Management of Pt1 tumours removed by endoscopy during colorectal cancer screening: Outcome and treatment quality indicators

MANAGEMENT OF pT1 TUMORS REMOVED BY ENDOSCOPY DURING COLORECTAL CANCER SCREENING: OUTCOME AND TREATMENT QUALITY INDICATORS

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Abbreviations: FS = sigmoidoscopy; TC = colonoscopy

Abstract

Introduction: Limited information is available about outcomes of patients with malignant adenomas endoscopically resected at screening. The aim of the study was to evaluate diagnostic and therapeutic quality indicators and to correlate them with clinical and surgical outcomes.

Materials and Methods: We reviewed endoscopic and histology characteristics of all pT1 tumours endoscopically removed at the time of colonoscopy assessment **in subjects** with a positive screening test result in the context of a population-based program.

Results: 392 pT1 tumours were completely removed by endoscopy (en-bloc= 86.7%, piecemeal= 13.3%) and the histology report was considered complete in 83.2% of cases. Treatment was limited to endoscopic excision for 120 patients (30.7%, Group 1), 272 (69.3%, Group 2) underwent radicalisation surgery. In patients who had at least 1 lymph node examined, the rate of nodal involvement was 5.4% (13/239); no metastatic node was found in the 21 (27.6%) out of 76 patients with low-risk adenomas, who underwent surgery.

Conclusion: Risk of nodal involvement in colorectal pT1 tumours is well predicted by known histologic features also in a screening setting, although it was lower than among patients from clinical series. Surgical overtreatment is still significantly present and there is ample room for improvement regarding diagnostic and therapeutic flow-chart.

Keywords: adenoma; cancer epidemiology; colorectal cancer screening; diagnosis; surgery

1 Introduction

Following the implementation of national colorectal cancer (CRC) screening campaigns, the incidence of malignant polyps, defined by submucosal invasion of cancer cells (pT1), is increasing [1,2]. The management of these cancerized adenomas is controversial and limited evidence is available about the long-term outcomes of patients with malignant polyps who undergo endoscopic removal in a screening setting, with or without subsequent surgical resection. Usually, additional surgery with lymph nodes (LN) dissection is required only for patients who present one or more adverse histological criteria [3]; according to these criteria, malignant polyps are stratified into 2 categories: 1) high risk for LN metastasis **(poor differentiation**, vascular or lymphatic invasion, margins of excision involved, presence of tumour budding, depth of tumour invasion >1000 μm) [4-8] 2) low risk for LN metastasis (absence of any of the abovementioned factors). However, there are cases where - even though potential risks for LN metastasis are not present – additional surgery is performed, as well as cases at high risk for LN metastasis not treated by additional surgical resection. Although surgery allows precise staging and treatment of both local and LN disease, it does harbour a definite risk of morbidity and mortality, especially in elderly patients, or in those with rectal disease [9]; for this reason, surgical radicalisation in low risk patients is not recommended. On the other hand, post-polypectomy surgical under-treatment in high risk patients may determine a poorer oncologic outcome although the quality of surgical procedures in these patients is not homogeneous and LN harvesting (at least 12 LNs examined) is often sub-optimal [10-15].

To assess the post-polypectomy oncological outcome of patients with pT1 malignancy recruited during CRC screening, we conducted a retrospective analysis aimed to assess the relationship of the characteristics of the lesion with the risk of recurrence and disease-free survival, as well as to evaluate quality indicators of endoscopic and surgical management.

2 Material and methods

We retrospectively evaluated data on all consecutive colorectal pT1 tumours removed by endoscopy between 2004 and 2014 in the context of seven centres in the Piedmont Regional screening program in North-Western Italy. Details of screening program were previously reported [16]. Briefly, the Piedmont program has adopted **flexible** sigmoidoscopy (FS), offered once in the life-time at age 58, as the primary screening test; subjects refusing FS, or those older than 58 at the starting date of the program, are offered biennial fecal immunochemical test (FIT) **until** age 69. General practitioners are asked to exclude from invitation subjects with personal, or family (>1 first degree relative with CRC, or hereditary syndrome) history of CRC, personal history of inflammatory bowel disease, severe psychiatric symptoms, or those unable to provide informed consent.

2.1 Screening procedure. FS exams are performed in hospital endoscopy units, by experienced gastroenterologists. Subjects detected at FS with one polyp ≥ 10 mm, or one advanced adenoma, or > 2 adenomas, are referred for **total** colonoscopy (TC) assessment.

The FIT system (OC-Sensor, Eiken, Tokyo, Japan) adopted in the program is an automated quantitative immuno-turbidimetric assay performed over a single sample with a 20 µg Hb/gr faeces positivity cut off.

All eligible subjects receive a personal invitation letter and those with a positive screening test results are contacted by the screening staff and they are offered an appointment for a TC. Patients **in whom a CRC is detected** are eventually referred for surgical treatment within the same hospital where the screening endoscopy unit is located. Within the Italian NHS, screening, assessment and treatment are free of charge for the patient, who can also choose an assessment centre different form the one indicated by the screening program.

The inclusion criterion for the analysis was complete treatment for malignant pT1 polyps with endoscopic resection as the first line of treatment. Data on patient's demographics, TC quality, number and site of removed polyps, type of polypectomy, **immediate complications of**

polypectomy, characteristics of detected lesions, as well as stage of screen detected CRC, type of surgical intervention, number of LNs examined, are routinely recorded on the screening data base. For the purposes of this analysis we performed a record linkage of the screening data base with the regional hospital discharge records database **to assess the frequency of late complications of the endoscopic procedure, of complications of surgical interventions, as well as CRC recurrence rate**. Immediate and 30-day complications **of surgery** were classified according to Clavien's classification [17]. **The vital status at the end of follow-up period was ascertained for all trial subjects through an automated record linkage with the regional mortality registries, which also record the causes of death. Cancer-free survival and overall survival were also assessed**.

The cancerized adenomas were classified as lesions at low/ high risk for LN metastasis according to international guidelines present at the time of diagnosis [18,19]; classification has changed throughout the years and – consequently – the histological reporting form of endoscopically removed lesions has changed. At the beginning of the screening program, the malignant polyps were considered as lesions at low risk for LN metastasis if the following criteria were fulfilled: 1) complete resection with no margin involved 2) not poorly differentiated lesion 3) no vascular or lymphatic involvement. Since 2010, two more features were considered: 1) no tumour budding 2) absence of submucosal invasion $\geq$ 1 mm. For this reason, we retrieved for all cases the pathology report which was re-evaluated according to the new criteria by a gastroenterology trainee under the supervision of a pathologist with special interest in gastrointestinal pathology and our final analysis considered high risk lesions those showing at least one of the five abovementioned features.

According to the screening protocol, no additional surgery was required if the polyp was at low risk for LN metastasis and was completely removed endoscopically. Patients with high risk lesions had to undergo segmental colon resection following standard oncologic principles and conforming to guidelines recommending removal and examination of at least 12 LNs [20].

Residual disease was defined as the presence of any residual carcinoma at the site of polypectomy. Recurrence of disease was defined as the presence of locally, or regionally recurrent, disease, or distant metastases after a curative resection.

We present monitoring data for a national health service program. The mandate of the program includes the follow-up of the participating subjects of all stages of the screening process. All the participating subjects sign, in each phase of the program (first and second level), a contribution that also includes access to the clinical documentation for the program monitoring procedures. For these activities it was therefore not foreseen, at least during the period of study recruitment (until 2014), an approval by ethics committees. This is an institutional mandate. The study protocol conforms to the ethical guidelines of the 1975 Declaration.

2.2 Statistical analysis. Chi-square tests were used for comparisons of proportions and t-tests for comparisons of means (for continuous variables). Univariate and multivariable odds-ratios (OR) were estimated using logistic regression models, to assess predictors of surgical referral and surgical complications. Disease free and overall survival were estimated for endoscopy and surgical patients using the Kaplan-Meier method. For the purposes of this analysis each subject contributed to the follow-up from the date of treatment to the date of recurrence, emigration, or death, or to December 31st 2014, whichever came first. To achieve a more reliable estimate of the risk of recurrent disease, we run also a sensitivity analysis excluding patients not diagnosed with a recurrence, who had not cumulated a minimum follow-up time of 24 months. All tests were 2-sided and statistical significance was set at 0.05.

3 Results

In the ten-year period under consideration, a total number of 520 malignant pT1 polyps in 520 patients were observed; of these, 128 (24.6%) were referred for direct surgical intervention and were not included in the analysis. The indications for direct surgery were: size of the lesion, depressed morphology, no-lifting sign, technical problems during endoscopic resection.

Of the remaining 392 malignant polyps, 340 (86.7%) were resected en-bloc and 52 (13.3%) by piece-meal technique. According to subsequent histological evaluation, 250 (63.8%) patients were considered at high risk for LN metastasis, or residual disease at the site of polypectomy, 76 (19.4%) at low risk and in 66 (16.8%) risk stratification was not possible due to sub-optimal histologic sample or incomplete histology report. In particular, out of 340 en-bloc removed lesions, 230 (67.6%) showed one, or more, high risk parameters, 67 (19.7%) could be classified in the low-risk group, while the level of risk could not be assessed in 43 (12.6%) cases with incomplete pathology report; the corresponding figures for the 52 polyps resected by piece-meal technique were 20 (38.5%), 9 (17.3%) and 23 (44.2% - OR for incomplete report: 0.18, 95% IC: 0.09-0.36; reference en-bloc). Out of 392 patients with endoscopically removed polyps, 120 (30.7%) did not undergo further treatments (Group 1) and 272 (69.3%) were referred for radicalisation surgery (Group 2). Demographic, clinical and procedural characteristics in both groups are shown in Table 1.

Table 1

No significant differences were found for age and gender. In patients who underwent radicalisation surgery, lesion size was significantly larger; right colon localization and sessile/flat morphology were significantly more frequent. Fifty-five patients in Group 1 (45.8%) were considered at high risk for LN metastases according to the new criteria, but 34 of them (61.8%) showed low risk parameters according to international guidelines present at the time of diagnosis; the remaining 21 patients refused surgery, or had significant comorbidities contraindicating surgery.

Out of 272 patients in Group 2, 195 (71.6%) showed high-risk and 21 (7.8%) low-risk histological features following endoscopic resection, while 56 (20.6%) had an incomplete histology report. At multivariable analysis (Table 2), factors independently associated with surgery referral were female sex, size larger than 25 mm, non-pedunculated shape, proximal site and the high-risk histology features.

Table 2.

3.1 Endoscopy quality indicators. Out of 392 patients undergoing endoscopic resection, 1 (0.26%) suffered from bleeding requiring hospitalization; no late complication of endoscopy was observed among the 120 patients who were not referred for surgery.

3.2 Surgery quality indicators. Thirty-eight of 272 patients (13.9%) sent to radicalisation surgery showed residual disease at the site of polypectomy and all of them belonged to the high-risk group. One more patient showed liver metastases, but no neoplastic LNs at the moment of surgery.

The median number of retrieved LNs per patient was 9 (mean: 9.89); a minority of patients had no LNs observed in the specimen (33, 12.1%), 73 (26.8%) had less than 7 LNs removed, 77 (28.3%) had 7-11 LNs removed and 89 (32.7%) ≥ 12 LNs.

Post-surgery complications were documented in 42 out of 272 patients (15.4%) (Table 3); 35 (83.3%) occurred immediately, or within 30 days after surgery, while 7 (16.7%) were observed after 30-days post-surgery.

Table 3.

Women seemed less prone to develop complications (OR: 0.30, 95% IC 0.16-0.58) while removal of ≥7 LNs was associated to a higher risk of complications (OR: 2.60, 95% IC 1.26-5.37). There

were no deaths related to surgery, but 5 (11.9%) patients had to undergo a second surgical procedure.

3.3 Residual disease and nodal involvement. In patients who underwent surgical resection and had at least 1 LN examined (239), the rate of LN positivity was 5.4% (13/239), but if only high-risk patients are considered, the rate increased up to 6.3% (11/173). Correlation between number of removed LNs and prevalence of neoplastic positivity stratified according to the risk class is reported in Table 4.

Table 4.

No positive LN was observed among low risk patients, irrespective of the number of retrieved LNs. Among high risk patients, those who had more than 6 LNs removed showed more frequently LN metastases (7.7%) compared with patients with lesser LNs retrieved (3.5%) (this difference was not statistically significant).

Residual disease in the bowel wall was observed in 13.8% of patients undergoing surgical resection: it was less frequent among subjects who had their lesion resected en bloc (10.4% as compared to piece-meal 33.3%; OR:0.23, 95%CI:0.10-0.54) and, among subjects with en-bloc resection, among those detected with pedunculated lesions (5.4% as compared to sessile 16.8%; OR:0.28, 95%CI:0.10-0.77).

Nodal involvement was more frequent (OR: 5.79; 95%CI:1.84-21.38) among subjects with residual disease (6 out of 38 patients, 15.8% versus 7 out of 223 patients, 3.1%);

Adjusting for age, gender and size of the lesion (Table 5), excision technique and morphology of the lesion emerged as predictors of residual disease, which was less likely when the lesions had been excised en-bloc (OR: 0.23; 95%CI: 0.10-0.54), as opposed to piecemeal resection, and, among lesions resected en-bloc, for pedunculated (OR: 0.28; 95%CI: 0.10-0.77), as compared to sessile/flat lesions.

Table 5.

3.3 Follow up. The mean follow-up time was 53.4 months (±33.4) in Group 1 and 57.1 months (±31.1) in Group 2. The follow-up protocol included an early endoscopic control (within 6 months) followed by a TC at 1-3 years. No recurrence was observed among the 55 low-risk patients treated by endoscopic resection alone, as well as among the 21 low-risk patients and the 56 patients with undetermined histologic features, who underwent additional surgery after endoscopic resection.

Recurrence free survival was similar for the two groups [Figure 1]: for the high-risk patients with radicalisation surgery, the recurrence rate was 1.5% (3/195); in each of them (100%), ≤7 LNs were removed during surgery; among patients with polypectomy only, one out of 55 high risk patients (1.8%) and one of 10 patients (10%) with incomplete histologic features showed neoplastic recurrence: both had refused surgery.

Figure 1.

Of the 272 patients who underwent surgery, 2 (0.7%) died from unrelated causes, while 3 (1.1%) died of disease progression (1 from local recurrence and 2 of metastatic disease): all belonged to the high-risk group. Among Group 1, 5 (4.1%) patients died from unrelated causes, none of disease progression.

4 Discussion

Our study showed a good oncologic outcome in patients with pT1 malignant polyps endoscopically removed during colorectal cancer screening confirming previous population-based data [21]. In particular, the results of this study indicate that in malignant polyps considered safe to **be removed** endoscopically by current guidelines [19], no LNs metastasis was observed during follow up with a recurrence-free survival rate of 100%.

Only two patients, out of 120 not referred for surgery, showed disease progression: one could be classified in the high-risk group, when considering those histological features introduced more recently, while in the second case the histology report was not including the necessary information to classify patient's level of risk. Among patients undergoing surgery, disease recurrence was found in 3 patients (1.5%) and all of them had high-risk malignant polyps.

CRC related deaths (due to disease progression) were observed only among Group 2 patients, while overall mortality was slightly higher in group 1 (4.1%) than in group 2 (1.8%), possibly as a result of higher prevalence of co-morbidity, contraindicating surgery; however, the difference did not reach the level of statistical significance.

Compared to previous studies on population-based data [6,22-23], we found a low rate (6.3%) of nodal metastases among subjects with lesions showing high-risk histological features as well as a low risk of residual disease among subjects with pedunculated lesions.

As compared to other similar studies, the direct surgery referral rate was higher both in a multicenter analysis of 5 screening programs [24] in North-Eastern Italy (30%) and in the UK [25] bowel cancer screening program (43%), with a lower referral rate for radicalisation surgery (57% and 53% respectively, as compared to 69%); the overall recurrence rate was similar in our program, as in the Italian multicenter study (1.3%), while it was higher (3.2%) in UK bowel screening program, over a shorter follow-up interval. Mortality data are comparable in our study as in the other reports from screening [24,25] or clinical settings [22]. **The incidence of residual disease in the subgroup of patients undergoing surgical intervention after endoscopic resection was**

within the range observed in other studies conducted in screening settings in North-Eastern Italy [24] and in UK [25]. A higher frequency of residual disease has been reported in clinical [26-28] and population based [29] series.

However, the adoption of different definitions (including only residual disease in the bowel wall, or also nodal metastases) limits the comparability of the reported findings. Also, the diffusion of screening, as well as the improvement of endoscopic techniques are likely to influence the pattern of presentation of the disease. Screen detected cases might show more favourable prognostic parameters (nodal involvement in pT1 CRCs seems less frequent in more recent screening series [24,25] as compared to reports dating back to the pre-screening era [26-28]) while the lower risk of recurrence observed among patients with sessile lesions in the more recent years [29] would suggest that excision technique has improved over time.

Our results are confirming that efforts to improve quality of pathologic evaluation and reporting of histologic specimens are needed also in the screening setting, as recently reported by an Italian study [30]. In spite of recommendations of the screening protocol and of EU and GISCoR guidelines, only a minority (<25%) of specimens related to malignant polyps were reviewed for a second opinion by a pathologist with a special interest in gastrointestinal pathology.

Also, about 16.8% of removed polyps had an incomplete histology report, in most cases related to lacking data from pathologic examination. The great majority of these patients (84.8%) underwent surgery showing a LNs positivity rate of 3.5%, suggesting that many of them probably had low risk malignant polyps.

An accurate pathology report was not necessarily taken into account when making decisions about patient's management. We still observed a fairly high surgery referral rate (27.6%) among patients with well characterised low-risk cancerized adenomas. Many studies [21,22,31,32] documented that endoscopic removal of these lesions is associated with very low rates of recurrence and with a high disease-free and overall survival, often approaching 100% at five-year follow-up, while surgical treatment may be associated with a high potential for morbidity. According to our data, about 15%

of patients experienced post-surgery complications, with a significant increase of direct and indirect costs. **Post-polypectomy and post-surgery complications rates observed in our patients are comparable with those reported by other studies [21,33,34] addressing the clinical and surgical outcomes in carriers of malignant colonic polyps.**

In our series the mean number of resected LNs at surgery was below the threshold indicated by guidelines [20] which suggest a minimum number of 12. Although other studies [33,35,36] have previously suggested that less than 12 LNs may be sufficient to adequately stage pT1 colon cancer, the rate of LN evaluation in our study (< 7 LNs in about 40% of patients) is probably inadequate. We are not able to explain this dismal LN evaluation which also has implications for adjuvant therapy discussions as well as cancer surveillance after resection.

This study has certain limitations. First, it is a retrospective study of clinical records; however, the data are likely to be reliable because all patients with malignant polyps removed by endoscopy at 7 Screening Centres between 2004 and 2014 were included and no one was lost to follow up. The second limitation is that it was not randomized; however, we think that the possible selection bias is minimal because the patients' characteristics and the median follow-up periods were not significantly different between the 2 groups.

In conclusion, the results of our study can be summarized as follows. First, in a screening setting, the oncologic outcome of patients with malignant pT1 polyps removed by endoscopy is excellent. Second, there is ample room for improvement regarding diagnostic accuracy, in order to reduce surgical overtreatment. Third, quality of surgical resection as measured by LNs counts is still sub-optimal and rigorous adherence to guidelines concerning LNs harvesting is strongly recommended to decrease the recurrence risks.

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‘The Author(s) declare(s) that there is no conflict of interest’.

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Figure 1. Recurrence free survival by type of treatment (Log-rank test p =0.80)

Table 1. Baseline characteristics of patients and polyps

	Polypectomy only (n = 120)	**Radicalisation surgery (n = 272)**	**OR (95%CI); p**
Age (mean ± SD)	64.45 (± 4.25)	64.74 (± 4.46)	p = 0.54
Gender			
Male (n, %)	86 (71.6%)	167 (61.4%)	1.5 (0.97 - 2.71)
Female (n, %)	34 (28.4%)	105 (36.6%)	
Site			
Right colon	14 (11.7%)	55 (20.2%)	1.94 (1.02 – 3.69)
Left colon	86 (71.7%)	174 (64%)	1
Rectum	20 (16.6%)	43 (15.8%)	1.06 (0.50-1.92)
Size (mm, mean ± SD)	16.13 (± 7.90)	20.14 (± 12.69)	p = 0.002
Morphology			
Pedunculated	87 (72.5%)	141 (51.8%)	2.45 (1.50 – 4.01)
Sessile/flat	33 (27.5%)	131 (48.2%)	
LNs metastases risk			
High risk	55 (45.8%)	195 (71.7%)	9.29 (5.17 – 16.67)
Low risk	55 (45.8%)	21 (7.8%)	1
Undetermined	10 (8.4%)	56 (20.5%)	14.67 (6.33 – 33.97)

OR = odd ratio; CI = confidence interval; p = p value; SD = standard deviation

Table 2. Multivariate analysis of factors associated with radicalisation surgery

Features	OR*	95%CI
Gender		
Male	1	
Female	1.78	1.05 – 3.02
Age		
< 65 years	1	
> 65 years	0.92	0.56 – 1.52
Polyp size		
1-15 mm	1	
16-25 mm	1.17	0.68 – 2.02
> 25 mm	2.9	1.46 - 5.78
Polyp morphology		
Sessile/flat	1	
Pedunculated	0.35	0.21 – 0.51
LNs metastases risk		
Undefined risk	1	
Low risk	0.17	0.09 – 0.31
High risk	2.01	1.03 – 3.90
Site		
Distal	1	
Proximal	2.13	1.08 – 4.24

*ORs adjusted for all the variables n the model

Table 3. Postoperative complications according to Clavien's classification

Post-surgical outcomes	Number of patients
Clavien grade I	
Abdominal pain	1
Vomiting	2
Biliary colic	2
Symptomatic hyperuricemia	1
Not specified	3
Clavien grade II	
Wound infection	7
Urinary infection	2
Acute pancreatitis	1
Pneumonia	2
Clavien grade III	
Gastrointestinal bleeding	11
Incisional hernia	3
Clavien grade IV	
Anastomotic leakage	2
Myocardial infarction	1
Hemoperitoneum	1
Pulmonary embolism	2
Anastomotic stenosis	1

Table 4. Pre-surgery histological risk parameters: correlation between number of LNs removed and nodal involvement

	Number of LNs removed		
	< 7	7-11	≥ 12
Low-risk patients	9	3	9
Positive LNs (n, %)	0 (0%)	0 (0%)	0 (0%)
High-risk patients	79	60	56
Positive LNs (n, %)	2 (2.5%)	5 (8.3%)	4 (7.1%)
Incomplete/undetermined report	18	14	24
Positive LNs (n, %)	0 (0%)	0 (0%)	2 (8.3%)

Table 5. Multivariate analysis of predictors of risk of residual disease

Features	OR*	95%CI
Gender		
Male	1	
Female	0.66	0.29 - 1.50
Age		
< 65 years	1	
> 65 years	0.74	0.35 - 1.58
Polyp size		
1-15 mm	1	
16-25 mm	1.10	0.39 - 3.14
> 25 mm	3.58	1.46 - 8.81
Polyp morphology		
Sessile/flat	1	
Pedunculated	0.34	0.15 – 0.76
Resection		
En-bloc	1	
Piece-meal	3.25	1.42 – 7.43

*ORs adjusted for all the variables in the model