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Diagnostic value of radiological staging and surveillance for T1 colorectal carcinomas: A multicenter cohort study

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Abstract

Background: The role of radiological staging and surveillance imaging is under debate for T1 colorectal cancer (CRC) as the risk of distant metastases is low and imaging may lead to the detection of incidental findings.

Objective: The aim of this study was to evaluate the yield of radiological staging and surveillance imaging for T1 CRC.

Jelle F. Huisman and Hao Dang, MD both authors contributed equally to this manuscript.

Methods: In this retrospective multicenter cohort study, all patients of 10 Dutch hospitals with histologically proven T1 CRC who underwent radiological staging in the period 2000–2014 were included. Clinical characteristics, pathological, endoscopic, surgical and imaging reports at baseline and during follow-up were recorded and analyzed. Patients were classified as high-risk T1 CRC if at least one of the histological risk factors (lymphovascular invasion, poor tumor differentiation, deep submucosal invasion or positive resection margins) was present and as low-risk when all risk factors were absent.

Results: Of the 628 included patients, 3 (0.5%) had synchronous distant metastases, 13 (2.1%) malignant incidental findings and 129 (20.5%) benign incidental findings at baseline staging. Radiological surveillance was performed among 336 (53.5%) patients. The 5-year cumulative incidence of distant recurrence, malignant and benign incidental findings were 2.4% (95% confidence interval (CI): 1.1%–5.4%), 2.5% (95% CI: 0.6%–10.4%) and 18.3% (95% CI: 13.4%–24.7%), respectively. No distant metastatic events occurred among low-risk T1 CRC patients.

Conclusion: The risk of synchronous distant metastases and distant recurrence in T1 CRC is low, while there is a substantial risk of detecting incidental findings. Radiological staging seems unnecessary prior to local excision of suspected T1 CRC and after local excision of low-risk T1 CRC. Radiological surveillance should not be performed in patients with low-risk T1 CRC.

KEYWORDS
cohort study, metastasis, radiological follow-up, radiological staging, T1 colorectal cancer

INTRODUCTION

The incidence of early colorectal cancer (CRC), that is, T1 CRC, has been rising since the implementation of bowel screening programs worldwide.[1] Patients with CRC often die due to distant metastases caused by lymphatic or hematological spread of tumor cells. Therefore, the standard diagnostic work-up for CRC includes radiological imaging of the chest and abdomen to exclude synchronous distant metastases and prevent unnecessary major surgery for patients with incurable disseminated disease. However, the risk of lymph node metastases (LNM) and synchronous distant metastases in T1 CRC is low, especially in the absence of histological high-risk features for LNM.[2–5]

In the Netherlands, there is large practice variation among physicians and hospitals whether radiological staging or follow-up should be performed for T1 CRC.[6] In international guidelines there is no consensus whether or not radiological staging and follow-up should be performed.[7–17] Radiological imaging can lead to the discovery of unexpected extra-colonic incidental findings. Although most of these unexpected anomalies are unlikely to be clinically relevant, many require further investigation or follow-up and can result in unnecessary treatments, anxiety for patients and physicians and increased healthcare costs.[18,19] An earlier study reported an incidental finding rate of 16% on radiological staging in patients with stage I-IV CRC.[20] The risk of detecting these findings should be discussed during an informed consent procedure prior to imaging.[21]

Key Summary

Summarize the established knowledge on this subject

- Low risk of synchronous distant metastases and distant recurrence of T1 colorectal cancer (CRC)
- Large practice variation among physicians whether radiological staging or follow-up should be performed for T1 CRC
- No guideline consensus

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

- Substantial risk of malignant (2%) and benign (19%) incidental findings during radiological staging and surveillance imaging
- Radiological staging seems unnecessary prior to local excision of suspected T1 CRC and after local excision of low-risk T1 CRC.
- Radiological surveillance should not be performed for low-risk T1 CRC

To date, there are no studies that have investigated the yield of radiological staging and follow-up imaging in patients with T1 CRC. The aim of this study was to evaluate the diagnostic value in terms of

distant metastases or distant recurrence, as well as the incidental finding rate of radiological staging and surveillance imaging in patients with T1 CRC.

MATERIALS AND METHODS

Study design and patient selection

The study design was a multicenter retrospective cohort study. Patients from 10 Dutch hospitals diagnosed with histologically proven T1 CRC between January 2000 and December 2014 were selected from the Dutch Cancer Registry. Patients were included in the study when they had undergone radiological staging of the abdomen and chest with Computed Tomography (CT), ultrasound (US), Magnetic Resonance Imaging, Positron Emission Tomography, or chest X-ray within 2 months after macroscopic or histological diagnosis of the T1 CRC. Patients referred for colonoscopy for a suspected asymptomatic colorectal lesion which was detected on prior imaging were excluded because most of these patients were already under examination or treatment for a secondary malignancy or had symptomatic incidental findings on performed imaging, which would distort the incidental finding rate. Other exclusion criteria were hereditary predisposition to CRC, inflammatory bowel disease, metachronous CRC (defined as CRC in the previous 5 years before detection of T1 CRC, synchronous CRC at the time of detection of T1 CRC), non-CRC-related death within 1 year after treatment, and non-adenocarcinoma or neo-adjuvant radiotherapy. The study was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (UMCU) (reference number: 15–487).

Endpoints

Primary outcomes were the presence of synchronous distant metastases at radiological baseline imaging and the presence of distant recurrence during follow-up. Distant metastases (synchronous metastases during baseline imaging as well as distant recurrence) were defined as metastases to extra-colonic organs, bones, peritoneum or distant lymph nodes outside the surgical plane, confirmed with histological examination, intra-operative findings (palpation or intra-operative ultrasound) or growth of lesions suspect for metastases during radiological follow-up.

Secondary outcomes were the presence of relevant extra-colonic incidental findings on radiological baseline imaging and during follow-up imaging. Relevant incidental findings were defined as malignant lesions (i.e. histologically proven or lesions suspect for malignancy which showed progression during radiological follow-up) which were not CRC-related, or benign lesions requiring additional treatment, diagnostic examinations, additional follow-up or referral to other medical specialties. Lesions that were already known before T1 CRC diagnosis were not counted as incidental findings.

Data collection

In each participating center, the patient and tumor characteristics, diagnostic and surveillance endoscopic reports, staging and follow-up radiological reports, and histology reports were collected from the electronic patient records. Patient characteristics included age and gender. Tumor characteristics included morphology, size and location of the tumor. Local excision was specified as (en-bloc or piecemeal) snare polypectomy (en-bloc or piecemeal) endoscopic mucosal resection, endoscopic submucosal dissection or transanal endoscopic microsurgery. Surgical resection was specified as surgical resection respecting oncological principles including draining lymph nodes. Radiology reports during baseline and follow-up imaging were analyzed to determine the presence of distant metastases and incidental findings. For the radiological follow-up, we only analyzed patients who underwent radiological follow-up performed in the context of T1 CRC surveillance and performed at least 2 months after T1 CRC diagnosis. For locally treated T1 CRCs with incomplete histological information in the histology reports, the original specimens were re-evaluated by the local pathologist of each participating hospital in order to provide complete histological information on the cases. For all pedunculated T1 CRCs, double reading by 2 blinded expert gastrointestinal pathologists (M.L. and J.O.) was performed in the context of another study. The data from these evaluations were also used for the current study.[22]

Histological evaluation

The tumors were assessed according to the World Health Organization of tumors.[23–25] T1 CRCs were classified as high-risk T1 CRC if 1 or more of the following risk factors was present: (1) lymphovascular invasion (LVI), (2) poor tumor differentiation, (3) deep submucosal invasion (≥1000 μm/SM2-3 in non-pedunculated and Haggitt 4 in pedunculated T1 CRCs), or (4) positive (R1) or undetermined resection margins (Rx). R0 resection was defined as a microscopically cancer-free resection margin, irrespective of the distance in millimeters, as the risk of local intramural residual cancer is comparable between 0.1 and 1.0 mm and >1.0 mm margins (in the absence of other histological high-risk features).[26] T1 CRCs were classified as low-risk when all these histological risk factors were absent and as undetermined-risk T1 CRC if at least one of the histological parameters was missing or could not be determined, while the other known risk factors were absent.

Statistics

All analyses were performed using the Statistical Package of Social Sciences version 26.0 (SPSS). A two-sided *p*-value of <0.05 was considered statistically significant. Normality was tested using

Kolmogorov-Smirnov test. Continuous variables were reported as means with standard deviations if the data were parametric or as medians with ranges if the data were non-parametric. Categorical data were analyzed using the chi-squared test or Fisher's exact test, as appropriate.

The incidence of distant recurrence and incidental findings during follow-up was calculated among patients who underwent abdominal or thoracic imaging, which was performed in the context of T1 CRC surveillance using survival analysis. Patients with distant metastases or a second primary malignancy during baseline imaging were excluded from follow-up analysis. The start of follow-up was the date of CRC diagnosis. Patients were censored during follow-up when endoluminal recurrence, distant metastases, or a second primary malignancy was found. We used Kaplan Meier and Cox proportional hazard regression analysis to estimate the risk of distant recurrences and incidental findings during follow-up. Since there was a shift from ultrasound or X-ray towards CT over the years, we performed a subgroup analysis to detect differences in radiological outcomes during the different time periods. We divided the patients into three time periods: 2000–2004, 2005–2009 and 2010–2014.

RESULTS

Baseline characteristics

A total of 1130 patients with T1 CRC were identified, of which 628 (55.6%) patients met the eligibility criteria and were included in the analysis (Figure 1). An overview of the baseline characteristics is presented in Table 1.

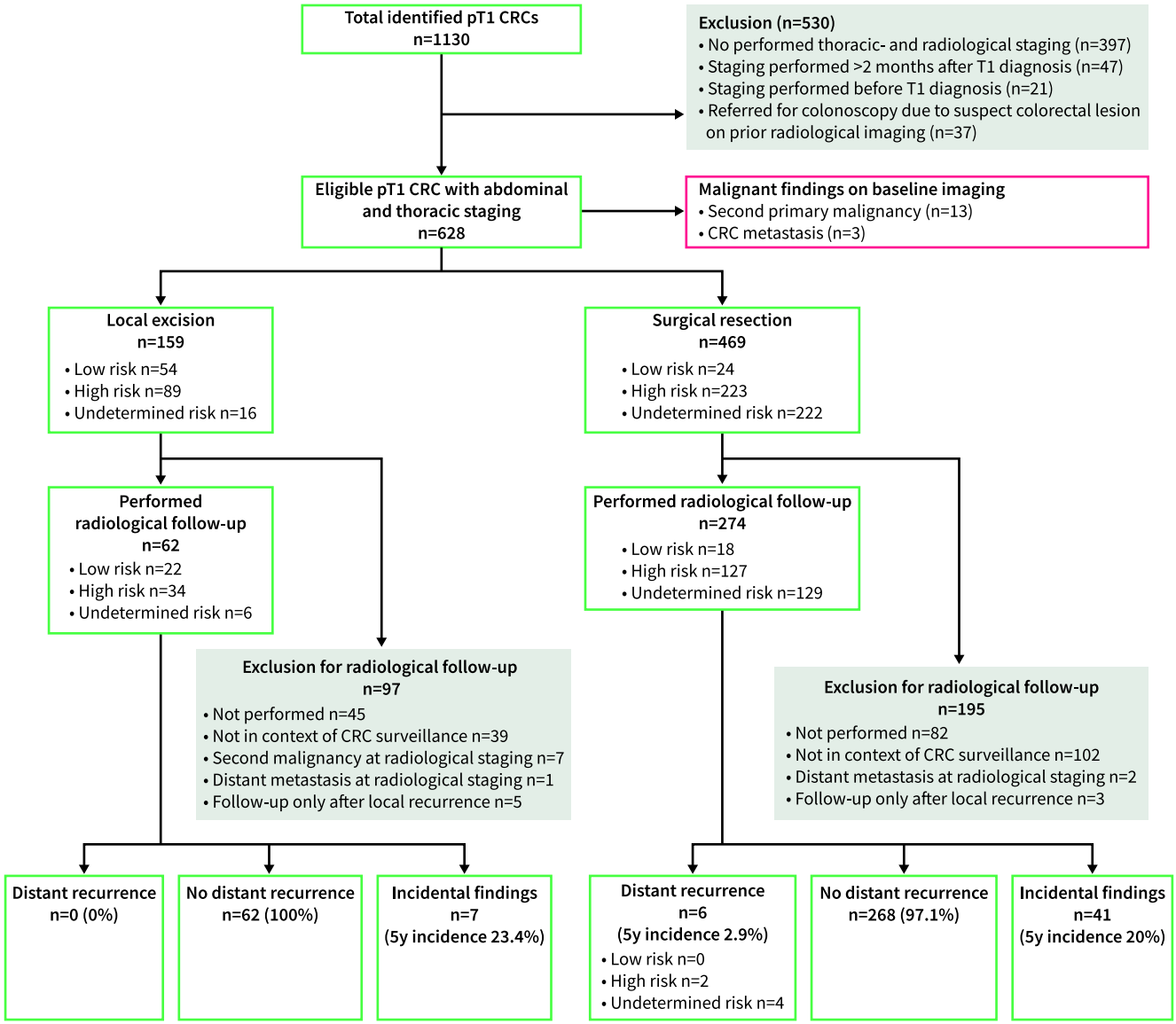

FIGURE 1 Flowchart of the included patients.

TABLE 1 Baseline characteristics.

Patient characteristics	Patients with radiological staging *n* (%)	Patients with local excision *n* (%)	Patients with surgical resection *n* (%)
Total patients	628	159	469
Male	357 (56.8)	102 (64.2)	255 (54.4)
Age	70 [38–91]	73 [41–88]	69 [38–91]
Histological risk status			
Low-risk	78 (12.2)	54 (34.0)	24 (5.1)
High-risk	312 (49.7)	89 (56.0)	223 (47.5)
Undetermined-risk (unknown)	238 (37.9)	16 (10.1)	222 (47.3)
Tumor size in millimeters—[range]	20 [4–160]	20 [5–60]	23 [4–160]
Tumor location			
Rectum	183 (29.1)	84 (52.8)	99 (21.1)
Left sided	310 (49.4)	65 (40.9)	245 (52.2)
Right sided	133 (21.2)	8 (5.0)	125 (26.7)
Unknown	2 (0.3)	2 (1.3)	-
Tumor morphology			
Pedunculated	197 (31.4)	80 (50.3)	117 (24.9)
Non-pedunculated	358 (57.0)	71 (44.7)	287 (61.2)
Unknown	73 (11.6)	8 (5.0)	65 (13.9)
Lymphovascular invasion			
Present	66 (10.5)	13 (8.2)	53 (11.3)
Absent	344 (54.8)	112 (70.4)	232 (49.5)
Unknown	218 (34.7)	34 (21.4)	184 (39.2)
Differentiation grade			
Grade 1 or 2	500 (79.6)	130 (81.8)	370 (78.9)
Grade 3	29 (4.6)	5 (3.1)	24 (5.1)
Unknown	99 (15.8)	24 (15.1)	75 (16.0)
Invasion depth			
Superficial	171 (27.2)	74 (46.5)	97 (20.7)
Deep	111 (17.7)	24 (15.1)	87 (18.6)
Unknown	346 (55.1)	61 (38.4)	285 (60.8)
Resection margin based on initial treatment			
R0	444 (70.7)	91 (57.2)	353 (75.3)[a]
R1 or Rx	184 (29.3)	68 (42.8)	116 (24.7)[a]
Definitive cancer treatment			
Local excision	159 (25.3)	159 (100.0)	-
Piecemeal snare polypectomy		15 (9.4)	
En-bloc snare polypectomy		64 (40.3)	
Piecemeal EMR		20 (12.6)	
En-bloc EMR		33 (20.8)	
ESD		1 (0.6)	

(Continues)

TABLE 1 (Continued)

Patient characteristics	Patients with radiological staging *n* (%)	Patients with local excision *n* (%)	Patients with surgical resection *n* (%)
TEM		23 (14.5)	
Unknown		3 (1.9)	
Primary surgical resection	295 (47.0)	-	295 (62.9)
Completion surgical resection	174 (27.7)	-	174 (37.1)
Lymph node metastases	49 (10.4)		49 (10.4)

Abbreviations: CRC, Colorectal cancer; CT, indicates Computed Tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TEM, transanal endoscopic microsurgery.

[a]the R0 resection was calculated on initial treatment and contained patients with irradical endoscopic resection with subsequently completion surgical resection.

Radiological findings in staging of T1 colorectal cancer patients

Of the included T1 CRC patients, synchronous distant metastases on radiological staging were confirmed in three of 628 patients (0.5%). These synchronous distant metastases were found in 0 of 78 (0%) low-risk cases, in 1 of 312 (0.3%) high-risk cases and in 2 of 238 (0.8%) undetermined-risk CRC cases. The histological characteristics of these metastatic cases are provided in Table 2. Two of these patients underwent palliative therapy and one patient underwent curative resection of the lung metastases.

A total of 162 incidental findings were detected at radiological staging in 142 of 628 patients (22.6%). Thirteen (2.1%) patients had a secondary primary extra-colonic malignancy and 129 patients (20.5%) had a benign incidental finding. Twenty patients had two incidental findings on baseline staging. An overview of all incidental findings can be found in Table 3.

Radiological and endoscopic surveillance of T1 colorectal cancer after local excision

Of the patients treated with local excision ($n = 159$), 54 had low-risk and 89 high-risk T1 CRC. For the remaining 16 cases with undetermined-risk T1 CRC, the presence or absence of histological risk factors for LNM remained unclear after histological revision ($n = 7$) or the revision could not be performed ($n = 9$).

Radiological surveillance after local excision was performed in 62 of 159 (39.0%) patients (Figure 1). During a median radiological follow-up period of 2.3 years [range: 0.3–5.6 years], no distant recurrence occurred. Malignant incidental findings were detected in 0 patients and benign incidental findings in seven of 62 patients. The 5-year cumulative incidence of benign incidental findings after local excision was 23.4% (95% confidence interval) (9.1%–54.1%). Details on radiological surveillance and a list of incidental findings can be found in Table 4 and Table 3, respectively.

Endoscopic surveillance was performed in 45 of 54 low-risk patients (83.3%) and in 81 of 89 high-risk patients (91%). Local recurrence occurred in 0 of 45 low-risk patients and in nine of 81 high-risk patients (Table 4). The 5-year cumulative incidence of local recurrence among the high-risk T1 CRCs was 23.8% (95%CI 11.5%–45.5%). All local recurrences were detected with endoscopy. Radiological imaging performed for tumor staging after detection of local recurrence showed synchronous distant metastases in two of 9 patients. Notably, one patient with endoscopically treated, completely resected low-risk T1 sigmoid carcinoma showed a newly detected malignant sigmoid tumor 2 years later. Local recurrence in this specific case could not be excluded.

Radiological and endoscopic surveillance of T1 colorectal cancer after surgical resection

Of the 469 patients treated with surgical resection, 274 (58.4%) underwent radiological surveillance (Figure 1). During a median radiological follow-up period of 3.4 years [range: 0.3–15.4 years], distant recurrence occurred in three of 57 rectal cancer patients (5.3%) and three of 217 colon cancer patients (1.4%). Malignant incidental findings occurred in 4 of 274 patients and benign incidental findings in 37 of 274 patients. The 5-year cumulative incidence of distant recurrence after surgical resection was 2.9% (95% CI 1.3%–6.4%). The 5-year cumulative incidence of malignant and benign incidental findings was 2.8% (95%CI 0.7%–11.2%) and 17.7% (95%CI 12.7%–24.4%), respectively. Details on histological status of distant recurrences, radiological surveillance and a list of incidental findings can be found in Table 2, Table 4 and Table 3, respectively. All distant recurrences were detected by radiological imaging and no local recurrence was found in these patients. Of the 6 distant recurrence cases, 4 underwent palliative therapy, and 1 patient underwent surgical resection with curative intent of the liver metastases. The last patient received therapy with curative intent for his peritoneal metastases, but developed lung metastases 1 year later. The histological characteristics, tumor location and treatment strategies of the original T1 CRC specimen are provided in Table 2. Of the 4 patients with a malignant incidental finding during follow-up, 1 had pancreatic cancer and underwent radical

TABLE 2 Original histological specimens of patients with synchronous or recurrent distant metastases.

Event	Histological risk status	Tumor location	Lympho-vascular invasion	Submucosal invasion	Resection	Tumor differentiation	Performed cancer treatment	Total lymph nodes harvested	Lymph node metastases	Location of distant metastases
#1 - Baseline metastases	High-risk	Sigmoid	[a]	SM3	R0	Grade 2	Primary surgical resection	1	1	Liver
#2 - Baseline metastases	Undetermined	Rectum	[b]	N/I	R0	Grade 2	Local excision	N/A	N/A	Lung
#3 - Baseline metastases	Undetermined	Sigmoid	N/I	N/I	R0	Grade 2	Primary surgical resection	1	1	Liver
#4 - Distant recurrence	High-risk	Ascending colon	[a]	SM2	R0	Grade 2	Completion surgical resection	7	4	Diffuse
#5 - Distant recurrence	High-risk	Cecum	[a]	N/I	R0	Grade 3	Primary surgical resection	14	2	Lung
#6 - Distant recurrence	Undetermined	Rectum	N/I	N/I	R0	Grade 2	Primary surgical resection	2	1	Liver
#7 - Distant recurrence	Undetermined	Rectum	N/I	N/I	R0	N/I	Primary surgical resection	3	0	Local extraluminal
#8 - Distant recurrence	Undetermined	Rectum	[b]	N/I	R0	N/I	Completion surgical resection	0	0	Local extraluminal
#9 - Distant recurrence	Undetermined	Ascending colon	N/I	N/I	R0	N/I	Completion surgical resection	0	0	Diffuse

Abbreviations: LNM, lymph node metastases; N/A, not applicable; N/I, not investigated; SM, submucosal invasion.

[a]indicates lymphvascular invasion present.

[b]lymphvascular invasion not present.

resection, 1 had prostate cancer, and the last 2 patients died from incurable lung cancer.

Endoscopic surveillance was performed in 341 of 469 patients (72.7%), with a median follow-up period of 27 [3–138] months (Table 4). Local recurrence occurred in 5 of 341 patients after a median of 25 [10–52] months. The 5-year cumulative incidence of local recurrence after surgical resection was 2.0% (95%CI 0.8%–5.0%). One of these 5 patients had newly detected distant metastases on radiological imaging, which was performed for tumor staging after endoscopic detection of local recurrence.

Differences over time

Subgroup analysis of the radiological staging and follow-up for the different time periods can be found in Table 5. We found significant differences in the presence of synchronous distant metastases ($p = 0.013$) and incidental findings ($p < 0.001$) during baseline radiological staging between the different time periods. We found no significant difference in the detection of distant recurrence or incidental findings during the follow-up period between the different time periods. The hazard ratios (HR) for distant recurrence for the period 2005–2010 and 2010–2015 compared to 2000–2005 were HR = 0.7 (95%CI 0.1–7.7) and HR = 0.6 (95%CI 0.1–5.3) and for incidental findings HR = 1.8 (95%CI 0.5–6.0) and HR = 1.7 (95%CI 0.5–5.7) respectively.

DISCUSSION

In this large multicenter study, we reported the radiological outcome of staging and follow-up imaging for endoscopically and surgically treated T1 CRCs. We found a very low risk of synchronous distant metastases (0.5%) and distant recurrence during follow-up (2.4%). Furthermore, this study revealed a substantial number of incidental findings detected on radiological staging and follow-up. Therefore, we believe that radiological staging and surveillance should not be routinely performed in all T1 CRC patients.

A recent survey showed that approximately 50% of clinicians perform baseline oncological staging after local excision of T1 CRCs, regardless of histological risk status.[6] For patients scheduled for major (primary or completion) surgical resection, it seems obvious to perform preoperative radiological staging to exclude distant metastases and prevent unnecessary surgery for patients with incurable disseminated disease. However, it is highly questionable whether or not radiological staging is also efficient for low-risk T1 CRCs. This is because these tumors have a negligible risk of metastatic disease, as confirmed by our current study. In addition, we show for the first time that in almost a quarter of T1 CRC patients, incidental findings were found on radiological staging. This percentage is in line with previous literature on incidental findings on radiological examinations performed for other medical conditions.[27] The percentage of incidental findings on radiological staging even appeared to rise over

TABLE 3 Incidental findings at baseline and during follow-up.

	Incidental findings during staging (n = 628) n	Incidental findings during follow-up (n = 336) n
Patients with incidental findings	142 (22.6%)	48 (20.4%, 95%CI: 15.0–27.5)
Total number of incidental findings	162	53
5y cumulative incidence malignant incidental findings: % (95%CI)	-	2.5% (0.6–10.4)
5y cumulative incidence benign incidental findings: % (95%CI)		18.3% (13.4–24.7)
Malignant incidental findings	13	4
Renal cell carcinoma	6	-
Lung cancer	3	2
Breast cancer	1	-
Urothelial carcinoma of the bladder	1	-
Gastrointestinal stroma cell tumor	1	-
Non-Hodgkin lymphoma	1	-
Prostate cancer	-	1
Pancreas cancer	-	1
Benign incidental findings	149	49
Hepatic cysts or hemangiomas	66	17
Benign thoracic lesion	30	14
Adrenal incidentaloma	14	-
Aortic abdominal aneurysm	11	2
Lymphadenopathy	5	5
Pancreatic cyst	4	-
Gynecological lesions (uterus/adnex/ovarium)	4	-
Symptomatic cholelithiasis	2	2
Thickened stomach wall	1	-
Thickened urinary bladder wall	1	-
Mucocele appendix	1	-
Renal cyst	1	1
Spinal degeneration	1	-
Hydronefrosis	1	1
Inguinal hernia	1	-
Myxoma	1	-
Thyroid nodule	1	-
Peri-urethal abnormality	1	-
Benign prostate hyperplasia	1	1
Lipoma	1	-
Hepatic cirrhosis	1	-
Hepatic steatosis	-	2
Colonic wall thickness	-	2
Surgical site infection	-	1
Abdominal soft tissue mass	-	1

Abbreviations: CI, confidence interval; y, indicates years.

TABLE 4 Local and distant recurrence during follow-up stratified by definitive cancer treatment.

	Local excision			Surgical resection	
Outcome radiological staging (*n* = 628)	**Low-risk pT1 CRC**	**High-risk pT1 CRC**	**Undetermined risk pT1 CRC**	**pT1N0**	**pT1N1**
	Radiological staging among locally treated T1 CRCs (*n* = 159)			**Radiological staging among surgically treated T1 CRCs (*n* = 469)**	
No. of patients (% of all enrolled patients)	54 (8.4%)	89 (14.2%)	16 (2.5%)	420 (66.9%)	49 (7.8%)
Synchronous distant metastases	-	-	1 (6.3%)	-	2 (4.1%)
Patients with incidental findings	17 (31.5%)	23 (25.8%)	5 (31.3%)	90 (21.4%)	7 (14.3%)
Benign incidental findings	14 (25.9%)	19 (21.3%)	5 (31.3%)	85 (20.2%)	6 (12.2%)
Malignant incidental findings	3 (5.6%)	4 (4.5%)	-	5 (1.2%)	1 (2.0%)
Lung cancer	1	-	-	2	-
Renal cell carcinoma	-	3	-	3	-
Gastrointestinal stroma cell tumor	1	-	-	-	-
Breast cancer	-	-	-	-	1
Urothelial carcinoma of the bladder	1	-	-	-	-
Lymphoma	-	1	-	-	-
Outcome endoscopic surveillance (*n* = 628)					
	Endoscopic surveillance after locally treated T1 CRCs (*n* = 141 of 159)			**Endoscopic surveillance after surgically treated T1 CRCs (*n* = 341 of 469)**	
No. of patients (% of all enrolled patients)	54 (8.4%)	89 (14.2%)	16 (2.5%)	420 (66.9%)	49 (7.8%)
At least 1 surveillance endoscopy	45 (83.3%)	81 (91%)	15 (93.8%)	309 (73.6%)	32 (65.3%)
Median follow-up surveillance endoscopy: months [range]	13 [3–76]	14 [1–63]	13 [2–139]	29 [3–138]	27 [4–90]
Local endoluminal recurrence cases	-	9	-	5	-
without distant recurrence	-	7	-	4	-
with distant recurrence	-	2[a]	-	1[a]	-
Median to local recurrence: months [range]	-	26 [4–62]	-	25 [10–52]	-
5 y cumulative incidence local recurrence (95%CI)	-	23.8% (11.5–45.5)	-	2.0% (0.8–5.0)	-
Outcome radiological surveillance (*n* = 336)					
	Performed radiological surveillance after locally treated T1 CRCs (*n* = 62 of 159)			**Radiological surveillance after surgically treated T1 CRCs (*n* = 274 of 469)**	
No. of patients with at least 1 radiological surveillance	22/54 (40.7%)	34/89 (38.2%)	6/16 (37.5%)	238/420 (56.7%)	36/49 (73.5%)
Median radiological follow-up: months [range]	23 [3–58]	29 [4–67]	41 [9–56]	38 [3–184]	55 [8–70]
Median number of radiological surveillance imaging procedures [range]	3 [1–8]	4 [1–17]	4 [1–8]	5 [1–20]	8 [1–21]
Distant recurrence cases	-	-	-	3	3
5y cumulative incidence distant recurrence (95%CI)	-	-	-	1.5% (0.5–4.6)	10.1% (3.3–28.3)
Median to distant recurrence: months [range]	-	-	-	12 [8–22]	28 [12–37]

(Continues)

TABLE 4 (Continued)

Outcome radiological surveillance (n = 336)					
	Performed radiological surveillance after locally treated T1 CRCs (n = 62 of 159)			Radiological surveillance after surgically treated T1 CRCs (n = 274 of 469)	
Patients with incidental findings	2	5	-	35	6
Benign incidental findings	2	5	-	31	6
Malignant incidental findings	-	-	-	4	-
Pancreas cancer	-	-	-	1	-
Prostate cancer	-	-	-	1	-
Incurable lung cancer	-	-	-	2	-

Abbreviations: CI, confidence interval; CRC indicates colorectal cancer; y, year.

[a]Patients with endoluminal recurrence were censored for distant recurrence analysis during follow-up on the date of local recurrence detection.

TABLE 5 Radiological staging and surveillance of T1 colorectal cancer (CRC) patients divided into three time frames.

	Overall cohort 2000–2014 n (%)	2000–2004 n (%)	2005–2009 n (%)	2010–2014 n (%)	p-value
No. of patients with pT1 CRC	1130	239	357	534	
No. of patients with radiological staging	628 (55.6)	80 (33.5)	184 (51.5)	364 (68.2)	
Performed abdominal staging					
CT	464 (73.9)	17 (21.3)	93 (50.5)	354 (97.3)	
Ultrasound	161 (25.6)	63 (78.8)	89 (48.4)	9 (2.5)	
MRI	2 (0.3)	-	1 (0.5)	1 (0.3)	
PET	1 (0.2)	-	1 (0.5)	-	
Performed thoracic staging					
CT	233 (37.1)	3 (3.8)	45 (24.5)	185 (50.8)	
X-ray	394 (62.7)	77 (96.3)	138 (75)	179 (49.2)	
PET	2 (0.2)	-	1 (0.5)	-	
Synchronous distant metastases	3 (0.5)	2 (2.5)	1 (0.5)	0 (0)	0.013[a]
Patients with incidental findings	142 (22.6)	12 (15)	26 (14.1)	104 (28.6)	<0.001[a]
Malignant	13	1	3	9	
Benign	129	11	23	95	
Radiological surveillance					
Performed follow-up imaging	336 (53.5)	33 (41.3)	95 (51.6)	208 (57.1)	
Distant recurrence cases	6	1	2	3	
5y cumulative incidence of distant recurrence (95%CI)	2.4% (1.1–5.4)				
Hazard rate distant recurrence (95%CI)		1	0.7 (0.1–7.7)	0.6 (0.1–5.3)	
5y cumulative incidence (benign and malignant) incidental findings (95%CI)	20.4% (15.0–27.5)				
Hazard rate (benign and malignant) incidental findings (95%CI)		1	1.8 (0.5–6.0)	1.7 (0.5–5.7)	
Incidental findings during follow-up	48	5	16	27	
Second primary malignancy	4	1	3	0	
Benign	44	4	13	27	

Note: All percentages are number of events divided by number of performed staging or follow-up imaging for each time period.

Abbreviations: CT indicates Computed Tomography; MRI, magnetic resonance imaging; PET, Positron Emission Tomography; y, years.

[a]Chi-squared test.

the years, probably due to the shift of imaging modalities from ultrasound or chest X-ray towards CT. Although incidental findings might occasionally be beneficial and lifesaving, they are often clinically irrelevant and potentially harmful and can cause burden and anxiety for patients and increased healthcare costs.[21,27] Based on the above, it would be reasonable to discourage radiological staging prior to local excision of suspected T1 CRC and after local excision of low-risk T1 CRC.

Endoscopic surveillance after local excision and surgical resection of T1 CRC should be performed according to national guidelines. A recent guideline recommends surveillance colonoscopy 1 year after resection (or up to 6 months, if colonoscopy has not yet been performed preoperatively).[28]

However, radiological follow-up to detect distant CRC recurrences is currently under debate as patients might not derive survival benefit from early detection of asymptomatic distant recurrence.[29–31] Our study suggests a limited yield of radiological follow-up for T1 CRC patients.

Of the patients treated with local excision in our study, no distant recurrence was primarily detected by radiological imaging, while incidental findings occurred in almost one of 4 patients (Figure 1). However, 2 censored high-risk T1 patients who underwent local excision had distant metastases on radiological imaging, which was performed for tumor staging after endoscopic detection of local recurrence with routine endoscopic surveillance. Our findings are supported by a recent meta-analysis, which also reported a low risk of distant recurrence after local excision (1.6% after local excision for any T1 CRC and 0.3% after local excision of low-risk T1 CRC).[32] Based on the results of this study and the previous literature, we strongly discourage radiological surveillance for low-risk pT1 CRC patients after local excision, as the risk of distant metastases does not outweigh the risk of incidental findings. For patients with high-risk or undetermined-risk T1 CRC in whom completion surgical resection is not performed, radiological follow-up could be considered according to national guidelines because of the relatively increased risk of metastatic disease. However, evidence that radiological surveillance improves survival outcomes of these CRC patients is currently lacking.

Of the patients treated with surgical resection, the distant recurrence rate was 2.9%. Distant recurrence occurred more frequently among rectal cancer patients and among lymph node-positive (T1N1) patients (10.1%). Histological reports demonstrated pT1N1 in 3 patients, pT1N0 in 1 patient and pT1Nx in the remaining 2 patients. Prior studies reported that intensified follow-up after oncological resection leads to earlier detection of distant recurrences with subsequent more curable treatment options. However, the therapeutic options for distant recurrence are still limited and there is no literature that supports survival benefit.[30,31] In this study, only one of the 6 metastatic patients underwent curative therapy. Incidental findings during follow-up were detected in one of 5 patients and might lead to anxiety, medicalization and healthcare costs. The risk of distant recurrence among pT1N0 CRC is very low, as confirmed by our current study. It is highly questionable whether radiological surveillance should be performed for these patients, as recommended in international guidelines.[8,9,12,14,16] In contrast, the risk of metastatic disease is much higher for patients with histologically proven LNM after surgical resection (pT1N1). We think that radiological surveillance imaging should only be considered for patients with histologically proven LNM after surgical resection (pT1N1) due to the relatively increased risk of metastatic disease (Figure 2). However, the patients should be informed about the risk and benefits of surveillance imaging.

This study has several limitations. First, we retrospectively analyzed a selected population of histologically proven T1 CRC patients. Patients with metastatic T1 CRC who did not undergo excision of the primary tumor were not included in the database. Furthermore, we excluded patients with radiological imaging performed >2 months before or after T1 CRC diagnosis and included only patients with radiological follow-up imaging that was performed in the context of CRC surveillance. This was mainly performed among high-

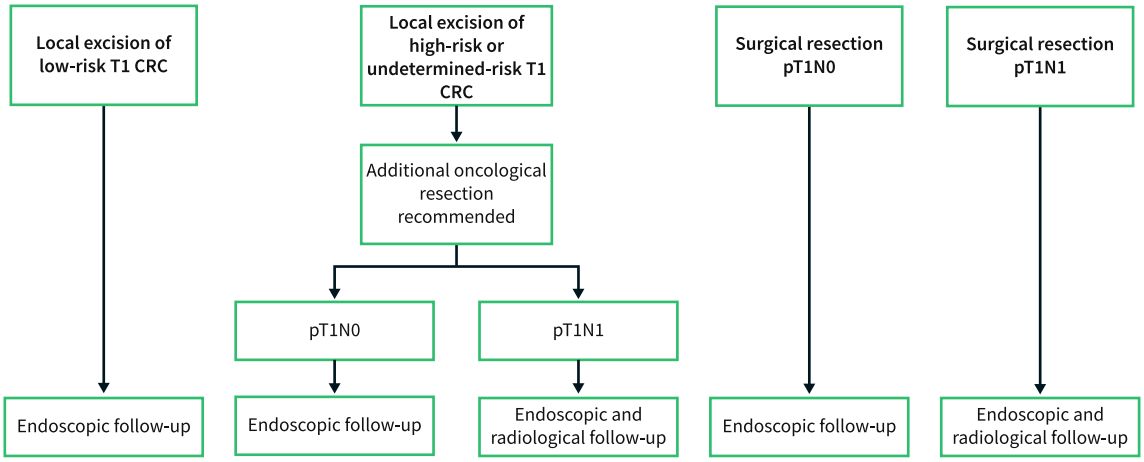

FIGURE 2 Follow-up recommendations after T1 colorectal cancer (CRC) therapy.

risk patients, which might have resulted in testing bias and might have influenced the rate of synchronous distant metastases or distant recurrence. Of the excluded T1 CRC cases in this study, 1 patient had synchronous distant metastases during baseline imaging and 9 patients had distant recurrence. However, none of them had low-risk T1 CRC, making our recommendation to omit radiological staging and surveillance for low-risk T1 CRC even stronger. Second, although our series is the largest T1 CRC cohort to date, the absolute number of distant metastases was low. Third, we found imaging heterogeneity due to increasing quality of CT and shift from the US toward CT over the years, especially for incidental findings. Also, there may be inter and intra-observer variability between different radiologists in different hospitals. Lastly, as we included patients diagnosed between 2000 and 2014, the histological features used to estimate the LNM risk were deep submucosal invasion, LVI and tumor differentiation. However, recent insights suggest that deep submucosal invasion may be omitted from risk stratification, whereas tumor budding emerged as a new risk factor for LNM.[14,22,33]

CONCLUSION

The risk of synchronous distant metastases and distant recurrence in T1 CRC is low, especially in low-risk T1 CRC. However, there is a substantial risk of detecting incidental findings leading to medicalization, burden for patients and increased health care costs. Radiological staging seems unnecessary prior to local excision of suspected T1 CRC and after local excision of low-risk T1 CRC. Radiological surveillance should not be performed in patients with low-risk T1 CRC.

AUTHOR CONTRIBUTIONS

Jelle F. Huisman planned the study, conducted data analysis and interpretation of the data, wrote the manuscript, critically revised the manuscript, submitted the manuscript, and gave final approval of the version to be published. Hao Dang planned the study, conducted data, analysis and interpretation of the data, writing of the manuscript, critical revision of the manuscript, give final approval of the version to be published. Yara Backes, Vincent K. Dik, Anouk Overwater, John N. Groen, Frank ter Borg, Jeroen D. van Bergeij, Joost M. J. Geesing, B. W. Marcel Spanier, Joachim S. Terhaar Sive Droste, Niels van Lelyveld, Koen Kessels, Frank P. Vleggaar conducted data, critical revision of the manuscript, give final approval of the version to be published. Miangela M. Lacle, G. Johan A. Offerhaus, Nikki Knijn, conducted data, histological revisions, critical revision of the manuscript, give final approval of the version to be published. Richard M. Brohet, analysis and interpretation of the data, writing of the manuscript, critical revision of the manuscript, give final approval of the version to be published. Leon M. G. Moons, Henderik L. van Westreenen, Wouter H. de Vos tot Nederveen Cappel, and Jurjen J Boonstra planned the study, analysis and interpretation of the data, writing of the manuscript, critical revision of the manuscript, give final approval of the version to be published.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The study was approved by the Medical Ethics Review Committee of the UMCU (reference number: 15–487).

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