Improvement in Treatment Results and Long-Term Survival of Patients With Esophageal Cancer

Impact of Chemoradiation and Change in Treatment Strategy

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Objective: To identify prognostic factors and reasons for improved survival over time in patients with esophageal cancer.

Summary Background Data: Management strategies for esophageal cancer have evolved with time. The impact of chemoradiation in the overall treatment results has not been adequately studied.

Methods: From 1990 to 2000, 399 (62.4%) of 639 patients with intrathoracic squamous cancers underwent resection. Two study periods were analyzed: period I (01/1990–06/1995), and period II (07/1995–12/2000); during period II, chemoradiation was introduced. Prognostic factors were identified by multivariate analysis and the 2 periods compared.

Results: Hospital mortality rate after resection decreased from 7.8% to 1.2%, $P = 0.002$. Five favorable prognostic factors were identified: female gender (female vs. male, HR = 0.66), infracarinal tumor location (infra vs. supra-carinal, HR = 0.63), low pTNM stage (III/IV vs. 0/I/II/T_0N_1, HR = 1.76), pM0 stage (M1a/b vs. M0, HR = 1.56), and R_0 category ($R_{1/2}$ vs. R_0, HR = 2.49). Median survival was 15.8 and 25.6 months in periods I and II, respectively, $P = 0.02$. More R_0 resections were evident in period II, being possible in 63% (period I) and 79% (period II) of patients, $P = 0.001$. This was attributed to tumor downstaging by chemoradiation and more stringent patient selection for resection in period II. Performing less $R_{1/2}$ resections in period II coincided with using primary chemoradiation in treating advanced tumors. In patients treated without resection, survival also improved from 3 (period I) to 5.8 months (period II), $P < 0.01$.

Conclusions: Survival has improved; chemoradiation enabled better patient selection for curative resections and also resulted in more R_0 resections by tumor downstaging. This treatment strategy led to overall better outcome for the whole patient cohort, even in those treated by nonsurgical means.

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Immediate surgical results of esophagectomy for cancer have improved. In dedicated centers, a mortality rate of below 5% can be achieved.[1] Prolonging long-term survival is a goal more difficult to attain. Prognosis for esophageal cancer remains poor throughout the world. In selected centers and in subgroups of patients who undergo radical esophagectomy, 5-year survival rates of 40% or above could be achieved.[2–4] A selection bias is difficult to disprove, and such encouraging results are infrequently seen. In most reports, a 20% 5-year survival rate is recorded.[5,6]

Change in surgical technique and treatment strategies, for example the use of preoperative chemoradiation in recent years, may improve prognosis. It was the objective of the present study to (1) identify prognostic factors for long-term survival in patients with esophageal cancer, (2) document if better immediate surgical results in the 1990s was paralleled by longer survival, and if so, (3) isolate factors that were responsible.

METHODS

Between January 1990 and December 2000, 1160 previously untreated patients with esophageal and gastric cardia cancer were managed at the Department of Surgery, University of Hong Kong Medical Center, Queen Mary Hospital. Patients who had gastric cardia cancers or cervical esophageal cancers were excluded because of their different oncological characteristics and treatment protocols. Only patients with squamous cell cancers were included to exclude the influence of cell type on prognosis. In addition, patients with

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synchronous or history of other nonesophageal tumors were also excluded so that the influence of other unrelated tumors on survival was prevented. A total of 639 patients thus satisfied the inclusion criteria. Of this cohort, 399 (62.4%) underwent surgical resection. They were the subjects of this study.

Management Protocols

Preoperative Staging and Treatment

Surgical treatment was the preferred treatment option. Patients were selected for nonsurgical treatment if they had locally advanced unresectable disease or nonlocal-regional metastases, when medical-surgical risks were prohibitive, or in those who declined surgery.

For tumor imaging and staging purposes, all patients had a barium contrast study, an endoscopy, bronchoscopy, and since May 1996, endoscopic ultrasound examination. An ultrasound of the neck and computed tomography scan of the thorax and abdomen were conducted. Positron emission tomography scans were not available during the study period.

Routine hematological and biochemistry tests, pulmonary function test, and electrocardiograph were studied. Chest physiotherapy and nutritional supplement were instituted. Further cardiological assessments including exercise electrocardiogram, echocardiogram, thallium myocardial scans, and cardiac catheterization were selectively applied when indicated.

Surgical Techniques

The surgical techniques have previously been described.[7,8] In brief, most tumors were located in the middle and lower third of the esophagus, so a Lewis-Tanner esophagectomy via an abdominal-right thoracotomy approach was preferred. For patients who had a tumor of the superior mediastinal segment, a 3-phase esophagectomy was conducted. In patients who had limited cardiopulmonary reserve for whom a thoracotomy was judged to be of high risk, a transhiatal esophagectomy was performed. This method was mainly used for tumors of the lower esophagus. A randomized study which compared transhiatal versus transthoracic esophagectomy for lower third tumors was conducted from 1990 to 1994.[9] Thoracoscopic esophageal mobilization was introduced since the latter part of 1994.[10,11] This procedure was primarily selected for poor risk patients, and it has largely replaced the need for transhiatal esophagectomy.

Lymphadenectomy usually involved a 2-field lymphadenectomy with dissection of lymph nodes around the celiac trifurcation and also an infracarinal mediastinal lymph node dissection. Lymph nodes of the superior mediastinum were sampled but no attempt was usually made to completely clear the paratracheal area of lymphatic tissue. In patients who underwent transhiatal resection, no formal lymphadenectomy was performed in the mediastinum and only sampling of accessible lymph nodes was possible. Cervical lymphadenectomy was not performed routinely because our study of recurrence patterns suggested limited value of neck dissection,[12] and that survival advantage of cervical lymphadenectomy was not proven.[13,14] In patients with obviously palliative resection, a more limited lymphadenectomy was performed.

Reconstruction of intestinal continuity was usually restored with a gastric conduit placed in the right thoracic cavity (after Lewis-Tanner esophagectomy), or via the orthotopic route when the anastomosis was carried out in the neck. In the obviously palliative cases where residual mediastinal disease was evident, the retrosternal route was chosen. The colon was used in patients with a previous gastrectomy, the right ileo-colon being the preferred conduit. A hand-sewn anastomosis was constructed by a 1-layer continuous technique with absorbable monofilament suture. The circular stapler was also used during the early part of the study period.[15]

During the study period, patients were not given neoadjuvant or adjuvant treatment except in the context of clinical trials. A randomized controlled trial comparing preoperative chemotherapy was carried out from 1989 to January 1995, the results of which have been published.[16] Currently, an ongoing randomized clinical trial compares neoadjuvant chemoradiation and surgical resection alone. Another prospective, nonrandomized clinical study is also in progress, offering patients with locally advanced tumor (cT4) or nonregional metastatic spread (eg, cervical lymph nodes) upfront chemoradiation therapy. In those who have good responses, surgical resection is conducted. Chemoradiation is also given with intent of cure to patients who because of medical reasons are excluded from surgery but who have potentially curative tumors. These studies involving chemoradiation commenced in mid 1995.

Statistical Analysis

Survival analyses were performed using the Kaplan–Meier method, and comparisons between groups assessed by the log-rank test. Both cancer-specific and noncancer-specific deaths were included in the analysis because the majority of patients died of cancer-related causes. Hospital deaths were not included in analyses of long-term survival to exclude the influence of reduction of hospital mortality rate during the study period. Outcome was analyzed with regard to 2 periods: period I, which covered January 1990 to June 1995, and period II, which covered July 1995 to December 2000. The reason for dividing the 2 periods in such a manner coincided with the introduction of chemoradiation therapy at that time, which resulted in substantial change in management strategies.

To evaluate the impact of various clinicopathologic parameters for long-term survival, potential prognostic factors were analyzed with univariate analyses, and then they

were further assessed by multiple stepwise regression analysis using a Cox regression model. The following factors were tested: age, gender, location of tumor, thoracotomy resection versus nonthoracotomy resection, blood loss, operation time, the organ used for esophageal substitution, site of anastomosis, the use of neoadjuvant therapy (chemotherapy and chemoradiation therapy), pT, pN, pM, overall pTNM stage, and the R category. Identified prognostic factors were compared for the 2 halves of the study period. Statistical significance was accepted at the 5% level. All statistical analyses were performed using the SPSS statistical package (SPSS Inc., Chicago, IL).

RESULTS

A total of 399 patients underwent surgical resection. Their demographics and the type of resections are shown in Tables 1 and 2. The overall resection rate was 62.4% (399/639); it was 70.4% (231/328) in period I and 54% (168/311) in period II, $P < 0.01$. In the later period, more patients underwent transthoracic resections, 93.5% compared with 74%, ($P < 0.01$), and more intrathoracic anastomoses (69% vs. 58%, $P = 0.021$) were performed. This correlated to fewer transhiatal resections in the later period. The retrosternal route of reconstruction was used more often in period I (18.2% vs. 7.7%, $P = 0.006$), reflecting the higher prevalence of advanced tumors, whereby the orthotopic route was avoided. R_0 resections were possible in 79.2% in period II compared with 63.2% in period I, $P = 0.001$, with corresponding lower pT-stage and overall pTNM stage distributions in period II (table 2). Overall, neo-adjuvant therapy was given to 33% of patients, in the form of chemotherapy in period I (26.8% of patients), and as chemoradiation in period II (42.3%), $P = 0.002$. Thirty-day mortality rates were 2.6% (6 patients) and 0 in period I and II respectively, $P = 0.04$. In-hospital death rates were 7.8% (18 patients) and 1.2% (2 patients), $P = 0.002$.

TABLE 1. Patient Demographics

	Period I	Period II	P Value
Number	231	168	–
Age in years (median, range)	63 (38–85)	64.5 (38–80)	0.7
Gender (M:F)	193:38	139:29	0.89
Level of tumor (Upper:middle:lower)	25:145:61	29:98:41	0.19
Type of resection			
Split-sternum	5	0	
Transhiatal	38	1	
3-phase	40	40	
Lewis-Tanner	117	89	–
Esophago-gastrectomy	16	25	
Thoracoscopic	15	10	
Staged resection	0	3	
Thoracotomy	171 (74)	157 (93.5)	<0.01
Reconstruction			
Stomach	222 (96.1)	160 (95.2)	
Colon	6 (2.6)	8 (4.8)	
Jejunum	3 (1.3)	0 (0)	0.20
Route of reconstruction			
Orthotopic	56 (24.2)	39 (23.2)	
Retrosternal	42 (18.2)	13 (7.7)	
Right chest	133 (57.6)	116 (69)	0.006
Site of anastomosis			
Neck	98 (42.4)	52 (31)	
Chest	133 (57.6)	116 (69)	0.021
Neoadjuvant therapy	62 (26.8)	71 (42.3)	0.002
R category			
R_0	146 (63.2)	133 (79.2)	
$R_{1/2}$	85 (36.8)	35 (20.8)	0.001

Numbers represent number of patients (%)

TABLE 2. Pathologic Staging After Resection

	Period I	Period II	*P* value
Number	231	168	
pT stage			
T0	4 (1.7)	32 (19)	
T1	14 (6.1)	17 (10.1)	
T2	19 (8.2)	22 (13.1)	
T3	148 (64.1)	69 (41.1)	
T4	46 (19.9)	28 (16.7)	<0.01
pN stage			
N0	114 (49.4)	98 (58.3)	
N1	117 (50.6)	70 (41.7)	0.08
pM stage			
M0	200 (86.6)	152 (90.5)	
M1a/M1b	31 (13.4)	16 (9.5)	0.27
pTNM stage			
Stage 0 (T0N0M0)	4 (1.7)	21 (12.5)	
Stage I	12 (5.2)	14 (8.3)	
Stage IIa	68 (29.4)	46 (27.4)	
Stage IIb	6 (2.6)	6 (3.6)	
Stage III	110 (47.6)	56 (33.3)	
Stage IV	31 (13.4)	16 (9.5)	
pT0N1M0	0 (0)	9 (5.4)	<0.01

Numbers represent number of patients (%).

Survival Results

The median follow-up period for surviving patients was 45 months. Overall 1-, 2-, 3-, 4-, and 5-year survival rates for all 399 patients were 62.4%, 41.8%, 31.1%, 24.9%, and 20.8%, and median survival was 16.3 months. Excluding hospital deaths the 1-, 2-, 3-, 4-, and 5-year survival rates were 65.4%, 43.7%, 32.6%, 26.1%, and 21.8%, and median survival was 17.5 months. Clear trends in survival with respect to pTNM stage and R category of resection are shown in Figures 1 and 2. Median survival figures were: stage 0 (pathologic complete response-pCR (median not reached yet), I (38.6 months), II (32.5 months), T0N1 (21.1 month), III (14.4 months), and IV (6.3 months), $P < 0.01$. The respective figures for R_0, and $R_{1/2}$ resections were 28.7 and 9.5 months, $P < 0.01$. When the 2 time periods were compared, median survival was 15.8 months for period I and was 25.6 months for period II, $P = 0.017$ (Fig. 3).

Univariate analyses of the clinicopathologic factors identified the following that were predictive of survival: gender, level of tumor, use of neoadjuvant therapy, site of anastomosis, amount of blood loss, pTNM stage, pT-stage, p-N stage, p-M stage and R-category (Table 3). Cox regression analysis identified the following variables as favorable independent prognostic factors: female gender, infracarinal tumor location, low pTNM stage, pM0 stage, and R_0 category of resection (Table 4).

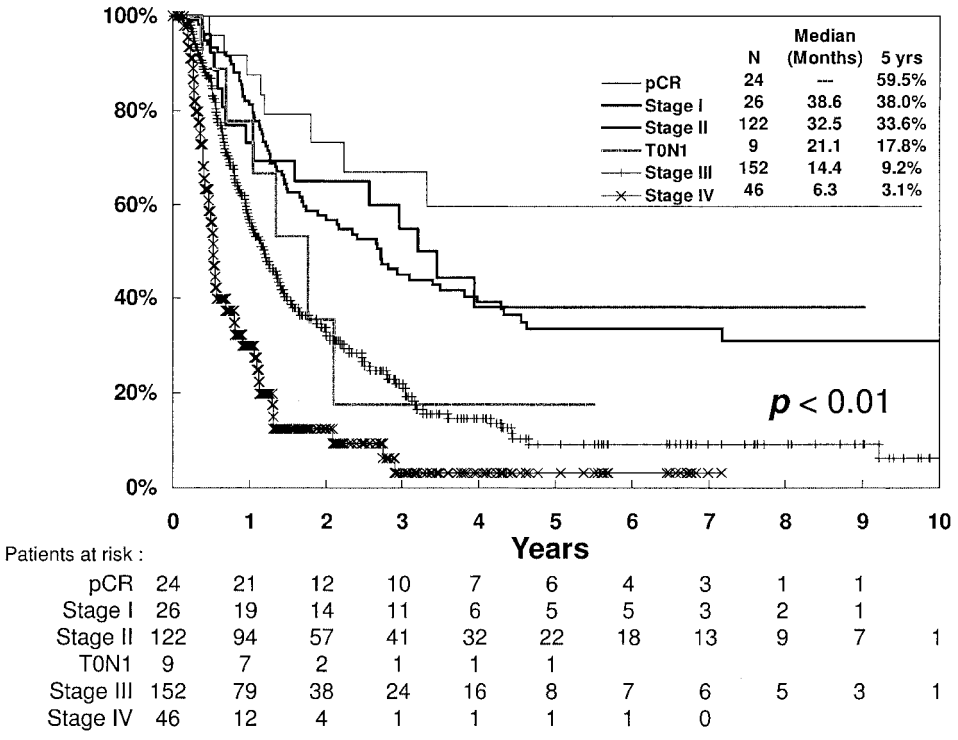

FIGURE 1. Survival curves with respect to pTNM stage.

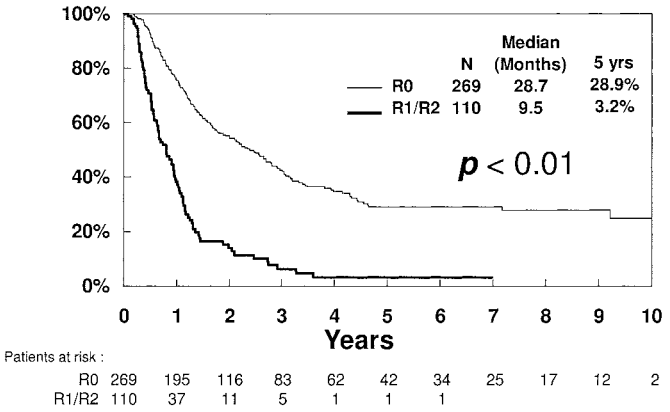

FIGURE 2. Survival curves with respect to R category of resection.

When period I and II were compared with respect to the 5 factors identified on Cox regression analysis, the later period had more R_0 resections, and stage groupings showed lower stage tumor distributions (table 2). Stage 0 to stage II, (including T0N1) tumors were found in 39% of patients in period I compared with 57.1% in period II, $P < 0.001$. The ability to perform a R_0 resection correlated with the pT stage. R_0 resection was possible in 97.2% (105/108) of patients who had pT0-pT2 tumors, compared with 59.8% (174/291) in those with pT3 / pT4 lesions, $P < 0.01$. Patients in period II had significantly lower pT stage. The prevalence of female sex, pM0 disease, and level of tumor distribution, did not differ between the 2 periods. When preoperative chemoradiation was given in period II, R0 resections were possible in 91.5% of patients (65/71), compared with only 70.1% (68/97) in patients who underwent surgical resection alone, $P = 0.001$.

No change in survival with time was noted for patients treated with surgery alone without neoadjuvant therapy having the same pathologic stage (pTNM). The median survival of patients with stage I disease was 30.8 months in period I (median not reached yet in period II, $P = 0.21$), and for stage II disease were 31.9 and 32.5 months for period I and II respectively, $P = 0.58$. The respective figures for stage III disease were 13.8 and 15.5 months, $P = 0.077$, and for stage IV: 6.6 months vs 6.2 months, $P = 0.74$.

The principle treatments given to all 639 patients in this study are shown in Table 5. To assess whether the improvement in long-term survival was better also in the nonresection group during the 2 periods, their survival were compared (Fig. 4). Even in this group of patients, survival in period II was better than in period I, median survival were 5.8 months and 3 months respectively, $P < 0.01$. If patients who received no treatment at all were excluded (mostly because of terminal status at presentation), median survival were 6.8 months and 3 months for period II and I respectively, $P < 0.01$.

The main difference in treatment strategy between the 2 periods was the use of chemoradiation therapy in period II. It appeared that the reduction in palliative resection and bypass procedures in the second period could largely be accounted for by a corresponding increase in primary chemoradiation therapy.

DISCUSSION

In this study, we have documented 5 favorable prognostic factors, which included female gender, infracarinal tumor location, tumor stage (both pTNM and pM), and R_0 resection. Better long-term prognosis with time after resection was also shown in the study period. Hospital mortality rate was lowered from 7.8% to 1.2%. Although a significant finding, better survival in period II was not solely related to

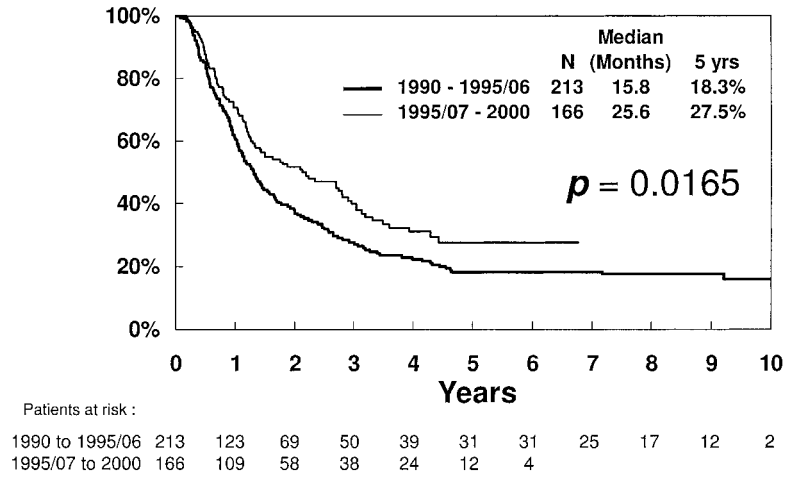

FIGURE 3. Survival curves with respect to periods I and II.

TABLE 3. Significant Prognostic Factors for Survival by Univariate Analysis

	Median Survival (Months)	*P* Value
Gender		
Male	16.2	
Female	24.7	0.0148
Level of tumor		
Upper	13.4	
Middle/lower	19.6	0.0294
Neoadjuvant therapy		
No	16.2	
Chemotherapy	21.3	
Chemoradiation	26.8	0.0384
Blood loss		
≤600 mL	25.2	
>600 mL	12.9	<0.01
Site of anastomosis		
Neck	15.2	
Chest	20.2	0.0318
pT stage		
T0/T1/T2	41.3	
T3/T4	14.4	<0.01
pN stage		
N0	30.8	
N1	15.6	<0.01
pM stage		
M0	21.3	
M1a/b	6.3	<0.01
pTNM stage		
Stage 0/I/II/T0N1	33.7	
Stage III/IV	12.3	<0.01
R category		
R0	28.7	
R1/2	9.5	<0.01

TABLE 4. Coc Regression Model of Prognostic Factors

Variable	P-value	Hazard Ratio	95% CI
Female vs. male	0.0202	0.6561	0.46–0.94
Level of tumor			
middle/lower vs. upper	0.01	0.63	0.45–0.90
pTNM stage			
III/IV vs. 0/I/II/T0N1	0.0001	1.76	1.32–2.35
pM1a/b vs. pM0	0.02	1.56	1.06–2.29
R category			
$R_{1/2}$ vs. R_0	<0.001	2.49	1.83–3.38

CI indicates confidence interval.

reducing immediate surgical mortality, since these deaths were excluded from survival analyses. The improvement in long-term prognosis was related to increase in the number of R_0 resections and lowering of tumor stage in patients who underwent resection. This was achieved by more appropriate selection of patients for surgical resection, and by tumor down-staging using neoadjuvant chemoradiation therapy.

Of the 5 prognostic factors identified, tumor stage and R category are widely accepted and are not debated; that gender and location of tumor are significant factors requires further discussion.

A survival advantage with the female gender has been observed. In a Japanese nationwide study, a significantly better survival rate was found for women.[17] It was hypothesized by 1 study that the endocrine milieu in premenopausal women inhibited the establishment of micrometastases.[18] Although an interesting concept, proof is lacking. Most patients suffer from esophageal cancer are also postmenopausal. A recent report also found that gender was an independent prognostic factor by multivariate analysis.[2] In our patients, slightly more R_0 resections were carried out in female patients (73% vs. 69%), and less stage III/IV disease were also found (46.3% versus 54.8%), but neither comparisons reached statistical significance.

Patients with tumors located above the tracheal bifurcation had worse prognosis. It is well recognized that radical resection of such tumors may be compromised because the proximity of trachea and recurrent laryngeal nerves. Lymphatic spread may be preferentially proximal,[19] which makes tumor clearance unlikely when superior mediastinal and bilateral cervical lymphadenectomy are not thoroughly performed. Worse survival rates have been reported for cancer of the upper esophagus.[20,21] In 1 study, proximal tumors had more pT4 stage, lower resection rate, less R_0 resections, more recurrent laryngeal nerve injury, and poorer overall survival.[22] Difficulty in performing radical operations for cancer of

TABLE 5. Main Treatment Given to 639 Patients in the Study Period

	Period I	Period II
Resection	231 (70.4)	168 (54)
Nonresection		
No intervention	17 (5.2)	25 (8)
Bypass/exploration	34 (10.4)	8 (2.6)
Intubation/laser	30 (9.1)	29 (9.3)
Chemotherapy or radiotherapy	14 (4.3)	18 (5.8)
Chemoradiation	2 (0.6)	63 (20.3)
Total	328 (100)	311 (100)

Numbers represent number of patients (%)

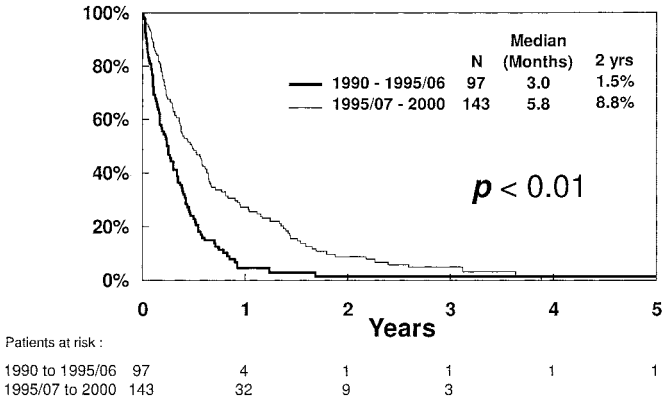

FIGURE 4. Survival curves with respect to periods I and II in the nonresection group.

the proximal esophagus has prompted other methods of treatment, such as adding intraoperative and postoperative radiotherapy.[23,24] The value of these regimens remains uncertain.

That tumor location has a bearing on prognosis has implications when studies from the East and West are compared. In studies from western countries, patients with squamous cell cancers and adenocarcinomas are different in their risk profile,[25] and in the likelihood of developing postoperative complications, especially after chemoradiation therapy.[26] For long-term prognosis, 1 study which involved 1059 patients showed that histologic cell type was an independent prognostic factor, the overall 5-year survival rates of patients with resected squamous and adenocarcinomas were 30.3% and 42.3%, respectively.[27] In another report of 800 patients, 5-year survival rates were 17% and 24% for squamous and adenocarcinomas.[28] Similar survival advantage for adenocarcinoma was seen even though radical esophagectomy was practiced by surgeons in the first study and nonradical transhiatal resections in the second. In both studies, adenocarcinomas were primarily lower esophageal in location while squamous cell tumors were more proximally located. If tumors located at or above the tracheal bifurcation have a poorer prognosis, as shown in the present study, then the survival advantage of adenocarcinomas reported may be a function of cancer location rather than the biologic behavior of different cell type.

Improvement of surgical results over time has been attributed variably to change in epidemiology, patient selection, staging methods, surgical technique, and the use of additional treatments.[2,5,29] Reports in the literature can span up to 30 years.[29] In the present study we have attempted to limit these possible confounding factors. Only squamous cell cancers were included, and the study period is relatively short (11 years). Although endoscopic ultrasound was introduced in 1996, we have not found it useful in altering clinical decisions, and CT scan was available throughout the study. It appeared that surgical procedures were different, in particular more thoracotomy resections were performed in the later period and thus more extensive lymphadenectomy may account for better survival. This was largely related to abandoning transhiatal resections in period II. However, transhiatal resections in period I were mainly performed in our randomized study in comparison with open transthoracic esophagectomy, and no significant prognostic difference was found,[9] similar to results recently published.[30] The number of thoracoscopic procedures also did not differ between the 2 periods. Patients with similar pathologic stages treated with resection alone had no difference in survival, suggesting no significant change in the natural history of the disease. We believe that the better result was primarily related to patient selection and the use of chemoradiation.

Patient selection no doubt played a part. The resection rate of period II in the present series was less than that in period I. In Hong Kong, most patients with esophageal cancer are treated primarily by surgical services. A recent estimate showed that the overall resection rate for the city was approximately 40%.[31] The authors' institution is a well-known tertiary referral center in Hong Kong, and an open-access system enables patients to self-refer through the emergency room. Most patients seen within its catchment area are therefore either self-referred, or are referred from general practitioners or other specialists directly regardless of tumor stage, often with minimal prereferral investigations. Indeed in recent years, referrals from other regions of Hong Kong are often those with advanced tumors or unfavorable physiological reserve, and the referral pattern could in part account for a lower resection rate in period II. Comparing to western reports with similar referral patterns, our resection rate of 54% (period II) is still high. In a 1-year survey of a single National Health Service in the United Kingdom (Wales), the resection rate for esophageal cancer was only 21%.[32]

In studies that report on improvement of surgical results over time, more stringent patient selection often comes into play. One study observed a reduction of 30-day mortality from 10% to less than 2%, and this coincided with the introduction of a "procedure-specific composite risk sore and strict exclusion of high-risk patients from surgical resection."[27,33] In another study that spanned a 15-year period, although resection rates were not significantly different over time, the proportions of T4 tumors in the second half of the study period was half that in the earlier one, and that $R_{1/2}$ resections also reduced from 14% to 6%. Patients with T4 cancers were referred for upfront chemoradiation therapy.[2] So again a selection bias was at least partly responsible for better results.

The main reason for a reduction in resection rate in period II coincided with the introduction of chemoradiation. Chemoradiation allowed patients with advanced and meta-

static tumors to be treated by nonoperative strategies, rather than palliative resections. In addition, patients with advanced disease can be downstaged, and those with significant response were selected for resection. In those with earlier resectable disease, they could also benefit from tumor downstaging, and this group is being studied in a randomized trial. Four randomized trials on neoadjuvant chemoradiation has been published,[34–37] 1 of which demonstrated a survival benefit.[35] This trial is often criticized because of its poor result in the surgery alone arm; the 3-year survival rate was only 6%.

It is interesting that the lower pTNM stage distribution in period II was mainly related to the lower pT stage. Although pN0 and pM0 stages were more prevalent in period II, it did not reach statistical significance, perhaps stressing that chemoradiation is still primarily a local treatment. From published trials of neoadjuvant chemoradiation therapy on resectable tumors, it is known that complete pathologic response can be achieved in more than 25% of patients,[34–37] this was found in 12.5% patients in period II. The complete response rate appears less because it also included patients with upfront advanced and metastatic cancers.

It is difficult to dissociate completely the relative contributions of more stringent patient selection and downstaging by chemoradiation to produce more R_0 resections and lower stage tumors in period II. However, the ability to perform R_0 resections (strongest prognostic factor) correlated with the pT stage, and that 18% of patients in period II had pT0 disease, which could only be produced after chemoradiation, compared with only 1.7% in period 1, suggesting that tumor downstaging by chemoradiation played a significant role. In period II, the ability to perform R_0 resections also correlated with preoperative chemoradiation.

True advances can only be made if the survival benefit in the resection group, now more selectively applied, is also paralleled by similar gain in those who are now denied of the chance of tumor extirpation. Median survival in the nonresection group was doubled in period II. Reducing palliative resections and bypass procedures paralleled with the use of palliative chemoradiation.

From the data presented, although it seems that patients with advanced tumors should be treated nonoperatively, the present study is not adequate to directly compare patients' quality of life undergoing different treatments. It may be argued that the apparent gain in survival (which is modest), is not justified by the inferior quality of life that these patients experience in undergoing chemoradiation, over a significant part of their limited survival period. Furthermore, the relative efficacy of neoadjuvant chemoradiation, surgical resection alone, and chemoradiation alone is not addressed by the data. It is a report on the overall change in management strategies for the whole spectrum of esophageal cancer patients, which is brought about by introducing chemoradiation.

The present study is of unique value in that most reports in the literature only examined selected groups of patients, either those who underwent operative or nonoperative treatments. This study showed that change in treatment strategies was beneficial to the whole cohort of patients. Chemoradiation therapy is certainly no panacea.[38] Further progress should be made by achieving better surgical care, by identifying reliable predictors of good response to chemoradiation therapy so that potentially harmful treatment are not given to nonresponsive patients, by seeking more effective treatment regimens,[39] and by being able to tailor the most appropriate approach to each individual patient.

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Discussions

DR. TOM R. DEMEESTER (Los Angeles, California): Dr. Law, the work of your unit is well known and we enjoyed hearing the results of your experience. I appreciated having the opportunity to have read the manuscript prior to the meeting. You told us that in the last group of patients operated upon the surgical mortality was 0. I compliment you and your group on this accomplishment. It is spectacular. In fact, I think it is the best mortality reported thus far for esophagectomy. I know the vigilance you put into the effort, and I compliment you on this achievement. I hope it is sustainable.

You said that there has been a change in outcome over the last 2 periods, and you would like us to believe that it is related to chemoradiation therapy rather than some form of selectivity. I would like to argue that it is selectivity.

We know from several randomized trials on esophageal carcinoma that there is little benefit from adjuvant or neo-adjuvant chemoradiation therapy. We also know that in chemotherapy trials patients who respond to neo-adjuvant therapy do better than the group average. As a consequence, patients who are nonresponders do worse than the group average and may have been harmed by the therapy. Our tendency in this situation is to be very enthusiastic and encouraged by responders and be less enthusiastic and discouraged by nonreaders. What assurances do we have that during the second period of your analysis you were not selective towards the patients who responded and unknowingly relegated the nonresponders to the nonoperative group?

This would explain why you observed in your second period of analysis a better outcome in both the operative and the nonoperative groups.

Lastly, I would ask if you were more apt to use esophageal stents in the second period of analysis and as a consequence excluded from the operative group patients you would have operated on in the initial group. This would explain the reduced operative mortality and the longer survival of the nonoperative patients during the second period of analysis.

DR. SIMON LAW (Hong Kong, China): I will answer the second question first because it is easier. For the stents, we compared the 2 periods, there was no difference in terms of their utilization. The stents are better designed now compared with the old ones of course, however the choice of using a stent for us has not changed. We only use them for palliation of patients who are not suitable for anything else. There was thus no difference in terms of the indication of stents in the 2 periods.

Now for the selection of patients, no doubt we were more selective in choosing our patients for resection in the second period. However, if patient selection was the only factor leading to better outcome in the resection group and the change in treatment strategy in fact had not made any impact,

then you would expect survival in the nonresection group to be correspondingly worse off compared with the first period. In our patients, better survival was seen in both groups, so that for the whole patient cohort, survival was improved.

I do agree that it is very difficult to dissect the relative contributions between patient selection and the effect of chemoradiation. Chemoradiation has not been convincingly shown to be superior to surgery alone in randomized trials. These trials were performed in patients who on preoperative investigations were shown to have resectable disease. In this group of patients we are currently running a randomized trial, and I am afraid that I cannot tell you the results because we have not stopped recruiting patients.

What we are suspecting is that the beneficial effects of chemoradiation lies with those who had advanced disease. We allow the patients who have very advanced (locally cT4 or those with metastatic disease, for example cervical lymph node) to undergo upfront chemoradiation. In those who respond well to chemoradiation we take them to surgery, in those who do not have a good response, we treat them otherwise. In the past, right or wrong, maybe we were too aggressive in resecting some of these patients. It became apparent that it is this group of patients who would do badly with surgery alone. Significant downstaging by chemoradiation selects the favorable ones for surgical resection, leaving the rest palliated, with or without additional treatment of palliation. This strategy led to better outcome for the whole patient cohort.

Are we being too selective? Our resection rate overall is about 63%, about 70% in period 1 and about 54% in period two. It is difficult to decide what is an appropriate resection rate if we read the literature, because a lot of papers do not tell you the overall referral pattern and the overall patient cohort that they see.

In Hong Kong, we have an open system of referral. Most of the patients with esophageal cancer are primarily looked after by surgical services, and generally they are not screened by oncologists or gastroenterologists. So we are seeing a representative spectrum of patients, with both early and advanced disease. If you look at our resection rate compared with data in the literature, for instance, 1 recent publication in the British Journal of Surgery looked at esophageal cancer in Wales, the resection rate was only 20%. And I am aware of some other papers which showed a figure of around 40%. Our resection rate is still high. We believe that chemoradiation is doing something to enhance overall results. But I do agree that its exact role requires more study and definition.

Dr. Carlos A. Pellegrini (Seattle, Washington): You have given us indirect, if you wish, circumstantial evidence of the effect of chemoradiation therapy on esophageal cancer. I wonder if you could share with us any data you may have on the direct effect of this treatment on the tumors you treated.

For example, we recommend radiation and chemotherapy for all patients with Stage II or higher. We stage these patients with CT, endoscopy, biopsy and endosonography, before and 6 weeks after chemoradiation to measure its effect. We see patients who experience complete regression, partial regression, no regression and even advancement of disease while under treatment. Could you tell us if you measured the effects of chemoradiation in these patients and if so how many responded and to what extent?

Dr. Simon Law (Hong Kong, China): For all the patients who underwent chemoradiation, they all had CT scans and endoscopic ultrasound before and after treatment, and then they went on to resection.

The pathologic response rate was about 13%. In the less advanced initial "resectable group," the complete response rate was around 25%. That is roughly what was also reported in randomized trials. The lower figure of 13% included those with upfront advanced tumors as well, like those with stage IV disease. This is already better compared with our previous chemotherapy trial, which showed a pathologic complete response rate of around 7% only.

Dr. William C. Krupski (Denver, Colorado): Dr. Law, knowing nothing about the topic whatsoever, I have the advantage of asking you a very dumb question. It didn't seem like there was a downside of giving chemoradiation to these groups of patients. As a vascular surgeon, this would be kind of like doing a randomized trial of giving antibiotics before and after surgery. What is the downside of just giving everybody chemoradiation, since the results seem to have been so impressive? Do you really need a randomized trial?

Dr. Simon Law (Hong Kong, China): The downside of it is that chemoradiation therapy has its morbidity and mortality. We do not have treatment-related mortality, I am happy to say, but the treatment is actually quite long. Our regimen only lasts for about a month, other regimens published could last for 3 months, sometimes even four.

If you look at the palliative resections or the nonresection patients, you have to remember that the median survival is only around 6 months or even less. So the patient would need to tolerate the chemoradiation therapy for a substantial period of their remaining life, especially if they do not respond well. At the moment, we do not have any reliable predictor of good response.

As far as palliation of symptoms is concerned, we still believe that if you can do a successful operation, get the patient out of the hospital quickly, they will have the most rapid and sustained recovery of the ability to eat. Chemoradiation therapy, even in those who respond, often results in a radiation stricture that requires dilatation, sometimes even stenting. So it is not all pluses, there are minuses to the treatment as well.