Systematic Review

Hepatocellular Carcinoma with Gastrointestinal Involvement: A Systematic Review

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Abstract: In this paper, we aimed to evaluate clinical and imagistic features, and also to provide a diagnostic algorithm for patients presenting with gastrointestinal involvement from hepatocellular carcinoma (HCC). We conducted a systematic search on the PubMed, Scopus and Web of Science databases to identify and collect papers on cases of HCC with gastrointestinal involvement. This search was last updated on 29 April 2022. One hundred and twenty-three articles were included, corresponding to 197 patients. The majority of the patients were male (87.30%), with a mean age of 61.21 years old. The analysis showed large HCCs located mainly in the right hepatic lobe, and highly elevated alfa-fetoprotein (mean = 15,366.18 ng/mL). The most frequent etiological factor was hepatitis B virus (38.57%). Portal vein thrombosis was present in 27.91% of cases. HCC was previously treated in most cases by transarterial chemoembolization (32.99%) and surgical resection (28.93%). Gastrointestinal lesions, developed mainly through direct invasion and hematogenous routes, were predominantly detected in the stomach and duodenum in equal measure—27.91%. Gastrointestinal bleeding was the most common presentation (49.74%). The main diagnostic tools were esophagogastroduodenoscopy (EGD) and computed tomography. The mean survival time was 7.30 months. Gastrointestinal involvement in HCC should be included in the differential diagnosis of patients with underlying HCC and gastrointestinal manifestations or pathological findings in EGD.

Keywords: hepatocellular carcinoma; gastrointestinal involvement; algorithm; esophagogastroduodenoscopy; gastrointestinal bleeding

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and the sixth most common cancer, according to GLOBOCAN 2020 data. Although both incidence and mortality rates declined in many high-risk areas, many patients have already reached an advanced stage at diagnosis, resulting in 830,000 deaths worldwide [1].

Hepatocellular carcinoma usually disseminates to the liver [2]. Although less common, in 30–50% of the cases, HCC can have extrahepatic spread. The most frequent areas are the lungs, followed by lymph nodes and bones [3–5]. Involvement of the gastrointestinal (GI) tract is a rare event, with a reported incidence of 0.5–2% of all HCCs. Higher rates of 4–12% have been recorded in autopsy cases [6,7].
Due to non-specific symptomatology or endoscopic features, GI involvement by HCC is underdiagnosed premortem [8]. The available data about this condition are provided mainly by case reports and only a few literature reviews. In 2004, Fujii, K. et al. reviewed the characteristics of 29 HCC patients with GI tract invasion [9]. Later on, in 2011, Lin, T.L. et al. assessed the course of disease and survival in 44 patients reported in the English literature with direct invasion of the GI tract by HCC [10]. In the same year, Kato, Y. et al. (2011) investigated the role of surgical treatment based on 18 cases from the literature (English literature and Japanese literature with English abstract), including his reported case [11]. In 2018, Harada, J. et al. also reviewed the clinical characteristics of esophageal metastases from HCC [12]. Recently, Yu, Y.M. et al. (2020) listed and analyzed 15 patients with metastases from HCC in the small bowel and large intestine, followed in 2021 by Mu, M. et al., who provided a literature summary of 21 HCC colonic metastases [13,14]. However, these studies included a limited number of cases and were focused on a specific route of metastasis, or the involvement of a particular segment of the GI tract. Additional cases have been reported since these previous publications.

The HCC survival rate has increased over the last three decades and we expect it to further increase as a result of improvements in therapy and early diagnosis [15]. For that reason, we also expect to see a more significant number of patients with atypical complications in our clinical practice [16]. An early diagnosis of GI involvement from HCC is a challenge for clinicians, and raising awareness of this issue is a crucial step toward it. Our systematic review complements previous studies and gives a bigger picture of the main clinical and imagistic characteristics of GI involvement from HCC. We also propose an algorithm diagnosis that would serve clinicians in making a rapid diagnosis.

2. Materials and Methods

A systematic review of case studies of gastrointestinal involvement from hepatocellular carcinoma was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Table S1) [17].

2.1. Data Sources

The systematic search was performed in the PubMed, Scopus and Web of Science databases up to November 2021, with the last search update on 29 April. A search in the Scopus and Web of Science database was also performed to avoid missing relevant articles up to 29 April. Randomly discovered searches, mainly from the manual search of references, were also included.

2.2. Inclusion and Exclusion Criteria

Our search strategy was developed on PICO (Patient/Population, Intervention, Comparison, Outcome) elements as follows: population: patients with an imagistic or histopathological diagnosis of hepatocellular carcinoma involving the gastrointestinal tract; intervention: none; comparison: none; outcomes: case studies that reported clinical presentation, diagnosis or survival of HCC with gastrointestinal involvement. All published case reports, case series or retrospective observational studies on the PubMed database concerning GI involvement from hepatocellular carcinoma were considered eligible for inclusion. We extended our search to editorial material that provided enough data for retrieval and analysis. No restriction for the time of publication was fixed. Only articles that addressed the specific clinical topic were selected for the examination. We excluded articles written in languages other than English, those not focused on the main issue, and papers not available as full text or papers with insufficient data to support the analysis.

2.3. Search Strategy

The search strategy included a combination of the following terms connected with the Boolean operators “AND” and “OR”: “hepatocellular carcinoma”, “esophagus”, “stomach”, “gastric”, “duodenum”, “jejenum”, “ileum”, “intestine”, “colon”, “rectum”, “invasion”, “HCC”.
“metastasis”. No filters were added. The search strategy is reported as Supplementary Materials (Table S2). In the first stage, duplicate references were removed from our results using EndNote 20 (Clarivate Analytics, Chandler, AZ, USA). Further, tiles/± abstracts of the records found in the first stage were screened by two reviewers, and reports that were not on the main subject were excluded. Cohen’s Kappa coefficient was calculated, obtaining a satisfactory value of 0.94. The next step was to eliminate non-English articles. The full text of the articles was retrieved when available and further analyzed. Articles containing insufficient data and those not related to the main topic were excluded.

Further, we composed a data-extracting sheet in Microsoft Excel (Microsoft Office Professional Plus 2019), Microsoft Excel® 2019 MSO (Version 2111 Build 16.0.14701.20204) 32-bit. One member of our team performed the initial data extraction and it was checked for reliability by a second member.

The following data were extracted: additional bibliographic information, including name of the first author, year of publication and type of study; number of patients reported in the paper; patient’s demographics, such as gender and age; etiology; location and size of HCC; previous treatment for HCC; AFP value (ng/mL); presence of portal vein thrombosis; the involved segment of the gastrointestinal tract; clinical presentation; involvement route; imagistic methods used for diagnosis of GI lesions; endoscopic features; methods used to obtain histological specimens and whether or not immunohistochemistry was used, as well as the survival time. The extracted data were further processed. Descriptive statistics (mean, standard deviation, percentages, minimum, maximum) were used to summarize the analyzed data.

Any discrepancy between reviewers was discussed, and a final consensus was reached.

In order to assess the risk of bias in our systematic review of case reports and case series, we used the Joanna Briggs Critical Appraisal Checklist for case reports and for case series (Tables S3 and S4) [18].

3. Results

3.1. Publication Characteristics

Figure 1 illustrates the PRISMA flow diagram of our search strategy. We initially identified 9474 record titles, from which we excluded 2727 duplicates. Further, from the remaining 6747 records, only 195 were sought for retrieval. Forty-seven articles were non-English publications. In the last stage, from the 148 reports considered eligible, one was an E-poster, 26 did not have full-text availability, three were not on discussed topic and five did not have sufficient detailed data to support the analysis (Table S5). We identified ten additional publications on manual search. One hundred twenty-three articles concerning 197 patients were included in the final analysis (Tables 1 and 2).

3.2. Patient Characteristics

We included 197 cases, with a mean age of 61.21 (standard deviation = 11.66), ranging from 22–86. The majority of patients were male (n = 172; 87.30%), with a ratio of man: woman of 6.88.

3.3. Etiology

Data concerning the etiology of liver disease in patients with HCC were described in 158 cases (Table 3). Hepatitis B virus (HBV) was incriminated in most patients (38.57%), followed by hepatitis C virus (HCV) (17.76%) and alcohol (7.61%). Coinfection with HBV and HCV was reported in 2.03% of cases, and only 0.5% of patients were identified with HBV, HCV, and hepatitis D virus (HVD) coinfection. Autoimmune etiology and non-alcoholic fatty liver disease (NAFLD) were suggested in one patient. In 19 cases, the underlying cause was unknown (9.64%).
Figure 1. PRISMA flow diagram for the selection process of the cases.
Table 1. Literature review of cases with gastrointestinal involvement from hepatocellular carcinoma—characteristics of HCC tumors.

| Author         | Year | Type of Paper | Segment of GI Tract Involved | No. of Patients Reported | Age | Gender | Etiology | Localization of HCC | Dimension of HCC (cm) | Previous Treatment for HCC | PVT | AFP (ng/mL) |
|----------------|------|---------------|-----------------------------|--------------------------|-----|--------|----------|--------------------|------------------------|----------------------------|-----|-------------|
| Sohn, D. et al. [19] | 1965 | Case report   | esophagus                   | 1                        | 74  | M      | N/A      | LHL                | 6                      | none                       | yes | N/A         |
| Hiraoka, T. et al. [20] | 1986 | Case report   | esophageal varices          | 2                        | 55  | M      | N/A      | RHL, LHL           | 1                      | none                       | yes | N/A         |
| Kume, K. et al. [21] | 2000 | Case report   | esophagus                   | 1                        | 56  | M      | HBV      | RHL                | N/A                    | TACE                       | yes | 12,200      |
| Sohara, N. et al. [22] | 2000 | Case report   | esophagus                   | 2                        | 54  | M      | HCV      | RHL                | N/A                    | TAI, PEI                   | yes | 7,820       |
| Tsubouchi, E. et al. [23] | 2005 | Case report   | esophagus + stomach         | 1                        | 63  | M      | HCV      | RHL, LHL           | 3; 2                   | PEI, IHAC                  | no  | 596.09      |
| Yan, S.L. et al. [24] | 2007 | Editorial material | esophagus                  | 1                        | 53  | M      | HBV      | LHL                | N/A                    | None                      | yes | 17,036      |
| Xie, L.Y. et al. [25] | 2008 | Case report   | esophagus                   | 1                        | 50  | M      | HBV      | RHL                | N/A                    | LT, TACE, systemic chemotherapy | yes | N/A         |
| Choi, C.S. et al. [26] | 2008 | Case report   | esophagus                   | 1                        | 66  | M      | UK       | RHL, LHL           | N/A                    | TACE, external beam radiotherapy | yes | 3.47        |
| Hsu, K.F. et al. [27] | 2009 | Editorial material | esophagus + gastric cardia | 1                        | 54  | M      | HBV      | N/A                | N/A                    | LT, TACE, systemic chemotherapy | no  | N/A         |
| Kahn, J. et al. [28] | 2009 | Letter to editor | esophagus                  | 1                        | 55  | M      | HCV      | RHL, LHL           | N/A                    | LT, TACE                   | yes | 1426        |
| Boonnuch, W. et al. [29] | 2011 | Case report   | esophagus                   | 1                        | 59  | M      | N/A      | No tumor recurrence | N/A                    | LT                         | no  | 510         |
| Skurla, B. et al. [30] | 2010 | Case report   | esophagus                   | 1                        | 56  | M      | alcohol  | RHL, LHL           | N/A                    | LT                         | yes | NR          |
| Fukatsu, H. et al. [31] | 2012 | Case report   | esophagus                   | 1                        | 63  | M      | NA       | RHL, LHL           | N/A                    | TACE, RFA                  | yes | N/A         |
| Chen, J.X. et al. [32] | 2016 | Case report   | esophagus                   | 1                        | 44  | M      | alcohol  | NA                 | N/A                    | LT, TACE                  | no  | 17.62       |
| Harada, J.-i. et al. [12] | 2018 | Case report   | esophagus                   | 1                        | 71  | M      | HBV      | RHL, LHL *         | N/A                    | surgical resection          | no  | 1800        |
| Kongam, P. et al. [33] | 2018 | Case report   | esophagus                   | 1                        | 59  | M      | N/A      | NA                 | N/A                    | LT                         | no  | 258.3       |
| Boinboire, R. et al. [34] | 2021 | Case report   | esophagus                   | 1                        | 66  | M      | alcohol  | RHL, LHL           | N/A                    | surgical resection, RFA     | no  | NR          |
| Subramanian, S.K. et al. [35] | 2021 | Editorial material | esophagus                  | 1                        | 53  | M      | alcohol  | No tumor recurrence in the liver | 5; 10 | systemic chemotherapy | no  | NR          |
| Shiota, T. et al. [36] | 1983 | Case report   | stomach                    | 1                        | 56  | M      | UK       | RHL, LHL           | 5; 10                  | systemic chemotherapy      | no  | NR          |
| Makino, H. et al. [37] | 1986 | Case report   | stomach                    | 1                        | 69  | M      | UK       | RHL, LHL           | N/A                    | none                       | yes | 1,136,800   |
Table 1. Cont.

| Author                  | Year  | Type of Paper          | Segment of GI Tract Involved | No. of Patients Reported | Age | Gender | Etiology | Localization of HCC | Dimension of HCC (cm) | Previous Treatment for HCC | PVT | AFP (ng/mL) |
|-------------------------|-------|------------------------|------------------------------|--------------------------|-----|--------|----------|---------------------|------------------------|----------------------------|-----|------------|
| Chen, L.T. et al. [6]   | 1990  | Retrospective analysis study | stomach                     | 3                        | 48  | M      | HBV      | LHL                 | 17                     | surgical resection         | UK  | N/A        |
|                         |       |                        |                              |                          | 86  | M      | UK       | RHL, LHL            | 25                     | none                       | yes | 221,920    |
|                         |       |                        |                              |                          | 59  | M      | HBV      | RHL                 | 18                     | TAE, IHAC                  | no  | 51,270     |
| De Nardi, P. et al. [38]| 1992  | Case report            | stomach                     | 1                        | 60  | M      | UK       | RHL                 | No tumor recurrence in the liver | surgical resection         | yes | 24,000     |
| Nicoll, A.J. et al. [39]| 1994  | Case report            | stomach                     | 1                        | 61  | M      | UK       | N/A                 | N/A                    | systemic chemotherapy     | no  | 6526       |
| Maruyama, A. et al. [40]| 1999  | Case report            | stomach                     | 1                        | 65  | M      | HCV      | RHL, LHL            | N/A                    | TAE, IHAC, radiotherapy    | no  | NR         |
| Srivastava, D.N. et al. [41]| 2000  | Case series            | stomach                     | 1                        | 58  | M      | HCV      | LHL                 | N/A                    | N/A                        | N/A | N/A        |
| Wang, M.H. et al. [42]  | 2000  | Case report            | stomach                     | 2                        | 57  | F      | HBV      | LHL                 | N/A                    | surgical resection, TACE  | no  | elevated   |
| Lin, C.P. et al. [7]    | 2000  | Retrospective analysis study | stomach                     | 5                        | 53  | M      | HCV      | RHL, LHL            | 9                      | none                       | yes | 719,110    |
|                         |       |                        |                              |                          | 66  | M      | HBV      | LHL                 | 12                     | surgical resection         | UK  | 1,159      |
|                         |       |                        |                              |                          | 60  | M      | HBV      | RHL, LHL            | 14                     | none                       | yes | 136,070    |
|                         |       |                        |                              |                          | 69  | M      | UK       | RHL, LHL            | 14                     | surgical resection, TACE  | no  | 50         |
|                         |       |                        |                              |                          | 63  | M      | HBV      | RHL, LHL            | 9                      | none                       | no  | 2,432      |
| Fujii, K. et al. [9]    | 2004  | Case report            | stomach + jejunum           | 1                        | 61  | M      | alcohol  | LHL                 | 10; 2                  | none                       | no  | 19,675     |
| Inoue, H. et al. [43]   | 2006  | Case report            | stomach                     | 1                        | 71  | M      | HCV      | LHL                 | 5                      | IHAC                       | yes | 45,630     |
| Ong, J.C.A. et al. [44] | 2007  | Case report            | stomach                     | 1                        | 67  | M      | HBV      | LHL                 | 10                     | none                       | No  | NA         |
| Kimura, K. et al. [45]  | 2008  | Case report            | stomach                     | 1                        | 54  | M      | HBV      | LHL                 | 7.5                    | TAE                        | no  | NR         |
| Korkolis, D.P. et al. [46]| 2009  | Case report            | stomach                     | 1                        | 70  | M      | HBV, alcohol | LHL                 | 15                     | none                       | no  | 2.1        |
| Hu, M.L. et al. [47]    | 2009  | Retrospective analysis study | stomach                     | 7                        | 48  | M      | HBV, alcohol | LHL                 | 12                     | TAE                        | yes | 969        |
|                         |       |                        |                              |                          | 54  | M      | HBV      | LHL                 | 6                      | TAE                        | yes | >87,500     |
|                         |       |                        |                              |                          | 68  | M      | HBV      | RHL, LHL            | N/A **                 | none                       | yes | 440        |
|                         |       |                        |                              |                          | 62  | M      | HBV      | RHL                 | 7                      | TAE                        | yes | 2          |
|                         |       |                        |                              |                          | 50  | M      | HBV, HCV, HDV, alcohol | RHL, LHL              | N/A **                 | TAE                        | no  | 218        |
### Table 1. Cont.

| Author          | Year | Type of Paper | Segment of GI Tract Involved | No. of Patients Reported | Age | Gender | Etiology         | Localization of HCC | Dimension of HCC (cm) | Previous Treatment for HCC | PVT | AFP (ng/mL) |
|-----------------|------|---------------|-----------------------------|--------------------------|-----|--------|------------------|----------------------|------------------------|----------------------------|-----|------------|
| stomach         | 51   | M             | HBV + alcohol               | LHL                      | 14  | TAE    | yes              | 6398                 |                         |                            |     |            |
| stomach         | 71   | M             | HBV + alcohol               | RHL, LHL                 | 8; 6| TAE    | yes              | 34.706               |                         |                            |     |            |
| Park, H. et al. | 2010 | Case report   | stomach                    | 1                        | 63  | M      | HBV             | RHL, LHL             | 8; 3                   | TACE                       | no  | 50.202     |
| Lin, T.L. et al.| 2011 | Case report   | stomach                    | 1                        | 57  | M      | HBV             | LHL                  | 9                      | TAE                        | no  | NA         |
| Tan, W.J. et al.| 2013 | Case report   | stomach                    | 1                        | 76  | F      | crypto-genic liver cirrhosis | NA ** | NA              | none                       | no  | >60.500    |
| Sayana, H. et al.| 2013 | Case report   | stomach                    | 1                        | 36  | M      | HBV + HCV       | LHL                  | 19                     | TACE, sorafenib            | no  | 7.6        |
| Okay, E. et al. | 2014 | Case report   | stomach + transverse colon | 1                        | 44  | M      | HBV             | LHL                  | 28                     | none                       | no  | >350.000   |
| Inagaki, Y. et al.| 2014 | Case report-Image of the month | stomach                    | 1                        | 62  | M      | HCV             | N/A                  | N/A                    | TACE, RFA                  | N/A | 6404       |
| Wu, W.D. et al. | 2014 | Case report   | stomach                    | 1                        | 75  | M      | HBV             | LHL                  | 11.5                   | surgical resection, TACE  | no  | NR         |
| Grover, I. et al.| 2014 | Case report   | stomach                    | 1                        | 51  | M      | HBV             | LHL                  | elevated               | TACE                       | no  | 2.82       |
| Li, L. et al.   | 2015 | Case report   | stomach                    | 1                        | 43  | M      | HBV             | N/A                  | N/A                    | LT                         | no  | 191        |
| Hot, S. et al.  | 2016 | Case report   | stomach                    | 1                        | 62  | M      | alcohol         | hepatic hilum        | 13                     | none                       | no  | 2.82       |
| Haruki, K. et al.| 2016 | Case report   | stomach                    | 1                        | 73  | M      | UK              | LHL                  | 17                     | none                       | no  | N/A        |
| Wu, D. et al.   | 2016 | Case report   | stomach + colon            | 1                        | 54  | M      | N/A             | RHL                  | 4                      | surgical resection        | N/A | N/A        |
| Abdul Hakim, M.S. et al. | 2017 | Case report   | stomach + duodenum         | 1                        | 73  | M      | N/A             | RHL                  | N/A                    | RFA                        | no  | 124.800    |
| Peng, L. et al. | 2018 | Case report   | stomach                    | 1                        | 22  | M      | HBV             | RHL, LHL             | 8; 1.5                  | surgical resection        | no  | >1200      |
| Kasi, M. et al. | 2018 | Case report   | stomach                    | 1                        | 43  | M      | HBV             | caudate lobe         | 3                      | LT, TACE                  | no  | 69         |
| Sakumura, M. et al. | 2018 | Editorial material | stomach                    | 1                        | 68  | F      | HBV             | N/A                  | N/A                    | TACE                       | yes | N/A        |
| Bale, A. et al. | 2018 | Editorial material | stomach                    | 1                        | 69  | M      | NAFLD           | LHl                  | N/A                    | TACE                       | no  | N/A        |
| Imai, M. et al. | 2019 | Case report   | stomach                    | 1                        | 62  | M      | alcohol         | RHL, LHL             | 17; 6                   | TACE                       | yes | 56.388     |
| Marques da Costa, P. et al. | 2019 | Editorial material | stomach + duodenum         | 1                        | 81  | F      | HCV             | RHL                  | N/A                    | none                       | no  | N/A        |
Table 1. Cont.

| Author                  | Year  | Type of Paper | Segment of GI Tract Involved | No. of Patients Reported | Age | Gender | Etiology | Localization of HCC | Dimension of HCC (cm) | Previous Treatment for HCC | PVT | AFP (ng/mL) |
|-------------------------|-------|---------------|-------------------------------|--------------------------|-----|--------|----------|---------------------|--------------------------|----------------------------|-----|-------------|
| Kim, R. et al. [66]     | 2020  | Case report   | stomach + ascending colon     | 1                        | 75  | M      | alcohol | N/A                 | N/A                      | surgical resection, TACE   | no  | NR (2.3)   |
| Abouzied, M.M. et al. [67] | 2021  | Case report   | stomach                      | 1                        | 69  | M      | N/A     | RHL                 | 10                       | surgical resection         | no  | NR (3.3)   |
| Eskarous, H. et al. [68] | 2022  | Case report   | stomach                      | 1                        | 82  | F      | NA      | RHL                 | N/A                      | surgical resection         | N/A | N/A         |
| Chen, L.-T. et al. [6]  | 1990  | Retrospective analysis study | duodenum                  | 4                        | 56  | M      | HBV     | RHL                 | 22                       | none                       |     | 3200        |
|                         |       |               |                               |                          |     |        |         |                     |                          | surgical resection, systemic chemotherapy |     | UK 15,435    |
| Arima, K. et al. [69]   | 1992  | Case report   | duodenum                      | 1                        | 61  | M      | NA      | RHL                 | 3                        | surgical resection         | yes | N/A         |
| Moriura, S. et al. [70] | 1995  | Case report   | duodenum                      | 1                        | 57  | M      | UK      | hepatic hilum        | 7                        | none                       | no  |             |
| Okusaka, T. et al. [71] | 1997  | Case report   | duodenum                      | 1                        | 60  | M      | alcohol | N/A **              | 11                       | surgical resection, TAE, PEI | no  | NA          |
| Hung, H.C. et al. [72]  | 1998  | Case report   | duodenum + stomach            | 1                        | 58  | M      | HBV     | RHL                 | 4                        | surgical resection, systemic chemotherapy | no  | 20,799      |
| Farrell, R. et al. [73] | 1999  | Case report   | duodenum                      | 1                        | 53  | M      | HCV     | N/A **              | 8                        | surgical resection         | no  | 5           |
| Srivastava, D.N. et al. [11] | 2000  | Case series   | duodenum                      | 1                        | 48  | M      | N/A     | RHL                 | N/A                      | none                       | N/A |             |
| Lin, C.P. et al. [7]    | 2000  | Retrospective analysis study | duodenum                  | 3                        | 64  | M      | HBV     | RHL, LHL            | 10                       | none                       | yes | 252         |
|                         |       |               |                               |                          |     |        |         |                     |                          | surgical resection, TAE, PEI |     |             |
|                         |       |               |                               |                          |     |        |         |                     |                          | TACE                       | yes | 12,420      |
| Del Natale, M. et al. [74] | 2001  | Case report   | duodenum                      | 1                        | 67  | M      | alcohol | N/A                 | N/A                      | TACE                       | yes | 24,935      |
| Cho, A. et al. [75]     | 2002  | Case report   | duodenum                      | 1                        | 50  | M      | HBV     | RHL                 | 22                       | none                       | no  | 3477        |
| Ohnishi, S. et al. [76] | 2003  | Letter to the editor | duodenum                  | 1                        | 73  | M      | N/A     | RHL                 | 9                        | surgical resection, TAE, RFA, PEI | radiotherapy | no  | N/A         |
| Uehara, K. et al. [77]  | 2003  | Case report   | duodenum                      | 1                        | 62  | M      | HCV     | RHL                 | 1                        | none                       | N/A | 2000        |
| Chung, C. et al. [78]   | 2009  | Case report   | duodenum                      | 1                        | 53  | F      | HCV, alcohol | N/A **              | none                      | yes | NR          |
| Kurtz, L.E. et al. [79] | 2009  | Editorial material | duodenum                  | 1                        | 78  | F      | HCV     | RHL                 | 8.5                      | RFA, sorafenib             | no  | N/A         |
Table 1. Cont.

| Author            | Year | Type of Paper | Segment of GI Tract Involved | No. of Patients Reported | Age  | Gender | Etiology | Localization of HCC | Dimension of HCC (cm) | Previous Treatment for HCC | PVT | AFP (ng/mL) |
|-------------------|------|---------------|-------------------------------|--------------------------|------|--------|----------|---------------------|------------------------|----------------------------|-----|------------|
| Kato, Y. et al. [11] | 2011 | Case report   | duodenum                      | 1                        | 63   | M      | UK       | RHL                 | 25; 2                  | none                       |     | 848        |
| Lin, T.L. et al. [10] | 2011 | Review        | duodenum                      | 1                        | 72   | M      | HBV      | RHL                 | 4.5                    | PEI, RAE, surgical resection |     | N/A        |
| Liang, J.D. et al. [80] | 2011 | Retrospective analysis study | duodenum-19 duodenum + stomach-1 duodenum + colon-1 | 21                       | 62.5 | M-17; F-4 | HBV-12; HCV-7; HBV + HCV-2; alcohol-2 LHL, RHL-3; RHL-7; LHL-4; peritoneum-1; no recurrent liver tumor = 1; NA = 4 | 8.6 | none-4; surgical resection-3; surgical resection + TACE-7; surgical resection + TACE + PEI-1, TACE + RFA-1, TACE-4, TACE + PEI-1 |     | 8051.6     |
| Kim, J.N. et al. [81] | 2012 | Case report   | duodenum                      | 1                        | 57   | M      | UK       | LHL                 | N/A                    | TACE                       |     | N/A        |
| Sauer, B.G. et al. [82] | 2012 | Editorial material | duodenum                      | 1                        | 68   | M      | N/A      | N/A                 | N/A                    | TACE, radiotherapy, systemic chemotherapy |     | N/A        |
| Arima, K. et al. [83] | 2015 | Case report   | duodenum                      | 1                        | 76   | F      | HCV      | RHL                 | 6                      | surgical resection         |     | 34,428     |
| Kashani, A. et al. [84] | 2015 | Case report   | duodenum                      | 1                        | 62   | M      | HCV      | N/A **              | N/A                    | TACE                       |     | N/A        |
| Lin, I.C. et al. [85] | 2017 | Editorial material | duodenum                      | 1                        | 83   | M      | N/A      | RHL                 | N/A                    | TACE                       |     | N/A        |
| Ito, T. et al. [86] | 2019 | Case report   | duodenum                      | 1                        | 65   | M      | HCV      | N/A                 | 10                     | TACE, sorafenib            |     | 13,300     |
| Liu, Y.H. et al. [87] | 2020 | Case report   | duodenum                      | 1                        | 62   | M      | HBV      | RHL                 | 2.4                    | RFA, surgical resection    |     | NR         |
| Wu, Y.H. et al. [88] | 2021 | Case report   | duodenum                      | 1                        | 80   | F      | N/A      | N/A                 | 25                     | none                       |     | N/A        |
| Bonboire, R. et al. [34] | 2021 | Case report   | duodenum                      | 1                        | 67   | M      | alcohol  | RHL                 | 79                     | none                       |     | 269        |
| Sawada, K. et al. [89] | 2021 | Editorial material | duodenum                      | 1                        | 72   | M      | alcohol  | caudate lobe        | N/A                    | TACE                       |     | N/A        |
| Lee, Y.J. et al. [90] | 2021 | Retrospective analysis study | duodenum-3 stomach-1 duodenum + stomach-3 | 7                        | 59.71 *** | M-7 | HBV-6 UK-1 | N/A | N/A | TACE, PEIT-4 TACE, RT-2 |     | N/A        |
| Tsujimoto, M. et al. [91] | 1984 | Case report   | intestinal tract              | 1                        | 62   | M      | alcohol  | RHL                 | 14                     | none                       |     | N/A        |
| Chen, L.T. et al. [6] | 1990 | Retrospective analysis study | jejunum                       | 1                        | 36   | M      | HBV      | RHL                 | NA                     | hepatic arterial ligation, UK |     | 309        |
| Narita, T. et al. [92] | 1993 | Case report   | small bowel-mostly ileum + stomach | 1                        | 73   | F      | HBV      | RHL                 | 6                      | TAE                        |     | 16,000     |
| Tanaka, A. et al. [93] | 2000 | Case report   | ileum                         | 1                        | 52   | M      | HBV      | Peritoneum+ small intestine *** | N/A | TACE, surgical resection, systemic chemotherapy, hyperthermia |     | 1160       |
| Byun, J.R. et al. [94] | 2005 | Case report   | ileum                         | 1                        | 27   | M      | none     | RHL, caudate lobe    | 2.4; 3.4; 4.5             | TACE                       |     | 6050       |
| Author                  | Year | Type of Paper | Segment of GI Tract Involved | No. of Patients Reported | Age | Gender | Etiology | Localization of HCC | Dimension of HCC (cm) | Previous Treatment for HCC | PVT | AFP (ng/mL) |
|------------------------|------|---------------|------------------------------|--------------------------|-----|--------|----------|---------------------|-------------------------|----------------------------|-----|-------------|
| Kim, H.S. et al. [95]  | 2006 | Case report   | jejunum                      | 1                        | 65  | M      | HBV      | N/A                 | N/A                     | none                       | N/A | 629         |
| Iwaki, K. et al. [96]  | 2008 | Case report   | jejunum                      | 1                        | 60  | M      | HCV      | N/A                 | N/A                     | surgical resection, TACE, RFA | no  | N/A         |
| Choi, J.H. et al. [97] | 2012 | Case report   | jejunum                      | 1                        | 54  | M      | HBV      | N/A                 | N/A                     | sorafenib, surgical resection | yes | N/A         |
| Kunizaki, M. et al. [98]| 2012 | Case report   | small bowel                  | 1                        | 60  | M      | HBV      | N/A                 | N/A                     | TACE, RFA                  | no  | 1345        |
| Igawa, A. et al. [99]  | 2013 | Case report   | ileum                        | 1                        | 60  | M      | HBV      | N/A                 | N/A                     | sorafenib                  | yes | 86.5        |
| Kanazawa, M. et al. [100]| 2018 | Case report   | jejunum                      | 1                        | 76  | M      | alcohol  | N/A                 | N/A                     | surgery, TACE, sorafenib  | N/A | N/A         |
| Shelat, V.G. et al. [101]| 2018 | Case report   | jejunum                      | 1                        | 75  | M      | HBV      | N/A                 | N/A                     | surgical resection          | no  | N/A         |
| Sun, W.C. et al. [102] | 2018 | Editorial material | ileum                      | 1                        | 72  | M      | N/A      | N/A                 | N/A                     | TACE, RFA                  | N/A | N/A         |
| Mashiko, T. et al. [103]| 2020 | Case report   | ileum                        | 1                        | 71  | M      | HBV      | RHL                 | N/A                     | surgical resection, sorafenib | no  | N/A         |
| Suzuki, N. et al. [104]| 2020 | Case report   | small bowel                  | 1                        | 75  | M      | alcohol  | LHL, caudate lobe | 2                       | Lenvatinib, RFA, surgical resection | no  | 2.2         |
| Fukui, H. et al. [105] | 1993 | Case report   | ascending colon              | 1                        | 57  | M      | HCV      | RHL                 | N/A                     | surgical resection, TAE    | no  | 7           |
| Hashimoto, M. et al. [16]| 1996 | Case report   | transverse colon             | 1                        | 72  | F      | HCV      | RHL                 | 4.5                     | surgical resection          | no  | 33          |
| Cosenza, C.A. et al. [106]| 1989 | Case report   | duodenum + ascending colon   | 1                        | 82  | F      | HCV      | RHL                 | NA                      | surgical resection, systemic chemotherapy, cryoablation | no  | 19          |
| Srivastava, D.N. et al. [41]| 2000 | Case series   | transverse colon             | 1                        | 32  | M      | HBV      | LHL                 | N/A                     | no                         | no  | N/A         |
| Lin, C.P. et al. [7]   | 2000 | Retrospective analysis study | colon                      | 3                        | 59  | M      | HCV      | RHL                 | 8                       | TAE                       | yes | 3319        |
|                        |      |               |                              |                          | 69  | M      | HBV      | RHL, LHL            | 20                      | none                      | no  | 698.346     |
|                        |      |               |                              |                          | 63  | M      | UK       | RHL, LHL            | 20                      | none                      | yes | 46          |
| Kurachi, K. et al. [107]| 2002 | Case report   | colon                        | 1                        | 43  | M      | UK       | LHL                 | 12                      | PEIT, surgical resection   | no  | 3           |
| Zech, C.J. et al. [108]| 2006 | Case report   | ascending colon              | 1                        | 57  | M      | HBV + HCV | RHL                 | N/A                     | TACE                      | no  | N/A         |
| Tapuria, N. et al. [109]| 2006 | Case report   | ascending colon              | 1                        | 67  | M      | autoimmune cirrhosis | RHL, LHL            | none                      | yes | 20.9        |
| Author                  | Year | Type of Paper   | Segment of GI Tract Involved | No. of Patients Reported | Age | Gender | Etiology | Localization of HCC | Dimension of HCC (cm) | Previous Treatment for HCC | PVT | AFP (ng/mL) |
|-------------------------|------|----------------|-----------------------------|-------------------------|-----|--------|----------|-------------------|------------------------|--------------------------------|-----|----------|
| Kaibori, M. et al. [110]| 2007 | Case report    | descending colon            | 1                       | 61  | M      | HCV      | RHL, LHL          | 2; 1.5                 | TAE, PEL, surgical resection | N/A | N/A      |
| Ng, D.S.C. et al. [111] | 2007 | Case report    | ascending and hepatic flexure of the colon | 1                       | 35  | M      | HBV      | RHL               | 12                    | surgical resection no    | 7   |          |
| Hirashita, T. et al. [112]| 2008 | Case report   | transverse colon            | 2                       | 79  | M      | HCV      | caudate lobe      | 7.5                   | TACE no                      | 331  |          |
| Nozaki, Y. et al. [113] | 2008 | Letter to the editor | hepatic flexure of colon    | 69                      | M   | HCV    | RHL      | N/A               | 5.5                   | TACE, RFA no                  | 370  |          |
| Yoo, D.J. et al. [114]  | 2010 | Case report    | sigmoid colon               | 1                       | 69  | M      | N/A      | LHL               | N/A                   | surgical resection no       | 686  |          |
| Huang, S.F. et al. [115]| 2011 | Editorial material | rectum                     | 1                       | 57  | F      | HCV      | RHL               | 3.8; 1.5              | TACE no                      | 800  |          |
| Shih, Y.J. et al. [116] | 2012 | Letter to the editor | sigmoid colon               | 1                       | 50  | M      | UK       | RHL               | 7; 6                  | none no                     | 800  |          |
| Haga, Y. et al. [117]   | 2013 | Case report    | cecum                       | 1                       | 75  | F      | HCV      | RHL               | 3.8; 1.5              | RFA no                       | 370  |          |
| Sun, L.H. et al. [118]  | 2013 | Case report    | ascending colon             | 1                       | 72  | F      | NA       | caudate lobe      | 6                     | none no                      | N/A  |          |
| Imada, S. et al. [119]  | 2013 | Case report    | appendix                    | 1                       | 66  | M      | N/A      | N/A               | N/A                   | surgical resection, TAE no | 37   |          |
| Ou, T.M. et al. [120]   | 2014 | Case report    | ascending colon + rectum    | 1                       | 62  | M      | HBV      | RHL, LHL          | N/A                   | surgical resection, RFA, PEL, stereotactic radiosurgery, TACE | N/A  | N/A      |
| Kohli, R. et al. [121]  | 2014 | Editorial material | splenic flexure of the colon | 1                       | 50  | F      | cryptogenic cirrhosis | RHL | 1.5                  | LT, Yttrium-90 radioembolization | N/A  | 43       |
| Zhu, X. et al. [122]    | 2016 | Letter to the editor | transverse colon            | 1                       | 47  | M      | HBV      | No tumor recurrence | 1.8                  | surgical resection, TACE, TAE no | NR   |          |
| Mitsialis, V. et al. [123]| 2018 | Letter to the editor | sigmoid colon               | 1                       | 67  | F      | N/A      | N/A               | N/A                   | TACE, surgical resection yes | N/A  |          |
| Repullo, D. et al. [124]| 2018 | Case report    | hepatic flexure of the colon | 2                       | 49  | M      | UK       | RHL               | 10                    | none no                      | NR   | NR       |
| Tagliabue, F. et al. [125]| 2019 | Case report    | sigmoid colon               | 1                       | 70  | M      | HBV      | RHL               | N/A                   | TACE no                      | 3    |          |
| Pham, B.V. et al. [126] | 2019 | Case report    | sigmoid colon               | 1                       | 60  | M      | HBV      | RHL, LHL          | 4.1                   | TACE no                      | 9.48 |          |
| Soni, A. et al. [127]   | 2019 | Case report    | hepatic flexure             | 1                       | 65  | M      | HCV      | RHL, LHL          | 12                    | none N/A                      | 633  |          |
| Yu, Y.M. et al. [13]    | 2020 | Case report    | sigmoid colon               | 1                       | 60  | M      | HBV      | RHL               | N/A                   | resection, TACE, RFA, PRFA, sorafenib, regorafenib, immunotherapy | 21,000 |          |
Table 1. Cont.

| Author               | Year | Type of Paper | Segment of GI Tract Involved | No. of Patients Reported | Age | Gender | Etiology | Localization of HCC | Dimension of HCC (cm) | Previous Treatment for HCC | PVT | AFP (ng/mL) |
|----------------------|------|---------------|------------------------------|-------------------------|-----|--------|----------|--------------------|------------------------|----------------------------|-----|------------|
| Mu, M. et al. [14]   | 2021 | Case report   | hepatic flexure             | 1                       | 86  | M      | HBV      | RHL                | 7                      | TACE, ablation             | no  | NR         |
| Miyauchi, T. et al. [128] | 2021 | Case report   | colon                       | 1                       | 80  | M      | HBV      | RHL                | N/A                    | TACE, surgical resection, RFA | no  | N/A        |
| Park, M.S. et al. [8] | 2002 | Retrospective analysis study | duodenum-4, colon-3, stomach-10, stomach and colon-1 | 18                       | 58  | M-15, F-3 | N/A | 11-LHL, 5-RHL, 2-LHL, RHL | mean ≈ 6 | 2-surgical resection, yes = 10; no = 8 | N/A | N/A        |
| Liu, K.W. et al. [129] | 2013 | Case report   | rectum                      | 1                       | 71  | M      | HBV      | RHL                | 1.5 cm | No liver tumor recurrence | RFA | no         |
| Nielsen, J.A. et al. [130] | 2014 | Case report   | rectosigmoid                | 1                       | 51  | M      | HBV      | N/A                | N/A | surgical resection       | no  | N/A        |
| Ikeda, A. et al. [131] | 2016 | Case report   | rectum                      | 1                       | 82  | F      | HCV      | RHL, LHL           | 3.5, 2.5, 1 | RFA, TACE                  | N/A | 3024       |

F: feminine; M: masculine; HCC: hepatocellular carcinoma; PVT: portal vein thrombosis; N/A: not available; UK: unknown; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; NAFLD: non-alcoholic fatty liver disease; LHL: left hepatic lobe; RHL: right hepatic lobe; AFP: alpha-fetoprotein; TACE: transarterial chemoembolization; TAE: transarterial embolization; RFA: radiofrequency ablation; PRFA: percutaneous radiofrequency ablation; LT: liver transplant; PEI: percutaneous ethanol injection; IHAC: intrahepatic arterial infusion chemotherapy. * Localization of HCC detected two months after esophageal metastasis diagnosis. ** Multinodular pattern of HCC. *** Mean age. **** Intraabdominal disseminated HCCs. ***** Elevated. ****** Localization of HCC recurrence.

Table 2. Literature review of cases with gastrointestinal involvement from hepatocellular carcinoma—features of GI metastases.

| Author            | Clinical Presentation         | Route of Involvement           | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|-------------------|------------------------------|--------------------------------|----------------------------------------------------------|-------------------|--------------------------------------|-----|-------------------------|
| Sohn, D. et al. [19] | anorexia, weight loss         | hematogenous, trans-lymphatic | UGI                                                      | not done          | NA                                   | no  | 7                       |
| Hiraoka, T. et al. [20] | hematemesis                  | hematogenous                   | autopsy                                                   | not done          | autopsy                              | no  | post-mortem diagnosis   |
| Kume, K. et al. [21] | dysphagia, tarry tools        | hematogenous                   | autopsy                                                   | not done          | autopsy                              | no  | 2                       |
| Sohara, N. et al. [22] | melena                       | hematogenous                   | EGD, CT                                                   | polypoid lesion   | autopsy                              | no  | 1                       |
| Tsubouchi, E. et al. [23] | epigastric discomfort       | hematogenous + direct invasion | EGD, EUS, CT                                             | polypoid lesion   | EGD                                  | yes | 3                       |
Table 2. Cont.

| Author | Clinical Presentation | Route of Involvement | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|--------|------------------------|----------------------|----------------------------------------------------------|-------------------|--------------------------------------|-----|-------------------------|
| Yan, S.L. et al. [24] | melena | hematogenous | EGD | polypoid lesion | EGD | yes | 1 |
| Xie, L.Y. et al. [25] | dysphagia, odynophagia | hematogenous | EGD, CT | polypoid lesion | EGD | yes | alive at eight-month follow-up |
| Choi, C.S. et al. [27] | hematemesis | hematogenous | EGD, EUS | submucosal mass | EGD | yes | 7 |
| Hsu, K.F. et al. [26] | hematemesis, tarry stools | hematogenous | EGD | polypoid | EGD | yes | 4 |
| Kahn, J. et al. [28] | dysphagia | undetermined | EGD | polypoid (submucosal) | EGD | yes | 9 |
| Boonnuch, W. et al. [29] | dysphagia | hematogenous | UGI series, EGD, EUS, CT, PET-CT | extrinsic compression | resected specimen | no | N/A |
| Skurla, B. et al. [30] | intermittent GI bleeding, anemia | hematogenous | EGD | flat and polypoid lesions | EGD | no | alive at two-month follow-up |
| Fukatsu, H. et al. [31] | progressive anemia | hematogenous | EGD | polypoid/submucosal mass | EGD | yes | 1 |
| Chen, J.X. et al. [32] | nausea, abdominal discomfort, dysphagia, tarry stools | undetermined-possible translymphatic | EGD, PET-CT, CT | ulcerative mass | EGD | no | 1 |
| Harada, J. et al. [12] | asymptomatic (increased AFP) | undetermined * | EGD, CT, UGI series | polypoid lesion | EGD + resected specimen | yes | 2 |
| Kongkam, P. et al. [33] | asymptomatic ** | hematogenous | EUS, PET-CT | not seen | EUS-FNA | no | 20 |
| Boinboire, R. et al. [34] | dysphagia | direct invasion from right atrium mass | EGD, CT | exophytic mass | EGD | yes | alive at fifteen-month follow-up |
| Subramanian, S.K. et al. [35] | hematemesis, melena | N/A | EDS, EUS | nodule | resected specimen | no | alive at five-month follow-up |
| Shiota, T. et al. [36] | hematemesis, melanoma, anasarca | direct invasion | autopsy | not done | autopsy | no | post-mortem diagnosis |
| Makino, H. et al. [37] | epigastralgia | hematogenous | EGD | Bormann type 2 tumor | autopsy | yes | 2 months + 10 days |
| Chen, L.T. et al. [6] | hematemesis | undetermined | EGD | ulcerated submucosal tumor | EGD | no | 1 |
| | bloody stool | hematogenous | EGD, CT, UGI series | Borman III-like ulcer | EGD | no | 1 |
| | fecal occult blood test+ | direct invasion | EGD, CT | ulcerated submucosal tumor | EGD | no | 2 |
| Author                  | Clinical Presentation                  | Route of Involvement | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|-------------------------|---------------------------------------|----------------------|-----------------------------------------------------------|-------------------|--------------------------------------|-----|--------------------------|
| De Nardi, P. et al. [38]| anorexia, weakness, weight loss, melena| hematogenous         | EGD                                                       | polyps            | EGD + resected specimen              | yes | 20                       |
| Nicoll, A.J. et al. [39]| melena, hematemesis, syncope          | direct invasion      | EGD                                                       | protuberant gastric nodule | resected specimen                  | yes | alive at seven-month follow-up |
| Maruyama, A. et al. [40]| melena                                | direct invasion      | EGD, CT, UGI series                                       | ulceration        | resected specimen                    | no  | 5                        |
| Srivastava, D.N. et al. [41]| hematemesis                           | direct invasion      | EGD, Angio-CT                                             | ulcerative lesion | none                                 | no  | death on the same day as diagnosis |
| Wang, M.H. et al. [42]   | tarry stools                           | undetermined-possible direct invasion | EGD                                                    | ulcerated, submucosal tumor | EGD                                | yes | N/A                      |
|                         | bloody sputum                          | undetermined-possible direct invasion | EGD                                                    | ulcerated, submucosal tumor | EGD                                | no  | 1                        |
| Lin, C.P. et al. [7]     | nausea, vomiting, fecal occult blood test+ | direct invasion      | EGD                                                       | submucosal tumor  | EGD                                 | no  | 0.7                      |
|                         | melena, abdominal fullness             | undetermined         | CT                                                        | not done          | none                                 | no  | 9.7                      |
| RUQ + epigastric pain   | hematemogenous                         | direct invasion      | EGD                                                       | ulcerative tumor  | EGD                                 | no  | 1.8                      |
|                         | melena                                | direct invasion      | EGD                                                       | submucosal tumor  | EGD                                 | no  | 4.7                      |
|                         | hematemesis, melena                    | direct invasion      | EGD, CT                                                   | penetrated ulcer  | none                                 | no  | 1.6                      |
| Fujii, K. et al. [9]     | anemia                                | direct invasion      | EGD                                                       | ulcerative tumor  | resected specimen                    | no  | 32                       |
| Inoue, H. et al. [43]    | LUQ pain, weight loss                  | translymphatic       | EGD, CT                                                   | protruding, necrotic tumor | EGD                                | yes | NA                       |
| Ong, J.C. et al. [44]    | epigastric pain, dizziness, dyspnea, GI bleeding | direct invasion      | EGD                                                       | ulcer (bleeding)  | resected specimen                    | no  | alive at two-year-and-nine-month follow-up |
| Kimura, K. et al. [45]   | progressive anemia, posprandial epigastric pressure, hematemesis | direct invasion      | EGD, CT                                                   | extrinsic compression | EGD                                 | no  | 2                        |
| Korkolis, D.P. et al. [46]| upper abdominal pain, gastric outlet obstruction | direct invasion      | EGD, CT                                                   | protrusive, infiltrating tumor | resected specimen | no  | alive at sixteen-month follow-up |
### Table 2. Cont.

| Author                  | Clinical Presentation                                                                 | Route of Involvement     | Imagistic Methods Used for the Diagnosis of GI Involvement                  | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|-------------------------|----------------------------------------------------------------------------------------|--------------------------|------------------------------------------------------------------------------|-------------------|---------------------------------------|-----|--------------------------|
| Hu, M.L. et al. [47]    | NA                                                                                     | hematogenous             | EGD                                                                          | ulcerative mass   | EGD                                   | no  | N/A                      |
|                         | NA                                                                                     | hematogenous             | EGD                                                                          | ulcerative mass   | EGD                                   | no  | N/A                      |
|                         | NA                                                                                     | hematogenous             | EGD                                                                          | ulcerative mass   | EGD                                   | no  | N/A                      |
|                         | NA                                                                                     | hematogenous             | EGD                                                                          | ulcerative mass   | EGD                                   | no  | N/A                      |
|                         | NA                                                                                     | hematogenous             | EGD                                                                          | ulcerative mass   | EGD                                   | no  | N/A                      |
|                         | NA                                                                                     | hematogenous             | EGD                                                                          | ulcer with irregular margin | EGD                 | no  | N/A                      |
| Park, H. et al. [48]    | dysphagia, postprandial epigastric pain, hematemesis                                   | direct invasion          | EGD, CT                                                                       | fistula           | EGD                                   | no  | 0.5                      |
| Lin, T.L. et al. [10]   | NA                                                                                     | direct invasion          | EGD, CT                                                                       | ulcerative tumor  | resected specimen                     | no  | >80                      |
| Tan, W.J. et al. [49]   | melena, hematemesis, abdominal distension, nausea, epigastric pain                    | direct invasion          | EGD, EUS, CT                                                                  | ulcer             | none                                  | no  | N/A                      |
| Sayana, H. et al. [50]  | hematemesis, melena                                                                     | direct invasion          | EGD, CT                                                                       | fistula           | none                                  | no  | alive at six months after diagnosis |
| Okay, E. et al. [51]    | dyspnea, abdominal distension, nausea, vomiting, abdominal pain, fever, weight loss   | direct invasion          | intraoperative diagnosis                                                       | not done          | resected specimen                     | yes | 12                       |
| Inagaki, Y. et al. [52] | hematemesis                                                                           | hematogenous             | EGD, CT                                                                       | polyoid lesions   | autopsy                               | no  | alive at twelve-month follow-up |
| Wu, W.D. et al. [53]    | GI bleeding                                                                            | direct invasion          | EGD, MRI                                                                      | mass mimicking    | resected specimen                     | yes | alive at twelve-month follow-up |
| Grover, I. et al. [54]  | melena, hematemesis                                                                    | direct invasion          | EGD, CT                                                                       | fistula           | no                                    | no  | N/A                      |
| Li, L. et al. [55]      | melena                                                                                 | translymphatic           | EGD, CT                                                                       | (polypoid) cauliflower like- mass | EGD                 | yes | 4                        |
| Hot, S. et al. [56]     | GI bleeding                                                                            | direct invasion          | EGD, CT                                                                       | ulcerated mass    | resected specimen + EGD               | yes | <1 m                      |
| Haruki, K. et al. [57]  | epigastric pain                                                                        | hematogenous             | EGD, CT, MRI                                                                  | submucosal tumor  | resected specimen                     | no  | alive at thirteen-month follow-up |
| Author                     | Clinical Presentation | Route of Involvement | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|---------------------------|-----------------------|----------------------|-------------------------------------------------------------|-------------------|--------------------------------------|-----|--------------------------|
| Wu, D. et al. [58]        | melena, anemia        | undetermined         | EGD, colonoscopy                                            | N/A               | resected specimen                    | no  | 50                       |
| Abdul Hakim, M.S. et al. [59] | anemia, melena        | hematogenous         | EGD                                                         | fungating, nodular mass | EGD | yes | 1                       |
| Peng, L. et al. [60]      | hepatalgia, asthenia  | undetermined *       | EGD, CT                                                     | protrusion like stromal tumor | resected specimen | yes | alive at six-month follow-up |
| Kasi, M. et al. [61]      | anemia                | needle track seeding (EUS) | EGD, MRI, PET-CT                                            | polypoid, ulcerated mass | EGD + resected specimen | yes | N/A                      |
| Sakumura, M. et al. [62]  | anemia, leg numbness  | hematogenous         | EGD                                                         | polyp             | EGD | yes | N/A                      |
| Bale, A. et al. [63]      | upper GI bleeding     | undetermined         | EGD, CT                                                     | fistula           | none | no  | N/A                      |
| Imai, M. et al. [64]      | anemia                | hematogenous         | EGD                                                         | elevated lesion   | EGD | yes | 5                       |
| Marques da Costa, P. et al. [65] | abdominal pain, melena | direct invasion     | EGD, CT                                                     | lobulated mass    | EGD | yes | <1 (0.75)                |
| Kim, R. et al. [66]       | dyspnea, melena       | hematogenous         | EGD, CT, colonoscopy                                         | fungating mass-stomach, ulcerofungating tumor—ascending colon | EGD + colonoscopy+ surgical resection | yes | 1.5                      |
| Abouzied, M.M. et al. [67] | weakness, anemia      | probably hematogenous | MRI, EGD, PET-CT                                            | polyps            | EGD | no  | alive at 15-month follow-up |
| Eskarous, H. et al. [68]  | dysphagia             | N/A                  | EGD                                                         | polyps            | EGD | yes | N/A                      |
| Chen, L.T. et al. [6]     | nausea, vomiting, fecal occult blood test+ | direct invasion | EGD                                                         | polypoid (cauliflower tumor) | EGD | no  | <1 (0.75)                |
|                           | melena                | direct invasion      | EGD, celiac angiography, CT                                 | ulcerated, submucosal tumor | none | no  | 1                       |
|                           | epigastric pain, fecal occult blood test+ | direct invasion | EGD, UGI series,                                            | penetrating ulcer | none | no  | 4                       |
|                           | melena                | direct invasion      | EGD, CT, UGI series                                        | polypoid (cauliflower tumor) | EGD | no  | 2                       |
| Arima, K. et al. [69]     | hematemesis, melena   | hematogenous         | EGD                                                         | Bormann 2 type elevation with large tumor | EGD + autopsy | no  | 17                      |
| Moriura, S. et al. [70]   | anemia                | direct invasion      | EGD, UGI series                                             | ulcer             | EGD + resected specimen | no  | alive at 22-month follow-up |
|                           |                       |                      |                                                             |                   |                                     |     |                          |
| Author                          | Clinical Presentation          | Route of Involvement | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|--------------------------------|--------------------------------|----------------------|-----------------------------------------------------------|------------------|---------------------------------------|-----|-------------------------|
| Okusaka, T. et al. [71]         | GI bleeding, abdominal pain    | direct invasion      | autopsy                                                    | duodenum not analysed at EGD | autopsy | no     | post-mortem diagnosis  |
| Hung, H.-C. et al. [72]         | abdominal pain, tarry stools   | direct invasion      | EGD, CT                                                    | ulcerative mass  | EGD                                  | no  | 6                       |
| Farell, R. et al. [73]          | GI bleeding, lethargy          | direct invasion      | EGD, EUS                                                  | persistent nodular ulcer | EGD-not suggestive | no  | N/A                     |
| Srivastava, D.N. et al. [41]    | GI bleeding                    | direct invasion      | EGD                                                        | ulcerative mass  | EGD                                  | no  | 2                       |
| Lin, C.P. et al. [7]            | RUQ pain, fecal occult blood test+ | direct invasion  | hematogenous                                               | ulcerative tumor | EGD                                  | no  | 2.2                     |
| Del Natale, M. et al. [74]      | abdominal pain, asthenia, dyspnea, anemia | direct invasion | CT                                                        | not done         | none                                 | no  | 1.5                     |
| Cho, A. et al. [75]             | palpable abdominal tumor, vomiting | direct invasion | CT, EGD                                                   | submucosal tumor | resected specimen                    | no  | N/A                     |
| Ohnishi, S. et al. [76]         | hematemesis                    | direct invasion      | CT, EGD, UGI series                                        | obstruction by the invading tumor | autopsy | no     | 2                       |
| Uehara, K. et al. [77]          | no symptoms described          | compression of a lymph node metastasis | CT, upper roentgenography                                   | normal duodenal mucosa | none                                 | no  | Alive—no signs of recurrence at 22-month follow-up |
| Chung, C. et al. [78]           | melena, abdominal pain         | undetermined *       | EGD                                                        | ulcerative tumor + nodule resembling liver parenchyma | EGD | yes | 7                       |
| Kurtz, L.E. et al. [79]         | melena, anemia                 | direct invasion      | EGD, CT                                                    | infiltrating mass | none                                 | no  | N/A                     |
| Kato, Y. et al. [11]            | painful epigastric mass        | direct invasion      | UGI series                                                 | not done         | resected specimen                     | yes | 8                       |
| Liang, J.D. et al. [80]         | GI bleeding-17, abdominal pain-2, anemia-1 | direct invasion-14; undetermined-1; metastases-6; (hematogeneous/translymphatic-5; peritoneal spreading-1) | CT-4; EGD-4; intraoperative diagnosis-1; CT + EGD-12; UGI series-2 | ulceration-13; tumor mass-10; fistula-1 | EGD-2; resected specimen-7; none-12 | no  | mean 10.5               |
Table 2. Cont.

| Author            | Clinical Presentation | Route of Involvement | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|-------------------|-----------------------|----------------------|------------------------------------------------------------|-------------------|--------------------------------------|-----|--------------------------|
| Lin, T.L. et al. [10] | tarry stools          | direct invasion      | CT, EGD                                                     | ulcerative mass   | resected specimen                    | no  | >68                      |
| Kim, J.N. et al. [81] | melena, dyspnea       | direct invasion      | CT, EGD                                                     | protrusive mass   | EGD                                  | no  | 3                        |
| Sauer, B.G. et al. [82] | GI bleeding, nausea, vomiting | direct invasion      | EGD, CT                                                     | large mass (liver) penetrating the pyloric channel causing gastric obstruction | EGD | yes | 1                        |
| Arima, K. et al. [83] | N/A                  | hematogenous         | CTHA, CTAP                                                  | not done          | resected specimen                    | no  | N/A                      |
| Kashani, A. et al. [84] | fatigue, GI bleeding | spread of HCC tumoral cells after biliary interventions | EGD, MRI         | peripartum mass | EGD                                  | yes | few months               |
| Lin, I.C. et al. [85] | melena                | direct invasion      | EGD, CT                                                     | mass              | EGD                                  | no  | N/A                      |
| Ito, T. et al. [86] | anemia                | direct invasion      | EGD, CT                                                     | ulcerative lesion | EGD + resected specimen             | no  | alive at three-year follow-up |
| Liu, Y.H. et al. [87] | hematemesis, tarry stools | direct invasion      | EGD, CT                                                     | ulcer             | resected specimen                    | no  | alive at seven-year follow-up |
| Wu, Y.H. et al. [88] | tarry stools          | direct invasion      | EGD, EUS                                                    | ulcerative mass   | EGD                                  | yes | N/A                      |
| Bonboire, R. et al. [34] | melena               | direct invasion      | EGD, abdominal arteriography, CT                           | submucosal mass   | no                                   | no  | 6                        |
| Sawada, K. et al. [89] | hematemesis          | direct invasion      | EGD, CT                                                     | ulcer-ulcerative lesion-submucosal tumor-like ulcer | EGD | yes | 7.5                      |
| Lee, Y.J. et al. [90] | nausea, vomiting, dysphagia | direct invasion-4 translymphatic-extraluminal compression due to metastatic lymph nodes/3 | EGD               | ulcerative mass-4 submucosal tumor-3 | N/A | N/A | <2 months               |
| Tsujimoto, M. et al. [91] | abdominal pain, vomiting, abdominal fullness | hematogenous         | autopsy                                                     | not done          | autopsy                              | yes | post-mortem diagnosis     |
| Chen, L.T. et al. [6] | melena                | hematogenous         | superior mesenteric angiography                             | not done          | laparotomy                           | no  | 0.5                      |
| Narita, T. et al. [92] | N/A                   | hematogenous         | autopsy                                                     | not done          | autopsy                              | no  | post-mortem diagnosis     |
| Tanaka, A. et al. [93] | increased AFP, palpable mass | peritoneal spread    | intraoperative diagnosis                                    | not done          | resected specimen                    | no  | 15                       |
Table 2. Cont.

| Author           | Clinical Presentation          | Route of Involvement | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|------------------|--------------------------------|----------------------|------------------------------------------------------------|-------------------|---------------------------------------|-----|--------------------------|
| Byun, J.R. et al. [94] | dysuria, fecaluria            | peritoneal spread    | CT, barium study                                           | not done          | resected specimen                     | no  | N/A                      |
| Kim, H.S. et al. [95]  | abdominal pain, nausea, vomiting | hematogenous         | CT, US, intraoperative diagnosis                           | not done          | resected specimen                     | yes | N/A                      |
| Iwaki, K. et al. [96]   | asymptomatic                  | hematogenous         | intraoperative diagnosis                                   | not done          | resected specimen                     | yes | alive at twenty-one months |
| Choi, J.H. et al. [97]  | abdominal pain, abdominal distension | hematogenous         | intraoperative diagnosis                                   | not done          | resected specimen                     | no  | 1                        |
| Kunizaki, M. et al. [98] | fatigue, anemia, melena       | hematogenous         | double-balloon enteroscopy                                  | protruding lesion | double balloon enteroscopy + resected specimen | yes | N/A                      |
| Igawa, A. et al. [99]  | melena, anemia                | hematogenous         | capsule endoscopy, double-balloon enteroscopy              | polypoid lesion   | double-balloon enteroscopy             | yes | 2                        |
| Kanazawa, M. et al. [100] | melena, light-headedness      | undetermined         | capsule endoscopy, double-balloon enteroscopy              | mass lesion       | double-balloon enteroscopy             | yes | 0.5                      |
| Shelat, V.G. et al. [101] | abdominal pain, vomiting, diarrhea | peritoneal spreading | CT                                                          | not done          | resected specimen                     | yes | alive at eight-month follow-up |
| Sun, W.C. et al. [102]  | melena                         | metastasis ***       | single balloon retrograde enteroscopy                      | protrusive mass   | single-balloon enteroscopy             | no  | N/A                      |
| Mashiko, T. et al. [103] | abdominal pain, vomiting      | hematogenous         | CT                                                          | not done          | resected specimen                     | yes | alive at eighty-two-month follow-up |
| Suzuki, N. et al. [104] | abdominal pain                | hematogenous         | intraoperative diagnosis                                   | not done          | resected specimen                     | no  | alive at two-month follow-up |
| Fukui, H. et al. [105]  | asymptomatic                  | possible hematogenous | CT, colonoscopy, scintigraphy Tc-99 MPT                    | elevated lesion   | colonoscopy                           | no  | N/A                      |
| Hashimoto, M. et al. [16] | melena                        | direct invasion      | colonoscopy, lower GI series superior mesenteric angiography | ulcerations       | colonoscopy + resected specimen       | no  | N/A                      |
| Cosenza, C.A. et al. [106] | weakness, fatigue, rectorrhagia | duodenum-direct invasion, colon-hematogenous | colonoscopy, lower GI series polypoid mass | colonoscopy       | no                                    | N/A |
| Srivastava, D.N. et al. [41] | bloody stools                 | direct invasion      | angio-CT                                                    | not done          | none                                  | no  | 0.75                     |
| Author                  | Clinical Presentation                  | Route of Involvement   | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect          | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|-------------------------|---------------------------------------|------------------------|----------------------------------------------------------|----------------------------|---------------------------------------|-----|--------------------------|
| Lin, C.P. et al. [7]    | bloody stools                         | direct invasion        | colonoscopy, CT                                          | polypod tumor              | colonoscopy                           | no  | 1.2                      |
| Lin, C.P. et al. [7]    | epigastric pain, fecal occult blood test+ | direct invasion       | CT, superior mesenteric angiography                      | not done                   | none                                  | no  | 4.7                      |
| Lin, C.P. et al. [7]    | bloody stools                         | direct invasion        | CT, superior mesenteric angiography                      | not seen                   | none                                  | no  | 4                       |
| Kurachi, K. et al. [107] | epigastric discomfort                | peritoneal spread      | intraoperative diagnosis                                  | not done                   | resected specimen                      | no  | alive at five-year-and-nine-month follow-up |
| Zech, C.J. et al. [108] | abdominal pain, fever, hemorrhagic diarrhea | direct invasion | CT, colonoscopy                                         | inflammatory mucosal lesions | resected specimen                    | no  | N/A                      |
| Tapuria, N. et al. [109] | rectorrhagia, anemia               | hematogenous           | CT, colonoscopy                                         | obstructing tumor          | colonoscopy                            | yes | few months               |
| Kailbori, M. et al. [110] | melena                               | metastasis ***         | intraoperative diagnosis                                  | not done                   | resected specimen                      | no  | 5                       |
| Ng, D.S.C. et al. [111] | rectorrhagia                         | hematogenous           | colonoscopy                                             | fungating tumor            | colonoscopy + resected specimen        | no  | alive at more than five years |
| Hirashita, T. et al. [112] | epigastric pain                     | direct invasion        | CT                                                       | not done                   | resected specimen                      | no  | 6                       |
| Nozaki, Y. et al. [113] | abdominal pain, hematochezia         | direct invasion        | colonoscopy, CT                                         | lobulated tumor            | resected specimen                      | no  | 1                       |
| Yoo, D.J. et al. [114]  | abdominal pain, hematochezia         | metastasis ***         | colonoscopy                                             | erosive tumor lesion       | colonoscopy                            | no  | alive at four-month follow-up |
| Huang, S.F. et al. [115] | bloody stools                        | hematogenous           | colonoscopy, CT                                         | bulging mass               | resected specimen                      | yes | N/A                      |
| Shih, Y.J. et al. [116] | abdominal pain, fever                | hematogenous           | CT                                                       | soft-tissue-like lesion    | resected specimen                      | yes | 6                       |
| Haga, Y. et al. [117]   | abdominal pain, vomiting             | peritoneal spreading   | CT                                                       | not seen                   | resected specimen                      | no  | N/A                      |
| Sun, L.H. et al. [118]  | abdominal pain                        | hematogenous           | CT                                                       | not done                   | resected specimen                      | yes | 8                       |
| Imada, S. et al. [119]  | asymptomatic                          | hematogenous           | US, CT, MRI, CT, PET-CT                                  | normal aspect              | resected specimen                      | yes | alive at 20-month follow-up |
| Ou, T.M. et al. [120]   | tenesmus                              | hematogenous           | colonoscopy                                             | polyps                     | resected specimen                      | no  | 1                       |
| Kohli, R. et al. [121]  | hematochezia                          | hematogenous           | colonoscopy                                             | friable, necrotic lesion   | colonoscopy                            | no  | N/A                      |
Table 2. Cont.

| Author                  | Clinical Presentation                                      | Route of Involvement | Imagistic Methods Used for the Diagnosis of GI Involvement | Endoscopic Aspect | Method of Histopathological Diagnosis | IHC | Survival Period (Months) |
|-------------------------|-----------------------------------------------------------|----------------------|------------------------------------------------------------|-------------------|---------------------------------------|-----|--------------------------|
| Zhu, X. et al. [122]    | fecal occult blood test+                                  | hematogenous         | colonoscopy                                                | mass              | resected specimen                     | yes | 12                       |
| Mitsialis, V. et al. [123] | abdominal pain, diarrhea, hematochezia                  | hematogenous         | colonoscopy                                                | ulceration        | resected specimen                     | no  | N/A                      |
| Repullo, D. et al. [124] | abdominal pain, fever, weight loss                       | direct invasion      | colonoscopy, CT                                            | mass              | resected specimen                     | no  | N/A                      |
| Tagliabue, F. et al. [125] | GI bleeding                                              | hematogenous         | colonoscopy, CT                                            | mass              | resected specimen                     | yes | N/A                      |
| Pham, B.V. et al. [126] | tenesmus, abdominal pain                                  | hematogenous         | colonoscopy, CT                                            | mass              | resected specimen                     | yes | N/A                      |
| Soni, A. et al. [127]   | rectorrhagia, anemia                                      | direct invasion      | colonoscopy, CT                                            | ulcerated lesion  | colonoscopy                           | no  | at diagnosis              |
| YU, Y.M. et al. [13]    | hematochezia                                              | hematogenous         | colonoscopy, CT                                            | protuberant mass  | resected specimen                     | yes | alive at three-month follow-up |
| Mu, M. et al. [14]      | abdominal pain, nausea, vomiting                         | direct invasion      | MRI                                                        | not seen          | resected specimen                     | no  | 10                       |
| Miyauchi, T. et al. [128]| abdominal pain, fever                                    | hematogenous         | CT                                                         | not done          | resected specimen                     | no  | 30                       |
| Park, M.S. et al. [8]   | GI bleeding-3; lower GI bleeding-1; epigastric discomfort (pain, nausea, vomiting)-9; palpable mass-5 | direct invasion-12; hematogenous-3; undetermined-2; peritoneal spreading-1 | CT-13, CT + UGI series-5, endoscopy = 13 | N/A                  | EGD-13; resected specimen-5 | no  | lost to follow up-12 patients; 2 months-3 patients; alive-3 patients. |
| Liu, K.W. et al. [129]  | tenesmus                                                  | direct seeding after RFA | CT                                                          | not seen          | resected specimen                     | yes | 19                       |
| Nielsen, J.A. et al. [130] | abdominal pain, diarrhea                                | hematogenous         | colonoscopy                                                | mass              | colonoscopy                           | yes | N/A                      |
| Ikeda, A. et al. [131]  | bloody stools                                             | hematogenous         | colonoscopy, lower GI series, CT                           | protruding tumor  | resected specimen, colonoscopy-not conclusive | yes | 5                        |

HCC: hepatocellular carcinoma; N/A: not available; RUQ: right upper quadrant; LUQ: left upper quadrant; GI: gastroenterology; CT: computed tomography; EGD: esophagogastroduodenoscopy; IHC: immunohistochemistry; UGI series: upper gastrointestinal series; US: ultrasound; EUS: endoscopic ultrasound; EUS-FNA: endoscopic ultrasound-fine needle aspiration; PET-CT: positron emission tomography-computed tomography; MRI: magnetic resonance imaging; CTHA: computed tomography angiography; CTAP: computed tomography arterial portography; Tc-99 m: technetium-99 m; PMT: pyridoxyl-5-methyltryptophan. * possible hematogenous. ** surveillance post-liver transplant. *** the specific route of metastasis was not clarified.
Table 3. Etiology of liver disease in patients with hepatocellular carcinoma.

| Risk Factor | n (%)                  |
|-------------|------------------------|
| HBV         | 76 (38.57%)            |
| HCV         | 35 (17.76%)            |
| Alcohol     | 15 (7.61%)             |
| HBV + HCV   | 4 (2.03%)              |
| HBV, Alcohol| 3 (1.52%)              |
| HCV, Alcohol| 1 (0.50%)              |
| HBV + HCV + HVD + Alcohol | 1 (0.50%) |
| NAFLD       | 1 (0.50%)              |
| Autoimmune  | 1 (0.50%)              |
| Cryptogenic | 2 (1.01%)              |
| Unknown     | 19 (9.64%)             |
| Not specified| 39 (23.35%)            |

HBV: hepatitis B virus; HCV: hepatitis C virus; HVD: hepatitis D virus; NAFLD: non-alcoholic fatty liver disease.

3.4. Clinical Findings in the Study Population

A summary of the clinical characteristics of the study population is described in Table 4. Most HCCs were bulky masses, with an average tumor size of 8.66 cm ($n = 92$ hepatic nodules). Liver tumor localization was described in 158 patients. Four patients did not have any tumor recurrence at the moment of diagnosis. Hepatocellular carcinoma was located as follows: right hepatic lobe (31.47%), left hepatic lobe (21.82%), both hepatic lobes (19.28%), caudate lobe (2.03%), hepatic hilum (1.01%), peritoneum (1.01%), left hepatic lobe and caudate lobe (0.50%), right hepatic lobe and caudate lobe (0.50%) and lymph nodes (0.50%). Portal vein thrombosis was found in 27.91% (55/197) of the evaluated cases. Regarding the tumoral markers, the mean value of serum AFP was 15,366.18 ng/mL ($n = 112$ available data, 14 patients were reported as having a normal value).

Table 4. Summary of clinical characteristics of study patients.

| Localization of HCC ($n = 158$) | [Mean ± SD] $8.66 ± 6.22$ cm |
|----------------------------------|-----------------------------|
| RHL                              | 62 (31.47%)                 |
| LHL                              | 43 (21.82%)                 |
| LHL, RHL                         | 38 (19.28%)                 |
| Caudate lobe                     | 4 (2.03%)                   |
| Peritoneum                       | 2 (1.01%)                   |
| Lymph nodes                      | 1 (0.50%)                   |
| LHL, caudate lobe                | 1 (0.50%)                   |
| RHL, caudate lobe                | 1 (0.50%)                   |
| Hepatic hilum                    | 2 (1.01%)                   |
| No tumor recurrence              | 4 (2.03%)                   |
| Portal vein thrombosis           |                             |
| Present                          | 55 (27.91%)                 |
| Absent                           | 109 (55.32%)                |
| Not available                    | 33 (16.75%)                 |
| AFP                              | Mean = 15,366.18 ng/mL      |

RHL: right hepatic lobe; LHL: left hepatic lobe; AFP: alfa-fetoprotein.

3.5. Previous Treatment for Hepatocellular Carcinoma

Information on prior therapy for HCC is supplied in detail below in Table 5. The percentage of patients who did not receive any specific therapy was 26.90% (53/197). A relatively high number of patients were treated with TACE (32.99%, 65/197) and surgical resection (28.93%; 57/197). Among locoregional therapies, TACE was followed by: transarterial embolization (TAE) (23/197; 11.67%), radiofrequency ablation (RFA) (10.15%, 20/197), percutaneous ethanol injection (PEI) (14/197, 7.10%) and intra-arterial chemother-
apy (4/197, 2.39%). Liver transplant was performed in 5.58% of included patients. Molecular targeted therapies and systemic chemotherapy were administered to 4.56% and 5.58% of the patients, respectively. Less commonly used treatment methods were yttrium-90 radioembolization, hepatic arterial ligation, cryoablation, immunotherapy, radiotherapy and ultrasound-guided percutaneous microwave ablation.

Table 5. Previous treatment of HCC.

| Methods of Treatment                              | n (%)  |
|--------------------------------------------------|--------|
| TACE                                             | 65 (32.99%) |
| Surgical resection                               | 57 (28.93%) |
| TAE                                              | 23 (11.67%) |
| Radiofrequency ablation                          | 20 (10.15%) |
| Liver transplant                                 | 11 (5.58%) |
| Systemic chemotherapy                            | 11 (5.58%) |
| Targeted molecular therapies                     | 9 (4.56%)  |
| Percutaneous ethanol injection                   | 14 (7.10%) |
| Radiotherapy                                     | 8 (4.06%) |
| Intra-arterial chemotherapy                      | 4 (2.03%) |
| Immunotherapy                                    | 1 (0.50%)  |
| Yttrium-90 radioembolization                     | 1 (0.50%) |
| Hepatic arterial ligation                        | 1 (0.50%) |
| Ultrasound guided percutaneous microwave ablation| 1 (0.50%) |
| Crioablation                                     | 1 (0.50%) |
| None                                             | 53 (26.90%) |
| N/A                                              | 7 (3.55%) |

TACE: transarterial chemoembolization; TAE: transarterial embolization; N/A: not available.

3.6. Involved GI Site and Presumed Mode of Involvement

The most commonly involved sites in the gastrointestinal tract were the stomach (55/197; 27.91%) and duodenum (55/197; 27.91%), followed by colon (32/197, 16.24%), esophagus (18/197; 8.92%), jejunum and ileum (14/197; 9.13%), and rectum (3/197; 1.52%). Synchronous localization occurred in 9.64% of patients. The sites with concomitant involvement were: stomach and esophagus, stomach and duodenum, stomach and colon, stomach and small bowel, duodenum and colon and rectum and colon. Our study suggested that in most cases, GI involvement occurred through direct invasion (87/197; 44.16%). HCC metastasized through the hematogeneous route in 31.97% of situations (63/197). Translymphatic dissemination was reported for 3.04% (6/197); meanwhile, peritoneal spreading was found in 3.55% of patients (7/197). We also detected three cases of iatrogenically induced metastases. Moreover, both direct invasion and hematogenous spread were considered in two patients with concomitant duodenal and colon involvement and esophagus and stomach involvement, respectively. Details of the segments of the GI tract involved and the routes of involvement are listed in Table 6.

3.7. Clinical Presentation

GI bleeding was the most common clinical presentation (49.74%), followed by abdominal pain (26.90%), nausea and vomiting (14.72%), fecal occult blood+ (4.06%), palpable abdominal mass (3.55%) and anemia (5.07%). Among the included patients, only 2.03% of them were asymptomatic. Other less frequent clinical characteristics are summarized in Table 7.
Table 6. Involved GI site and involvement route.

| GI Site Involved by HCC (n = 197) | n (%) |
|-----------------------------------|-------|
| Stomach                           | 55 (27.91%) |
| Duodenum                          | 55 (27.91%) |
| Colon                             | 32 (16.24%) |
| Esophagus                         | 18 (8.92%)  |
| Small bowel                       | 14 (9.13%)  |
| Esophagus + Stomach               | 2 (1.01%)   |
| Stomach + colon                   | 4 (2.03%)   |
| Stomach + duodenum                | 7 (3.55%)   |
| Stomach + small bowel             | 2 (1.01%)   |
| Duodenum + Colon                  | 3 (1.52%)   |
| Rectum                            | 3 (1.52%)   |
| Rectosigmoid                      | 1 (0.50%)   |
| Rectum and colon                  | 1 (0.50%)   |

**Involvement route**

| Involvement route                  | n (%) |
|-----------------------------------|-------|
| Direct invasion                   | 87 (44.16%) |
| Hematogenous route                | 63 (31.97%) |
| Translymphatic route              | 6 (3.04%) |
| Peritoneal spreading              | 7 (3.55%) |
| Iatrogenic                        | 3 (1.52%) |
| Direct invasion + Hematogenous route | 2 (1.19%) |
| Hematogenous + translymphatic route | 1 (0.50%) |
| Metastasis (hematogenous or translymphatic) | 17 (8.62%) |
| Undetermined                      | 9 (4.56%) |
| N/A                               | 2 (1.19%) |

Table 7. Clinical features of included patients.

| Symptom                          | n (%) |
|----------------------------------|-------|
| GI bleeding                      | 98 (49.74%) |
| Abdominal pain                   | 53 (26.90%) |
| Nausea/Vomiting                  | 29 (14.72%) |
| Dysphagia                        | 15 (7.61%) |
| Anemia                           | 10 (5.07%) |
| Fecal occult blood+              | 8 (4.06%) |
| Gastrointestinal outlet obstruction | 8 (0.50%) |
| Palpable abdominal mass          | 7 (3.55%) |
| Weight loss                      | 5 (2.53%) |
| Dyspnea                          | 5 (2.53%) |
| Abdominal distension             | 5 (2.53%) |
| Fever                            | 5 (2.53%) |
| Fatigue                          | 4 (2.03%) |
| Diarrhea                         | 4 (2.03%) |
| Abdominal fulness                | 2 (1.01%) |
| Tenesmus                         | 2 (1.01%) |
| Anorexia                         | 1 (0.50%) |
| Anasarca                         | 1 (0.50%) |
| Syncope                          | 1 (0.50%) |
| Dizziness                        | 1 (0.50%) |
| Asymptomatic                     | 4 (2.03%) |
| Not available                     | 11 (5.58%) |

3.8. Diagnosis of GI Lesions

The most frequently used diagnostic tools were upper GI endoscopy (112/197; 56.86%) and CT (112/197; 56.86%), followed by colonoscopy (24/197; 12.18%), upper GI series (18/197; 9.13%) and endoscopic ultrasound (EUS) (9/197; 4.56%). Other less frequent diagnostic methods were: magnetic resonance imaging (MRI) (7/197; 3.55%), positron emission tomography-computed tomography (PET-CT) (6/197; 3.04%), double/single-balloon...
enteroscopy (5/197; 2.53%), superior mesenteric angiography (4/197; 2.03%), lower GI series (3/197; 1.52%), angio-CT (3/197; 1.52%), capsule endoscopy (2/197; 1.01%), scintigraphy TC-99 pyridoxyl-5-methyltryptophan (PMT) (1/197; 0.50) and celiac angiography (1/97; 0.50%). In 15 patients, the diagnosis was made either intraoperatively (9/168, 4.56%) or at autopsy (6/197; 3.04%). The full palette of the combination of diagnostic tools used is summarized in Table 8.

Table 8. Palette of diagnostic tools used for GI lesion.

| Diagnostics Tools                                                                 | n (%)       |
|----------------------------------------------------------------------------------|-------------|
| Upper GI endoscopy                                                              | 47 (23.85%) |
| Upper GI endoscopy, CT                                                           | 55 (27.91%) |
| CT                                                                               | 13 (6.59%)  |
| Lower GI endoscopy, CT                                                           | 10 (5.07%)  |
| Lower GI endoscopy                                                              | 8 (4.06%)   |
| CT, upper GI series                                                              | 7 (3.55%)   |
| Upper GI endoscopy, CT, upper GI series                                          | 5 (2.53%)   |
| Upper GI endoscopy, EUS                                                          | 4 (2.03%)   |
| Upper GI series                                                                  | 4 (2.03%)   |
| Double balloon/single balloon enteroscopy                                        | 3 (1.52%)   |
| CT, superior mesenteric angiography                                              | 2 (1.01%)   |
| Capsule endoscopy + double balloon enteroscopy                                  | 2 (1.01%)   |
| Upper GI endoscopy, MRI, PET-CT                                                  | 2 (1.01%)   |
| Lower GI endoscopy, lower GI series                                              | 2 (1.01%)   |
| Upper GI endoscopy, EUS, CT                                                      | 2 (1.01%)   |
| Upper GI endoscopy, MRI                                                          | 2 (1.01%)   |
| Upper GI endoscopy, upper GI series                                              | 2 (1.01%)   |
| Upper GI series, upper GI endoscopy, EUS, CT, PET-CT                             | 1 (0.50%)   |
| EUS, PET-CT                                                                      | 1 (0.50%)   |
| Upper GI endoscopy, MRI, CT                                                      | 1 (0.50%)   |
| MRI                                                                              | 1 (0.50%)   |
| Upper GI endoscopy, lower GI endoscopy, CT                                       | 1 (0.50%)   |
| Upper GI endoscopy, lower GI endoscopy                                           | 1 (0.50%)   |
| Upper GI endoscopy, celiac angiography, CT                                       | 1 (0.50%)   |
| Upper GI endoscopy, CTA                                                           | 1 (0.50%)   |
| CT, CTA                                                                          | 1 (0.50%)   |
| CTA                                                                              | 1 (0.50%)   |
| CT, lower GI endoscopy + Tc-99 m PMT Scintigraphy                               | 1 (0.50%)   |
| CT, lower GI endoscopy, lower GI series                                         | 1 (0.50%)   |
| Lower GI endoscopy, lower GI series, superior mesenteric angiography             | 1 (0.50%)   |
| Superior mesenteric angiography                                                   | 1 (0.50%)   |

GI: gastroenterology; CT: computed tomography; EUS: endoscopic ultrasound; PET-CT: positron emission tomography-computed tomography; MRI: magnetic resonance imaging; CTA: computed tomography angiography; Tc-99 m: technetium-99 m; PMT: pyridoxyl-5-methyltryptophan.

Endoscopic features of GI lesions are listed in Table 2. GI endoscopic procedures were used for diagnosis in 86.78% of cases (169/197). Detailed descriptions of the endoscopic aspect of the GI lesions were related in 84.61% (143/169). In two cases there was no endoscopic evidence of GI lesions. The most common endoscopic findings were: exophytic mass (15.73%), polypoid lesions (14.72%), ulcerative lesions (14.21%), submucosal tumor (8.62%), ulcer (5.58%), fistula (2.53%) and extrinsic compression (1.52%). Non-specific aspects (ulcerations, erosions etc.) were seen in 9.64% of cases.

Specimens for pathological diagnosis (n = 159) were obtained through endoscopic biopsies (76/197; 38.57%), surgical intervention (61/197; 30.96%), endoscopic biopsies and resected specimens (10/197, 5.07%), endoscopic ultrasound-fine needle aspiration (1/197; 0.50%) and autopsy (11/197; 5.58%). The diagnosis was not confirmed through histopathology in 15.22% of cases (30/197). Immunohistochemistry techniques were used in 26.39% of patients (52/197).
3.9. Prognosis of Gastrointestinal Involvement in Patients with HCC

Prognosis of patients with hepatocellular carcinoma and GI tract involvement (n = 158 available data; from which 12 were lost to follow-up) was dismal, with an average survival of 7.30 months. In 3.04% of cases (6/197), the diagnosis was made post-mortem at autopsy, and 1.01% (2/197) survived for less than 24 h. In the present study, only 14.72% (29/197) were still alive at the moment of the last follow-up.

4. Discussion

Hepatocellular carcinoma yields high recurrence rates, even after radical resection. Liver transplantation is the best treatment method because it also cures the underlying liver disease, but it is not broadly applicable [132]. However, other available therapeutic approaches, such as locoregional therapies, have been developed with the purpose of increasing the survival rate in patients with unresectable HCC [133]. Improvements in the survival period are associated with a higher risk of developing extrahepatic metastases. Among them, gastrointestinal involvement from hepatocellular carcinoma is rare [118].

In our study, both stomach and duodenum were the areas of the GI tract most frequently affected. In reviews reported in literature, the stomach was most commonly involved, followed by duodenum [10]. On the other side, esophagus metastases were very uncommon in our analysis, accounting for less than 9% of cases. Sites of the lower part of the gastrointestinal tract, such as the colon, jejunum, ileum and rectum were also less affected. In exceptional cases, a liver tumor can simultaneously involve more than one segment of the GI tract [7,51,58,65,66,80].

As in most reports, direct invasion was the predominant spread pattern. Factors favoring GI involvement were growth mode, size and localization of hepatic tumors [14]. Due to the anatomical relationship between the liver and GI tract segments, HCCs localized in the right hepatic lobe tend to invade the duodenum, and those located in the left lobe usually involve the stomach [84]. The role of TACE is controversial. TACE can induce tumor adherence to the liver capsule and GI tract through necrosis and inflammation. On the other hand, HCC was diagnosed concomitant with the GI invasion in many cases, and these patients had not received any previous treatment [14]. In our analysis, TACE was previously performed in 32.99% of cases, and 26.90% did not receive any treatment.

The hematogenous route was the second most frequent path. Although it can be detected in liver cirrhosis, reverse portal flow is more frequently observed in primary hepatocellular carcinoma due to arteriovenous communications and arterial neovascularization [134]. Tumor emboli can be disseminated from the liver to the gastrointestinal tract by the hepatofugal portal flow [131]. Portal vein thrombosis is also a significant contributing element that can exacerbate the reversal of the flow [119]. This aspect is supported by the fact that 27.91% of the assessed cases in our study presented portal vein thrombosis. It is hypothesized that endoscopic therapy of esophageal varices, in particular esophageal band ligation, can promote the development of esophageal metastasis by trapping the tumoral thrombi [31]. Hiraoka, T. et al. (1986) presented two cases of hepatocellular carcinoma with invasion of the portal vein branches, in which microscopic tumoral thrombi were found in sclerosed esophageal varices [20]. Kume, K. et al. also presented a case of HCC metastases developed at the place of variceal band ligation [21].

In our review of the literature, GI tract involvement in HCC was also reported to develop after liver transplant [25,28,29,32,41,55,121]. The risk of developing uncommon metastases of HCC, including gastrointestinal metastases, can increase after a liver transplant due to a delicate physiological state or to the administration of immunosuppressive agents [32].

In exceptional cases, dissemination of tumor cells through needle track following endoscopic ultrasound-fine needle aspiration (EUS-FNA) performed for the confirmation of HCC has also been described [61]. Moreover, periampullary metastasis from HCC has been reported after biliary interventions in a patient with HCC invaded in the biliary tract [84].
Several authors also reported GI tract involvement from peritoneal spreading or lymph node metastases [8,43,55,77,80,93,101,117].

Gastrointestinal bleeding, either frank or occult, was the most common presenting feature among the studied cases. Similarly to our results, in an analysis of 30 cases with direct GI involvement from HCC, reported in the English literature, Korkolis, D.P. et al. (2009) also concluded that gastrointestinal bleeding was the main clinical presentation [46]. Besides GI bleeding, the spectrum of clinical manifestations was vast in our study results. It included abdominal pain, palpable mass, chronic anemia, dysphagia, fatigue, weight loss, nausea, vomiting, diarrhea and gastric outlet obstruction.

Algorithm of Diagnosis

On the basis of data found in the literature and the results of our research, we propose a diagnostic algorithm (Figure 2).

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**Figure 2.** Algorithm for diagnosis of GI tract involvement from HCC. HCC: hepatocellular carcinoma; GI: gastrointestinal; CT: computed tomography; PVT: portal vein thrombosis; IHC: immunohistochemistry; EUS: endoscopic ultrasound; EUS-FNA: endoscopic ultrasound-fine needle aspiration; PET-CT: positron emission tomography-computed tomography.
The diagnosis can be extremely challenging and clinicians must be aware of this condition, as early detection and prompt treatment are crucial for a better prognosis. In patients with a known clinical context of cirrhosis and hepatocellular carcinoma, with new-onset gastrointestinal symptoms, especially GI bleeding, gastrointestinal involvement from HCC should be considered as a possible etiology if other common causes are excluded [47,71]. Clinical examination plays a key role in identifying an abdominal mass [100]. In the next stage, risk-factor assessment should be conducted: tumor size, location, growth pattern, presence of portal vein thrombosis and previous locoregional therapies for the primary liver tumor, or even liver transplant and endoscopic therapy for esophageal varices [14,31,32,119]. Endoscopic examination is the standard gold method for identifying GI lesions [7]. As evidenced by the various aspects described, endoscopic features are not specific and can pose differential diagnosis problems. However, the following aspects should draw suspicion in a patient with HCC: polypoid mass, a submucosal tumor/extrinsic compression, ulcerative lesions or even the presence of a fistula [8,48,50,63,80]. The histopathologic examination is mandatory for a certain diagnosis. In some situations where there is uncertainty, investigations should include immunohistochemical tests [7,114,126]. Hepatocyte paraffin-1 (Hep par-1), glypican-3 (GPC-3), arginase-1 and polyclonal carcinoembryonicantigen (pCEA) effectively differentiate GI metastases of HCC from other types of tumors [126]. EUS and EUS-FNA are the alternative diagnostic methods for GI submucosal lesions or for when endoscopy fails to identify the tumor [33]. Radiological investigations are an excellent guidance modality. CT can describe the localization, size and extension of primary liver tumor, the status of the portal vein and lymph nodes, the site of invasion, the contiguity of HCC with the GI tract lesions and the severity of underlying liver cirrhosis, and can also exclude other metastases [8,118]. GI metastases of HCC usually display hyperenhancement in the arterial phase on CT scans, similarly to liver tumors [8]. FDG-PET/CT and angiography can complete the diagnostic workup [6,7,29,32,33,71].

Based on our reviewed articles, the mean survival was 7.30 months. Fujii, K. et al. (2004) evaluated median survival in 29 patients with HCC invading the GI tract. The estimated median survival time was 1.2 months for patients who received supportive treatment, and three months for nonsurgical treatment; meanwhile, patients treated with curative surgery showed an average survival of 9.7 months [9].

Although it may improve the clinical approach of cases with HCC and GI involvement, our study has a number of limitations. Subjectivity in data interpretation, lack of a large control group and the fact that only English-language articles were included are just some of these limitations, and may have influenced the final results.

5. Conclusions

In conclusion, to our knowledge, we are reporting the most extensive systematic review of case reports to date on the involvement of the gastrointestinal tract in HCC. Gastrointestinal involvement in HCC could be included in the differential diagnosis of patients with underlying HCC and gastrointestinal manifestations or pathological findings in EGD.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diagnostics12051270/s1. Table S1: PRISMA 2020 checklist. Table S2: Complete search strategy. Table S3: Methodological quality of included case reports using JBI Critical Appraisal Checklist for case reports. Table S4: Methodological quality of included case reports using JBI Critical Appraisal Checklist for case series. Table S5: Relevant studies excluded from the systematic review.

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