Original article

Patterns of recurrence in early-stage oesophageal cancer after chemoradiotherapy and surgery compared with surgery alone

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Background: **Patterns of disease recurrence in patients with oesophageal cancer following treatment with neoadjuvant chemoradiotherapy and surgery (nCRTS) or surgery alone are poorly reported. An understanding of patterns of disease recurrence is important for subsequent treatment planning.**

Methods: **An analysis was undertaken of patterns of disease recurrence from a phase III multicentre randomized trial (FFCD9901) comparing nCRTS with surgery alone in patients with stage I and II oesophageal cancer.**

Results: **Some 170 patients undergoing surgical resection were included in the study. R0 resection rates were similar in the two groups: 94 per cent following nCRTS *versus* 92 per cent after surgery alone ($P = 0{\cdot}749$). After a median follow-up of 94·2 months, recurrent disease was found in 39·4 per cent of the overall cohort (31 per cent after nCRTS *versus* 47 per cent following surgery alone; $P = 0{\cdot}030$). Locoregional recurrence was diagnosed in 41 patients (17 *versus* 30 per cent respectively; $P = 0{\cdot}047$) and distant metastatic recurrence in 47 (23 *versus* 31 per cent respectively; $P = 0{\cdot}244$). Metastatic recurrence was more frequent in patients with adenocarcinoma than in those with squamous cell cancer (40 *versus* 23·1 per cent respectively; $P = 0{\cdot}032$). ypT0 N0 category was associated with prolonged time to mixed locoregional and metastatic recurrence ($P = 0{\cdot}009$), and time to locoregional ($P = 0{\cdot}044$) and metastatic ($P = 0{\cdot}055$) recurrence. In multivariable analysis, node-positive disease predicted both locoregional ($P = 0{\cdot}001$) and metastatic ($P < 0{\cdot}001$) recurrence.**

Conclusion: **Locoregional disease control following nCRTS indicated a local field effect not related solely to completeness of resection. pN+ disease was strongly predictive of time to locoregional and metastatic disease recurrence.**

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Introduction

The prognosis for patients with oesophageal cancer remains bleak. Despite advances in diagnosis and treatment, surgical resection may be appropriate in as few as 15–20 per cent of patients, and only 15–34 per cent of these patients can be expected to survive 5 years[1]. Although improved survival has been gained through neoadjuvant treatments[2], with estimated 5-year survival rates of 41–47 per cent in recent trials[3,4], most patients who undergo oesophagectomy continue to die from disease recurrence[5].

Meta-analysis of randomized clinical trials comparing neoadjuvant chemoradiotherapy followed by surgery (nCRTS) with surgery alone has shown that trimodal therapy improves survival in patients with locally advanced disease as a result of tumour downstaging facilitating more

complete (R0) resections, and better regional and systemic control of disease[2]. Reports documenting patterns of disease recurrence after nCRTS are scarce, yet understanding this is important for subsequent treatment planning. If recurrence through distant metastases predominates then better systemic treatments would seem logical, whereas if locoregional recurrence is most common then radiotherapy fields and the quality of surgical resection required may merit greater attention.

Few data exist regarding the patterns of disease recurrence in early disease (stage I and II). In 2000, the Fédération Francophone de Cancérologie Digestive (FFCD) completed a multicentre randomized clinical phase III trial (FFCD9901) comparing nCRTS with surgery alone in patients with stage I or II oesophageal cancer[4]. Unlike preceding trials comparing these treatments, R0 resection rates were equivalent between the groups. This, together with a long median follow-up of 93·6 months, provided an ideal background to evaluate patterns of disease recurrence and identify predictive factors for locoregional and metastatic recurrence in stage I and II oesophageal cancer.

Methods

The primary objective of FFCD9901 was to determine whether nCRTS improves survival in early-stage oesophageal cancer. The trial design was registered on the ClinicalTrials.gov website under the identifying number NCT00047112. Detailed methodology and the main outcomes have been reported previously[4]. Patients less than 75 years of age, judged suitable for curative resection, with untreated stage I and II (T1 or T2, N0 or N1, and T3 N0, M0) oesophageal adenocarcinoma or squamous cell carcinoma (SCC) were included. Patients with junctional Siewert type II and III tumours were excluded. Staging was performed systematically by CT of the thorax, abdomen and pelvis, as well as by endoscopic ultrasonography. PET, cervical ultrasound imaging and radionucleotide bone scanning were optional. Only patients who underwent surgical resection were included in the present analysis.

Patient randomization and treatment

Patients were assigned randomly by telephone at the FFCD Data Centre by means of a minimization programme. Stratification was done by institution, histology, stage of disease (I *versus* IIA *versus* IIB) and tumour location (above or below the carina).

Surgery

Patients in the surgery-alone group had their operation within 4 weeks of randomization, and those receiving nCRTS proceeded to surgery 4–8 weeks after completion of the neoadjuvant treatment. All resections involved open thoracotomy, with a three-stage procedure and cervical anastomosis for tumours with a proximal margin above the carina. The trial protocol required the performance of an extended two-field lymphadenectomy.

Neoadjuvant chemoradiotherapy

Chemotherapy and radiotherapy were delivered concomitantly. Details of the schedules and radiation fields have been described previously[4]. For tumours with a proximal margin more than 30 cm from the dental arch, inclusion of the coeliac area in the clinical target volume was obligatory.

Histopathological examination

Pathological examination described tumour type, extension, number of lymph nodes retrieved and involved, and resection margin status. Curative (R0) resection was defined as no evidence of tumour at any resection margin[6]; R1 indicated residual microscopic disease; and R2 the presence of macroscopic tumour. Pathological response to nCRTS was defined by tumour regression grade (TRG) according to the Mandard classification[7].

Patient follow-up and identification of recurrent disease

Patients were seen every 4 months during the first 2 years from randomization, then 4-monthly for 2 years, 6-monthly until 5 years and annually thereafter. At each follow-up, patients underwent CT and clinical examination. Endoscopic surveillance was performed when indicated clinically, with PET, radionucleotide scanning or ultrasonography when indicated by new findings on surveillance CT, or by new symptoms.

Disease recurrence was defined as locoregional (oesophageal bed, anastomotic or regional lymph nodes) or metastatic (supraclavicular nodes, para-aortic nodes below the renal veins, peritoneal metastases or distant organ metastases), and was established on the basis of histological or cytological sampling. When this was not possible, definitive radiological evidence of disease recurrence was required.

Statistical analysis

Time to recurrence was defined as the time from date of randomization to date of first recurrence (locoregional, metastatic or mixed) and was estimated using the Kaplan–Meier method. Curves were compared with the

Table 1 Patient, tumour and pathological characteristics

	Resected population ($n = 170$)	nCRTS ($n = 81$)	Surgery alone ($n = 89$)	P†
Age (years)*	57·8 (36·9–76·4)	57·8 (40·1–76·4)	57·6 (36·9–74·3)	0·813§
Sex ratio (M : F)	146 : 24	73 : 8	73 : 16	0·130
Tumour histology				0·795‡
Squamous cell carcinoma	121 (71·2)	57 (70)	64 (72)	
Adenocarcinoma	48 (28·2)	23 (28)	25 (28)	
Undifferentiated	1 (0·6)	1 (1)	0 (0)	
Tumour location				0·245
Above carina	15 (8·8)	5 (6)	10 (11)	
Below carina	155 (91·2)	76 (94)	79 (89)	
WHO performance status				1·000‡
0	127 (74·7)	61 (75)	66 (74)	
1	41 (24·1)	20 (25)	21 (24)	
2	1 (0·6)	0 (0)	1 (1)	
Missing	1 (0·6)	0 (0)	1 (1)	
cT category				0·770
cT1	42 (24·7)	21 (26)	21 (24)	
cT2	97 (57·1)	47 (58)	50 (56)	
cT3	31 (18·2)	13 (16)	18 (20)	
cN category				0·587
cN0	125 (73·5)	58 (72)	67 (75)	
cN1	45 (26·5)	23 (28)	22 (25)	
cTNM stage				0·856
I	33 (19·4)	15 (19)	18 (20)	
IIA	92 (54·1)	43 (53)	49 (55)	
IIB	45 (26·5)	23 (28)	22 (25)	
pT category				< 0·001‡
pT0	34 (20·0)	33 (41)	1 (1)	
pT1	49 (28·8)	21 (26)	28 (31)	
pT2	32 (18·8)	12 (15)	20 (22)	
pT3	43 (25·3)	13 (16)	30 (34)	
pT4	12 (7·1)	2 (2)	10 (11)	
pN category				0·016
pN0	98 (57·6)	56 (69)	42 (47)	
pN1	38 (22·4)	15 (19)	23 (26)	
pN2	22 (12·9)	8 (10)	14 (16)	
pN3	12 (7·1)	2 (2)	10 (11)	
pTNM stage				< 0·001‡
0	31 (18·2)	29 (36)	2 (2)	
I	38 (22·4)	14 (17)	24 (27)	
II	56 (32·9)	28 (35)	28 (31)	
III	45 (26·5)	10 (12)	35 (39)	
R0 resection				0·749‡
Yes	158 (92·9)	76 (94)	82 (92)	
No	10 (5·9)	4 (5)	6 (7)	
Missing	2 (1·2)	1 (1)	1 (1)	
No. of lymph nodes invaded				0·001
0	97 (57·1)	56 (69)	41 (46)	
1–3	47 (27·6)	21 (26)	26 (29)	
> 3	24 (14·1)	4 (5)	20 (22)	
Missing	2 (1·2)	0 (0)	2 (2)	
No. of lymph nodes resected				
≥ 15	114 (67·1)	48 (59)	66 (74)	0·021
< 15	54 (31·8)	33 (41)	21 (24)	
Missing	2 (1·2)	0 (0)	2 (2)	
≥ 23	67 (39·4)	25 (31)	42 (47)	0·021
< 23	101 (59·4)	56 (69)	45 (51)	
Missing	2 (1·2)	0 (0)	2 (2)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). The fifth edition of the TNM classification of malignant tumours was used[8]. nCRTS, neoadjuvant chemoradiotherapy followed by surgery; WHO, World Health Organization. †χ^2 test, except ‡Fisher's exact test and §Wilcoxon test.

Table 2 Patterns of disease recurrence

	nCRTS ($n = 81$)	Surgery alone ($n = 89$)	P*
Recurrence at any site	25 (31)	42 (47)	0·030
Locoregional recurrence			
≥ 1 locoregional recurrence	14 (17)	27 (30)	0·047
Metastatic recurrence			
≥ 1 metastatic recurrence	19 (23)	28 (31)	0·244
Single site	12 (15)	20 (22)	
Lung	4 (5)	7 (8)	
Liver	4 (5)	3 (3)	
Bone	2 (2)	5 (6)	
Other	2 (2)	5 (6)	
Multiple sites	7 (9)	8 (9)	
Squamous cell carcinoma ($n = 121$)	($n = 57$)	($n = 64$)	
≥ 1 locoregional recurrence	11 (19)	20 (31)	0·133
≥ 1 metastatic recurrence	14 (25)	14 (22)	0·727
Adenocarcinoma ($n = 48$)	($n = 23$)	($n = 25$)	
≥ 1 locoregional recurrence	3 (13)	7 (28)	0·202
≥ 1 metastatic recurrence	5 (22)	14 (56)	0·015

Values in parentheses are percentages. nCRTS, neoadjuvant chemoradiotherapy followed by surgery. *χ^2 test.

log rank test. The Fleming–Harrington weighted log rank test ($\rho = 0$, $\lambda = 3$) was also used to estimate whether the treatment effect was more pronounced in the later part of the follow-up interval. Corresponding hazard ratios (HRs) were calculated with 95 per cent c.i. using the Cox proportional hazards model. The influence of potential predictive factors for time to locoregional recurrence and metastatic recurrence was analysed using univariable and multivariable Cox regression models. Treatment group, variables in univariable analysis with $P \leq 0{\cdot}100$ and non-duplicated variables were entered into the multivariable Cox regression model. Median follow-up was calculated according to reverse Kaplan–Meier estimates. Qualitative variables were described as numbers and percentages, and quantitative variables as median (range) values. χ^2 or Fisher's exact test was used to compare proportions between treatment groups; continuous data were compared with the Wilcoxon test. Analyses were performed using SAS® version 9.4 software (SAS Institute, Cary, North Carolina, USA).

Results

Between June 2000 and June 2009, 195 patients from 30 French centres were assigned randomly to nCRTS (98 patients) or surgery alone (97). Compared with surgery alone, nCRTS did not improve the R0 resection rate or survival, but was associated with increased postoperative mortality in patients with stage I/II disease. Of the 195 recruited patients, only 170 who underwent surgical resection (89 nCRTS, 81 surgery alone) were included in the present study.

Individual and tumour characteristics were similar in the two groups (*Table 1*). The median age of patients was 57·8 years. Most patients had SCC (71·2 per cent) located below the carina (91·2 per cent), and the majority (92·9 per cent) had an intrathoracic anastomosis. Of included patients, 19·4 per cent were classified before treatment as having stage I (cT1 N0 M0), 54·1 per cent stage IIA (cT2–T3 N0 M0) and 26·5 per cent stage IIB (T1–2 N1 M0) disease.

Of the patients allocated to nCRTS, 76 (94 per cent) of 81 received the total radiation dose per protocol (45 Gy), 77 (95 per cent) completed one cycle of chemotherapy and 71 (88 per cent) completed the second cycle. No patient was lost to follow-up.

Disease downstaging and histopathological analysis in resected patients

R0 resection rates were similar in the two groups: 94 per cent following nCRTS *versus* 92 per cent after surgery alone ($P = 0{\cdot}749$) (*Table 1*). Histopathological examination showed that 45 patients had pTNM stage III disease (10 in the nCRTS group and 35 of those having surgery alone; $P < 0{\cdot}001$). Significant disease downstaging was observed following nCRTS (*Table 1*).

The median number of lymph nodes analysed was 16 (0–47) after nCRTS and 22 (3–58) after surgery alone ($P = 0{\cdot}001$), and the median number of lymph nodes with tumour involvement was 0 (0–10) and 1 (0–25) respectively ($P < 0{\cdot}001$). Node-positive (pN+) disease was found in 25 patients (31 per cent) after nCRTS and 47 (53 per cent) after surgery alone ($P = 0{\cdot}004$).

Disease recurrence and patterns related to histology

After a median follow-up of 94·2 months, and a median survival of 41·5 months for the 170 patients who proceeded to surgery, recurrent disease was identified in 67 patients (39·4 per cent): 25 (31 per cent) following nCRTS and 42 (47 per cent) after surgery alone ($P = 0{\cdot}030$).

Locoregional recurrence was diagnosed in 41 patients: 14 (17 per cent) after nCRTS *versus* 27 (30 per cent) after surgery alone ($P = 0{\cdot}047$). Metastatic recurrence was identified in a total of 47 patients (27·6 per cent): 19 (23 per cent) *versus* 28 (31 per cent) respectively ($P = 0{\cdot}244$). Mixed locoregional/metastatic recurrence was seen in 21 of the 67 patients: 8 (10 per cent) after nCRTS *versus* 13 (15 per cent) after surgery alone ($P = 0{\cdot}349$). Isolated locoregional recurrence occurred in 20 patients (6 (7 per cent)

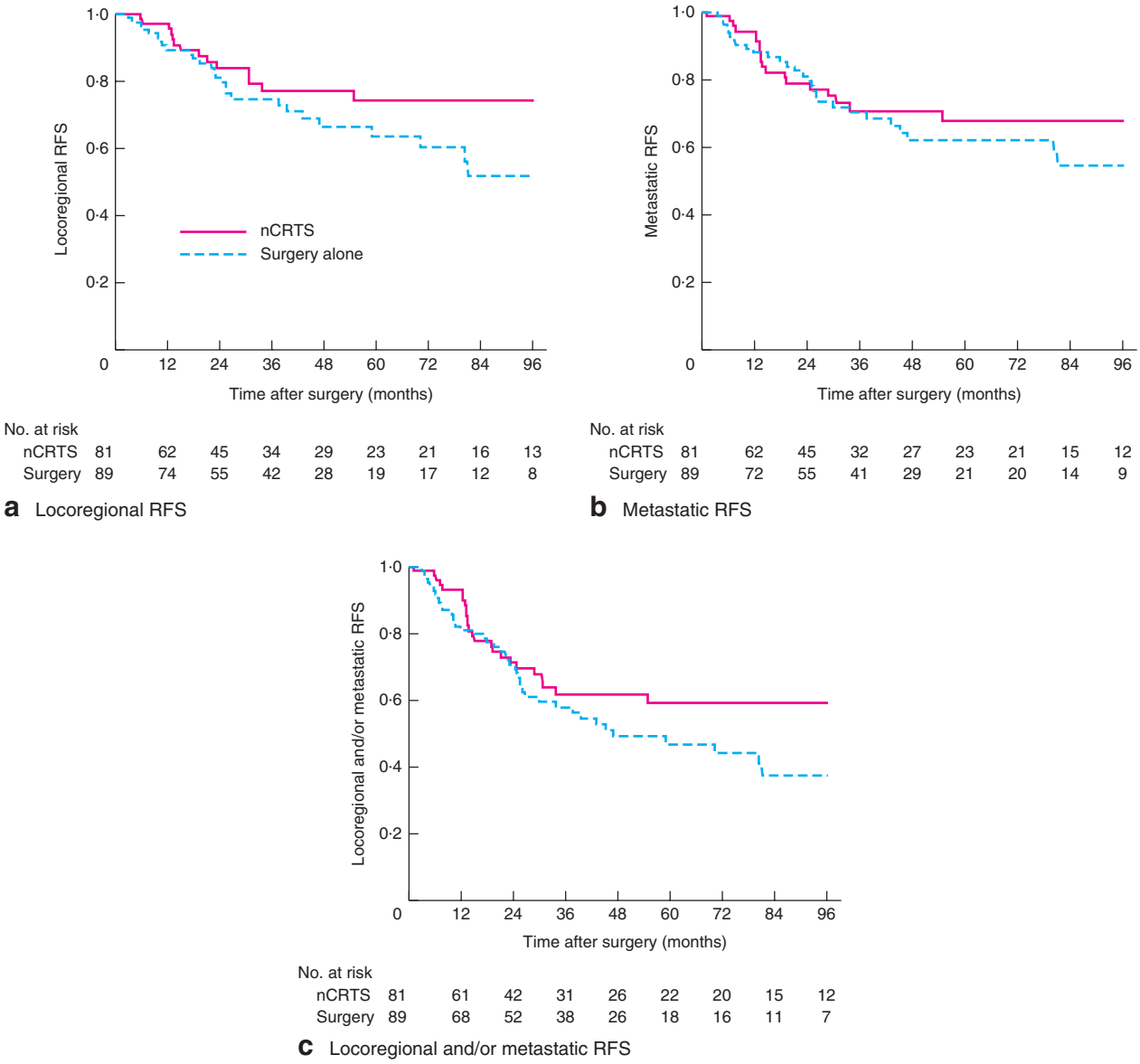

Fig. 1 Time to recurrence after neoadjuvant chemoradiotherapy followed by surgery (nCRTS) or surgery alone in 170 patients with oesophageal cancer: **a** locoregional recurrence-free survival (RFS); **b** metastatic RFS; **c** locoregional and/or metastatic RFS. **a** Hazard ratio (HR) 0·60 (95 per cent c.i. 0·31 to 1·14; $P = 0·113$, log rank test; $P = 0·032$, Fleming–Harrington test); **b** HR 0·80 (0·45 to 1·43; $P = 0·443$, log rank test; $P = 0·106$, Fleming–Harrington test); **c** HR 0·68 (0·41 to 1·12; $P = 0·124$, log rank test; $P = 0·016$, Fleming–Harrington test)

versus 14 (16 per cent) respectively; $P = 0·093$), whereas 26 had isolated metastatic recurrence (11 (14 per cent) *versus* 15 (17 per cent) respectively; $P = 0·554$). Site-specific disease recurrence is detailed in *Table 2*. Of patients who had an R1 resection, only one of four patients in the nCRTS group developed metastatic recurrence, and one of six in the surgery-alone group developed mixed locoregional/metastatic recurrence.

At 5 years, the locoregional recurrence rate was 74 and 64 per cent in the nCRTS and surgery-alone groups respectively ($P = 0·113$), and the metastatic recurrence rate was 68 and 62 per cent ($P = 0·443$) (*Fig. 1*). When recurrence rates were compared using the Fleming–Harrington test, time to both locoregional ($P = 0·032$) and mixed ($P = 0·016$) recurrence was decreased significantly after nCRTS, but not time to metastatic recurrence ($P = 0·106$).

Table 3 Univariable and multivariable Cox regression analysis of factors predictive of locoregional recurrence in 170 patients

	Locoregional recurrence	Univariable HR	Multivariable HR	*P*
At randomization				
Treatment group (nCRTS *versus* surgery alone)	14 *versus* 27	0·60 (0·31, 1·14)	0·79 (0·40, 1·57)	0·505
Age (> 60 *versus* ≤ 60 years)	19 *versus* 22	1·49 (0·81, 2·76)		
Sex (F *versus* M)	4 *versus* 37	0·68 (0·24, 1·90)		
Histology (adenocarcinoma *versus* SCC)	10 *versus* 31	0·96 (0·47, 1·96)		
Tumour location (below *versus* above carina)	38 *versus* 3	1·09 (0·34, 3·52)		
WHO performance status (≥ 1 *versus* 0)	9 *versus* 32	0·97 (0·46, 2·04)		
cT category				
3 *versus* 1	11 *versus* 7	3·34 (1·29, 8·66)	n.i.	
2 *versus* 1	23 *versus* 7	1·87 (0·80, 4·35)		
cN category (1 *versus* 0)	9 *versus* 32	0·82 (0·39, 1·71)		
After surgery				
pT category (2–4 *versus* 0–1)	26 *versus* 15	1·91 (1·01, 3·60)	0·85 (0·38, 1·93)	0·704
pN category (N+ *versus* 0)	25 *versus* 16	5·06 (3·01, 8·52)	3·76 (1·69, 3·86)	0·001
No. of lymph nodes invaded				
> 3 *versus* 0	3 *versus* 15	1·28 (0·37, 4·44)		
≤ 3 *versus* 0	22 *versus* 15	5·66 (2·88, 11·13)	n.i.	
No. of lymph nodes resected				
≥ 15 *versus* < 15	26 *versus* 14	0·83 (0·43, 1·59)		
≥ 23 *versus* < 23	11 *versus* 29	0·62 (0·31, 1·24)		
Resection (R0 *versus* R1–2)	39 *versus* 1	0·76 (0·10, 5·56)		

Values in parentheses are 95 per cent c.i. HR, hazard ratio; nCRTS, neoadjuvant chemoradiotherapy followed by surgery; SCC, squamous cell carcinoma; WHO, World Health Organization; n.i., not included to avoid duplication of included variables.

At least one focus of recurrent disease was found in 44 (36·4 per cent) of the 121 patients with SCC, identified in 19 (33 per cent) of 57 following nCRTS compared with 25 (39 per cent) of 64 after surgery alone ($P = 0·513$). By comparison, 23 (48 per cent) of the 48 patients with adenocarcinoma had at least one focus of recurrent disease: six (26 per cent) of 23 patients with adenocarcinoma in the nCRTS group and 17 (68 per cent) of 25 in the surgery-alone group ($P = 0·004$).

Locoregional and metastatic recurrence rates based on tumour histology are shown in *Table 2*. In total, 31 (25·6 per cent) of the 121 patients with SCC had locoregional recurrence, compared with ten (21 per cent) of the 48 with adenocarcinoma ($P = 0·513$), whereas metastatic recurrence was seen in 19 patients (40 per cent) with adenocarcinoma compared with only 28 (23·1 per cent) with SCC ($P = 0·032$). Estimated time to locoregional recurrence did not differ between histological subtypes ($P = 0·911$), whereas time to metastatic recurrence was significantly shorter for patients with adenocarcinoma ($P = 0·007$).

Pathological response and disease recurrence

A pathological complete response (ypT0 N0) was seen in 28 patients (16·5 per cent). Data on TRG were available for 76 of 81 patients who received nCRTS. Complete response of the primary tumour (TRG1) occurred in 33 patients, rare residual cancer cells (TRG2) in 23, ten patients were classified as TRG3, eight as TRG4 and two showed a complete absence of tumour response (TRG5). When patients with a complete tumour response (TRG1) were compared with those with an incomplete treatment response (TRG2–5), there were no differences in 5-year rates of locoregional (79 *versus* 72 per cent respectively; $P = 0·321$) or metastatic (70 *versus* 67 per cent; $P = 0·623$) recurrence. When the 28 patients who had a complete pathological response (ypT0 N0) were compared with the other 142 patients (those with an incomplete response plus patients having surgery alone), ypT0 N0 was associated with prolonged time to mixed locoregional and metastatic recurrence ($P = 0·009$), time to locoregional recurrence ($P = 0·044$) and time to metastatic recurrence ($P = 0·055$).

Factors predicting locoregional and metastatic recurrence

Univariable and multivariable analyses of predictive factors for the development of locoregional and metastatic recurrence are shown in *Tables 3* and *4* respectively. In multivariable analysis, only pN+ disease predicted time to locoregional recurrence ($P = 0·001$), whereas adenocarcinoma ($P = 0·021$) and pN+ disease ($P < 0·001$) predicted time to metastatic recurrence. nCRTS was not found to be protective against either locoregional or metastatic recurrence.

Discussion

The final analysis of the FFCD9901 trial showed that nCRTS did not provide any survival advantage compared with surgery alone in patients with stage I and

Table 4 Univariable and multivariable Cox regression analysis of factors predictive of metastatic recurrence in 170 patients

	Metastatic recurrence	Univariable HR	Multivariable HR	*P*
At randomization				
Treatment group (nCRTS *versus* surgery alone)	19 *versus* 28	0·80 (0·45, 1·43)	1·03 (0·56, 1·93)	0·917
Age (> 60 *versus* ≤ 60 years)	17 *versus* 30	0·88 (0·49, 1·60)		
Sex (F *versus* M)	2 *versus* 45	0·26 (0·06, 1·09)	0·35 (0·08, 1·47)	0·152
Histology (adenocarcinoma *versus* SCC)	19 *versus* 28	2·18 (1·21, 3·90)	2·04 (1·12, 3·71)	0·021
Tumour location (below *versus* above carina)	43 *versus* 4	0·91 (0·33, 2·55)		
WHO performance status (≥ 1 *versus* 0)	8 *versus* 39	0·67 (0·31, 1·43)		
cT category				
3 *versus* 1	11 *versus* 8	2·74 (1·10, 6·84)	n.i.	
2 *versus* 1	28 *versus* 8	1·94 (0·89, 4·27)		
cN category (1 *versus* 0)	11 *versus* 36	0·88 (0·45, 1·73)		
After surgery				
pT category (2–4 *versus* 0–1)	29 *versus* 18	1·74 (0·97, 3·14)	0·51 (0·23, 1·11)	0·090
pN category (N+ *versus* 0)	33 *versus* 14	5·54 (2·92, 10·49)	7·84 (3·50, 17·61)	< 0·001
No. of lymph nodes invaded				
> 3 *versus* 0	14 *versus* 14	7·72 (3·64, 16·38)	n.i.	
≤ 3 *versus* 0	18 *versus* 14	4·21 (2·07, 8·58)	n.i.	
No. of lymph nodes resected				
≥ 15 *versus* < 15	33 *versus* 13	1·19 (0·63, 2·27)		
≥ 23 *versus* < 23	20 *versus* 26	1·31 (0·73, 2·35)		
Resection (R0 *versus* R1–2)	44 *versus* 2	1·32 (0·32, 5·46)		

Values in parentheses are 95 per cent c.i. HR, hazard ratio; nCRTS, neoadjuvant chemoradiotherapy followed by surgery; SCC, squamous cell carcinoma; WHO, World Health Organization; n.i., not included to avoid duplication of included variables.

II oesophageal cancer[4]. Patterns of disease recurrence after oesophagectomy are poorly reported and recurrence patterns in early-stage disease are not known. In the Dutch CROSS trial[9], R0 resection rates of 92 and 69 per cent were seen after nCRTS and surgery alone respectively ($P < 0·001$) – a result typical of studies comparing these treatment strategies in patients with more advanced tumours, and where comparative analysis of the relative contributions of surgery and radiotherapy to local disease control are difficult to separate. In FFCD9901, R0 resection rates were comparable in both groups[4]. This, together with a prolonged median follow-up of 94·2 months, provided an acceptable background to assess the relative contribution of neoadjuvant chemoradiotherapy to local and distant disease control.

Despite being limited to early-stage disease, 67 (39·4 per cent) of the 170 patients who underwent resection were found to have disease recurrence during follow-up, emphasizing that, even with early diagnosis, recurrence remains a significant problem. Despite the similarity of surgery in the two groups, there were fewer locoregional recurrences following nCRTS ($P = 0·047$), although there was no effect on the number of metastatic recurrences ($P = 0·244$). Other studies[10–12] have also shown a reduction in locoregional recurrence after nCRTS. It is, however, difficult to distinguish whether this is a local sterilizing effect of radiotherapy, its tumour downstaging effect or a synergistic effect. The patterns of disease recurrence reported from the CROSS study[11] suggest that radiotherapy reduced the 'in-field' mediastinal recurrence rate from 20·5 to 7 per cent after nCRTS, yet recurrence rates were similar at sites not included in the radiation field (coeliac and supraclavicular nodes). Both groups in the present study had comparable R0 resection rates, but with more locoregional recurrences after surgery alone. This suggests that chemoradiotherapy does improve locoregional disease control beyond simply facilitating a complete resection.

Despite improved local control with nCRTS, neither the estimated time to locoregional nor metastatic recurrence rate at 5 years was different between the groups. This probably reflects the inclusion of patients with early-stage disease in the trial as well as the quality of the surgery in both arms. It appears that the estimated time to locoregional recurrence curves diverged after 2 years (*Fig. 1a*), suggesting that a proportion of patients were destined to develop early recurrence. The beneficial effect of neoadjuvant chemoradiotherapy appears to accrue in those who are disease-free beyond 2 years. Identification of predictive factors for early recurrence may identify a subgroup of patients who do not benefit from aggressive treatment designed to cure.

If the local control advantage that follows radiotherapy is to translate into a survival advantage, the risk of distant metastatic disease must also be minimized. A previous suggestion[13] that lower-third adenocarcinomas have

higher potential for haematogenous spread is supported by the present results. Although caution has to be exercised in subgroup analysis, a greater proportion of patients with adenocarcinoma developed recurrent metastatic disease. Metastatic failures after trimodal therapy are theoretically due to a combination of unrecognized micrometastatic disease, persistent local disease acting as the nidus for subsequent metastases, and failures of systemic treatment. Improved systemic and targeted treatments are needed.

For of all stages of oesophageal cancer, there is strong evidence that patients who achieve a complete pathological response to neoadjuvant treatment have improved outcomes[14–16]. This was confirmed in the present study, where a pathological complete response was associated with prolonged time to recurrence. In contrast to other studies[15], complete response in the primary tumour (TRG1) had no effect on time to locoregional or metastatic recurrence, although this may also reflect the fact that the present study was confined to patients with early-stage disease.

Although the prognostic value of the number of resected lymph nodes after neoadjuvant therapy for oesophageal cancer remains unclear[11,17], the number of positive lymph nodes in the resected specimen after nCRTS retains strong prognostic value[17]. Regardless of treatment, the present study confirmed the observation that patients with pN+ disease have poorer overall survival and shorter time before disease relapse[11,15,17]. Multivariable analyses confirmed that pN+ disease was predictive of time to locoregional and metastatic disease recurrence. As response to treatment cannot be predicted reliably before operation, and as surgery optimizes local disease control even with a complete clinical response to neoadjuvant chemoradiotherapy[18], it seems logical to advocate radical surgery even for small tumours.

It is important to acknowledge that the present results are confined to patients with early tumours and may not be generalizable to other disease stages. It seems reasonable to suggest that the observed differences may be exaggerated in more advanced disease where incomplete resection is more common, particularly after surgery alone. Differences between this trial and the CROSS study, with which some comparisons have been made, need to be highlighted. Differences in histology, stages of disease, primary tumour locations, the chemoradiotherapy schedule and its tolerance, and definition of an R0 resection mean that such comparisons must be made with caution[19].

Although the present findings suggest that nCRTS improves local disease control in patients considered to have stage I and II oesophageal cancer compared with surgery alone, this approach may contribute towards incremental improvements in cure rates by eliminating occult micrometastatic disease. Equally, pN+ disease remains strongly predictive of recurrence, even in early disease, and advocating the routine use of neoadjuvant chemoradiotherapy for early disease must be tempered by the possibility of greater toxicity with an associated risk of higher postoperative mortality[20], with no demonstrable gain in complete resection rates. Identification of subgroups of patients with early disease likely to benefit from trimodal treatment remains a challenge.

Contributors

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