Comprehensive genomic profiling of “The German Registry of Incidental Gallbladder Carcinoma” cases (IKF-t043)

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Background and Design

Gallbladder cancer (GBC) is one of the most frequent cancers of the biliary tract with an aggressive progression and poor prognosis. The GBC related studies are rather limited due to low incidence rate of the disease, or all biliary tract cancer (BTC) studies are combined rather than isolated GBC cases. The multicenter German Registry of Incidental Gallbladder Carcinoma (IGBC) trial evaluates clinical real-world data and comprehensive genomic profiling together. Here we retrospectively analyzed the clinical, histopathological and molecular spectrum of patients from German Registry of IGBC.

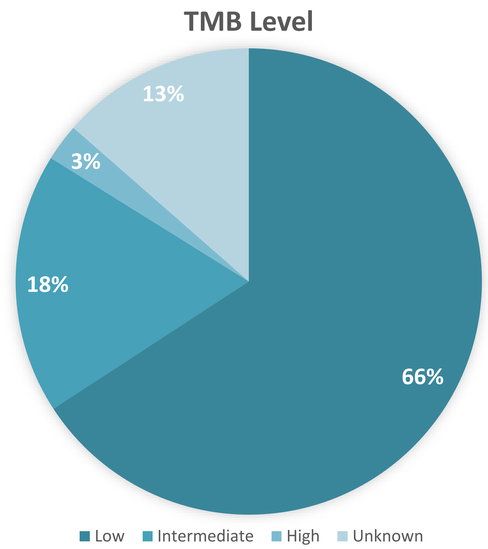
Materials and Methods

A total of 1,054 patients who had undergone resection for GBC were retrospectively analyzed and cases with available FFPE samples (n=200) were studied for their mutational status by the FoundationOne Heme Dx. For each patient, the following variables were described in the molecular report provided by FMI: alteration type (SNV, deletion, amplification, fusion), alteration name, actionable gene alteration, therapies approved in EU (patient tumor type and other tumor types), tumor mutational burden (TMB) and microsatellite instability (MSI) status.

Table 1: Clinical findings and pathogenic TP53 status of patients with MGPT (n=155)

	TP53 status		
	Positive	Negative	*p value*
Gender			
Female	51	66	*0.574*
Male	19	19	
Age			
<60	9	17	*0.383*
60-75	25	33	
>75	34	34	
TMB			
High/Intermediate	18	14	*0.226*
Low	44	58	
Metastasis			
Yes	16	15	*0.481*
No	18	25	
High-Level Amp			
Yes	33	31	*0.193*
No	37	54	
Low-Level Amp			
Yes	18	15	*0.242*
No	52	70	

Figure 1. TMB status of tumors



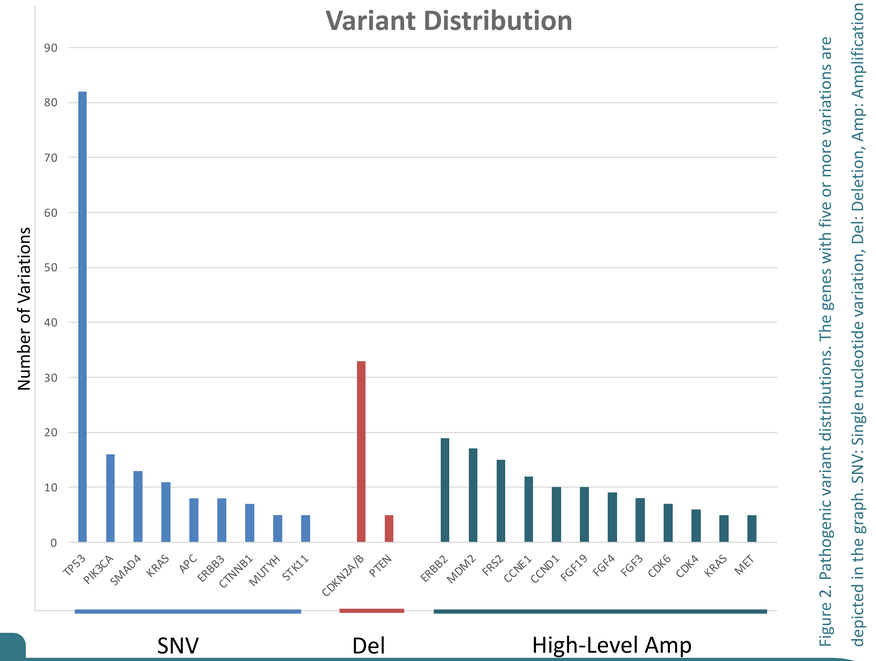


Figure 2. Pathogenic variant distributions. The genes with five or more variations are depicted in the graph. SNV: Single nucleotide variation, Del: Deletion, Amp: Amplification

Results and Conclusion

Clinical Findings: Among 1,054 patients, there were 250 male and 804 female, with a mean age of 70.83 (min:30-max:98). The average survival following surgery was 27.14 months for patients with available data (n=975), and 30 of the cases were deceased within the 30 days following surgery. There were 200 available FFPE samples, and 155 could already be analyzed by MGPT. For molecularly analyzed patients, the average survival following surgery was 22.04 (n=150, with available data) months. **Molecular Findings:** Among 155 samples, 127 (82%) showed at least one pathogenic variation. We have determined a total of 288 pathogenic and 212 likely pathogenic variations among 155 patients. The highest number of SNVs were detected in the *TP53* gene (28.47%), and more than 88% of those were concurrent with another gene variation. *TP53, PIK3CA, SMAD4, KRAS, APC, ERBB3, and APC* were also the most frequently altered genes within the cohort. We have also detected high- and low-level amplifications, as well as homozygous deletions. Among these, *ERBB2* exhibited the highest count of high-level amplifications, present in 19 patients. Additionally, *MDM2* and *FRS2* were frequent high-level amplifications seen in 17 and 15 patients, respectively. The most prevalent homozygous deletion was *CDKN2A/B,* which was detected in 33 patients. The average TMB was 3.64 (min:0.81-max:52.95). Survival rates were also assessed based on age, gender, metastasis status, TMB levels, and mutated genes. Significant differences were only observed in age comparison and ERBB2 variation carriers. Patients less than 60 years old had higher survival rates than 60-75 and >75 age groups (*p=0.043)*. *ERBB2* positive cases had higher survival than negative cases (*p=0.025*). **Conclusion:** Currently, clinical trials mostly evaluate targeted therapies in BTC cases, and GBC-specific studies are urgently needed. Here, we retrospectively analyzed the clinical, histopathological, and molecular spectrum of a large series of GBC patients. These findings will provide insights into a rare but severe type of upper GI cancer.

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