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doi: 10.3748/wjg.14.3165

World J Gastroenterol 2008 May 28; 14(20): 3165-3173
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Treatment and survival in a population-based sample of patients diagnosed with gastroesophageal adenocarcinoma

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Supported by The Health Research Board of Ireland, N01-PC-35133, N01-PC-35135, N01-PC-35136, N01-PC-35137, N01-PC-35138, N01-PC-35139, N01-PC-35141, N01-PC-35142, N01-PC-35143, N01-PC-35145, N02-PC-15105, N02-PC-15106 and N02-PC-15107
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Received: September 27, 2007 Revised: April 12, 2008
Accepted: April 19, 2008
Published online: May 28, 2008

Abstract

AIM: To examine the extent of use of specific therapies in clinical practice, and their relationship to therapies validated in clinical trials.

METHODS: The US National Cancer Institutes' Patterns of Care study was used to examine therapies and survival of patients diagnosed in 2001 with histologically-confirmed gastroesophageal adenocarcinoma (n = 1356). The study re-abstracted data and verified therapy with treating physicians for a population-based stratified random sample.

RESULTS: Approximately 62% of patients had stomach adenocarcinoma (SAC), while 22% had gastric-cardia adenocarcinoma (GCA), and 16% lower esophageal adenocarcinoma (EAC). Stage Ⅳ/unstaged esophageal cancer patients were most likely and stage Ⅰ-Ⅲ stomach cancer patients least likely to receive chemotherapy as all or part of their therapy; gastric-cardia patients received chemotherapy at a rate between these two. In multivariable analysis by anatomic site, patients 70 years and older were significantly less likely than younger patients to receive chemotherapy alone or chemoradiation for all three anatomic sites. Among esophageal and stomach cancer patients, receipt of chemotherapy was associated with lower mortality; but no association was found among gastric-cardia patients.

CONCLUSION: This study highlights the relatively low use of clinical trials-validated anti-cancer therapies in community practice. Use of chemotherapy-based treatment was associated with lower mortality, dependent on anatomic site. Findings suggest that physicians treat lower esophageal and SAC as two distinct entities, while gastric-cardia patients receive a mix of the treatment strategies employed for the two other sites.

Key words: Adenocarcinoma; Esophageal adenocarcinoma; Gastroesophageal; Gastric adenocarcinoma; Survival; Chemotherapy; Radiotherapy

Peer reviewers: Emad M El-Omar, Professor, Department of Medicine & Therapeutics, Aberdeen AB25 2ZD, United Kingdom; Dr. Bernardino Rampone, Department of General Surgery and Surgical Oncology, University of Siena, viale Bracci, Siena 53100, Italy; Dino Vaira, Professor, Department of Internal Medicine and Gastroent, University of Bologna, S.Orsola-Malpighi Hospital-Nuove Patologie, Pad. 5-via Massarenti 9, Bologna 40138, Italy; Shotaro Nakamura, MD, Department of Medicine and Clinical Science, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan

Cronin-Fenton DP, Mooney MM, Clegg LX, Harlan LC. Treatment and survival in a population-based sample of patients diagnosed with gastroesophageal adenocarcinoma. *World J Gastroenterol* 2008; 14(20): 3165-3173 Available from: URL: http://www.wjgnet.com/1007-9327/14/3165.asp DOI: http://dx.doi.org/10.3748/wjg.14.3165

INTRODUCTION

The incidence and mortality of esophageal and gastric-cardia adenocarcinoma (GCA) has increased dramatically since the 1970s in western countries, while that of stomach cancer has decreased[1-3]. Gastroesophageal

adenocarcinomas have a poor prognosis[4-8]. However, numerous randomized clinical trials (RCTs) have evaluated, and continue to evaluate, the survival benefit of various treatment regimens.

Surgery remains standard care for early stage esophageal cancer. The MAGIC trial, a large phase Ⅲ European RCTs found that patients with resectable lower esophageal or gastric adenocarcinomas treated with peri-operative chemotherapy had better progression-free and overall survival rates compared to surgery only[9]. This benefit was supported by the Fédérale Nationale des Centres de Lutte Contre Le Cancer (FNLCC) for patients with gastroesophageal adenocarcinoma who received pre-operative chemotherapy compared to surgery alone[10]. However, RCTs evaluating pre-operative chemoradiation compared to surgery alone have had conflicting results; some indicate better survival for esophageal cancer patients[11,12]. For locally advanced esophageal cancer, a phase Ⅲ RCT, RTOG 85-01, demonstrated improved survival in patients who received chemoradiotherapy compared to radiation alone[13], although most of these patients had squamous esophageal cancer. Another small RCT in patients with locally advanced esophageal cancer found chemoradiation superior to radiation alone[14]. These trials support the use of definitive chemoradiotherapy for locally advanced disease and its potential use for some patients with resectable disease. Current National Comprehensive Cancer Network (NCCN) guidelines for patients who are medically unfit for surgery or have unresectable disease recommend radiation and concurrent chemotherapy as treatment or best supportive care if patients cannot tolerate chemotherapy[15].

Surgery is also the standard of care for early stage gastric cancer. A US Intergroup phase Ⅲ trial, INT-0116, demonstrated post-surgical chemoradiation improved overall and disease-free survival in patients with stomach adenocarcinoma (SAC) and GCA[16]. The MAGIC and FNLCC trials also included patients with SAC and GCA. RCTs have also evaluated various chemotherapy treatments for patients with advanced or metastatic stomach and gastric-cardia cancer and have demonstrated improved survival for particular regimens[17,18]. The current NCCN guidelines for patients with metastatic stomach cancer recommend chemotherapy as treatment or best supportive care for those unable to tolerate chemotherapy[19].

Few studies have examined community-based patterns of care for these cancers. A study on esophageal adenocarcinoma (EAC) and squamous cell carcinoma patients diagnosed between 1996 and 1999 found that chemoradiation was most frequently given although patients with chemoradiation followed by surgery had better survival compared to definitive chemoradiation[20]. Research suggests, however, that community-based use of treatment and the observed survival of patients in the community can vary depending on clinical and non-clinical factors[21-26].

We present a population-based study, analyzing the receipt of various treatment strategies among a stratified random sample of patients with gastroesophageal adenocarcinoma. This study aims to determine whether treatment strategies used in routine community practice are based on anatomic location or cancer origin and to examine community-based use of specific chemotherapy regimens, especially those evaluated in RCTs. Finally, we assess factors that influence treatment receipt and patient survival.

MATERIALS AND METHODS

We included individuals aged ⩾ 20, newly diagnosed during 2001 with histologically-confirmed lower esophageal (EAC), GCA and SAC. Patients were ineligible if diagnosis was by death certificate only, autopsy, if they had a previous cancer diagnosis, other than non-melanoma skin, or were simultaneously diagnosed with another cancer. Patients were sampled from the National Cancer Institute's Surveillance, Epidemiology and End-Results Program (SEER) including Atlanta, Detroit, Seattle, New Mexico, Iowa, Louisiana, New Jersey, Connecticut, Utah, and California (Los Angeles County, San Francisco/Oakland, San Jose/Monterey, and greater California). Individuals were stratified by registry and race/ethnicity, and randomly sampled within strata. Non-Hispanic blacks, Hispanics, Asians/Pacific Islanders and Native Americans were over-sampled to obtain more stable estimates.

Data from medical records were re-abstracted to verify patient demographics, tumor characteristics, and treatment. Abstractors from each registry were centrally trained to ensure consistency of abstracting and coding. Because therapy is frequently provided in an outpatient setting, each patient's physician was contacted to verify treatment received, and provide names of any other physician who may have administered therapy. That physician was then contacted. All co-morbid conditions recorded at the hospitalization for most definitive treatment were abstracted. These were coded centrally by a single Registered Health Information Technologist and analyzed using the Charlson score[27]; an index of nineteen conditions, weighted according to the adjusted risk of one-year mortality.

We included 1411 cases. Patients were grouped by anatomic sites based on ICD-O2 codes; EAC (ICD-O: C15.2, C15.5, n = 165), GCA (the portion of the stomach surrounding the gastroesophageal junction) (C16.0, n = 246), and SAC (C16.1-C16.9, n = 1000) and stage, Ⅰ-Ⅲ and Ⅳ/unstaged. Because of small numbers (18) of Ⅳb EAC, these were grouped with Ⅳ/unstaged.

Treatments were defined as the receipt of surgery, radiotherapy, chemotherapy, in any combination. Non-adenocarcinoma cases were excluded from the therapy analyses (n = 55); 1356 adenocarcinoma patients were included in the treatment analyses.

Data analyses were performed using Stata 8.0 and SUDAAN (Research Triangle Institute, Research Triangle Park, NC). Analyses were weighted to reflect the SEER population from which the sample was drawn. Multivariable analyses were conducted using logistic

and multinomial logistic regression. Cancer survival was analyzed using Cox regression models with a maximum two-year follow-up (through December 2003). All *P*-values were two-sided.

RESULTS

Approximately 62% of patients had SAC, 22% GCA, and 16% lower EAC (Table 1). Median age was highest (76 years) for stage I-Ⅲ SAC patients and lowest (67 years) for stage Ⅳ/unstaged GCA (data not shown).

Lower EAC

Over 12% of stage I-Ⅲ patients with EAC received surgery alone (Table 2). About 27% of patients with stage I-Ⅲ EAC received tri-modality therapy (surgery, radiation and chemotherapy), while 36.5% of these patients received chemotherapy plus radiation therapy with no surgery. One-quarter of stage I-Ⅲ EAC patients received no chemotherapy. The most frequently administered agent was 5-FU, frequently with cisplatin. Few patients with late/unstaged EAC received surgery, in any combination. Chemoradiotherapy, however, was given to nearly 47% of these patients. In multinomial logistic regression, age ⩾ 70 was associated a 70%-80% decreased use of chemotherapy and chemoradiation in patients with EAC (Table 3).

Non-Hispanic blacks and Asian/Pacific Islanders with EAC had significantly higher hazards of cancer deaths than non-Hispanic white patients (Table 4). Patients age < 70 with a Charlson score of ⩾ 1 had a significantly increased risk as did those with late/unstaged disease. EAC patients who received chemotherapy had better survival, although not statistically significant. In a separate model, EAC patients who received chemoradiation had decreased hazards (HR = 0.69, 95% CI = 0.43-1.06 model not presented). The prognostic factors in the Cox proportional hazards model containing chemoradiation were otherwise the same as those significantly associated with death in the model which adjusted for chemotherapy.

GCA

Patients with GCA received therapies at a rate between that of EAC and SAC patients. Surgery alone was provided to 34% of stage I-Ⅲ GCA patients (Table 2). One-quarter of stage I-Ⅲ GCA patients received trimodal therapy. Nearly twice as many GCA patients as EAC patients but less GCA than SAC patients received no chemotherapy. Fewer patients received chemoradiotherapy compared to EAC patients. 5-FU was the most frequently used chemotherapeutic agent. Nearly twice as many late/unstaged GCA patients as EAC received no therapy. In multinomial logistic regression, age ⩾ 70 was associated with a 70%-80% decrease in chemotherapy alone or chemoradiotherapy (Table 3). Women and patients with a Charlson Score of ⩾ 1 were significantly less likely to receive chemotherapy, but not chemoradiation. In the Cox proportional hazards models patients, with late/unstaged disease or poorly/undifferentiated tumors had an increased risk of cancer deaths while married individuals had a decreased risk (Table 4).

SAC

Of the three anatomic sites, patients with SAC were most likely to receive surgery alone (Table 2). Nearly 50% of stage I-Ⅲ SAC patients received surgery alone. Less than 20% of stage I-Ⅲ SAC patients received trimodal therapy. Fewer SAC patients than EAC or GCA patients received chemotherapy. As with the other two anatomic sites, 5-FU was most frequently administered. Of the three anatomic sites, late/unstaged SAC patients received no definitive cancer treatment most often. In multinomial regression, age ⩾ 70 was associated with 80% less chemotherapy alone or chemoradiation (Table 3). Late/unstaged disease was associated with decreased use of chemoradiation but a substantial increased use of chemotherapy alone. Proportional hazards models for cancer deaths showed that in non-surgical patients, late/unstaged disease or a poor/undifferentiated tumor was associated with increased risk of cancer death (Table 4). However, patients receiving chemotherapy had a significantly decreased risk. Among surgical patients, a Charlson Score of ⩾ 1, regardless of age and having late/unstaged disease was associated with increased hazards. Lower risks were seen among Asian/Pacific Islanders, and a non-significant decreased risk among patients who received chemotherapy (Table 4). Patients who received chemoradiation had a statistically significant decreased risk both with (HR = 0.56, 95% CI = 0.35-0.89) and without surgery (HR = 0.62, 95% CI = 0.43-0.92) (model not presented) but all other prognostic factors had similar associations with hazard ratios as the Cox models which adjusted for chemotherapy.

DISCUSSION

RCTs have demonstrated that certain treatment strategies and regimens improve survival for patients with esophageal and gastric cardia adenocarcinoma. Variation in gastroesophageal cancer survival, however, has sometimes been attributed to case mix[28]. We therefore selected adenocarcinoma cases only and categorized patients by anatomic site to assess rates of treatment and survival among a population-based sample of patients treated in the community. We found significant differences in treatment and survival by anatomic site, stage, age, and race/ethnicity. This study highlights the considerably varied approach that community physicians take to treat adenocarcinomas at each anatomic site.

Lower EAC

While there is no consensus definition of the optimal therapy for patients with resectable EAC, clinical trials have indicated survival improvements when surgery is supplemented with additional therapies. Of the three cancer sites investigated in the current study, stage I-Ⅲ EAC patients had the lowest rates of surgery alone

Table 1 Percentage distribution (weighted for the sampling fraction) of clinical and non-clinical characteristics for gastroesophageal cancer patients diagnosed in 2001 NCI: Patterns of care study (n = 1411) (Wt%)

	Lower esophagus		Gastric cardia		Stomach	
	I-III (n = 86)	IV-V (n = 79)	I-III (n = 119)	IV-V (n = 127)	I-III (n = 491)	IV-V (n = 509)
Age						
< 70	57.5	46.4	57.2	54.0	36.7	42.4
⩾ 70	42.5	53.6	42.8	46.0	63.3	57.6
Marital status						
Other	39.9	43.6	37.9	41.0	46.4	48.9
Married	60.1	56.4	62.1	59.0	53.6	51.1
Race						
NH White	93.9	87.8	78.0	75.1	51.0	47.9
NH Black	1.0	3.3	4.3	5.8	13.4	14.2
Hispanic	4.1	7.9	11.6	12.0	15.8	20.5
A/PI	1.0	1.0	6.2	6.8	19.1	17.0
NA/AI	0.0	0.0	0.0	0.4	0.6	0.3
Charlson score						
Zero	72.3	81.0	77.7	86.5	79.5	78.9
1+	27.7	19.0	22.3	13.5	20.5	21.1
Vital status Dec 2003						
Deceased	69.6	88.8	70.0	88.3	53.9	89.9
Histology						
Adeno, NOS	92.8	81.0	79.5	70.4	50.4	50.7
A. intestinal	0.0	3.7	9.1	4.1	14.6	7.2
A. diffuse	0.0	0.0	1.8	4.4	4.0	3.0
Signet	6.0	12.0	8.0	18.9	20.6	28.9
Mucinous	1.2	2.4	0.9	1.0	5.5	5.5
Papillary	0.0	0.9	0.7	0.0	0.9	1.5
Tubular	0.0	0.0	0.0	1.0	2.2	0.6
Linus plastica	0.0	0.0	0.0	0.2	1.8	2.6
Linitis plastica/Signet ring						
Linitis plastica	3.9	0.0	0.0	4.1	5.3	7.2
Signet	13.9	13.1	15.2	22.4	24.4	33.6
No mention	81.6	86.9	78.3	71.3	69.5	58.5
Unknown	0.6	0.0	6.5	2.2	0.8	0.7
Intestinal metaplasia in resected tumor						
None	31.3	28.5	36.7	17.9	25.4	24.3
Metaplasia	7.9	3.0	18.4	5.9	31.2	9.6
No mention	36.6	29.9	30.6	37.5	30.1	28.0
Unknown	24.2	38.6	14.3	38.8	13.3	38.1
Grade						
Well differentiated	4.1	12.0	2.9	4.9	6.9	2.3
Moderate	18.9	39.6	31.3	33.4	28.1	19.4
Poor/Undif	57.1	28.5	59.0	51.3	56.5	60.7
Unknown	19.8	20.0	6.8	10.4	8.4	17.7
Barrett's esophagus						
No	21.3	27.7	39.1	19.9	43.4	28.4
Yes	33.2	9.3	11.0	3.8	0.0	0.6
Other	3.9	1.1	1.3	0.0	0.0	0.0
No mention	16.8	21.8	27.8	35.2	43.7	31.5
Unknown	24.8	40.1	20.7	41.1	12.9	39.5
History of Barrett's						
No history	19.3	22.6	27.5	25.6	29.4	29.4
History	22.7	14.0	6.0	8.7	1.7	0.5
No mention	54.5	60.0	59.5	61.8	67.2	67.9
Unknown	3.4	3.4	7.0	3.9	1.8	2.1
H pylori						
Negative	22.6	39.2	32.3	29.6	37.6	33.1
Positive	2.1	13.5	10.0	15.9	18.6	15.9
No mention	73.3	41.9	51.1	52.6	41.4	49.0
Pernicious anemia						
No history	25.9	33.1	26.9	31.5	31.1	28.7
Pernicious Anemia	0.6	0.0	8.2	0.4	6.1	3.9
No mention	71.5	62.0	60.4	65.4	59.6	64.9
Unknown	2.0	4.9	4.5	2.7	3.2	2.6
History of ulcers						
No history	23.5	32.6	28.2	29.5	19.6	23.1
Peptic ulcers, NOS	7.9	11.6	5.8	4.7	12	10.5
Duod/pyloric ulcer	2.1	1.7	0.4	1.3	1.1	2.9
Gastric ulcer	4.3	0	8.6	9.6	22.7	13.3
Other	6.5	7.1	0.4	1.4	0.9	0.8
No mention	55.1	44.7	50.1	51	40.6	46.9
Unknown	0.6	2.4	6.6	2.4	3.1	2.5

American Indians/Native American are included in Table 1 for completeness of reporting. Histology groupings were created according to the following: Adenocarcinoma-NOS = 8140, 8210, 8255, 8261 (n = 842), Adeno-Intestinal = 8144 (n = 122), Adeno-Diffuse = 8145 (n = 45), Signet Cell = 8490 (n = 295), Mucinous/mucin-producing = 8480 + 8481 (n = 48), Papillary/Serous = 8260 + 8460 + 8461 (n = 12), Tubular = 8211 (n = 17), Linitis plastica = 8142 (n = 23).

Table 2 Percentage distribution (weighted for the sampling fraction) of treatment characteristics and survival for gastroesophageal adenocarcinoma patients diagnosed in 2001 NCI: Patterns of care study (n = 1356)[1] (Wt%)

	Lower esophagus		Gastric cardia		Stomach	
	I-III	IV-V	I-III	IV-V	I-III	IV-V
Therapy received						
Surgery only	12.3	1.3	34	2.2	49.6	15.7
Radiation only	8.1	3.5	4.7	7.2	2	3.3
Chemotherapy only	0.5	24	1.2	21.9	3.6	22.1
Surgery and radiation	0.8	0	2.6	0.9	3.9	0.4
Surgery and chemo	2.5	1.3	8.6	4.8	3.2	5.6
Surgery, rad, chemo	27	4.6	25	11.2	19.2	6.1
Chemo and radiation	36.5	46.8	9.8	12.4	1.5	3.4
None	12.4	18.7	14.1	39.4	17.1	43.4
Chemotherapy						
No chemo	25.1	21.5	48.7	40.8	64.9	54.5
Single agent	5.4	25.5	11.4	9.9	10.3	8.4
Multi-agent	61.1	50.9	31.4	39.6	17.1	29
Refused	5.9	1.5	4.3	7.2	4	4.3
Rec, unknown if given	1.9	0	1	2.1	1.8	2.3
Unknown	0.6	0.6	3.2	0.4	2	1.5
Chemotherapy agent						
5-FU	58.6	37.9	35.7	34.7	23.2	26.4
Doxorubicin	0.5	0	0.3	1	0.5	3.4
Capecitabine	1.2	0	0.7	7.4	0.6	4
Cisplatin	38.7	37.2	22	17.2	2.8	10.8
Etoposide	1	0	0.7	10.7	1.4	5.8
Irinotecan	0.7	12.9	0.5	5.9	1.6	5.6
Leucovorin	4.1	0.9	6.1	21.8	12.1	15.1
Mitomycin-C	13.7	4.3	0.5	0.6	0.2	1.8
Oxaliplatin	No one					
Epirubicin	0	0	0	1	0	1.2
Paclitaxel	11.8	20.8	5.9	7.3	2.2	4.6
Docetaxel	0	1.6	0.7	2.1	0.6	1.4
Chemotherapy plus surgery (with or without radiation)						
No	70.5	94.2	68.3	84	77.7	87.8
Pre-op	23.7	4.9	16.8	6.4	0.3	0.5
Post-op	5.8	0.9	9	8.5	20.3	11.2
Unknown	0	0	5.9	1.1	1.7	0
Surgery plus chemotherapy and radiation						
No	73	95.4	75	88.5	80.9	93.9
Pre-op	21.9	4.6	13.4	4.3	0.2	0.5
Post-op	5.1	0	8.6	6.9	17.4	5.6
Unknown	0	0	3	0	1.5	0
Median survival time (mo)						
Non-surgical pts	13	8	8	6	5	4
Surgical patients	22	13	19	13	26	6

[1]13 American Indians/Native Americans excluded.

Table 3 Therapy among patients with gastroesophageal adenocarcinoma by anatomic site, 2001: Multinomial logistic regression for the receipt of chemoradiation (Chemo + RT) and chemotherapy alone

Site characteristic	Lower esophagus					Gastric-cardia					Stomach				
	Chemo + RT		Chemo			Chemo + RT		Chemo			Chemo + RT		Chemo		
	OR	95% CI	OR	95% CI	*P*	OR	95% CI	OR	95% CI	*P*	OR	95% CI	OR	95% CI	*P*
Age					0.05					< 0.001					< 0.001
< 70	1		1			1		1			1		1		
⩾ 70	0.3	0.1-0.96	0.2	0.03-0.9		0.2	0.1-0.4	0.3	0.1-0.7		0.2	0.1-0.4	0.2	0.1-0.3	
Race/ethnicity					0.33					0.64					0.24
Non-hispanic white	1		1			1		1			1		1		
Non-hispanic black	1.1	0.1-10.2	0.9	0.1-14.5		0.5	0.1-1.7	1	0.2-6.7		1.3	0.6-2.5	0.6	0.3-1.0	
Hispanic	0.1	0.01-0.9	0.3	0.02-3.6		0.4	0.1-1.6	1.6	0.3-7.4		1.2	0.6-2.5	0.6	0.3-1.4	
Asian/Pacific Islander						0.5	0.1-1.9	1.4	0.4-4.9		1.7	0.9-3.4	0.8	0.4-1.4	
Gender					0.32					0.01					0.64
Male	1		1			1		1			1		1		
Female	1.2	0.5-3.3	0.3	0.04-2.1		1.2	0.4-3.3	0.3	0.1-0.8		1.3	0.8-2.1	1.1	0.7-1.8	
Marital status					0.28					0.86					0.74
Not married	1		1			1		1			1		1		
Married	2.1	0.7-6.5	1	0.3-3.9		1	0.4-2.6	1.4	0.4-4.6		1.2	0.7-2.0	1.2	0.7-1.9	
Stage					0.12					0.01					< 0.001
Ⅰ-Ⅲ	1		1			1		1			1		1		
Ⅳ & unknown	1	0.4-2.7	3.6	0.9-13.6		0.7	0.3-1.7	3.8	1.3-11.4		0.6	0.4-0.9	5.2	3.0-8.8	
Differentiation grade					0.57					0.36					0.38
Well/Moderately differentiated	1		1			1					1		1		
Poorly/Undifferentiated	1.2	0.4-3.6	0.9	0.2-3.7		0.8	0.3-1.9	1	0.3-3.1		1.3	0.7-2.2	1.3	0.7-2.5	
Unknown	0.6	0.2-1.9	0.2	0.03-1.4		1.5	0.3-7.3	0.2	0.03-1.8		0.7	0.3-2.0	1.6	0.8-3.5	
Charlson score					0.25					0.02					0.35
0	1		1			1		1			1		1		
1+	2	0.6-6.7	0.6	0.1-3.1		0.4	0.1-1.3	0.1	0.02-0.6		0.7	0.4-1.2	0.9	0.5-1.7	
H pylori					0.02					0.004					0.65
No	1		1			1		1			1		1		
Yes	0.1	0.02-0.8	0.4	0.03-5.6		1	0.2-4.2	0.4	0.1-2.1		1.2	0.6-2.5	1.3	0.6-2.8	
Unknown	0.1	0.03-0.4	0.2	0.03-0.8		0.2	0.1-0.7	0.8	0.3-2.3		1	0.6-1.7	1.5	0.9-2.5	

Model also adjusted for registry.

as their primary treatment, but highest rates of pre-operative chemotherapy and chemoradiation as well as definitive chemoradiation. This may reflect the significant morbidity associated with esophageal surgery[29-32]. However, toxicities associated with pre-operative chemotherapy or chemoradiation can preclude a patient from further treatment[33].

RCTs and a meta-analysis have suggested a survival benefit associated with pre-operative and adjuvant chemoradiation compared to surgery alone[11,33-37]. The US-Intergroup trial, CALGB-9781, closed early due to poor accrual, but an intent-to-treat analysis on the 56 enrolled patients, demonstrated better median survival in favor of trimodal therapy[12]. In our study, over a quarter of stage Ⅰ-Ⅲ EAC patients received trimodality therapy. The MAGIC and FNLCC phase Ⅲ trials support the use of perioperative or preoperative chemotherapy; however, we found that few (2.5%) stage Ⅰ-Ⅲ EAC patients received surgery and chemotherapy as primary treatment. Chemoradiation was the treatment strategy received by the largest percentage of patients with stage Ⅰ-Ⅲ EAC (36.5%) and late/unstaged EAC patients (47%).

GCA

Optimal therapy for GCA is not clear. Most RCTs have included patients with this cancer in trials conducted for either or both of the other two anatomic sites[18,38]. Reflective of this, we found that GCA patients seemed to receive treatment at a rate that fell midway between the other two anatomic sites. In the current population-based study, stage Ⅰ-Ⅲ GCA patients were most frequently treated with surgery alone (34%) or trimodal therapy (22%). For late/unstaged disease less than 25% received chemotherapy alone and a significant percentage received no therapy (39%).

SAC

In contrast to EAC and GCA patients, SAC patients received surgery alone most frequently (50% of stage Ⅰ-Ⅲ and 16% of stage Ⅳ/unstaged disease) and radiotherapy and chemotherapy less frequently than the other two anatomic sites. Although the MAGIC and FNLCC trials demonstrated a survival advantage for patients with gastroesophageal adenocarcinoma[9], this was not evident in the current population-based study, where less than 20% of stage Ⅰ-Ⅲ SAC patients received chemoradiation with surgery.

With respect to advanced disease, several RCTs for SAC have demonstrated survival benefits for chemotherapy compared to best supportive care for stage Ⅳ (late-stage) disease[17]. However, we found that only 22% of patients with late/unstaged SAC received chemotherapy alone, with an additional 15% receiving chemotherapy with surgery, with surgery and radiation, or as chemoradiation. Furthermore, for late/

Table 4 Cox proportional hazards model for cancer death among lower esophageal and GCA patients overall (Model 1) and among SAC patients who did or did not receive surgery (Model 2)

	Model 1						Model 2					
	Lower esophagus (n = 164) With & Without surgery			Gastric-cardia (n = 241) With & Without surgery			Stomach					
							No surgery (n = 461)			With surgery (n = 490)		
Characteristic	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age & co-morbidity			0.02			0.44			0.97			0.01
< 70, Charlson score = 0	1			1			1			1		
< 70, Charlson score = 1	2.7	1.4-5.2		1	0.4-2.1		0.9	0.6-1.4		2	1.1-3.7	
70+, Charlson score = 0	1.5	0.9-2.6		1.4	0.9-2.3		0.9	0.6-1.4		1.5	0.9-2.5	
70+, Charlson score = 1	1.5	0.7-3.3		1.1	0.5-2.4		1	0.6-1.6		2.4	1.4-4.0	
Race			< 0.001			0.08			0.39			0.003
Non-Hispanic White	1			1			1			1		
Non-Hispanic Black	3.4	1.8-6.7		0.8	0.5-1.2		1.1	0.8-1.5		1.1	0.6-1.7	
Hispanic	1	0.5-2.0		1.3	0.8-2.2		0.8	0.5-1.2		1.3	0.8-2.1	
Asian/Pacific Islander	6.4	2.9-14.4		0.4	0.2-1.0		0.9	0.6-1.2		0.5	0.3-0.9	
Gender			0.78			0.87			0.84			0.18
Male	1			1			1			1		
Female	0.9	0.6-1.5		1	0.6-1.4		1	0.8-1.4		0.8	0.5-1.1	
Marital Status			0.43			0.01			0.39			0.33
Not married	1			1			1			1		
Married	0.8	0.5-1.3		0.6	0.4-0.9		1.2	0.8-1.6		1.2	0.8-1.9	
Stage			< 0.001			< 0.001			0.004			< 0.001
Stage Ⅰ-Ⅲ	1			1			1			1		
Stage Ⅳ & unknown	2.5	1.5-4.2		2.6	1.6-4.0		1.7	1.2-2.3		5	3.4-7.4	
Differentiation grade			0.11			0.049			0.01			0.14
Well/Moderately	1			1			1			1		
Poorly/Undifferentiated	1.8	1.0-3.3		1.7	1.1-2.6		1.8	1.2-2.6		1.4	0.9-2.2	
Unknown	1.7	0.9-3.2		1.3	0.6-2.8		1.5	1.0-2.3		0.7	0.3-1.7	
Chemotherapy			0.09			0.68			< 0.001			0.12
No	1			1			1			1		
Yes	0.6	0.4-1.1		1.1	0.7-1.8		0.6	0.4-0.8		0.7	0.5-1.1	

unstaged disease, SAC patients received no therapy most frequently (43%).

Overall, our results do suggest that RCT-validated therapies have been incorporated into community practice, albeit at low levels. However, a significant percentage of patients, especially those with stage Ⅳ/unstaged disease, across all anatomic sites received no cancer-directed therapy. Our findings also highlight that the sequence and combination of chemotherapy, radiotherapy and surgery in the adjuvant setting was distinct for each anatomic site. For example, of stage Ⅰ-Ⅲ EAC patients who received surgery plus chemotherapy and radiation, 81% received this therapy pre-operatively [most frequently with 5-fluorouracil (5-FU) and cisplatin], while of stage Ⅰ-Ⅲ SAC patients who received surgery plus chemotherapy and radiation, 91% received this therapy post-operatively (most frequently with 5-FU and leucovorin). These sequences of therapy as well as the chemotherapeutic agents selected were also consistent with RCTs conducted in these disease sites[11].

Chemotherapeutic agents

Overall, the most frequently administered chemotherapeutic agents in our study were 5-FU, cisplatin, and leucovorin. Newer agents (paclitaxel, irinotecan) have been investigated in phase Ⅱ trials[39,40] for use in EAC patients. We found that these drugs were used in community practice (Table 2). Use of these compounds was much lower among patients with SAC and GCA cancers. No patients received oxaliplatin, possibly because these cases were diagnosed in 2001 and findings advocating oxaliplatin for esophageal cancer were only presented in 2006[38]. Specific chemotherapeutic agents used alone or in combination with surgery and radiation are listed in Table 5. Whether patients received chemotherapy alone, chemoradiation, or trimodal therapy, the majority of patients received 5-FU in combination with another chemotherapeutic agent.

Age disparities

Less frequent treatment of elderly patients has been widely reported[21-25,41]. Sabel *et al*[31] reported that 50% of patients age < 70 and 32% of those age ⩾ 70 were suitable for surgery at diagnosis. Similar to this, we found that in stage Ⅰ-Ⅲ EAC, 30% of patients aged ⩾ 70 compared to 51% of those age < 70 underwent cancer-directed surgery and 56% of gastric-cardia patients aged ⩾ 70 compared to 80% of those age < 70. The age-related treatment decline is likely attributable to a number of factors: (1) Potentially higher morbidity among elderly patients; (2) Compromised treatment options due to delayed presentation by elderly patients; (3) Increased anesthesiological risk[31,42]; and (4) A higher prevalence of co-morbidities.

Median age at diagnosis for stomach cancer is approximately 70 years[43], an age when patients have a reasonable life-expectancy[43]. Selected medically-fit elderly patients do as well as younger patients after surgical or adjuvant therapy[44,45]. Our models indicate

Table 5 Percentage distribution (weighted for the sampling fraction) of chemotherapy agents by selected therapeutic combinations gastroesophageal adenocarcinoma patients diagnosed in 2001; NCI: Patterns of care study (n = 1356)[1] (Wt%)

	Lower esophagus		Gastric-cardia		Stomach	
	I-III	IV-V	I-III	IV-V	I-III	IV-V
Chemotherapy only						
Etoposide + Doxorubicin + Cisplatin	1 patient	0	0	0	0	0.6
5-FU only	0	3.2	0	3.3	15.9	5.1
Mitomycin only	0	16.7	0	0	0	0
Paclitaxel only	0	2.1	19.2	3.3	0	0
Capcitabine only	0	0	0	0	0	4.4
Gemcitabine only	0	0	0	3.1	0	1.2
5-FU + 1 agent	0	18	56	16.6	25.5	18.8
5-FU + 2 agents	0	4	24.8	40	26.6	23.3
5-FU + 3 agents	0	0	0	7.9	0	15.6
5-FU + 4 agents	0	0	0	2.6	0	2.2
Irinotecan + Paclitaxel	0	20.6	0	1.2	0	0.6
Irinotecan + Cisplatin	0	15.4	0	1.7	0	8.4
Irinotecan + Cisplatin + Paclitaxel	0	0	0	0	20.4	0
Other	0	20	0	20	11.7	19.7
Radiation and chemotherapy						
5-FU only	2.1	9.2	34.8	29.2	5.6	20.6
Cisplatin only	0	17.1	0	3.3	0	0
5-FU + Leucovorin	0	1.2	0	0	0	14.3
5-FU + Cisplatin	50.6	28	61.5	32.6	7.9	0
5-FU + Mitomycin	25.1	0.7	0	0	0	0
5-FU + Irinotecan	0	0	0	0	30.1	0
Paclitaxel + Carboplatin	0	13.6	0	4.7	0	0
Chemo, NOS	4.6	8.9	0	7.5	20	13.1
Other	17.6	21.3	3.7	22.7	36.4	52
Surgery, radiation & chemotherapy						
5-FU only	5	0	9.4	0	32.4	26.5
5-FU + Leucovorin	13.3	0	17.6	31.7	46.5	40.9
5-FU + Cisplatin	41.1	15.6	27.7	7.3	2.3	0
5-FU + Paclitaxel + Carboplatin	15.3	44.6	1.6	0	0.7	0
Other agents/Combos	25.3	39.8	43.7	61	18.1	32.6

[1]13 American Indians/ Native Americans excluded; NOS: Not otherwise specified.

that in EAC or GCA patients, being age < 70 with a Charlson score of 1+ was significantly and inversely associated with surgery (data not shown). Older patients (≥ 70) were also less likely to have surgery even with a Charlson score of 0. In our multinomial models, being age ≥ 70 was associated with a decreased use of chemotherapy or chemoradiation even after adjusting for co-morbid conditions. Although we saw this disparity in the use of chemotherapy or chemoradiation by age group, there was no evidence of treatment-related differences by racial/ethnic groups. This suggests that in a community-based setting, age, in addition to co-morbidity, influences whether or not a patient receives surgery, chemotherapy, and chemoradiation.

Survival

Survival from gastric adenocarcinoma is extremely poor[46]. Theuer *et al*[46] reported that patients aged ≥ 70 had higher risk of death even after adjusting for clinical, non-clinical and treatment-related factors. In contrast, we observed that in GCA and non-surgical SAC patients, age and co-morbidity were not significant predictors of survival, perhaps due to the poor prognosis for these patients. We noted higher mortality in non-Hispanic blacks and Asian/Pacific Islanders with EAC. Such racial disparities have been reported in other cancers[47,48], however the underlying cause for this poorer survival is not clear.

A US-based survey of 59 radiotherapy facilities indicated improved survival associated with pre-operative chemoradiation for patients with esophageal cancer[20]. In the current study, chemotherapy and chemoradiation were associated with decreased mortality for SAC and EAC patients, although not GCA patients. This suggests that the receipt of chemotherapy and/or radiotherapy may improve outcome in these poor prognosis cancers. This analysis was not a randomized study of therapy and although we adjusted for Charlson comorbidity score and additional potential confounders, patients who had better baseline health and who were selected for chemotherapy, may have been more likely to respond to such treatment or may have had better survival regardless of the use of chemotherapy.

In conclusion, RCTs have demonstrated that specific treatment strategies prolong survival in certain patient groups. We note that the use of these therapies was very low in US community-based practice despite their demonstrated survival benefits. Our study shows lower mortality among patients with EAC and SAC who received chemotherapy and significant disparities in terms of age in treatment receipt. Our findings highlight the distinctly individualized approach taken by community physicians in treating adenocarcinoma at these three anatomic sites. Community physicians appear to differentiate gastroesophageal adenocarcinoma as two distinct entities (i.e. EAC and SAC) and use different treatment strategies and chemotherapeutic agents for each, while patients with GCA are treated with a mixture of those employed for the other two anatomic sites. Improvements in community-based treatment of gastroesophageal adenocarcinoma will require better differentiation of treatments for the different anatomic sites and more extensive incorporation of those treatments proven effective in clinical trials. Future RCTs should be designed and appropriately powered to account for differences related to the anatomic site or origin of the tumor as well as the underlying tumor biology.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of the participating SEER registries and staffs. Without their dedicated efforts this research could not be conducted.

COMMENTS

Background

Randomized clinical trials (RCTs) have demonstrated that specific treatment strategies prolong survival in certain patient groups with gastric, gastro-esophageal and esophageal adenocarcinomas. However, the extent of use of these treatments in routine clinical practice is not clear. Research suggests that community-based use of treatment and the observed survival of patients in the

community can vary depending on clinical and non-clinical factors.

Research frontiers

To determine whether treatment strategies used in routine community practice are based on anatomic location or cancer origin. To examine community-based use of specific chemotherapy regimens especially those evaluated in RCTs. To assess factors that influence treatment receipt and patient survival.

Innovations and breakthroughs

We document relatively low community-based use of treatments tested in RCTs in patients with gastroesophageal adenocarcinoma. The use of these therapies was very low despite their demonstrated survival benefits. Our study shows lower mortality among patients with esophageal adenocarcinoma (EAC) and stomach adenocarcinoma (SAC) who received chemotherapy and significant disparities in terms of age in treatment receipt. Community physicians appear to take an individualized approach in treating adenocarcinoma at these three anatomic sites; differentiating between gastric and EAC and using different treatment strategies and chemotherapeutic agents for each, while patients with gastric cardia adenocarcinoma are treated with a mixture of those employed for the other two anatomic sites.

Applications

Improvements in community-based treatment of gastroesophageal adenocarcinoma will require better differentiation of treatments for the different anatomic sites and more extensive incorporation of those treatments proven effective in clinical trials. Future RCTs should be designed and appropriately powered to account for differences related to the anatomic site or origin of the tumor as well as the underlying tumor biology.

Peer review

This is a retrospective study of a large number of patients with gastroesophageal adenocarcinoma focusing on treatment modalities and survival. This is an excellent and relevant study, which was well conducted and presented.

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