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Perugia, 05 Luglio 2019

Characterization of mismatch repair deficiency in biliary tract cancer

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Our work: a multicentric work



Background

- **Biliary tract cancer (BTC)** represents a rare and heterogenic tumour with aggressive behaviour¹.
- **Mismatch repair deficiency (dMMR)** seems to be associated with better prognosis in different gastrointestinal cancer types² compared to mismatch repair proficiency (pMMR).
- Its prevalence and correlation with clinical and pathological features in BTC remains unclear³.

Objectives

- 1) To evaluate the incidence of dMMR in BTC
- 2) To evaluate the correlation between the presence of dMMR and different clinical and pathological characteristics.
- 3) To evaluate the putative prognostic role of dMMR in both resectable and advanced BTC, in terms of association with Disease Free Survival (DFS), Progression Free Survival (PFS) and Overall Survival (OS)

Materials and Methods

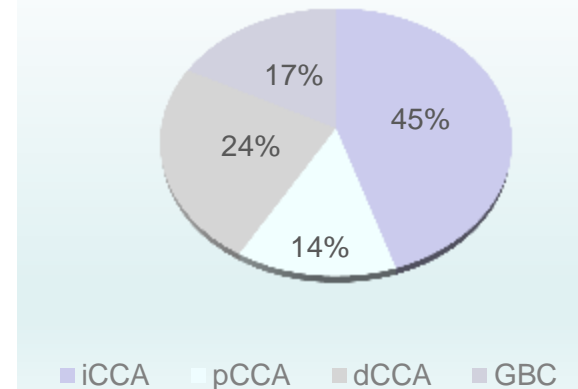
- We retrospectively evaluated MMR status in a cohort of **149 patients with BTC** - intrahepatic (iCCA), perihilar (pCCA), distal (dCCA) cholangiocarcinoma and gallbladder cancer (GBC).
- Tumour sections were assessed **by IHC** for MLH1, PMS2, MSH2, and MSH6.
- A dMMR tumour was defined by the **loss of expression** of any of the four MMR proteins.

Patients Characteristics

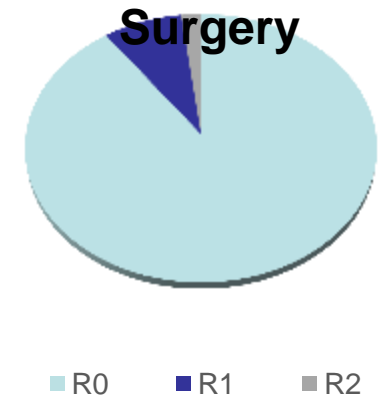
Patients Characteristics	N=149	%
Gender,		
male	89	59.7
female	60	40.3
Age,		
median (range)	66 years (29-87)	
Tumor location,		
iCCA	67	45
pCCA	20	13.4
dCCA	36	24.2
GBG	26	17.4
Stage at diagnosis (TNM 8° ed)		
I	33	22.1
II	40	26.8
III	23	15.4
IV	53	35.6
Surgery on primary tumor		
yes	111	74.5
no	38	25.5
MMR status		
MMR proficient	140	94
MMR deficient	9	6
Histology		
adenocarcinoma	130	87.2
mucinous adenocarcinoma	8	5.4
signet ring cells carcinoma	3	2
other	8	5.4
Tumor grade		
1	8	5.4
2	57	38.2
3	48	32.2
4	1	0.7
not available	35	23.5
First-line chemotherapy		
yes	80	53.7
no	69	46.3
Type of first-line chemotherapy		
gemcitabine + platinum	49	61.2
other	31	38.8



Tumour location

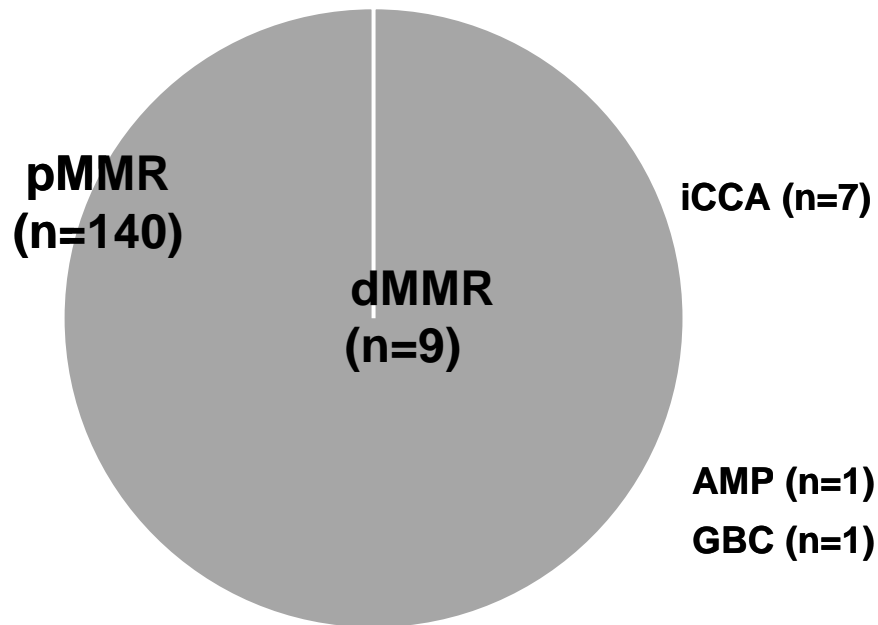


Surgery



Results – Incidence of dMMR in all population

- MMR deficiency was found in 6% of BTC (9 patients)



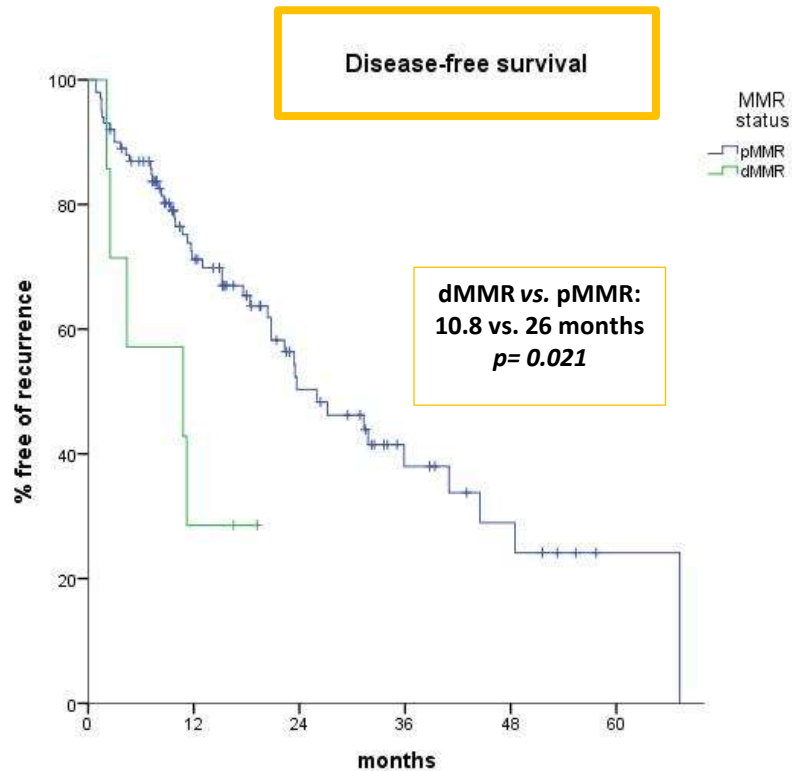
	MLH1	PMS2	MSH2	MSH6
1	x	✓	✓	✓
2	x	x	x	✓
3	✓	✓	✓	x
4	x	x	x	✓
5	x	x	x	✓
6	x	x	x	✓
7	✓	✓	✓	x
8	x	x	x	x
9	x	x	x	✓

- 7 pts (78%) presented **resectable** disease and 2 pts (22%) **metastatic** disease

Results – Correlation with baseline characteristics

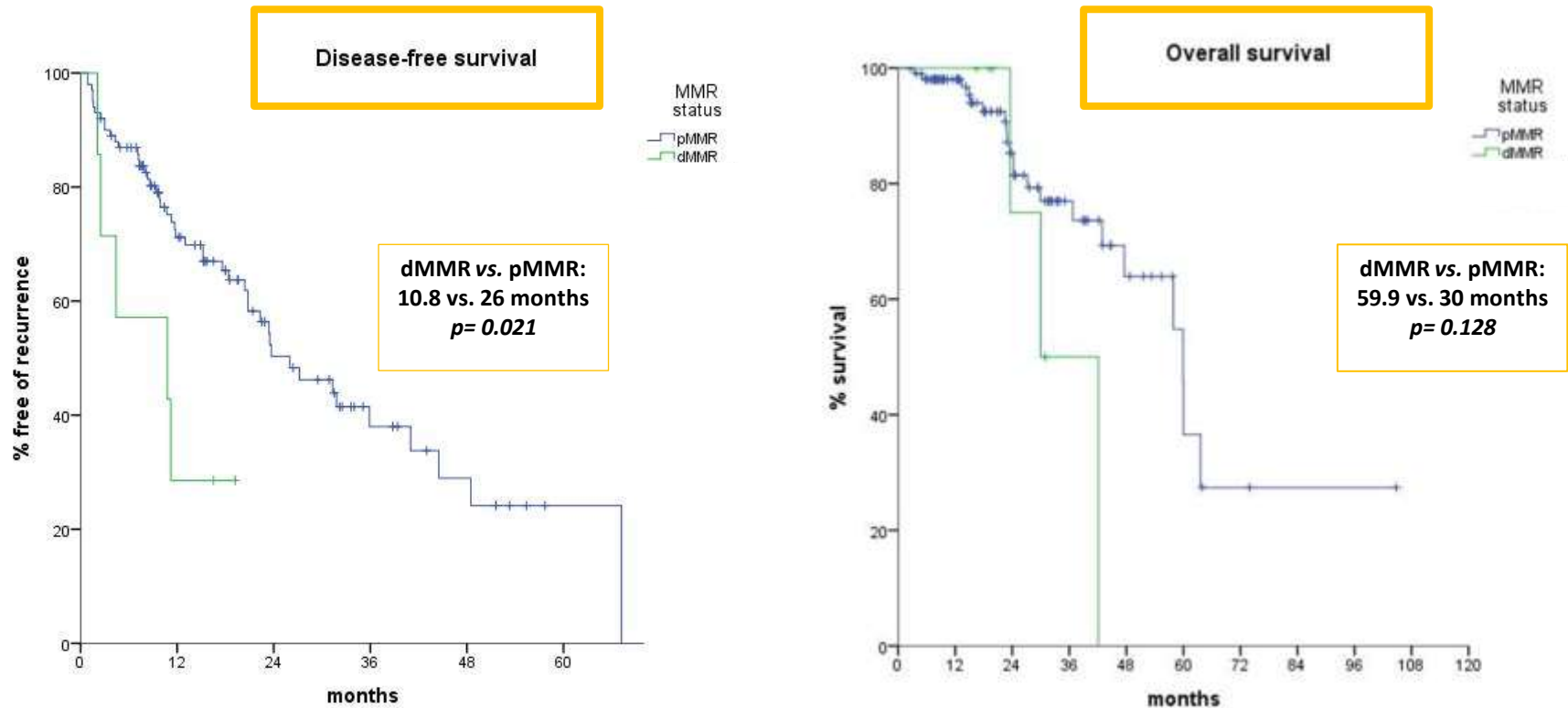
- Among the investigated characteristics, dMMR status was significantly correlated with:
 - 1) tumour site (iCCA 11% vs others 2.4 %, $p=0.041$)
 - 2) mucinous histology (yes 50% vs no 4%, $p<0.001$).
- Median age was apparently lower in dMMR subset (58 vs 68 years, $p=NS$).

Results - Role of dMMR in resectable disease



At a median follow up of 22.5 months after resection, 52/107 patients experienced recurrence (median DFS 23.7 months).

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DFS: Multivariate analysis

Multivariate analysis	HR (95% CI)	<i>p</i>
MMR status dMMR vs pMMR	4.4 (1.48-13.1)	0.008
Nodal involvement N0 vs other	0.31 (0.16-0.60)	0.001
Resection margin R0 vs other	0.28 (0.094-0.817)	0.020

Results - Role of dMMR in advanced BTC

Median follow up= 17,4 months

	dMMR	pMMR	<i>p</i>
mPFS	8.6	7.4	0.46
mOS	33.2	20.1	0.66

Conclusions

- Deficiency of MMR was reported in a little but relevant proportion **(6%) of BTC** patients
- This feature seems to be more prevalent among patients with **iCCA** and tumours with **mucinous histology**
- Putative poor prognostic role after potentially curative resection needs to be confirmed at longer follow up and in independent **larger cohorts**.

Grazie per l'attenzione!



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