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● *Clinical Investigation*

PREOPERATIVE RADIOTHERAPY IN ESOPHAGEAL CARCINOMA: A META-ANALYSIS USING INDIVIDUAL PATIENT DATA (OESOPHAGEAL CANCER COLLABORATIVE GROUP)

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Purpose: 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.

Methods and Materials: This quantitative meta-analysis included updated individual patient data from all properly randomized trials (published or unpublished) comprising 1147 patients (971 deaths) from five randomized trials.

Results: With a median follow-up of 9 years, 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.

Conclusion: 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 would be needed to reliably detect such an improvement (15→20%).

Meta-analysis, Systematic review, Randomized controlled trials, Esophageal neoplasms, Radiotherapy.

INTRODUCTION

Surgical resection is standard therapy for patients with carcinoma of the esophagus (5), but the prognosis for these patients remains poor, with 5-year survival of approximately 10% (4). Local recurrences are frequent even after intended curative resection. Following the results of numerous uncontrolled historical studies [reviewed (8)] 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 (3, 8, 10, 15), resectability appeared to be unaffected in all trials and a conventionally significant survival benefit was detected in only the most recent (11). 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 (12) 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,

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Cambridge and carried out on behalf of the Oesophageal Cancer Collaborative Group.

METHODS AND MATERIALS

The general methods for the meta-analysis were outlined prospectively in a protocol.

Trial eligibility

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.

Trial identification

Trials were identified by computerized searching of MEDLINE and CANCERLIT, using the optimal search strategy for identifying randomized controlled trials developed by the Cochrane Collaboration (6), 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 Clinical Trials and Physicians Data Query Clinical Protocols) were also consulted to help identify unpublished trials.

Seven potentially eligible trials were identified. Of these, five were eligible for inclusion in the meta-analysis. The eligibility of two remaining trials (one published (17) and one 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.

Data obtained

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. 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.

Analysis

The role of preoperative radiotherapy was investigated in four trials (3, 8, 10, 15) and a fifth trial (11) used a factorial design to examine the role of preoperative radiotherapy while 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 log rank expected number of deaths and variance used to calculate individual and an overall pooled hazard ratio (HR) using the fixed effects model (16). 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) compared to control (no preoperative radiotherapy). A simple (nonstratified) Kaplan-Meier curve was also generated (9). 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 (7). To investigate the effect of preoperative radiotherapy within prespecified subgroups, similar stratified analyses were performed.

Chi-square (χ^2) tests for heterogeneity were used to test for gross statistical heterogeneity over all trials (χ^2 Heterogeneity) and between subgroups (χ^2 Interaction). 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 chi-square test for trend (χ^2 Trend) was used.

RESULTS

The meta-analysis is based on five trials including 1147 patients. This represents 98.5% of patients from all known randomized trials, because data were not available for 17 patients in one (10) of the five trials. All trials included patients with potentially resectable cancer of the thoracic esophagus and with the exception of one (3), 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 (Table 1). In all trials, the overall rates of resection and complete resection were broadly similar in the treatment and control arms (Table 1).

The overall hazard ratio of 0.89, although not conventionally significant ($\chi^2(1) = 3.48$, $p = 0.06$), suggests a moderate benefit from preoperative radiotherapy (Fig. 1 and 2). This 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 (χ^2 In-

Table 1. Characteristics of trials included in the meta-analysis

Trial	Recruitment period	No. of patients	Radiation dose (Gy)	No. of fractions	Treatment duration (days)	Delay (days)	% Resections		% Complete resections	
							RT (± CT) + S	(± CT) + S	RT (± CT) + S	(± CT) + S
Launois	1973–1976	107	40	?	8–12	<8	89	89	74	78
Gignoux	1976–1982	229	33	10	28	<8	68	78	43	55
Wang	1977–1988	418	40	10	12	14–28	90	86	74	65
Arnott	1979–1983	176	20	10	14	21	84	75	76	72
Nygaard (a)	1983–1988	108	35	20	28	21	46	62	34	32
Nygaard (b)	1983–1988	109	35	20	28	21	62	55	53	41

RT = radiotherapy; CT = chemotherapy; S = surgery.

teraction(1) = 1.49, $p = 0.22$) and no clear evidence of a large difference in effect across all trials (χ^2 Heterogeneity(5) = 0.37, $p = 0.06$).

Predefined subgroups of patients were analyzed 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 tumor 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 (8) used a different method of classification. Based on these data, there was little evidence to suggest that any patient group, specified by sex (χ^2Interaction(1) =3.15, $p = 0.08$), age (χ^2Trend(1) =0.76, $p = 0.38$) or tumor location (χ^2Interaction(1) =1.32, $p = 0.25$), benefited more or less from preoperative radiotherapy (Fig. 3).

DISCUSSION

This meta-analysis was based on five 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

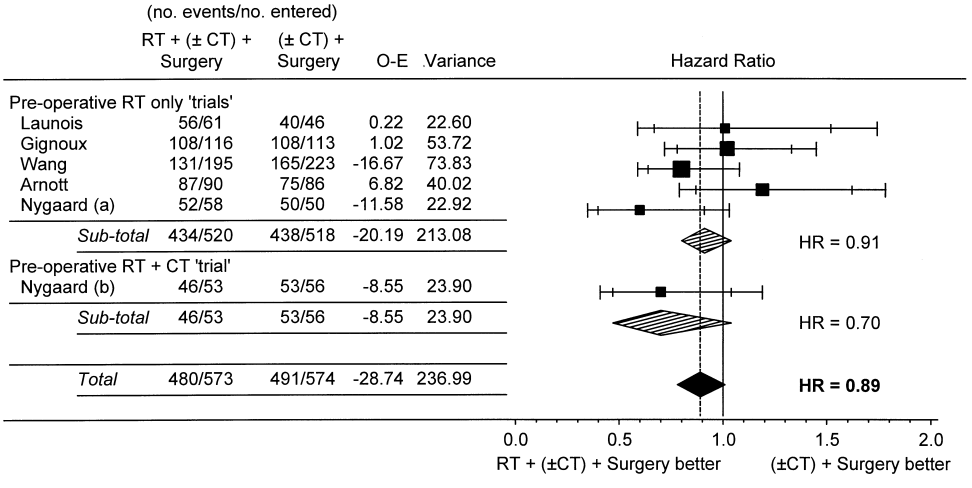

Fig. 1. Results of meta-analysis of randomized trials of preoperative radiotherapy with or without chemotherapy vs. (with or without chemotherapy) surgery. The hazard ratio for each trial is represented by the square on each bar, the size of which is proportional to the amount of information available in the trial. The inner and outer limits of the bar indicate the 95 and 99% confidence intervals, respectively. The center of the black diamond gives the overall hazard ratio when the results of all trials are combined. The extremes of the diamond give the 95% confidence interval. The shaded diamonds represent the hazard ratios and confidence intervals for the preoperative radiotherapy only ''trials'' and the preoperative radiotherapy plus chemotherapy ''trial.'' The overall HR estimate of the effect of preoperative radiotherapy is 0.89 ($\chi^2(1) = 3.48$, $p = 0.06$).

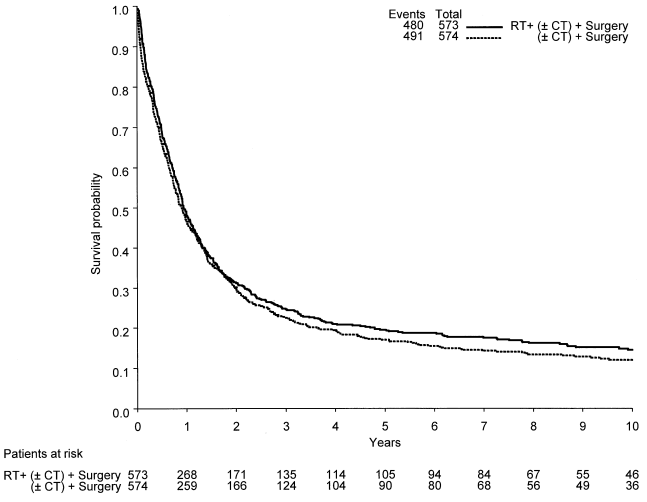

Fig. 2. Survival in randomized trials of preoperative radiotherapy with or without chemotherapy vs. (with or without chemotherapy) surgery.

patient age and sex and the location of the tumor 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 (2, 14). In addition, the advent of new diagnostic techniques, in particular electronic ultrasonography, seems to offer the potential for more accurate clinical staging (13). It is, therefore, possible that with modern staging approaches and better patient selection a more substantial benefit of preoperative radiotherapy might be found.

It is also possible that in these trials the radiotherapy dose was insufficient [particularly (3, 8, 11)] or the delay between radiotherapy and surgery was too short to allow the inflammatory response to subside and tumor shrinkage to take place. Indeed, the expected improvement in resectability was not evident in these studies. Furthermore, 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.

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 evidence to suggest that this therapy is detrimental. 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,

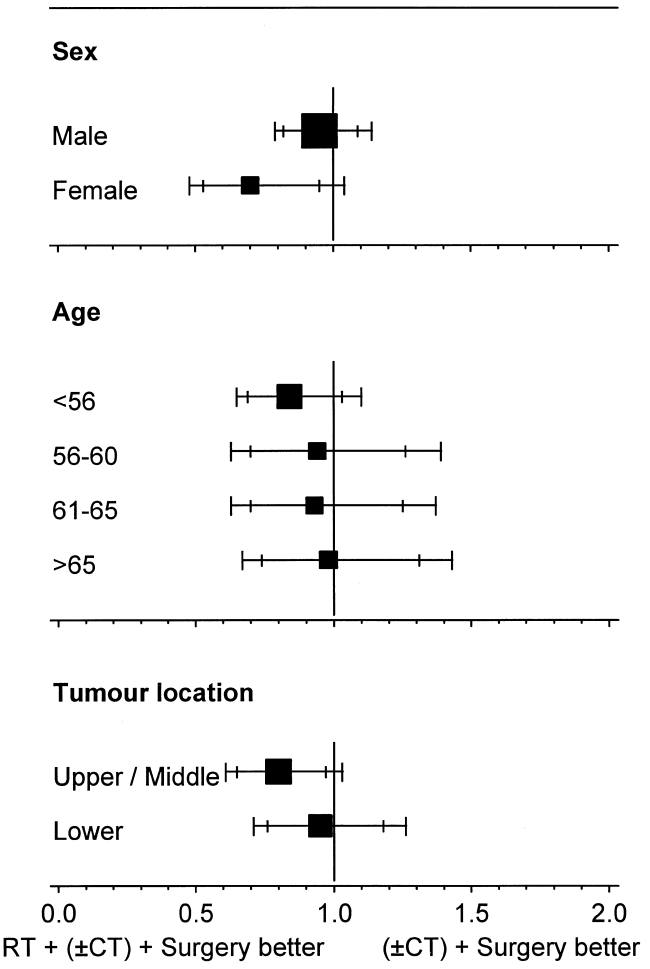

Fig. 3. Effect of preoperative radiotherapy according to sex, age, and tumor location. Symbols and conventions as for Fig. 1. Sex: χ^2Interaction(1) =3.15, p = 0.08. Age: χ^2Trend(1) =0.76, p = 0.38. Tumor location: χ^2Interaction(1) =1.32, p = 0.25.

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 (1), but this meta-analysis has failed to demonstrate conclusively that preoperative radiotherapy improves survival. Therefore, if more effective means of loco-regional 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 delay to surgery, in carefully selected patients could reveal more substantial survival benefits. However, any such trials would need to be substantially larger than those in the meta-analysis. To reliably detect an absolute survival benefit of 5% would require 2000 patients, and of 10% would require 600 patients. Such large trials would almost certainly necessitate large-scale international collaboration.

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