Preoperative radiotherapy for esophageal carcinoma (Review)

Arnott SJ, Duncan W, Gignoux M, Girling DJ, Hansen HS, Launois B, Nygaard K, Parmar MKB, Rousell A, Spiliopoulos G, Stewart LA, Tierney JF, Wang M, Rhugang Z (Oeosphageal Cancer Collaborative Group)

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TABLE OF CONTENTS

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ABSTRACT

Background
The existing randomized evidence has failed to conclusively demonstrate the benefit or otherwise of preoperative radiotherapy in treating patients with potentially resectable esophageal carcinoma.

Objectives
This meta-analysis aimed to assess whether there is benefit from adding radiotherapy prior to surgery and whether or not any pre-defined patient subgroups benefit more or less from preoperative radiotherapy

Search strategy
Medline and CancerLit searches were supplemented by information from trial registers and by hand searching relevant meeting proceedings and by discussion with relevant trialists, organisations and industry. The search strategy was run again in Medline, Embase and the Cochrane Library on 30th April 2001, two years after original publication. No new trials were found. The search strategy was re-run 8th August 2002 and August 2003 on Medline, Embase, CancerLit and The Cochrane Library, and and July 2004 on Medline, Embase and the Cochrane Library. No new relevant trials identified on any of these occasions.

Selection criteria
Trials were eligible for inclusion in this meta-analysis provided they randomized patients with potentially resectable carcinoma of the esophagus (of any histological type) to receive radiotherapy or no radiotherapy prior to surgery. Trials must have used a randomization method which precluded prior knowledge of treatment assignment and completed accrual by December 1993, to ensure sufficient follow-up by the time of the first analysis (September 1995).

Data collection and analysis
A quantitative meta-analysis using updated data from individual patients from all properly randomized trials (published or unpublished) comprising 1147 patients (971 deaths) from five randomized trials. This approach was used to assess whether preoperative radiotherapy improves overall survival and whether it is differentially effective in patients defined by age, sex and tumour location.

Main results
With a median follow-up of 9 years, in a group patients with mostly squamous carcinomas, the hazard ratio (HR) of 0.89 (95% CI 0.78-1.01) suggests an overall reduction in the risk of death of 11% and an absolute survival benefit of 3% at 2 years and 4% at 5 years. This result is not conventionally statistically significant (p=0.062). No clear differences in the size of the effect by sex, age or tumor location were apparent.

Authors' conclusions
Based on existing trials, there was no clear evidence that preoperative radiotherapy improves the survival of patients with potentially resectable esophageal cancer. These results indicate that if such preoperative radiotherapy regimens do improve survival, then the effect

is likely to be modest with an absolute improvement in survival of around 3 to 4%. Trials or a meta-analysis of around 2000 patients (90% power, 5% significance level) would be needed to reliably detect such an improvement (from 15 to 20%).

SYNOPSIS

Radiotherapy before surgery for cancer of the esophagus does not seem to improve patient's chances of survival.

If the tumour has not spread, surgery is usually the standard treatment for cancer of the esophagus (the tube between the throat and stomach). Surgery to remove the cancer can help people to live longer, but the prognosis is still very poor. Trials have tried using radiotherapy (x-ray treatment) before the operation. It was hoped that this would make the tumour smaller, less likely to spread and let people live longer. However, the review of trials found no clear evidence that radiotherapy before surgery for cancer of the esophagus increases a patient's chances of survival.

BACKGROUND

Most patients with esophageal carcinoma have loco-regional or more advanced disease at diagnosis, with overall 5-year survival of approximately 10% (Boring 1993). Surgical resection is standard therapy for patients with localized tumours (DeMeester 1988) and while their prognosis is better, it is still poor (15%). One reason being that loco-regional recurrences are frequent even after intended curative resection. Following the results of numerous uncontrolled historical studies (reviewed in Gignoux 1988) there has been interest in the use of preoperative radiotherapy as a possible means of reducing local spread, thereby, improving survival. By downstaging the tumor, it may also increase resectability and perhaps alleviate symptoms.

Five prospective randomized controlled trials have investigated the effects of preoperative radiotherapy. Although pathological responses were reported in four of these trials (Arnott 1992; Gignoux 1988; Launois 1981; Wang 1989) resectability did not appear to be substantially affected and a conventionally significant survival benefit was detected in only the most recent (Nygaard 1992). All but one of these trials involved fewer than 250 patients, and they were therefore, too small to detect moderate treatment effects. However, combining the results of these trials quantitatively in a meta-analysis of updated individual patient data, increases the statistical power to detect such differences and is the most reliable and unbiased way to evaluate the evidence (Parmar 1996) from these trials.

Such a meta-analysis was therefore suggested by the Medical Research Council (MRC) Oesophageal Cancer Working Party, initiated by the MRC Cancer Trials Office (CTO), Cambridge (now the Cancer Division of the MRC Clinical Trials Unit) and carried out on behalf of the Oesophageal Cancer Collaborative Group (OCCG). Data was collated, checked and analysed by the MRC CTO. The collaborative group met in September 1995 to discuss the preliminary results. This review was first published by OCCG in the International Journal of Radiation Oncology Biology Physics (OCCG 1998) and is reproduced with their permission.

OBJECTIVES

The existing randomized evidence has failed to conclusively demonstrate the benefit or otherwise of preoperative radiotherapy in treating patients with potentially resectable esophageal carcinoma. This meta-analysis aimed to assess whether there is benefit from adding radiotherapy prior to surgery. It also investigated whether any pre-defined patient subgroup would benefit more or less from preoperative radiotherapy.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Trials (published or unpublished) were eligible for inclusion in this meta-analysis provided they randomized patients with potentially resectable carcinoma of the esophagus (of any histological type) to receive radiotherapy or no radiotherapy prior to surgery. Trials must have used a randomization method, which precluded prior knowledge of the treatment assignment and accrual had to be completed by December 1993. This cut-off date was to allow time for sufficient follow-up by the time of analysis in 1995.

Types of participants

Individuals with potentially resectable carcinoma of the esophagus (of any histological type). Individual data from all randomized patients were included in the meta-analysis. Where possible data were obtained for individuals who had been excluded from the original trial analyses and they were included in the meta-analysis.

Types of intervention

Trials that compared radiotherapy prior to surgery with surgery alone.

Types of outcome measures

Survival

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

Trials were identified by computerized searching of MEDLINE and CANCERLIT, using a modification of the optimal search strategy for identifying randomized controlled trials developed by the Cochrane Collaboration (Dickersin 1995), and EMBASE and by examining the reference lists of trial publications, review articles, and books. Trial investigators collaborating in the meta-analysis and trial registers (United Kingdom Coordinating Committee on Cancer Research Register of Cancer Clinical Trials, Physicians Data Query Clinical Protocols and the Cochrane Controlled Trials Register) were also consulted to help identify unpublished and other published trials. These searches were last updated in May 1999. The search strategy was run again in Medline, Embase and the Cochrane Library on 30th April 2001, two years after original publication. No new relevant trials were identified. The search strategy was re-run 8th August 2002 and August 2003 on Medline, Embase, CancerLit and The Cochrane Library, and and July 2004 on Medline, Embase and the Cochrane Library. No new relevant trials identified on any of these occasions.

Search Strategy for MEDLINE and CANCERLIT (modified for Probase software)

1 PT=RANDOMIZED-CONTROLLED-TRIAL
2 RANDOMIZED-CONTROLLED-TRIALS.DE
3 RANDOM-ALLOCATION.DE
4 DOUBLE-BLIND-METHOD.DE.
5 SINGLE-BLIND-METHOD.DE.
6 1 OR 2 OR 3 OR 4 OR 5
7 PT=CLINICAL-TRIAL
8 CLINICAL-TRIALS#.DE.
9 CLIN$ WITH TRIAL$).AB,TI.
10 ((SINGL$ OR DOUBL$ OR TREBL$ OR TRIPL$) WITH (BLIND$ OR MASK$)).AB,TI.
11 PLACEBO$.DE.
12 PLACEBO$.AB,TI.
13 RANDOM$.AB,TI.
14 RESEARCH-DESIGN.DE.
15 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16 CARCINOMA#.DE.
17 ESOPHAGEAL-NEOPLASMS.DE.
18 16 and 17
19 (ESOPHAG$ ADJ CARCINOMA$).AB,TI.
20 (ESOPHAG$ ADJ CANCER$).AB,TI.
21 (ESOPHAG$ ADJ NEOPLASM$).AB,TI.
22 (OESOPHAG$ ADJ CARCIMOMA$).AB,TI.
23 (OESOPHAG$ ADJ CANCER$).AB,TI.
24 (OESOPHAG$ ADJ NEOPLASM$).AB,TI.
25 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
26 Radiotherapy.DE.
27 QS Neoplasms WITH RT
28 26 or 27
29 15 and 25 and 28

Please note: Format shown is for Knight-Ridder Probase version 1.1
$ is a truncation symbol
# denotes an exploded term

METHODS OF THE REVIEW

This review is based on individual patient data obtained directly from the responsible trialist or data centre. The methods used were prespecified in a protocol.

For all eligible trials, information on the following were requested: sex; date of birth or age; tumor location; disease stage; histology; extent of resection; date of randomization; allocated treatment; survival status and updated information on date of death or last follow up. Such information was sought also for patients who had been excluded from the investigators' own analysis, to prevent the potential bias of patient exclusions. No quality of life data were available. Following transfer, each trial dataset was checked thoroughly to ensure both the accuracy of the meta-analysis database and the quality of randomization and follow-up. Queries were resolved by, and the final database entries verified by, the responsible trial investigator or data manager.

The role of preoperative radiotherapy was investigated in four trials (Arnott 1992; Gignoux 1988; Launois 1981; Wang 1989) and a fifth trial (Nygaard 1992) used a factorial design to examine the role of preoperative radiotherapy whilst controlling for the effect of chemotherapy. For this reason, the latter trial was split into two allowing separation of preoperative radiotherapy only 'trials' and preoperative radiotherapy plus chemotherapy 'trials' in the meta-analysis.

All analyses were carried out on an intention-to-treat basis. Survival analyses were stratified by trial and the logrank expected number of deaths and variance used to calculate individual and an overall pooled hazard ratio (HR) using the fixed effects model (Yusuf 1985). Thus the time to death for individual patients was used within trials to calculate HRs representing the overall risk of dying on treatment (preoperative radiotherapy) as compared to control (no preoperative radiotherapy). These HRs are plotted in the main analysis of survival and the subgroup analysis (although still

labelled as odds ratios in the Cochrane Library). A simple (non-stratified) Kaplan-Meier curve was also generated (Kaplan 1958). These are not currently reproducable in the Cochrane Library, but can be found in the meta-analysis publication. Baseline survival at 2 and 5 years, as derived from the survival curve, together with the overall HR was used to calculate the absolute effect of treatment (Freedman 1982). To investigate the effect of preoperative radiotherapy within pre-specified subgroups, similar stratified analyses were performed.

Chisquare tests for heterogeneity were used to test for gross statistical heterogeneity over all trials (heterogeneity chisquare) and between subgroups (interaction chisquare). These tests are aimed primarily at detecting quantitative differences (differences in size rather than direction), because there was no a priori reason to expect qualitative differences. Where subgroups had a natural order (e.g. categories of increasing age) the chisquare test for trend (trend chisquare) was used.

DESCRIPTION OF STUDIES

At the time of analysis (1995), 8 potentially eligible trials were identified. Of these, 5 were eligible for inclusion in the meta-analysis. One was excluded, because it compared preoperative chemoradiotherapy plus surgery with surgery alone (Le Prise 1994). The eligibility of 2 remaining trials (1 published, Zhang 1988, and 1 with no known publication details) could not be assessed fully and it was not clear that they were actually randomized controlled trials. It proved impossible to establish adequate communication with the trial investigators. Updated searches (May 1999) did not uncover any new eligible trials, but rather 2 further trials comparing preoperative chemoradiotherapy plus surgery with surgery alone (de Pree 1995; Urba 1995).

The meta-analysis is based on five trials including 1147 patients (Table of included studies). This represents 98.5% of patients from all known randomised trials, because data were not available for 17 patients in one (Launois 1981) of the 5 trials. All trials included patients with potentially resectable cancer of the thoracic esophagus and with the exception of one (Arnott 1992), restricted entry to patients with squamous carcinoma. Trials included both men and women of most age groups. In general, the majority of patients in the meta-analysis were men (78%), younger than 65 years (80%) with squamous carcinomas (86%) of the middle or lower third (74%) of the thoracic esophagus. The total planned dose of radiotherapy ranged from 20-40 Gy given in 10-20 fractions over a period of 1-4 weeks, with the delay from the end of radiotherapy to surgery ranging from less than 8 days to 4 weeks. In all trials, the overall rates of resection and complete resection were broadly similar in the treatment and control arms.

METHODOLOGICAL QUALITY

Trials must have used a randomization method, which precluded prior knowledge of treatment assignment and completed accrual by December 1993 (to allow time for sufficient follow-up by the time of analysis in 1995). Following transfer, each trial dataset was checked thoroughly to ensure both the accuracy of the meta-analysis database and the quality of randomisation and follow-up. Queries were resolved by, and the final database entries verified by, the responsible trial investigator or data manager.

RESULTS

The overall hazard ratio of 0.89, although not conventionally significant (chisquare=3.48, df=1, p=0.06), suggests a moderate benefit from preoperative radiotherapy. It should be noted, however, that the meta-analysis had only about 75% power to detect such an effect. This effect represents an 11% reduction in the risk of death and an absolute benefit of 4% (95% CI 0 to 9%) at 2 years and 3% (95% CI 0 to 8%) at 5 years, improving survival from approximately 30 to 34% and 15 to 18% respectively. There was no evidence that this result varied when chemotherapy was used in conjunction with radiotherapy (interaction chisquare=1.49, df=1, p=0.22), but there was some bordeline evidence of a difference in effect across the trials (heterogeneity chisquare=10.37, df=5, p=0.06). This seems to be mainly because of the extreme result of the Scandinavian trial (Nygaard 1992). Removing this trial reduces the overall heterogeneity (heterogeneity chisquare=4.557, df=3, p=0.21), while keeping the results comparable (HR=0.96, p=0.53).

Pre-defined subgroups of patients were analysed to determine whether the size of the effect of preoperative radiotherapy varied across these groups. Only two trials had information on clinical staging and most patients (89%) had squamous carcinomas. Thus analyses by clinical stage and tumour histology were uninformative. Data on sex and age were available for at least 99% of patients, but on tumor location for only 80%, because one trial (Gignoux 1988) used a different method of classification. Based on these data, there was little evidence to suggest that any patient group, specified by sex (interaction chisquare=3.15, df=1, p=0.08), age (trend chisquare=0.76, df=1, p=0.38) or tumor location (interaction chisquare=1.32, df=1, p=0.25), benefited more or less from preoperative radiotherapy.

DISCUSSION

This meta-analysis was based on 5 trials comparing preoperative radiotherapy with no preoperative radiotherapy. It included 1147 patients representing 98.5% of patients from all confirmed eligible randomized trials. Most of the survival data for these trials were

updated for the meta-analysis, many years after the publication of the results and up to 20 years after recruitment had stopped. Therefore, currently, the meta-analysis provides the most comprehensive and reliable assessment of the effect of preoperative radiotherapy in potentially resectable esophageal cancer. Based on this existing evidence, there is a suggestion that preoperative radiotherapy may offer a modest benefit to patients, reducing the risk of death by 11% and improving absolute survival at 2 years, from 30 to 34% and at 5 years, from 15 to 18%. This effect was consistent irrespective of patient age and sex and the location of the tumour in the thoracic esophagus.

As a major aim of preoperative radiotherapy is to downstage the tumor and increase resectability, optimal results may rely on selecting appropriate patients. This will largely depend on accurate clinical staging. The rate of resection in the control arm varied between trials, which may suggest that clinical staging and so patient selection was also variable. Since these trials were performed, there have been two major changes in the staging of esophageal cancer, with international consensus (AJC 1988; UICC 1987). In addition, the advent of new diagnostic techniques, in particular endoscopic ultrasonsography seems to offer the potential for more accurate clinical staging (Thompson 1994). It is possible, therefore, that with modern staging approaches, those patients most likely to benefit from preoperative treatment will be identified. Perhaps in these patients any effect of preoperative radiotherapy on the rate of resection and survival will be easier to detect.

It is also possible that in these trials the radiotherapy dose was insufficient (particularly Arnott 1992; Gignoux 1988; Nygaard 1992) or the delay between radiotherapy and surgery was too short to allow the inflammatory response to subside and tumor shrinkage to take place. Alternatively, it may have been that surgery was carried out too late, allowing fibrosis to occur. Indeed, based on a simple analysis, the expected improvement in resectability was not evident in these studies. However, it is hoped that a future update of this review will include a more detailed and informative analysis of the rates of resection. Over time, the methods for administration of radiotherapy have changed and perhaps larger total doses to the tumor site or the same doses in a shorter time scale might be more effective.

AUTHORS' CONCLUSIONS

Implications for practice

This meta-analysis suggests that preoperative radiotherapy, as given in these trials, may provide a small survival advantage for patients with potentially resectable cancer of the esophagus and moreover, there is no clear evidence to suggest that this therapy is detrimental, at least for survival. However, any small benefit of preoperative radiotherapy could be offset by the increased morbidity, cost, and duration of treatment associated with giving radiotherapy preoperatively. Therefore, preoperative radiotherapy, cannot currently be routinely recommended outside of controlled clinical trials.

Implications for research

A major focus of current research is combined preoperative radiotherapy and chemotherapy (Ajani 1995), but this meta-analysis has failed to demonstrate conclusively that preoperative radiotherapy improves survival. Therefore, if more effective means of locoregional control using preoperative radiotherapy with surgery can be found, the potential of additional systemic therapy could be assessed. Perhaps then trials of newer radiotherapy regimens followed by a longer (or shorter) delay to surgery, in carefully selected patients could reveal more substantial survival benefits. These would need to be considered alongside any changes in patient-reported quality of life. However, any such trials (or indeed a meta-analysis) would need to be substantially larger than those in the current meta-analysis. To reliably detect an absolute survival benefit of 5% would require 2000 patients and of 10% would require 600 patients (both 90% power, 5% significance). Such large trials would almost certainly necessitate large-scale international collaboration.

POTENTIAL CONFLICT OF INTEREST

There is no known conflict of interest.

ACKNOWLEDGEMENTS

We would like to thank all those patients who took part in the trials and contributed to this research. The meta-analysis would not have been possible without their help or without the collaborating institutions who kindly supplied their trial data.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Medical Research Council UK

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xSub 1. Female *{published and unpublished data}*

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xSub 1. Male *{published and unpublished data}*

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xSub 2. 56-60 *{published and unpublished data}*

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xSub 2. 61-65 *{published and unpublished data}*

.

xSub 2. <56 *{published and unpublished data}*

.

xSub 2. >65 *{published and unpublished data}*

.

xSub 3. Lower *{published and unpublished data}*

.

xSub 3. Upper/Middle *{published and unpublished data}*

.

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TABLES

Characteristics of included studies

Study	**Arnott 1992**
Methods	RCT, 1979-1983
Participants	176 patients with potentially resectable squamous cell or adenocarcinoma
Interventions	Surgery with or without prior radiotherapy* *20Gy in 10 fractions over 14 days. 21 days delay to surgery
Outcomes	Survival
Notes	84% resections, 76% complete resections on treatment 75% resections, 72% complete resections on control

Characteristics of included studies (*Continued*)

Allocation concealment	A

Study	**Gignoux 1988**
Methods	RCT, 1976-1982
Participants	229 patients with potentially resectable squamous cell carcinoma
Interventions	Surgery with or without prior radiotherapy* *33Gy in 10 fractions over 28 days. <8 days delay to surgery
Outcomes	Survival
Notes	68% resections, 43% complete resections on treatment 78% resections, 55% complete resections on control
Allocation concealment	A

Study	**Launois 1981**
Methods	RCT, 1973-1976
Participants	107 patients with potentially resectable squamous cell carcinoma
Interventions	Surgery with or without prior radiotherapy* *40Gy in ? fractions over 8-12 days. <8 days delay to surgery
Outcomes	Survival
Notes	89% resections, 74% complete resections on treatment 89% resections, 78% complete resections on control
Allocation concealment	A

Study	**Nygaard 1992 (a)**
Methods	RCT, 1983-1988
Participants	108 patient with potentially resectable squamous cell carcinoma
Interventions	Surgery with or without prior radiotherapy* *35Gy in 20 fractions over 28 days. 21 days delay to surgery
Outcomes	Survival
Notes	46% resections, 34% complete resections on treatment 62% resections, 32% complete resections on control
Allocation concealment	A

Study	**Nygaard 1992 (b)**
Methods	RCT, 1983-1988
Participants	109 patients with potentiall resectable squamous cell carcinoma
Interventions	Surgery with or without prior chemotherapy and radiotherapy* *35Gy in 20 fractions over 28 days. 21 days delay to surgery
Outcomes	Survival
Notes	62% resections, 53% complete resections on treatment 55% resections, 41% complete resections on control
Allocation concealment	A

Study	**Wang 1989**
Methods	RCT, 1977-1988

Characteristics of included studies (*Continued*)

Participants	418 patients with potentially resectable squamous cell carcinoma
Interventions	Surgery with or without radiotherapy* *40Gy in 10 fractions over 12 day. 14-28 days delay to surgery
Outcomes	Survival
Notes	90% resections, 74% complete resections on treatment 86% resections, 65% complete resections on control
Allocation concealment	A

Study	**xSub 1. Female**
Methods	Subgroup analysis by sex (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	D

Study	**xSub 1. Male**
Methods	Subgroup analysis by sex (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	D

Study	**xSub 2. 56-60**
Methods	Subgroup analysis by age (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	D

Study	**xSub 2. 61-65**
Methods	Subgroup analysis by age (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	D

Study	**xSub 2. <56**
Methods	Subgroup analysis by age (stratified by trial)
Participants	
Interventions	

Outcomes	
Notes	
Allocation concealment	D

Study	**xSub 2. >65**
Methods	Subgroup analysis by age (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	D

Study	**xSub 3. Lower**
Methods	Subgroup analysis by tumor location (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	D

Study	**xSub 3. Upper/Middle**
Methods	Subgroup analysis by tumor location (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	D

Characteristics of excluded studies

Study	**Reason for exclusion**
China	Eligibility uncertain: No contact could be made with investigator. Therefore, not clear that it was RCT.
Le Prise 1994	Compared preoperative chemoradiotherapy plus surgery with surgery alone
Urba 1995	Compared preoperative chemoradiotherapy plus surgery with surgery alone
Zhang 1988	Eligibility uncertain: Unsure that it was RCT
de Pree 1995	Compared preoperative chemoradiotherapy plus surgery with surgery alone

GRAPHS

Comparison 01. Main effects of preoperative radiotherapy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Survival	6	1147	Peto Odds Ratio 95% CI	0.89 [0.78, 1.01]

Comparison 02. Subgroup Analyses

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Survival			Peto Odds Ratio 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Esophageal Neoplasms [*radiotherapy; surgery]; Meta-Analysis; Radiotherapy, Adjuvant; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

Title	Preoperative radiotherapy for esophageal carcinoma
Authors	Arnott SJ, Duncan W, Gignoux M, Girling DJ, Hansen HS, Launois B, Nygaard K, Parmar MKB, Rousell A, Spiliopoulos G, Stewart LA, Tierney JF, Wang M, Rhugang Z (Oeosphageal Cancer Collaborative Group)
Contribution of author(s)	All reviewers participated in the design, execution, and analysis of the review and twice commented on the overall intellectual content.
Issue protocol first published	/
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Date of most recent amendment	25 August 2004
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What's New	Search strategy re-run 8th August 2002 and August 2003 on Medline, Embase, CancerLit and The Cochrane Library, and and July 2004 on Medline, Embase and the Cochrane Library. No new relevant trials identified on any of these occasions.
Date new studies sought but none found	08 July 2004
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author

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GRAPHS AND OTHER TABLES

Comparison 02. 01 Survival

Review: Preoperative radiotherapy for esophageal carcinoma

Comparison: 01 Main effects of preoperative radiotherapy

Outcome: 01 Survival

Study	Preoperative RT n/N	No Preoperative RT n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Preoperative RT only 'trials'					
Arnott 1992	87/90	75/86		16.5	1.19 [0.87, 1.62]
Gignoux 1988	108/116	108/113		22.2	1.02 [0.78, 1.33]
Launois 1981	56/61	40/46		9.3	1.01 [0.67, 1.53]
Nygaard 1992 (a)	52/58	50/50		9.5	0.60 [0.40, 0.91]
Wang 1989	131/195	165/223		32.6	0.81 [0.65, 1.01]
Subtotal (95% CI)				90.1	0.91 [0.80, 1.04]
Test for heterogeneity chi-square=8.69 df=4 p=0.071 I=54.0%					
Test for overall effect z=1.37 p=0.2					
02 Preoperative RT + CT 'trials'					
Nygaard 1992 (b)	46/53	53/56		9.9	0.70 [0.47, 1.04]
Subtotal (95% CI)				9.9	0.70 [0.47, 1.04]
Test for heterogeneity: not applicable					
Test for overall effect z=1.75 p=0.08					
Total (95% CI)				100.0	0.89 [0.78, 1.01]
Test for heterogeneity chi-square=10.20 df=5 p=0.071 I=51.0%					
Test for overall effect z=1.85 p=0.06					

Comparison 02. 01 Survival

Review: Preoperative radiotherapy for esophageal carcinoma

Comparison: 02 Subgroup Analyses

Outcome: 01 Survival

Study	Preoperative RT n/N	No Preoperative RT n/N	Peto Odds Ratio 95% CI	Peto Odds Ratio 95% CI
01 Sex				
xSub 1. Female	97/131	100/119		0.70 [0.53, 0.95]
xSub 1. Male	383/441	391/455		0.95 [0.82, 1.09]
02 Age				
xSub 2. 56-60	91/106	98/115		0.94 [0.70, 1.26]
xSub 2. 61-65	96/104	96/108		0.93 [0.70, 1.25]
xSub 2. <56	180/235	204/246		0.84 [0.69, 1.03]
xSub 2. >65	107/118	89/101		0.98 [0.74, 1.31]
03 Tumor location				
xSub 3. Lower	172/185	159/172		0.95 [0.76, 1.18]
xSub 3. Upper/Middle	194/265	220/285		0.80 [0.65, 0.97]