RESEARCH COMMUNICATION

Neoadjuvant Chemotherapy for Resectable Esophageal Carcinoma: A Meta-analysis of Randomized Clinical Trials

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Abstract

Neoadjuvant chemotherapy for resectable esophageal carcinoma has been a focus of study, but no agreement has been reached on clinical randomized controlled trials and relevant systematic evaluation. The purpose of this study was to perform a meta-analysis on published randomized controlled trials (RCTs) that compared neoadjuvant chemotherapy and surgery with surgery alone for resectable esophageal carcinoma. Medline and manual searches was conducted in PubMed, ASCO (American Society of Clinical Oncology) meeting summary, Embase, the Cochrane Library (up to October 2010), Chinese Biomedical Literature Database, China National Knowledge Infrastructure, VIP Database, Wanfang Database. The selection contents were to identify all published and unpublished RCTs that compared neoadjuvant chemotherapy and surgery with surgery alone for resectable esophageal carcinoma. Sixteen RCTs which included 2,594 patients were selected. The risk ratio (RR) (95% confidence interval [CI]; P value), expressed as neoadjuvant chemotherapy and surgery versus surgery alone (treatment versus control), was 1.02 (0.95, 1.10; P=0.54) for 1-year survival, 1.29 (1.13, 1.47; P=0.0001) for 3-year survival, 1.31 (1.13, 1.51; P=0.0003) for 5-year survival, 1.00 (0.95, 1.04; P= 0.85) for rate of resection and 0.89 (0.64, 1.23; P=0.48) for operative mortality. The results showed that neoadjuvant chemotherapy for resectable esophageal carcinoma can raise the overall survival rate of patients with esophageal carcinoma, but it does not affect treatment-related mortality.

Keywords: Esophageal neoplasms - surgery - neoadjuvant chemotherapy - randomized controlled trial - meta-analysis

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Introduction

Esophageal cancer is the eighth most common malignancy and sixth most fatal, with approximately 460,000 new diagnoses and 380,000 mortalities annually around the world (Kamangar et al., 2006). It has a high incidence in Asia, southern and eastern Africa, and northern France (Parkin and Muir, 1992; Crew and Neugut, 2004). Esophageal cancer is the most rapidly increasing tumor type in the Western world, and the histology of esophageal cancer varies worldwide, with more than half of new cases being adenocarcinoma in the United States (Bollschweiler et al., 2001; Pohl and Welch, 2005; Eslick, 2009; Jemal et al., 2009). Surgery has always been considered as the standard treatment for patients with resectable esophageal cancer, but the effectiveness of surgery alone was unsatisfactory and the median survival of patients rarely exceeded eighteen months (Khushalani, 2008). Thus clinicians always make efforts to seek for new treatment strategies to prolong the survival time of patients with resectable esophageal cancer. Many experiments show apparent improvements in survival often reflect advances in preoperative staging, patient selection, and postoperative care, as opposed to the effectiveness of surgical therapy itself (Orringer et al., 1999; Ando et al., 2000; Whooley et al., 2001). Most patients with resectable esophageal cancer have little prospect for cure because they have micrometastatic systemic disease at the time of clinical examination and diagnosis. It is not surprising that tumor had already invaded the adjacent organs or tissues after surgical resection. Chemotherapy including cisplatin and 5-fluorouracil has shown activity in advanced esophageal cancer. Combining systemic chemotherapy and local-regional surgery could improve survival in patients with resectable esophageal cancer (Sutton and Clark, 2000). In the past 20 years, neoadjuvant chemotherapy for resectable esophageal carcinoma has been a research hotspot. In Japan, since the results of the Japan Clinical Oncology Group (JCOG) 9907 study (Igaki et al., 2008) were reported, neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil followed by surgery has emerged as a new standard treatment. Neoadjuvant chemotherapy for resectable esophageal carcinoma becomes one of the most common methods of esophageal cancer treatment.

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Debate regarding the current standard of care for the management of esophageal cancer is ongoing (Iyer et al., 2004; Shah and Kelsen, 2004; Greil and Stein, 2007). Internationally, an agreement has been reached on preoperative adjuvant therapy for common tumors, such as breast, lung and colorectal cancer, but there is no consensus about the effect of neoadjuvant chemotherapy for resectable esophageal carcinoma. Neoadjuvant chemotherapy theoretically offers early treatment of micrometastatic disease, and it can facilitate surgical resection by downstaging cancers (Sutton and Clark, 2000). In addition, esophageal cancer patients generally tolerate neoadjuvant chemotherapy better than postoperative chemotherapy. Based on these theories many trials of neoadjuvant chemotherapy followed by surgery have been done. Most trials have generated promising results, and these patients had dramatic responses to chemotherapy. A significant survival benefit was evident for these responders with esophageal cancer. However, neoadjuvant chemotherapy has associated with treatment toxicity, and it may contribute to perioperative morbidity and mortality. Furthermore, it may be harmful by delaying definitive and effective treatment with surgery. RCTs have been performed to address these issues. However, many of the RCTs enrolled small numbers of patients, and it is limited to detect a treatment benefit through these RCTs, even if a benefit actually exists. We got different experimental results from these RCTs. The existing three meta-analysis (Urschel et al., 2002; Kaklamanos et al, 2003; Malthaner and Fenlon, 2003) did not find consistent experimental results due to few selected RCTs, missing unpublished RCTs, and the short age of follow-up time. In the recent three years, the follow-up results of original large-scale population tests and new randomized controlled trial results published successively with increased the data of experiment, so we can comprehensively observe the curative effect of neoadjuvant chemotherapy with resectable esophageal cancer. Thereupon, meta-analysis can be useful in this situation. We performed a meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy plus surgery to surgery alone in patients with resectable esophageal cancer.

Materials and Methods

By applying a combination of controlled vocabulary and text word terms, the simple search utilized Boolean search combined with search terms. The advanced search was in accordance with the handbook recommended by the Cochrane Collaboration (Higgins et al., 2009). Two studies used "esophageal neoplasms/surgery or esophagectomy or oesophagectomy or esophageal cancer or oesophageal cancer" combined with "antineoplastic agents" to search in Medline (1966–October 2010), Embase (1986–October 2010), the Cochrane Library (up to October 2010), ASCO (American Society of Clinical Oncology) meeting summary. And we did search in the Chinese Biomedical Literature Database (1975–October 2010), the China National Knowledge Infrastructure (1994–October 2010), the VIP database (1989–October 2010), the Wanfang database (1980-October 2010), and the National Research Register for ongoing trials. This set was limited to "randomized controlled trial" in the "publication type" search field to yield 244 documents. Trials were not excluded because of cancer histology (squamous or adenocarcinoma) or language of publication or trial quality or insufficient number of patients. Manual searches were performed by reviewing articles and abstracts cited in the published meta-analysis and quoted related literatures.

The eligible studies must meet the following inclusion criteria: (1) It must be a prospective RCT which compares neoadjuvant chemotherapy plus surgery with surgery alone; (2) Outcomes must have included survival data; (3) There was no statistical significance in factors such as sex, age, type of pathology, tumour stage between the two groups; (4) It was the initial management of resectable esophageal cancer; and (5) Pathologic diagnosis of invasive squamous cell carcinoma (SCC) or invasive adenocarcinoma (AC) of the esophagus including the gastroesophageal junction. The following studies were excluded from the analysis: (1) These results were reported on a mixed group of randomized and nonrandomized patients; (2) The survival analysis was reported only for patients who completed treatment; (3) Esophageal cancer cannot be resected only by surgery treatment; and (4) The therapy measures that be adopted in RCTs are not in accord with inclusion criteria. Multiple publications reporting the same group of participants, or their subsets, were excluded. In addition, colleagues and experts in the field were contacted to ascertain unpublished or ongoing studies.

Quality assessment and data extraction were independently fulfilled by two authors. Any discrepancies between authors arising at any stage were resolved by discussion or with a third party, when necessary. A structured tabulation was used for data extraction from the included studies. Possible results from studies were entered into Revman Manager (Version 5.0.2, Cochrane Collaboration). Data analysis followed the guidelines in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2009). The domain-based evaluation criteria recommended by the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2 (Higgins et al., 2009) was used to assess the quality of included studies (Table 1).

Outcomes assessed by meta-analysis included 1-year survival, 3-year survival, 5-year survival, rate of resection and operative mortality. The intention to treatment principle was used in calculating frequency of events. Survival data was obtained from individual trials which possess reliable data. Original data was considered as the most reliable data, followed by survival percentages and derivation of survival from graphically presented survival rate curves. Surgical resection was defined as any resection, curative or palliative, but esophageal bypass and exploratory surgery were not included. Usually operative mortality was expressed as 30-day mortality, as opposed to in-hospital mortality in most of the trials, thus 30-day mortality was used for the meta-analysis. If is not accurate

Table 1. Quality Assessment of Included Studies

Study (author-year)"	Adequate sequence generation	Allocation concealment	Blinded method	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
1 Liao, 1993	Unclear	Unclear	No	Unclear	Unclear	Unclear
2 Wang, 2001	Unclear	Unclear	No	Unclear	Unclear	Unclear
3 Cao, 2001	Unclear	Unclear	No	Unclear	Unclear	Unclear
4 Peng, 2007	Unclear	Unclear	No	Unclear	Unclear	Unclear
5 Ma, 2007	Unclear	Unclear	No	Yes	Unclear	Unclear
6 Roth, 1988	Yes	Yes	Yes	Yes	Unclear	Unclear
7 Nygaard, 1992	Unclear	Unclear	No	Unclear	Unclear	Unclear
8 Schlag, 1992	Unclear	Yes	No	Yes	Unclear	Unclear
9 Maipang, 1994	Unclear	Unclear	No	Yes	Unclear	Unclear
10 Law, 1997	Unclear	Yes	No	Unclear	Unclear	Unclear
11 Kelsen, 1998	Yes	Yes	Yes	Yes	Unclear	Unclear
12 Baba, 2000	Yes	Yes	Yes	Unclear	Unclear	Unclear
13 Ancona, 2001	Yes	Yes	Yes	Unclear	Unclear	Unclear
14 MRC, 2002	Yes	Yes	No	Unclear	Unclear	Unclear
15 David, 2006	Yes	Yes	Yes	Unclear	Unclear	Unclear
16 Okhyan, 2009	Unclear	Unclear	No	Unclear	Unclear	Unclear

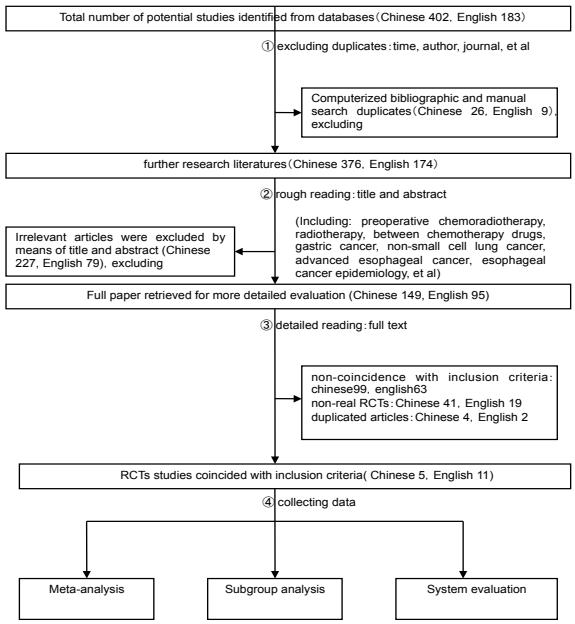

Figure 1. The Flow of Selection of Studies

in the literature, we take method: (1) direct connection with corresponding author (such as Dr. Kelsen), trying to get original data; (2) if there are survival curves, according to the literature data, getting survival rates and subgroups number, and then calculating incidents and difference than (Roth et al., 1988; Law et al., 1997).

Data were analyzed by RevMan 5.0.2. According to the type of outcome index, measurement data were assessed by weighted mean difference or standardized mean difference (SMD) and a 95% confidence interval (95% CI). Numeration data was estimated by the relative risk and 95% confidence interval. Q test methods were used to assess heterogeneity of study results and a planned cut-off for significance of $P \leq 0.05$. If $P > 0.05$, we used a fixed effect model, otherwise we used a random effect model. The Risk ratios (RR) among the frequency of events in both neoadjuvant chemotherapy plus surgery group and surgery alone group was calculated and these RR are presented as a point estimate with 95% confidence intervals (CI) and P values in parentheses. The significance level was set at 5%. Funnel plot analysis did not suggest publication bias against negative trials.

Results

Features of RCTs

A total of 244 studies were identified. Only sixteen studies (Roth et al., 1988; Nygaard et al., 1992; Schlag, 1992; Liao et al., 1993; Maipang et al., 1994; Law et al., 1997; Kelsen et al., 1998; Baba et al., 2000; Ancona et al., 2001; Cao et al., 2001; Wang et al., 2001; Medical Research Council Oesophageal Cancer Working Group, 2002; Cunningham et al., 2006; Ma et al., 2007; Peng et al., 2007; Bokhyan et al, 2009) were in accordance with the above-mentioned inclusion criteria (Figure 1). Eleven was published in English and five in Chinese. The sixteen RCTs included 2,594 patients, 1,302 of whom received neoadjuvant chemotherapy before surgery, and the remaining 1,292 patients received surgery alone. The literatures were published between 1988 and 2009. Of these sixteen studies, seven (Nygaard et al., 1992; Schlag, 1992; Maipang et al., 1994; Law et al., 1997; Baba et al., 2000; Ancona et al., 2001; Ma et al., 2007) were restricted to patients with esophageal squamous cell carcinoma only, one (Cunningham et al., 2006) was restricted to patients with esophageal adenocarcinoma only, and the remaining eight trials enrolled patients with SCC and AC. Nearly all the patients in the surgery alone group underwent surgery, yet there were more patients in the chemotherapy group who had not completed the planned chemotherapy regimen for various causes such as side effects of chemotherapy or metastasis of cancer before surgery. In the neoadjuvant chemotherapy group, surgery will be done early after one week, lately six weeks, chemotherapy regimen including 2-4 cycles. The tumor stage of the most patients in the sixteen studies ranged from II-III, but more advanced tumor stage (IVa) was also seen in three RCTs (Law et al., 1997; Baba et al., 2000; Cunningham et al., 2006), total 82 patients. Finally, tumor stage was not reported in two RCTs (Roth et al., 1988; Bokhyan et al., 2009). The main features of the

Table 2. Features of All Trials Included in the Meta-analysis

Study (author-year)	Sample size	country	Tumor type	tumor stage (TNM) I	II	III	IV	Schedule of chemotherapy	Time of surgery	Median survival (months)
Liao, 1993	64	China	SCC and AC	Not report				Two cycles: vinblastine 1 mg/week; cyclophosphamide 600mg/week;5-fluorouracil 500 mg/week; bleomycin 10 mg/day(im days 1–15)	7-10d after CT	Not report
Wang, 2001	100	China	SCC and AC	0	91	9	0	One cycles: cisplatin 30 mg/day(days 1-5)	10d after CT	Not report
Cao, 2001	87	China	Not report	0	30	57	0	Three cycles: bleomycin 6 mg/day(days 1–3) cisplatin 20 mg/day(days 1-5);5-fluorouracil 1000 mg/day(days 1–3)	2 W after CT	Not report
Peng, 2007	264	China	SCC and AC	Not report				Two cycles: cisplatin 40 mg/m2 days 1–5; 5-fluorouracil 500 mg/m2 days 1–5	2 W after CT	Not report
Ma, 2007	67	China	SCC	0	0	67	0	Two cycles: cisplatin 100 mg/m2 day 1,5; bleomycin 10 mg/m2 days 2–7	2-4 W after CT	34/24
Roth, 1988	39	USA	SCC and AC	Not report				Three cycles: cisplatin 120 mg/m2 day 1; vindesine 3 mg/m2 days 1, 8; bleomycin 10 U/m2 days 3–6	4 W after CT	9/9
Nygaard, 1992	106	Norway	SCC	106			0	Two cycles: cisplatin 20 mg/m2 days 1–5; bleomycin 5 mg/m2 days 1–5	3 W after CT	Not report
Schlag, 1992	46	Germany	SCC	Not report				Three cycles: cisplatin 20 mg/m2 days 1–5; 5-fluorouracil 1000 mg/m2 days 1–5	2-3 W after CT	10/10
Maipang, 1994	46	Thailand	SCC	3	43	0	0	Two cycles: cisplatin 100 mg/m2 day 1; bleomycin 10 mg/m2 days 3–8; vinblastine 3 mg/m2 days 1, 8	2 W after CT	17/17
Law, 1997	147	China	SCC	0	9	90	48	Two cycles: cisplatin 100 mg/m2 day 1; 5-fluorouracil 1000 mg/m2 days 1–5	D42	16.8/13
Kelsen, 1998	467	USA	SCC and AC	467			0	Three cycles: cisplatin 100 mg/m2 day 1; 5-fluorouracil 1000 mg/m2 days 1–5	D93	14.9/16.1
Baba, 2000	42	Japan	SCC	10	10	12	10	Two cycles: cisplatin 70 mg/m2 day 1; 5-fluorouracil 700 mg/m2 days 1–5; folinic acid 20 mg/m2 days 1–5	28-42d after CT	34.1/41.0
Ancona, 2001	96	Italy	SCC	0	73	23		Two cycles: cisplatin 100 mg/m2 day 1; 5-fluorouracil 1000 mg/m2 days 1–5	3-4 W after CT	24/25
MRC, 2002	802	UK	SCC and AC	Not report				Two cycles: cisplatin 80 mg/m2 day 1; 5-fluorouracil 1000 mg/m2 days 1–4	3-5 W after CT	16.8/13.3
David, 2006	131	UK	AC	0	32	75	24	Three cycles: epirubicin 50 mg/m2 day 1; cisplatin 60 mg/m2 day 1; 5-fluorouracil 200 mg/m2 days 1–21	3-6 W after CT	Not report
Bokhyan, 2009	90	Russian	SCC and AC	Not report				Three cycles: cisplatin 80 mg/m2 day 1; 5-fluorouracil 500 mg/m2 days 1–3; folinic acid 20 mg/m2 days 1–3; etoposide 100 mg/m2 days 1–3	4W after CT	Not report

SCC, squamous cell carcinoma; AC, adenocarcinoma; CT, chemotherapy; W, week; n1/n2:n1 chemotherapy group median survival, n2 surgery alone group median survival

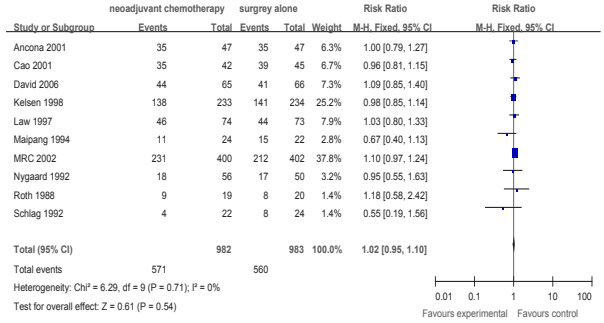

Figure 2. One-Year Survival Rate in Neoadjuvant Chemotherapy and Surgery Compared with Surgery Alone (Forest Plot)

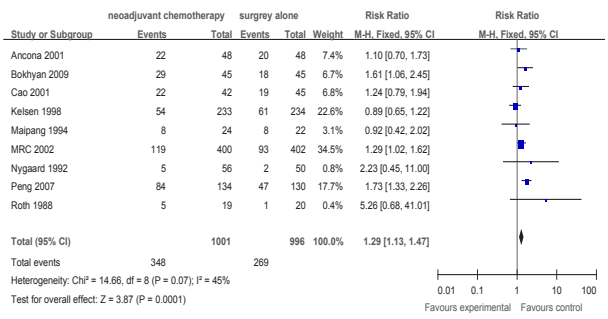

Figure 3. Three-Year Survival Rate in Neoadjuvant Chemotherapy and Surgery Compared with Surgery Alone (Forest Plot)

trials included in the meta-analysis are shown in Table 2. Nine countries including China, Thailand, Japan, United States of America, the United Kingdom, Norway, Italy, Russia, and Germany were involved in the RCTs.

A total of sixteen articles were evaluated as RCTs. Only six trials (Kelsen et al., 1998; Roth et al., 1988; Baba et al., 2000; Ancona et al., 2001; Medical Research Council Oesophageal Cancer Working Group, 2002; Cunningham et al., 2006) described details of the methods used, and eight trials (Roth et al., 1988; Schlag, 1992; Law et al., 1997; Kelsen et al., 1998; Baba et al., 2000; Ancona et al., 2001; Medical Research Council Oesophageal Cancer Working Group, 2002; Cunningham et al., 2006) provided information of allocation concealment. Five studies reported information of blinding between practitioners and participants, or blinding of outcome assessors. All trials which provided patient characteristics in the chemotherapy and surgery alone groups were free of selective reporting and other bias, and all studies provided insufficient information to determine as judgment of 'Yes' or 'No' (Table 1). Because double blinding can not be performed and the method of randomization was not reported in some trials, some RCTs quality is lower than others.

Survival rate

The effect of neoadjuvant chemotherapy on survival rate is shown in Figure 2-4. 1-year survival was similar for the treatment and control group. The review of ten studies that investigated neoadjuvant chemotherapy and enrolled a total of 2,337 patients resulted in estimates of 1-year

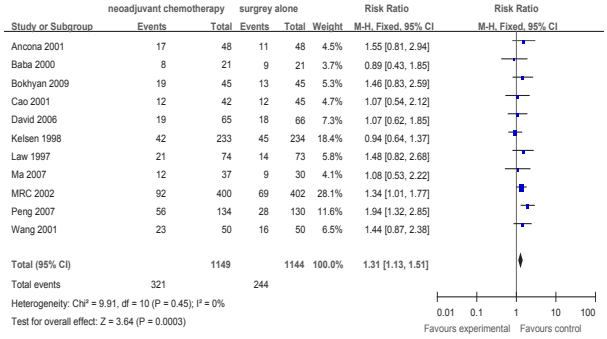

Figure 4. Five-year Survival Rate in Neoadjuvant Chemotherapy and Surgery Compared with Surgery Alone (Forest Plot)

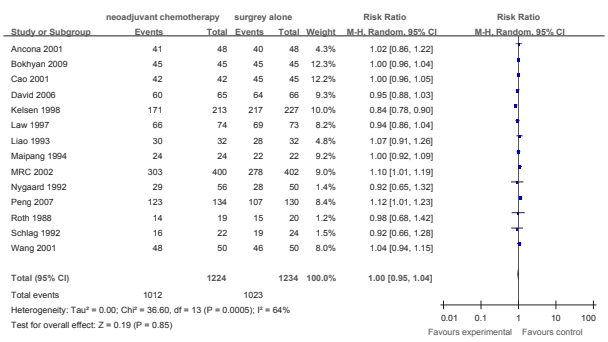

Figure 5. Overall Rate of Resection in Neoadjuvant Chemotherapy and Surgery Compared with Surgery Alone (Forest Plot)

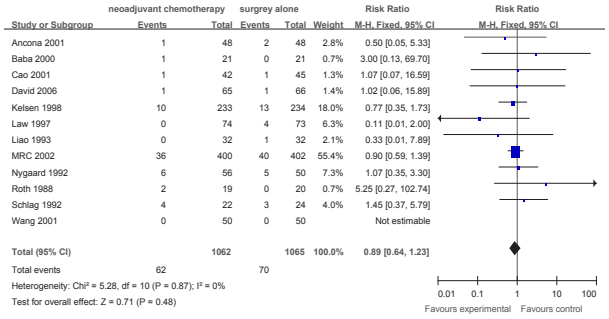

Figure 6. Operative Mortality in Neoadjuvant Chemotherapy and Surgery Compared with Surgery Alone (Forest Plot)

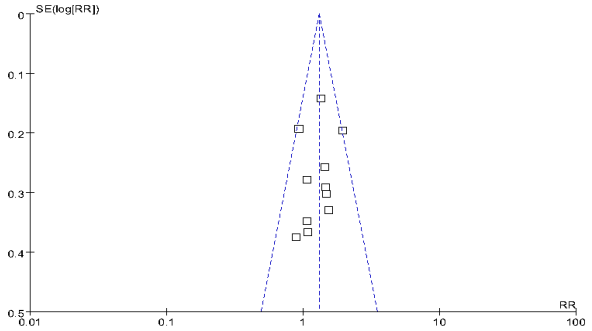

Figure 7. Five-Year Survival Rate in Neoadjuvant Chemotherapy and Surgery Compared with Surgery Alone (Funnel Plot)

survival ranging from 17% to 82.2% in the treatment group and from 30% to 86.7% in the control group. Risk ratio (95% CI; P value), expressed as neoadjuvant chemotherapy and surgery versus surgery alone, was 1.04(0.97, 1.11; P=0.30) for 1-year survival. Nonetheless, 3-year survival was higher in the treatment group than control group. The review of nine studies that investigated neoadjuvant chemotherapy and enrolled a total of 1,997 patients resulted in estimates of 3-year survival ranging from 9% to 62.9% in the treatment group and from 3% to 41% in the control group. Risk ratio (95% CI; P value), expressed as neoadjuvant chemotherapy and surgery versus surgery alone, was 1.29 (1.13, 1.47; P=0.0001) for 3-year survival. Same as above, 5-year survival was higher in the treatment group than control group. The review of eleven studies that investigated neoadjuvant chemotherapy and enrolled a total of 2,293 patients resulted in estimates of 5-year survival ranging from 13% to 46% in the treatment arm and from 6% to 32% in the control arm. Risk ratio (95% CI; P value), expressed as neoadjuvant chemotherapy and surgery versus surgery alone, was 1.31 (1.13, 1.51; P=0.0003) for 5-year survival.

Morbidity after surgery

The resection rate and operative mortality were similar for the treatment and control group (Figure 5 and 6). Risk ratio was 1.00 (95% CI: 0.95-1.04; P=0.85) for rate of resection, the review of fourteen studies that investigated neoadjuvant chemotherapy and enrolled a total of 2,458 patients resulted in estimates of resection rate ranging from 58% to 100% in the treatment group and from 69% to 100% in the control group. Analogously, operative mortality varied from 0% to 19% in treatment group (over average 5.9%) and from 0% to 10% in control group (over average 6.6%). Risk ratio was 0.89 (95% CI: 0.64-1.23; P=0.485) for operative mortality, a total of twelve studies including 2,127 patients.

Discussion

Our analyses are based on 16 randomized clinical trials studying the effect of neoadjuvant chemotherapy on patients with esophagus cancer. The total number of patients represented here is 2,594, of which 1,302 received preoperative treatment and 1,292 were treated with surgery alone. The meta-analysis indicated that patients treated by neoadjuvant chemotherapy had more survival benefit compared with patients treated by surgery alone, including 3-year survival and 5-year survival. The meta-analysis performed by Malthaner et al. (2003) including eleven randomised trials comprising 2,051 patients suggested 1 and 2 years the risk ratios showed no difference in overall survival, at 3 and 4 years there appeared to be a trend towards increased survival in the neoadjuvant chemotherapy patients, and total operation resection rate and pathologic complete resection rate did not differ on the two groups. Another meta-analysis performed by Urschel et al (2002) including 11 randomised trials and 1,976 patients demonstrated no advantage to neoadjuvant chemotherapy over surgery alone, survival estimates were available only at 1, 2 and 3 years, and local recurrence and distant metastasis rate did not differ too. The third meta-analysis performed by Kaklamanos et al. (2003) including seven trials and 1,683 patients of neoadjuvant chemotherapy versus surgery alone demonstrated improved 2-year survival of patients treated with neoadjuvant chemotherapy compared with

surgery alone. The absolute difference was 4.4% (95% CI 0.3% to 8.5%). Our meta-analysis shows that there was no evident difference in 1-year survival, the resection rate and operative mortality, but there was a statistically significant survival advantage at 3-year and 5-year survival of esophageal cancer patients with neoadjuvant chemotherapy comparing with surgery alone. The result of 1-year survival is the same as before, but 5-year survival was not studied in previous analyses because of the limit of sample size and short of follow-up time. The 5-year survival rate is an extremely important indicator to reflect the curative effect of malignant tumor, and can present the role of neoadjuvant chemotherapy in esophageal cancer patients. Compared with the previous studies, our study included sixteen randomized controlled trials with larger sample size, wider distribution range, especially including many Asian cases, filled with two large randomized controlled trials late follow-up results , namely the UK Medical Research Council (MRC) OE02 study and the US National Cancer Institute (NCI)-sponsored Intergroup trial 0113 (Kelsen et al., 2007; Allum et al., 2009), added to a new clinical randomized controlled trial (Bokhyan et al., 2009), and provided more efficacy evidence of neoadjuvant chemotherapy for esophageal cancer. This system analysis, using such detailed and true research data, is expected to produce more accurate results.

Neoadjuvant chemotherapy for resectable esophageal carcinoma can raise 3-year and 5-year survival rate of patients with esophageal carcinoma. This is consistent with the rationale that neoadjuvant chemotherapy is to downstage or downsize the primary tumour in order to ensure complete surgical resection, and to pre-emptively destroy any distant foci of micrometastatic disease. Among literatures that we selected to evaluate 3-year or 5-year survival rate, there is a pathologic diagnosis of AC only for 131 patients, so we separated them to do subgroup analysis, and the 5-year survival rate is also significantly different. For the treatment of esophageal cancer, we found that neoadjuvant chemotherapy have had positive curative effect for squamous cell carcinomas or adenocarcinoma. But Gebski et al (Gebski et al., 2007) thought neoadjuvant chemotherapy is effective only for adenocarcinoma, the view only coming from a randomized controlled trial, maybe questionable.

In our study, neoadjuvant chemotherapy for resectable esophageal carcinoma is usually a systemic therapy combining cisplatin with other chemotherapy drugs, cisplatin chemotherapy doses ranging from 40 to 120 mg/m^2, chemotherapy regimen ranging from 2 to 4 cycles, the surgery time after chemotherapy ranging from one to six weeks. This will affect neoadjuvant chemotherapy curative effect for esophageal cancer patients, potentially changing the result of randomized controlled trial, but we didn't make a concrete analysis. Zhu et al. (2008) believe that new BPF chemotherapy regimens can effectively increase the resection rate in middle-late esophageal cancer. Millar et al. (2005) and Van et al. (2007) reported new chemotherapy drug, for example gemcitabine and oxaliplatin that could further improve survival in patients with esophageal cancer. With the development of esophageal neoadjuvant chemotherapy scheme and drug, the curative effect of neoadjuvant chemotherapy will become more and more obvious in esophageal cancer patients.

A lot of studies indicated that 40%-75% of patients with resectable esophageal cancer diagnosed according to clinical examination or surgery had subclinical metastasis or tumor that had already invaded the adjacent organs or tissues (Katlic et al., 1990; Kelsen, 1997). Accurate tumor staging is crucial to the prognosis of esophageal cancer patients receiving surgical resection. Therefore, further measures should be taken to improve the accuracy of tumor stages. Nowadays, endoscopic ultrasound (EUS) is the most accurate method for staging esophageal cancer for T and N stage (Meyenberger and Fantin, 2000). Helical computed tomography still appears insensitive for the identification of T4 or metastatic involvement of celiac lymph node disease in esophageal cancer, but EUS with fine needle aspiration and FDG-PET [fluorine 18-labeled fluorodeoxyglucose (FDG) positron emission tomography (PET)] can make up for this shortcoming. As a result, we can accurately differentiate tumor stages from esophageal cancer patients before surgical resection. The 82 patients in RCTs (Law et al., 1997; Baba et al., 2000; Cunningham et al., 2006) included in this meta-analysis had metastasis of forane lymph nodes, and they belong to IV according to TNM staging. Using neoadjuvant chemotherapy before radical resection of esophageal cancer could also improve survival in these patients with esophageal cancer. We suggest that esophageal cancer patients with IV stage should not give up the chance to operate, and they will also benefit from neoadjuvant chemotherapy plus surgery.

The quality of these studies including 16 clinical randomized controlled trials is generally high, but there are four studies with low quality. These trials seldom provided details of the randomized techniques and allocation concealment. These may produce selection bias, measurement bias of the implementation and results, thereby affecting the results and argumentation intensity. Four studies did not undertake an intention-to-treat analysis, so there is no guarantee for a truly randomized purpose, and cannot reflect the actual effect for neoadjuvant chemotherapy in patients with esophageal cancer. It is easy to produce results bias. To publication bias, we adopt funnel plot analysis (Figure 7). All studies are roughly around symmetrical arrangement in the chart, and publication bias is not obvious, thus the affected quantity in the combined effect is little.

In our results analysis, we removed these experiments because the test method is not specifically blinded, to restart result analysis, but there was no difference in sensitivity analysis results about esophageal cancer over survival rate and operative mortality rate between the two results. This explains the stability of the original results. Our study including a piece of grey literature, we removed this literature data to analyze experimental result that is same as the original results, further explaining the stability of experimental results. This renew included studies with large sample size, wider distributed crowd, every part of the esophagus, various pathologic types, and more clinical cases including tumor TNM stage. It can be widely used in clinical research and therapy of esophageal cancer.

In conclusion, neoadjuvant chemotherapy for resectable esophageal carcinoma can improve the overall survival rate of patients with esophageal carcinoma, but it does not increase surgical risk and treatment related mortality. It is an effective therapy method of esophageal cancer.

Acknowledgements

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