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# Proposal of a Classification System for Adenocarcinoma Involving the Ileocecal Valve (Bauhin's Valve): A Retrospective Study of 689 Right Hemicolectomized Patients

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**Abstract.** *Background/Aim: As of 2020, adenocarcinoma arising in the ileocecal valve (ICV-A) has been examined along with cecal and right colon cancer (RCC) under the collective heading "ileocecal" tumor. We propose a new classification system for this cancer. Patients and Methods: We retrospectively analyzed RCC patients from 2003 to 2019. The scheme was: i) Type I cancer for adenocarcinomas residing in ICV; ii) Type II, if they reside 1 to 5 mm from ICV; iii) Type III, 6 mm to 10 mm from ICV; iv) Type IV, at 1,1 to 5 cm; v) Type V, at more than 5 cm (ascending colon cancer). Results: Of 689 hemicolectomized patients, there were 91 (13.2%) Type I, 87 Type II (12.6%), 38 (5.5%) Type III, 157 (22.8%) Type IV and 314 (45.6%) Type V. Each type was associated with at least one clinicopathologic feature. Conclusion: ICV-A was classified into five types (I-V) according to the distance from ICV. Further studies are needed in order to corroborate our findings.*

Currently, assessing the clinicopathologic and prognostic characteristics of the adenocarcinoma occurring in the ileocecal valve (ICV-A) is a laborious task. This is mainly due to three important reasons. First, as of 2020, compared with cancers arising in other intestinal regions, those arising in ICV-A have been rarely investigated (1, 2). Most studies on colorectal cancers (CRCs), in fact, classified and statistically analyzed cecal, ascending colon and ICV malignancies under the collective heading "ileocecal" tumors: as a consequence, ICV-A real incidence, carcinogenesis and clinical evolution are unknown (2-6). Second, the particularity of ICV structure (which is formed by a duplication of the wall of the small and large bowels) as well as the long-running dispute between the passive *versus* the active nature of its sphincter have always created difficulties in finding a common definition in respect with the anatomy, histology and physiology (7). In this regard, it is noteworthy that information about ICV neuroanatomy is sparse and the myenteric interstitial cells of Cajal network have been examined only in pigs so far (7). Moreover, although unanimously considered an epithelial transitional zone (TZ) in which the small and the large intestinal mucosa merge, there is no agreement on the topographic definition of ICV and, consequently, for ICV-A: tumor epicenter has been described within 5 (1), 4 (8), 2 to 3 (9) or 1 cm (10) of the ICV. Third, ICV-A appears an orphan malignancy since no international guideline on large or small bowel cancer specific cites, regards or includes it (4, 11-14). However, irrespective of the intestinal or colonic custody, prognostic references and the type of surgical resection for ICV-A do not change (12). In this study we compared the clinicopathologic data of ICV-A patients with those of subjects with right colon cancer in order to better assess the anatomic and histopathologic characteristics of ICV-A and designate a classification system for this rare malignancy as accurately as possible.

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*Key Words:* Ileocecal valve, Bauhin's valve, colorectal cancer, small bowel adenocarcinoma.

## Patients and Methods

*Patients.* We retrospectively examined the clinical records of patients with right colon adenocarcinoma who underwent hemicolectomy at St. Andrea Hospital, University Sapienza of

Rome, Italy, from 2003 to 2019. Collection and analysis of data were performed in accordance with the ethical standards described in the Declaration of Helsinki (as revised in Brazil 2013). No other type of primary malignancy but adenocarcinoma of the right colon (also arising in the appendix) was included in the study; metastatic and recurrent cancers were not considered (15). All the adenocarcinomas were related to the distance from the Bauhin's valve following a 5-tier classification system: i) Type I cancer (or true valve cancer) for adenocarcinomas residing in ICV only; ii) Type II (or very close) ICV-A, for tumors residing 1 to 5 mm from ICV; iii) Type III (or close) cancer, residing 6 mm to 10 mm from ICV; iv) Type IV (or distant or peripheral) ICV-A, localized 1,1 to 5 cm from ICV; v) Type V (or very distant) lesions if located at more than 5 cm from ICV (ascending colon cancers). We also combined the close (Type I with II with/without III) and peripheral cancer (Type IV plus V) subgroups among themselves to obtain further results. Macroscopically, tumors were assessed as follows: ulcerated, perforated, polypoid, vegetant, flat/depressed, ring-shaped, infiltrating and stenosing. Histology of surgical specimens was described following the 8th AJCC TNM Staging System (16). The analyzed histomorphologic prognostic indicators were: tumor border configuration (infiltrative *versus* pushing), tumor budding, presence of mucinous/colloid component, necrosis, peri-tumoral inflammation, solid cords and signet ring cells (17). The ratio between the total number of positive-metastatic lymph nodes and the total number of the nodes examined in the surgical specimens (lymph node ratio, LNR) were sub-divided into 4 categories in accordance with the parameters used by Ferri and co-authors: LNR1 <0.11, LNR2 0.12-0.18, LNR3 0.19-0.40 and LNR4 >0.41 (18). Genetic analysis included investigation of microsatellite instability (MSI), Lynch syndrome and Familial Adenomatous Polyposis (FAP) as formerly addressed (19).

*Statistics*. Statistical analysis was performed using MedCalc Statistical Software version 19.1.7 (MedCalc Software Ltd, Ostend, Belgium). Categorical variables were examined through Chi-square test and continuous variables using one-way analysis of variance (ANOVA) or Kruskal-Wallis test when compared with categorical variables. *p*-Values <0.05 were considered statistically significant.

## Results

Adenocarcinoma of the right colon was found in 689 Caucasian patients submitted to hemicolectomy. The main clinicopathologic features of the examined population are listed in Table I. There were 91 (13.2%) Type I ICV-As, 87 Type II (12.6%), 38 (5.5%) Type III, 157 (22.8%) Type IV and 314 (45.6%) Type V. Type I ICV-A showed the largest tumor size (53 mm) and this finding achieved statistical significance ($p$=0.004). Type II ICV-A was statistically associated with FAP (2 out of 3 patients, $p$=0.004) whereas Type III cancers had the highest number of metastatic lymph nodes (mean: 3.1 per specimen, $p$=0.025). Type IV ICV-As were found in the oldest patients (mean age: 73.1 years, $p$=0.005) while Type V in the youngest ones (69.3 years, $p$=0.006). Type V class was also associated with advanced tumor depth (T4, $p$=0.005), infiltrative border configuration in samples with cancer-free margins ($p$=0.0001) and in those with infiltrated surgical edges (R1, $p$=0.008). The distant subgroup taken together (Type IV plus Type V) strongly related with advanced disease (N2 with $p$<0.0001 and Stage 3 with $p$=0.012) but had the lowest number of metastatic nodes (mean count: 1.5 with $p$=0.002).

## Discussion

Gaspard (or Caspar) Bauhin (1560-1624), a Swiss Professor of anatomy, medicine, botany and also Ancient Greek, was the first to described the ICV (20). Similarly to other epithelial transitional zones (TZs), curvatures or regions of great constriction such as gastro-esophageal, ano-rectal, endo-ectocervix and cornea-conjunctiva junction, ICV is often associated with increased cancer susceptibility (1, 3). Primary cancers at this site include adenocarcinoma, lymphoma, melanoma, sarcoma, neuroendocrine and granular cell tumor (1-6, 21-23) whereas, concerning metastatic localization, there are several reports describing ICV involvement from breast cancer and gallbladder adenocarcinoma (24, 25). Among primitive forms, adenocarcinoma is the most frequent histologic type but, at the same time, it represents the rarest carcinoma of the colon: in fact, literature reports an incidence from 1.32 to 22% (1, 3, 10, 26). There are three main reasons for the low rate of ICV-A: the inclusion (and confusion) of cecal, ascending colon and confinement of ICV malignancies under the collective heading "ileocecal" tumors elaborated by previous studies, the fact that such lesions are discovered at a late stage of disease and the prophylactic presence of a lymphatic block or barrier at the summit of the ileocecal papilla (3, 10). Incidence heterogeneity can be also affected by the differences in ICV-A assessment: in fact, since no standardized definition exists about the size of ICV-A and its distance from ICV, tumor epicentre has been described within 5, 4, 2 to 3, and 1 cm of the valve (1, 4, 8-10, 12-14). In this study, we propose a new 5-tier scheme, distinguishing cancer arising in the valve (Type I ICV-A: 91 cases, 13.2%) from those located in the close proximity (Type II: 87 cases, 12.6%), in the vicinity (Type III: 38 lesions, 5.5%), distant (Type IV: 157 cancers, 22.8%) and very distant (Type V: 314 tumors, 45.6%). Each cancer type was statistically associated with at least one clinicopathologic feature: Type I ICV-A showed the largest tumor size (53 mm, $p$=0.004), Type II related to FAP ($p$=0.004), Type III had the highest number of metastatic lymph nodes (mean: 3.1 per specimen, $p$=0.025), Type IV correlated with oldest mean age of the patients (73.1 years, $p$=0.005) while Type V was most frequent among the youngest subjects (69.3 years, $p$=0.006). Type V was also associated with advanced disease (N2 with $p$<0.0001 and Stage III with $p$=0.012). Comparison between our results and those available in the literature appears interesting. In the study by Lee *et al*., ICV-A correlated with N2 but, differently from our study, the authors considered under this term all the tumors whose

Table I. *Associations between types of ileocecal valve cancer and clinicoanatomopathologic features of the examined patients*.

| Clinicopathologic feature | Type of ileo-cecal valve adenocarcinoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Type I | Type II | Type III | Type IV | Type V | Type I+II | Type I+II+III | Type IV+V |
| Patients' number (%) | 91 (13.2%) | 87 (12.6%) | 38 (5.5%) | 157 (22.8%) | 314 (45.6%) | 178 (25.8%) | 216 (31.3%) | 471 (68.4%) |
| Gender | M:47<br>F:44 | M: 50<br>F: 37 | M: 21<br>F: 17 | M: 82<br>F: 75 | M: 163<br>F: 151 | M: 97<br>F: 81 | M: 118<br>F: 98 | M: 245<br>F: 226 |
| Age°, years | 69.5 | 71.9 | 72.7 | 73.1 $p$=0.005 | 69.3 $p$=0.006 | 70.3 | 71.0 | 70.6 |
| Size°, mm | **53.0 $p$=0.004** | 46.5 | 50.3 | 43.4 | 45.6 | **49.8 $p$=0.024** | **22.1 $p$=0.024** | **44.9 $p$=0.010** |
| T0 (T *in situ*) | 6 | 2 | 2 | 9 | 28 | 8 | 10 | 37 |
| T1 | 4 | 2 | 1 | 10 | 14 | 6 | 7 | 24 |
| T2 | 7 | 8 | 4 | 22 | 22 | 15 | 19 | 44 |
| T3 | 53 | 49 | 24 | 96 | 254 | 102 | 126 | 350 |
| T4 | 21 | 26 | 7 | 20 | 91 $p$=0.005 | 47 | 54 | 111 |
| N0 | 47 | 39 | 17 | 94 | 180 | 86 | 103 | 274 |
| N1 | 23 | 21 | 11 | 43 | 89 | 44 | 55 | 132 |
| N2 | 21 | 27 | 10 | 20 | 44 | 48 | 58 | **64 $p$<0.0001** |
| N3 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| N° LNs° | 21.9 | 24.8 | 21.2 | 22.3 | 24.4 | 23.4 | 23.0 | 23.7 |
| N° Metastatic LNs° | 2.1 | **2.6 $p$=0.030** | **3.1 $p$=0.025** | 1.5 | 1.5 | **2.3 $p$=0.032** | **2.5 $p$=0.002** | **1.5 $p$=0.002** |
| LNR1 | 67 | 58 | 24 | 126 | 256 | 125 | 149 | **382 $p$=0.0005** |
| LNR2 | 5 | 10 | 4 | 12 | 17 | 15 | 19 | 29 |
| LNR3 | 9 | 16 | 3 | 11 | 24 | 25 | 28 | 35 |
| LNR4 | 6 | 3 | 6 | 7 | 12 | 9 | 15 | 19 |
| M1 | 6 | 4 | 6 | 7 | 21 | 10 | 16 | 28 |
| Stage 0 | 6 | 2 | 2 | 10 | 27 | 8 | 10 | 37 |
| Stage 1 | 10 | 7 | 4 | 24 | 26 | 17 | 21 | 50 |
| Stage 2 | 30 | 29 | 10 | 58 | 122 | 59 | 69 | 180 |
| Stage 3 | 40 | 45 | 16 | 57 | 115 | 85 | 101 | **172 $p$=0.012** |
| Stage 4 | 6 | 4 | 6 | 7 | 22 | 10 | 16 | 29 |
| R1 | 0 | 0 | 0 | 1 | **8 $p$=0.008** | 0 | 0 | **9 $p$=0.040** |
| G1 | 7 | 7 | 3 | 13 | **43 $p$=0.016** | 14 | 17 | 56 |
| G2 | 30 | 32 | 9 | 53 | 98 | 62 | 71 | 151 |
| G3 | 54 | 48 | 26 | 89 | 171 | 102 | 128 | 260 |
| LVI | 33 | 33 | 14 | 52 | 123 | 66 | 80 | 175 |
| PnI | 7 | 11 | 4 | 7 | 35 | 18 | 22 | 42 |
| Mucinous pattern | 29 | 37 | 11 | 55 | 86 | 66 | 77 | 141 |
| Colloid pattern | 4 | 15 | 5 | 21 | 28 | 19 | 24 | 49 |
| Solid nests/cords | 4 | 2 | 1 | 3 | 14 | 6 | 7 | 17 |
| Signet ring cells | 2 | 2 | 1 | 2 | 4 | 4 | 5 | 6 |
| Infiltrative border | 5 | 16 | 6 | 33 | **89 $p$=0.0001** | 21 | 27 | 132 |
| Pushing border | 13 | 23 | 6 | 45 | 50 | 36 | 42 | 95 |
| Tumor deposits | 6 | 5 | 2 | 0 | 12 | 11 | **13 $p$=0.023** | 12 |
| Inflammation | 11 | 11 | 3 | 29 | 58 | 22 | 25 | **87 $p$=0.021** |
| Appendix absence | 45 | 25 | 16 | 48 | **136 $p$=0.045** | 70 | 86 | 184 |
| Appendix NET | 0 | 1 | 0 | 0 | 2 | 1 | 1 | 2 |
| Additional CRC | 0 | 3 | 0 | 3 | 6 | 3 | 3 | 9 |
| Peritumoral polyps | 21 | 26 | 5 | 53 | 105 | 47 | 52 | **158 $p$=0.011** |
| Ulcerated aspect | 27 | 31 | 13 | 35 | 83 | 58 | 71 | **118 $p$=0.033** |
| Perforation | 4 | 2 | 1 | 1 | **18 $p$=0.013** | 6 | 7 | 19 |
| Serosal alteration | 18 | 22 | 7 | 27 | 64 | 40 | 47 | 91 |
| Polypoid aspect | 19 | 18 | 6 | 36 | 60 | 37 | 43 | 96 |
| Vegetant aspect | 39 | 23 | 17 | 39 | 95 | 62 | 79 | 134 |
| Infiltrative aspect | 20 | 21 | 7 | 53 | 74 | 41 | 48 | 127 |
| Annular aspect | 11 | 16 | 8 | 8 | **86 $p$=0.003** | 27 | 35 | **118 $p$=0.009** |
| Stenosing aspect | 12 | 4 | 2 | 17 | **64 $p$<0.0001** | 16 | 18 | **81 $p$=0.002** |
| MSI | 5 | 4 | 3 | 7 | 24 | 9 | 12 | 31 |
| Lynch syndrome | 2 | 1 | 1 | 1 | 5 | 3 | 4 | 6 |
| FAP | 0 | **2 $p$=0.004** | 0 | 0 | 1 | 2 | 2 | 1 |

°Age and size: mean values; LNR: metastatic lymph node ratio; LVI: lymphovascular invasion; PnI: perineural invasion; NET: neuroendocrine tumor; MSI: microsatellite instability; FAP: familial adenomatous polyposis. Features achieving statistical significance are written in bold type ($p$<0.05).

epicenter was within 5 cm of the ICV (1). In a previous article by Honma (10), the presence of mucinous/colloid component has been associated with shorter survival for ICV-A patients: in our study, however, the association between ICV-A close types and such a pattern was not statistically significant ($p$=0.131). Clinical presentation with small bowel obstruction has been correlated with low-stage ICV-As and good prognosis whereas in our population stenosis did not achieve statistical significance ($p$=0.099) (4, 5). Right hemicolectomy represents the gold standard treatment for ICV-A and this practice has been adopted by all the studies present in the pertinent literature (12); recently, 2 ICV-As were treated with a minimally invasive endoscopic approach (27). From a genetic point of view, MSI associated with defects in DNA mismatch repair (MMR) system and p53 gene mutations have been identified in some cases of ICV-A (1, 13); in our series, we found correlation of Type II ICV-A with FAP ($p$=0.004) (19).

Our study suffers from few important limitations: the absence of survival and prognostic data appears the most serious. Analyzing patients' perioperative conditions and outcomes as well as distinguishing open from laparoscopic hemicolectomy could also provide interesting information.

## Conclusion

Our study highlights the lack of a standardized method for classifying ICV-A and aims to bridge such a gap of knowledge. In light of our results, ICV-A shows particular clinicopathologic characteristics and deserves a more tailored clinical and prognostic investigation. Further studies are needed in order to corroborate our findings.

## Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

## Authors' Contributions

All the Authors agreed with the content of this article. Dr. Virgilio conceived the presented research and wrote the manuscript. Dr. Virgilio and Dr. Montali performed the statistical analyses. Dr. Cavallini and Dr. Costi contributed in the supervision of the entire project.

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