

Original article

Chemotherapy for carcinoma of the esophagus: A comparison of evidence from meta-analyses of randomized trials and of historical control studies

M. S. Bhansali, J. S. Vaidya, R. G. Bhatt, P. K. Patil, R. A. Badwe & P. B. Desai

Department of Thoracic Oncology, Tata Memorial Centre, Bombay, India

Summary

Background: Chemotherapy (CT) has been used as an adjunct to local treatment (surgery or radiotherapy) in esophageal carcinoma. A meta-analysis of all published randomized clinical trials and historical control studies which have used cisplatinum-based combination CT was carried out to assess the effect of chemotherapy on survival for esophageal cancer.

Materials and methods: A computer-based literature search was performed for the period from January 1988 to March 1995 using the index terms 'Esophageal neoplasms' and 'Chemotherapy'. The frame of reference was further narrowed to include only cisplatinum-based combination chemotherapy. Twelve randomized clinical trials (RCT) and eight historical control (HC) studies were included in the meta-analysis.

Results: In the overview of HC studies a highly significant reduction in odds of death with CT was observed ($68\% \pm 8\%$ OR = 0.32, 95% CI 0.24-0.42). On the other hand, the overview of RCTs showed a relative reduction in odds of death for the CT group of $4.2\% \pm 23.7\%$ (OR = 0.96, 95% CI 0.75-1.22).

Conclusions: There was a gross overestimation of treatment effect in the studies using HC as compared to RCTs, despite the use of cisplatinum-based chemotherapy in both groups. The meta-analysis of RCTs reveal no significant survival benefit from cisplatinum-based adjuvant/neoadjuvant chemotherapy in esophageal cancer.

Key words: chemotherapy, historical controls, oesophageal neoplasms, randomized controlled trials

Introduction

Treatment for patients with esophageal cancer remains unsatisfactory, as presentation is usually delayed until the onset of dysphagia, by which time the disease is usually at a late stage of its natural history. Surgery and/or radiation are considered standard treatment modalities for esophageal cancer [1, 2]. In the past decade radical surgery [3] and chemotherapy as an adjunct to local treatment [4] have been emphasized as potential avenues to survival benefit. Radical surgery has been studied only in the historical control and non-randomized setting, whereas chemotherapy has been tested in randomized controlled studies. Chemotherapeutic agents in combination have been used since 1970 in various schedules and regimens. All of these agents are moderately effective in present therapeutic trials as far as response to treatment is concerned but have failed to confer survival advantage [4]. Some studies have compared benefit against historical controls (HCs) and others in the setting of randomized controlled trials (RCTs). The RCTs have shown modest benefit [5] at best and small deleterious effect at worst [6]. Studies using HCs have shown large benefits [7, 8].

We carried out a meta-analysis of all published

RCTs and HC studies using cisplatinum-containing combination therapy for esophageal cancer to compare results from studies using HCs with evidence from RCTs which are considered to be the 'gold standard' for assessing treatment efficacy. A spin-off from such an exercise would be collation of published data on efficacy of chemotherapy in esophageal cancer and quantification of benefit, if it existed.

Materials and methods

Literature search

An initial list was obtained by a computer search of Cancerlitt-Silverplatter Information (National Cancer Institute) for January 1988-March 1995. The index terms 'Esophageal neoplasm' and 'Chemotherapy' were used. Six hundred sixty-eight abstracts were scanned. Cis-platinum-based combinations have had the highest response rates in esophageal cancer [4] and the search was therefore further narrowed to include only cisplatinum-based chemotherapy. The list was updated by hand search of references from original articles, review articles and cross references from chemotherapy-based articles. Articles written in English and other languages with an English abstract were also scanned. The data from the most recent article were used for studies that had resulted in several publications.

Data synthesis

Meta-analysis of randomized clinical trial (RCT)

Articles which met the following criteria were included in the meta-analysis: (1) cis-platinum-based combination chemotherapy, (2) Randomized clinical trial, (3) distinct chemotherapy and non-chemotherapy groups (4) survival as end point. Twelve articles were included in the meta-analysis [5, 6, 9–18], 10 with operable esophageal cancer and two with inoperable esophageal cancer (Table 1). One study was excluded as it was a cross over study with the surgery arm receiving post-operative chemotherapy in T3/4 and node-positive tumours [19].

In each study, the non-chemotherapy group was considered as the 'control' group and the chemotherapy group was considered as the 'treatment' group. The meta-analysis was designed to assess survival advantage with the addition of chemotherapy to the presently accepted standard therapy, namely, surgery and/or radiotherapy.

Meta-analysis of historical control (HC) studies

Studies in which prospectively collected treatment groups were compared with either previous published series or previously-treated patients at the same institution, considered as historical controls, were included if the authors drew conclusions about relative efficacy from these comparisons. Articles which met the following criteria were included: (1) Cisplatin-based combination chemotherapy and (2) survival as end point. Eight studies were included in the meta-analysis [7, 8, 20–25] (Table 2).

End point

Survival was calculated from life table analysis or noted from the actual numbers published. Two-year survival figures were available

Table 1. Esophageal cancer and chemotherapy. Randomized control trials.

Author	Stage and cell type	Treatment arm (D/N)	Control arm (D/N)	Follow up
Schlag	O, Sq	CT+SURG (22/22)	SURG (20/24)	20 months
Roth	O, Sq	CT+SURG+CT (14/19)	SURG (17/20)	2 years
Maipong	O, Sq	CT+SURG (17/24)	SURG (13/22)	2 years
Hatlevoll	LA, Sq	CT+RT (43/46)	RT (45/51)	2 years
Herskovic	O, Sq/ Ad	CT+RT (39/61)	RT (53/60)	2 years
Zhou	NA, Sq	CT+RT (23/32)	RT (23/32)	2 years
Roussel	LA, Sq	CT+ (88/110)	RT (93/111)	2 years
Nygaard*	O, Sq	CT+SURG (83/97)	SURG (72/89)	2 years
Le Prise	O, Sq	(CT+RT)+SURG (30/41)	SURG (30/45)	2 years
Apinop	O, Sq	(CT+RT)+SURG (25/35)	SURG (26/34)	2 years
Iizuka (Jeog)	O, Sq	SURG+CT (50/126)	SURT+RT (50/127)	2 years
Bosset	O, Sq	(CT+RT)+SURG (54/107)	SURG (54/108)	20 months

* Pooled treatment of arms of adjuvant CT *versus* no CT.

(D) – number of deaths; (N) – number of patients; CT – chemotherapy; RT – radiotherapy; SURG – surgery; O – operable; LA – locally advanced; NA – not available; Sq – squamous carcinoma; Ad – adenocarcinoma.

Table 2. Esophageal cancer and chemotherapy. Historical control studies.

Author	Stage and cell type	Treatment arm (D/N)	Control arm (D/N)	Follow up
Wright	O, Ad	CT+SURG (9/22)	SURG (69/91)	2 years
Orringer	O, Sq/ Ad	CT+SURG (17/43)	SURG (284/417)	2 years
Hoff	O, Sq/ Ad	(CT+RT)+SURG ((33/68)	SURG (114/137)	2 years
Saito	O, Sq	(CT+RT)+SURG (19/35)	SURG (35/48)	2 years
Naunheim	O, Sq/ Ad	(CT+RT)+SURG (25/47)	SURG (20/25)	2 years
Vogel	O, Sq/ Ad	CT/RT+SURG (22/59)	SURG (42/66)	2 years
Carey	O, Sq	CT+SURG+CT/RT (42/59)	SURG (203/257)	5 years
Badwe	O, Sq/ Ad	SURG+CT (60/83)	SURG (306/350)	2 years

(D) – number of deaths; (N) – number of patients; CT – chemotherapy; RT – radiotherapy; SURG – surgery; O – operable; LA – locally advanced; Sq – squamous carcinoma; Ad – adenocarcinoma.

for most of the studies. Ten studies in RCT were analyzed at two-year follow-up, and two at 20-month follow-up. Bosset reported a median survival of 20 months, in both arms [18]. In the study by Schlag all patients in the treatment arm had died by the time of the 20-month follow-up [6]. In HC studies results were analyzed at two years in seven trials [7, 8, 20–23, 25] and five years in one trial [24].

Indirect comparison between the treatment or control arms of RCT *versus* C studies

Indirect comparison between outcomes in treatment or control groups (RCT *versus* HC), was carried out using survival at two years in all 12 studies in the RCT group (those by Schlag and Bosset included) and for the seven studies in HC group [7, 8, 20–23, 25].

Confounding factors

The studies had several confounding factors. The first was the addition of radiation over and above CT in the treatment group. Four of the in RCTs [12, 13, 16, 18] and three of the HC [7, 20, 23] studies had used radiation in addition to CT, so in these studies it may appear that the comparison of treatment *versus* control includes more than CT alone. The second factor was inclusion of adenocarcinoma. Only one of the RCTs included adenocarcinoma along with squamous carcinoma [10], whereas six HC studies included squamous carcinoma and/or adenocarcinoma [7, 8, 20–22, 25]. The third confounding factor was the fact that in the study by Vogel et al., 70% (42/59) received adjuvant CT while the remaining patients in the treatment group received adjuvant radiotherapy [21]. The fourth factor in 11 RCTs was that a criterion for inclusion was localized and resectable tumors. Two RCTs [9, 1] for inoperable esophageal carcinoma were conducted. Overview analysis was performed including and excluding the above two. The fifth factor was that seven historical control studies and 11 randomized trials compared neoadjuvant CT *versus* no CT, whereas the trial from JEOG compared postoperative adjuvant CT. A meta-analysis was carried out excluding the JEOG trial. One study in the HC group had used CT in the neoadjuvant and adjuvant setting, with most patients (70%) receiving only adjuvant therapy [25]. A meta-analysis was carried out excluding this trial.

Meta-analysis of RCTs with a three-year follow-up was carried

out separately to assess the efficacy of CT with a longer duration of follow-up. Eight trials were included in the analysis [5, 9, 10, 12–16].

Statistical methods

The difference between the observed and expected [O–E] number of deaths and variance was calculated for each study using standard methodology [26]. The odds ratio [OR] defined as the ratio of the odds of death in the treatment compared with the control group was estimated for each trial. The individual variances and O–E differences were combined to obtain a pooled odds ratio [POR] with confidence intervals [CI]. OR and POR less than 1.00 indicate a reduction in odds of death associated with the use of CT. The percent of reduction in odds of death is a measure of treatment effect calculated as $[(1.00 - \text{POR}) \times 100]$.

The results were expressed graphically, indicating the OR, CI (horizontal bar) and statistical information content [square on each horizontal bar reflecting the variance, event rate and sample size] of each study. The POR, CI of the overview were expressed as a diamond at the bottom. The large square in the corner represents the overall information content of all the trials. The studies were tested for heterogeneity using the Mantel–Haenszel chi-square test. If the result of the test of heterogeneity was positive ($P < 0.05$), the significance of the result did not change but the magnitude of the effect indicated by meta-analysis was not reliable.

The indirect comparison between the treatment and control arms of the RCT *versus* the HC studies was carried out using the conventional chi-square test.

Results

Twelve RCT and eight HC studies were included in the meta-analysis. In the meta-analysis of RCT four of 12 studies showed improvement in survival following CT [O–E negative or $\text{OR} < 1.00$], but the result was statistically significant in only one study. In seven studies patients in the control group did better than those in the treatment arm [O–E positive or $\text{OR} > 1.00$] although in none was statistical significance reached. One study showed equivalent results [O–E zero or $\text{OR} = 1$]. In the overview of all 12 studies, the POR for survival in the CT group was 0.96 (95% CI 0.75–1.22, $2P > 0.1$) i.e., the reduction in the odds of death with adjuvant CT was $4.2\% \pm 23.6\%$ ($2P = \text{NS}$). The chi-square test for heterogeneity was 17.80 (degree of freedom = 11, $P = \text{NS}$) (Figure 1).

Results of analysis excluding two studies performed on patients with inoperable esophageal carcinoma [9, 17] did not differ from the above [POR = 0.96, 95% CI 0.74–1.25, $2P > 0.1$ and RR in odds of death = $3.60\% \pm 26\%$]. Results of meta-analysis excluding the JEOG trial was similar, [POR = 0.94, 95% CI 0.72–1.24, $2P > 0.1$ and RR in odds of death = $5.74\% \pm 26.6\%$]. Results of meta-analysis of trials with three years of follow-up revealed a better survival but this was not statistically significant [POR = 0.74, 95% CI 0.53–1.02 $2P < 0.07$ and RR in odds of death = $26.17\% \pm 29\%$].

All eight HC studies showed improvement in survival following adjuvant CT. In six studies there was significantly better survival in the treatment group. In the overview, the OR in the CT group was 0.32 [95% CI,

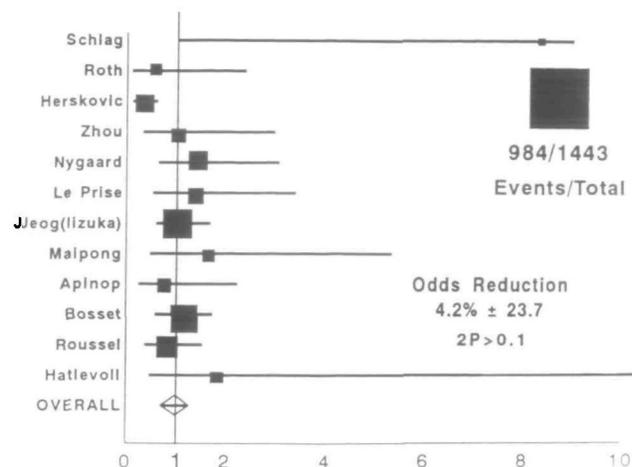


Figure 1. Meta-analysis of randomised clinical trials for cisplatin based adjuvant/neo-adjuvant chemotherapy in esophageal carcinoma. χ^2 for heterogeneity = 17.80 ($P = \text{NS}$).

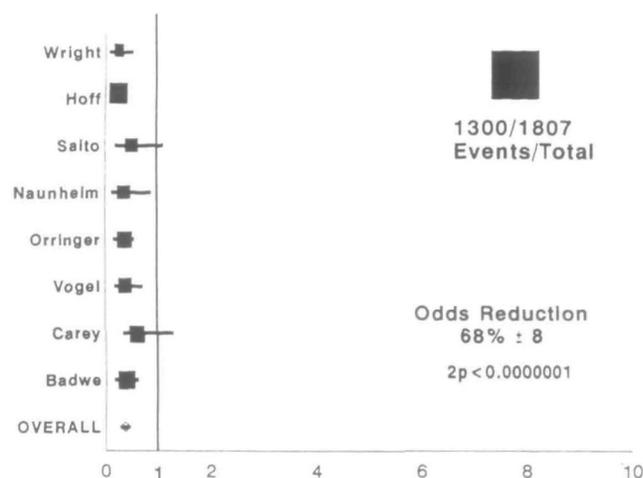


Figure 2. Meta-analysis of historical control studies for cisplatin based chemotherapy in esophageal carcinoma. χ^2 for heterogeneity = 8.6 ($P = \text{NS}$).

0.24–0.42, $2P < 0.0000001$] i.e., the percent of reduction in odds of death with CT was $68 \pm 8\%$. The test result for heterogeneity was not significant (Figure 2). The result of meta-analysis excluding the study which used adjuvant CT was similar (POR = 0.32, 95% CI 0.24–0.42, $2P < 0.0000001$ and RR in mortality = $67.9\% \pm 8.7$).

To assess the gross difference in the estimated benefit in RCT and HC, we carried out an indirect comparison between treatment arms of the RCT and the HC studies and the control arms of the RCT and the HC studies. The treatment arm of RCT had higher odds of death than the treatment arm of the HC studies 67.8% (488/720) *versus* 51.8% (185/357, $P = 0.0000004$). The control arm of RCT had lower odds of death than the control arm of the HC studies (68.6% (496/723) *versus* 76.7% (870/1134), $P = 0.0001$).

Discussion

Results from the overview suggest that adjuvant/neoadjuvant cisplatin-based combination CT reduced the relative odds of death from esophageal cancer by $4.2\% \pm 23.7\%$ in RCT whereas in HC studies the percent of reduction in odds of death was $68\% \pm 8\%$. This clearly showed a gross overestimation of treatment effect in studies based on HC as compared to the one in RCTs, although all of the studies had used cisplatin-based CT. It has been customary to rely on historical controls for large treatment effects where it would be deemed unnecessary or unethical to run an RCT, and HC studies are also useful to determine whether a new treatment is promising and should be tested in an RCT. Our study suggests that large treatment effect shown by HCs does not necessarily reflect true benefit from newer treatment, but rather a flawed design.

Historical control studies are known to be misleading for various reasons [27]. Development of better diagnostic modalities and pathological processing improves precision of staging. This 'stage migration' of patients from lower to higher stage can manifest itself as improvement in survival in patients without any addition to change in therapy [28]. The bias introduced by the use of HC may also be due to difficulty in distinguishing treatment effect from improvement in ancillary care, diagnostic criteria, referral pattern or trend over time. Indirect comparison showed an outcome of controls in the HC studies inferior to that of controls of RCTs. We also found the outcome of treatment arms in HC studies to be far superior to the outcome of treatment arms in RCTs. This could be due to a selection bias involving all patients considered for surgery, and a further bias introduced while selecting patients for adjuvant treatment. All HC studies and most of the RCTs involved surgical treatment, supporting our contention that selection for surgery itself introduced a major bias.

The results of meta-analysis can be distorted by many confounding factors. In four RCTs and three HC studies radiation was added to the treatment arm over and above CT. To assess the magnitude of this confounding factor of the addition of RT to surgery, we carried out a separate meta-analysis of RCTs dealing with comparison of the combination of RT and surgery *versus* surgery alone. There was no significant difference in outcome between the arms and hence, in these confounding studies, it is assumed that the combination is equivalent to both of the modalities alone. The inclusion of adenocarcinoma in the study may be argued to be a factor which reduces the overall efficacy of CT. One trial of the RCT group included adenocarcinoma, whereas six HC studies included squamous carcinoma and/or adenocarcinoma. Response of cisplatin-based combination CT in squamous carcinoma is similar to or slightly better than in adenocarcinoma [4]. Benefit from this confounding factor should have clear-

ly favoured the treatment arm in RCT rather than overestimating the treatment arm in HC. Timing of CT in relation to surgery for esophageal cancer has been studied in laboratory models showing a better survival when CT was given before the operation (neoadjuvant) [29]. The rationale for timing of CT has been reviewed in the clinical setting with the neoadjuvant approach offering some advantages [30]. All but one of the RCTs (JEOG group) [15] had used neoadjuvant CT. Benefit from this confounding factor should clearly favor the treatment arm in RCTs, but the present analysis did not substantiate this.

The results of our meta-analysis are uniformly collated at two years of follow-up. It may be argued that longer follow-up could add a few more events and reveal a difference in the two arms. We carried out a meta-analysis of eight RCTs with three years of follow-up which showed no significant benefit (percent of reduction in odds of death = $26\% \pm 29\%$). Although the magnitude of benefit seems to have increased, it is only after exclusion of large trials and in those in which all patients in the treatment arm had died prior to 2 years.

Results from the overview of RCTs revealed no significant benefit from CT, and the overall effect was not significant (OR = 0.96, 95% CI 0.75–1.22). These results, based on the total number of 1443 patients, with 984 deaths (68.2%), rule out a major beneficial effect of CT, which should be reason enough not to change clinical practice at present. The meta-analysis has a 53% power to detect a 5% benefit and an 85% power to detect a 10% benefit. A single large study to detect a 5% difference with 90% power should include over 3500 patients. Two large RCTs which are still accruing patients in the U.S. and Europe might define the exact role and magnitude of benefit from adjuvant CT, including the difference in benefit between squamous and adenocarcinoma [18, 31].

Meta-analyses of this kind are useful in assessing modest treatment effects. Our meta-analysis has the limitation of being confined to published literature rather than the use of raw patient data which are more reliable and less biased [32]. Meta-analysis of published literature is known to overestimate treatment effect. Despite this overestimation, the meta-analysis of RCTs at present shows no significant impact of CT. Nevertheless, it does reveal gross overestimation of benefit unrelated to treatment in studies using historical controls.

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Correspondence to:

Dr. R. A. Badwe
Assistant Surgeon
Dept. of Thoracic Oncology
Dr. Ernest Borges Marg, Parel
Bombay 400 012, India