Current Status of Metastatic Colorectal Cancer in East Europe and Middle East

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Introduction:

- Colorectal cancer is the second leading cause of cancer-related deaths among men and women.
- 20%, advanced stage.
- 20-25% were relapsed

(Torre LA, 2012. CA Cancer J Clin, Song X, Zhao Z, BaAm J ManagCare2011)

Introduction:

- Oxaliplatin and irinotecan to fluorouracil based regimens.
- The OS was increased from 12 months to 20 months.
- Molecular pathways: Anti-VEGF, Anti-EGFR

*(*Sridharan M, Oncology (Williston Park) 2014*)*, CALGB/SWOG 80405)

Introduction:

- K-RAS, N-RAS and BRAF tests are important milestones
- Cetuximab, panitumumab, bevacizumab, afatinib, regarofenib
- In different countries; numerous prognostic factors like biology of the disease, stage at diagnosis and practice patterns might be different.

Aim:

- To demonstrate the differences in biology, prognostic factors and practice patterns in mCRC at country level and their impact on survival rates in our region.

Study Design

- This will be multinational, retrospective registry study.

- The data will be obtained from patient files.

Eligibility Criteria:

- Patients with mCRC at time of diagnosis or relapsed CRC during follow-up period

- Those patients with at least 3 year follow up data OR died before 3 year follow up time period: The diagnosis should be made in between 2005 – 2012.

Primary End Point

- Descriptive analysis of factors affecting survival and treatment efficacy among the regional countries.

Secondary End Points

- Progression free survival
- RAS testing rates
- Availability of drugs
- Characteristics of multiple lines of therapy
- Patients' demographics
- Surgical procedures
- Metastasectomy rates
- Pathological features
- Locations of primary tumor
- Tumor marker levels
- Laboratory parameters
- Treatment patterns

Sample Size

- Consecutive patients meet inclusion criteria will be recruited. Each country will evaluate the number of patients that they are going to include in the study.

Financial Support

- There is no budget for the study.
- The most important work will be collecting data. Recruitment of local stuff to collect data may be needed. If any participant center needs budget for the study, the center's investigator can apply local potential resources for financial support. Full disclosure of supporting funds must be declared.

Study Centers:

- Major centers in participant countries.

Data Colection

- An excel spreadsheet template will be formed for data collection.
- The coding system will be created for identifying patients.(Confidential)
- The codes will be shared by Dr. Ozan Yazıcı (Ankara Numune Hospital, Turkey) who will be responsible for data collection.
- Coding tables must be kept separate from the data table by a third party within each center in order to maintain patient anonymity.

Coding Rules:

- 1 (1 represents the first participated patient),
- I (Israel),
- TASMC (represents Tel-Aviv Sourasky Medical Center),
- RG (initials of researcher: Ravit Geva) .
- MV (patients' name surname initials: Moshe Vardi) .
- Code of first patients will be: 1-I-TASMC-RG-MV

Participated Number of Pateinst	Country	Center	Name-Surname of researcher	Name-Surname of patient	Created Code For Each Patient	National Identification Number	Hospital Computing ID of patient
1.	Israel	Tel-Aviv Sourasky Medical Center	Ravit Geva	Moshe Vardi	1-I-TSMC-RG-MV		
2	.....	.....	.....	.....	.....		
3	.....	.....	.....	.....	.....		
4	.....	.....	.....	.....	.....		
5	.....	.....	.....	.....	.....		
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299	Israel	Tel-Aviv Sourasky Medical Center	Ravit Geva	Jonathan Rosenblum	299- I-TSMC-RG-JR		
300	Israel	Tel-Aviv Sourasky Medical Center	Ravit Geva	Ram Avrahami	300-I-TSMC-RG-RA		

Trial Form

Table 1: Conditions of Country

Country Name	
Name of Hospital	
Is K-RAS test available in country?	Yes No
Is N-RAS test available in country?	Yes No
K-N-RAS test is easily accessible?	Yes No
Is BRAF test available in country?	Yes No
BRAF test is easily accessible	Yes No
The following drugs are available in country;	
Oxaliplatin	Yes No
Irinotecan	Yes No
Capecitabin	Yes No
Bevacizumab	Yes No
Cetuximab	Yes No
Panitumumab	Yes No
Aflibercept	Yes No
Regorafenib	Yes No

Table 2: Patient characteristics

Metastatic at time of diagnosis	Yes or No
Primary Operated	Yes_or No
Type of operation	Low anterior resection Right hemicolectomy Total colectomy
Date of Operation	dd_mm_year
Grade	1-2-3
Histological type	Adenocarcinoma-mucinous
Lymphovascular invasion	Yes No
Perineural invasion	Yes No
T stage	
N stage	
Total number of excised lymph nodes	
Number of pathological lymph nodes	
MSI	Stable instable-not determined
Adjuvant Chemotherapy	Yes No
Type of Adjuvant tx	FOLFOX, XELOX, Infusinal FU-FA, Mayo, Other (Explain……..)
If Rectal primary	
(Chemo-)Radiotherapy	Yes-No
Advuvant-Neoadjuvant	
Accompanying agent	Infusional FU, IV push FU, Capecitatbine, None, Other

Table 3: Clinical and Therapy Features of Advanced Stage Disease

Relapse	Yes – No – Metastatic at time of diagnosis
Date of Relapse or metastasis	dd_mm_year
Regions of metastasis	Liver , Lung, Central nervous system Peritoneal , Bone ,Lymph nodes, Other
Number of Metastatic Regions	
Metastasectomy at time of advanced disease diagnosis	Yes or No
Organ of Metastasectomy	Liver, Lung, Other
Local Therapies for liver metastasis	Radio frequency ablation – Transarterial chemoembolization (TACE)-Other (Explain…….)
CEA _Ca 19-9 at time of relapse or metastasis	
K-N-RAS –BRAF status	Wild-mutant-Not applicable
First line chemotherapy	Oxaliplatin combination+bevacizumab Oxaliplatin combination+cetuximab, combination+panitumumab, Irinotecan combination+ bevacizumab Irinotecan combination+ cetuximab
Total Cycle numbers	
Best response to chemotherapy	Complete-partial-stable-progression
Date of Progression	dd_mm_year

Table 4. Patient Outcome

Date of Last Visit	
Status	Alive or exitus or lost to follow up
Date of Last contact	dd_mm_year

Results

- Totally 364 patients were included in study population.
- Participating Countries: Turkey and Greece (University of Athens)
- Metastasectomy was done in 140 patients (38.5%).
- Metastasectomy regions were liver (22.3%), lung (4.7%), other (%11.5)
- Second-time metastasectomy was done in 10.2% of patients.

Results

Table 1: Demographic and clinical features of patient population

Features	N	%
Gender		
Female	156	42.9
Male	208	57.1
Age (Median)	62 years	Min:23-Max:85
ECOG Status		
0-1	226	62.1
2	63	17.3
At time of diagnosis		
Metastatic	217	59.6
Relapsed	144	39.5
Tumor Location		
Right	71	19.5
Transverse	13	3.6
Left	276	75
Site of Metastasis		
Liver	253	69.7
Lung	100	27.4
Local Relapse	45	12.6
Peritoneum	43	12
Distant Lymph Node	36	10
Brain	6	1.6
Ras Test Available	305	84.6
Ras Test Accessible	258	71.4
K-Ras Wİld	136	37.4
N-Ras Wild	60	16.5
Braf Wild	52	14.3
K-N Ras Wild	129	35.4
K-N Ras- Braf Wild	49	13.5
MSI Instability	6	1.6

Results

- Most (96.2%) of patients had first-line chemotherapy (FLC);

First line Chemotherapy (most common)	Frequency (%)
oxaliplatin-based combination	29.9
irinotecan combination with bevacizumab	16.5
Oxaliplatin combination with bevacizumab	16.5

Results

Response to First Line Chemo

Response to First line Chemotherapy	Frequency (%)
Complete	8
Partial	30.5
Stable	28.3
Progression	24.7

Disease control rate: 66.8%

Results

First-line Chemotherapy

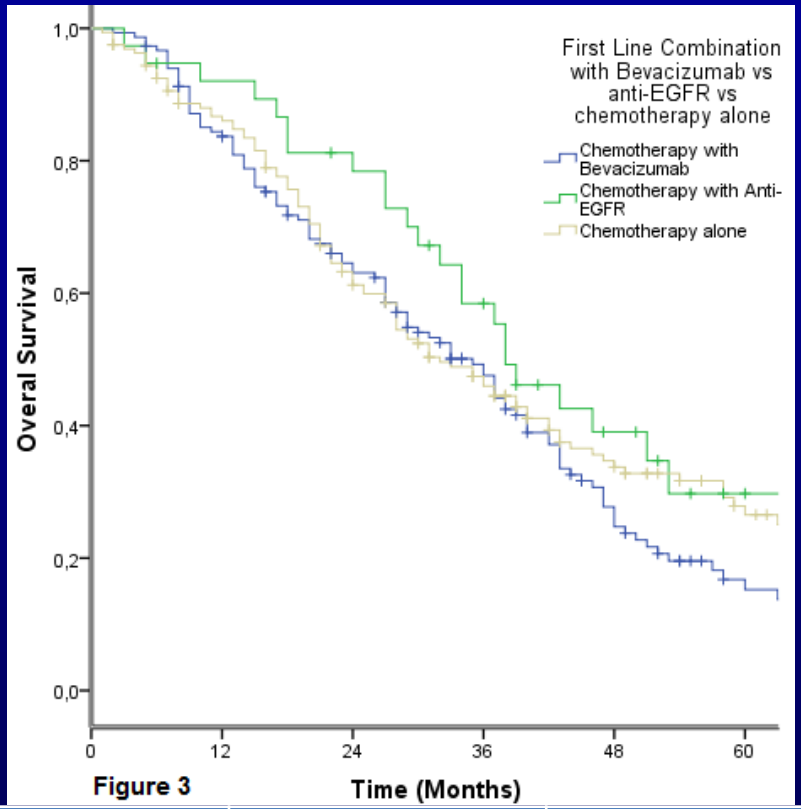


Figure 3

First Line Chemotherapy	OS	95% CI	p
Chemo+Anti-EGFR	38	30.1 – 45.8	0.24
Chemo+Bevacizumab	35	29.1 – 40.8)	
Chemo	32	26.3 - 37.6	

Results

Progression Free Survival

- Median PFS of first, second and third line chemotherapy was;

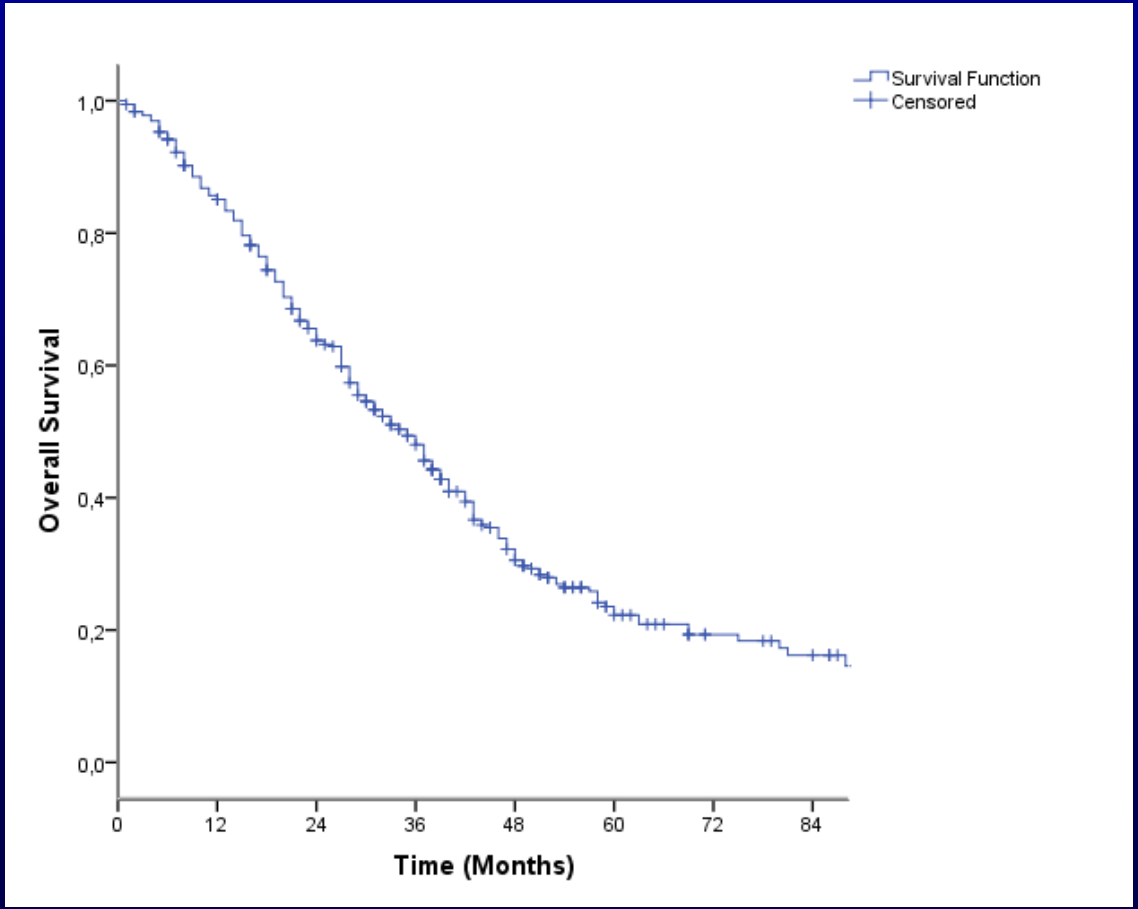
  -PFS1: 10 m (95%CI 8.3 – 11.6),

  -PFS2: 7 m (95%CI 6.2 – 7.7),

  -PFS3: 6 m (95% CI 4.6 – 7.3).

Results

Median OS of all patients was **35 m** (95% CI 30.7 – 39.2).



Results

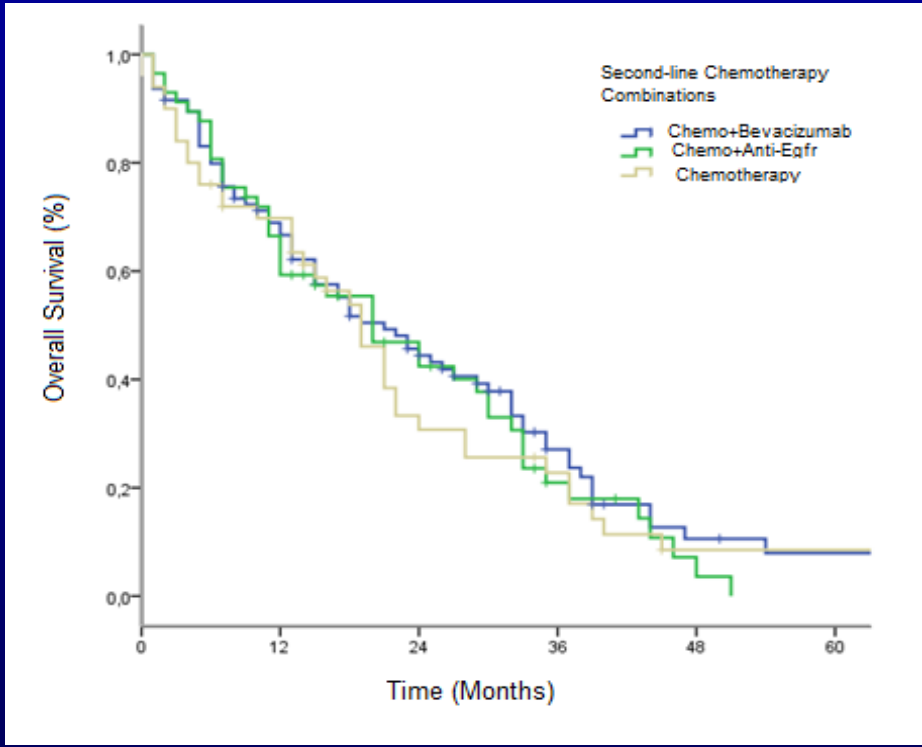
Second-line Chemotherapy

- Most (66.7 %) of patients had second-line chemotherapy ; İrinotecan combination with bevacizumab (24.5%) was the most common.

Response to Second line Chemotherapy	Frequency (%)
Complete	4.9
Partial	15.1
Stable	13.2
Progression	29.1

Results

Second-line Chemotherapy



Second-line Chemo	OS	95% CI	p
Chemo+Anti-EGFR	20	11.7 – 28.2	0.65
Chemo+Bevacizumab	21	14.2 – 27.7	
Chemo	19	14.8 – 23.1	

Results

K-N Ras Wild

- In K-N Ras wild group median OS was 40 m (95%CI, 34.7 – 45.2), compared with mutant patients 29 m (95%CI, 23.9–34), (p=0.004).

- In K-N Ras wild group median PFS of FLC with
  *anti-EGFR combination was 13 m (95 % CI, 9.3 - 16.6),
  *bevacizumab combination was 13 m (95 % CI, 4.4 - 21.5),
  *FLC alone was 9m (95 %CI, 6.3 - 11.6),
  (p: 0.3).

Results

Metastasectomy vs Non-metastasectomy

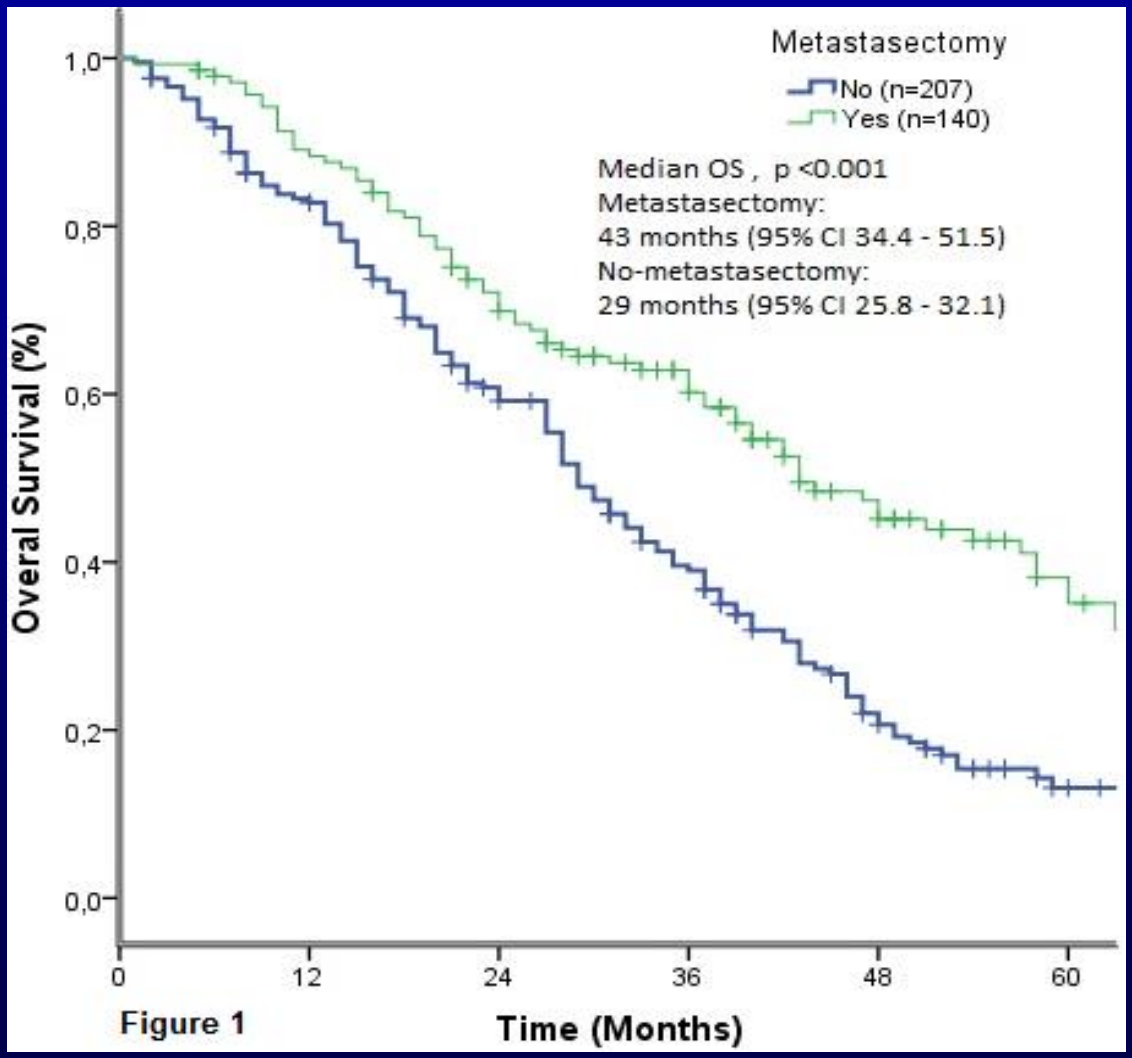


Figure 1

Results

Right vs Left

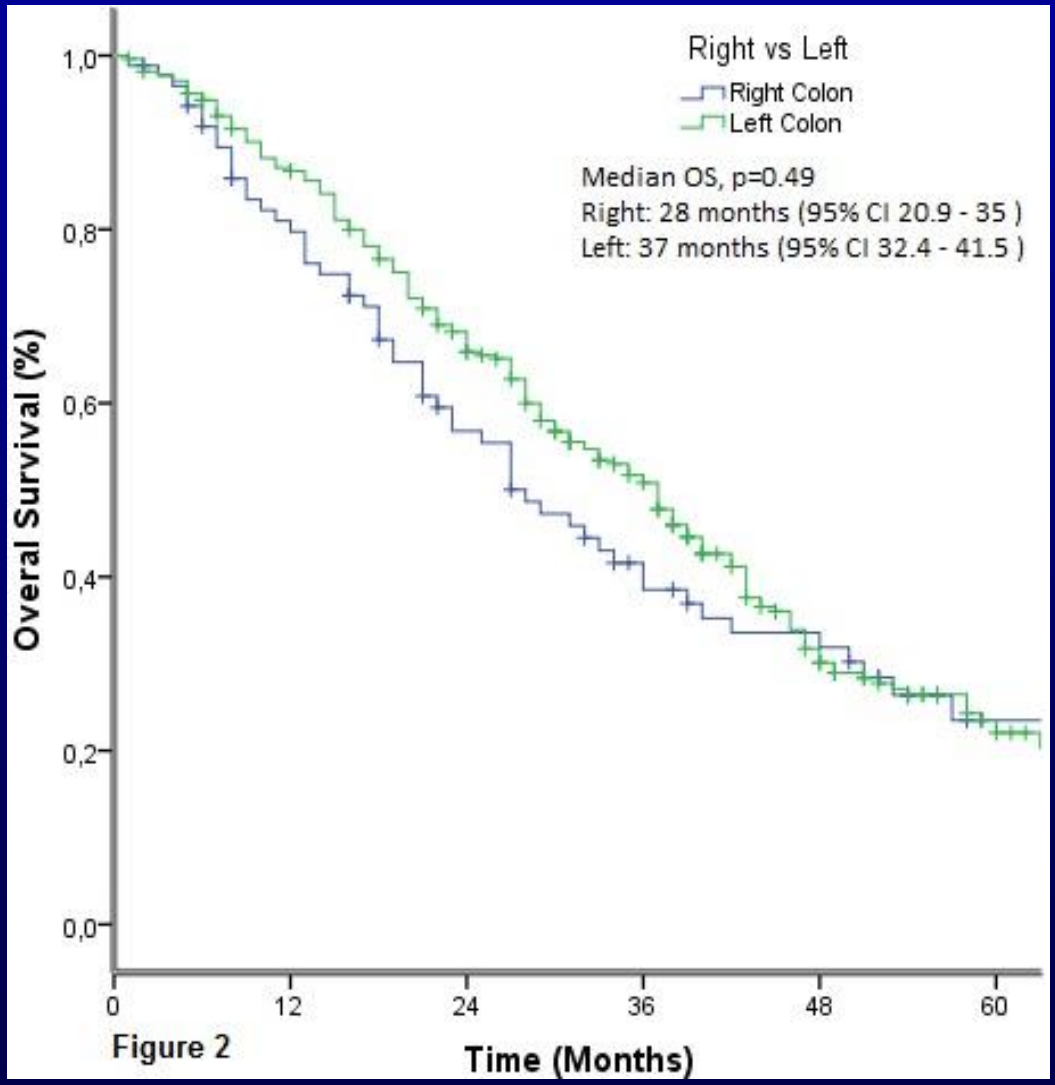


Figure 2

Univariate Analysis

- Age (<65 years vs ≥65 years),
- Smoking status,
- Tumor location (right vs left),
- At time of diagnosis metastatic or relapsed status,
- ECOG performance status (ECOG 0-1 vs 2),
- Number of metastatic regions (1 vs 2 vs 3 vs 4),
- First-time metastasectomy,
- First line chemotherapy (anti-EGFR vs bevacizumab combination vs chemotherapy alone),
- Second line chemotherapy (anti-EGFR vs bevacizumab combination vs chemotherapy alone),
- K-N Ras-BRAF status (all ras+ BRAF wild or one of them mutant),
- Second-time metastasectomy

Multivariate Analysis

Table 2: Cox regression analysis of factors significantly effecting OS in univariate analysis

Variables	Hazard Ratio	95% Confidence interval	p
Performance status			0.002
ECOG 0-1	1		
ECOG 2	4.45	1.76 – 11.26	
Number of Metastatic Region			0.03
One region	1		
Two region	1.48	1.02 - 2.16	
K/N-Ras –Braf Status			0.047
Mutant	1		
Wild (all ras +braf)	0.59	0.35 - 0.99	
Second Metastasectomy			<0.001
No	1		
Yes	0.3	0.16 - 0.57	

Limitations

- One of the limitations in our study we could not collect the data of toxicity.

Conclusion

- Our data showed that RAS, BRAF tests are widely avaliable and metastasectomy is a widely adopted practice in colorectal cancer management.
- Median PFS and OS of the current study similar to PFS reported in randomized trials . The current study also demonstrated that median OS of left and right colon was consistent with the CALGB and Fire-3 trials .

CALGB/SWOG 80405: ASCO meeting 2014 //FIRE-3) Lancet Oncol. 2014;15(10):1065-75.

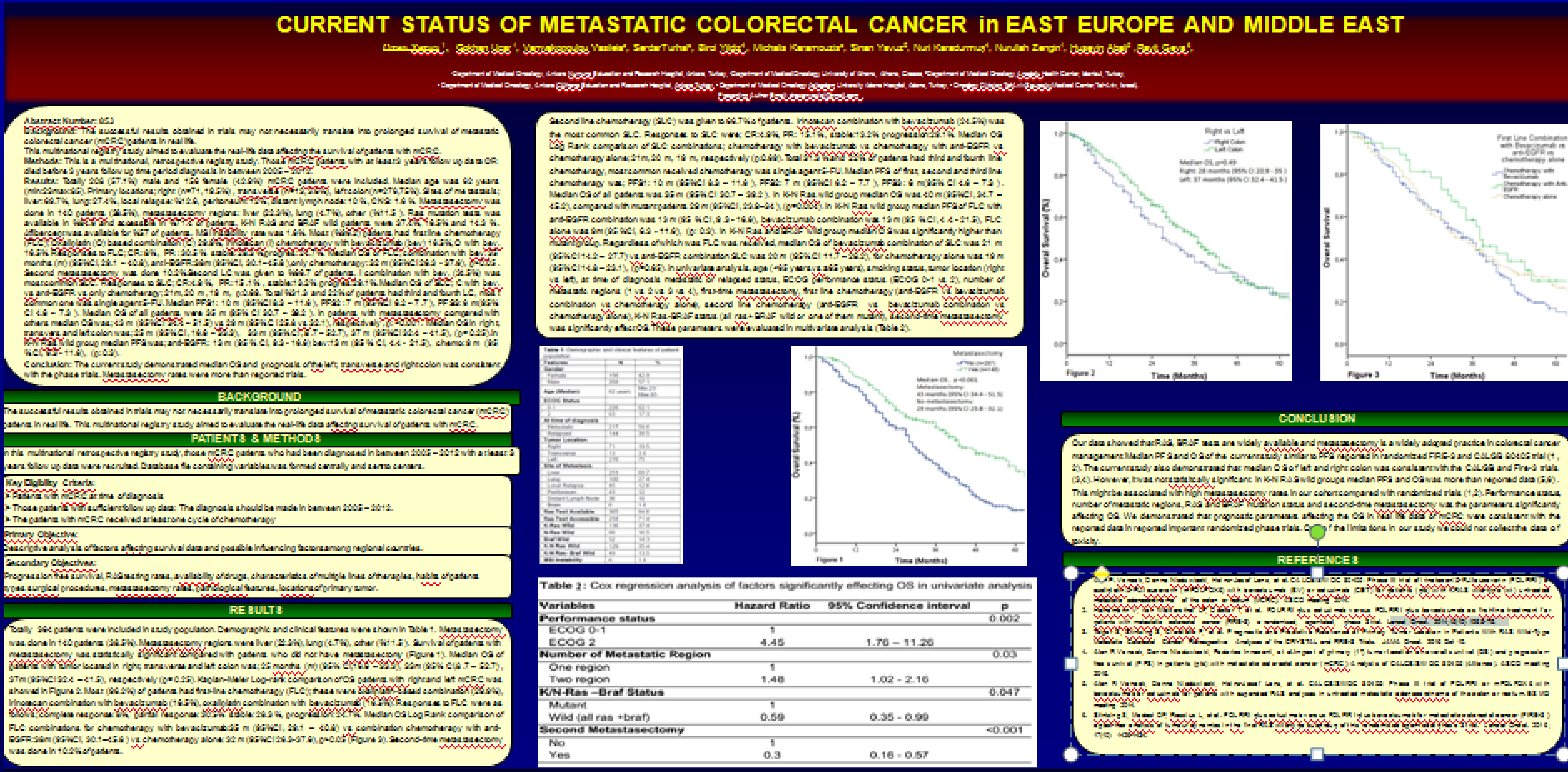
Conclusion

- In K-N RAS wild groups median PFS and OS was more than reported data . This might be associated with high metastasectomy rates in our cohort compared with randomized trials.
- Performance status, number of metastatic regions, RAS and BRAF mutation status and second-time metastasectomy was the parameters significantly affecting OS.

Conclusion

- We demonstrated that prognostic parameters affecting the OS in real life data of mCRC were consistent with the reported data in reported important randomized phase trials.

Presented in ASCO GI, San Francisco,2018



If anyone prefer to participate the study,

Email: drozanyazici@gmail.com


THANK YOU FOR YOUR ATTENTION!!!!