

TABLE OF CONTENTS

TABLE OF CONTENTS ..... 3

1. INTRODUCTION ..... 4

2. THE ROLE OF SMALL NERVE FIBERS IN HEPATO-PANCREATICO-BILIARY CANCER..... 8

    BACKGROUND – THE ROLE OF SMALL NERVE FIBERS IN HEPATO-PANCREATICO-BILIARY CANCER ..... 8

        2.1. Nerve Fibers in the Tumor Microenvironment as a novel Biomarker for Oncological Outcome in Patients Undergoing Surgery for Perihilar Cholangiocarcinoma..... 11

        2.2. The Presence of Small Nerve Fibers in the Tumor Microenvironment as Predictive Biomarker of Oncological Outcome Following Partial Hepatectomy for Intrahepatic Cholangiocarcinoma..... 15

        2.3. Limitations of Nerve Fiber Density as a Prognostic Marker in Predicting Oncological Outcomes in Hepatocellular Carcinoma..... 18

        2.4. Nerve Fibers in the Tumor Microenvironment Are Co-Localized with Lymphoid Aggregates in Pancreatic Cancer. .... 20

3. THE TUMOR MICROENVIRONMENT IN CHOLANGIOCARCINOMA..... 22

    BACKGROUND – THE TUMOR MICROENVIRONMENT IN CHOLANGIOCARCINOMA ..... 22

        3.1. PD-1+ T-Cells Correlate with Nerve Fiber Density as a Prognostic Biomarker in Patients with Resected Perihilar Cholangiocarcinoma. .... 23

        3.2. Expression of checkpoint molecules in the tumor microenvironment of intrahepatic cholangiocarcinoma: implications for immune checkpoint blockade therapy. .... 26

4.DISCUSSION ..... 30

5. FUTURE PERSPECTIVES ..... 39

6.ORIGINAL RESEARCH ..... 40

    6.1. ORIGINAL RESEARCH RELATED TO THE PRESENT THESIS ..... 40

7. APPENDIX ..... 127

    7.1. REFERENCES..... 127

    7.2. CURRICULUM VITAE..... 133

    7.3. LIST OF PUBLICATIONS AND RESEARCH FUNDING ..... 137

8. ACKNOWLEDGEMENTS..... 148