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Review

Evolution in sentinel lymph node biopsy in breast cancer

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ABSTRACT

Sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging in clinically node-negative (cN0) breast cancer patients without neoadjuvant chemotherapy (NAC). The application of SLNB in patients receiving NAC has also been explored. Evidence supports its use after NAC in pretreatment cN0 patients. Nonetheless, its routine use in all the pretreatment node-positive patients who become cN0 after NAC is unjustified due to the unacceptably high false-negative rate, which can be improved in a subset of patients. Axillary surgery omission in selected patients with a low risk of ALN metastasis has gained more and more research interest because the SLNs are tumor-free in more than 70% of all patients. To avoid drawbacks of conventional mapping methods, novel techniques for SLN detection have been developed and shown to be highly accurate in patients with early breast cancer. This article reviews the progress in SLNB in patients with breast cancer.

1. Introduction

Axillary staging is an important component of the surgical procedure performed in patients with breast cancer. This was initially performed as axillary lymph node dissection (ALND). This procedure has changed since randomized trials showed that sentinel lymph node biopsy (SLNB) reflects the overall axillary lymph node (ALN) status. No difference in regional control, disease free survival (DFS) and overall survival (OS) was found between SLNB and ALND in patients with clinically negative nodes (Veronesi et al., 2006a; Krag et al., 2010). Moreover the SLNB group experienced an improved quality of life (QoL) and upper extremity function (Mansel et al., 2006; Ashikaga et al., 2010). These results made SLNB the standard of care for ALN staging in patients with early breast cancer and clinically negative ALNs (Lyman et al., 2005). In about 75% of the patients who undergo SLNB, this biopsy does not contain tumor cells (Krag et al., 2007). There is now increasing interest, based on "*Primum non nocere*", in properly selecting patients with a low probability of ALN metastasis and therefore might not even require a SLNB (Gentilini and Veronesi, 2012).

Neoadjuvant chemotherapy (NAC) is offered to patients with locally advanced diseases in order to downstage the tumor and is increasingly being used for large operable tumors for decreasing the extent of surgery needed (Senkus et al., 2015). ALND has been standard treatment of the axilla after NAC for many years (Lyman et al., 2005). However, around 40% of those patients with a clinically or biopsy-proven positive lymph node get a histopathologically complete response (pCR) after NAC (Fisher et al., 1997) and rates increased to more than 70% with using of anti-HER2 therapy (Dominici et al., 2010). Moreover, axillary staging after NAC has been reported to be more meaningful in predicting locoregional recurrence than the axillary staging before NAC, and therefore can be used to guide adjuvant locoregional treatment (Mamounas et al., 2012). These data supports the application of SLNB after NAC in order to reduce the extent of axillary surgery without compromising the prognostic and predictive value of axillary staging. Argument against the application of SLNB after NAC is that the lymphatic drainage alteration after NAC could decrease the SLN identification rate and increase the false-negative rate (FNR) (Jatoi et al., 2016). However, increasing data showed that the SLN identification rate and FNR were comparable between SLNB before and after NAC in patients with pretreatment clinically negative nodes. In general, the SLN identification rate and FNR of SLNB after NAC are less satisfactory in patients with pretreatment positive nodes. However, in subset of patients the accuracy of SLNB in this setting has been reported to be similar with that in patients without NAC (Boughey et al., 2013;

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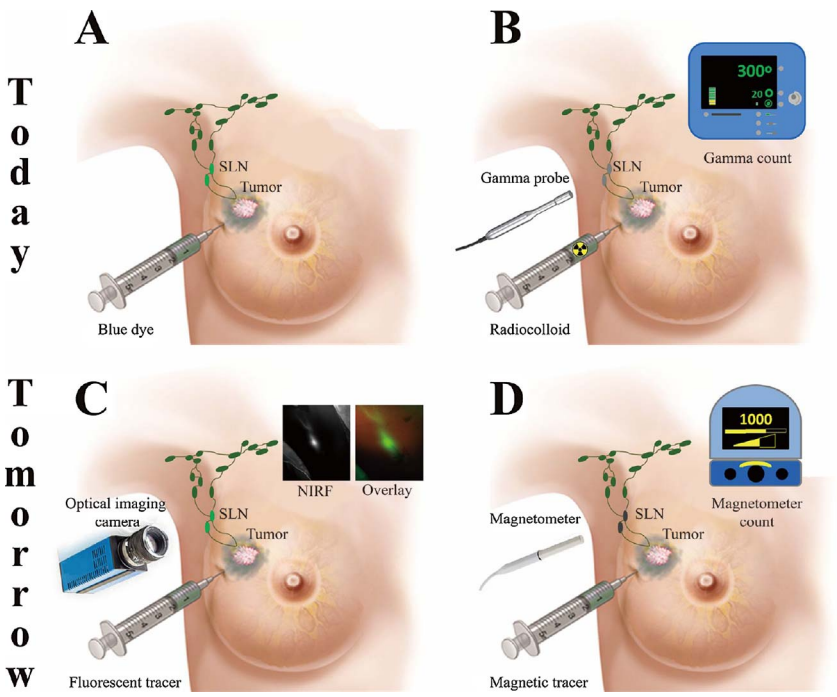

Fig. 1. Four sentinel lymph node (SLN) detecting methods. (A & B) current standard of care for SLN detection: A) the blue dye method relies on the visual detection of the blue stained SLNs; B) the radioisotope method locates the SLNs by using a gamma probe for detecting the radiation emitted from the radioactive tracer accumulated in the SLNs. (C & D) novel methods for SLN detection: C) optical imaging guided SLN detection provides a real-time map for locating the SLNs; D) magnetic tracer guided SLN detection locates the SLNs by using a hand-held magnetometer to magnetize the magnetic tracer and detect the particles' magnetic response.

Kuehn et al., 2013; Boileau et al., 2015).

For optimal SLN detection, tracers are applied. The current standard tracers have limitations. For example, the logistic and legislative issues of using a radioisotope limit the application of radioactive tracer method in many countries/regions in the world. In several developing countries, including China (Li et al., 2015), only blue dye is available for SLNB. Blue dye carries a risk of allergic reactions in around 1% of the patients (Cady, 2002) for the whole spectrum and 0.2% (Krag et al., 2007) for severe reactions. Besides, the performance of SLNB using a blue dye is highly dependent on a surgeons' experience (Ang et al., 2014), lacking the guidance of devices such as a gamma probe used in radioisotope guided SLNB, and relies, obviously, on visual detection of the SLN (Fig. 1). The above-mentioned potential limitations of both standard tracers have led to the development of alternative methods for SLNB. Data from studies on indocyanine green (ICG) optical imaging or superparamagnetic iron oxide (SPIO) guided SLNB in early breast cancer is encouraging.

This review therefore focuses on SLNB in early breast cancer patients, feasibility of SLNB in patients receiving NAC, novel techniques for SLNB, and ongoing clinical trials about SLNB in breast cancer.

2. Search strategy and quality assessment of studies

We searched English language literature/abstracts in PubMed and San Antonio Breast Cancer Symposium and ongoing trials in the ClinicalTrials.gov database. The American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines for breast cancer were also referred. The search strategy focused on SLNB in breast cancer. Reference lists of articles were manually searched for relevant articles. The details of search terms are showed in Supplementary Table S1.

For studies on indocyanine green (ICG) guided SLNB, we included studies which reported SLN identification rate and/or FNR of SLNB and number of SLN removed. The Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011) was used to evaluate the quality of randomized studies. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al., 2007) was used to assess the quality of cohort studies. We judged six items of the STROBE statement relevant to quality assessment. Studies with overall quality score of 4 out of 6 or higher were included in this review (Ahmed et al., 2014). The quality assessment of studies was showed in Supplementary Tables S2 and S3.

3. SLNB in patients with early breast cancer

3.1. Clinical trials comparing SLNB and ALND

Since late 20th century, five randomized clinical trials have been performed to evaluate the efficacy and safety of SLNB in early breast cancer patients (Mansel et al., 2006; Krag et al., 2007; Zavagno et al., 2008; Veronesi et al., 2010; Gill, 2009). The primary and secondary outcome measures of those trials mainly focused on arm morbidity and QoL, with the National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trial (Krag et al., 2007), Milan trial (Veronesi et al., 2010) and Gruppo Interdisciplinare Veneto di Oncologia Mammaria (GIVOM) trial (Zavagno et al., 2008) also assessed DFS and OS. The NSABP B32 trial, which had the largest patient population, randomized 2807 patients into the ALND group and 2804 patients into the SLNB group. The study showed that the SLN identification rate was 97.2%, and the FNR was 9.8% (Krag et al., 2007). The SLN identification rates and FNRs reported by the Milan trial (Veronesi et al., 2006b), Sentinel Node Biopsy versus Axillary Clearance (SNAC) trial (Gill, 2009), GIVOM trial (Zavagno et al., 2008) and Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial (Goyal et al., 2006) were 99%, 94%, 95%, 96.1% and 8.8%, 5.5%, 16.7%, 6.7%, respectively. The ALMANAC trials demonstrated that combination of blue dye and radioisotope (dual mapping method) permitted an improved SLN identification (combined 96% versus blue dye 85.6% versus radioisotope 85.6%) and positive SLN identification (combined 93.5% versus blue dye 90.9% versus radioisotope 89.1%) (Goyal et al., 2006). A systematic review by the American Society of Clinical Oncology (ASCO) confirmed a lower FNR using dual mapping method, compared with use of only one (7% versus 9.9%) (Lyman et al., 2005).

The NSABP B32 trial, the only trial with sufficient power to answer the impact of SLNB on survival, showed that DFS, regional control and OS were equivalent between SLNB and ALND groups in breast cancer patients with clinically negative ALN at a median follow-up 95.6