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Cisplatin-based chemoradiotherapy *versus* cetuximab-based bioradiotherapy for p16-positive oropharyngeal cancer: An updated meta-analysis including trials RTOG and De-ESCALaTE

Running title: Cisplatin CRT *vs*. cetuximab BRT for p16+ OPC

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Abstract

Purpose: Human papilloma virus (HPV) associated oropharyngeal cancer (OPC) is a special entity among head and neck squamous cell carcinomas (HNSCCs). Given its favourable prognosis, one of the de-escalating strategies in the treatment of OPC includes the introduction of cetuximab (C225) instead of cisplatin (CDDP) in conjuction with radiotherapy. An updated meta-analysis of published studies has been performed, which directly compared the efficacy of CDDP *vs.* C225 given concurrently with radiotherapy as definitive treatment of p16-positive OPC.

Methods: A systematic literature search was performed for studies published between 2006 and 2018. A total of 1490 citations were obtained and 8 studies met inclusion criteria, with a total of 1665 patients.

Results: The data from 7 studies were available for the analysis of 2-year overall survival. Calculated pooled OR for CDDP based chemoradiotherapy *vs.* C225 based bioradiotherapy, was 0.45 ($P<0.0001$). The data from 8 studies were available for the analysis of 2-year locoregional recurrence (LRR). Calculated pooled OR for CDDP based chemoradiotherapy *vs.* C225 based bioradiotherapy, was 0.35 ($P<0.0001$). Patients receiving CDDP with irradiation had 2.2 and 2.9-fold decreased risk for death from any cause and LRR, respectively.

Conclusions: For patients with HPV-positive OPC, radiotherapy plus C225 showed inferior OS and higher LRR rates compared with radiotherapy plus CDDP. CDDP-based chemoradiotherapy should remain standard of definitive treatment of p16-positive OPC.

Key words: oropharyngeal cancer, human papilloma virus, cisplatin, cetuximab, survival, recurrence

Introduction

The sixth most common cancer worldwide is head and neck squamous cell carcinoma (HNSCC) [1]. It is associated with high morbidity and mortality rates and represents a challenging subsite of cancer to treat, while maintaining the function of the vital healthy structures. Multiple phase III randomized clinical trials (RCT) have demonstrated that cisplatin (CDDP) given at 100 mg/m2 every 3 weeks concurrently with radiotherapy (RT) improves locoregional control (LRC) and overall survival (OS) compared to radiotherapy alone for non-metastatic, locally advanced head and neck squamous cell carcinoma (LA HNSCC) [2, 3]. Similarly to CDDP, in a phase III RCT (IMCL-9815), epidermal growth factor receptor (EGFR) inhibitor cetuximab (C225) demonstrated a beneficial effect regarding OS and LRC given concurrently with RT in patients with LA HNSCC compared to RT alone, without significantly worsening common acute radiation toxicity such as mucositis, dysphagia, or pain [4]. Subgroup analysis showed, that the effect was the most pronounced among oropharyngeal cancer (OPC) patients receiving altered fractionated RT with the consistence of this finding in the re-analysis of the trial published in 2010 [5]. These favorable outcomes have led the medical community to examine de-escalation treatment opportunities in this specific population. One of the most promising strategies is replacement of CDDP with C225. Although human papilloma virus (HPV) status has been established as a positive and favorable prognostic factor in OPC [6], with p16 positivity as surrogate marker of its viral aetiology, the utilization and benefit *vs.* risk ratio of bioradiotherapy compared to chemoradiotherapy remains unknown. Recently, two phase III RCTs (RTOG 1016, De-ESCALaTE), addressing direct comparison of CDDP-based chemoradiotherapy and C225-based bioradiotherapy in OPC patients with positive HPV status, demonstrated beneficial effect of the CDDP over C225 in terms of both overall survival (OS) and recurrence (locoregional relapse and distant failure) rates [7, 8]. Similarily to the latter results, we have

reported a meta-analysis in which patients receiving CDDP with irradiation had a 2.9 and 4-fold decreased risk for death from any cause and locoregional recurrence (LRR), respectively [9].

The aim of this study was to perform an updated meta-analysis of the studies, with inclusion of recently published RCTs (RTOG 1016 and De-ESCALaTE) which directly compared the efficacy of CDDP *vs.* C225 given concurrently with RT as definitive treatment of p16-positive, non-metastatic and locally advanced/unresectable OPC in order to guide treatment decision-making in this subgroup of patients.

Methods

Data collection

Systematic literature search has been done using the MEDLINE, EMBASE, PubMed, ScienceDirect, Scopus databases and Web of Science, for all studies published between March 2006 (month and year of regulatory approval of C225 by Food and Drug Administration (FDA) in the treatment of LA HNSCC and December 2018. The literature search process was conducted by using the key words cisplatin, cetuximab, head and neck cancer, HPV, p16, and OPC.

Selection criteria

Studies meeting inclusion criteria satisfied the following criteria:(1) pathologically proven OPC, (2) non-metastatic, locally advanced/unresectable disease, (3) p16-positivity determined by either immunohistochemisty (IHC) or in-situ hybridization (ISH), (4) prospective or retrospective research directly comparing outcome of patients treated with definitive CDDP +RT *vs.* C225 + RT, (5) conventionally accepted RT schedules, (6) studies which included at least 15 patients. Studies were excluded if (1) no data on OS and/or LRR at 2-year was reported/available, (2) non-CDDP + RT was applied (3) induction chemotherapy was administered, (4) oncologic surgery any kind prior to definitive management. Surgery after definitive treatment was allowed. A flow-chart diagram of the study is presented in **Figure 1**.

Data extraction

Two independent reviewers (the first and second authors) extracted the data from all of the included trials. Any disagreements or differences in the data extraction between the 2 authors

were resolved through consensus after rechecking the source data and consultations with additional investigators (., Z.R., S.D., I.L.).

The completed database contained the following data: name of the first author, year of publication, type of study, treatment details, number of patients in each group, and the 2-year OS and LRR rates per arm.

Statistical analysis

Data (events) were derived directly from each selected article or extracted from survival curves using Digitizelt - Plot Digitizer Software, if not available in text. This graphic digitizer has been proven to be a reliable tool for meta-analysis and cost-effectiveness analyses reporting time-to-event data [10]. In cases in which no survival curves and data with respect to OS or LRR were available, the corresponding authors were contacted.

Primary endpoints assessed by this meta-analysis were 2-year OS and 2-year LRR.

Statistical heterogeneity was assessed using the Cochrane Q test and I^2 statistic. Statistically significant heterogeneity was considered present at $P<0.10$ and $I^2>50\%$. When homogeneity was minimal ($P\geq0.10$, $I^2\leq 50\%$), a fixed-effects model was applied for meta-analysis of disease outcome (OS and LRR); otherwise, a random effects model was used. Egger's test was used to estimate potential publication bias. A pooled odds ratio (OR) was reported with 95% confidence interval (CI). Analyses were conducted using statistical software Stats Direct version 3.0.165 (Stats Direct Ltd., Altrincham, United Kingdom).

Results

A total of 1490 citations were obtained from the electronic search. Final analysis included eight studies with a total of 1665 patients (range 18 - 805). Studies were selected after reading titles and abstracts, followed by a review of potentially relevant articles (**Figure 1**). Among the included studies, 5 studies were retrospective ones and three studies (one was secondary analysis of phase II study) had prospective design [7,8,11-16]. The study characteristics are listed in the **Table 1**.

2-year OS

The analysis of pooled studies showed no significant heterogeneity (I^2=46.1%, Cochran Q=11.13, *P=0.08*) without publication bias (Egger: bias = -0.73, *P=0.48*) (**Figure 2**). Therefore, the fixed effect model was used. The data from 7 studies were available for the analysis of 2-year OS **(Figure 3)**. Analysis included 885 patients in the CDDP based chemoradiotherapy group and 680 patients in the C225 based bioradiotherapy group., Calculated pooled OR for CDDP based chemoradiotherapy *vs.* C225 based bioradiotherapy was 0.45 (95% CI, 0.31-0.65; *P<0.0001*).

2-year LRR

The analysis of pooled studies showed no significant heterogeneity (I^2=31.4%, Cochran Q=10.20, *P=0.18*) without publication bias (Egger: bias = -0.07, *P=0.94*) (**Figure 4**). Therefore, the fixed effect model was used. The data from 8 studies were available for the analysis of 2-year LRR **(Figure 5)**. Analysis included 954 patients in the CDDP based chemoradiotherapy group and 711 patients in the C225 based bioradiotherapy group. Calculated pooled OR CDDP based chemoradiotherapy vs. C225 based bioradiotherapy, was 0.35 (95% CI, 0.25-0.49; *P<0.0001*).

Discussion

In the past, extensive surgical resection of the primary tumour and regional lymph nodes was the standard of care for LA HNSCC worldwide. However, the introduction of organ-preserving strategies in the form of definitive radiotherapy or chemoradiotherapy has led to clinical investigation which proved that these regimens are associated with similar OS rates compared to surgery [17]. Additionally, numerous trials comparing chemoradiotherapy to radiotherapy alone proved the superiority of concurrent treatment which eventually culminated in meta-analysis demonstrating an absolute survival advantage of 6.5% at 5-years with concurrent chemoradiotherapy compared to irradiation alone [18]. Therefore, for the last two decades, definitive platinum-based (chemo)radiotherapy has become the cornerstone of treatment for patients with LA HNSCC. However, one should bear in mind that the addition of platinum-based chemotherapy to RT increases acute and late toxicity of the treatment with the latter one having major negative implications for the quality of life of the cancer survivors [19, 20].

Bonner et al. published their results in a randomized trial comparing concurrent C225 and RT versus RT alone in LA HNSCC and found that C225 improved both LRC and OS [4]. C225 is a monoclonal antibody directed at the epidermal growth factor receptor (EGFR), which is often overexpressed in LA HNSCC. This has led to the inclusion of C225 with RT as a definitive treatment option for LA HNSCC in NCCN guidelines as category 1 [21]. Furthermore, a study follow-up with 5-year results, continued to demonstrate a difference of 9.2% benefit in survival within the C225 cohort [5]. However, evidence of the direct comparison of these two agents (CDDP *vs.* C225) were scarce [22-26], until recently published RCTs data suggesting significant advantage of CDDP over C225 in terms of both recurrence rates and final outcome in cohort with HPV positive OPC [7, 8].

A special entity among HNSCC is represented by HPV-associated OPC. In numerous studies, HPV positivity was associated with improved prognosis for patients with OPC compared with patients with similar stage HPV-negative tumours [27-29]. Given its favorable prognosis, there has been a significant interest in the introduction of de-escalating strategies in treatment of this unique tumor subsite.

Among these ‘’less toxic’’ strategies, the replacement of the CDDP with C225, seemed to offer a possibly safer treatment option without compromising final outcome in HPV-driven OPC. Recently, after median follow up of 4.5 years, Gillison et al. [7], found that C225 plus RT was associated with inferior OS (hazard ratio (HR) = 1.45 one-sided 95% upper CI 1.94; p=0.5056 for non-inferiority) and progression-free survival (PFS) (HR 1.72, 95% CI 1.29–2.29; p=0.0002), compared to the CDDP + radiation.

In addition, LRR/distant metastasis rates were also considerably higher with radiation plus C225 (HR 2·05, 95% CI 1.35–3.10) than with radiation plus C225.

Consistent with previous reports, Mehanna et al. [8], documented in their RCT detrimental effect of C225 arm in form of significantly lower 2-year OS compared to those receiving CDDP (HR 5.0 [95% CI 1.7-14.7]; p=0.001) with concomitant radiotherapy respectively.

The difference in OS was driven by a difference in locoregional control and distant control. Patients assigned to C225 had increased risk of recurrence 6.0% *vs* 16.1%, (HR 3.4 [1.6-7.2]; p=0.0007) in 2 years compared with CDDP.

This is an updated meta-analysis on the direct comparison of the efficacy among patients with HPV-associated OPC receiving either CDDP or C225 with definitive irradiation. Although, it aggregates all study types, it is focused on only studies which directly compared two

schedules (CDDP *vs.* C225) in specific head and neck cancer subsite with predictable biological behavior and comparable disease stage (p-16 positive and LA OPC) treated with conventional fractionated schedule (use of 1.8 to 2 Gy per fraction, delivered once daily, 5-6 days a week, to a total dose of 70 Gy being administered to gross disease). Therefore, to our knowledge this is the largest meta-analysis focusing solely on this topic. According to our results, patients receiving CDDP with irradiation had a 2.2 and 2.9-fold decreased risk for death from any cause and locoregional recurrence respectively.

This meta-analysis has several limitations. In these studies, multiple factors could influence the selection of treatment options such as: subjects performance status, comorbidities, age, patients preferences, and the cost of therapy. Secondly, data regarding therapy completion rates among p16-positive subjects were unavailable and this could influence outcome in terms of both OS and LRR rates.

While in past C225 was often administered due to patient and physician preference, according to the evidence demonstrated by both RCTs and our meta-analysis, C225 should be prescribed only to patients who are thought to be suboptimal candidates for high-dose CDDP due to baseline renal dysfunction or hearing impairment.

In conclusion, CDDP-based chemoradiotherapy should be considered as first line therapy option and standard of treatment in p16-positive locally advanced/unresectable OPC.

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Figure legend

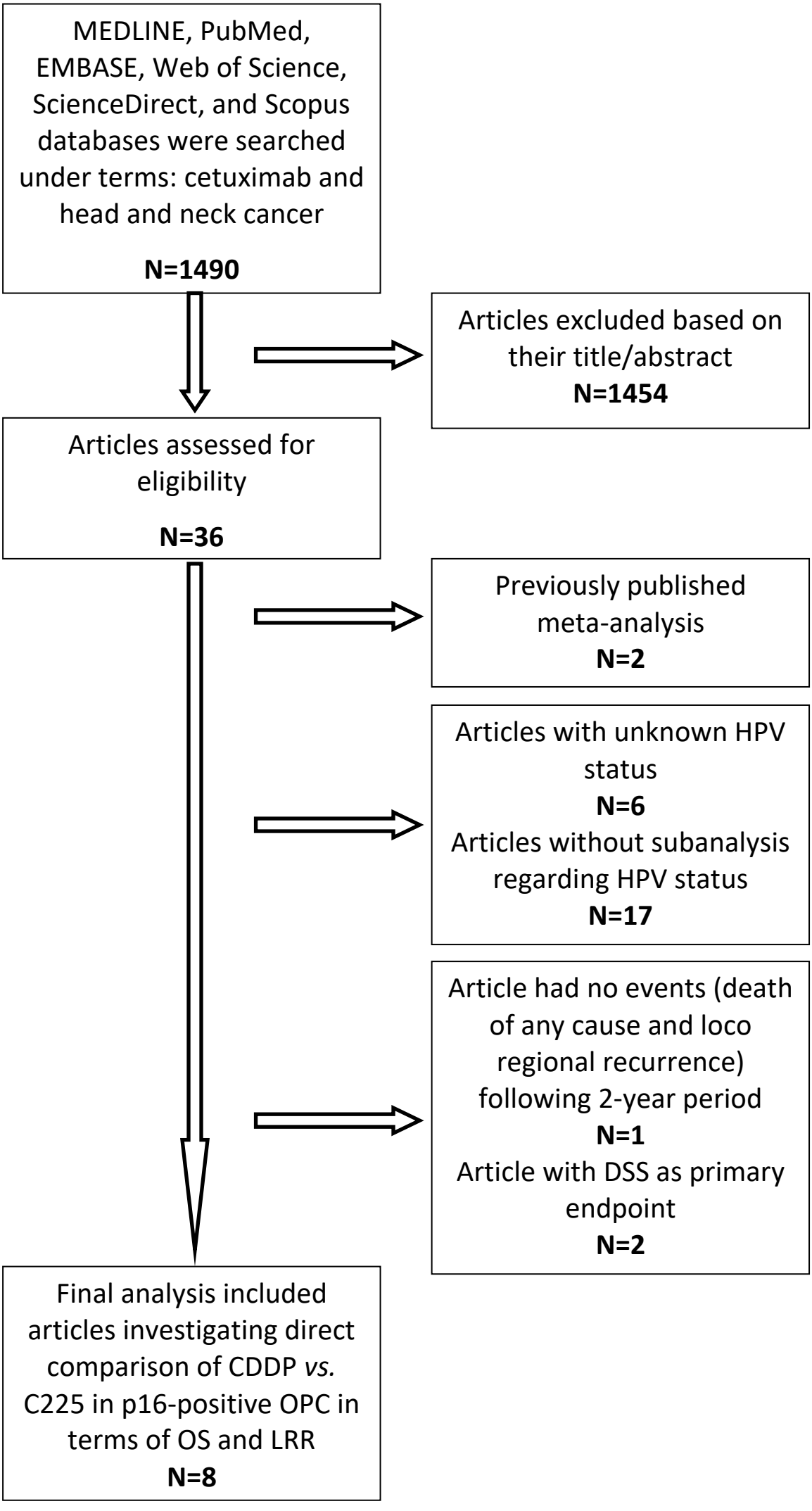
Figure 1. Study selection flow chart

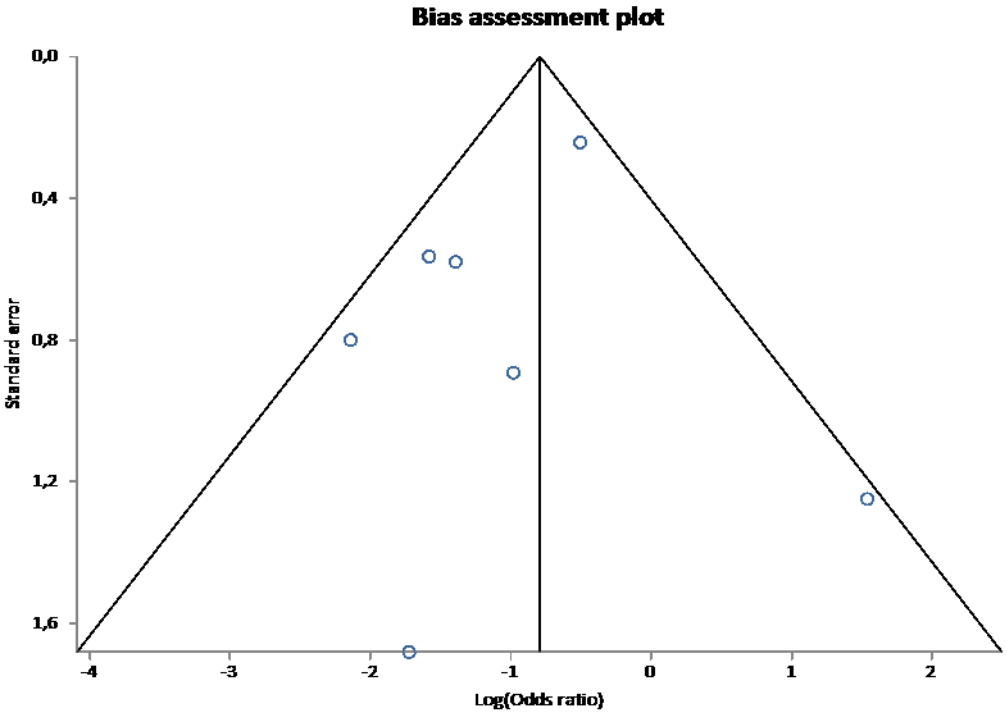
Figure 2. Bias asessment plot for 2-year OS

Figure 3. Meta-analysis of 2-year OS (forrest plot)

Figure 4. Bias assessment plot for 2-year LRR

Figure 5. Meta-analysis of 2-year LRR (forrest plot)


MEDLINE, PubMed, EMBASE, Web of Science, ScienceDirect, and Scopus databases were searched under terms: cetuximab and head and neck cancer
N=1490
Articles excluded based on their title/abstract
N=1454
Articles assessed for eligibility
N=36
Previously published meta-analysis
N=2
Articles with unknown HPV status
N=6
Articles without subanalysis regarding HPV status
N=17
Article had no events (death of any cause and loco regional recurrence) following 2-year period
N=1
Article with DSS as primary endpoint
N=2
Final analysis included articles investigating direct comparison of CDDP vs. C225 in p16-positive OPC in terms of OS and LRR
N=8


Bias assessment plot
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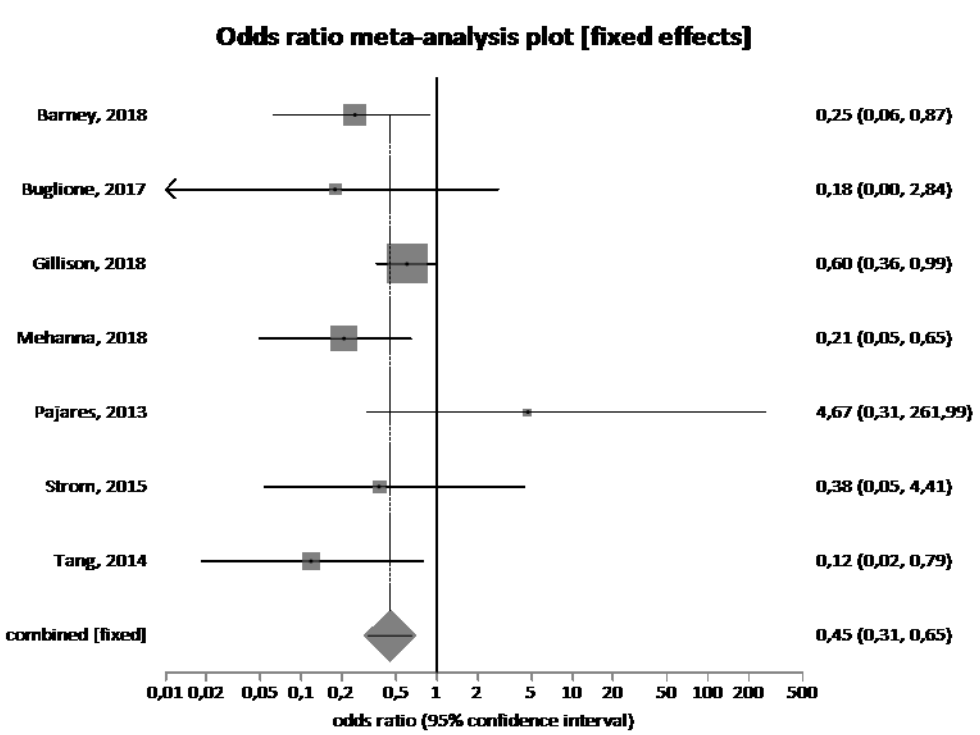
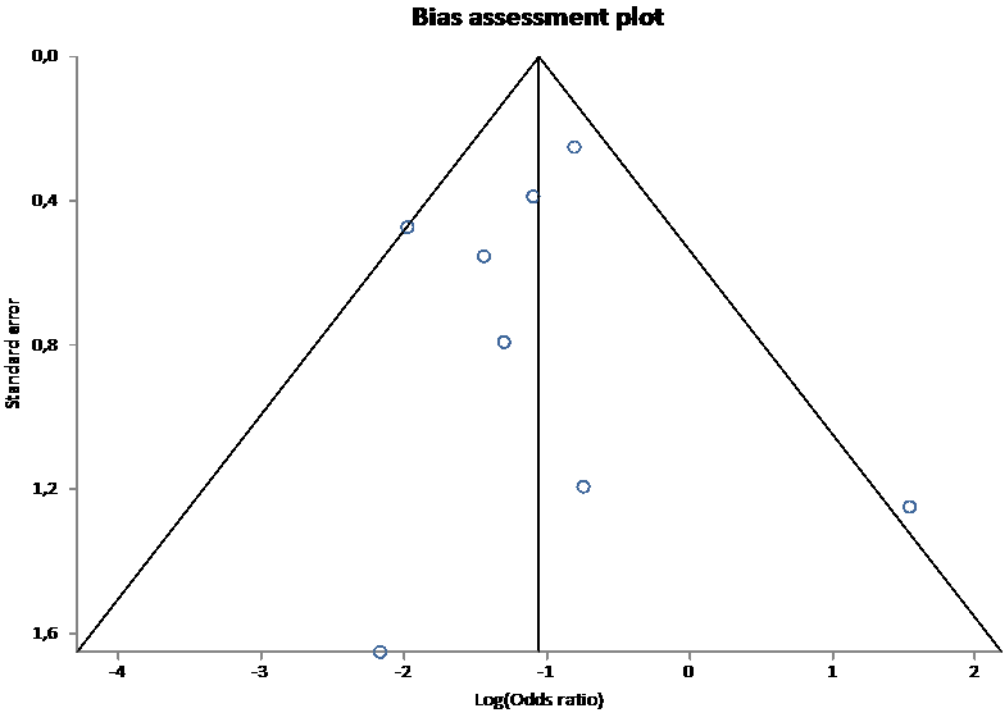
0,8
1,2
1,6
Standard error
-4
-3
-2
-1
0
1
2
Log(Odds ratio)


Odds ratio meta-analysis plot [fixed effects]
Barney, 2018
Buglione, 2017
Gillison, 2018
Mehanna, 2018
Pajares, 2013
Strom, 2015
Tang, 2014
combined [fixed]
0,25 (0,06, 0,87)
0,18 (0,00, 2,84)
0,60 (0,36, 0,99)
0,21 (0,05, 0,65)
4,67 (0,31, 261,99)
0,38 (0,05, 4,41)
0,12 (0,02, 0,79)
0,45 (0,31, 0,65)
0,01 0,02 0,05 0,1 0,2 0,5 1 2 5 10 20 50 100 200 500
odds ratio (95% confidence interval)


Bias assessment plot
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0,8
1,2
1,6
Standard error
-4
-3
-2
-1
0
1
2
Log(Odds ratio)

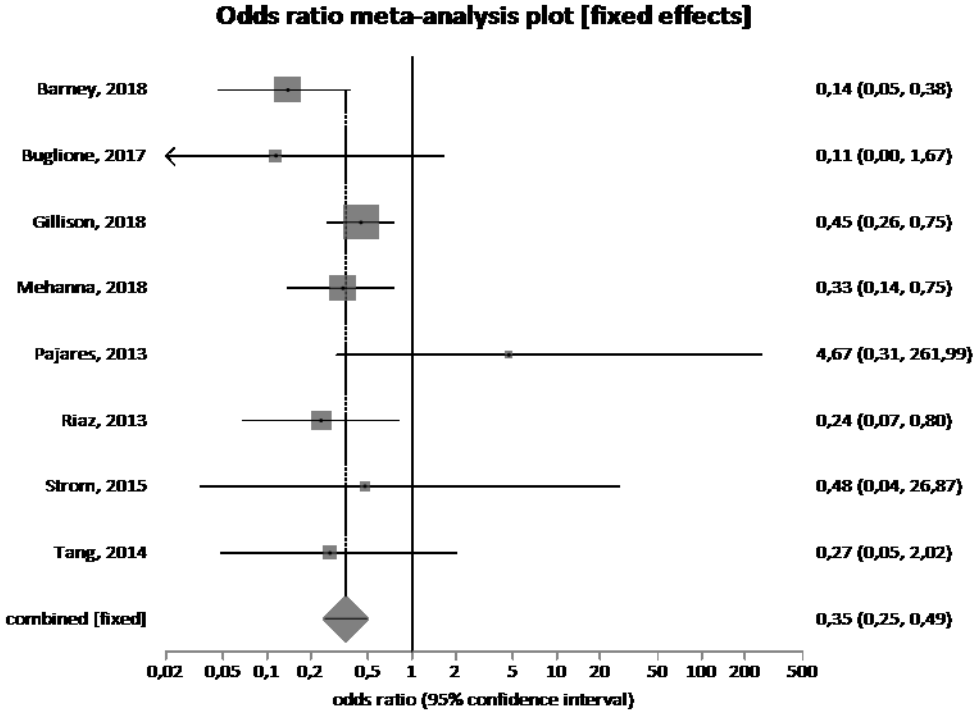
Odds ratio meta-analysis plot [fixed effects]
Barney, 2018
Buglione, 2017
Gillison, 2018
Mehanna, 2018
Pajares, 2013
Riaz, 2013
Strom, 2015
Tang, 2014
combined [fixed]
0,14 (0,05, 0,38)
0,11 (0,00, 1,67)
0,45 (0,26, 0,75)
0,33 (0,14, 0,75)
4,67 (0,31, 261,99)
0,24 (0,07, 0,80)
0,48 (0,04, 26,87)
0,27 (0,05, 2,02)
0,35 (0,25, 0,49)
0,02 0,05 0,1 0,2 0,5 1 2 5 10 20 50 100 200 500
odds ratio (95% confidence interval)

Table 1. Characteristics of included studies.

Author, year	Study type	No. of pts CDDP + C225	Treatment	2y OS (%) CDDP *vs.* C225	2y LRR (%) CDDP *vs*. C225
Barney, 2018	RS	137 + 68	RT (70 Gy/35 fr) + CDDP (q 3 weeks or weekly)[a] vs C225	96.3 / 86.4[c]	5 / 28.3[c]
Buglione, 2017	Phase II (secondary analysis)	9 + 11	RT (70 Gy/35 fr) + CDDP (q 3 weeks or weekly)[b] vs C225	100 / 77.8	0 / 27.1
Gillison, 2018	Phase III	406 + 399	RT (70 Gy/35 fr) + CDDP (q 3 weeks or weekly) vs C225	92.3 / 87.9	6.3 / 13.2
Mehanna, 2018	Phase III	166 + 168	RT (70 Gy/35 fr) + CDDP (q 3 weeks or weekly) vs C225	97.5 / 89.4	6 / 16.1[d]
Pajares, 2013	RS	10 + 8	RT + CDDP (q 3 weeks or weekly) vs C225	60 / 88	53 / 25[d]
Riaz, 2013	RS, abstract	69 + 31	CDDP vs C225 (RT schedule NA)	-	10.4 / 33.6
Strom, 2015	RS	85 + 14	RT + CDDP[b] (q 3 weeks or weekly) vs C225	94 / 85	3 / 7
Tang, 2014	RS	72 + 12	RT + CDDP (q 3 weeks or weekly) vs C225	95 / 69	8 / 27[e]

[a] in 17 (12.4%) patients chemotherapy was swithed to single agent carboplatin due to cisplatin-related toxicity

[b] cisplatin dose 75-100mg/m^2

[c] determined using DigitizeIt - Plot Digitizer Software

[d] both locoregional and distant relapses were included in LRR meta-analysis

[e] freedom from relapse was included in 2-year LRR meta-analysis