

ORIGINAL ARTICLE

End-of-study results of Turkish gastric cancer patients from the global REGATE study

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Summary

Purpose: Registry of Gastric Cancer Treatment Evaluation (REGATE) study was an international, prospective study including over 10000 patients from 22 countries, designed to describe the pattern of care in gastric cancer globally. The aim of this study was to summarize the data of the Turkish arm and compare them with the global results.

Methods: Ten centers from Turkey took part in the REGATE registry. Between 2004 and 2008, 395 patients (median age, 60 years; range, 18-91, 67.6% men) with newly diagnosed primary adenocarcinoma of the stomach were followed at initial visit and 8-10 months later, at the time of treatment completion. Data on patient demographics, medical history, histopathology, cancer stage, planned and realized treatments was prospectively collected. Data processing and analysis were conducted centrally.

Results: In Turkey, the majority of patients were diagnosed at an advanced stage, while the rate of surgery was lesser

compared with the rest of the world. Realized treatment included more palliative-only therapy than initially planned (63.3%), while no therapy was recommended in 21.8%. Surgery involved total gastrectomy (46.3%) or distal subtotal gastrectomy (51.9%), with 87% R0 resection, 51.0% D1 and 44.9% D2 lymph node dissection. Combination chemotherapy was administered in more than half of the patients receiving palliative therapy (57.9%). Chemoradiotherapy was used in 66.7% of the cases receiving adjuvant therapy. Radiotherapy was applied to 32% of the cases receiving palliative therapy.

Conclusion: Advanced stage gastric cancer is highly prevalent in Turkey. Increasing public awareness and implementing screening programs in high risk groups may help identify gastric cancer at earlier stages.

Key words: cancer staging, cancer treatment protocols, epidemiology, gastric cancer, registry, Turkey

Introduction

Gastric cancer is the fourth most common cancer and the second leading cause of cancer mortality in the world, with nearly one million new cases and 738,000 deaths estimated in 2008 [1]. There is great geographical variation in gastric cancer incidence with high rates seen in Eastern Asia, Eastern Europe and Central and South

America, while low rates are seen in North America, North and East Africa, Australia and New Zealand [2]. Gastric cancer trends are susceptible to change with time: in the United States gastric cancer incidence and mortality decreased considerably since 1930s. On the other hand, esophageal and distal gastric cancer rates have been on the rise in developed Western countries [2-4]. Environmental or life-style factors such as consump-

tion of salty, pickled foods, chronic *Helicobacter pylori* (*H.pylori*) infection, and prior family history, especially genetic syndromes such as hereditary nonpolyposis colon cancer and Li Fraumeni syndrome are thought to be important risk factors for gastric cancer development [4,5]. Gastric cancer is diagnosed twice more commonly in men than in women [6].

With the exception of Eastern Asia where community screens implemented due to high incidence allow for early detection, gastric cancer is usually diagnosed at advanced stage and prognosis is poor. Total or partial gastrectomy with disease-free margins is currently the only curative treatment. Limited (D1) or extended (D2 or D3) lymph node dissection is required as nodal involvement occurs at early disease stages. There is no worldwide consensus regarding the use of neoadjuvant (preoperative) and adjuvant (postoperative) chemotherapy and radiotherapy. Based on the success of Intergroup 0016 study, adjuvant chemoradiotherapy consisting of 4500 cGy of radiation and fluorouracil-leucovorin chemotherapy is standard following D1 surgery in the United States [6]. Perioperative chemotherapy consisting of preoperative (neoadjuvant) and postoperative (adjuvant) treatment cycles of epirubicin-cisplatin-fluorouracil (ECF) was successful in improving survival in a UK study of stomach and gastroesophageal cancer [7]. Surgery with extended (D2) nodal dissection is the standard therapy in Japan and Eastern Asia [8]. S-1 adjuvant monotherapy was the only chemotherapy conferring increased survival benefit on surgery with D2 in a Japanese trial [9].

REGATE was an international prospective survey involving 223 investigators in 22 countries from 5 regions [10,11]. Included countries were (in order of patient contribution for each region): Russia, Poland, Turkey, Portugal, Spain, Serbia, FYROMacedonia, and Switzerland from Europe; Korea, Malaysia, Taiwan, Thailand and Philippines from Asia Pacific; Colombia, Chile and Venezuela from Latin America; India, Pakistan and Bangladesh from Indian Subcontinent; Egypt and Tunisia from North Africa. Over 10,000 patients with newly diagnosed gastric cancer were enrolled between 2004 and 2008. The percentage of patients registered by region was 31.6% from Europe, 30.9% from Asia Pacific, 19.5% from Latin America, 11.4% from Indian Subcontinent, and 6.3% from North Africa. The primary objective of the REGATE study was to describe real-world practice patterns for patients with gastric cancer.

Secondary objectives were to determine regional differences in gastric cancer characteristics and treatments, and to investigate changes in these parameters over time between 2004 and 2008.

Turkey is a developing country with a population of 74 million, residing on the Mediterranean coast, between Europe and Asia [2]. In Turkey, gastric cancer is the second most common malignancy after lung cancer in men, and the third most common malignancy after breast and colorectal cancers in women. According to GLOBOCAN 2008, age-standardized incidence is estimated at 18.9 per 100,000 for men and 8.8 per 100,000 for women [12]. Gastric cancer is the second leading cause of cancer-related deaths for both genders in Turkey, with 17.0 and 7.9 per 100,000 mortality for men and women, respectively [13].

In the present article we present analyses from the REGATE registry database describing the pattern of care for gastric cancer in Turkey, in comparison with European, Asian and global results.

Methods

Details regarding center and patient sampling were described before [12]. Basically, male or female patients 18 years or older, newly diagnosed with primary gastric adenocarcinoma were included. Patients with history of other neoplasm, except curatively treated non-melanoma skin cancer or adequately treated in situ carcinoma of the cervix, were excluded from the registry. Written informed consent was obtained from all participants. Investigators were asked to collect data on patient's demographics, diagnosis and planned treatment at baseline visit and on the actual treatment applied at the end-of-study visit.

The number of patients to be enrolled in the Turkish arm of REGATE was based on the available information on gastric cancer incidence in Turkey at the time of registry initiation. The centers involved were representative of the general trend in gastric cancer presentation and treatment in Turkey: two centers in Eastern Turkey with a higher incidence of gastric cancer; four centers in Western Turkey and four centers in Central Turkey.

Statistics

Considering country-specific characteristics and feasibility aspects, the proposed sample size ranged from 50 to 1,000 across the participating countries. The precision (reported in terms of 95% exact binomial confidence intervals) that may be expected in estimating outcomes of various frequencies depended on the sample size. For example, with a sample size of 200, an outcome of 10% frequency could be estimated with a

95% confidence interval of 6.2-15.0%.

The statistical analysis was performed using the SAS (SAS Institute; North Carolina) software, version 9 on Windows. All tests were 2-sided, alpha being fixed at 5%. Continuous variables were by the frequency distribution (histogram), mean, median, standard deviation and extreme values. Categorical (nominal/ordinal) variables were described by counts of each modality. Missing data were not included in the calculation of percentages. Parameters for which several boxes could be ticked (initially, count and percentage) were described for each modality. Each modality was considered as a categorical variable (yes/no) and count and percentage of "response=yes" (box ticked) was described. All combinations were then described by the count and percentage.

Results

Four hundred and twelve newly diagnosed gastric cancer patients from 10 centers were enrolled in the Turkish arm of the REGATE study. Excluding 14 patients who withdrew consent, baseline analysis included data from 398 patients while end-of-study analysis included data from 395 patients who completed the end-of-study visit.

Baseline analysis

Patient demographics and medical history are summarized in Table 1. The mean age of patients was 59.1±12.5 years (median 60; range 18-91) and 67.6% were men. Endoscopy was previously performed in 60% of the patients. Family history of gastric cancer was present in 12.2% of the Turkish patients compared to 7.2% in Europe, 4.4% in Asia and 6.1% globally. The majority of the Turkish patients (83.4%) were not tested for *H. pylori* infection and only 5.8% among overall Turkish patients were proven to be *H. pylori* positive. Similar rates were seen in Europe, whereas in Asia about half of the patients were tested for *H. pylori* and 17.7% were found to be positive.

Participation in clinical trials was lower in Turkey, compared with Europe, Asia and the global rate (1.7% vs 4.1 %, 7.6%, 4.6%).

The median time from first symptoms to diagnosis was 3 months (range 0.07-240) in Turkey, compared with 3 months (range, 0.03-240) in Europe, 2 months (0-250 months) in Asia and 3 months (0-312 months) globally. Of the patients, 52.2% received treatment within 30 days of diagnosis, while 7.4% waited for more than 90 days to receive treatment (Table 1).

Table 1. Patient demographics and history (N=395)

Demographics and history	N (%)
Age, years, mean±SD (median, range)	59.1±12.5 (60, 18-91)
Age distribution (years)	
< 40	29 (7.3)
40-49	56 (14.2)
50-59	107 (27.1)
60-69	121 (30.6)
≥70	82 (20.8)
Males	267 (67.6)
Gastric symptoms	368 (93.2)
Time from first symptoms to diagnosis, months, mean±SD (median, range)	6.96±16.88 (3, 0.07-240)
Time between diagnosis and visit (days) mean±SD (median, range)	38.4±41.2 (28, 0-367)
0	8 (2.0)
1-30	205 (52.2)
31-60	115 (29.3)
61-90	36 (9.2)
>90	29 (7.4)
Previous endoscopy	220 (59.8)
Family history of gastric cancer	48 (12.2)
<i>Helicobacter pylori</i> infection	22 (5.6)
Participation in a clinical (cancer treatment) study	6 (1.7)

SD: standard deviation

Tumor site, histopathology and stage

The primary tumor site was antrum (45.8%) and body (30.6%), followed by proximal stomach (18%) and entire stomach (5.6%) (Table 2). Diagnosis was based on endoscopy in the majority of the cases (Table 2).

At baseline, signet ring cell was the most common adenocarcinoma in Turkey according to WHO classification (54.8%, Table 3). The most common types were adenocarcinoma not otherwise specified (38.5%) and signet ring cell (32.4%) in Europe, signet ring cell (41.1%) and tubular (40.3%) adenocarcinoma in Asia, and signet ring cell (40.8%), followed by adenocarcinoma not otherwise specified (22.5%), tubular (21.9%), mucinous (6.6%) and undifferentiated (5.8%) adenocarcinomas globally [10,11].

Diffuse type was slightly more common than intestinal type (53.3 vs 45.7%) in Lauren classification, while infiltrating type was more common than expanding type in Ming classification (73.5 vs 26.5%, Table 3). Distribution of tumor types according to Ming or Lauren classification was

Table 2. Primary tumor site and diagnosis

Primary site/diagnosis	N (%)
Primary tumor site	
Proximal	71 (18.0)
Antrum	181 (45.8)
Body	121 (30.6)
Entire stomach	22 (5.6)
Method of diagnosis	
Endoscopy	356 (90.1)
Laparoscopy	3 (0.8)
Postsurgical intervention	32 (8.1)
Biopsy	4 (1.0)
Operation	1 (0.25)

not significantly different between Turkey, Europe, Asia and the global results. Histopathological grading was performed in 57% of the patients (Table 3). The majority of the tumors were grade 2 (moderately differentiated, 36.4%) and grade 3 (poorly differentiated, 50.2%).

Clinical stage information was present in less than half of the patients at baseline visit, while

nearly three quarters of patients in Europe and Asia had complete information on disease stage. A very large proportion of patients (146/167, 87.4%) in Turkey were classified as having stage IV cancer, compared to 41.6% in Europe, 27.9% in Asia/Pacific and 37.4% in the world (Table 4 and Figure 1). In Turkey, staging was based mostly on CT scan (84.1%) and physical examination (63.6%, Table 4), while in Europe physical examination (78.6%), abdominal ultrasound (65.1%), abdominal X-rays (59.9%) and endoscopy (53.2%) were used more frequently than CT scan (46.6%). In Asia, CT scan was the most frequent test for cancer staging (93.6%), along with X-ray (57.0%) and physical examination (57.1%). Globally, CT scan (75.8%), physical examination (71.7%), X-ray (58.2%) and abdominal ultrasound (41.9%) were the most frequently used tests for clinical staging of gastric cancer [10,11].

Therapy plan

Palliative/non-curative chemotherapy was planned for 54.2% of the patients, followed by

Table 3. Histopathology at baseline and histopathology of resected tumor in the subset of patients subjected to surgery

Histopathology	Baseline evaluation N=316 N (%)	Post-surgery evaluation N=56 N (%)
WHO classification	259 (82.0)	42 (79.2)
Signet ring cell	108 (54.8)	19 (55.9)
Mucinous	18 (9.1)	4 (11.8)
Undifferentiated	10 (5.1)	2 (5.9)
Tubular	7 (3.6)	5 (14.7)
Papillary	2 (1.0)	-
Adenocarcinoma not otherwise specified	52 (26.4)	4 (11.8)
Not known	62 (19.6)	8 (14.3)
Lauren classification	198 (62.7)	37 (69.8)
Diffuse	49 (53.3)	17 (63.0)
Intestinal	42 (45.7)	10 (37.0)
Mixed	1 (1.1)	-
Not known	106 (33.5)	10 (17.8)
Ming classification	155 (49.1)	28 (52.8)
Infiltrating	36 (73.5)	13 (72.2)
Expanding	13 (26.5)	5 (27.8)
Not known	106 (33.5)	10 (17.8)
Histopathological grade available	225 (71.2)	50 (89.2)
Gx: Differentiation not available	2 (0.9)	17 (34.0)
G1: Well differentiated	19 (8.4)	1 (2.0)
G2: Moderately differentiated	82 (36.4)	15 (30.0)
G3: Poorly differentiated	113 (50.2)	17 (34.0)
G4: Undifferentiated	9 (4.0)	-

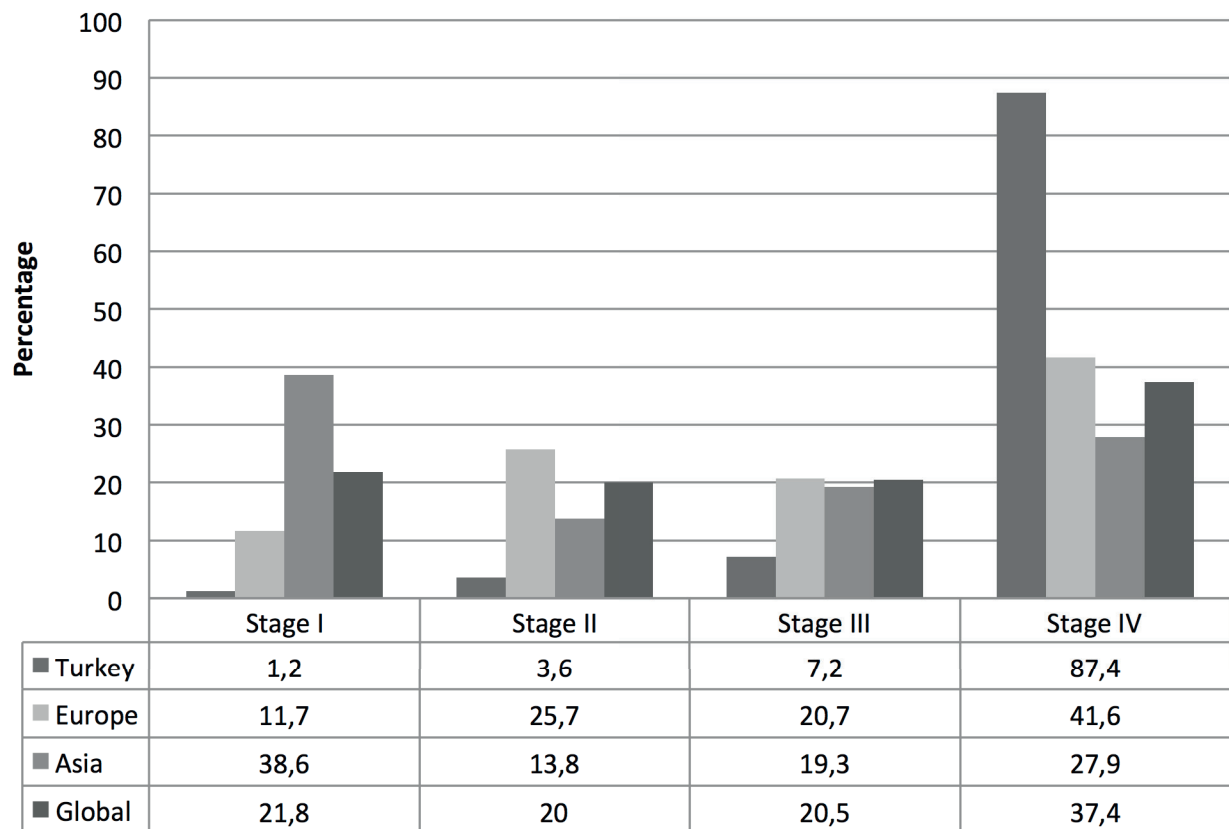


Figure 1. Clinical disease stage according to AJCC/UICC classification in Turkey compared with Europe, Asia and global results. Stage IV cancer was highly prevalent in Turkey. AJCC/UICC classification data was available as follows: Turkey (42.5%), Europe (55.6%), Asia (68.1%), and global (62.4%).

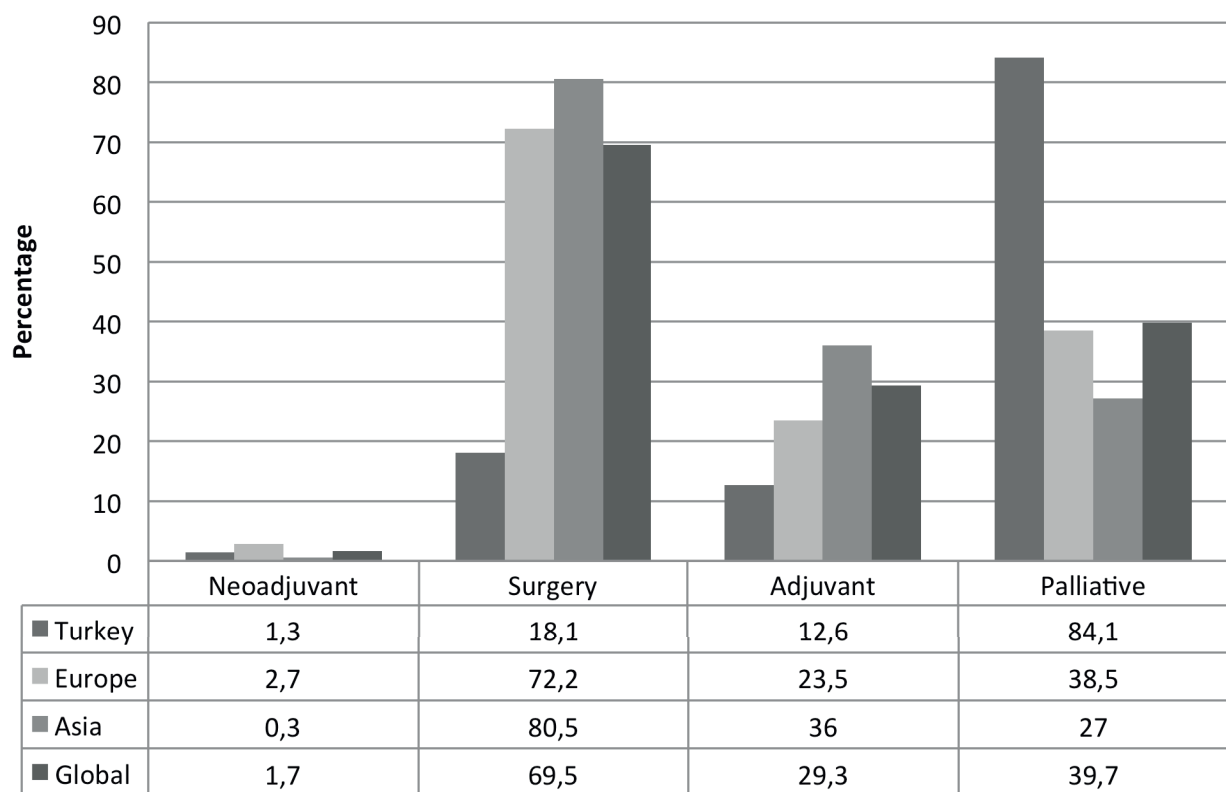


Figure 2. Gastric cancer therapy in Turkey compared with Europe, Asia and global results. Palliative therapy was more common in Turkey, while surgery and adjuvant therapy were less prevalent.

Table 4. Clinical stage at baseline evaluation and histopathological stage by postoperative evaluation in the subset of patients subjected to surgery

Clinical stage and staging methodology	Baseline evaluation	Postoperative evaluation
	N=195 N (%)	N=56 N (%)
AJCC/UICC classification only	22 (13.1)	4 (7.3)
Japanese classification only	1 (0.6)	-
Both	145 (86.3)	51 (92.7)
AJCC/UICC classification	167 (99.4)	55 (98.2)
0	1 (0.6)	-
I	2 (1.2)	8 (14.5)
II	6 (3.6)	3 (5.5)
III	12 (7.2)	27 (49.1)
IV	146 (87.4)	17 (30.9)
Japanese classification	146 (86.9)	51 (91.1)
I	2 (1.4)	9 (17.6)
II	6 (4.1)	1 (2.0)
III	8 (5.5)	26 (51.0)
IV	130 (89.0)	15 (29.4)
Work-up for disease staging		
CT scan	164 (84.1)	
Physical examination	124 (63.6)	
Abdominal ultrasound	65 (33.3)	
X-Ray	25 (12.8)	
Post-surgical intervention	7 (3.5)	
MRI	6 (3.1)	
Bone scintigraphy	6 (3.1)	
Peritoneal cytology	6 (3.1)	
Endoscopic ultrasound	4 (2.1)	
Laparoscopy	4 (2.1)	
PET scan	2 (1.0)	
Endoscopy	1 (0.5)	
Biopsy	1 (0.5)	

palliative and /or adjuvant surgery (45.1%), adjuvant chemotherapy±radiotherapy (30.4%), and neoadjuvant chemotherapy (8.9%, Table 5). These rates were globally 31.2%, 67.7%, 17.5%, and 6.5%, respectively, showing that surgery was less preferred while palliative/non-curative therapy and adjuvant therapy were applied more in Turkey compared to global data. Investigators were asked to rank the reasons for initial choice of therapy: clinical staging was the number one factor in decision making in 75% of the cases, while general status (co-morbidity) and age ranked second and third as reasons for treatment choice, followed by histology and tumor location (Table 5). Therapy plan was chosen by the medical oncologist in 58.5% of the cases, while a multidisciplinary team was involved in decision making in only 31.1% of the cases. Globally, therapy plan was chosen by

multidisciplinary team (41.1%), surgeons (36.9%), and medical oncologists (14.5%).

End-of-study analysis

The median time between first visit and end-of-study visit was 7.9 months (range, 0.1-43.9 months). The type of treatment or combination of treatments used are summarized in Table 6 and Figure 2. In total, 21.8% (N=86) patients received no therapy in Turkey, while this rate was 12.3%, 8.2% and 14.8% in Europe, Asia and globally, respectively.

Realized treatment: neoadjuvant therapy

Only 4 patients received neoadjuvant therapy (Table 7). All 4 patients received combination therapy with either ECF or docetaxel-cispla-

Table 5. Planned therapy at baseline

Therapy	N=395 N (%)
Neoadjuvant chemotherapy	35 (8.9)
Surgery	178 (45.1)
Adjuvant chemoradiotherapy	120 (30.4)
Palliative/Non curative chemotherapy	214 (54.2)
Reasons for initial choice	
1st rank: Clinical staging	295 (75.1)
2nd rank: General status/co-morbidity	188 (50.3)
3rd rank: Age	148 (40.4)
4th rank: Histology	197 (55.8)
5th rank: Tumor location	244 (72.2)
Therapy plan chosen by	
Medical oncologist	231 (58.5)
Multidisciplinary team	123 (31.1)
Radiotherapist	39 (9.9)
Surgeon	2 (0.5)

Table 7. Neoadjuvant treatment received

Neo-adjuvant therapies	N=4 N (%)
Chemotherapy	4 (100)
5-FU	3 (75)
UFT	1 (25)
Cisplatin	4 (100)
Docetaxel	2 (50)
Epirubicin	2 (50)
Radiotherapy	1 (25)
Chemoradiotherapy	1 (25)

Table 9. Adjuvant therapies received

Adjuvant therapies	N=39 N (%)
Chemotherapy-monotherapy	30 (76.9)
5-FU	29 (96.7)
UFT	1 (3.3)
Chemotherapy-combination therapy	9 (23.1)
5-FU	8 (88.9)
UFT	1 (11.1)
Cisplatin	9 (100.0)
Docetaxel	1 (11.1)
Epirubicin	4 (44.4)
Radiotherapy	26 (66.7)
Intergroup 0116 regimen	25 (64.1)

Table 6. Actual therapy received

Therapies	N=395 N (%)
Therapy received	309 (78.2)
Neoadjuvant chemotherapy	4 (1.3)*
Surgery	56 (18.1)*
Adjuvant chemoradiotherapy	39 (12.6)*
Palliative/non-curative chemotherapy	260 (84.1)*
Treatment combination	
Palliative chemotherapy only	250 (63.3)
Adjuvant/palliative chemotherapy	1 (0.3)
Surgery only	12 (3.0)
Surgery/palliative chemotherapy	6 (1.5)
Surgery/adjuvant chemotherapy	34 (8.6)
Surgery/adjuvant/palliative chemotherapy	2 (0.5)
Neoadjuvant/palliative chemotherapy	1 (0.3)
Neoadjuvant/adjuvant chemotherapy	1 (0.3)
Neoadjuvant/surgery	1 (0.3)
Neoadjuvant/surgery/adjuvant chemotherapy	1 (0.3)
No therapy	86 (21.8)

* percent within patients receiving treatment

Table 8. Surgical treatment

Surgical treatment	N=56 N (%)
Type of surgery	
Total gastrectomy	25 (46.3)
Proximal subtotal gastrectomy	1 (1.9)
Distal subtotal gastrectomy	28 (51.9)
Missing data	2 (3.6)
Residual tumor after resection	
R0	47 (87.0)
R1	4 (7.4)
R2	3 (5.6)
Missing data	2 (3.6)
Lymph node dissection	53 (94.6)
D1	25 (51.0)
D2	22 (44.9)
D3	2 (4.1)
Missing data	4 (7.1)
Number of resected nodes mean±SD (median, range)	23.1±12.8 (21, 4-60)
Number of positive nodes mean±SD (median, range)	10.4±9.8 (7, 0-42)

SD: standard deviation

tin-fluorouracil (DCF). In addition, one patient received 7 weeks of neoadjuvant radiotherapy to the epigastric area.

Realized treatment: curative surgery

Only 18.1% (N=56) were subjected to curative surgery as opposed to the planned operations for 45.1% of the patients. Surgery was four times less common in Turkey compared to the rest of the world (18.1 vs 69.5%). Among operated patients, total gastrectomy was performed in 46.3%, distal subtotal gastrectomy in 51.9% and proximal subtotal gastrectomy in 1.9% (Table 8). R0 resection was achieved in 87%, R1 in 7.4% and R2 in 5.6% (Table 8). Histological profile of the resected tumors was similar to the general profile at baseline (Table 3). Lymph node dissection was performed in 98% of the cases undergoing surgery, at the level of D1 (51%), D2 (44.9%) and D3 (4.1%, Table 8). Extended lymph node dissection (D2) was more common globally (67.2%), in Europe (65.8%), and in Asia (77.1%). The median number of nodes removed was 21 (range 4-60) and 7 (range 0-42) positive nodes were identified (Table 8). The median number of positive nodes were lower globally (2; range, 0-90), in Europe (3; range 0-66), and in Asia (0; range 0-76). The majority of the operated patients had pathological stage III and IV disease (Table 4). In Europe stage II was slightly more common and stage III less common among resected cases (15.3%, 18.2%, 33.1%, 32.1%, for stages I through IV). In contrast, 45.4% of the patients had stage I cancer in Asia (14.3%, 21.1%, and 18.3% for stages II through IV).

Among the 56 surgically treated patients, 12 were subjected to surgery alone, 39 received adjuvant chemotherapy and the rest received palliative or neoadjuvant chemotherapy.

There were only 10 patients staged both clinically at baseline visit and pathologically following surgical resection, and all of them were staged identically in both classifications. Globally 3239 patients had both clinical and pathological classification results, with postoperative pathological evaluation indicating 64% having identical, 28% more advanced and 8% less advanced disease stage.

Realized treatment: adjuvant therapy

Adjuvant therapy is summarized in Table 9. Adjuvant chemotherapy (N=39) was administered as monotherapy of 5-FU in 29 patients and monotherapy of UFT in 1 patient. The remaining 9

Table 10. Palliative therapies received

<i>Palliative therapies</i>	<i>N=260 N (%)</i>
Palliative chemotherapy	252 (97.3)
Chemotherapy-monotherapy	105 (40.4)
5-FU	93 (88.6)
UFT	13 (12.4)
Chemotherapy-combination therapy	146 (56.2)
5-FU	112 (76.7)
UFT	33 (22.6)
Cisplatin	137 (93.8)
Docetaxel	63 (43.2)
Epirubicin	47 (32.2)
Doxorubicin	4 (2.7)
Irinotecan	6 (4.1)
Antrex	2 (1.4)
Radiotherapy	83 (32.0)
Chemoradiotherapy	82 (31.5)
Symptomatic surgery	1 (0.4)

patients had combination therapy of CF, with or without epirubicin (ECF) or docetaxel (DCF). Combination therapy use was more common globally (44.6%), in Europe (46.7%) and in Asia (50.9%), compared with Turkey (23.1%). Postoperative adjuvant radiotherapy was delivered to 26 (66.7%) patients to the epigastric area for a median of 5 weeks (range 4-7). Postoperative radiotherapy use was less common globally (33.5%), in Europe (30.4%) and especially in Asia (13.1%), compared to Turkey. Intergroup 0116 regimen of chemoradiotherapy with 5-FU was used in 25 patients, such that 45% of the operated patients in Turkey received Intergroup 0116 regimen, compared to 9% in Europe, 5% in Asia and 14% globally.

Realized treatment: palliative therapy

Palliative chemotherapy was administered to 260 patients and it was the only treatment in 250 patients (Table 6). The rate of patients receiving only palliative chemotherapy (63.3%) was significantly higher in Turkey compared with Europe (23.5%), Asia (17.4%) and global results (25.4%).

Palliative monotherapy was administered to 41.7% (N=105) and combination therapy to 57.9% (N=146) patients (Table 10). Compared to Turkey, combination chemotherapy was more prevalent in the rest of the world (77% in Europe, 82% in Asia and 82% globally). Monotherapy consisted of 5-FU (93/105) or UFT (13/105). Combination chemotherapy was mostly based on 5-FU

(112/146) or UFT (33/146) together with cisplatin (137/146). Other agents used in combination chemotherapy included docetaxel (63/146), epirubicin (47/146), doxorubicin (4/146), irinotecan (6/146), and antrex (2/146). Palliative radiotherapy was added to chemotherapy in 82 patients. Radiotherapy was applied to epigastric area for a median of 5 weeks (range 1-8). Only one patient had symptomatic surgery.

Eight patients received palliative supportive care not including chemotherapy or radiotherapy.

Discussion

In this study we analyzed the Turkish results of the REGATE in comparison with European, Asian and global results. Age and sex distribution in Turkey was similar to the rest of the world, while the mean time from appearance of the first symptoms to diagnosis was nearly 7 months compared with 5 months in Europe and Asia and 6 months globally [10,11]. Delay in diagnosis may account for the increased prevalence of advanced disease in our country. In addition, genetic make-up of the patients may contribute to more aggressive tumor development. Family history of cancer was associated with larger and more aggressive tumors in a study [14]. Family history of gastric cancer (12.2%) was twice the global rate (6.1%) in our study [10,11]. Familial clustering of gastric carcinoma was also observed in a Turkish study from Eastern Black Sea region where gastric cancer incidence is high [14]. Other gastric cancer-associated risk factors such as dietary habits, *H. pylori* prevalence, or environmental factors may also be responsible for more aggressive tumors in Turkish population.

H. pylori testing was done in only a small percent of our patients. However, in a study *H. pylori* seroprevalence was high (more than 60%) in Turkish adults and early childhood acquisition was common [15]. In a Turkish survey of gastric cancer, significantly lower resectability was found in the Eastern region, along with higher prevalence of *H. pylori* infection and intestinal metaplasia, compared to Western regions [16].

Surgery was performed considerably less in our country compared with Europe and Asia (14.2% vs 63% and 74%, respectively) [10,11]. The high prevalence of advanced stage may have limited the number of resectable cancers. Additionally, a large proportion of patients did not undergo surgery despite initial surgery recommendation. A recent analysis of stage IV gastric cancer patients in the United States SEER database deter-

mined that patients who were recommended but did not undergo surgery had similar survival as the patients for whom no operation was recommended, and that survival was significantly better for the patients who did undergo surgery (3 vs 9 months, $p < 0.0001$) [17]. Since survival outcome was not among the objectives, we cannot assess the effect of changing the initial therapy recommendation in this study.

Resection of stage IV gastric cancer is still a matter of debate. In current guidelines, palliative care is recommended for large locally advanced tumors, extensive nodal disease, hepatic or peritoneal involvement or other distant metastasis [7,8,19]. On the other hand, some studies suggest that all resectable stage IV cancers should be resected to improve survival and that subclassification of stage IV tumors may help in specific tailoring of the type and extent of surgery [20-22]. A retrospective study from Eastern Turkey on 138 stage IV gastric cancer patients with or without distant metastasis found that surgery was the most significant independent prognostic factor improving both overall and progression-free survival [23]. Another study from Turkey, showed improved survival with palliative surgery in advanced-stage gastric cancer, but perioperative mortality was relatively high [24]. The present registry revealed a conservative palliative care approach in most cases of gastric cancer. Combination chemotherapy was administered in more than half of the patients receiving palliative therapy. There appeared to be a shift towards increased use of DCF as per the efficacy and quality of life results obtained in the V325 study [25,26]. Palliative surgery was not preferred. Instead, radiotherapy was used in approximately one third of the patients receiving palliative therapy to relieve cancer-related symptoms such as obstruction, pain and bleeding.

In terms of curative surgery, either D1 or D2 lymph node dissection was performed in the majority of the patients, with less than 10% undergoing D3 lymphadenectomy. Extended lymph node removal is the standard in Eastern Asia, but initial attempts at D2 dissection in Western countries had resulted in high perioperative morbidity and mortality [27]. European guidelines recommend D2 dissections to be performed in specialized centers by experienced surgeons, for selected patients who are fit enough to tolerate the procedure. Rates of morbidity and mortality for D2 dissection show variation among Turkish centers depending on patient characteristics and exper-

tise of the surgeon, but are generally similar to European rates [28-30].

Adjuvant chemoradiotherapy was preferred in approximately half of the patients undergoing surgery in Turkey, while surgery only, combination adjuvant chemotherapy, palliative chemotherapy, and neoadjuvant chemotherapy were used in lesser proportion of patients, suggesting that chemoradiotherapy is an integral part of gastric cancer treatment in Turkey, in accordance with the American guidelines [31,32].

In conclusion, the majority of gastric cancers in Turkey are diagnosed at advanced stage. A conservative palliative approach is preferred in most cases, while surgery with curative intent is performed in a minority. Use of Intergroup 0116 regimen and D1 lymph node dissection among

surgically treated patients is more common in Turkey than in Europe or Asia. Given the high rate of advanced-stage gastric cancer in Turkey, public awareness should be increased and screens should be considered, especially in high risk groups in the Eastern region. Additionally, the outcome of current standard of care should be assessed to determine whether increasing the rate of surgical therapy would lead to better survival.

Conflicts of interest statement

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