4]. Since then, several independent studies have investigated the prognostic significance of LBVI in breast cancer in both lymph node negative and positive tumors.

In 1999, the College of American Pathologists (CAP) consensus accepted peritumoral LBVI as prognostic factor of local failure and reduced overall survival in breast cancer, and recommended that vascular invasion should be assessed in peritumoral breast tissue. However, not all commentators agreed on its clinical importance [5]. At the 9th St. Gallen meeting in January 2005, LBVI accepted as sufficiently reliable to define risk category of relapse and death form the disease in patients with node negative breast cancer. The consensus from the meeting was that the presence of LBVI defined intermediate risk and its absence defined low risk for node-negative disease. The importance of LBVI in patients with node-positive cancers was considered uncertain, and more studies were still required [6].

Based on both the CAP consensus (1999) and 9th St. Gallen meeting (2005), there was no agreement on the need for specific stains to identify vascular spaces or the necessity to distinguish LVI from BVI. However, one of the major challenges in the field has been to distinguish LVI and BVI on hematoxylin and eosin (H&E) stained sections from retraction artifacts caused by tissue handling and fixation [7–10].

Therefore, the aim of the present systematic review was to examine the prognostic significance of LVI and BVI separately and together (LBVI), and how they are detected.

2. Materials and methods

The review of published literature was undertaken according to a pre-defined protocol. The primary area of interest was the relationship between the lymphovascular invasion (either general, lymphatic vessel invasion or blood vessel invasion) and outcome (cancer specific, relapse free and overall survival) in patients with primary operable breast cancer. A literature search, using appropriate key words (breast cancer, lymphovascular/lymphatic/blood vessel invasion and survival) was made of the US National Library of Medicine (MEDLINE), the Excerpta Medica database (EMBASE), the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts and Reviews (DARE) for articles reporting the prognostic value of lymphovascular invasion (May 1964–August 2012).

From this search, the titles and abstracts were examined and if relevant, the full text papers were obtained. Studies in which sample size was $\leq$100 patients, median/mean follow-up was not reported or less than 5 year and studies not available in English language. Where there were duplicate publications of the same patient dataset from same center were only the most recent study was considered. The bibliographies of all included articles were subsequently hand searched to identify additional studies. It was taken that vascular invasion was ascertained in H&E sections if no other detection method was specified. All papers included in the review were examined by F G and one or more of the co-authors. For each group of studies a weighted average for the invasion rate using H&E, H&E and/or classical staining and immunostaining was calculated by multiplying the invasion rate reported in the study by the number of patients in the study. The product of this multiplication was added to the products of other studies in the group and the total was divided by the total number of all the patients in the group studies.

3. Results

3.1. Study selection process

The study selection process is summarized in Fig. 1. The initial literature search returned 227 articles of potential interest. After title and abstract review, full text was obtained for 129 studies. Hand searching bibliographies identified 25 additional studies. Of these, 95 were excluded (32 did not examine the prognostic value of lymphovascular invasion,