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.



• 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							
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	
	Low anterior resection	
Type of operation	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
	Liver , Lung, Central nervous system
Regions of metastasis	Peritoneal, Bone, Lymph nodes, Other
Number of Metastatic Regions	
Metastasectomy at time of advanced disease	Yes or No
diagnosis	
Organ of Metastasectomy	Liver, Lung, Other
	Radio frequency ablation – Transarterial
Local Therapies for liver metastasis	chemoembolization (TACE)-Other (Explain)
CEA _Ca 19-9 at time of relapse or metastasis	
K-N-RAS –BRAF status	Wild-mutant-Not applicable
	Oxaliplatin combination+bevacizumab
	Oxaliplatin combination+cetuximab,
First line chemotherapy	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

- 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.

Table 1: Demographic a	and clinical f	eatures of patient			
population					
Features	N	%			
Gender	Γ				
Female	156	42.9			
Male	208	57.1			
Age (Median)	62 years	Min:23- Max:85			
ECOG Status	T				
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			

 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



Response to First Line Chemo

Response to First line Chemotherapy		Frequency (%)		
Complete	8			
Partial	30.5	 Disease control rate: 66.8% 		
Stable	28.3			
Progression	24.7			

First-line Chemotherapy





Progression Free Survival

Median PFS of first, second and third line chemotherapy was;
-PFS1: 10 m (95%Cl 8.3 – 11.6),
-PFS2: 7 m (95%Cl 6.2 – 7.7),
-PFS3: 6 m (95% Cl 4.6 – 7.3).

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





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

Second-line Chemotherapy



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



- In K-N Ras wild group median OS was 40 m (95%Cl, 34.7 – 45.2), compared with mutant patients 29 m (95%Cl, 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 % Cl, 4.4 - 21.5),

*FLC alone was 9m (95 %CI, 6.3 - 11.6),

(p: 0.3).

Metastasectomy vs Non-metastasectomy



Right vs Left



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	р
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	
No Yes	1 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.

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

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Abstract Number: 053

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Conclusion: The curvantscoly demonstrated median OS and prognosis of the left, transverse and right colon was consistent with the phase trials. Negoticscopy, rates were more than reported trials.

BACKGROUND
he successful results obtained in trials may not necessarily translate into prolonged survival of measurals colorectal cancer (mCRC) atems in real life. This multinational registry study almed to evaluate the real-life data affecting survival of patients with mCRC.
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his multinational remospective registry study, those mCRC patients who had been diagnosed in between 2005 – 2012 with a tieser 5 ans follow up data were recruited. Database file containing variables was formed centrally and sentro centers.
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the most common SLC. Responses to SLC were; CR:(19%, PR: 15.1%, stable:19.2% progression:29.1% Nedian OS (b) Rank comparison of SLC combinations; chemotheragy with bevacitures vs chemotheragy with ant-EGFR vs. chemotherapy alone; 21 m, 20 m, 19 m, respectively (p:0.69). Total 21.9 Wand 20% of patents had third and fourth line chemotherapy, most common received chemotherapy was single agent S-FU. Median PFS of first, second and third line chemotheragy was; PF21: 10 m (85WCI 8.3 - 11.6), PF22: 7 m (95WCI 6.2 - 7.7), PF20: 6 m(85W CI 6.6 - 7.5). Nedlan OS of all gatens was SS m (95% CI S0.7 - S9.2). In K-N Ras wild group median OS was 40 m (95% CI, S4.7 -(\$32), compared with mutanzpatients 29 m (\$5%C1, 23.9–34.), (p=0,000). In K-N Ras wild group median PF9 of FLC with and-EGFR combination was 15 m (95 WCI, 9.5 - 19.6), bevacibureab combination was 15 m (95 WCI, 4.4 - 21.5), FLC sione was \$m (\$5 %21, 6.3 - 11.6), (p: 0.3). In K-N Ras and BROF wild group median O Swas significantly higher than Nutrin Shour, Recordeds of which was FLC was received, median OS of bevacizuratic combination of SLC was 21 mil (95% CI14.2 - 27.7) ys and EGFR combinator SLC was 30 m (95% CI 11.7 - 29.2), for chamotherapy alone was 19 m. (95% CI14.8 – 29.1), (240.65). In universas analysis, age (465 years vs. a65 years), amoking sasus, sumor location (right is left, at the of diagnosis medicate of relayed status, \$2000 geformance status (\$2000 0-1 vs 2), number of Restato regions (1 vs. 2 vs. 5 vs. 4), franche metastasectory, frat line chemotherapy (and-EGFR Vs. bevacitumab combination vs chemotherapy alone, second line chemotherapy (ant-EGFR) vs, bevacizumab combination vs chemotherapy alone), K-N Ras-GRAF status (all ras+ GRAF wild on one of them mutanty, Second-the metastasectory) was significantly effection. These parameters were evaluated in multivariate analysis (Table 2).



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

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If anyone prefer to participate the study,

Email: drozanyazici@gmail.com

THANK YOU FOR YOUR ATTENTION!!!!