Clinical management of endoscopically resected pT1 colorectal cancer

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ABSTRACT

Background Implementation of colorectal cancer (CRC) screening programs increases endoscopic resection of polyps with early invasive CRC (pT1). Risk of lymph node metastasis often leads to additional surgery, but despite guidelines, correct management remains unclear. Our aim was to assess the factors affecting the decision-making process in endoscopically resected pT1-CRCs in an academic center.

Methods We retrospectively reviewed patients undergoing endoscopic resection of pT1 CRC from 2006 to 2016. Clinical, endoscopic, surgical treatment, and follow-up data were collected and analyzed. Lesions were categorized according to endoscopic/histological risk-factors into low and high risk groups. Comorbidities were classified according to the Charlson comorbidity index (CCI). Surgical referral for each group was computed, and dissociation from current European CRC screening guidelines recorded. Multivariate analysis for factors affecting the post-endoscopic surgery referral was performed.

Results Seventy-two patients with endoscopically resected pT1-CRC were included. Overall, 20 (27.7%) and 52 (72.3%) were classified as low and high risk, respectively. In the low risk group, 11 (55%) were referred to surgery, representing over-treatment compared with current guidelines. In the high risk group, nonsurgical endoscopic surveillance was performed in 20 (38.5%) cases, representing potential under-treatment. After a median follow-up of 30 (6–130) months, no patients developed tumor recurrence. At multivariate analysis, age (OR 1.21, 95%CI 1.02–1.42; $P = 0.02$) and CCI (OR 1.67, 95%CI 1.12–3.14; $P = 0.04$) were independent predictors for subsequent surgery.

Conclusions A substantial rate of inappropriate post-endoscopic treatment of pT1-CRC was observed when compared with current guidelines. This was apparently related to an overestimation of patient-related factors rather than endoscopically or histologically related factors.

Introduction

The progressive enforcement of colorectal cancer (CRC) screening programs and the improvement in endoscopic resection techniques are leading to a growing number of early CRCs that are diagnosed and treated endoscopically and this number is expected to increase [1, 2].

Endoscopic resection without subsequent surgery appears to be a more conservative treatment, but the potential hazard of lymph node metastasis may jeopardize its efficacy [3, 4]. Endoscopic and histological variables have been shown to be reliable predictors of lymph node metastasis [5–9]; in particular, poor differentiation, tumor budding, lymphovascular inva-

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E1462

Antonelli Giulio et al. Clinical management of … Endoscopy International Open 2018; 06: E1462–E1469

sion, deep submucosal invasion, and positive resection margins have been associated with a higher risk of lymph node disease.

European CRC guidelines recommend additional surgical resection only for high risk lesions, while a conservative approach appears more suitable for low risk lesions. However, such recommendations are based on weak evidence, leaving residual uncertainty on the best treatment [10 – 12]. In addition, implementation of such guidelines in clinical practice is unclear, and large variability may be expected. [5, 13].

The aim of this retrospective study was to assess the clinical management of endoscopically resected pT1-CRC in an academic center and to identify the main factors affecting the decision-making process.

Patients and methods

Study population

The hospital charts of patients who underwent a complete endoscopic resection of a histologically proven pT1 lesion between June 2006 and December 2016 were reviewed, cross-referencing histological and endoscopic databases to marginalize selection bias. In addition, we collected data on patients who in the same time frame were sent from our endoscopy unit to upfront surgery for a colonic lesion which resulted pT1 at pathology. Additional information on index and surveillance colonoscopies, histological data and possible surgical procedures, and hospital stay were collected.

After the initial data collection, all patients were given an identification number to guarantee anonymity and information entered in a dedicated data base for statistical analysis. All patients gave informed consent for the use of clinical and laboratory data at the time of the first examination or procedure.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local institutional review board.

Center policy in the study period

Endoscopy – characterization and resection

In the study period, it was routine practice in our endoscopy unit to use Paris criteria to morphologically classify the lesions [14, 15]. Resection techniques were performed to ensure, whenever possible, an en bloc, R0 resection. Polypectomy and endoscopic mucosal resection (EMR) were available throughout the entire study period, while endoscopic submucosal dissection (ESD) was started in 2013.

Polyps were sent to upfront surgery when morphological, vascular or pit pattern characteristics suggested a high risk of deeply invasive cancer.

Pathology staging

Tumor differentiation, presence of lymphovascular invasion, depth of invasion (Haggitt and Kikuchi) [16, 17], and/or submucosal infiltration in millimeters were regularly reported in the study period, while the presence of budding was evaluated starting from 2012.

It was general policy to classify lesions as low or high risk polyps according to the presence of one or more of the above mentioned pathology risk factors, and according to the resection modality (en bloc vs piece-meal) and presence of positive resection margins (R1). For the purposes of this study, presence of R1 at pathology was considered to be an exclusion criteria, as potentially indicative of a cancer deeper than T1.

Multidisciplinary decision – surgery vs endoscopy

In the study period, patients with pT1-CRC were routinely referred to a multidisciplinary group involving gastroenterologists, oncologists, colorectal surgeons, radiologists, and pathologists that would propose a treatment approach based on pathological and clinical risk factors. The risk of surgery was classified according to the presence of comorbidities using the Charlson comorbidity index (CCI) [18]. When surgery was not indicated, endoscopic surveillance was performed at 1 year, and then after 3 and 5 years [19].

Study end points

To assess:
1. Management of endoscopically resected low risk pT1 (follow-up vs subsequent surgery).
2. Management of endoscopically resected high risk pT1 (subsequent surgery vs follow-up).
3. Main polyp- or patient-predictors of the endoscopic/surgery approach.
4. Management of upfront surgically resected pT1.

In order to assess the appropriateness of our recommendations, we used the European CRC Screening Guidelines as reference standard [10].

Statistical analysis

Continuous data were reported as mean ± SD or as median (range) and compared using the Student's t test or Mann-Whitney test as appropriate. Categorical variables were expressed as number (percentage) and compared using the chi-squared test with Fisher's exact test using Yates correction as appropriate. Overall survival (OS) was considered to be the time from pT1 lesion resection to death or last follow-up. Patients' survival times were evaluated using Kaplan-Meier curves and compared with the log-rank test. A backward stepwise logistic regression model was performed to identify factors affecting the decision to perform surgical resection. Statistical analysis was performed using IBM SPSS Statistics for Mackintosh, Version 20.0 (IBM Corp., Armonk, NY).

Results

In the study period, 93 pT1-CRC were identified, corresponding to 1.4% (93/6440) of all the endoscopic resections performed in the study period. In addition, 24 colonic lesions that were sent from our endoscopy unit to upfront surgery subsequently resulted as pT1 at pathology.
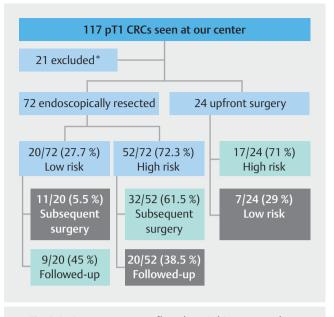
For the purpose of this study, 21 patients were excluded (5 for neuroendocrine tumors, 3 for R1, 3 for previous or synchro-

Antonelli Giulio et al. Clinical management of … Endoscopy International Open 2018; 06: E1462–E1469

E1463

▶ **Table 1** Patient demographics and endoscopic characteristics.

Gender (F/M)	46/50
Age, median (range), years	70 (36 – 94)
Comorbidities (CCI[1]), mean ± SD	2.6 (± 1.28)
Tumor site	
▪ Right colon	16 (17 %)
▪ Left colon	17 (18 %)
▪ Sigma	30 (31 %)
▪ Rectum	33 (34 %)
Tumor size, mean ± SD, mm	20.4 (± 1.9)
Paris classification	
▪ 0-Ip	41 (42 %)
▪ 0-Is	32 (34 %)
▪ 0-Isp	5 (5 %)
▪ 0-IIa	2 (2 %)
▪ 0-IIb	5 (5 %)
▪ 0-IIc	1 (1 %)
▪ LST-G	7 (8 %)
▪ LST-NG	3 (3 %)
Resection	
▪ Upfront surgery	24 (25 %)
▪ Endoscopy and surgery	43 (45 %)
▪ Endoscopy	29 (30 %)
Lymph node metastasis	4 (4.1 %)

[1] CCI = Charlson comorbidity Index.

▶ **Fig. 1** Patient management flow chart. White squares show patients managed according to guidelines. Black squares show patients managed outside guidelines. *Exclusion criteria listed in Methods section.

nous advanced CRC, 10 lost to follow-up). Finally, 96 patients were included in the final analysis, 72 (75 %) with endoscopic resection and 24 (25 %) patients sent to upfront surgery. Demographics and clinical characteristics are shown in ▶ **Table 1**, while a patient management flow chart is shown in ▶ **Fig. 1**.

Endoscopically resected low risk polyps

Overall, 20/72 (27.8 %) patients presented with a low risk pT1-CRC after endoscopic resection. Of these, 11/20 (55 %, 95 %CI: 0.34 – 0.74) were referred to surgery and 9/20 (45 %, 95 %CI: 0.25 – 0.65) to endoscopic follow-up. This corresponds to an inappropriate management of 55 %, compared with the reference standard. In particular, 9/11 operated patients had a pedunculated polyp while two were Laterally Spreading Tumors. Eight patients underwent a videolaparoscopic emicolectomy, while three underwent open emicolectomy. When surgical risk was considered, 6/11 patients were found to have an increased surgical risk (CCI ≥ 3). As for the 9/20 patients referred to endoscopic surveillance, 8/9 (89 %) had a pedunculated polyp, while the surgical risk was low in 4/9 (44 %) patients.

Endoscopically resected high risk polyps

Overall, 52/72 patients (72.2 %) presented with high risk pT1-CRC after endoscopic resection. The presence of histologic risk factors is detailed in ▶ **Table 2**. In detail, 20/52 (38.5 %, 95 %CI: 0.26 – 0.52) were followed up endoscopically, while 32/52 (61.5 %, 95 %CI: 0.48 – 0.73) underwent surgical intervention. This corresponds to an inappropriate management of 38.5 % of patients according to the reference standard. Among those followed up at endoscopy, 16/20 (80 %) patients were found to have an increased surgical risk (≥ 3 CCI). Of the remaining four patients, two had a very low rectal localization. Among patients referred to surgery, 5/32 had a CCI ≥ 3.

One patient from the high risk group who underwent subsequent surgery had lymph node metastasis (LNM) in 1 out of 20 lymph nodes dissected (N1). The percentage of LNM in endoscopically resected pT1-CRC sent to subsequent surgery was 2.3 %.

Predictors of clinical management of endoscopically resected pT1-CRC (post polypectomy surgery vs follow-up) and survival

When considering cumulatively the low and high risk groups, after endoscopic resection, 43/72 (59.7 %) were referred for subsequent surgical resection, while 29/72 (40.3 %) were followed up with only endoscopic surveillance. The main demographic and clinical characteristics of the two groups are shown in ▶ **Table 3**. In detail, the median age in the endoscopy group appeared to be significantly higher than that of the surgery group (74, range: 43 – 94 vs 67, range 36 – 83; P = 0.008), and a lower number of patients surgically treated appeared to have comorbidities (mean CCI value: 2.3 ± 1.3 vs 3.1 ± 1.3 P = 0.01).

E1464

Antonelli Giulio et al. Clinical management of … Endoscopy International Open 2018; 06: E1462–E1469

▶ **Table 2** Histopathological characteristics and risk factors.

Grading G1/G2/G3	21/53/22
Haggitt	
▪ 1	8 (8 %)
▪ 2	15 (15 %)
▪ 3	7 (7 %)
▪ 4	11 (11 %)
Kikuchi score	
▪ Sm1	14 (14 %)
▪ Sm2	11 (11 %)
▪ Sm3	7 (7 %)
Submucosal infiltration, mean ± SD, mm	4.6 (± 5.4)
Lymphovascular invasion	24 (23 %)
Budding	
▪ 0 – 4 Buds	11 (11 %)
▪ 5 – 9 Buds	6 (6 %)

No additional differences were found concerning endoscopic and histological characteristics (▶ **Table 4**), with the only exception being Haggitt 1 lesions, which were more prevalent in the group on endoscopic surveillance (24.1 % vs 2.3 %; P = 0.003). After a median follow-up of 30 (2 – 130) months, the 1-, 3-, and 5-year overall survival of patients undergoing surgery was 100 %, 96 %, and 89 %, respectively while it was 96 %, 90 %, and 90 % for patients undergoing endoscopic surveillance (P = 0.47; ▶ **Fig. 2**). No patients developed cancer recurrences. During follow-up colonoscopies, 17 polyps in 13 (18 %) patients were endoscopically removed, all adenomas with low or high grade dysplasia.

The logistic regression model showed that only age (OR 1.21, 95 %CI 1.02 – 1.42; P = 0.02) and comorbidities (CCI) (OR 1.67, 95 %CI 1.12 – 3.14; P = 0.04) were independently associated with post-endoscopic surgery (▶ **Table 5**).

Upfront surgery group

Among the 24 patients who were sent to upfront surgery for pT1-CRC, 7/24 (29 %) harbored low risk polyps, while 17/24 (71 %) polyps had at least one histological risk factor for LNM. Indeed, 3/24 (12.5 %) had at least one pathologically proven LNM, all from high risk polyps. This highlights potential mismanagement in 29 % of patients who were sent to upfront surgery with a low risk lesion. Four low risk lesions had endoscopic risk factors for deep submucosal invasion (3 depression, 1 non-lifting sign), while 3 lesions were evaluated as non endoscopically approachable for size.

▶ **Table 3** Demographics and endoscopic characteristics of patients with endoscopically resected pT1 CRCs.

	Endoscopy + surgery	Endoscopy (n = 29)	P value
Gender (F/M)	20/23	16/13	0.31
Age	67 (36 – 83)	74 (43 – 94)	0.008
Comorbidities (Charlson Comorbidity Index), mean ± SD	2.3 ± 1.3	3.1 ± 1.3	0.01
Tumor site			
▪ Right colon	5 (11.6 %)	5 (17.2 %)	0.5
▪ Left colon	4 (9.3 %)	1 (3.4 %)	
▪ Sigma	21 (48.8 %)	11 (37.9 %)	
▪ Rectum	13 (30.2 %)	12 (41.3 %)	
Tumor size, mean ± SD, mm	17.2 ± 9	17.5 ± 8	0.89
Paris classification			
▪ 0-Ip	22 (51.1 %)	14 (48.2 %)	0.39
▪ 0-Is	9 (20.9 %)	10 (34.4 %)	
▪ 0-Isp	4 (9.3 %)	1 (3.4 %)	
▪ 0-IIa	1 (2.3 %)	0 (0 %)	
▪ 0-IIb	4 (9.3 %)	1 (3.4 %)	
▪ 0-IIc	0 (0 %)	1 (3.4 %)	
▪ LST-G	1 (2.3 %)	2 (6.8 %)	
▪ LST-NG	2 (4.6 %)	0 (0 %)	

Antonelli Giulio et al. Clinical management of … Endoscopy International Open 2018; 06: E1462–E1469

E1465

▶ **Table 4** Histopathological characteristics of endoscopically resected pT1 CRCs.

	Endoscopy + surgery (n = 43)	Endoscopy (n = 29)	P value
Grading G1/G2/G3	7/24/12	6/18/5	0.56
Haggitt			
▪ 1	1 (2.3 %)	7 (24.1 %)	0.003
▪ 2	12 (27.9 %)	3 (10.3 %)	
▪ 3	5 (11.6 %)	0 (0 %)	
▪ 4	16 (37.2 %)	15 (51.7 %)	
Kikuchi score			
▪ Sm1	7 (16.2 %)	8 (27.5 %)	0.7
▪ Sm2	5 (1.6 %)	4 (13.7 %)	
▪ Sm3	4 (9.3 %)	2 (6.8 %)	
Submucosal infiltration, mm	3.3 ± 2	2.5 ± 3	0.28
Lymphovascular invasion	9 (20.9 %)	5 (17.2 %)	0.47
Budding			
▪ 0 – 4 Buds	5 (11.6 %)	6 (20.6 %)	0.32
▪ 5 – 9 Buds	2 (4.6 %)	0 (0 %)	
En bloc resection	37 (86 %)	24 (82.8 %)	0.74

Discussion

According to our data, an unexpected high rate of discordance exists between real-life clinical management and current guidelines when dealing with endoscopically resected pT1-CRC. In particular, a high rate of over-treatment of low risk lesions was reported, with an apparently unnecessary use of surgical resources. On the other hand, more than 1 in every 3 patients with high risk lesions were not operated on, potentially remaining at risk of tumor progression. In addition, we showed that clinically related factors, such as age and comorbidities, played a dominant role in the decision-making process, while the role of endoscopic and histological factors appeared to be somewhat downgraded.

Our results are relevant for the following considerations. First, most of the low risk lesions sent to surgery disappointingly presented with a pedunculated morphology. Thus, indication to surgery was apparently related to a clinical choice, as the risk of incomplete resection is to be ruled out. In this regard, it must be admitted that the evidence in favor of a conservative approach for low risk lesions is weak, mostly based on retrospective historical series.

Second, there is compelling evidence that such patients never have a 0 % risk of LNM, and inconstant risk ratios have been described [5, 20]. Thus, it may be suggested that when comparing such risk with the mortality risk from CRC surgery in patients at low risk of surgery, the surgical choice still appeared attractive: young and healthy patients were more likely referred to surgery considering long life expectation and low procedure-related morbidity; conversely, patients with high
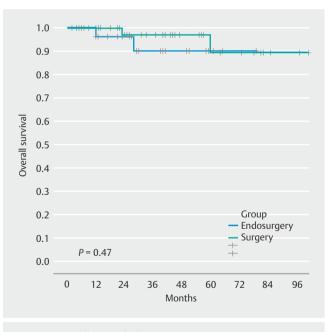

▶ **Fig. 2** Overall survival of patients.

risk pT1 lesions were more likely followed up endoscopically when the risk for morbidity and mortality of the surgical procedure was high.

Third, oncological benefit of post-endoscopic surgical referral was questionable in both low and high risk lesions. Surgical approach does not seem to benefit the outcome, since survival in both groups was comparable, and no patient developed re-

E1466

Antonelli Giulio et al. Clinical management of … Endoscopy International Open 2018; 06: E1462–E1469

▶ Table 5 Predictive factors for surgical approach after endoscopic resection.

	Univariate analysis		Multivariate analysis	
	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value
Female sex	0.38 (0.03 – 3.77)	0.41		
Age	1.24 (1.05 – 1.46)	0.009	1.21 (1.02 – 1.42)	0.02
Comorbidities	2.21 (1.01 – 5.27)	0.05	1.67 (1.12 – 3.14)	0.04
Tumor site				
▪ Right colon	1	0.70		
▪ Left colon	0.63 (0.05 – 7.07)			
▪ Sigma	0.03 (0.00 – 3.10)			
▪ Rectum	0.23 (0.02 – 2.61)			
Tumor size	1.02 (0.93 – 1.11)	0.67		
Parigi classification				
▪ 0-Ip	1	0.99		
▪ 0-Is	6.26 (0.00 – 9.75)			
▪ 0-Isp	0.97 (0.00 – 1.23)			
▪ 0-IIa	0.92 (0.00 – 9.70)			
▪ 0-IIb	0.98 (0.00 – 1.63)			
▪ 0-IIc	1.26 (0.00 – 1.28)			
▪ LST-G	1.06 (0.00 – 6.71)			
▪ LST-NG	1.09 (0.00 – 6.26)			
Grading				
▪ G1	1	0.20		
▪ G2	1.02 (0.32 – 1.42)			
▪ G3	8.01 (0.00 – 11.4)			
Haggitt				
▪ 1	1	0.79		
▪ 2	1.03 (0.00 – 6.8)			
▪ 3	1.05 (0.03 – 8.8)			
▪ 4	6.06 (0.00 – 11.5)			
Kikuchi score				
▪ Sm1	1	0.93		
▪ Sm2	1.47 (0.04 – 3.43)			
▪ Sm3	2.22 (0.91 – 5.16)			
Submucosal infiltration, mm	0.95 (0.68 – 1.34)	0.79		
Lymphovascular invasion	0.03 (0.00 – 1.78)	0.53		
Budding 5 – 9 buds	2.49 (0.88 – 3.28)	0.07		
En bloc resection	1.28 (0.35 – 4.68)	0.70		

currence. This is crucial in the clinical decision-making process, since it is well known that surgical resection harbors higher risks [21].

The lack of benefit of surgical resection could be ascribable to the small sample size in our cohort; however, a recent multicenter Asian retrospective study on high risk pT1-CRCs with

Antonelli Giulio et al. Clinical management of … Endoscopy International Open 2018; 06: E1462–E1469

E1467

long-term follow-up also found no survival benefit in patients treated with additional surgery [22]. Furthermore, it could be a clue to the great heterogeneity of histological risk factors and the lack of standardization in reporting them, as suggested previously [5]. Indeed, most available studies are based on Asian data, where histological workout is thorough and yields more certain results. Thus, to safely identify patients who can be spared from surgical intervention, it is necessary to establish cutoffs, risk stratification models and clear definitions for every risk factor, increasing reproducibility.

It is possible that, in the near future, a refined risk stratification capability will expand indications for endoscopic resection and surveillance of pT1-CRCs. Until then, our data indicate that the final decision-making is still predominantly driven by clinical factors, as well as patient preferences. Since real life management of patients largely differs from available guidelines, it is possible that these do not yet fully address clinical needs. Indeed, it is conceivable that the mismanagement we highlighted may be ascribable to the lack of high quality evidence to guide informed choices.

To the best of our knowledge, this is the first recent Italian study that investigates pT1-CRC management in a real life consecutive cohort of unselected patients from a single center. The inclusion of patients outside the age range of screening programs could be the main cause of discrepancy between our study and that of Fasoli et al., who found no age difference between the different treatment approaches [23]. We believe however that inclusion of these patients is of great importance when investigating a real life approach, since it is in the treatment of the very young or the very old that the most challenging decisions lie.

Our study also highlighted a quota of patients with low risk pT1 that were sent to upfront surgery, potentially exposing them to unnecessary risks. This was mainly driven by endoscopic characteristics that suggested increased risk of invasive cancer or by perceived technical difficulties. Indeed, all these patients were sent to surgery before 2010. We can assume that this fraction of patients is decreasing along with the improvement in endoscopic diagnosis and resection techniques.

The present study has some limitations. First, having the objective of analyzing the decision-making process, it has a retrospective design based on clinical and procedural records, and as such, may be affected by selection bias, which was marginalized by cross-referencing histological and endoscopic records. Second, the sample size is not sufficient to guarantee a satisfactory statistical power useful to discern small differences between groups. Indeed, our comprehensive LNM rate was 4.1 %, lower than mean rates reported in the literature. However, expressing LNM rate was not among the main purposes of this study.

Conclusion

A substantial rate of inappropriate post-endoscopic treatment of pT1-CRC was observed, when compared with current guidelines. This was apparently related to an overestimation of patient-related factors rather than endoscopically or histological-

ly related factors. A large multicenter study would be of great interest to further analyze clinical management of pT1-CRC and as a starting point for its standardization.

Competing interests

None

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E1468

Antonelli Giulio et al. Clinical management of ... Endoscopy International Open 2018; 06: E1462–E1469

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Antonelli Giulio et al. Clinical management of … Endoscopy International Open 2018; 06: E1462–E1469

E1469