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Abstract: Induction chemotherapy (ICT) is a controversial treatment for head and neck squamous cell carcinomas (HNSCC). Despite numerous randomized controlled trials (RCTs), a majority do not have enough statistical power alone to conclude ICT's treatment value among oral squamous carcinoma patients (OSCC) since many addressed HNSCC as one entity instead of by specific subtypes. By performing a systematic review and cumulative meta-analysis, we aim to determine the benefits of ICT in OSCC therapy. A literature search identified for RCTs comparing OSCC patients who received ICT against those without. Log-hazard ratio, and relative risk were used for comparison. Heterogeneity was determined using the I2 statistic package. The primary endpoint was overall survival (OS), followed by disease-free survival (DFS), locoregional recurrence (LRR) and distant metastasis (DM) as secondary endpoints. RESULTS: 27 randomized trials were included for analysis (n= 2872 patients). The shortest median follow-up was 15 months whereas the longest was 11.5 years. ICT does not improve OS (HR = 0.947, 95% CI 0.85-1.05, p= 0.318), DFS (RR= 1.05, 95% CI 0.92-1.21, p= 0.462) and DM (RR= 0.626, CI 95% 0.361-1.086, p= 0.096) compared to locoregional treatment alone. However, there was a significant improvement to LRR (RR= 0.778, 95% CI 0.622-0.972, p= 0.027). There is no evidence ICT improves survival outcomes for OSCC patients. However, ICT reduces locoregional recurrence of OSCC, which may need further verification.

Highlights:

- ICT provides no additional benefit to OS, DFS, and DM endpoints for OSCC survival
- LRR may be improved with the addition of ICT in OSCC treatment
- A cumulative meta-analysis is an effective tool to visualize and identify survival trends over time and should be considered for use in conjunction with the traditional meta-analysis format

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Induction Chemotherapy for Squamous Cell Carcinomas of the Oral Cavity: A Cumulative Meta-analysis

Abstract

Induction chemotherapy (ICT) is a controversial treatment for head and neck squamous cell carcinomas (HNSCC). Despite numerous randomized controlled trials (RCTs), a majority do not have enough statistical power alone to conclude ICT's treatment value among oral squamous carcinoma patients (OSCC) since many addressed HNSCC as one entity instead of by specific subtypes. By performing a systematic review and cumulative meta-analysis, we aim to determine the benefits of ICT in OSCC therapy. A literature search identified for RCTs comparing OSCC patients who received ICT against those without. Log-hazard ratio, and relative risk were used for comparison. Heterogeneity was determined using the I^2 statistic package. The primary endpoint was overall survival (OS), followed by disease-free survival (DFS), locoregional recurrence (LRR) and distant metastasis (DM) as secondary endpoints. RESULTS: 27 randomized trials were included for analysis (n= 2872 patients). The shortest median follow-up was 15 months whereas the longest was 11.5 years. ICT does not improve OS (HR = 0.947, 95% CI 0.85-1.05, p= 0.318), DFS (RR= 1.05, 95% CI 0.92-1.21, p= 0.462) and DM (RR= 0.626, CI 95% 0.361-1.086, p= 0.096) compared to locoregional treatment alone. However, there was a significant improvement to LRR (RR= 0.778, 95% CI 0.622-0.972, p= 0.027). There is no evidence ICT improves survival outcomes for OSCC patients. However, ICT reduces locoregional recurrence of OSCC, which may need further verification.

Key Words: oral cancers, mouth neoplasm, induction chemotherapy, adjuvant chemotherapy, meta-analysis, systematic review

INTRODUCTION

Squamous cell carcinomas of the oral cavity (OSCC) is the 10th most common malignancy worldwide[1]. The aggressive nature of advanced OSCC usually indicates a poor prognosis, requiring a multi-nodal treatment strategy of chemotherapy, surgery and radiotherapy. Despite advances in treatment options, locoregional recurrence (LRR) and distant metastasis (DM) rates remain high at around 30% and 25% respectively with minimal improvement to 5-year survival rates as they remain approximately at 50%[1,2]. While guidelines from the National Comprehensive Cancer Network recommend surgical excision followed by concurrent single–agent cisplatin chemo-radiotherapy in T3 or T4 lesions demonstrating adverse features of extrascapular spread and/or positive margins[3], the most optimal approach for managing advanced OSCC is still unclear.

The introduction of induction chemotherapy (ICT) showed promise for improving survival in advanced head and neck cancers from the high response rates to ICT demonstrated by trials in the 1990s[4,5]. It was hypothesized ICT would increase overall survival (OS), disease-free survival (DFS) and progression free survival by improving distant control[6]. Shrinking tumor volume prior to definitive treatment with ICT could enhance radiotherapy feasibility and tolerability whilst reducing the disfiguring effects of surgery and radiation[6].

Multiple randomized trials (RCT) have evaluated OSCC response to ICT. Integration of data from independent studies is performed through meta-analysis where data from individual trials are pooled simultaneously to provide a summary for evidence-based care. Despite its perceived advantages, multiple meta-analyses did not find significant improvements to OS when ICT was added to treatment[7-12]. However, interest in ICT has been renewed by the improved efficacy to survival using a taxane regimen, and improved loco-regional control by concomitant chemo-radiotherapy (CCRT)[10].

Complementary to the 'traditional' method of meta-analysis, the 'cumulative' meta-analysis approach creates repeated poolings as each new study is added[13]. The overall analysis becomes a continuum of accumulating data, offering a visual depiction of trends and when significance, or if any significance of an endpoint had been achieved over the years for safety and ethical monitoring.

Due to the enduring uncertainty of ICT's role and the continued publications of RCTs investigating ICT in OSCC treatment, this paper aims to summarize the effect of ICT in OSCC treatment by performing an updated systematic review and cumulative meta-analysis from the earliest to most recent published studies.

METHODS AND MATERIALS:

This systematic review followed the Cochrane Collaboration Handbook of Interventions Systematic Reviews and the PRISMA statement checklist and flowchart. Cumulative meta-analysis was performed where studies were added in order of date to summarize the evaluated endpoints.

Search Methods

A sensitive search protocol was developed to retrieve RCTs published in peer-reviewed journals from 1980 to March 2016 using MEDLINE via Pubmed (1970–March 2016), EMBASE via Ovid (1980–March 2016), The Cochrane Central Register of Controlled Trials (CENTRAL) (1970- March 2016), and Web of Science (1956- 2016).

Search queries included MeSH terms for *"Head and Neck Neoplasms", "mouth neoplasms", "gingival neoplasms", "palatal neoplasms", "tongue neoplasms", "lip neoplasms", "mouth squamous cell carcinoma", "induction chemotherapy", "neoadjuvant therapy"*, and *"anti-neoplastic drugs"* in combination with free text phrases such as *"primary chemotherapy", "initial chemotherapy"* and *"oral cavity"*. The syntax input was revised for each database. The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity maximizing version (revision): PubMed Format was applied for the MEDLINE search whilst the EMBASE search strategy was combined with the Cochrane Oral Health Groups' RCT filter to maximize retrieving clinical trial articles.

To identify for any current ongoing or missed trials from the search queries, ClinicalTrials.gov and manual searches of reference lists from relevant systematic reviews and meta-analyses, and abstract conferences were screened. No language restrictions were imposed.

Study Selection Criteria

Studies included had the following characteristics:

1. **Participants:** Patients diagnosed only with previously untreated primary OSCC with or without nodal involvement or metastasis.
2. **Types of interventions:** Patients randomized to either receive or not receive ICT with their definitive treatment. All types of chemotherapeutic agents and routes of administration were included. Definitive treatment describes treatment best suited for the patient at the time after all other choices have been considered to eliminate the disease. This could be surgery alone, radiotherapy alone, concurrent chemo-radiotherapy alone, or any of the three in combination.
3. **Outcomes:** Primary outcome is to assess whether ICT improves OS. Secondary outcomes will evaluate DFS, LRR, and DM. If a study only provided figures on secondary outcomes, it was still included only into relevant sections of this analysis.
4. **Studies:** RCTs

Studies were excluded if:

1. Trial was not a RCT
2. Patients had received prior intervention
3. Secondary or recurrent OSCC
4. Other histological types of oral cancer
5. ICT was not compared to locoregional treatment alone
6. Radiotherapy was included in the induction protocol

Study selection and data extraction

Two authors independently reviewed for studies that met the eligibility criteria. An initial screen was performed through reading the title/abstract. If the title/abstract was unclear whether a study fulfilled the inclusion criteria, a full article was obtained. Characteristics of excluded studies were documented and counterchecked by each author. Any disagreements or inconsistencies were resolved amongst group discussion.

The corresponding author was contacted for the availability of individual data on OSCC patients in trials which included general head and neck cancer patients, or if clarifications were required. Studies comparing multiple ICT regiments against one control had the interventions combined into a large cohort to avoid inflating sample size data from double-counting the control groups.

Assessment of Bias

Following the Cochrane Collaboration's Tool (Cochrane Handbook version 5.1.0), a risk of bias assessment was conducted from the following domains: sequence generation, allocation concealment, complete outcome data, selective outcome reporting and other potential bias. Outcome data was considered complete if less than 20% of patients randomized were excluded from the trial data with appropriate reasoning described. Blinding of participants, personnel and outcome assessors was not measured due to the difficulty and unethicality of performing a double-blinded trial under such circumstances. The absence of blinding should not affect OS statistics but may influence DFS, LRR and DM reporting. If it was difficult to interpret bias risk from the published article, the study authors were contacted for clarification. An "unclear risk of bias" would be concluded if the author could not be reached and if the available information was insufficient for a proper bias assessment. The Beggs and Egger's

regression test would also be used for OS, and for any endpoints that achieved significance as a supplement to compensate for studies categorized with an “unclear risk” from the Cochrane risk of bias assessment tool.

Data analysis

OS was expressed as log hazard ratios (HR). If HR were not reported yet other statistics were available (observed events, expected events, variance), HR, standard error and 95% confidence intervals were calculated using various formulas provided by Hackshaw 2009[14] and the GraphPad Software Statistics Guide[15].

Other dichotomous outcomes including DRS, LRR and DM were expressed as risk ratios (RR) together with 95% confidence intervals based on the availability of data from these endpoints. A p value of < 0.05 indicated a significant result for all outcomes measured.

Data analysis was performed using STAT/SE ®, version 11 [Stat Crop., College Station, TX, USA]. Heterogeneity was evaluated based on the I^2 statistic percentage or p-value ($p< 0.05$ indicates significant heterogeneity) to evaluate whether variability in results were attributed to heterogeneity rather than by sampling error.

If heterogeneity was not significant, the Fixed-Effects Model of Mantel and Hanszel with the assumption all trials shared a common effect size would be used.

RESULTS

Selection of trials

From the database query, 2021 reports were organized into a bibliographic database (Figure 1). After removing duplicate articles, 1876 articles were excluded based on assessing the title and abstract. The remaining 145 texts were appraised by full-text. OSCC data published by the MACH-NC Collaborative Group from a meta-analysis performed by Blanchard et al[7] were also included.

Description of included studies and data analysis

31 RCTs conducted from 1974 to 2015 were initially included. After systematic review, four trials were excluded. One study[16] had high overall bias risk, one did not state whether randomization was performed[17] and two trials from Blanchard's[7] meta-analysis had no abstract to verify the study data since they were unpublished trials. 22 RCTs included were from the published meta-analysis by the MACH-NC Collaborative Group[7]. Five trials were further identified from the literature search and had data extracted directly from the article. 27 trials were included in the meta-analysis.

Nine studies originated from establishments in France, six from the United States of America, three from Italy, and one each from Australia, Argentina, Brazil, Sweden, Germany Japan, China, India, and Thailand. The earliest trial started recruitment in 1965[18] whilst the most recent completed recruitment in 2008[19]. 1484 participants were pooled in the ICT group whereas the control group had 1388 patients for the meta-analysis. 14 RCTs compared the addition of ICT to surgery with/without radiotherapy[20-33], 10 against radiotherapy alone[18,25,26,33-39], one for CCRT[19], and one study[40] did not specify the standard therapy given. Regarding ICT regimen, twelve trials evaluated a Cisplatin-5-Fluorouracil containing protocol[20,21,25,26,32,36-38,40-42], eight used a Cisplatin-Bleomycin containing protocol[22,24,28,33,34,36,38,39], two administered Bleomycin and

Vinicristine[23,27], one included Cisplatin, Bleomycin and 5-Fluorouracil (5-FU)[38] and four had other ICT combinations[18,29-31] where one trial used Cisplatin, 5-FU and Doxetaxel (TPF)[30]. All trials had OS figures excluding one[23]. Five trials reported data for DFS[19,22,27,30,41], five for LRR[19,23,27,30,41], and four for DM analysis[19,27,30,41]. OS and DFS were reported from Zhong et al's 2013 paper[44] instead of the most recent 2015 article[30] since the 2015 paper did not provide enough data for OS analysis. The shortest follow-up was at a median of 15 months[19], whereas the longest follow-up period was a median of 11.5 years[41]. Further descriptions of the trials included are available in the supplementary data, Table 1.

Risk of Bias assessment

Using the Cochrane risk of bias assessment tool (Figure 2), 7 out of 27 RCTs[18,22,26,27,29,30,41] were considered low risk of bias. However many studies had insufficient descriptions on how allocations into treatment groups during randomization was performed. 9 Trials[20,21,23,25,32,37,39,42,43] had large proportions (at least three out of the five domains) of the risk assessment criteria categorized as unclear since insufficient information was provided for an analysis to be made.

One trial[16] had a high risk for bias and subsequently excluded from the analysis. The symmetrical pattern in the funnel plot derived from the Begg's test and calculations from the Egger's test, suggested no evidence of publication bias (see supplementary data figure 1, 2, 3, 4).

Overall Survival

ICT provided no advantage compared to definitive treatment alone for OS (HR= 0.947, 95% CI 0.85-1.05, p= 0.318). Heterogeneity between these groups were not significant (I^2: 32.3%, p= 0.059). The cumulative meta-analysis plot shows the addition of ICT to locoregional treatment favours neither ICT nor definitive treatment for OS (Figure 3).

Disease Free Survival

There was no significant difference in DFS between patients treated with ICT and patients who only received definitive treatment (RR= 1.05, 95% CI 0.92-1.21, p= 0.462) (Figure 4). Heterogeneity between trials groups were not significant (I^2 =0%, p= 0.556)

Loco-regional recurrence

There was a significant reduction in LRR (RR= 0.778, 95% CI 0.622-0.972, p= 0.027) amongst patients who treated with ICT compared those who only received definitive therapy (Figure 5). Heterogeneity in these trials was not significant (I^2= 11.3%, p=0.342). When data from Luboinski et al[23] was excluded in a sensitivity analysis, results were not significant (RR= 0.842, 95% CI 0.669-1.060, p= 0.143) and remained non-significant for heterogeneity (I^2= 0%, p= 0.868) (Figure 6).

Distant metastasis

DM[19,27,30,41] reduction was not significant between patients in the ICT and control group (RR= 0.626, CI 95% 0.361-1.086, p= 0.096) where heterogeneity between trials was not significant (I^2 = 0%, p= 0.720) (Figure 7).

Discussion

Our paper is the first to include 27 RCTs over a 40-year period, investigating ICT on survival endpoints in a cumulative meta-analysis format. The addition of ICT does not offer an improved OS for OSCC patients. There was also no benefit to DFS, or DM using ICT, with the exception of a significant decrease in LRR for patients receiving ICT.

There continues to be a lack of evidence supporting ICT for routine management in advanced OSCC patients. Previous meta-analyses by Blanchard et al[7] and Marta et al[9] found no advantage for OS in patients who had ICT added to their treatment. Although we did not investigate OS based on clinical response to ICT, three studies[24,30,41] highlighted a correlation between a high clinical response to ICT and improved OS. Whilst it is difficult to ascertain whether the sensitivity was all attributed to chemotherapy, certain HNSCCs such as HPV-positive oropharyngeal cancers are associated with a better therapeutic response to chemo-radiation[45]. This raises the possibility a select group of OSCCs, namely HPV-positive, are more sensitive to ICT. While the role of HPV regarding treatment response and prognosis of OSCC is still controversial and inconclusive, a recent retrospective study demonstrated an improved 2-year OS amongst HPV-positive OSCC patients compared to HPV-negative patients[46]. Therefore, clinical response and HPV status may be important factors contributing towards the success of ICT treatment in OSCC patients. Future studies should investigate these subgroup of patients in correlation with OS to understand whether ICT can truly play a role in OSCC treatment.

The significance observed in LRR reduction for ICT patients may need to be interpreted with caution. When Luboinski et al's [23] trial was excluded in the sensitivity analysis, the effect of ICT on LRR failed to achieve significance (p= 0.143). It is important to note

Luboinski et al[23] only reported preliminary results where the trial also had multiple domains categorized as 'unclear' for bias risk. Varying prognostic factors amongst the patient pools could have influenced the sensitivity analysis, and accounted for the unchanged OS despite LRR reduction between the experimental and control cohorts. Luboinski et al[23] had more patients with T2 disease compared to other studies which had a greater number of patients with T3 and T4 disease. Meanwhile, Richard et al[27] had more patients with T4 disease assigned to the ICT cohort whilst Bossi et al[41] reported a higher incidence of patient death from unknown causes or treatment toxicity.

Despite an observed reduction in DM for patients who received ICT, our results only approached but never achieved significance (Figure 9). Yet, since Ma et al[8] demonstrated a significant reduction for DM in HNSCC patients receiving TPF, future studies should further investigate this endpoint for a more conclusive result as our analysis only included 4 trials.

In our meta-analysis, a taxane regimen did not seem to benefit OS considering a shift favoring LRT alone from the forest plot (Figure 3) was observed when a study[30] with TPF was included. Meta-analyses by Zhang et al[12] and Kim et al[47] showed ICT using TPF did not improve OS for HNCC patients, with adverse events cited as a possible risk for increased morbidity and mortality[12,47]. However, it is too soon to discredit TPF, considering we only included one trial. Kim et al found a significant improvement in OS and PFS for non-oropharyngeal head and neck cancer patients who had received TPF treatment[47]. Given oral cancer was the second most prevalent HNSCC subtype included in 3 of the 6 studies within Kim et al's meta-analysis, perhaps ICT using TPF

may provide a breakthrough for OSCC survival. More studies are required to conclude whether TPF has a future role for increasing OSCC survival rates.

A cumulative meta-analysis is frequently criticized for potentially replicating and amplifying biases. Yet, a cumulative and a conventional meta-analysis will present identical results since they are using the same metrics and statistical model. Hence, heterogeneity and the quality of studies will affect both types of analysis equally. A cumulative meta-analysis is reliable for presenting evidence from multiple trials conducted over an extended period of time and should be considered in use with a conventional meta-analyses. As demonstrated in our study, it can aid identifying when and if an intervention ever reaches significance whilst summarizing trends (or the lack of). To tackle concerns about incorporating bias and poor quality studies that would skew the analysis outcomes, systematic reviews should be carried out in conjunction to minimize these risks.

Conclusion

ICT has never provided an improvement to OS for OSCC patients, which can be effectively visualized through a cumulative meta-analysis approach. Although our analysis is the first to demonstrate a statistically significant reduction in LRR amongst patients who received ICT, indicating ICT is possibly effective in managing microscopic disease, these results should also be interpreted with caution.

Figure Legends

Figure 1: A Flow Chart of Literature Search Methods

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Figure 1 - literature search
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Figure 1: A flow chart of literature search methods

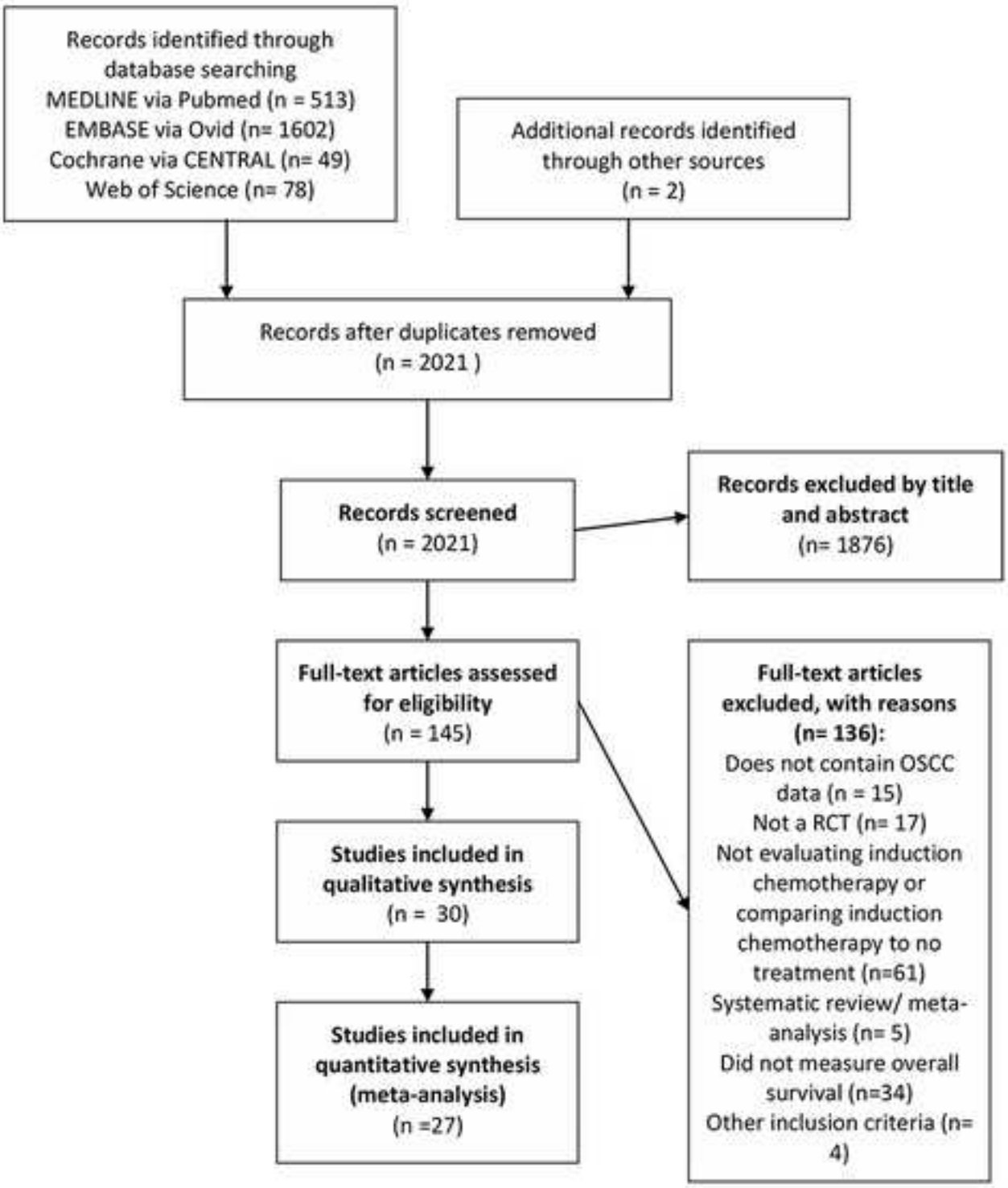

Figure 2 -risk of bias assessment
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Figure 2: Quality assessment of studies gathered from the literature search

Figure 3- Overall survival
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Figure 2: Overall Survival between induction chemotherapy and Locoregional treatment compared to locoregional treatment alone (a) standard meta-analysis (b) cumulative meta-analysis

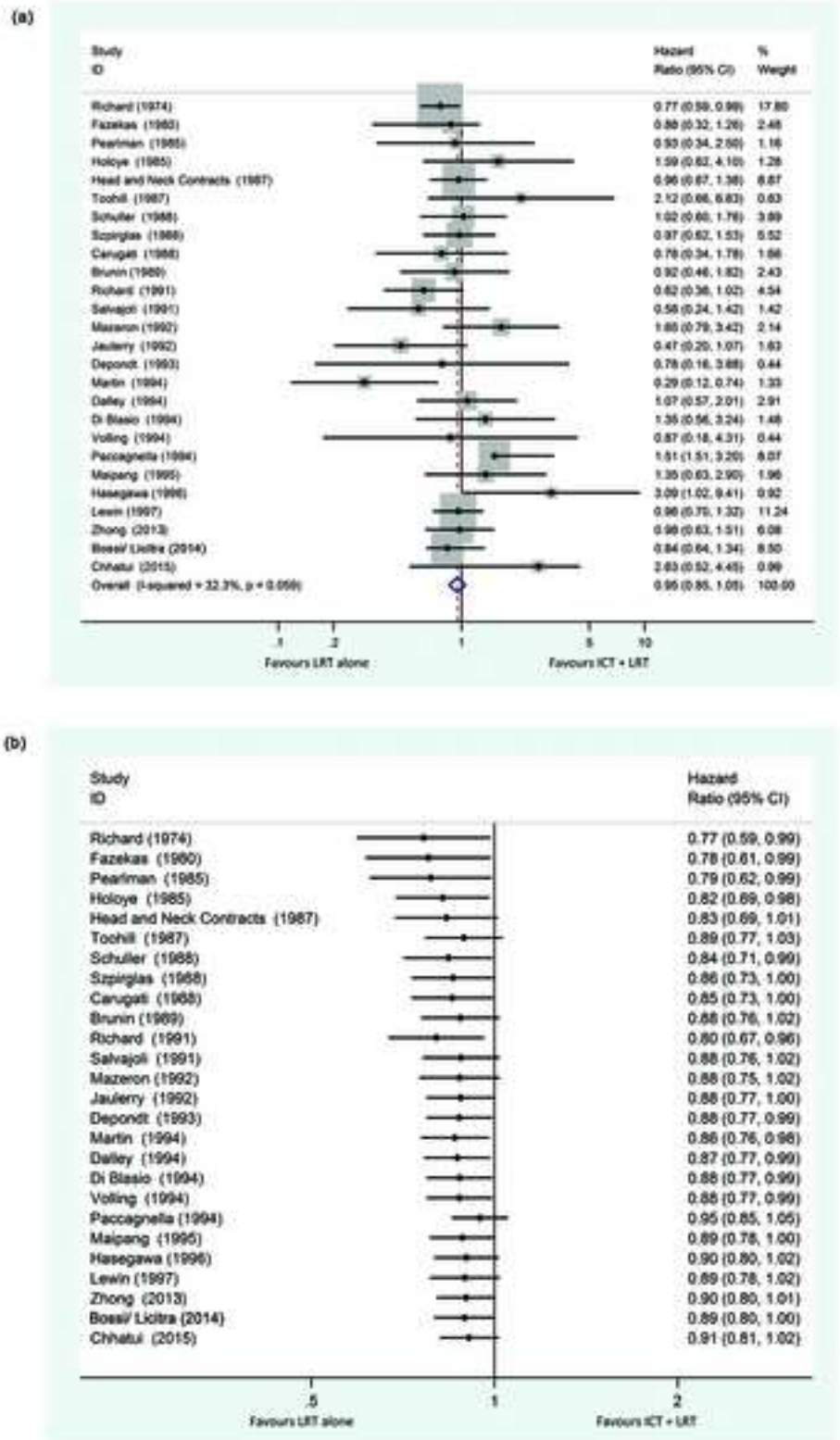

Figure 4 -Disease free survival
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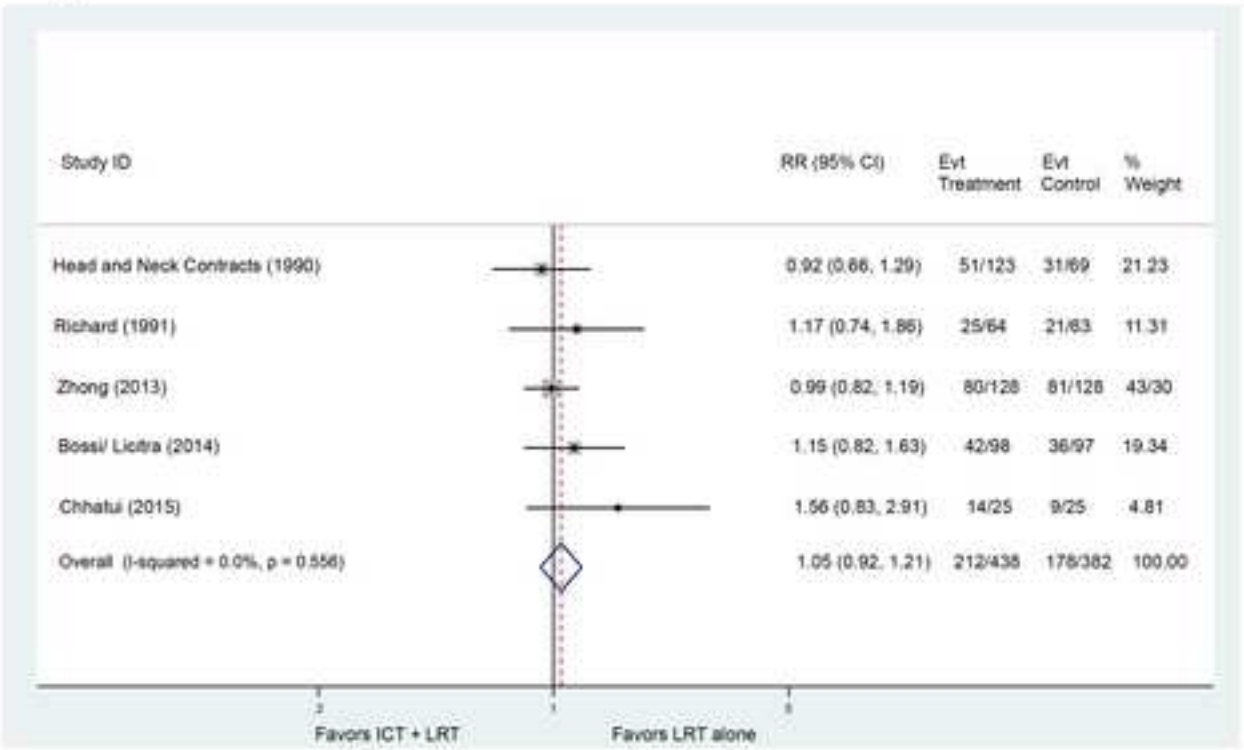
Figure 4: Disease Free Survival among OSCC patients recieving induction chemotherapy and locoregional treatment versus locoregional treatment alone (a) standard meta-analysis (b) cumulative meta-analysis

(a)



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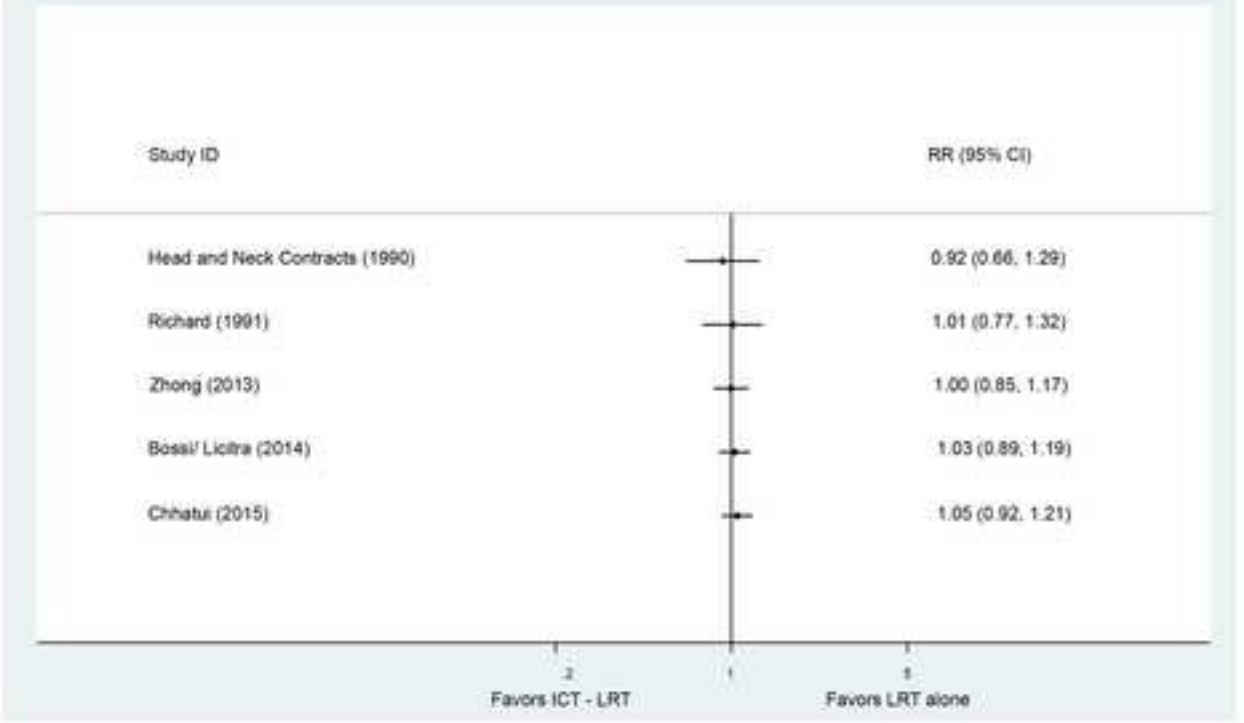

Figure 5- LRO

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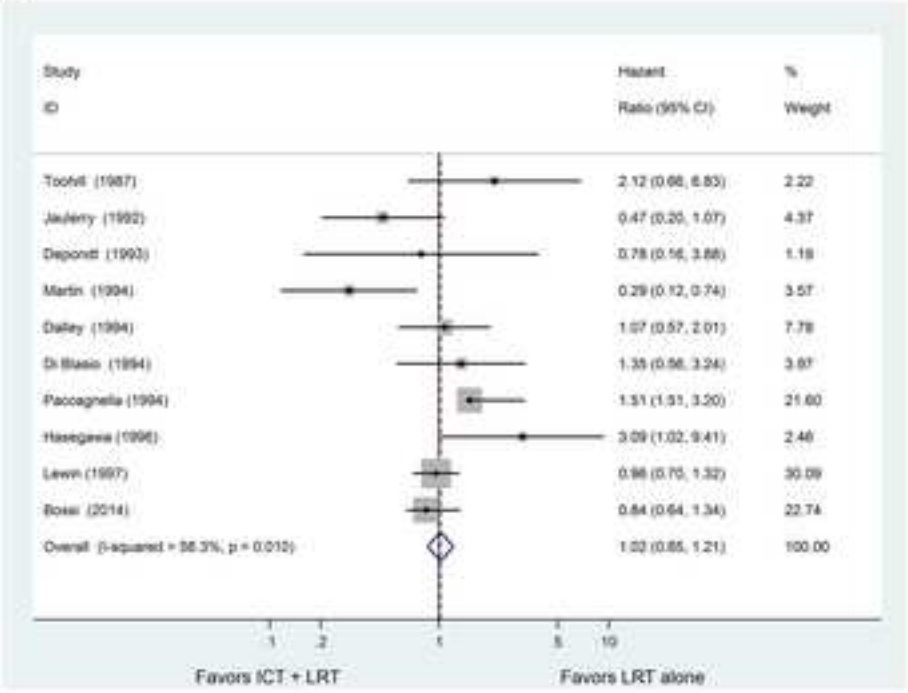
Figure 4: Subset analysis of cisplatin - 5FU containing induction chemotherapy protocol in overall survival amongst patients recieving induction chemotherapy and locoregional treatment compared to locoregional treatment alone (a) standard meta-analysis (b) cumulative meta-analysis

(a)



(b)

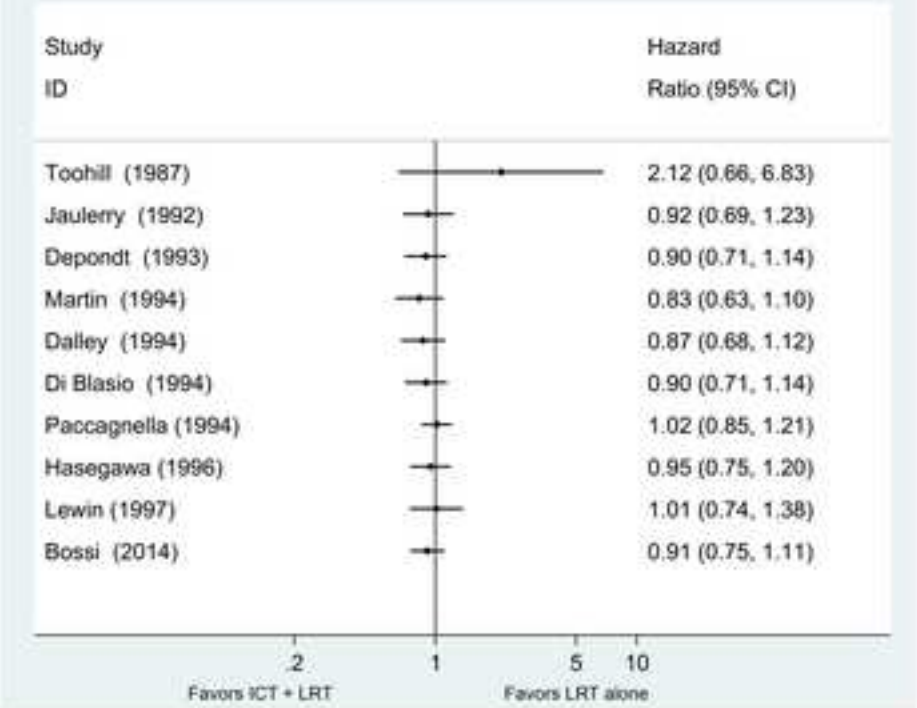


Figure 6- LRO sensitivity analysis
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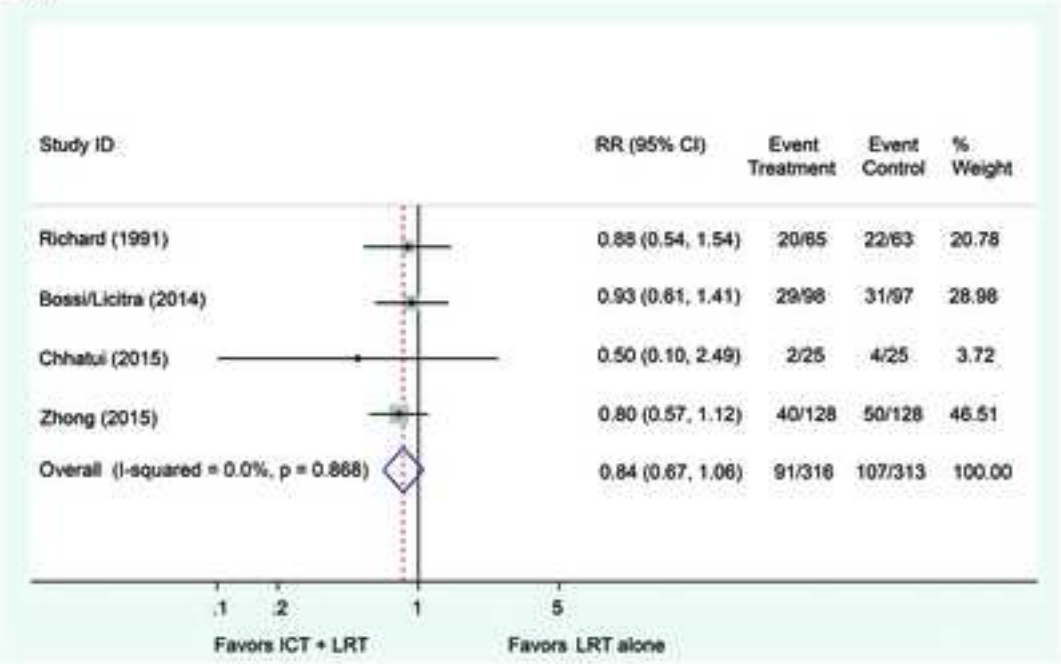
Figure 8: Sensitivity analysis of locoregional recurrence amongst patients recieving ICT and locoregional treatment compared to locoregional treatment alone (a) standard meta-analysis (b) cumulative meta-analysis

(a)



(b)

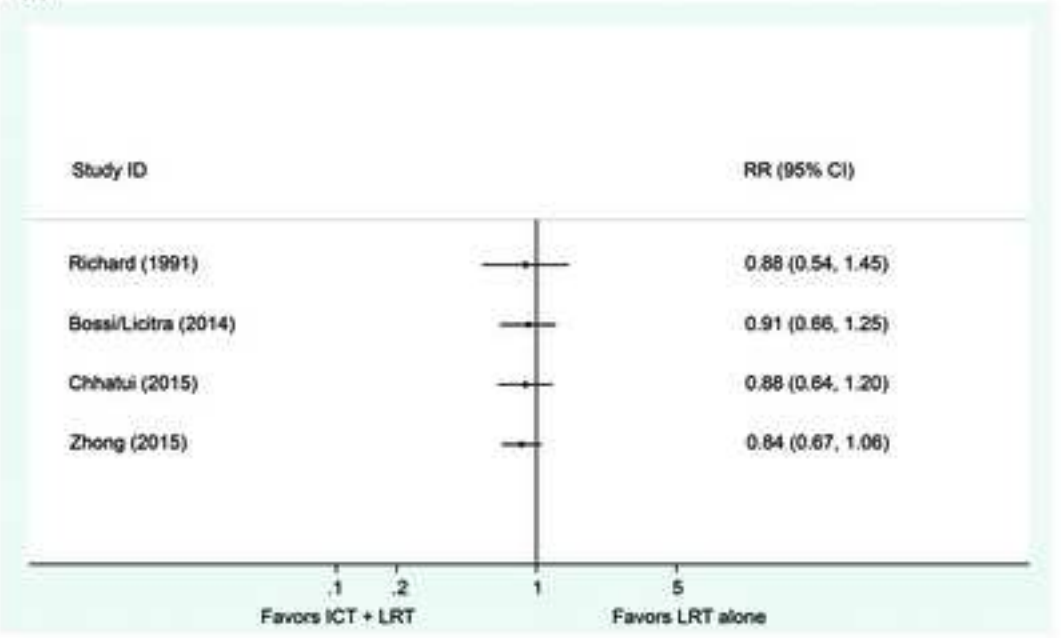


Figure 7- DFS
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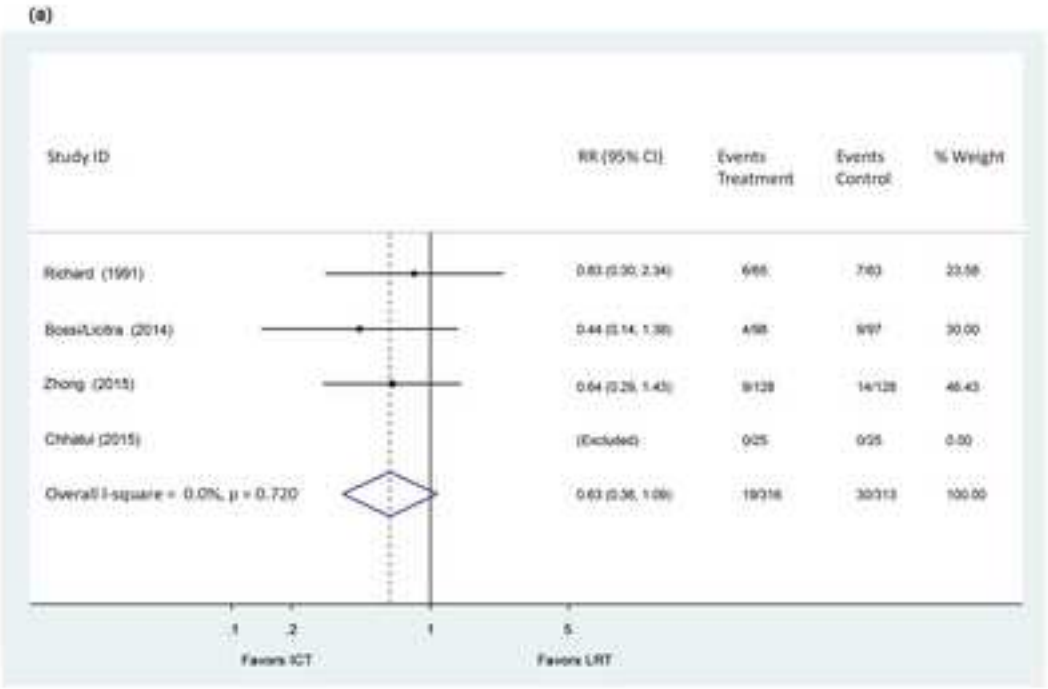
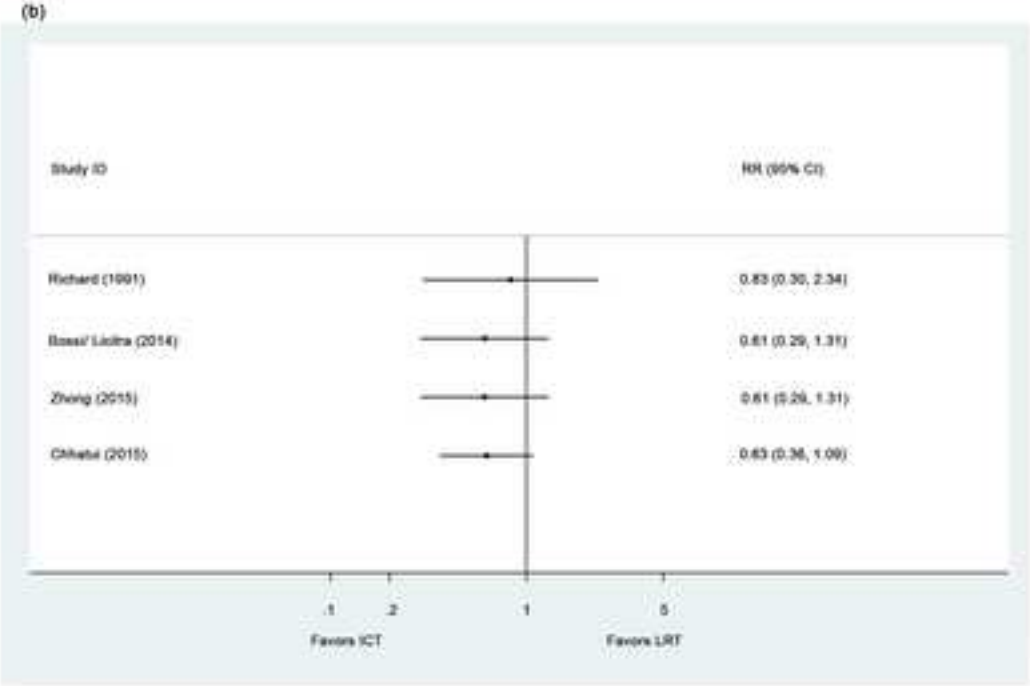
Figure 7 : Distant metastasis amongst OSCC patients who recieved Induction chemotherapy and locoregional treatment compared to locoregional treatment alone
(a) standard meta-analysis (b) cumulative meta-analysis





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