· 论著 ·

Is it necessary to do axillary dissection in old women with breast cancer? A meta-analysis of randomized clinical trials

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【Abstract】 **Objective** To assess the effectiveness and safety of axillary dissection in old women with breast cancer. **Methods** All randomized controlled trials on axillary dissection in old woman were retrieved in the Cochrane Library, PubMed, EMBASE and Chinese Biomedical Literature Database. Meta-analyses were completed using RevMan 5.1. **Results** Three eligible randomized controlled trials (RCTs) including 5337 patients were involved. There were weak evidences in favor of axillary dissection in old woman. The meta-analysis showed that the overall survival (OS) in 1, 3, 5 and 7 years and the disease-free survival (DFS) in 1, 3 and 5 years were not statistically different between axillary dissection patients and non-axillary dissection patients. However there was a statistical difference in 7-year DFS. **Conclusions** Axillary dissection does not show a survival benefit in the old women with breast cancer. Therefore it is not well-founded to do axillary dissection in old women with breast cancer.

【Key words】 breast neoplasms; axillary dissection; meta-analysis; randomized controlled trials

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[1]. Conventional axillary lymph node dissection (ALND) was central to the treatment of operable breast cancer[2]. According to the rationale, there were four reasons for performing axillary dissection, i.e., 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[3-6]. So most authorities recommended ALND for the treatment of breast cancer[7-10] in order to classify the tumor stage, achieve regional control of the disease, establish a good prognosis and identify the patients who might benefit from adjuvant therapy and especially from intensified chemotherapy[11-12].

Due to an earlier diagnosis of breast cancer, approximate 60% -70% of breast cancer patients showed lymph node negative[13]. In the old women with axillary lymph node negative breast cancer, the role of axillary dissection (AD) remained

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controversial[14-15]. There were no statistical differences in overall survival or distant metastases in NSABP-04 when old women with breast cancer were randomized to axillary dissection, axillary radiotherapy, or no axillary treatment[16]. However, Gardner and Feldman[17] argued that B-04 and other studies lacked sufficient statistical power to confirm survival advantage from axillary dissection. Furthermore, Harris and Osteen[18] 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. Moreover several clinical studies demonstrated that the incidence of axillary recurrence was high (ranging from 18% to 35%), when clinically negative axillary nodes in old woman were observed without axillary dissection or radiotherapy[19-21]. Also the axillary dissection had harmful side-effects of varying intensity in 40% of cases, including lymphedema, swelling and weakness of the arm[2, 22]. Therefore we did this systematic review to assess the effectiveness and safety in axillary dissection versus non-axillary dissection treatment in the old women with breast cancer.

1 METHODS

1.1 Study selection

We searched PubMed, Cochrane Library, EMBASE, Chinese Biomedical Literature Database and other three websites (www.asco.org, www.esmo.org and www.google.com) up to August 2011, for relevant clinical trials published in English and Chinese with the following MeSH terms and textwords: "randomized controlled trials", "axillary dissection", "axillary lymph node dissection", "axillary clearance(AC)", "AD", "ALND", "AC", and "breast cancer" and "breast neoplasms".

Randomized clinical trials (RCTs) on axillary dissection in old women 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* non-axillary dissection; (2) axillary dissection plus primary surgery *vs* only primary surgery (3) axillary clearance *vs* non-axillary clearance; (4) ALND *vs* sentinel lymph node dissection (SLND). If the disease was combined with other tumors, bone metastasis, local skin invasion and inflammatory breast cancer, the studies should be excluded.

1.2 Outcomes

The primary outcomes included overall survival (OS) and disease-free survival (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 metastasis and non-breast malignancy, which failed to demonstrate statistical differences.

1.3 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 performed according to the Cochrane handbook 5.1.

1.4 Statistical analysis

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

2 RESULTS

2.1 Literature search

We identified 2133 potentially relevant articles in the primary literature search, and involved three RCTs[23-25] that met the inclusion criteria and included a total of 5337 old women with breast cancer and were published in English(Figure 1). The basic characteristics of the studies included cases, tumor size, ER status, follow-up period, interventions and outcomes (Table 1).

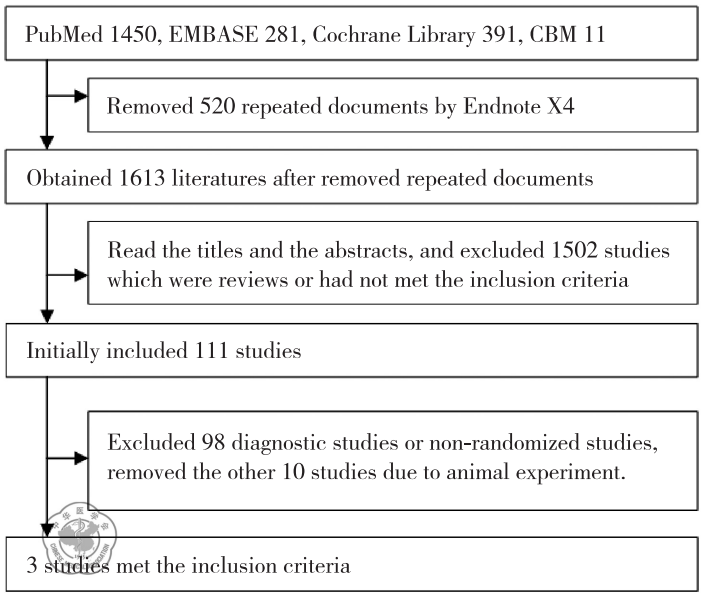

Figure 1 The screening flow chart

Table 1 The basic characteristics of the included studies

Literature	Total(AD/Non-AD)	Age (years)	Tumor size (AD/Non-AD,%)			ER status (AD/Non-AD,%)			Intervention type		Follow-up (years)
			≤2 cm	>2 cm	Unknown	+	−	Unknown	Experimental	Control	
IBCSG[23]	473(234/239)	74(60-91)	54/57	43/42	3/1	76.0/84.0	20.0/13.0	4.0/3.0	Sx+Ax	Sx	7
Martelli[24]	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	Non-AD	5
Krag[25]	3986(1975/2011)	≥ 65	83.7/84.0	16.3/16.0	unclear	unclear	unclear	unclear	SNR+AD	SNR	8

Sx: primary surgery; Ax: axillary clearance; AD: axillary dissection; SNR: sentinel node resection.

2.2 Quality assessment

Table 2 showed that the methodological qualities of the included studies were assessed by the Cochrane handbook 5.1. All three trials described a proper 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".

Table 2 The methodological qualities of included studies

Included studies	Randomization	Allocation concealment	Incomplete outcome	Selective reporting	Other bias
IBCSG[23]	Low risk	Low risk	Low risk	Low risk	Low risk
Martelli[24]	Low risk	Unclear risk	Low risk	Low risk	Low risk
Krag[25]	Low risk	Low risk	Low risk	Low risk	Low risk

2.3 Primary outcomes

2.3.1 OS: OS was reported in three RCTs[23-25]. There was no heterogeneity in the trials, therefore, the fixed-effects model was used to pool data, there was no statistically significant difference between axillary dissection group and non-axillary dissection 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, $P=0.46$, $I^2=0$) (Figure 2).

2.3.2 DFS: Two studies[23, 25] reported DFS in 4459 randomized patients. Between axillary dissection and non-axillary dissection 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 a difference in 7 years DFS ($RR=1.03$, 95% CI: 1.01−1.06, $P=0.42$, $I^2=0$) (Figure 3).

2.4 Secondary outcomes

2.4.1 First events: Three of the studies[23-25] 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, $P=0.56$, $I^2=0$) (Figure 4).

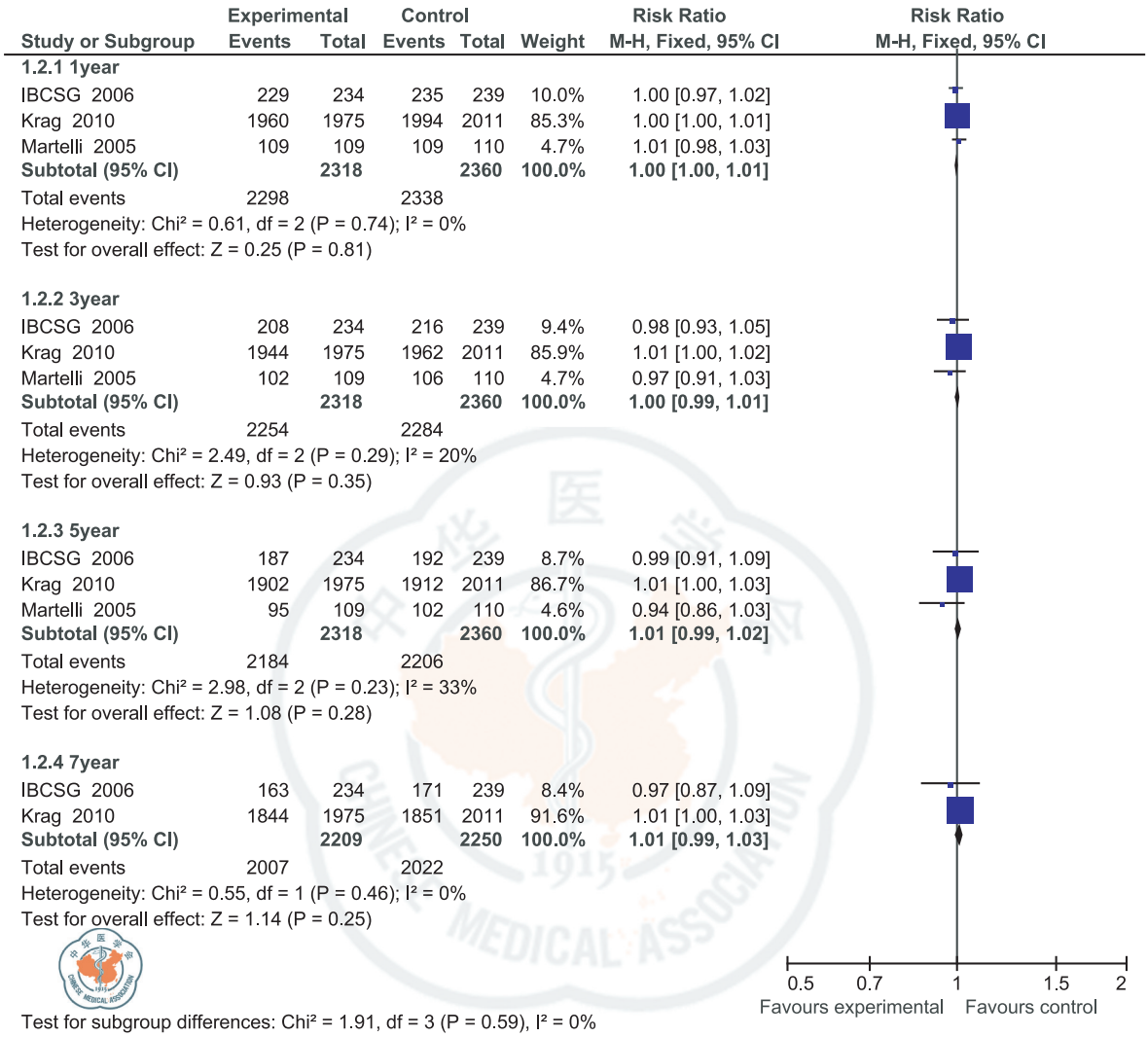

Figure 2 Overall survival

2.4.2 QOL: One study[23] reported the QOL. In both the patients' subjective assessment of their QOL and the physicians' perception of the patients' QOL, the largest adverse effects of axillary dissection in the respect of QOL were observed from baseline to the first postoperative assessment. However, the differences tended to disappear in 6 to 12 months after operation.

3 DISCUSSION

3.1 Summary of key findings

The necessity of axillary dissection in the old women with breast cancer was still under debate[26]. This meta-analysis examined the option of avoiding axillary surgery in old women with breast cancer. The included three studies demonstrated that axillary dissection had little survival benefits in old women with breast cancer. Only the 7 years DFS in axillary dissection group was superior to non-axillary dissection group. The first events, including local, contralateral, distant, non-

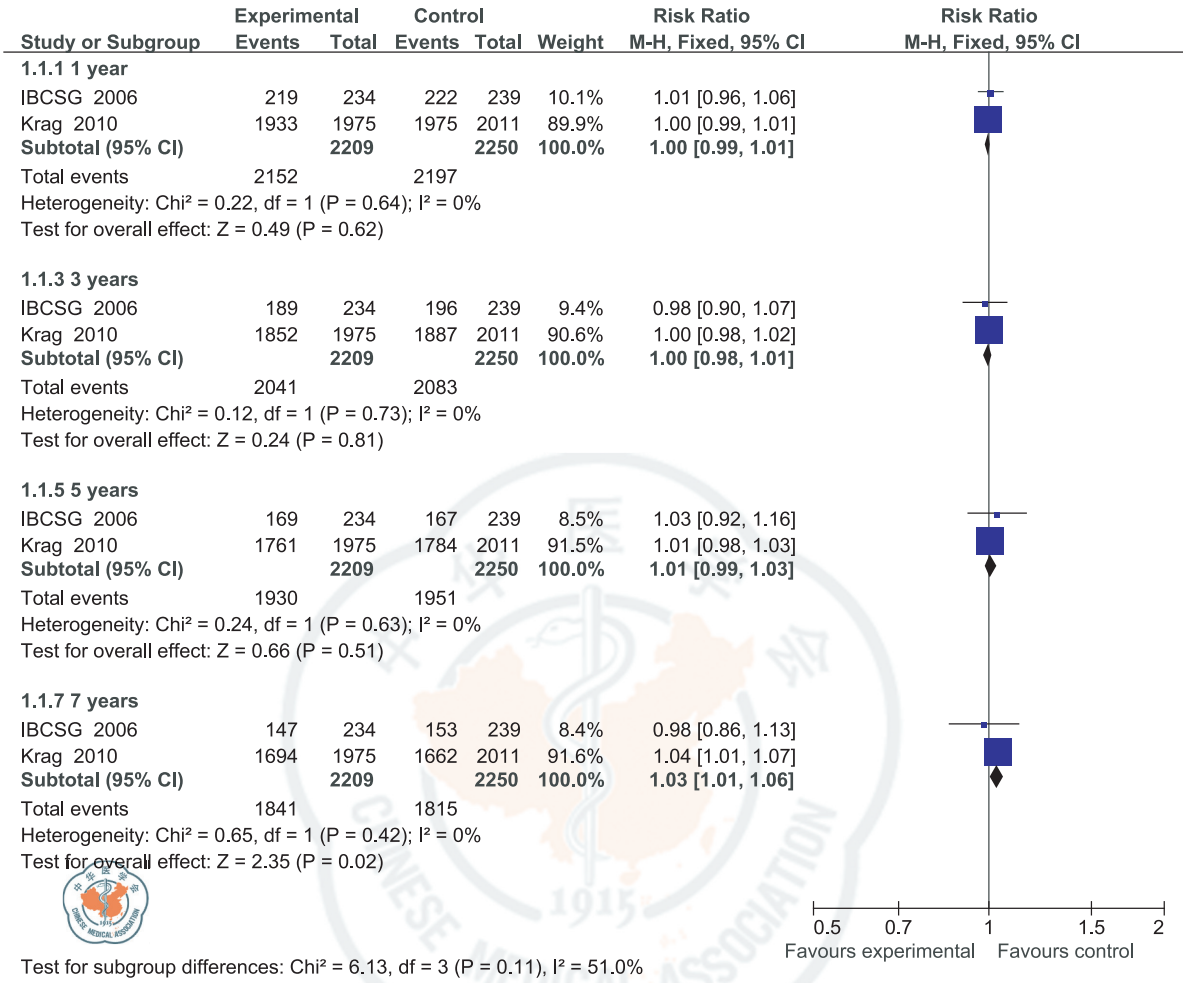

Figure 3 Disease free survival

breast malignancy etc, failed to demonstrate any difference. Only one study reported QOL. The difference turned to disappear in 6 to 12 months.

3.2 Strengths and limitations

This meta-analysis had several potential limitations. Only three studies accorded with the included criteria. The quantity of included RCTs was less. Moreover the sample size was contributed by one study[25], which might increase the risk of the inclusion. The sample size 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 to identify clinical trials. However, it was possible that not all the relevant studies be identified from computerized searching. Survival data at 7 years follow-up were lacking in one trial, which may lead to a biased estimate in favor of OS. 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 methodology of allocation concealment in Martelli's research may show unclear risk (Table 2). However, according to the Cochrane handing book, we made the search strategy and did our best to reduce the selection biases. By this meta-analysis, what role can axillary

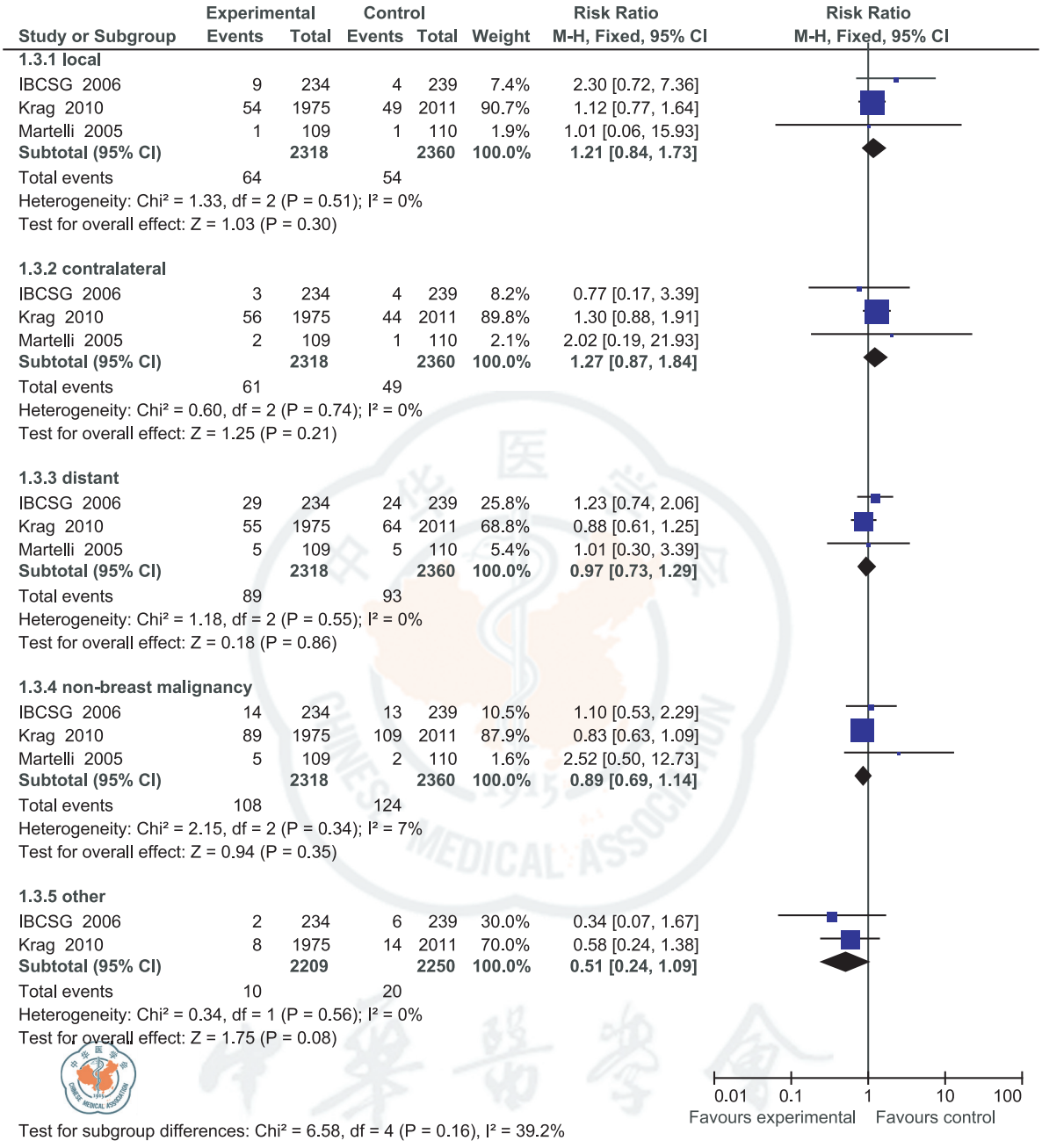

Figure 4 First events

dissection play in clinical axillary node negative patients became clear.

3.3 Clinical implications

This meta-analysis showed that axillary dissection for the treatment of old women with breast cancer did not improve both DFS and OS compared with non-axillary dissection. On the contrary, the 7 years DFS in non-axillary dissection group was superior to axillary dissection group. With the technique improvement, SLND can be rapidly implemented in routine practice and make it possible to replace the axillary dissection in old women with negative axillary lymph node, based on the low false-negative rate[27]. Therefore, if the axillary lymph nodes were

truly negative, the old women patients maybe show no benefits from axillary dissection.

3.4 Future directions

Our meta-analysis demonstrated that the survival benefit and the first event of axillary dissection and non-axillary dissection were similar. If SLND can confirm the axillary lymph node as negative[28], it seems unnecessary to do the axillary dissection in old women with breast cancer. Only one study reported QOL. Some researches focused on quality of life of patients after axillary dissection[29], however, further studies are needed to address this issue.

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