Evolving progress in oncologic and operative outcomes for esophageal and junctional cancer: Lessons from the experience of a high-volume center

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Objective: Modern series from high-volume esophageal centers report an approximate 40% 5-year survival in patients treated with curative intent and postoperative mortality rates of less than 4%. An objective analysis of factors that underpin current benchmarks within high-volume centers has not been performed.

Methods: Three time periods were studied, 1990 to 1998 (period 1), 1999 to 2003 (period 2), and 2004 to 2008 (period 3), in which 471, 254, and 342 patients, respectively, with esophageal cancer were treated with curative intent. All data were prospectively recorded, and staging, pathology, treatment, operative, and oncologic outcomes were compared.

Results: Five-year disease-specific survival was 28%, 35%, and 44%, and in-hospital postoperative mortality was 6.7%, 4.4%, and 1.7% for periods 1 to 3, respectively ($P < .001$). Period 3, compared with periods 1 and 2, respectively, was associated with significantly ($P < .001$) more early tumors (17% vs 4% and 6%), higher nodal yields (median 22 vs 11 and 18), and a higher R0 rate in surgically treated patients (81% vs 73% and 75%). The use of multimodal therapy increased ($P < .05$) across time periods. By multivariate analysis, age, T stage, N stage, vascular invasion, R status, and time period were significantly ($P < .0001$) associated with outcome.

Conclusions: Improved survival with localized esophageal cancer in the modern era may reflect an increase of early tumors and optimized staging. Important surgical and pathologic standards, including a higher R0 resection rate and nodal yields, and lower postoperative mortality, were also observed. (J Thorac Cardiovasc Surg 2012;143:1130-7)

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The curative approach to esophageal and junctional cancer is historically associated with poor outcomes, with cure rates of approximately 20% and a risk of operative morbidity and mortality greater than for any other cancer operation.[1] Of note, several reports from high-volume centers suggest significant recent advances in outcomes, with cure rates of approximately 40% and an in-hospital postoperative mortality of less than 4%.[2-4] General factors that may underpin this improvement include more accurate staging enabling precise treatment planning, improved physiologic risk assessment for surgery, advances in perioperative care, earlier diagnosis through greater awareness of Barrett's esophagus and strict surveillance, lower thresholds for endoscopy, and the use of neoadjuvant and adjuvant therapies.[5-7] The key organizational element underpinning improved outcomes may be the increasing trend for oncologic resections to the domain of specialist high-volume surgeons working in multidisciplinary teams in high-volume hospitals.[5,8]

The evidence in support of restricting esophageal cancer surgery to high-volume centers is unassailable, but within high-volume centers the structure and process factors associated with improved oncologic and operative outcomes are rarely studied. In addition to volume, measures of structure include specialization, organization, and centralization. Process measures include staging, multidisciplinary decision-making and planning, neoadjuvant and adjuvant therapies, type of surgery, perioperative care, and pathologic reporting. The Esophageal and Gastric Cancer Center at St James's Hospital in Dublin is a high-volume esophageal center. The pattern of disease in Ireland, with adenocarcinoma the most common cancer, is representative of what is observed in North America and much of Europe.[6] There is no national

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Abbreviations and Acronyms
AEG = adenocarcinoma of the esophagogastric junction
CT = computed tomography
EUS = endoscopic ultrasound
PET = positron emission tomography
TRG = tumor regression grade

centralization or a national Barrett's surveillance program. With no major structural changes, a significant quality improvement in operative and oncologic outcomes was nonetheless observed over time, and the aim of this study was to analyze patterns of care and key factors that may be associated with the outcomes evident in the current era.

MATERIALS AND METHODS

Patients attending the Center between 1990 and 2008 with a diagnosis of cancer of the esophagus or esophagogastric junction were included. The study focused on patients treated with curative intent, defined as pretreatment staging of $T_{0–3}$, N any, and M_0, and considered fit enough to undergo treatment. Selected patients with cT4 disease were also treated with curative intent. Adenocarcinoma of the esophagogastric junction (AEG) included tumors that had their center within 5 cm proximal or distal of the anatomic cardia, identified endoscopically, and were classified per the Siewert criteria.[9] All data are prospectively recorded in a database (Dendrite, London, UK). The study was approved by the institutional review board.

Structures

The St James's Hospital is a high-volume center for esophageal and junctional cancer operating since the mid-1970s. Surgeons are defined as upper gastrointestinal surgeons, not thoracic surgeons, and undertake at minimum 30 major esophageal resections each per annum. The esophageal program has been aligned with dedicated intensive care specialists and thoracic anesthetists throughout the study period.

Process

Computed tomography (CT) of the neck, thorax, and abdomen became standard in 1995 but was used only sporadically between 1990 and 1995. The use of ^{18}-F-deoxyglucose positron emission tomography (PET) scans was introduced in 2003 and has been performed as a combined CT-PET since early 2006. Endoscopic ultrasound (EUS) was available on an inconsistent basis since 1993 and has been routine since 2007 with the appointment of a dedicated EUS specialist. Laparoscopy is standard for locally advanced tumors below the diaphragm.

A formal multidisciplinary team was established in 1999, including an advanced nurse specialist and defined lead clinicians in surgery, medical and radiation oncology, radiology, pathology, and gastroenterology. A weekly conference to discuss all new cases has been in place since 1999, and conference proceedings have been audited since 2004. A weekly esophageal clinic with attendance by surgeons, nurse specialists, and nutritionists, and same-day linkage to gastroenterology, medical, and radiation oncologists has been operational since 2004.

Preoperative chemoradiation is the preferred multimodal approach for patients with predicted locally advanced tumors. A randomized trial of multimodal therapy versus surgery alone was performed at this center between 1990 and 1995.[6] There have been no changes to the chemoradiation regimen or dosing schedule over the study period since the time of this trial and no other trial performed. Patients with AEG type III tumors have been considered for postoperative chemoradiation and more recently for pre- and postoperative chemotherapy.[10,11]

For surgery, the principle of wide clearance and a radical lymphadenectomy is the goal in all cases, with the extent of resection influenced by the location of the tumor, comorbidities, cardiac and respiratory function, and local extent of the tumor.[12,13] The usual standard for esophageal tumors is an abdominal–thoracic en bloc esophagectomy. A transhiatal esophagectomy is considered for patients with clinical T1 and predicted node-negative disease or for higher-risk operative cases due to age or respiratory comorbidity. For patients with AEG type III tumors, an extended total gastrectomy and an anastomosis via a transmediastinal approach or separate thoracotomy is performed. Endoscopic mucosal resection was introduced in 2007 and is applied to patients with high-grade dysplasia or tumors that by EUS assessment do not invade the submucosa (uT1a).

Patient assessment for fitness for surgery or multimodal therapy has been largely unchanged since 1990, with the absence of major respiratory disease being the key clinical criteria, as well as satisfactory pulmonary function test results (forced expiratory volume in 1 second > 1.5 L) and performance status as previously described.[13] Thoracic epidurals have been used since 1992. All patients are extubated immediately postoperatively and managed in a high-dependency unit or intensive care unit before transfer to a specialist surgical ward. All patients receive early enteral nutrition via a needle catheter jejunostomy. Perioperative care protocols have been relatively uniform since 1996 but were not standardized or audited during this study period. All complications, major and minor, were defined and prospectively audited, as previously described.[13]

Pathologic assessment is performed per standard guidelines.[14] All margins (proximal, distal, and circumferential) were assessed, as well as tumor differentiation, lymphovascular invasion, and perineural invasion. An R1 deep (circumferential) margin denotes tumor within 1 mm of the resection margin. The database was adapted and retrospectively classified in 2010 to include the new 7th edition *AJCC Cancer Staging Manual* N staging classification for esophageal and junctional tumors.[15] In patients treated with neoadjuvant therapy, the extent of residual carcinoma in the esophagectomy specimen was assigned per Mandard and colleagues[16]: Tumor regression grade (TRG) 1 represents a complete response; TRG2 represents rare residual cancer cells scattered throughout the fibrosis; TRG3 represents an increase in the number of residual cancer cells, but fibrosis still predominates; TRG4 represents residual cancer cells outgrowing fibrosis; and TRG5 represents a complete absence of regression.

Patients are followed at the Esophageal Clinic at 3 monthly intervals for the first year and at 4 to 6 monthly intervals for the subsequent 4 years. All patients had CT scans in the first and second post-treatment years or as clinically indicated.

Statistics

Three time periods were compared: period 1, from 1990, when prospective records commenced, and a randomized clinical trial (1990–1995), to 1998 inclusive; period 2, from 1999, when a defined multidisciplinary team was established, with nurse specialization, to 2003; and period 3, from 2004 to 2008 inclusive, where multidisciplinary team structure was well established and processes audited. Statistical analysis was performed using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc, Chicago, Ill). Continuous variables were compared using unpaired *t* tests, and categoric variables were assessed using the chi-square test. Survival statistics were calculated using the Kaplan–Meier method, and the log-rank test was used to assess differences in disease-specific survival between groups. Survival time was measured from the date of diagnosis to the date of an event or last follow-up. Independent variables were entered into a multivariate Cox proportional hazards model with a forward likelihood ratio selection procedure. A significance level of .05 was used for all analyses, and all *P* values reported are 2-tailed.

TABLE 1. Tumor site and morphology in patients treated with curative intent

Time period	1990–1998		1999–2003		2004–2008		*P* value
Morphology	n	%	n	%	n	%	
Adenocarcinoma	271	57.5	154	60.6	222	64.9	.17
Squamous cell	187	39.7	93	36.6	109	31.8	
Small cell	2	0.004	2	0.8	4	1.1	
Lymphoma	0	0	1	0.4	1	0.3	
Other	7	0.015	4	1.5	6	1.9	
Missing	4	0.008	0	0	0	0	
Tumor site	n	%	n	%	n	%	
AEG	271	56.7	154	62.3	222	65.8	.492
SCC lower third	110	23.4	45	18.2	33	10.0	
SCC middle third	54	11.5	38	15.4	62	18.7	
SCC upper third	23	4.9	10	4.1	14	4.2	
AEG junction	n = 271	%	n = 154	%	n = 222	%	
AEG type 1	88	39.6	57	37.0	118	53.2	<.001
AEG type 2	91	33.6	54	35.1	51	22.9	
AEG type 3	74	27.3	42	27.3	53	23.9	
Unspecified	18	6.6	1	0.06	0	0	
Barrett's surveillance	8	3.0	5	3.3	24	10.8	.035

AEG, Adenocarcinoma of the esophagogastric junction.

RESULTS

Volumes, Pathology, and Treatment Intent

Between 1990 and 2008, 1787 patients were referred with esophageal or junctional cancer, 704 in period 1, 494 in period 2, and 589 in period 3 (Table E1). The sex distribution and mean age were similar across the time periods. There was a significant ($P = .003$) increase in the incidence of adenocarcinoma, from 55.5% and 53.2% in periods 1 and 2, respectively, to 62%, in period 3. There was a significant ($P < .001$) decrease in the percentage of patients treated with curative intent, from 68% in period 1 to 53% and 58% in periods 2 and 3, respectively.

For patients treated with curative intent (n = 1067), the tumor site and morphology are shown in Table 1. Adenocarcinoma was the dominant pathology in each time period, with a nonsignificant increase ($P = .17$) from 57.5% to 60.6% to 64.9% over each time period, respectively. Within the AEG cohort, AEG type 1 represented 53% in the most current time period compared with 39.6% in period 1 and 37.0% in period 2 ($P < .001$). In period 3, 24 patients, representing 10.8% overall and 20.3% of patients with AEG 1, were on Barrett's surveillance compared with 3% overall in the 2 previous time periods.

Staging

Staging modalities in the different periods are shown in Table E2. In patients treated with curative intent, just 31% of patients underwent CT imaging in period 1, compared with 100% in periods 2 and 3. For PET imaging, this was performed in 82% of patients in period 3 and 11% in period 2. EUS increased from 10% and 9% in periods 1 and 2, respectively, to 32% in period 3, and 85% since 2007. Since 2004, 100% of patients treated with curative intent were discussed at the weekly multidisciplinary meeting.

Treatment of Patients With Curative Intent

In patients treated with curative intent, there was a significant ($P < .001$) decrease in the use of surgery, from 94.6% in period 1 to 80.7% in period 2 and 71.1% in period 3 (Table 2). A corresponding increased use of radical chemoradiotherapy was observed, from 2.5% to 16.1% and 23.4% in periods 1 to 3, respectively. The use of endoscopic mucosal resection for high-grade dysplasia and uT1a tumors is exclusive to the recent period, representing 5.3% of operative approaches.

The use of multimodal therapy as a percentage of all surgical approaches increased from 28% in period 1 to 37% in period 2 and 41% in period 3 ($P < .001$). In patients undergoing multimodal therapy, a similar percentage did not progress to surgery in each time period because of progressive disease or worsening performance status (9.4% period 1, 9.6% period 2, and 16% period 3). In period 3, the use of transhiatal esophagectomy increased, representing 5.8% of resections, compared with 1.8% in period 1 and 2.4% in period 2 ($P = .027$).

Pathologic Stage and Response to Neoadjuvant Therapy

Surgery-only cohort. The incidence of early esophageal cancer, defined as cancer confined to the mucosal or submucosa, and including high-grade dysplasia, pT1a, and pT1b, was 6.6%, 10.0%, and 34.3% ($P < .001$) in periods 1 to 3, respectively. pT3 tumors represented 77%, 57%, and 45% of resections in periods 1 to 3, respectively (Table 3).

TABLE 2. Treatment details

Time period	1990–1998		1999–2003		2004–2008		*P* value
Treatment details of patients treated with curative intent	n = 471	%	n = 254	%	n = 342	%	
Radical chemoradiotherapy	12	2.5	41	16.1	80	23.4	<.001
Surgery:	446	94.6	205	80.7	243	71.1	<.001
Surgery first	320	71.7	130	63.4	131	54	<.001
Multimodal completed	126	28.3	75	36.6	99	40.7	.05
Endoscopic mucosal resection	0		0		13	5.3	.0001
Failed to progress to surgery after multimodal therapy (of total multimodal therapy)	13	9.4	8	9.6	19	16	NS
Type of surgery							
2 Phase esophagectomy	269	60.3	110	53.6	132	54.3	NS
3 Phase esophagectomy	91	20.4	42	20.5	51	21.0	
Transhiatal*	8	1.8	5	2.4	14	5.8	
Total gastrectomy	37	8.3	34	16.6	22	9.1	
Extended proximal gastrectomy	8	1.8	2	1.0	5	2.1	
Open/close	2	0.5	2	1.0	5	2.1	
PLO	31	7.0	10	4.9	14	5.8	

PLO, Pharyngo-laryngo-esophagectomy. *Transhiatal esophagectomy rate $P = .027$.

Node-negative status was evident in 42.3%, 35.7%, and 48.1% for periods 1 to 3, respectively ($P = .446$). A heavy nodal burden (N2/N3) was evident in 37% in period 1, 37% in period 2, and 36% in period 3 (0.546). The R0 resection rate was significantly ($P < .01$) improved in periods 2 and 3 compared with period 1.

Multimodal cohort. A complete pathologic response (TRG1) was observed in 22%, 24%, and 21% of patients in periods 1 to 3, respectively. A major response (TRG1 and TRG 2) was evident in 49%, 51%, and 46% in periods 1 to 3, respectively. Node negativity was 71% in period 1, 57% in period 2, and 40.4% in period 3 ($P < .001$). The R0 resection rate was 81.8% in period 3 compared with 88.1% and 85.7% in periods 1 and 2, respectively ($P = .427$). N2/3 nodal burden represented 12%, 21%, and 30% in periods 1 to 3, respectively ($P = .01$) (Table 4).

Nodal Yield and Involvement

For all groups, including surgery and multimodal cohorts, the median (range) number of nodes harvested was 11 (1–44) in period 1, 18 (4–52) in period 2, and 22 (8–62) in period 3 ($P < .05$). The percentage of patients with a nodal yield greater than 15 was 50%, 78%, and 90% in periods 1 to 3, respectively ($P < .05$).

Operative Outcomes

There were 4 (1.7%) in-hospital postoperative deaths in period 3, a significant ($P < .001$) improvement compared with 30 (6.7%) in period 1 and 9 (4.4%) in period 2

TABLE 3. Pathologic T and N stage: Patients treated with surgery only

	1990–1998	2003–2008	2004–2008	
Pathology	**Surgery n = 320 (%)**	**Surgery n = 130* (%)**	**Surgery n = 131* (%)**	***P* value**
HGD/in situ	5 (1.1)	2 (1.5)	5 (3.8)	Early cancer rate (Tis/T1/T2) <.001
T0	0	0	0	
T1	19 (5.5)	11 (8.5)	40 (30.5)	
T2	28 (8.0)	28 (21.5)	22 (16.8)	
T3	254 (77.0)	74 (56.9)	59 (45.0)	
T4	14	15 (11.5)	5 (3.8)	
Nodal status				
N0	132 (42.3)	46 (35.7)	63 (48.1)	.108
N1	65 (20.8)	35 (27.1)	21 (16.0)	.082
N2	65 (20.8)	30 (23.3)	24 (18.3)	.519
N3	50 (16.0)	18 (14.0)	23 (17.6)	.628
R0 resection				
R0	232 (73)	98 (75)	106 (81)	$P < .05$ 2004–2008 vs others
R1	87 (27)	32 (25)	25 (19)	

HGD, High-grade dysplasia. *Excludes open and close laparotomy and endoscopic mucosal resection.

TABLE 4. Pathologic T and N status and response to neoadjuvant treatment: Multimodal treatment group

	1990–1998	2003–2008	2004–2008	
Pathology	**Multimodal n = 126, (%)**	**Multimodal n = 75, (%)**	**Multimodal n = 99, (%)**	***P* value**
HGD/in situ	0	0	0	Early cancer rate (Tis/T1/T2) <.001
T0	29 (23)	14 (18.7)	24 (24)	
T1	26 (20.6)	16 (19.3)	11 (11)	
T2	21 (16.7)	15 (20.0)	17 (17)	
T3	47 (37.3)	29 (38.7)	46 (46)	
T4	3 (2.4)	1 (0.01)	1 (1)	
Nodal status				
N0	89 (71.2)	43 (57.3)	40 (40.4)	<.001
N1	21 (16.8)	15 (20.0)	29 (29.3)	.062
N2	12 (9.6)	10 (13.3)	17 (17.2)	.205
N3	3 (2.4)	5 (6.7)	13 (13.1)	.01
Response				
TRG 1	24 (21.6)	18 (24.3)	21 (21)	.521
TRG 2	30 (27.0)	20 (26.7)	25 (25)	
TRG 3	23 (20.7)	17 (22.7)	26 (26)	
TRG 4	21 (18.9)	17 (22.7)	18 (18)	
TRG 5	13 (11.7)	2 (2.7)	9 (9)	
Missing	15	1	0	
R0 resection				
R0	111 (88.1)	64 (85.7)	81 (81.8)	.427
R1	15 (11.9)	11 (14.7)	18 (18.2)	

HGD, High-grade dysplasia; *TRG*, tumor regression grade.

(Table 5). There was no significant difference across time periods in the incidence of pneumonia, anastomotic leaks, arrhythmias, myocardial infarction, or thromboembolic events, but the incidence of respiratory failure was significantly ($P < .05$) decreased in period 3 compared with both other time periods.

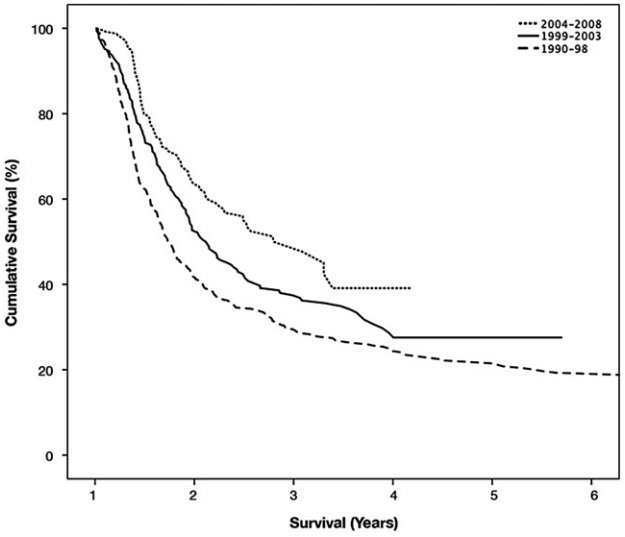
Survival

In patients treated with curative intent, the median disease-specific survival in period 3 was significantly ($P < .05$) increased at 33 months compared with 17 and 23 months for periods 1 and 2, respectively (Figure 1). At a median follow-up of 46 months and a minimum of 24 months, the actuarial 1-, 3-, and 5-year disease-specific survival for period 3 was 80%, 55%, and 44%, respectively. This compares with disease-specific survival of 65%, 36%, and 28% for period 1, and 75%, 43%, and 35% for period 2. The overall 5-year survival for period 1 was 25%, 29% for period 2, and 37% for period 3.

In a univariate analysis of disease-specific survival (Table E3), age, sex, pT stage, pN stage, number of involved nodes, R status, venous invasion, and period of treatment were significantly ($P < .05$) associated with survival. In multivariate analysis, age, nodal status, T stage, and venous invasion were significant, as well as the time period, with a hazard ratio of 0.415 (0.315–0.547) for period 3, compared with 0.717 (0.576–0.891) for period 2 and 2.41 (1.829–3.176) for period 1.

TABLE 5. Postoperative morbidity and mortality

	1990–1998		1999–2003		2004–2008		
Time period	**n**	**%**	**n**	**%**	**n**	**%**	***P* value (χ^2)**
30-d mortality	24	5.4	5	2.4	3	1.3	
90-d mortality	6		3		1		
Total in-hospital mortality	30	6.7	9	4.4	4	1.7	<.0001
Respiratory							
Pneumonia	74	16.6	21	10.2	31	12.8	
Respiratory failure	42	9.4	17	8.3	9	3.7	<.05
Cardiovascular							
Atrial fibrillation	32	7.2	13	6.3	30	12.3	NS
Myocardial infarction	3	0.006	2	0.01	4	1.6	
Anastomotic							
Radiologic or clinical leak	38	8.5	8	3.9	10	4.1	NS
Graft ischemia	5	1.1	1	0.5	1	0.4	



	1990-98		1999-2003		2004-08		p-value (log-rank)
	N	95% CI	n	95% CI	n	95% CI	
Median survival (months)	17.38	14.89-19.87	22.93	18.29-27.58	32.85	24.34-38.15	0.001

Survival	1990-98			1999-2003			2004-2008		
	No at risk	Deaths	% survival	No at risk	Deaths	% survival	No at risk	Deaths	% survival
0 years	471	0	100	254	0	100	342	0	100
1 year	462	151	65	208	51	75	253	65	80
3 years	241	103	36	144	60	43	144	60	55
5 years	151	27	27	99	13	35	84	13	44
10 years	102	15	19	63	8	28	n/a	n/a	n/a

FIGURE 1. Disease-specific survival in patients treated with curative intent. *CI*, Confidence interval.

DISCUSSION

In the modern era, there is a consistent reported trend of markedly improved operative and oncologic outcomes from high-volume esophageal programs within academic medical centers.[1-4] The current benchmark survival in patients treated with curative intent is 35% to 50%, not 20% as commonly quoted, and postoperative deaths are rare, usually less than 4%.[17,18] The argument in favor of esophageal cancer being the exclusive domain of high-volume surgeons in high-volume centers is compelling,[9] and there is evidence from Europe that organizational reform and centralization of esophageal cancer care may improve outcomes.[19] Within high-volume centers, there is also evidence of improved outcomes over time, but factors that underpin such improvement are rarely studied or reported.[18,20,21] Where significant improvements in oncologic and operative outcomes occur, does this reflect increased percentages of patients with early stage disease, improved staging, better treatment planning, better cancer surgery, greater use of multimodal approaches, advances in perioperative care, a combination of factors, or elements that cannot easily be measured? In this study of 1067 patients treated with curative intent, where all operations were performed by high-volume surgeons in a high-volume center, the most recent 5-year period is associated with markedly improved oncologic and operative outcomes. An increase in early cancers, the introduction of formal multidisciplinary processes, improved staging, an increased use of nonoperative therapies, and improvements in proxy measures of cancer surgery are all features of the current period that may underpin the attainment of improved outcomes.

A 5-year survival of 44% for the period 2004–2008 is consistent with other series.[2-4] A shift toward early-stage disease may be central to this finding, which now represents close to one fifth of patients presenting for curative therapy, compared with 1 in 20 a decade ago. Adenocarcinoma represented 38 of 42 early tumors in the recent time period; of these, 25 (65%) were on Barrett's surveillance programs. In a report of 263 patients with adenocarcinoma treated over a 13-year period by Portale and colleagues[2] at the University of Southern California, the overall 5-year survival was 50%, and pT1N0 represented approximately 50% of tumors in the final 2 years of the study. In this and our own series we do not know whether the increase in early tumors reflects a referral bias to a specialist center or a national trend consequent on improved awareness of Barrett's esophagus and early detection, and this demands further study. Similar trends internationally may exist for esophageal squamous cell cancer. From a multicenter study in Italy of predominantly squamous cell cancer, Ruol and colleagues[21] reported approximately 10% of patients with T0/T1 tumors in 1980–1987, compared with 15% in 1988–1995, and 28% in 1996–2004, with 5-year survival of 19%, 23%, and 42%, respectively.

Improved staging represents a key process measure that has significantly changed over the time periods, enabling better definition of patient cohorts who can be selected for treatment with curative intent. The decrease in patients treated with curative intent compared with the first time period suggests that staging and case selection have influenced decision-making. CT-PET would be expected to identify 5% to 17% of patients whose treatment plan may be altered compared with CT alone.[22] The impact of EUS on the outcomes observed is unclear. EUS has the greatest value for staging of early cancer and has been available throughout each period but underused until 2007. It is now standard in combination with CT-PET for patients with localized disease, and in parallel with an increase in early cancer there has been increased use of EUS in combination with endoscopic mucosal resection for microstaging and curative therapy.

The approach to surgery and its extent did not significantly change over successive time periods, although quality indicators including nodal yield and negative margins were improved. Transthoracic esophagectomy with abdominal and thoracic lymphadenectomy is the dominant operation throughout. There is an increasing use of transhiatal

esophagectomy for higher-risk patients and early disease, an approach that may be associated with lower respiratory risks compared with open thoracic surgery, and accounted for 5.4% of surgery in the recent period, compared with 1.7% in period 1 and 2.3% in period 2.[18] The use of multimodal therapy significantly increased to 41% in period 3 compared with 27% in period 1 and 36% in period 2. The same regimen spans the 3 time periods, based on the randomized trial conducted between 1990 and 1995, and combines cisplatin and fluorouracil and 40 to 44 Gy radiation therapy.[6] Consistent treatment efficacy is shown by equivalent major (TRG 1 and 2) histomorphologic regression at the primary site at 48%, 51%, and 45% for periods 1 to 3, respectively. The patterns of care and pathology indicate that the indication for use has changed, consequent on improved staging and the lack of a randomized trial, suggesting that the use of multimodal therapy in the modern era in this center is predominantly in patients with predicted locally advanced disease or node-positive disease. This is shown by node-positivity rates in 29% of patients in period 1 compared with 40% in period 2 and 60% in period 3 despite a uniform regimen and identical effects at the primary site. There has also been an increased use of radical radiation therapy in combination with chemotherapy over time, because a number of recent series suggest that this approach may be equivalent to approaches involving surgery, particularly for squamous cell cancers.[23]

The operative mortality in the recent time period was less than 2%, consistent with modern benchmarks from large single-center experience reported in the international literature, and markedly improved compared with collected series.[1-4] Many factors may be important, including the improved case selection, selective use of transhiatal esophagectomy or nonoperative approaches for higher-risk patients, and development of relatively standardized care pathways in combination with anesthetists, critical care specialists, cardiologists, and specialist nurses. The lowest reported mortality rate from a large series is from Low and colleagues[4] at the Virginia Mason Medical Center in Seattle, with 1 death in 340 patients (0.3%) in a 17-year series, results underpinned by standardized clinical pathways. Several key elements, including the use of thoracic epidurals, restricted intraoperative fluid, early mobilization, and enteral nutrition, are in place at this center.[4] In this current series, the most significant change is reduced deaths and reduced respiratory failure, but other major morbidities remained constant, a finding consistent with other series.[21]

We acknowledge that changes in staging and decision-making make the time periods not exactly comparable. Moreover, elements of quality of care are difficult to measure. The most significant impact on improved outcomes may be from the surgeons, oncologists, and other specialist staff working closely together in defined multidisciplinary teams, a so-called virtuous circle of shared experience.[24] This philosophy, focus, and drive are embedded widely in modern multidisciplinary care in cancer and complex surgery, and although these are nuanced and difficult to measure, they are likely to be a key factor where major quality improvements are observed.[24] We suggest that the modern high-volume esophageal cancer program targets stage for stage cure rates consistent with the best reported benchmarks, and the avoidance of any postoperative death, and that this philosophy is the driving force in most high-volume centers dealing with esophageal or other complex cancers or surgery.[25]

CONCLUSIONS

This study addressed factors that may relate to a continuously evolving improvement in oncologic and operative outcomes in a high-volume center where adenocarcinoma is the dominant cancer and the lessons learned may apply to similar centers in the West. A marked increase in early cancers is likely to be a key factor, as well as improved clinical and pathologic staging, and the integration of the multidisciplinary team. The modern team has a shared commitment to standardized care pathways and a drive to avoid any postoperative death and achieve adequate nodal harvest and negative margins, and all these factors are likely to affect this encouraging trend.

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TABLE E1. Demographics: All patients

	1990–1998		1999–2003		2004–2008		
Time period	**n = 704**	%	**n = 494**	%	**n = 589**	%	***P* value**
Mean age (range)	64 y	(28–86 y)	62 y	(26–83 y)	65	(36–86 y)	NS
Male:female ratio	2:1		2:1		2.2:1		NS
Pathology							.003
Adenocarcinoma	391	55.5	263	53.2	365	62	
Squamous cell	293	41.6	221	44.9	196	33.3	
Other	21	3	10	2	28	4.8	
Treatment intent:							<.05
Curative	471	68	254	53	342	58	
Palliative	233	32	240	47	247	42	

TABLE E2. Staging and radiologic investigations

	1990–1998		1999–2003		2004–2008		
	n	%	**n**	%	**n**	%	***P* value (χ^2)**
Total patients staged	704		494		589		
CT scan	165	23.4	467	94.5	579	98.3	<.001
PET scan/CT-PET	0	0	33	6.7	399	67.7	<.001
EUS	66	9.4	27	5.5	106	18.0	<.001
Barium study	348	49.4	130	26.3	69	11.7	<.001
Total patients treated with curative intent	471		254		342		
CT scan	145	30.8	254	100	342	100	<.001
PET scan/CT-PET	0	0	30	11.8	296	86.5	<.001
EUS	50	10.6	24	9.5	105	30.7	<.001
Barium study	257	54.6	64	25.1	36	10.5	<.001

CT, Computed tomography; *EUS*, endoscopic ultrasound; *PET*, positron emission tomography.

TABLE E3. Univariate and multivariate analysis of disease-specific survival of patients treated with curative intent

	Univariate analysis		Multivariate analysis	
Factor	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Sex (male vs female)	1.208 (1.025–1.423)	.024	1.258 (1.036–1.527)	.05
Age at diagnosis (>70 vs <70 y)	1.017 (1.009–1.024)	<.001	1.017 (1.008–1.026)	<.001
Adenocarcinoma	1.05 (0.90–1.224)	.536	Not in model	
Node negative versus node positive	0.445 (0.379–0.552)	<.001	0.461 (0.379–0.561)	<.001
T1 vs T2/3	0.395 (0.324–0.483)	<.001	0.521 (0.415–0.655)	<.001
R0 resection	0.505 (0.417–0.61)	<.001	0.706 (0.572–0.87)	.001
Neoadjuvant treatment (yes)	0.858 (0.726–1.015)	.074	Not in model	
Did not undergo resectional surgery	1.449 (1.197–1.755)	<.001		n/a
Postoperative complications (yes)	0.916 (0.785–1.069)	.265	Not in model	
Junction tumor (yes)	0.986 (0.843–1.152)	.855	Not in model	
Lymphatic invasion	2.46 (2.053–2.947)	<.001	$\chi^2 = 0.573$	.484
Venous invasion	1.49 (1.195–1.857)	<.001	1.445 (1.117–1.868)	.005
Perineural invasion	1.47 (1.177–1.836)	.001	$\chi^2 = 0.49$	.484
Time period of surgery: for trend		<.001		<.001
1990–1998 vs others	1.457 (1.209–1.757)	<.001	2.41 (1.829–3.176)	<.001
1999–2003 vs others	0.819 (0.68–0.986)	.035	0.717 (0.576–0.891)	.003
2004–2008 vs others	0.686 (0.569–0.827)	<.001	0.415 (0.315–0.547)	<.001

CI, Confidence interval.