

Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer

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Background: The prognostic role and definition of circumferential resection margin (CRM) involvement in operable oesophageal cancer remain controversial. The College of American Pathologists (CAP) and Royal College of Pathologists (RCP) define CRM involvement as tumour found at the cut resection margin and within 1 mm of the cut margin respectively. This systematic review and meta-analysis was performed to determine the influence of CRM involvement on survival in operable oesophageal cancer.

Methods: PubMed, MEDLINE and the Cochrane Library (January 1990 to June 2012) were searched for studies correlating CRM involvement with 5-year mortality. Statistical analysis of dichotomous variables was performed using the odds ratio (OR) as the summary statistic.

Results: Fourteen studies involving 2433 patients with oesophageal cancer who had undergone potentially curative oesophagectomy were analysed. Rates of CRM involvement were 15.3 per cent (173 of 1133) and 36.5 per cent (889 of 2433) according to the CAP and RCP criteria respectively. Overall 5-year mortality rates were significantly higher in patients with CRM involvement compared with CRM-negative patients according to both CAP (OR 4.02, 95 per cent confidence interval (c.i.) 2.25 to 7.20; $P < 0.001$) and RCP (OR 2.52, 1.96 to 3.25; $P < 0.001$) criteria. CRM involvement between 0.1 and 1 mm was associated with a significantly higher 5-year mortality rate than CRM-negative status (involvement more than 1 mm from CRM) (OR 2.05, 95 per cent c.i. 1.41 to 2.99; $P < 0.001$).

Conclusion: CRM involvement is an important predictor of poor prognosis. CAP criteria differentiate a higher-risk group than RCP criteria, but overlook a patient group with similar poor outcomes.

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Introduction

Although prognosis after oesophageal cancer resection has improved over the past decade, long-term survival remains poor^{1,2}. Traditionally, the depth of tumour invasion and the number of lymph node metastases have been the most important prognostic indicators following curative oesophagectomy³, but more recently increasing interest has developed in the prognostic value of circumferential resection margin (CRM) involvement.

Although CRM involvement is a well established independent prognostic indicator in patients with rectal cancer^{4,5}, reports on its role in oesophageal cancer have been conflicting⁶⁻⁹. The two largest series of over 300 patients both found that CRM involvement was not an

independent predictor of prognosis^{9,10}, in contrast to smaller studies^{6,7,11}.

On the basis of evidence available at the time suggesting that CRM involvement resulted in higher rates of local recurrence and poorer survival¹², the UK Royal College of Pathologists (RCP) included CRM status as a required data item in its 1998 minimum data set for oesophageal cancer^{13,14}. The RCP defined CRM involvement as tumour involvement within 1 mm of the cut margin, whereas the College of American Pathologists (CAP) considered CRM involvement as tumour found at the cut margin of resection¹⁵. The optimum definition for CRM involvement in predicting outcome remains uncertain, and several studies^{6,16-19} have supported each classification.

The aim of this study was to perform a systematic review and meta-analysis of the influence of CRM involvement on overall survival in patients with operable oesophageal cancer. Secondary aims included determining the optimum definition of CRM involvement and the prognostic significance of CRM involvement in patients with T3 tumours with and without nodal involvement, and in those undergoing neoadjuvant therapy before surgery.

Methods

Literature search strategy

A systematic review of published work was conducted according to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines²⁰. A systematic search of PubMed, MEDLINE and the Cochrane Library databases was performed from January 1990 to June 2012 using the following terms to identify studies investigating the influence of CRM involvement on survival in patients with operable oesophageal cancer: oesophageal neoplasm, oesophagectomy, surgery, circumferential resection margin, outcomes and survival. The searches were limited to articles published in the English language. Further articles were identified by handsearching reference lists of all articles retrieved to identify potentially relevant studies. Searches were cross-referenced on PubMed using the related articles function. The last search date was 30 June 2012.

Data extraction

Data were extracted independently by three authors using a standard protocol. Any discrepancies were dealt with by discussion among all authors and consensus was reached. The following information was extracted from each study: first author, year of publication, study design, country of origin, definition of CRM involvement used, number of subjects with CRM involvement, histological subtype (adenocarcinoma or squamous cell carcinoma), use of neoadjuvant chemotherapy and/or chemoradiotherapy, mean follow-up, quality of study and outcome measures (all-cause mortality). Subgroup analysis was performed according to classification of CRM involvement, T3 tumours and use of neoadjuvant chemotherapy or chemoradiotherapy.

Inclusion and exclusion criteria

Studies comparing overall survival outcomes in patients with operable oesophageal cancer with and without CRM involvement were included. Where there were multiple articles by the same authors analysing data from the same

or a similar patient group, the most recent publication was included if the study periods overlapped. Review articles, case reports, experimental studies and studies that did not report outcomes were excluded. Unpublished data from conference abstracts were excluded. Only high-quality studies, or studies with more than 100 patients were included.

Statistical analysis

The meta-analysis was performed in line with the recommendations from the Cochrane Collaboration and PRISMA guidelines²⁰ using Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Statistical analysis of dichotomous variables was carried out using the odds ratio (OR) as the summary statistic. The decision to use a fixed-effects model was made in advance as minimal heterogeneity was expected. The pooled ORs were reported with 95 per cent confidence intervals (c.i.). ORs represent the odds of death during the study interval in a patient who was CRM-positive compared with a patient who was CRM-negative. An OR greater than 1 indicated a higher mortality rate in patients who had CRM involvement, and the point estimate of the OR was considered significant at the $P < 0.050$ level if the 95 per cent c.i. did not include 1.

The quality of non-randomized studies was assessed using the Newcastle–Ottawa scale²¹, which examines patient selection methods, comparability of study groups and assessment of outcome. A score of at least seven stars from a maximum of nine was considered to indicate higher quality. Heterogeneity was assessed using the I^2 value that was reported for each analysis.

Funnel plots were used to assess publication bias²², where asymmetry implied that results were subject to reporting or publication bias.

Results

The full texts of 30 papers were obtained, of which 14 cohort studies fulfilled the criteria for review (Fig. 1). Analysis was carried out on 2433 patients (1884 men; median age 64 years) with oesophageal carcinoma (adenocarcinoma, 1789; squamous cell carcinoma, 623; other histology, 21), all of whom had undergone attempted curative oesophagectomy (transthoracic, 1929; transhiatal, 277; three-stage, 124; laparoscopically assisted, 103).

Characteristics of included studies (Table 1)

All studies analysed were observational cohorts, of which two had a prospective design^{6,7}. Of the

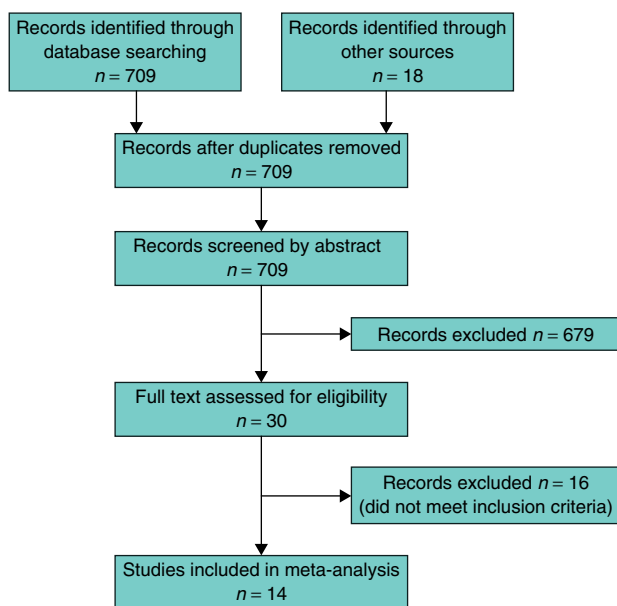


Fig. 1 Identification process for eligible studies

14 studies, 13^{6-9,11,16-19,23-26} reported 3-year and ten^{6,8,9,11,16,17,19,23,24,27} reported 5-year mortality outcomes. Only two studies reported local recurrence rates^{8,23}. The RCP classification was used in all studies to define CRM involvement. Eight studies used both the RCP and CAP classifications^{6,8,16-19,23,24}. Nine studies reported CRM involvement to be a significant predictor of poor prognosis in univariable²³ and multivariable^{6,7,11,16,17,19,25,26} analysis. In six studies, the significance of CRM involvement was negated by other factors, such as the number of lymph node metastases^{8,9,18,24,27}, T stage⁹, lymphovascular invasion¹⁰ and tumour grade^{10,27}.

Characteristics of excluded studies

Four studies were excluded from analysis^{12,28-30}. Two studies had small sample sizes (less than 100) with short durations of follow-up and Newcastle–Ottawa scores of less than 7^{12,29}. Although CRM involvement was reported in these two studies as a predictor of poor prognosis, other factors were not corrected for in multivariable analysis. Two other studies examined the influence of other factors, such as the degree of involvement of oesophageal circumference³⁰ and longitudinal resection margins²⁸.

Method of examining circumferential resection margin involvement

In 11 studies^{6,7,9,11,16-19,23,25,26}, the specimen was delivered fresh and unopened to the pathology department with

no dissection of lymph nodes. Specimens were then painted with Indian ink to allow better microscopic assessment followed by fixation in formalin for 24–48 h. Specimens were cut to between 3 and 5 mm in thickness, and assessed by one to three consultant histopathologists for CRM involvement according to the RCP and CAP criteria. Three studies did not detail the method of specimen preparation before assessment of CRM involvement^{8,24,27}. In 12 studies, the specimens were reviewed by either a single specialist pathologist^{6,8,19,23,25,27} or a team of up to three pathologists^{9,11,17,18,24,26}.

Circumferential resection margin involvement in all patients

The rates of CRM involvement were 15.3 per cent (173 of 1133) and 36.5 per cent (889 of 2433) according to the CAP and RCP criteria respectively. Overall 3-year mortality was significantly higher in patients with CRM involvement compared with CRM-negative patients according to the CAP (OR 3.13, 95 per cent c.i. 2.12 to 4.63; $P < 0.001$) and RCP (OR 2.49, 2.02 to 3.06; $P < 0.001$) criteria (Table 2). Overall 5-year mortality rates were also significantly higher in patients with CRM involvement with both CAP (OR 4.02, 2.25 to 7.20; $P < 0.001$) and RCP (OR 2.52, 1.96 to 3.25; $P < 0.001$) criteria (Table 3, Figs 2 and 3). The CAP criteria resulted in larger ORs than the RCP criteria.

Circumferential resection margin involvement in patients with T3 tumours

Overall, ten studies reported separate outcomes for patients with T3 tumours^{6,8,9,11,17,19,23-26}. The rate of CRM involvement was 14.6 per cent (110 of 754) and 42.5 per cent (597 of 1405) according to the CAP and RCP criteria respectively.

Of the ten studies, three^{11,17,26} reported separate outcomes according to node status using the RCP criteria. Positive node status negated the importance of CRM involvement in the 3-year but not the 5-year mortality analysis (Tables 2 and 3).

Circumferential resection margin involvement in patients having surgery alone

Five studies reported separate outcomes for patients who had undergone surgery alone^{7,9,16,19,27}. The rate of CRM involvement was 22.2 per cent (51 of 230) and 40.1 per cent (325 of 810) according to CAP and RCP criteria respectively.

Table 1 Characteristics of studies included in the meta-analysis

Reference	Country	Definition of CRM	Total no. of patients	Tumour at CRM	Tumour ≤ 1 mm of CRM	No. with stage \geq T3	Neoadjuvant therapy	Survival related to CRM positivity in multivariable analysis	Mean follow-up (months)	NO
Chao <i>et al.</i> ²³ (2011)	Taiwan	CAP* and RCP	151	26 (17.2)	51 (33.8)	151 (100)	CRT	No	50.0	7
Deeter <i>et al.</i> ⁶ (2009)	USA	CAP* and RCP	135	16 (11.9)	83 (61.5)	135 (100)	CRT	Yes	37.2	8
Dexter <i>et al.</i> ⁷ (2001)	UK	RCP	135	NA	64 (47.4)	95 (70.4)	None	Yes	19.0	8
Griffiths <i>et al.</i> ¹¹ (2006)	UK	RCP	249	NA	79 (31.7)	145 (58.2)	CT	Yes	70.0	9
Harvin <i>et al.</i> ⁸ (2012)	USA	CAP* and RCP	160	8 (5.0)	42 (26.3)	160 (100)	CRT	No	NA	7
Khan <i>et al.</i> ⁹ (2003)	UK	RCP	329	NA	67 (20.4)	267 (81.2)	None	No	60.0	9
Pultrum <i>et al.</i> ¹⁶ (2010)	The Netherlands	CAP and RCP*	98	25 (26)	47 (48)	58 (59)	None	Yes	37.0	9
Rao <i>et al.</i> ²⁴ (2012)	UK	CAP and RCP*	115	17 (14.8)	57 (49.6)	80 (69.6)	CT	No	38.0	8
Saha <i>et al.</i> ²⁵ (2009)	UK	RCP	105	NA	38 (36.2)	70 (66.7)	CT	Yes	26.0	8
Salih <i>et al.</i> ¹⁸ (2012)	UK	CAP and RCP*	232	38 (16.4)	89 (38.4)	171 (73.7)	CT	No	18.0	8
Scheepers <i>et al.</i> ¹⁷ (2009)	The Netherlands	CAP and RCP*	110	17 (15.5)	42 (38.2)	86 (78.2)	CT	Yes	NA	8
Sujendran <i>et al.</i> ²⁶ (2008)	UK	RCP	242	NA	56 (23.1)	151 (62.4)	CT and CRT	Yes	NA	8
Thompson <i>et al.</i> ²⁷ (2008)	Australia	RCP	240	NA	85 (35.4)	127 (52.9)	CRT	No	NA	8
Verhage <i>et al.</i> ¹⁹ (2011)	The Netherlands	CAP* and RCP	132	26 (19.7)	89 (67.4)	132 (100)	None	Yes	28.4	8

Values in parentheses are percentages. *Indicates the definition that was more prognostically significant in studies that used both definitions of circumferential resection margin (CRM) involvement. NO, Newcastle–Ottawa study quality score; CAP, College of American Pathologists (tumour at CRM); RCP, Royal College of Pathologists (tumour within 1 mm of CRM); CRT, neoadjuvant chemoradiotherapy; NA, data not available; CT, neoadjuvant chemotherapy.

Table 2 Three-year mortality related to circumferential resection margin involvement according to Royal College of Pathologists and College of American Pathologists criteria

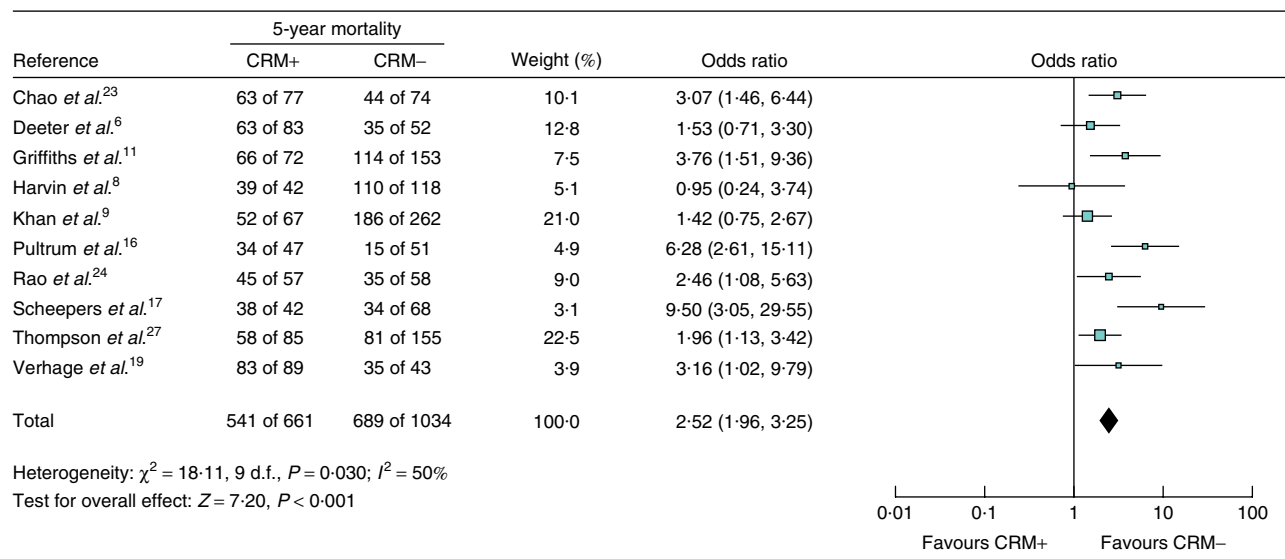
	No. of studies	CRM-positive		CRM-negative		Odds ratio	P	Heterogeneity	
		Events	Total	Events	Total			I ² (%)	P
RCP criteria									
All	13	607	861	652	1178	2.49 (2.02, 3.06)	< 0.001	38	0.080
Surgery	4	191	267	247	427	2.11 (1.47, 3.03)	< 0.001	68	0.020
NCT	6	267	392	257	507	2.88 (2.11, 3.92)	< 0.001	0	0.590
NCRT	3	149	202	148	244	2.34 (1.51, 3.61)	< 0.001	54	0.120
T3	9	430	556	364	582	2.35 (1.79, 3.10)	< 0.001	0	0.700
T3 N0	3	55	73	43	82	2.88 (1.43, 5.77)	0.003	0	0.550
T3 N1	3	86	97	99	121	1.92 (0.87, 4.26)	0.110	0	0.830
CAP criteria									
All	8	128	173	515	960	3.13 (2.12, 4.63)	< 0.001	13	0.330
Surgery	2	39	51	101	179	3.69 (1.65, 8.29)	0.002	0	0.850
NCT	3	45	72	163	385	2.40 (1.41, 4.08)	0.001	60	0.080
NCRT	3	44	50	251	396	4.51 (1.91, 10.7)	< 0.001	0	0.840
T3	6	94	110	420	669	3.83 (2.20, 6.69)	< 0.001	0	0.350
T3 N0	0					NA			
T3 N1	0					NA			

Values in parentheses are 95 per cent confidence intervals. CRM, circumferential resection margin; RCP, Royal College of Pathologists; NCT, neoadjuvant chemotherapy; NCRT, neoadjuvant chemoradiotherapy; T, tumour stage; N, node stage; CAP, College of American Pathologists; NA, data not available.

Table 3 Five-year mortality related to circumferential resection margin involvement according to Royal College of Pathologists and College of American Pathologists criteria

	No. of studies	CRM-positive		CRM-negative		Odds ratio	P	Heterogeneity	
		Events	Total	Events	Total			I ² (%)	P
RCP criteria									
All	10	541	661	689	1034	2.52 (1.96, 3.25)	< 0.001	50	0.030
Surgery	4	219	261	263	414	3.08 (2.04, 4.66)	< 0.001	74	0.009
NCT	3	149	171	183	279	4.06 (2.39, 6.89)	< 0.001	44	0.170
NCRT	4	185	229	241	341	2.08 (1.34, 3.22)	0.001	2	0.380
T3	8	438	529	492	659	1.94 (1.43, 2.63)	< 0.001	36	0.140
T3 N0	2	50	58	42	60	2.65 (1.03, 6.83)	0.040	0	0.490
T3 N1	2	55	56	45	54	7.63 (1.33, 40.6)	0.020	60	0.110
CAP criteria									
All	7	121	135	560	766	4.02 (2.25, 7.20)	< 0.001	21	0.270
Surgery	2	44	51	123	179	4.25 (1.66, 10.9)	0.003	0	0.820
NCT	2	29	34	130	191	2.50 (0.96, 6.53)	0.060	73	0.050
NCRT	3	48	50	307	396	6.34 (1.92, 20.9)	0.002	0	0.500
T3	6	102	110	515	669	3.78 (1.88, 7.57)	< 0.001	30	0.210
T3 N0	0					NA			
T3 N1	0					NA			

Values in parentheses are 95 per cent confidence intervals. CRM, circumferential resection margin; RCP, Royal College of Pathologists; NCT, neoadjuvant chemotherapy; NCRT, neoadjuvant chemoradiotherapy; T, tumour stage; N, node stage; CAP, College of American Pathologists; NA, data not available.

**Fig. 2** Influence of circumferential resection margin (CRM) involvement on 5-year mortality in all patients with oesophageal carcinoma according to the Royal College of Pathologists criteria. A Mantel–Haenszel fixed-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

Circumferential resection margin involvement in patients undergoing neoadjuvant chemotherapy

Six studies^{11,17,18,24–26} included patients who had undergone neoadjuvant chemotherapy before surgery according

to the Medical Research Council OEO2 regimen³¹. The rate of CRM involvement was 15.8 per cent (72 of 457) and 34.3 per cent (361 of 1053) according to CAP and RCP criteria respectively.

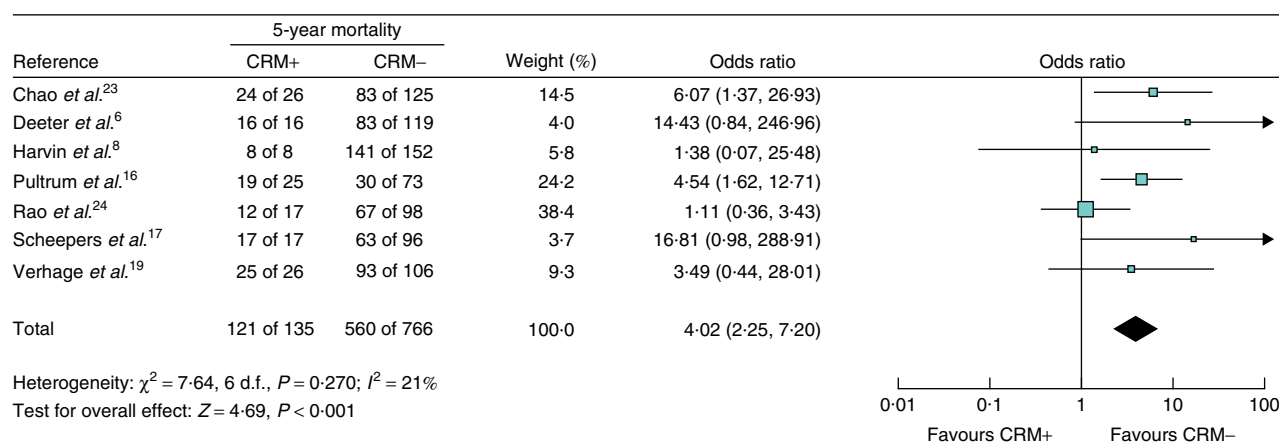


Fig. 3 Influence of circumferential resection margin (CRM) involvement on 5-year mortality in all patients with oesophageal carcinoma according to the College of American Pathologists criteria. A Mantel–Haenszel fixed-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

Table 4 Overall 3- and 5-year mortality in patients with circumferential resection margin involvement between 0.1 and 1 mm

	No. of studies	CRM 0.1–1 mm		CRM > 1 mm		Odds ratio	P	Heterogeneity	
		Events	Total	Events	Total			I^2 (%)	P
3-year mortality									
All	8	211	327	265	569	2.15 (1.59, 2.91)	< 0.001	31	0.180
Surgery	2	62	85	39	94	2.66 (1.36, 5.20)	0.004	76	0.040
NCT	3	66	116	78	231	2.70 (1.68, 4.33)	< 0.001	0	0.660
NCRT	3	83	126	148	244	1.53 (0.94, 2.49)	0.090	0	0.390
T3	5	159	229	202	345	1.75 (1.19, 2.56)	0.004	0	0.440
T3 N0	0					NA			
T3 N1	0					NA			
5-year mortality									
All	7	220	276	308	464	2.05 (1.41, 2.99)	< 0.001	52	0.050
Surgery	2	73	85	50	94	3.81 (1.72, 8.45)	0.001	0	0.420
NCT	2	54	65	69	126	3.89 (1.85, 8.18)	< 0.001	0	0.500
NCRT	3	93	126	189	244	1.03 (0.59, 1.79)	0.910	0	0.880
T3	5	184	229	259	345	1.50 (0.97, 2.33)	0.070	22	0.280
T3 N0	0					NA			
T3 N1	0					NA			

Values in parentheses are 95 per cent confidence intervals. CRM, circumferential resection margin; NCT, neoadjuvant chemotherapy; NCRT, neoadjuvant chemoradiotherapy; T, tumour stage; N, node stage; NA, data not available.

Circumferential resection margin involvement in patients receiving neoadjuvant chemoradiotherapy

Five studies included patients who had undergone neoadjuvant chemoradiotherapy before surgery^{6,8,23,26,27}, one of which did not report combined outcomes²⁷. One study²⁶ included only nine patients who had received neoadjuvant chemoradiotherapy, and was therefore excluded from the analysis. The rate of CRM involvement was 11.2 per cent (50 of 446) and 31.9 per cent (259 of 812) according to CAP and RCP criteria respectively.

Outcome in patients with circumferential resection margin involvement of 0.1–1 mm

Meta-analysis of the eight studies that used both definitions was performed to determine the outcome in patients separated by the RCP but not the CAP criteria (Table 4, Figs 4 and 5). Three- and 5-year mortality rates were significantly higher in this group of patients compared with rates in those with no involvement within 1 mm of the cut margin (OR 2.15, 95 per cent c.i. 1.59 to 2.91, $P < 0.001$ and OR 2.05, 1.41 to 2.99, $P < 0.001$ respectively).

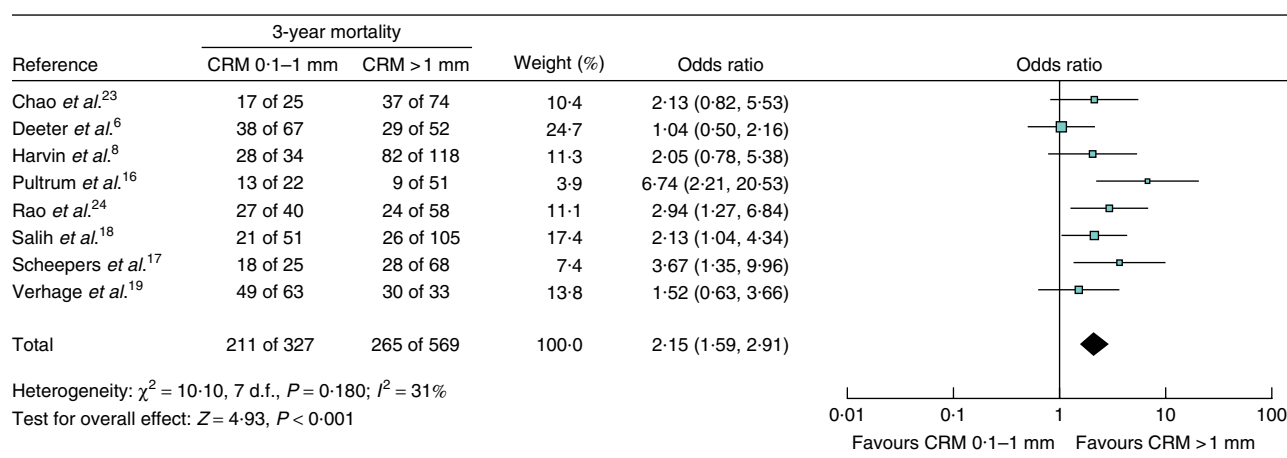


Fig. 4 Influence of circumferential resection margin (CRM) involvement of 0.1–1 mm on 3-year mortality in all patients with oesophageal carcinoma. A Mantel–Haenszel fixed-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

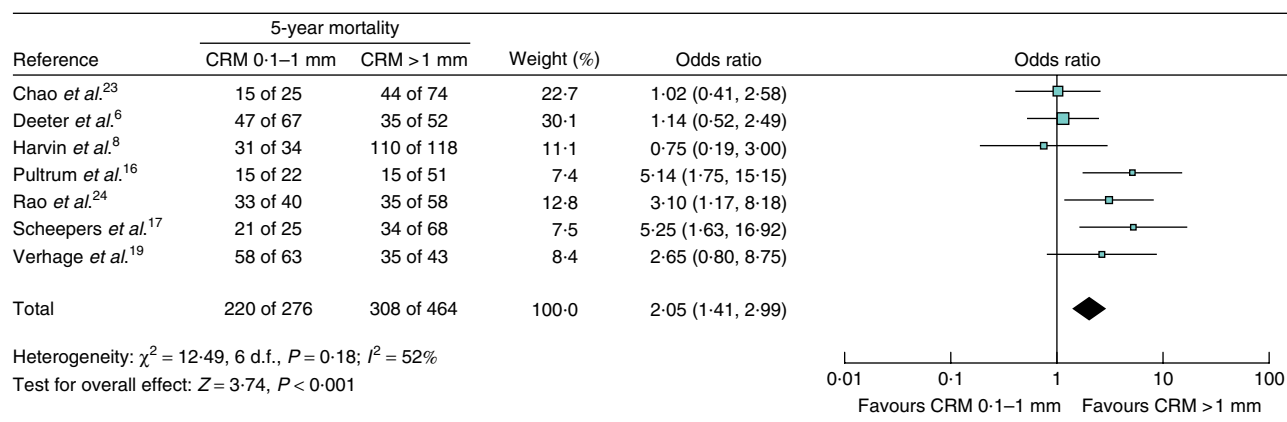


Fig. 5 Influence of circumferential resection margin (CRM) involvement of 0.1–1 mm on 5-year mortality in all patients with oesophageal carcinoma. A Mantel–Haenszel fixed-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

However, this difference in outcome was not significant in patients who had had neoadjuvant chemoradiotherapy.

Heterogeneity and publication bias

Statistical heterogeneity was identified in only three analyses using the RCP criteria: 3- and 5-year mortality in patients who had undergone surgery alone, and 5-year mortality in all patients. There was no heterogeneity among analyses using the CAP criteria.

The funnel plots for 3- and 5-year mortality rates for all patients were symmetrical, indicative of the absence of publication bias.

Discussion

The main findings from the 14 studies identified were that 3- and 5-year mortality rates in patients with CRM involvement according to both CAP and RCP criteria were significantly higher than rates in patients without CRM involvement. CRM involvement as defined by the CAP criteria differentiated a higher-risk group of patients than the RCP criteria, as evidenced by the larger OR values in the 3- and 5-year mortality analysis of all patients. However, the group of patients not considered by the CAP criteria did have a significantly poorer outcome than patients without CRM involvement.

The RCP criteria therefore give important additional information compared with the CAP criteria. CRM involvement remained an important prognostic indicator despite being lower in patients who had undergone neoadjuvant chemoradiotherapy.

The presence of lymph node metastases appeared to negate the importance of CRM involvement, with the OR for 3-year mortality in patients with lymph node metastases straddling 1, indicating that CRM involvement was not associated with poorer outcomes. Conversely, the ORs for 5-year mortality were greater than 1, indicating that CRM involvement remained important. However, these outcomes should be interpreted with caution as only three studies that used the RCP criteria stratified for the presence of lymph node metastases^{11,17,26}.

The strengths of this study are the large sample size analysed. Two of the 14 studies were ostensibly about other prognostic variables such as histological grade of tumour and the number of lymph node metastases^{10,27}. The inclusion of such studies reduced concern about publication bias as the decision to publish was unrelated to CRM involvement and outcome. Moreover, in most analyses, heterogeneity was low and there was no publication bias. Only high-quality studies as assessed by the Newcastle–Ottawa score and studies with more than 100 patients were included, thereby strengthening the conclusions. Most studies used similar histopathological specimen preparation and analysis, thus allowing comparison of CRM measurements.

This study has limitations. Meta-analysis of retrospective cohort studies is regrettably sensitive to confounding. Many factors influence prognosis following surgery such as age, stage of disease, surgical technique, and use of neoadjuvant chemotherapy or chemoradiotherapy. In attempts to reduce confounding, 12 studies adjusted for two or more of these variables during analysis. Subgroup analysis was limited, as not all studies reported separate outcomes according to stage of disease and treatment, and not all reported 5-year mortality. Three-year mortality rates were therefore analysed, as this allowed the inclusion of four additional studies^{7,18,25,26}.

CRM involvement is an important and significant predictor of poor prognosis. The issue of a threatened CRM forms an integral part of the wider argument relating to the most appropriate neoadjuvant therapy regimens for patients with operable yet locally advanced oesophageal cancer. Although CRM involvement as defined by the CAP criteria differentiates a higher-risk group of patients than the RCP criteria, this system overlooks the group of patients with poorer outcomes identified by the RCP system where there is tumour within 1 mm of the margin.

Consensus regarding the most accurate and prognostically important definition of CRM involvement would be welcome; in the interim, arguably the exact nearest distance of the oesophageal tumour from the CRM should form part of routine pathology reporting in oesophageal cancer.

Disclosure

The authors declare no conflict of interest.

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