RESEARCH ARTICLE

Is Axillary Dissection Necessary for Breast Cancer in Old Women? A Meta-analysis of Randomized Clinical Trials

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Abstract

Background: We performed this meta-analysis to assess the effectiveness and safety of axillary dissection in old women. Methods: The Cochrane Library, PubMed, EMBASE and Chinese Biomedical Literature Database were searched and all randomized controlled trials of axillary dissection in old women (at least 60 years old) were considered. Meta-analyses were completed using RevMan5.1. Results: Three eligible randomized controlled trials (RCTs) including 5,337 patients were considered. There was weak evidence in favour of axillary dissection (AD) in old women. The meta-analysis showed that the overall survival (OS) after 1, 3, 5 and 7 years and the disease free survival (DFS) after 1, 3 and 5 year were not statistically significantly different between AD and no AD groups. However, there was a difference in the 7 year DFS. Conclusions: Axillary dissection did not provide survival benefit to the old women with breast cancer analysed. Therefore, axillary dissection is not well-indicated in old women with breast cancer.

Keywords: Breast cancer - old women - axillary dissection - meta-analysis - randomized controlled trials

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Introduction

For many years, axillary dissection was part of the standard treatment of breast cancer following the pioneering studies by Halsted, early in the 20th century (Halsted, 1907). Conventional axillary lymph node dissection (ALND) was central to the treatment of operable breast cancer (Liljegren, 1997). According to the rationale, there were four reasons for performing axillary dissection, including determining the role of systemic therapy, particularly cytotoxic drugs, local control in the axillary, providing prognostic information to the patients and a possible survival benefit (Fisher et al., 1983; Smith et al., 1990; Fisher et al., 1995; Anderson et al., 2006; Sofi et al., 2012). So most authorities recommended axillary lymph node dissection for the treatment of breast cancer (NIH, 1991; Balch, 1993; Eberlein, 1994; Ruffin et al., 1995) in order to classify the tumors stage, achieve regional control of the disease, establish a prognosis and identify patients who might benefit from adjuvant therapy and especially from intensified chemotherapy (Fisher et al., 1981; Dees et al., 1997; Bai et al., 2012).

Due to an earlier diagnosis of breast cancer, approximate 60-70% of breast cancer patients had node negative disease (Siesling et al., 2003). In the axlliary lymph node negative breast cancer in old woman, the role of axillary dissection (AD) remained controversial (Deckers, 1991; Silverstein et al., 1994). There were no differences in overall survival or distant metastases in NSABP-04 when old woman with breast cancer were randomized to axillary dissection, axillary radiotherapy, or no axillary treatment (Fisher et al., 2002). However, Gardner argued that B-04 and other studies lacked sufficient statistical power to confirm survival advantage from AD (Gardner, 1993). Furthermore, Harris and Osteen proposed that 35% of the patients in the control arm of B-04 actually had a limited axillary dissection, which might have hidden a small survival advantage (Harris, 1985). Moreover several clinical studies demonstrated that the incidence of axillary recurrence was very high (ranging from18 to 35%), when clinically negative axillary nodes in old woman were observed without axillary dissection or radiotherapy (Lythgoe, 1982; Fisher et al., 1985; Ribeiro et al., 1993). Also the axillary dissection had harmful side-effects of varying intensity in 40% of cases, including lymphedema, swelling and weakness of the arm (Ashikaga et al., 2010). Therefore we did this systematic review to assess the effectiveness and safety in AD versus no AD group of breast cancer in old woman.

Materials and Methods

Study selection

We searched PubMed (1966-2011.08), the Cochrane Library (2011 08 issue), EMBASE (1974-2011.08), Chinese Biomedical Literature Database (1978-2011.08) and other website (www.asco.org, www.esmo.org and www.google.com), for relevant clinical trials published

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Table 1. The Basic Characteristic of the Included Studies

The Basic Items	Total	Age	Tumor Size (%)			ER Status (%)		Types of Intervention			Followed
	(AD/No AD)		≤ 2 cm	> 2 cm	Unknow	+	-	Unknow	Experimental	Control	
IBCSG2006	473(234/239)	74(60-91)	54/57	43/42	13-3-1	76.0/84.0	20.0/13.0	4.0/3.0	Sx+Ax	Sx	7 years
Martelli 2005	219(109/110)	70	92.7/92.7	7.3/7.3	unclear	85.4/89.1	14.6/10.0	0.0/0.9	AD	No AD	5 years
Krag2010	3986(1975/2011)	≥ 65	83.7/84.0	16.3/16.0	unclear	unclear	unclear	unclear	SNR+AD	SNR	8 years

Sx, primary surgery; Ax, axillary clearance; AD, axillary dissection; SNR, sentinal node resection

Table 2. The Methodological Qualities of Included Studies

Include studies	Randomization	Allocation concealment	Incomplete outcome data	Selective Reporting	Other bias
IBCSG 2006	Low risk	Low risk	Low risk	Low risk	Low risk
Martelli 2005	Low risk	Unclear risk	Low risk	Low risk	Low risk
Krag 2010	Low risk	Low risk	Low risk	Low risk	Low risk

in any language with the following MeSH terms and textwords: "randomized controlled trails", "axillary dissection", "axillary lymph node dissection", "axillary clearance", "AD", "ALND", "AC", and "breast cancer" and "breast neoplasms".

Randomized clinical trials (RCTs) about axillary dissection in old woman with breast cancer were considered eligible. The breast cancer was diagnosed by pathological methods. The following types of intervention were included: (1) axillary dissection vs no axillary dissection; (2) axillary dissection plus primary surgery vs only primary surgery (3) axillary clearance vs no axillary clearance (4) axillary lymph node dissection vs sentinel lymph node dissection. Further review led to the exlusion of studies in which the patients combine other tumors, bone metastasis, local skin invasion and inflammatory breast cancer.

Outcomes

The primary outcomes included OS and DFS. OS defined as the length of time from the date of randomization to death for any cause and DFS defined as the time to the earliest occurrence of any of the following events: locoregional recurrence or distant metastasis, second breast cancer, new primary other than squamous or basal cell carcinoma of the skin. Secondary outcomes were first events and the quality of life (QOL). The first events included local, contralateral, distant, non-breast malignancy and other failed to demonstrate any difference.

Data extraction

Data were extracted and potentially relevant citations for inclusion were assessed by two reviewers independently. Disagreements were resolved by consensus. We extracted the following data from each included article: the authors, publication year, intervention, outcome etc. Quality assessment was according to the Cochrane handbook 5.1.

Statistical methods

We analyzed the data using Review Manager (version 5.1). Significance set at P value 0.05 and I^2 50% statistic was measured to evaluate statistical heterogeneity among studies. According to the heterogeneity in treatment effect existed in studies, we used fixed effects model or random effect model. Then we grouped studies and pooled data in meta-analyses; otherwise, we presented a narrative synthesis. Dichotomous outcomes results were expressed as relative risk (RR) with 95% confidence intervals (CI).

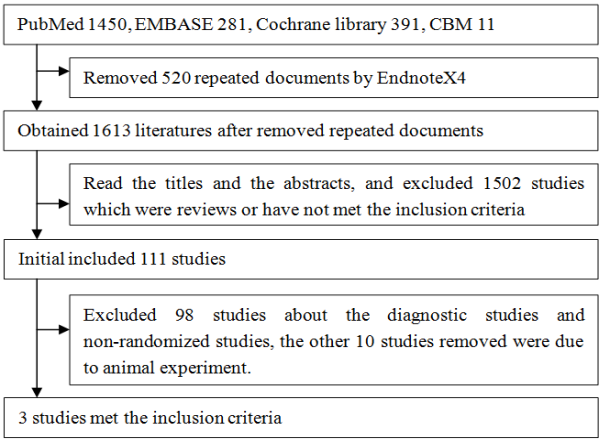

Figure 1. The Screening Flow Chart

Results

Literature search

We identified 2133 potentially relevant articles in the primary literature search (Figure 1), three RCTs (Martelli et al., 2005; IBCSG et al., 2006; Krag et al., 2010) that met the inclusion criteria and included a total of 5,337 old woman with breast cancer and were published in English. The basic characteristic of the studies included cases, tumor size, ER status, follow–up period, interventions and outcomes (Table 1).

Quality assessment

Table 2 showed that the methodological qualities of included studies were assessed by the Cochrane handbook 5.1. All three trials described a satisfactory method of randomization. Two of the trials provided information on allocation concealment methods. The incomplete outcome data, selective reporting and other bias in three included studies were evaluated as "low risk".

Primary outcomes

OS: Overall survival(OS) was reported in three RCTs (Martelli et al., 2005; IBCSG et al., 2006; Krag et al., 2010), There was no heterogeneity across the trials, therefore, the fixed-effects model was used to pool data, there were no statistically significant differ¬ence between AD group and no AD group in 1 year OS

(RR=1.00, 95%CI:1.00-1.01, P=0.74, I^2=0%), 3 years OS (RR=1.00, 95%CI:0.99-1.01, P=0.29, I^2=20%), 5 years OS (RR=1.01, 95%CI:0.99-1.02, P=0.23, I^2=33%), 7 years OS (RR=1.01, 95%CI:0.99-1.03, P= 0.46, I^2=0%).

DFS: Two studies (IBCSG et al., 2006; Krag et al., 2010) reported disease free survival data on 4459 randomized patients. Between AD and no AD group, there was no significant difference in 1, 3, 5 years DFS. 1 year: (RR=1.00, 95% CI:0.99-1.01, P=0.64, I^2=0%), 3 years: (RR=1.00, 95% CI:0.98-1.01, P=0.73, I^2=0%), 5 years: (RR=1.01, 95% CI:0.99-1.03, P=0.63, I^2=0%). But there was difference in 7 years diseases free survival (RR=1.03, 95% CI:1.01-1.06, P=0.42, I^2=0%).

Secondary outcomes

First event: Three of the studies (IBCSG et al., 2006;Krag et al., 2010)reported the first events. There was no statistically significant difference in two groups. Local: (RR=1.21, 95% CI:0.84-1.73, P=0.51, I^2=0%), Contralateral: (RR=1.27, 95% CI: 0.87-1.84, P=0.74, I^2=0%), Distant: (RR 0.97, 95% CI: 0.73-1.29, P=0.55, I^2=0%), Non-breast malignancy: (RR= 0.89, 95% CI: 0.69-1.14, P=0.34, I^2=7%), Other: (RR=0.51, 95% CI: 0.24-1.09, P=0.56, I^2=0%).

QOL: One studies (IBCSG et al., 2006) reported the quality of life. In both the patients' subjective assessment of their QOL and the physicians' perception of the patients' QOL, the largest adverse QOL effects of axillary dissection were observed from baseline to the first postoperative assessment. However the differences tended to disappear in 6 to 12 months.

Discussion

Summary of key findings: The necessary of axillary dissection in the old woman with breast cancer was still under debate (Parmigiani et al., 1999). This Meta-analysis examined the option of avoiding axillary surgery in old woman with breast cancer. Included three studies demonstrated that axillary dissection had little survival benefits on breast cancer in old woman. Only the 7years DFS in AD group was superior to no AD group. Also the first events including local, contralateral, distant, non-breast malignancy and other failed to demonstrate any difference. Only one studies reported QOL. The difference turned to disappear in 6 to 12 months.

Strengths and limitations: This Meta-analysis had several potential biases. Only three studies were in accord with the included criteria. The quantity of included RCTs was less (Tian, 2012). Moreover the sample size was contributed by one study (Krag et al., 2010), which might increase the risk of the inclusion. The weight in the study was major, but other studies also devoted the size. So we demanded the other large sample size studies to confirm. Computerized searching was essential for identifying clinical trials. It was, however, possible that not all the relevant studies be identified from computerized searching. Survival data at 7 years of follow-up were lacking in one trial, which may lead to a biased estimate in favor of overall survival. Among articles cited in the present study, some authors referred to adopted axillary dissection as axillary clearance, which may slightly sway the reliable conclusion. The methodological of allocation concealment in Martelli's research was unclear risk (Table 2). However according the Cochrane handing book, we made the search strategy and did our best to reduce the selection biases. Refer to the problem the disputes were in clinical diagnosis and treatment. By this Meta-analysis, what role of the axillary dissection played in clinical axillary node negative patients were clear.

Clinical implications: This Meta-analysis showed that axillary dissection for the treatment of old women with breast cancer did not improve both disease-free and overall survival compared with no axillary dissection. On the contrary, the diseases free survival of 7 years in no axillary dissection was superior to axillary dissection group. With the improvement of the method of sentinel lymph node biopsy (SLND), the sentinel lymph node biopsy procedure was rapidly implemented in routine practice and could replace the axillary dissection in old woman who had a negative axillary lymph node, which based on the low false-negative rate (Pepels et al., 2011). Therefore if the axillary lymph nodes were truly negative, there could be no possible benefit from performing an axillary dissection in old woman.

Future directions

Our Meta-analysis demonstrated that the survival benefit and the first event of axillary dissection and no axillary dissection were similar. Now that the sentinel lymph node biopsy to confirm the axillary lymph node as negative (Veronesi et al., 2003), it seemed unnecessary to do the axillary dissection in old woman with breast cancer. Only one study reported the quality of life. However more researches focused on quality of life in axillary dissection or no (Chan, 2010). Therefore the further studies' designs were needed to concern the estimation of benefit and harm in this intervention of the quality of life.

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