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Metachronous neoplasms in patients with laterally spreading tumours during surveillance

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Abstract

Background: Laterally spreading tumours represent a major challenge for endoscopic detection and resection.

Objective: To examine synchronous and metachronous neoplasms in patients with laterally spreading tumours.

Methods: We prospectively collected colonoscopy and histopathology data from patients who underwent colonoscopy in our centre at up to 6 years' follow-up. Post-resection surveillance outcomes between laterally spreading tumours, flat colorectal neoplasms 10 mm or greater, and large polypoid colorectal neoplasms, polypoid colorectal neoplasms 10 mm or greater, were compared.

Results: Between 2008 and 2012, 8120 patients underwent colonoscopy for symptoms (84.6%), screening (6.7%) or surveillance (8.7%). At baseline, 151 patients had adenomatous laterally spreading tumours and 566 patients had adenomatous large polypoid colorectal neoplasms. Laterally spreading tumour patients had more synchronous colorectal neoplasms than large polypoid colorectal neoplasm patients (mean 3.34 vs. 2.34, $p < 0.001$). Laterally spreading tumour patients significantly more often developed metachronous colorectal neoplasms (71.6% vs. 54.2%, $p = 0.0498$) and colorectal neoplasms with high grade dysplasia/submucosal invasion than large polypoid colorectal neoplasm patients (36.4% vs. 15.8%, $p < 0.001$). After correction for age and gender, laterally spreading tumour patients were more likely than large polypoid colorectal neoplasm patients to develop a colorectal neoplasm with high grade dysplasia or submucosal invasion (hazard ratio 2.9, 95% confidence interval 1.8–4.6). The risk of metachronous colorectal cancer was not significantly different in laterally spreading tumours compared to large polypoid colorectal neoplasm patients.

Silvia Sanduleanu-Dascalescu and Ad A. M. Masclee are shared last authors.

Conclusion: Patients with laterally spreading tumours developed more metachronous colorectal neoplasms with high grade dysplasia/submucosal invasion than large polypoid colorectal neoplasm patients. Based on these findings endoscopic treatment and surveillance recommendations for patients with laterally spreading tumours should be optimised.

KEYWORDS
colorectal neoplasms, laterallyspreadingtumours, metachronousneoplasms, non-polypoidcolorectal neoplasms, training

Key Summary

Summarize the established knowledge on this subject

- Laterally spreading tumours (LSTs) are a heterogeneous group of large, predominantly benign flat neoplasms that can be endoscopically treated, requiring additional time and expertise
- LSTs consist of different endoscopic subtypes which are predictive of the risk of submucosal invasion (SMI)
- Patients with LSTs harbour more synchronous neoplasms than patients with large polypoid colorectal neoplasms (LP-CRNs)

What are the significant and/or new findings of this study?

- Patients with LSTs more frequently have metachronous neoplasms than patients with LP-CRNs, justifying strict surveillance
- LSTs can be effectively managed by conventional endoscopic resections in most cases

INTRODUCTION

Non-polypoid (flat and depressed) colorectal neoplasms (NP-CRNs) are common precursors of colorectal cancer (CRC).[1–4] Up to 15% of patients undergoing elective colonoscopy have NP-CRNs.[1,3] A significant subset of NP-CRNs are the Laterally Spreading Tumours (LSTs), which are lesions minimally 10 mm in size, growing laterally along the mucosa, rather than luminal or submucosal growth.[5] LSTs have a high risk of containing SMI[6] and a risk of local recurrence after endoscopic resection,[7,8] emphasising the need for an effective treatment. Endoscopic resection of LSTs is challenging and requires additional expertise.[9] Endoscopic mucosal resection (EMR) frequently results in piecemeal resection with LST residue and high local recurrence rates[7,10] leading to superfluous colonoscopies, resection procedures and surgery referrals.[11]

Previous studies have shown that patients with LSTs have a higher risk of synchronous neoplasms.[12,13] This finding could affect the surveillance strategy for LST patients. At our academic endoscopy unit, we examined the prevalence of LSTs, endoscopic subtypes and histology in our prospective colonoscopy database. We aimed to explore whether LST patients more frequently develop synchronous and metachronous neoplasms, compared to patients with LP-CRNs.

METHODS

From 2007 onwards, all endoscopists (faculty and trainees) receive regular extensive training in the detection, diagnosis and resection of NP-CRNs.[14] The training curriculum consists of lectures, video training using accredited programmes and personal feedback during colonoscopy.[14] Special attention is given to the application of selective chromo-endoscopy and EMR. The present study was approved by the Medical Ethical Review Committee of the Maastricht University Medical Centre (MEC 14-4-046), Dutch trial register (NTR4844). The need for individual informed consent was waived.

Cohort

Between February 2008 and February 2012, all patients who underwent colonoscopy for screening, surveillance or symptoms, were included. This was before the start of the national CRC screening programme. Patients aged less than 18 years, with hereditary polyposis syndrome, inflammatory bowel disease or prior colectomy were excluded. All findings within the first 6 months after the first colonoscopy were regarded as baseline findings. The majority of colonoscopies were performed by endoscopy trainees under direct supervision of 11 senior endoscopists, who ensured quality and

helped with resections. All patients received split-dose bowel cleansing. High definition Pentax endoscopes were used.

Post-polypectomy surveillance colonoscopy was performed according to national[15] and international guidelines.[16,17] Three and 5-year surveillance intervals were recommended after resection of LSTs or LP-CRNs. Piecemeal resection was additionally followed by surveillance colonoscopies within 6 months to ensure radicality of resection. Clinical and surgical follow-up data were collected for each patient with large (10 mm) colorectal neoplasms (CRNs) at index colonoscopy up until 6 years after inclusion or until death occurred.

Definitions

LSTs are colonic lesions growing laterally along the mucosa rather than upward (luminal) or downward (submucosal), with a minimal diameter of 10 mm (Paris 0-IIa, 0-IIb, 0-IIaþIIc or 0-IIaþIs).[5] Serrated lesions were included for descriptive purposes, but excluded in the risk analyses. LP-CRNs are defined as polypoid neoplasms (Paris 0-Ip, 0-Is or 0-Isp) of at least 10 mm in size. The colonic location was referred to as either proximal or distal from the splenic flexure. Lesion size was measured using a biopsy forceps/minisnare. Patients with both LSTs and LP-CRNs were considered as LST patients.

LSTs were classified based on their endoscopic appearance using the Kudo classification into granular and non-granular.[5] Granular LSTs are classified into granular homogeneous subtype (LST-G-H) and granular nodular mixed subtype (LST-G-NM). Non-granular LSTs are classified into non-granular flat elevated subtype (LST-NG-FE) and non-granular pseudo-depressed subtype (LST-NG-PD).

Detection of LSTs

Colonoscopy records including photo documentation were independently reviewed by two study investigators (RMMB and LCC). In case of uncertainty, data were reviewed by the study supervisor (SSD) and discussed to achieve consensus. The location of neoplasms, size, shape (Paris classification,[18] Kudo classification of LSTs),[5] histopathology and resection modality (i.e., endoscopic resection [en bloc vs. piecemeal] or surgery) were recorded.

The histopathology of all CRNs was addressed by GE pathologists according to the World Health Organization classification.[19] CRNs comprised adenomas, serrated lesions and early cancers. Large flat lesions that turned out to be advanced carcinoma (T2–4) after biopsy or resection were not classified as LSTs. Suspected CRNs with normal or inflammatory histology were excluded from analysis. Adenomas were subdivided into tubular, tubulovillous and villous adenomas. SMI was defined as carcinogenic cells invading the muscularis mucosae. Serrated lesions were subdivided into hyperplastic polyps, sessile serrated lesions with and without dysplasia and traditional serrated adenomas.

Endoscopic resection was considered complete when careful visual inspection showed no residual neoplastic tissue. All reports of follow-up colonoscopy were reviewed for the presence/absence of neoplastic tissue at the previous location of the LST. The presence of visually and/or histologically confirmed neoplastic tissue after successful resection was considered as residue/recurrence. Surgery reports and referral letters were reviewed and surgery was categorised into primary surgery (without endoscopic resection attempt) and additional surgery (after endoscopic resection attempt).

Statistical analysis

Numerical variables were presented with means (standard deviation [SD]), while numbers (%) were used for categorical variables. Time trends in LST prevalence were tested using a chi-square or Fisher's exact test, and time trends in treatment were tested using a binary logistic regression model for surgical referral (yes/no) and endoscopic en bloc resection (yes/no) correcting for year of study, LST size and the presence of SMI. Colonoscopic findings at index colonoscopy between LST patients and LP-CRN patients were compared using chi-square tests for binary variables and independent samples *t*-tests for numeric variables. We compared findings during follow-up colonoscopy between both groups using a multivariable logistic regression model for binary variables. Because of the excessive zero count in some numerical variables, Poisson regression analysis with zero inflation correction was used to compare the means between groups. In addition, the number of CRNs at index colonoscopy and the number of follow-up colonoscopies were accounted for in both models. In a sub-analysis, the same afore-mentioned models were applied in LST patients to compare subtypes and size (LSTs < 20 and 20 mm). In the case of small groups ($n < 20$) an additional Fisher's exact test was performed. The death-censored event-free rate was compared between LST and LP-CRN patients using a Cox regression model correcting for age and sex, in which event is the detection of CRNs with high grade dysplasia (HGD) or SMI. Two-sided p values of 0.05 or less were considered statistically significant. IBM SPSS version 23 was used for all analysis, except for the zero inflation corrected model, which was analysed using R statistics version 3.1.2 by using the Political Science Computational Laboratory package (PSCL).[20]

RESULTS

Figure 1 shows the study flowchart. Between February 2008 and February 2012, 8120 patients were examined (mean age 58.9 years [SD 16.0], 46.0% men).

Indications for colonoscopy were symptoms (84.6%), screening (6.7%) or surveillance (8.7%). At the index colonoscopy, 223 LSTs in 188 patients were found (2.3% of all patients). Furthermore, 810 LP-CRNs were found in 610 patients at index colonoscopy (7.5% of all patients). The mean LP-CRN size was 19.0 mm (SD 14.4, range 10–130 mm) and did not significantly differ from that of LSTs, namely 19.4 mm (SD 10.3, range 10–70 mm, p=0.686).

Photo documentation was available in 96.4% of LST cases. The proportion of LST-G-H, LST-G-NM, LST-NG-FE and LST-NG-PD LSTs was 18.6%, 8.8%, 62.8% and 9.8%, respectively. Table 1 shows the patient characteristics and histopathology, by LST subtype at baseline. The LST detection rate and rate of HGD or SMI within LSTs did not significantly change over time ($p = 0.935$, $p = 0.760$ and $p = 0.277$, respectively; Table 2).

Resection

Of the 223 LSTs found, 152 were resected endoscopically; 38 LSTs were left in place (older age, comorbidities, frailty, patient's preference). Twenty-two LSTs were primarily referred for surgical resection (suspected malignancy, technical difficulty for endoscopic resection). In 11 cases, additional surgery was performed after attempted endoscopic resection. Logistic regression after correction for lesion size and the presence of SMI showed that the proportion of surgical referrals remained stable over time (odds ratio [OR] per year 0.8, 95% confidence interval [CI] 0.5–1.2, $p = 0.220$) while the proportion of endoscopic en bloc resections increased (OR per year 1.5, 95% CI 1.1–1.9, $p = 0.007$; Figure 2). Among LST patients who underwent surveillance, 15 (14.2%) showed residue/recurrence.

Synchronous neoplasms

We compared 151 patients with one or more adenomatous or SMI LSTs at index colonoscopy, with 566 patients with one or more adenomatous or SMI LP-CRN at index colonoscopy (Table 3). At index colonoscopy, the mean number of synchronous CRNs, adenomas and CRNs with HGD or SMI were significantly higher ($p < 0.001$, $p < 0.001$ and $p = 0.001$, respectively) in LST patients than in LP-CRN patients. The mean number of synchronous CRCs was significantly lower in LST patients versus LP-CRN patients (0.17 vs. 0.28, $p = 0.003$). LST patients had significantly more NP-CRNs versus LP-CRN patients (mean of 1.52 vs. 0.09; $p < 0.001$).

Metachronous neoplasms

LST patients more often had a surveillance colonoscopy within 6 years than LP-CRN patients (58.3% vs. 45.9%, $p = 0.007$) and the interval between index and surveillance was significantly shorter (1.85 vs. 2.55 years, $p < 0.001$). During the first surveillance colonoscopy, LST patients more often had an advanced adenoma than LP-CRN patients (22.7 versus 12.7%, $p = 0.024$). Five CRCs were found at first surveillance colonoscopy, all in LP-CRN patients and none in LST patients ($p = 0.336$).

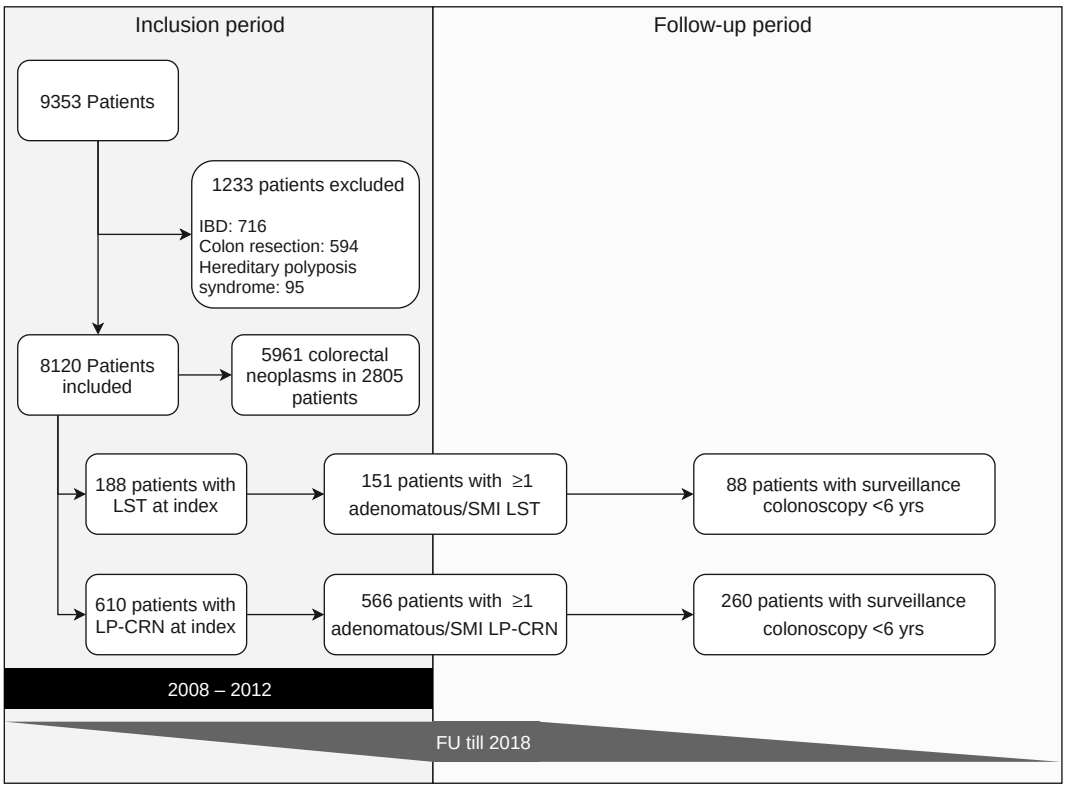

FIGURE 1 Flowchart explaining the data collection. Some excluded patients presented with not one but two exclusion criteria. SMI, submucosal invasion

TABLE 1 Endoscopic and histological characteristics of LSTs

	LST-G-H (*n*=40)	LST-G-NM (*n*=19)	LST-NG-FE (*n*=135)	LST-NG-PD (*n*=21)	Unknown (*n*=8)	Total (*n*=223)
Mean size in mm (SD)	22.2 (9.7)	26.8 (9.3)	16.9 (9.0)	21.9 (10.3)	27.6 (20.1)	19.4 (10.3)
Location, *n* (%)						
Caecum	18 (45.0)	7 (36.8)	31 (23.0)	6 (28.6)	3 (37.5)	65 (29.1)
Ascending colon—splenic flexure	17 (42.5)	5 (26.4)	78 (57.7)	9 (42.9)	2 (25.0)	111 (49.3)
Descending colon—sigmoid	3 (7.5)	2 (10.6)	18 (13.3)	2 (9.6)	2 (25.0)	26 (11.6)
Rectum	2 (5.0)	6 (31.6)	8 (5.9)	4 (19.0)	1 (12.5)	21 (9.4)
Histopathology, *n* (%)						
Submucosal invasion	1 (2.5)	3 (15.8)	4 (2.9)	5 (23.8)	1 (12.5)	14 (6.2)
Adenoma HGD	8 (20.0)	9 (47.4)	18 (13.3)	7 (33.3)	2 (25.0)	44 (19.7)
Adenoma LGD	24 (60.0)	4 (21.1)	68 (50.4)	7 (33.3)	3 (37.5)	106 (47.5)
SSL	3 (7.5)	1 (5.3)	24 (17.7)	1 (4.8)	0 (0)	29 (13.0)
TSA	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.4)
Hyperplastic polyp	4 (10.0)	2 (10.5)	20 (14.8)	1 (4.8)	2 (25.0)	29 (13.0)
Resection, *n* (%)						
En bloc resection	13 (32.5)	2 (10.5)	63 (46.7)	5 (23.8)	2 (25.0)	85 (38.1)
Piecemeal resection	13 (32.5)	7 (36.8)	37 (27.4)	8 (38.1)	2 (25.0)	67 (30.0)
Surgery	6 (15.0)	8 (42.1)	10 (7.4)	5 (23.8)	4 (50.0)	33 (14.8)
No resection	8 (20.0)	2 (10.6)	25 (18.5)	3 (14.3)	0 (0)	38 (17.1)

Abbreviations: HGD, high grade dysplasia; LGD, low grade dysplasia; LST, laterally spreading tumour; LST-G-H, homogenous granular LSTs; LST-G-NM, nodular mixed granular LSTs; LST-NG-FE, flat elevated non-granular LSTs; LST-NG-PD, pseudo-depressed non-granular LSTs; SD, standard deviation; SSL, sessile serrated lesion; TSA, traditional serrated adenoma.

TABLE 2 Time trends in LST diagnosis

Findings	Year 1	Year 2	Year 3	Year 4
Number of colonoscopies	1941	2098	2074	2007
Number of CRNs (mean per colonoscopy)	1521 (0.8)	1856 (0.9)	1718 (0.8)	2150 (1.1)
Number of LSTs (% of lesions)	54 (3.6)	55 (3.0)	54 (3.1)	60 (2.8)
Indication of colonoscopy (% of colonoscopies) screening	161 (8.3)	145 (6.9)	130 (6.3)	108 (5.4)
Surveillance[a]	204 (10.5)	162 (7.7)	181 (8.7)	155 (7.7)
Symptoms	1576 (81.2)	1791 (85.4)	1763 (85.0)	1744 (86.9)
Submucosal invasion (% of LSTs)	1 (1.9)	5 (9.1)	5 (9.3)	3 (5.0)
High grade dysplasia (% of LSTs)	9 (16.7)	13 (23.6)	9 (16.7)	11 (18.3)
Proximal location (% of LSTs)	45 (83.3)	36 (65.5)	46 (85.2)	50 (83.3)
10–19 mm (% of LSTs)	27 (50.0)	30 (54.5)	27 (50.0)	36 (60.0)
20–29 mm (% of LSTs)	15 (27.8)	7 (12.7)	15 (27.8)	16 (26.7)
30 mm (% of LSTs)	12 (22.2)	18 (32.7)	12 (22.2)	8 (13.3)

Abbreviation: CRN, colorectal neoplasm; LST, laterally spreading tumour.

[a]Surveillance indicated before the start of the study.

During follow-up, LST patients more often underwent surveillance colonoscopies than LP-CRN patients (58.3 vs. 45.9%). Overall, 36.4% of all patients with adenomatous LSTs at baseline developed one or more CRNs with HGD or SMI during follow-up compared with 15.8% of patients with LP-CRNs at baseline. After correction for the number of CRNs at index and the number of follow-up colonoscopies, HGD or SMI was significantly more often found during follow-up in LST patients than LP-CRN patients (36.4 vs. 15.8%, $P < 0.001$). A Cox

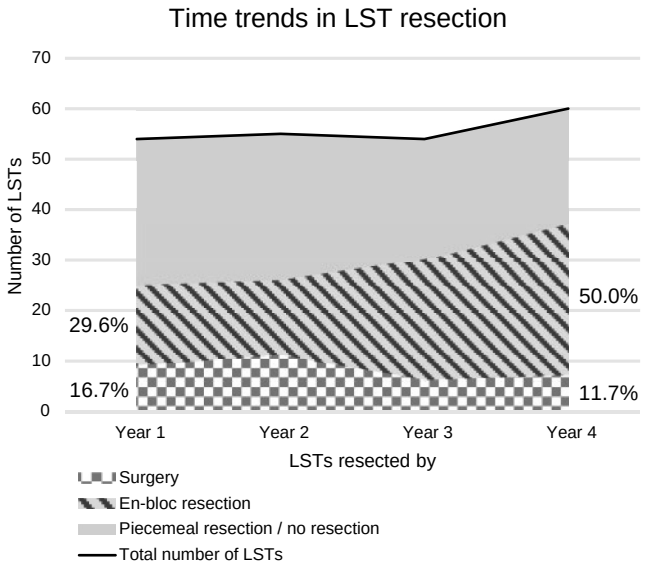

FIGURE 2 Time trends in resection of LSTs after training at our institution. LSTs, laterally spreading tumours

regression model correcting for age and gender showed a hazard ratio of 2.9 (95% CI 1.8–4.6) for LST patients to develop a CRN with HGD or SMI within 6 years (Figure 3). This association was not materially influenced by the initial indication for colonoscopy. The mean number of adenomas found during follow-up was significantly higher for LST patients versus LP-CRN patients (1.82 vs. 1.24, $P = 0.032$; Table 4). During follow-up, LST patients more often had metachronous NP-CRNs than LP-CRN patients (44.3 vs. 20.0%, $P < 0.001$).

Within LST patients, patients with LST-NG-PD developed fewer adenomas during follow-up than patients with other subtypes (mean 0.82 vs. 2.08, P=0.018). LST patients with LSTs of 20 mm or greater developed only slightly more neoplasms (mean 2.00 vs. 1.89, $P = 0.045$) than patients with smaller LSTs (< 20 mm). There was no significant effect of LST size on the number of adenomas.

DISCUSSION

In this population-based colonoscopy cohort, the prevalence of LSTs was low and remained stable over time. After training, endoscopic resection of LSTs became more efficient, along with increasing endoscopists' experience.

An important finding of our study is that LST patients not only have more synchronous but also more metachronous neoplasms (including more HGD/SMI) compared to LP-CRN patients. The number of surveillance colonoscopies performed was also higher in LST patients. This may have been the result of technical difficulties with endoscopic resection of LSTs and of more synchronous CRNs found in such patients. Therefore, more intensive surveillance could detect additional small CRNs. After correction for the number of surveillance colonoscopies, however, the number of metachronous CRNs with HGD or SMI remained significantly higher in LST patients.

Hypothetically, longer surveillance intervals facilitate adenomas to progress and become more advanced. LP-CRN patients had longer intervals between the index and first surveillance colonoscopy than LST patients, but fewer metachronous CRNs with HGD or SMI were found. Of note is that all five cases of CRC detected at first surveillance colonoscopy were diagnosed in LP-CRN patients, while we previously found a low rate of post-colonoscopy CRCs in our region (0.8 per 1000 colonoscopies, 0.34 per 1000 person-years of follow-up).[21]

Little is known about the influence of neoplasm shape on the rate of metachronous CRNs. A previous study in a US-based population compared findings of the first surveillance colonoscopy in patients

TABLE 3 Synchronous findings in patients with one or more LSTs at index colonoscopy compared with patients with one or more LP-CRNs at index colonoscopy

Clinical features	Patients with 1 ≥ neoplastic LST (*n*=151)	Patients with 1 ≥ LP-CRN (no LSTs; *n*=566)	*p* value
Mean age, years (SD)	67.6 (10.7)	67.9 (11.5)	0.800
Men (%)	83 (55.0)	313 (55.3)	0.942
Mean FU time, years (SD)	5.11 (1.76)	4.90 (1.92)	0.189
Mean time till last FU scopy, years (SD)	3.59 (1.65)	3.55 (1.70)	0.881
Mean number of FU scopies (SD)	2.15 (1.36)	1.51 (0.79)	<0.001
Mean number of CRNs at index (SD)	3.34 (2.61)	2.34 (2.38)	<0.001
Mean number of non-polypoid CRNs at index (SD)	1.52 (1.00)	0.09 (0.37)	<0.001
Mean number of CRNs with HGD/SMI at index (SD)	1.96 (1.56)	1.51 (1.17)	0.001
Mean number of adenomas at index (SD)	2.71 (2.33)	1.90 (2.04)	<0.001
Mean number of CRCs at index (SD)	0.17 (0.42)	0.28 (0.47)	0.003
Mean number of serrated neoplasms at index (SD)	0.50 (1.14)	0.37 (0.88)	0.221

Abbreviations: CRC, colorectal cancer; CRN, colorectal neoplasm; FU, follow-up; HGD, high grade dysplasia; LP-CRN, large polypoid colorectal neoplasm; LST, laterally spreading tumour; SD, standard deviation; SMI, submucosal invasion.

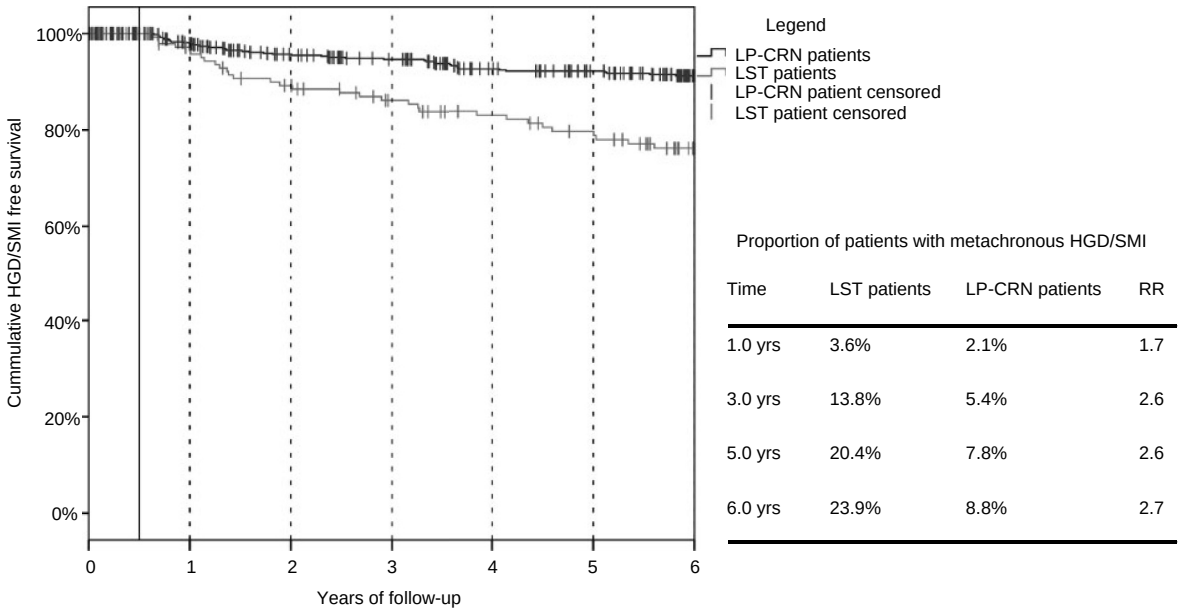

FIGURE 3 Colorectal neoplasm (CRN) with HGD or SMI-free survival of 6 years of follow-up in patients with large CRNs at index (Kaplan–Meier). Follow-up started after 0.5 years (vertical line) as all CRNs found within 6 months were counted as index CRNs. HGD, high grade dysplasia; SMI, submucosal invasion

with NP-CRNs at index with those of patients with polypoid CRNs at index.[22] Patients with NP-CRNs more often had advanced neoplasms at baseline (63% vs. 25%) and were more often diagnosed with advanced neoplasms (relative risk 1.6, 95% CI 1.05–2.6) during the first surveillance colonoscopy than patients with polypoid CRNs. Cohorts of LSTs show high numbers of synchronous CRNs in patients with NP-CRNs and LSTs.[12,13,22,23] Our findings confirm and expand on these data in comparison with polypoid neoplasms of comparable size. In a cohort of LST patients, synchronous CRNs were common among patients with large LSTs.[13] Most patients in that study were referred for endoscopic resection of LSTs. Unfortunately, a control group was lacking. One may speculate that endoscopists stop looking for additional CRNs after the detection of a large LST.[13] In our population, the number of synchronous CRNs was much lower and the average size of LSTs was smaller than in the US study. We cannot exclude the possibility that some of the metachronous CRNs in our cohort may actually have been missed synchronous CRNs. Nevertheless, strict surveillance is required in LST patients to

TABLE 4 Metachronous lesions in patients with LSTs and patients with LP-CRNs at index

Clinical features during follow-up	Patients with ≥ 1 neoplastic LST (*n*=88)	Patients with ≥ 1 LP-CRN (no LSTs; *n*=260)	*p* value
Patients with 1 CRN (%)	63 (71.6)	141 (54.2)	0.050[a]
Mean number of CRNs (SD)	2.80 (4.99)	1.45 (2.36)	0.002[b]
Patients with 1 adenoma (%)	63 (71.6)	134 (51.5)	0.015[a]
Mean number of adenomas (SD)	1.82 (2.09)	1.24 (1.93)	0.032[b]
Patients with 1 CRN with SMI (%)	1 (1.1)	5 (1.9)	0.824[a]
Mean number of CRNs with SMI (SD)	0.01 (0.11)	0.02 (0.14)	0.411[b]
Patients with 1 CRN with HGD/SMI (%)	32 (36.4)	41 (15.8)	<0.001[a]
Mean number of CRNs with HGD/SMI (SD)	0.51 (1.03)	0.22 (0.57)	0.002[b]
Patients with 1 non-polypoid CRN (%)	39 (44.3)	52 (20.0)	<0.001[a]
Mean number of non-polypoid CRNs (SD)	1.16 (2.73)	0.34 (0.90)	<0.001[b]

Notes: Patients without any follow-up were excluded. *p* values after correction for the number of follow-up colonoscopies and number of neoplasms at index.

Abbreviations: CRN, colorectal neoplasm; HGD, high grade dysplasia; LST, laterally spreading tumour; LP-CRN, large polypoid colorectal neoplasm; SD, standard deviation; SMI, submucosal invasion.

[a]Logistic regression model.

[b]Poisson regression corrected for zero inflation.

diagnose CRNs and prevent development into advanced CRNs. According to current international post-polypectomy surveillance guidelines, a 3-years surveillance interval is recommended after complete removal of advanced adenomas.[24,25] No specific advice has been provided regarding LST patients. In our study, the number of CRCs found during surveillance was low and did not differ significantly between LST and LP-CRN patients. On the other hand, we more frequently found advanced neoplasia in LST patients. Most recent surveillance guidelines have become more conservative than before, based on a lower than previously estimated absolute risk of CRC.[25,26] The guidelines state that further improvements in the quality of index colonoscopy would be more effective. Perhaps new detection and determination techniques such as artificial intelligence could result in an even lower risk of CRC.[27] Until then, data investigating the long-term CRC risk in the LST subgroup are necessary to reveal whether this subgroup may benefit from stricter surveillance.

An explanation for the increased risk of metachronous CRNs in LST patients remains unknown. Underlying genetic predisposition and yet undiscovered environmental factors[22] may play a role. Different molecular pathways may be involved in LSTs.[28] Of note is that patients with LST-NG-PD, the subtype with the highest risk of SMI, have the lowest number of metachronous neoplasms. In the present study, special attention was given to distinguish suspected residue/recurrence from metachronous CRNs. Hence, residue/recurrence does not explain our findings. The detection of NP-CRNs is strongly dependent on high-quality bowel preparation.[29,30] In our study, only patients with adequate bowel preparation and complete visualisation of the colonic mucosa were included.

The 2.3% LST prevalence in our population was higher than the pooled prevalence of 0.8% found in a meta-analysis.[31] A possible explanation is that our endoscopists were trained in the detection and resection (EMR) of NP-CRNs.[14] The detection rate of LSTs was stable over time. Of note, our university hospital functions as a secondary care referral centre for colonoscopies. Between 2008 and 2012, the number of referred LST cases was low.

Large flat serrated lesions were considered to be LSTs, but were excluded in the risk analysis. The discussion as to whether serrated lesions should be included or not as LSTs is ongoing. Some LST studies have excluded serrated lesions[32] while others did not.[33]

Resection skills seemed to improve at group level over time, as shown by an increase in en bloc resection rates. In our study we found a relatively high (14.2%) residue/recurrence rate after endoscopic resection of LSTs, which is in line with previous data.[10] Endoscopic submucosal dissection (ESD) was not available in our centre between 2008 and 2012. The use of ESD may increase en bloc resection rates and thereby reduce recurrence rates.[34]

The strengths and limitations of the current study should be acknowledged. To our knowledge, this is the first study examining time trends in LST diagnosis and treatment, and studying the metachronous findings of LSTs compared to a control group of comparable sized neoplasms. Furthermore, individual quality measures for colonoscopy (e.g., cecal intubation and adenoma detection rate) were recorded. Given the trained environment in which the study was performed, our data cannot be extrapolated to general clinical practice. In addition, most colonoscopies were performed by trainee endoscopists, arguably leading to lower adenoma detection rates. In a recent study the adenoma detection rates in trainees was not much different from their supervisors, and was dependent on the performance of their supervisor.[35] Furthermore, neoplasm prevalences may be different in other patient populations, for instance in screening colonoscopy populations.

An important limitation of our study is that surveillance colonoscopies were not performed in all patients. Older patients, patients with comorbidities and patients who declined surveillance were lost to follow-up. Although this reflects the real-life situation, we recognise that this might have biased the results. To mitigate bias, we adjusted the logistic regression model by baseline neoplasms and the number of follow-up colonoscopies performed. In addition, at the time of data collection the endoscopic Kudo classification was not widely used. To identify potentially misclassified lesions, photo documentation of all large sessile CRNs was systematically reviewed. Another limitation is that complete resection rates were primarily estimated based on endoscopic findings without the routine use of dye, possibly resulting in an underestimation of residues.[36]

CONCLUSION

In this population-based cohort, LSTs have a low and stable prevalence over time. Patients with LSTs had a higher risk of developing metachronous CRNs with HGD or SMI than patients with LP-CRNs, suggesting that these patients may benefit from stricter surveillance. Based on these findings, endoscopic treatment and surveillance recommendations for LST patients should be optimised.

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CONFLICT OF INTERESTS

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ETHICS APPROVAL

The present study was approved by the Medical Ethical Review Committee of the Maastricht University Medical Centre (MEC 14-4-046), Dutch trial register (NTR4844).

AUTHOR CONTRIBUTIONS

Roel MM Bogie, Ad AM Masclee and Silvia Sanduleanu-Dascalescu conceived the study. Roel MM Bogie, Sean JJ Retra, Marielle W Bouwens and Eveline JA Rondagh collected the data. Roel MM Bogie, Bjorn Winkens, Li-Chun Chang and Silvia Sanduleanu-Dascalescu analysed and interpreted the data. Roel MM Bogie, Bjorn Winkens, Ad AM Masclee and Silvia Sanduleanu-Dascalescu drafted the manuscript. All authors critically reviewed the manuscript. All authors have approved the final draft of the manuscript. Ad AM Masclee and Silvia Sanduleanu-Dascalescu are guarantors of this article.

INFORMED CONSENT

The need for individual informed consent was waived.

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