Virchows Archiv (2019) 475:665–668
https://doi.org/10.1007/s00428-019-02603-y

BRIEF REPORT

Pathologist second opinion significantly alters clinical management of pT1 endoscopically resected colorectal cancer

Gian Luca Rampioni Vinciguerra[1,2] · Giulio Antonelli[3] · Francesca Citron[2] · Giammauro Berardi[3] · Stefano Angeletti[3] · Gustavo Baldassarre[2] · Andrea Vecchione[1] · Emilio Di Giulio[3] · Emanuela Pilozzi[1]

Received: 10 April 2019 / Revised: 31 May 2019 / Accepted: 6 June 2019 / Published online: 17 June 2019

Abstract

We retrospectively collected a series of 82 endoscopically removed early colorectal cancers. Histological specimens were revised by two gastrointestinal pathologists, performing a re-evaluation of all risk factors for lymph node metastasis. The comparison between second opinion and first pathological report revealed that lymphovascular invasion and tumor grading showed a lower level of concordance than other parameters. Our results demonstrated that second opinion modified risk assessment in about 10% of cases. It was mainly due to a lack in reporting of some parameters at the first diagnosis and a different evaluation in second opinion for updated guidelines. Considering the subgroup of patients with modified risk assessment, clinical data revealed that tumors, re-classified as low risk, did not develop lymph node metastasis that, conversely, occurred in patients identified as high risk by second opinion. In conclusion, second opinion significantly alters risk perception of endoscopically removed early colorectal carcinomas representing a valuable tool for their appropriate clinical management.

Keywords Colorectal carcinoma · Prognostic factors · Second opinion · Early colorectal carcinoma · Lymph node metastasis

Introduction

Worldwide implementation of colorectal cancer (CRC) screening programs has significantly increased the percentage of tumors endoscopically treated at early stage, and this amount is expected to rise [1].

Early CRC (eCRC) is classified as pT1 and defined by invasion limited to the submucosa [2]. In eCRC patients, endoscopic resection showed to be safer than surgery, although lymph node metastasis (pN+) still occurs in 5–15% of cases limiting its success [3].

Many histological parameters have been proposed to stratify the pN+ risk and identify lesions that may benefit from additional surgical resection [3, 4]. Despite improvements in stratification and novel guidelines, an intrinsic variability in histological analyses, pN+ rates, and clinical management still exists [5], ascribed to the lack of standardization and inter-observer agreement in reporting risk factors [3].

Gastrointestinal pathology is recognized as a critical field attracting a high rate of diagnostic mistakes and discordances. Thus, a second opinion has been proposed to minimize possible misdiagnosis [6]. However, second opinion is rarely reported, although *European CRC screening Guidelines* suggest its employment, especially when a surgical resection is considered [7].

Our aim was to assess how a second opinion affects clinical management of endoscopically resected eCRC and which histological risk factors are mostly influenced.

Gian Luca Rampioni Vinciguerra and Giulio Antonelli contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00428-019-02603-y) contains supplementary material, which is available to authorized users.

✉ Gian Luca Rampioni Vinciguerra
gianluca.rampionivinciguerra@uniroma1.it

[1] Faculty of Medicine and Psychology, Department of Clinical and Molecular Medicine, University of Rome "Sapienza", Santo Andrea Hospital, via di Grottarossa 1035, 00189 Rome, Italy

[2] Division of Molecular Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, National Cancer Institute, 33081 Aviano, Italy

[3] Faculty of Medicine and Psychology, Department of Surgical and Medical Sciences and Translational Medicine, University of Rome "Sapienza", Santo Andrea Hospital, 00189 Rome, Italy

Materials and methods

Sample collection and analyses

We retrospectively collected 82 eCRC specimens from patients who underwent endoscopic resection in our Institute from June 2006 to December 2017. The study protocol conforms to ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local institutional review board. Clinical, endoscopic, and follow-up data were recorded.

eCRC was defined by submucosal infiltration [2]. A pathologist (GLRV) performed a systematic revision of H&E staining from each sample, blinded to the primary diagnosis. Challenging cases were discussed with a second pathologist (EP) to achieve consensus.

The examined parameters were polyp architecture, type of adenoma, grading, and Kikuchi and Haggitt levels, respectively, for sessile/flat and pedunculated polyps, invasion depth, budding, lymphovascular invasion (LV), and margin status.

Grading was defined according to the percentage of gland formation: > 95% G1, 50–95% G2, < 49% G3. Haggitt and Kikuchi scores were respectively subdivided in four and three levels as recommended [8, 9].

Invasion depth was measured in millimeters. Budding was defined as single cell up to four, evaluated in a × 20 power field at the invasive front and graded in a three-tier system (0–4 Buds: Bd1; 4–9 Buds: Bd2; > 10 Buds: Bd3) [10]. Involvement of resection margins was considered at or within 1 mm [11].

Statistical analyses

Data were reported as mean (±S.D.) or median (with range). The weighted Kappa statistic test (quadratic weights) was used to quantify inter-observer agreement between first diagnosis and second opinion. The values of Kappa strength agreements and intra-class correlations were interpreted as follows: < 0.20 poor, 0.21–0.40 fair, 0.41–0.6 moderate, 0.61–0.80 sufficient, and 0.81–1.00 satisfactory agreement [12]. Statistical analysis was performed using MedCalc 18.3 statistical software.

Results

Our cohort comprised 82 cases of eCRC (48.8% female; mean age 67.5 ± 10.9 years), the majority of them derived from the sigmoid-rectum tract (73.2%) (Table 1).

A non-homogeneity in reports was present, and some evaluations were missing. Grading and resection margins were reported in 96.3% and 100% of cases, respectively, while invasion depth and Haggitt/Kikuchi levels were considered in 65.9% and 2.4% of cases. In two cases, invasion depth was described (e.g., "superficial invasion of submucosal layer") but not measured. Budding was specified in 23.2% of cases as "positive" or "negative."

Table 1 Clinical parameters and risk assessment are summarized

Clinical parameters		
Patients		82
Sex	Male	42 (51.2%)
	Female	40 (48.8%)
Age	Mean (years old)	67.5
	SD	± 10.9
Tumor site	Right bowel	10 (12.2%)
	Left bowel	10 (12.2%)
	Sigmoid rectum	62 (75.6%)
Risk stratification (first diagnosis)	High risk	51 (62.2%)
	Low risk	31 (37.8%)
Risk stratification (2nd opinion)	High risk	47 (57.3%)
	Low risk	35 (42.7%)
Polyp size	Mean (mm)	19.42
	SD	± 10

In second opinion, all risk factors were expressed. Risk stratification was evaluated according to guidelines [13] for first and second opinions (Table 2).

As a result of the first diagnosis, 51 of 82 (62.2%) patients were considered at high risk and underwent additional surgical resection. One of them (2%) resulted pN+. The others 31 of 82 (37.8%) were considered low risk and underwent clinical follow-up with one evidence of nodal recurrence (1/31, 3%).

When second opinion was performed, 2 of 31 (6.45%) low-risk patients were reconsidered as high risk, including the case with nodal recurrence (Fig. 1), previously underestimated due to a poorly differentiated infiltrative component not reported in the first diagnosis.

Conversely, 6 of 51 (11.8%) of patients originally classified with a high-risk lesion were reconsidered as low risk: in 2 cases, class modification was ascribable to a different evaluation of grading and margin status. The remaining 4 cases were modified by Haggitt level evaluation and tumor budding. A second opinion description of a low (i.e., 1 or 2) Haggitt level, not reported in the first diagnosis, reduced the perceptive risk of LNM with infiltration depth ranging from 1 to 2 mm. In the same way, tumor budding originally reported only as "positive," upon second opinion was appropriately evaluated as Bd1, using the three-tier system in which only Bd2–3 lesions are considered as high risk. To date, none of these patients has developed recurrences.

Table 2 Histological parameters are reported and their concordance between the first diagnosis and the evaluation derived by second opinion

Histological parameters	Not reported in first diagnosis	Reported in first diagnosis	Concordance with second opinion	*k*-factor*	*k*-factor**
Polyp architecture	23 (28.0%)	59 (72.0%)	48 (81.3%)	N/A	N/A
Type of adenoma	16 (19.6%)	66 (80.5%)	59 (89.4%)	N/A	N/A
Tumor grading	3 (3.7%)	79 (96.3%)	74 (93.7%)	0.73 ± 0.08 (95% CI 0.56–0.90)	0.73 ± 0.08 (95% CI 0.56–0.90)
Depth invasion	28 (34.1%)	54 (65.9%)	53 (98.1%)	0.73 ± 0.07 (95% CI 0.60–0.91)	0.92 ± 0.05 (95% CI 0.80–1)
Haggitt/Kikuchi	80 (97.6%)	2 (2.4%)	2 (100%)	N/A	N/A
LV	15 (18.3%)	67 (81.7%)	61 (91.0%)	0.30 ± 0.11 (95% CI 0.07–0.53)	0.60 ± 0.12 (95% CI 0.36–0.84)
Pn	82 (100%)	0 (0%)	0%	N/A	N/A
Budding	63 (76.8%)	19 (23.2%)	19 (100%)	N/A	N/A
Margin of resection	0 (0%)	82 (100%)	78 (95.1%)	0.82 ± 0.07 (95% CI 0.69–0.97)	0.82 ± 0.07 (95% CI 0.69–0.97)

**k*-factor is calculated considering all cases (lack of information in the first diagnosis is interpreted as a divergent result)

***k*-factor is calculated considering only cases in which the analyzed parameter is expressed in the first diagnosis

Concordance level

Considering only cases in which risk parameters were expressed both in the first and second opinions, the concordance levels expressed by Kappa strength were high (Table 2).

In detail, concordance strength was satisfactory for depth of invasion and resection margin status, and sufficient for LV and tumor grading.

Discussion

This study was a useful internal quality control of our Pathology Unit, since concordance levels between first diagnosis and second opinion range from sufficient to satisfactory. The small gap between the evaluations could be overcome by a pathologist training that could represent a valid alternative to the second opinion in an institution where inter-observer concordance is satisfactory.

From a clinical point of view, second opinion modified risk stratification and clinical management in about 10% of eCRC. The discrepancy between the high level of concordance and the significant impact on risk-assessment could be attributed both to a lack in reporting of some parameters at the first diagnosis and to their different evaluations based on new guidelines.

Indeed, tumor budding represents an emblematic example: its simple description, without any grade, puts Bd1 and Bd3 lesions at the same level, leading to a misinterpretation of patients' risk. The second opinion, where guidelines from the International Tumor Budding Consensus Conference of 2016 [10] were adopted, permitted minimizing the risk perception of Bd1 tumors.

Interestingly, we observed how reporting the Haggitt's level is helpful for a proper interpretation of infiltration depth,

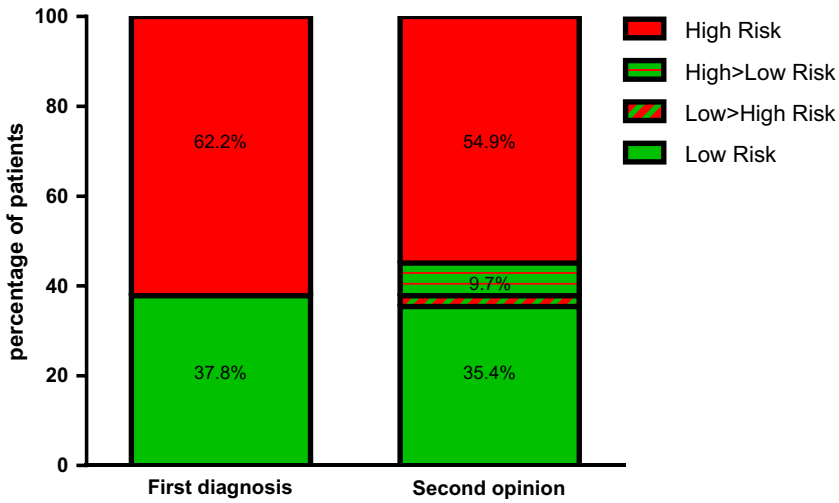

Fig. 1 The comparison between first diagnosis and second opinion modified risk assessment in 9.7% of patients that switched from low- to high-risk class (2.4%) and from high- to low-risk class (7.3%) (realized with GraphPad Prism 6)

sometimes scaling down a risk perception initially classified as high.

Thus, in a percentage of lesions firstly considered high risk, second opinion appears to prevent overtreatment.

Conversely, our revision highlighted an increased risk in two cases, showing clearly how second opinion better refines patients who benefit from surgery, preventing a dismal outcome of LN.

Our results underline the difficulties in risk stratification, encouraging to expand consensus on pathology reports. Indeed, a low accuracy results in misclassification and impinges on economic gains and patients' quality of life achieved by a conservative approach [14]. Moreover, we showed how many variables were missing. This flaw could not only undermine the prognosis of patients, but also reduce the possibility of data pooling and analysis of literature reports. Accordingly, we proposed a form to standardize eCRC report in order to simplify the risk assessment (Supplementary 1). Further studies will verify the impact of this tool on inter-observer agreement in our institution.

In conclusion, our data showed how nearly 10% of endoscopically resected eCRCs in daily practice would benefit from a pathological second opinion, significantly influencing clinical decision making even in institutes where a high level of concordance is achieved. Systematic implementation of this practice, as seen in other fields of pathology, may help clinicians and patients in making a more informed management choice.

Author contributions GLRV conceived and designed the study, researched and analyzed pathological data, and wrote and edited the manuscript. GA conceived and designed the study, researched and analyzed clinical data, and wrote and edited the manuscript. FC analyzed pathological data and edited the manuscript. G Berardi researched clinical data and edited the manuscript. SA provided and analyzed clinical data and reviewed the manuscript. G Baldassarre edited and reviewed the manuscript. AV provided pathological data, and edited and reviewed the manuscript. EDG conceived and designed the study, analyzed data, and reviewed the manuscript. EP conceived and designed the study, provided and analyzed pathological data, and reviewed the manuscript. All authors gave final approval for publication. GLRV and GA take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Lopez A, Bouvier AM, Jooste V, Cottet V, Romain G, Faivre J, Manfredi S, Lepage C (2019) Outcomes following polypectomy for malignant colorectal polyps are similar to those following surgery in the general population. Gut. 68(1):111–117
2. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP (2017) The eighth edition AJCC Cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67(2):93–99
3. Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID (2013) Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy. 45(10):827–834
4. Ueno H, Mochizuki H, Hashiguchi Y, Shimazaki H, Aida S, Hase K, Matsukuma S, Kanai T, Kurihara H, Ozawa K, Yoshimura K, Bekku S (2004) Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology. 127(2):385–394
5. Antonelli G, Berardi G, Rampioni Vinciguerra GL, Brescia A, Ruggeri M, Mercantini P, Corleto VD, D'Ambra G, Pilozzi E, Hassan C, Angeletti S, Di Giulio E (2018) Clinical management of endoscopically resected pT1 colorectal cancer. Endoscopy Int Open 6(12):E1462–E14E9
6. Peck M, Moffat D, Latham B, Badrick T (2018) Review of diagnostic error in anatomical pathology and the role and value of second opinions in error prevention. J Clin Pathol 71(11):995–1000
7. Steele RJ, Pox C, Kuipers EJ, Minoli G, Lambert R (2012) International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition–management of lesions detected in colorectal cancer screening. Endoscopy. 44(Suppl 3):SE140–SE150
8. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD (1985) Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology. 89(2):328–336
9. Kikuchi R, Takano M, Takagi K, Fujimoto N, Nozaki R, Fujiyoshi T, Uchida Y (1995) Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. Dis Colon Rectum 38(12):1286–1295
10. Lugli A, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H et al (2017) Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Modern pathology : an official journal of the United States and Canadian Academy of Pathology. Inc. 30(9):1299–1311
11. West NP, Langman G, Haboubi N, Carey F, Henry J, Morgan M, Sheahan K (2019) Significant polyps and early colorectal cancer: the importance of high-quality standardized histopathology. Color Dis : Off J Assoc Coloproctol G B Irel 21(Suppl 1):53–56
12. McHugh ML (2012) Interrater reliability: the kappa statistic. Biochem Med 22(3):276–282
13. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A et al (2013) Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol : Off J Eur Soc Med Oncol 24(Suppl 6):vi64–vi72
14. Hassan C, Pickhardt PJ, Di Giulio E, Hunink MG, Zullo A, Nardelli BB (2010) Value-of-information analysis to guide future research in the management of the colorectal malignant polyp. Dis Colon Rectum 53(2):135–142