Is the assessment of submucosal invasion still useful in the management of early rectal cancer? A study of 91 consecutive patients

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Original Article

Is the assessment of submucosal invasion still useful in the management of early rectal cancer? A study of 91 consecutive patients

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Running-Head: Lymph node metastasis in early rectal cancer

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KEY WORDS

Early rectal cancer – Lymph node metastasis – T1 rectal cancer – Submucosal invasion – Surgery

Abstract

Aim: Only former studies, including colic and rectal cancers, exist on the prognosis of T1 tumours. Very few studies use Kikuchi's classification, dividing submucosa in 3 strata, to evaluate the depth of the submucosal invasion. This study aimed to assess the pathological risk factors for lymph nodes metastasis (LNM), pathologic and oncologic results of patients with early rectal cancer (ERC, pT1 tumour).

Methods: Between 2000 and 2014, 91 consecutive patients undergoing surgery (primary total mesorectal excision (TME) or local excision (LE) alone or LE followed by TME) for ERC were included.

Results: Surgery was LE for 18 patients, LE followed by TME for 22 and primary TME for 51 patients. After TME (n=73), 16 patients (23%) had LNM. LNM rate was 15%, 14% and 30% for Sm1, Sm2 and Sm3 tumours. In multivariate analysis, lymphovascular invasion (p=0.027) and high tumour budding (p=0.037) were the only independent factors of LNM. The depth of submucosal invasion was not associated with an increased risk of LNM. After a mean follow-up of 56±46 months, 5-year overall survival, specific survival and disease-free survival were respectively 82%, 93% and 75%. No significant difference of survival was found according to the depth of submucosal invasion or to the surgical management.

Conclusions: More than depth of submucosal invasion, histological features seem to be risk factors for LNM. Considering the LNM rate, TME should be discussed after local excision in terms of one of these pathological criteria.

What does this paper add to the literature?

We present one of the largest series of rectal pT1 tumours, assessing the risk of lymph node metastases based on several histological criteria. The depth of submucosal invasion is probably no longer a relevant factor when determining the risk of LNM. Total mesorectal excision (TME) should be discussed after histopathological examination of a local excision specimen in more terms of lymphovascular invasion and tumour budding.

INTRODUCTION

Early rectal cancer (ERC) is defined as carcinoma that only invades the submucosa. This corresponds to a T1 tumour in the tumour-node-metastasis (TNM) classification [1, 2] and its incidence varies between 3 and 9% of all the resected colorectal cancers [3-5]. The management of ERC depends on the histopathological classification of the tumour, the depth of submucosal invasion and the risk of lymph node metastases (LNM). Often, the best plan is made retrospectively once the tumour has been removed and the histopathological stage confirmed.

Many studies have focused on the risk of lymphatic dissemination in ERC and possible risk factors of LNM have been studied including the depth of submucosal invasion, tumour location in the rectum, tumour budding, lymphovascular invasion, cribriform-type structural atypia and tumour size [3, 6-9]. The reported overall rate of LNM varies between 6% and 29% [10, 11]. The main studies are listed in the Table 1 [3, 5-33]. LNM rate increases with the depth of submucosal invasion from 0 to 18% in Sm1 tumours, 0% to 25% in Sm2 and 12% to 38% in Sm3. Most seriesare however old and include a heterogeneous population of colonic and rectal tumours often of T1 and T2 stage. There is often no mention of the Kikuchi classification [6]. Furthermore, the two most recent studies, including only T1 rectal tumours, show that LNM rate is above 10%, even for Sm1.

Curative treatment of rectal cancer is based on rectal resection with total mesorectal excision (TME). In the treatment of ERC, this may be overtreatment for patients with a low risk of LNM. Because of the risk of perioperative complications, the possibility of poor bowel function and mortality [34-38], some patients have undergone local excision (LE) as the definitive surgical alternative. LE retains anal function and preservation of the organ but is associated with a potential risk of leaving involved lymph nodes behind. LE does indeed have fewer post-operative complications and a lower mortality but it does not offer oncologic

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results comparable to TME [39]. The choice of LE for a T1-Sm1 tumour and TME for a T1-Sm3 tumour is reasonably well established, but there is still controversy regarding the treatment of T1-Sm2 tumours and there are no clear guidelines. The present study aimed to assess the histopathological risk factors for LNM in pT1 rectal cancer and the cancer specific results after surgery.

METHOD

Study population

From January 2000 to December 2014, all consecutive patients who underwent a surgical resection for primary rectal adenocarcinoma in Saint-Antoine Hospital (Paris, France) were identified from a pathological prospective database. Only patients with a pT1 rectal cancer were included in the study. Synchronous colorectal cancers and those receiving neoadjuvant treatment with ypT1 tumour were excluded.

Demographic features (age, gender, body mass index), preoperative clinical features (American Society of Anesthesiologists score, tumour location), surgical features (procedure performed), pathological features including the pTNM classification, depth of submucosal invasion, the presence of vascular embolism and perineural invasion, margin involvement and long-term oncologic results (death, overall and disease free survival, locoregional recurrences and distant metastases) were collected retrospectively from a prospectively maintained database. Follow-up was assessed using medical files or by telephone interview with the general practitioner or the patient.

Perioperative findings and surgery

Preoperative assessment included digital rectal examination, endorectal ultrasound and/or magnetic resonance imaging (MRI). Surgery was by total mesorectal excision (TME) or local excision, according to the preoperative staging.

Mesorectal excision is well described [40, 41]. A laparoscopic approach was used according to the surgeon's practice but was systematically advocated. For a tumour in the upper third of the rectum, rectal dissection was carried out 5 cm below the lower border of the tumour with partial mesorectal excision and colorectal anastomosis (CRA). For a tumour in the mid or lower rectum, TME dissection was carried out to the pelvic floor and a coloanal anastomosis (CAA) performed. For rectal cancers located less than 10 mm from the dentate line, an abdominoperineal excision with permanent colostomy was performed. All extraperitoneal anastomoses were diverted by a defunctioning ileostomy.

Local excision (LE) was carried out in patients diagnosed with a T1 rectal cancer on preoperative endorectal ultrasound. It was performed either through transanal approach for very low rectal tumours or by transanal endoscopic microsurgery (TEM) for higher lesions. In the case of adverse histoipathological findings, LE was followed by radical surgery.

Histopathologic examination

Histopathologic examination of the resected specimen was performed according to a standardized protocol [42] following the pTNM classification [2]. The depth of invasion into the submucosa was defined according to the Kikuchi classification (Sm1, Sm2 and Sm3) [6]. The circumferential resection margin was defined as positive if the primary tumour or an involved lymph node were found to be less than or equal to 1mm from the margin of the specimen. The distal margin was considered R1 when invaded by tumour cells. Available histopathological slides were reviewed by a specialist intestinal histopathologist.

Tumour budding was defined as the presence of a isolated single cancer cells or a small cluster composed of fewer than five cancer cells scattered in the stroma at the advancing edge of the invasive tumour [43]. After choosing the block containing the highest degree of budding by standard diagnostic slide review, tumour buds were detected using a pan-cytokeratin AE1-

AE3 stain (Dako, mouse monoclonal, 1:200, enzyme pretreatment 5 min; DAB chromogen) [44]. More than ten buds per high-power-field (40x) were regarded as positive.

Follow-up

Adjuvant chemotherapy was discussed during a multidisciplinary meeting for patients with lymph node invasion on the histopathological examination. All patients were followed every three months during the first two years after surgery then every 6 months during the next three years and annually thereafter. During follow-up, the patients underwent clinical examination, a thoraco-abdomino-pelvic computerised tomographic (CT) scan and blood was taken for the estimation of carcinoembryonic antigen and carbohydrate antigen 19.9. Colonoscopy was performed one year after surgery, then every three years.

Locoregional recurrence was defined as recurrent disease within the pelvis, including recurrence at the site of the anastomosis and of the perineal wound. In cases with suspected locoregional recurrence, a pelvic MRI was performed and a pathological diagnosis of cancer was always confirmed by biopsy. Metastatic recurrence, diagnosed mainly by imaging, included liver metastasis, metastasis at other extra-abdominal sites and nodal metastasis beyond the regional nodes.

Statistical analysis

Data were presented as median ± standard deviation (range) for quantitative data and as number of cases (percentage of cases) for categorical variables. Comparisons were carried out using, Student's t test and Pearson's χ^2 or Fisher exact test as appropriate.

Survival was estimated using the Kaplan-Meier method and the log-rank test was used to compare survival curves. Overall survival was defined as the interval from the date of surgery to the date of death or the date of last follow-up for patients still alive. All causes of death, including postoperative deaths were considered for overall estimation of survival. All tests

were two sided with a level of significance set at $p < 0.05$. All analyses were performed using JMP9 (SAS Institute Inc, Cary, NC, USA).

This study was conducted according to the ethical standards of the Committee on Human Experimentation of our institution and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [45].

RESULTS

Study population

From January 2000 to December 2014, 121 consecutive patients with pT1 rectal cancer on histopathological examination of the excised specimen were operated on at Hôpital Saint-Antoine, Paris. Of these, ten had a synchronous colorectal cancer. Twenty patients received neoajuvant treatment and were also excluded from the analysis. The remaining 91 patients with early rectal cancer were included in the study (Figure 1). The baseline characteristics of the population are given in Table 2.

Fifty-one (56%) patients were treated by a primary TME, 18 (20%) underwent local excision (LE) alone and 22 (24%) underwent LE followed by a secondary TME. Secondary surgery was performed: in two Sm1 patients (n=2/17, 12%) owing to an R1 resection, in 12 Sm2 patients (n=12/18, 67%), in six Sm3 patients (n=6/8, 75%) and for the two patients with unknown Sm status. The reasons for choosing not to perform a secondary TME in Sm2 and Sm3 patients were age over 75 years (n=4), associated severe comorbidity (n=7) and the absence of poor histopathological criteria in one Sm2 patient.

Histopathological features

The histopathological features are shown in Table 2. Macroscopic analysis showed piece-meal resection in nine (10%) patients. This occurred only after LE: including three after endoscopic resection (n=3/4, 75%), five after transanal excision (n=5/29, 17%) and one after TEM (n=1/7, 14%).

The proportions of Kikuchi stages Sm1, Sm2 and Sm3 were 34% (31), 32% (29) and 32% (29) (32%). The depth of submucosal invasion could not be classified in 2 (2%) patients. An R0 resection was achieved in 81 (89%) patients and was R1 in the remaining ten (11%) including two patients after LE and eight after TME. Five patients having a TME had circumferential involvement from a mesorectal involved lymph node, two patients had distal margin involvement and one had involvement of both circumferential and distal margins.

Lymph node involvement

Of the 73 patients with TME, lymph node status was known in 70. The number of examined lymph nodes was 22 [8-167] per specimen. Sixteen (23%) patients had lymph node metastases (Table 3). Patients with LNM had an average of 3 ± 2 [1-9] involved nodes. The node positive rate was 15%, 14% and 30% in Sm1, Sm2 and Sm3 patients (p=0.326).

Histomorphological parameters were evaluated for statistical correlation with LNM (Table 4). Univariate analysis showed that piece-meal resection (p=0.001), lymphovascular invasion (p=0.001) and high tumor budding (p=0.043) were associated with a significantly increased risk of LNM. The depth of submucosal invasion was not significantly associated with increased LNM. In multivariate logistic regression (Table 4), only lymphovascular invasion (Odds-Ratio (OR)=6.3 [1.2 − 50.8] ; p=0.027) and high tumour budding (OR=7.6 [1.1 − 152.2] ; p=0.037) were independent risk factors for LNM. Considering these two risk factors identified in multivariate analysis, we evaluated the risk of LNM according to the presence or absence of these risk factors in the same patient (Table 5). The risk was 0%

(n=0/18) when there was no factor whatever the depth of submucosal invasion, and 36% (n=14/39) when one or two factors were present.

Survival analysis

After a mean follow-up of 56 ± 46 [0-178] months, 10 (11%) patients had died, including 4 (4%) patients with cancer-related death. Nine (10%) patients had developed recurrence including six with distant metastasis, two with local recurrence and one with both. The five-year overall survival (OS), specific survival (SS) and disease-free survival (DFS) were 82%, 93% and 75%. There was no statistical difference in five-year DFS, according to the surgical management (p=0.87) or the depth of submucosal invasion. (p=0.168) (Figure 2).

DISCUSSION

In the present study, 91 patients with pT1 rectal cancers underwent surgery. After TME (n=73), LNM were detected in 16 (23%) patients. The rate of lymph node involvement was 15%, 14% and 30% in patients with Sm1, Sm2 and Sm3 tumours. In univariate analysis, lymphovascular invasion, piece-meal resection and a high degree of tumour budding were predictive factors for LNM. In multivariate analysis, lymphovascular invasion and high tumour budding were both independent risk factors. After a mean follow-up of 56 months, 10 (11%) patients had died and nine (10%) had recurrence, including three with local recurrence. The five-year overall survival (OS), specific survival (SS) and disease-free survival (DFS) were 82%, 93% and 75%.

In the literature, many studies have focused on the prognosis of small colorectal cancers, especially pT1 tumours. These series include 5938 patients (Table 1) with an overall rate of LNM of 12% but over half of these had colonic cancer in which the LNM rate seems to be higher than in the rectum [6, 8, 46]. Our literature review is in agreement with this report with a

LNM rate of 13% and 10% in rectal and colonic cancers (p=0.009). ERC is different from early colonic cancer and LNM appear to be more common in these tumours. These results highlight the need for specific studies on ERC. Consequently, we present one of the largest series of specifically rectal pT1 tumours.

In our series, three of the 20 patients who underwent TME for a pT1-Sm1 tumour had LNM amounting to a rick of 15%. These had unfavorable histopathological features such as lymphovascular invasion. This result is in contradiction with the initial rates published by Kikuchi, who found no case of LNM among the 35 patients with pT1-Sm1 rectal cancer [6]. Nevertheless, this publication is old and two more recent studies, including 55 and 68 patients with ERC, have also found a LNM rate above 10% for Sm1 tumours [24, 32]. Despite the small sample size, these figures indicate nevertheless that the risk of lymph node involvement in Sm1 cancer may have been underestimated. For Sm2 tumours, no clear guidelines exist and the different therapeutic options are often discussed case by case. The 14% rate of LNM in the present study is consistent with the published data [6, 24, 32]. At least, one third of our patients with a Sm3 tumour had LNM. After LE, only two patients with Sm3 cancer did not n Have a subsequent TME, largely owing to comorbidity and age. One of these presented with local recurrence at six months. Total mesorectal excision is the gold standard for an Sm3 tumour and LE should be an exception, reserved for older patients and / or with serious comorbidity.

The results of the present study and of others indicate, therefore, that the depth of submucosal invasion is probably not a relevant factor to define the risk of LNM and determine the surgical management. Indeed, many studies have identified pathological criteria that are related to LNM and permit division into "high" or "low" risk. TME after a local excision should be discussed when the relevant these pathological features are present. For Sm3 tumours where the risk is 30%, TME must be the basic ttreatment. IN the casse of Sm2

and Sm1 tumours, the rate of LNM is 0% when there are no risk factors and 36% when there is at least one. Consequently, the presence of a single poor histopathological factor on examination of an LE specimen, should lead to an immediate discussion of TME. Local excision should be reserved for patients with an Sm1 and Sm2 tumour when there is no lymphovascular invasion,tumour budding, piecemeal resection and tumour at the margin of the specimen (R1 resection).

There has been much interest in ERC and its risk of LNM, but it is difficult to identify predictors of LNM with confidence, because of the heterogeneity of patients. In many studies, the number of patients is small and, some series include either colonic or rectal cancers or both and many combine pT1 and pT2 tumours. Subdivision of submucosal penetration may be irrelevant in many studies because location of tumour in the rectum [6, 8, 46] and pT2 stage [10, 29, 31] have been identified as undoubted factors associated with lymph node involvement. Only one study looked specifically at risk factors for LNM in early rectal cancer and none was demonstrated [32]. Lymphovascular invasion has been consistently reported in the literature to have high-risk of LNM in pT1 carcinoma [8, 9, 12, 14, 24] and this was confirmed to be statistically significant in the present study in which, furthermore, tumours with lymphovascular invasion had deeper submucosal invasion than those without (data not shown). This could explain why in other series the depth of submucosal invasion and not lymphovascular invasion that seemed to increase the risk of LNM.

Another risk factor identified in the present study is piece-meal resection where there was a great difference in LNM for tumours removed piecemeal (75%) or whole (16%). The nine cases of piece-meal resection occurred after LE and eight of these had been operated on before 2011, mostly by endoscopic removal or trans-anal excision. All these patients, except one 80-year-old woman with cardiac comorbidity, had a subsequent TME at a median of 47 days after the LE [21-77]. Of these six had LNM and two did not. One patient died of

metastatic disease in each of these groups. Piece-meal resection could cause release of cancer cells into the circulation with a metastatic potential favored by local trauma of the surgery. In the case of LE, a complete resection is a major quality criterion and given the availability of new surgical technologies. piecemeal excision should not be performed. For this reason, transanal endoscopic microsurgery (TEM) should be preferred to conventional transanal surgery whenever possible. Fragmentation of the tumour significantly less likely with TEM than with conventional transanal excision [47-49]. Recently, Clancy et al published a meta-analysis of six comparative studies, including 927 patients. This confirmed the superiority of the TEM over transanal excision in achieving complete monobloc resection (OR=0.096, p<0.001) and R0 resection (OR=5.281, p<0.001) and minimizing local recurrence (OR=0.248, p<0.001) [50].

Tumour budding is correlated with the risk of lymph node invasion and survival[43, 51]. In a series of 56 patients with pT1 CRC, Kazama et al reported a LNM rate of 38% in the presence of budding and zero when it was absent (p=0.004)[20]. Similarly, in focusing specifically on ERC, Masaki et al showed that budding was not only a risk factor for LNM, but also for local recurrence after LE only of ERC (p=0.048) [52]. Tumour budding would be important in the evaluation and surgical management of pT1 carcinoma, but the lack of standardized methods for its identification has been responsible for the low use. Tumour budding should be assessed after staining with a pan-cytokeratine antibody as in the present study; this greatly improves the identification of buds [16]. Using this method, our results are concordant with those reported by Ueno et al [16]. One of the weaknesses of our study is the lack of multivariate analysis, but the small size of the groups do not allow a valid analysis.

The current study used three surgical strategies for treating ERC including primary TME, LE alone and LE followed by salvage TME. No significant difference was found between them in the risk of regional LNM or survival. In the current era of 'organ

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preservation', LE is attractive as it avoids the morbidity of the TME and preserves satisfactory bowel function. Two meta-analyses have shown superiority of LE, compared with TME, in various end points including postoperative morbidity (8% vs. 47%, p=0.01), major postoperative morbidity (4% vs. 16%, p<0.001) and mortality (0.4% vs. 2%, p=0.005) [39, 53], but on the other hand LE offers poorer oncologic results owing to the risk of involved nodes in the mesorectum which are not removed by the surgery. This results in lower overall and cancer-specific survival (p>0.001) and higher local recurrence rates than TME. The absence of a significant difference in our study may be related to the small size of the groups despite a 14-year study period, and secondly to the rigorous selection of patients for LE.

In conclusion, we highlight the specific natural history of ERC with a higher rate of regional lymph node involvement than in early colon cancer. Contrary to the findings of Kikuchi et al [6] the depth of submucosal invasion does not predict the presence of LNM in ERC. Other histopathological factors, such as lymphovascular invasion and budding are the best histopathological indicators of regional lymphadenopathy.

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Table 1: Review of the literature of colorectal T1 carcinoma and lymph node involvement

Authors	Year	Tumor localisation	Patients	Lymph node involvement rate			
				N+	Sm1	Sm2	Sm3
Brodsky et al.	1992	Rectum	26	3 (12%)	-	-	-
Huddy et al.	1993	Rectum	27	3 (11%)	-	-	-
Kikuchi et al.	1995	Colon – Rectum	182	13 (7%)	0/64 (0%)	4/82 (5%)	9/36 (25%)
Tanaka et al.	1995	Colon – Rectum	177	21 (12%)	-	(4%)	(20%)
Sitzler et al.	1997	Rectum	35	2 (6%)	-	-	-
Nascimbeni et al.	2002	Colon – Rectum	353	46 (13%)	2/70 (3%)	9/120 (8%)	35/154 (23%)
Bayar et al.	2002	Rectum	59	5 (8%)	-	-	-
Kitajima et al.	2004	Colon – Rectum	865	87 (10%)	-	-	-
Okabe et al.	2004	Colon – Rectum	428	43 (10%)	-	-	-
Shimomura et al.	2004	Colon – Rectum	171	18 (10%)	-	-	-
Egashira et al.	2004	Colon – Rectum	140	13 (9%)	-	-	-
Ueno et al.	2004	Colon – Rectum	251	33 (13%)	-	-	-
Yamamoto et al.	2004	Colon – Rectum	301	19 (6%)	-	-	-
Bentrem et al.	2005	Rectum	168	31 (18%)	-	-	-
Wang et al.	2005	Colon – Rectum	159	16 (10%)	2/70 (3%)	3/46 (6%)	11/43 (26%)
Kazama et al.	2006	Colon – Rectum	56	8 (14%)	-	-	-
Landmann et al.	2007	Rectum	21	6 (29%)	-	-	-
Sohn et al.	2007	Colon – Rectum	48	7 (15%)	4 /22 (18%)	1/13 (8%)	2/13 (15%)
Yasuda et al.	2007	Colon – Rectum	86	21 (24%)	-	-	-
Choi et al.	2008	Colon – Rectum	168	24 (14%)	4/95 (4%)	10/47 (21%)	10/26 (38%)
Rasheed et al.	2008	Rectum	55	7 (13%)	2/15 (13%)	1/7 (14%)	4/33 (12%)
Son et al.	2008	Colon – Rectum	147	25 (17%)			
Yamauchi et al.	2008	Colon – Rectum	164	16 (10%)	-	-	-
Tateishi et al.	2010	Colon – Rectum	322	46 (14%)	-	-	-
Komori et al.	2010	Colon – Rectum	111	17 (15%)	-	-	-
Kobayashi et al.	2010	Rectum	233	20 (9%)	-	-	-
Salinas et al.	2011	Rectum	35	4 (11%)	-	-	-

Saraste et al.	2013	Rectum	205	24 (12%)	-	-	-
Kulu et al.	2015	Rectum	68	9 (13%)	2/17 (12%)	4/16 (25%)	3/22 (14%)
Kawachi et al.	2015	Colon – Rectum	806	97 (12%)	-	-	-

Colon	1816	189 (10%)*	0/29 (0%)	0/40 (0%)	2/10 (20%)
Rectum	2151	283 (13%)*	4/67 (6%)	9/65 (14%)	14/81 (17%)
Total	5938	722 (12%)	16/353 (5%)	32/331 (10%)	74/327 (23%)

* p = 0,009

Table 2: Characteristics and histopathological features of 91 patients with early rectal cancer

(ERC)

TME total mesorectal excision

CRA colorectal anastomosis

	Early Rectal Cancer (pT1) n = 91
Male	65 (71%) [a]
Age	62 ± 12 [b]
Body Mass Index	26 ± 4
ASA [c] score	
I-II	77 (85%)
III-IV	14 (15%)
Digestive comorbidity	
Familial adenoma polyposis	2 (2%)
Inflammatory bowel disease	3 (3%)
Tumour location	
Upper rectum	12 (13%)
Middle rectum	19 (21%)
Lower rectum	50 (55%)
Unknown (polyposis)	10 (11%)
Pre-operative tumour stage	
Stage I (T1/T2 N0)	48 (53%)
Stage II (T3/T4 N0)	1 (1%)
Stage III (N+)	6 (7%)
Stage IV (Synchronous metastasis)	2 (2%)
Unknown	34 (37%)
Surgical procedure	
Endoscopic resection	4 (4%)
Local excision	36 (40%)
Transanal excision	29
TEM [d]	7
TME [e]	73 (80%)
Proctectomy with CRA [f]	10
TME with CAA [g]	47
Ileo-pouch anal anastomosis	12
Hartmann procedure	1
Abdominoperineal excision	1
Adjuvant chemotherapy	12 (13%)
Tumour size (mm)	23 ± 14
Polypoid tumour	36 (39%)

Piecemeal excision	9 (10%)
Histopathological grade	
Well – Moderate	80 (88%)
Poor	4 (4%)
Unknown	7 (8%)
Depth of submucosal invasion	
Sm1	31 (34%)
Sm2	29 (32%)
Sm3	29 (32%)
Unknown	2 (2%)
Lymphovascular invasion	30 (33%)
Perineural invasion	2 (2%)
Tumour budding	
None	13 (14%)
Low	19 (21%)
High	35 (38%)
R1 resection	10 (11%)

(a) number of patients (percentage); (b) mean ± standard deviation; (c) American society of anesthesiology grade; (d) transanal endocopic microsurgery; (e) total mesorectal excision; (f) colorectal anastomosis; (g) coloanal anastomosis.

Table 3: Histopathological features of the primary tumour in 16 patients with lymph node metastasis

	Sex	Age	Tumour location	Polypoid	Diameter (mm)	Primary LE [a]	Piece-Meal	Histological Grade	Sm	Lymphovascular invasion	Perineural invasion	Tumour budding	R0 R1	Recurrence	Survival
1	M	76	Upper	No	15	-	-	Moderate	Sm1	Yes	Yes	High	1	Distant	Dead
2	M	19	-	Yes	4	-	-	Well	Sm1	Yes	No	High	0	-	Alive
3	M	63	Low	No	10	TEM [b]	No	Moderate	Sm1	Yes	No	Low	1	-	Alive
4	M	59	Low	No	40	Transanal	Yes	Well	Sm2	Yes	No		0	-	Alive
5	M	72	Low	No	12	Transanal	Yes	Well	Sm2	No	No		0	-	Alive
6	F	42	Middle	No	23	Transanal	Yes	Well	Sm2	Yes	No		0	-	Alive
7	F	43	Low	No	25	-	-	Moderate	Sm3	Yes	No	High	0	-	Alive
8	M	67	Upper	Yes	30	Endoscopy	Yes	Moderate	Sm3	Yes	No	None	0	Distant	Dead
9	F	56	Middle	No	30	-	-	Moderate	Sm3	Yes	No	High	1	-	Alive
10	M	60	Middle	No	30	-	-	Moderate	Sm3	Yes	No	High	0	-	Alive
11	M	72	Upper	No	-	Transanal	Yes	Well	Sm3	Yes	No	High	0	-	Alive
12	M	53	Low	Yes	25	-	-	Well	Sm3	No	No	High	0	Distant and Local	Dead
13	M	41	-	Yes	20	-	-	Poor	Sm3	No	No		0	-	Alive
14	F	68	Low	No	75	-	-	Moderate	Sm3	Yes	No	High	0	Distant	Alive
15	F	51	Low	Yes	15	Endoscopy	Yes	Well	Unknown	Yes	No		1	-	Alive
16	F	61	Middle	Yes	20	-	-	Moderate	Unknown	No	No	High	0	-	Alive

(a) local excision; (b) transanal endoscopic microsurgery

Table 4: Univariate and multivariate analysis of risk factors for lymph node metastasis in 70 patients undergoing TME for early rectal cancer

			Univariate analysis		Multivariate analysis	
		n	Lymph node involvement	P	OR [CI 95%]	p
Tumour size	≥ 25mm	30	7 (23%)	0.999		
	< 25mm	30	8 (27%)			
Tumour location	Low	35	7 (20%)	0.805		
	Middle-Upper	27	7 (26%)			
Polypoid	Yes	26	6 (23%)	0.822		
	No	29	7 (24%)			
Primary local excision	Yes	19	7 (37%)	0.167		
	No	51	9 (18%)			
Piecemeal resection	Yes	8	6 (75%)	**0.001**	**NS**	**NS**
	No	62	10 (16%)			
Histopathological grade	Well-Moderate	63	15 (24%)	0.435		
	Poor	2	1 (50%)			
Depth of invasion	Sm1	20	3 (15%)	0.326		
	Sm2	21	3 (14%)			
	Sm3	27	8 (30%)			
Lymphovascular invasion	Yes	26	12 (46%)	**0,001**	**6.3 [1.2 – 50.8]**	**0.027**
	No	42	4 (9%)			
Perineural invasion	Yes	1	1 (100%)	0.235		
	No	67	15 (22%)			
Tumour budding	High	28	9 (32%)	**0.031**	**7.6 [1.1 – 152.2]**	**0.037**
	None-Low	25	2 (8%)			
Margin involvement	R1	8	4 (50%)	0.077		
	R0	61	12 (20%)			

(a) lymph node metastasis

Table 5: Rate of lymph node metastasis according to the presence or absence of risk factors including lymphovascular invasion and tumour budding.

	No risk factor	**One or 2 risk factors**
Overall	0/18 (0%)	14/39 (36%)
Depth of submucosal invasion		
Sm 1	0/8 (0%)	3/6 (50%)
Sm 2	0/8 (0%)	2/10 (20%)
Sm 3	0/2 (0%)	7/21 (33%)
Unknown	-	2/2 (100%)
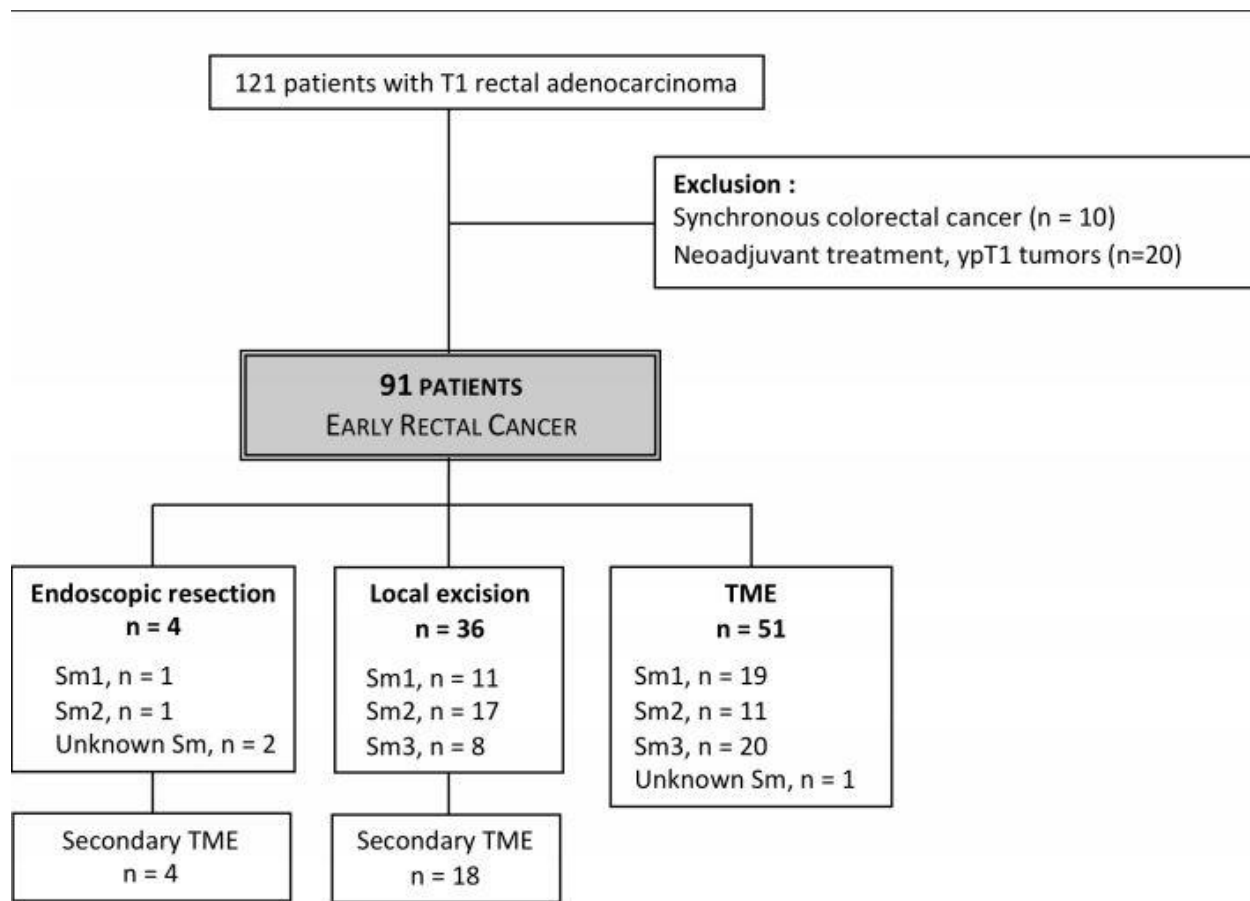
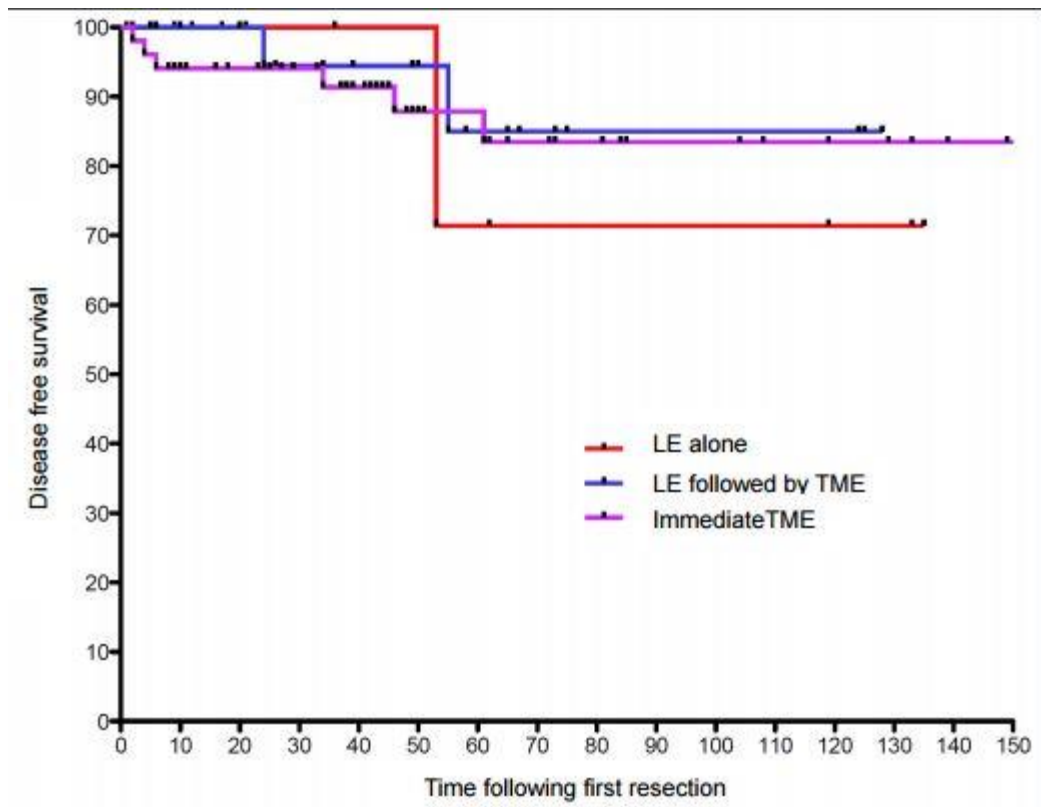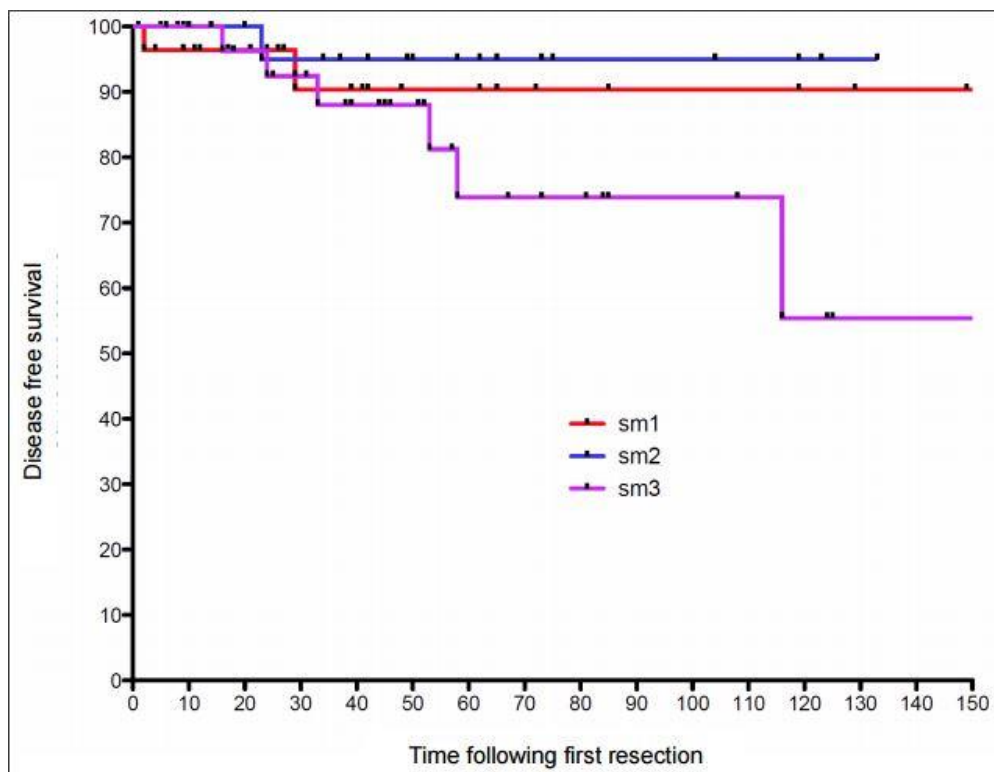Figure 1: Flow-diagram of 121 patients with pT1 rectal cancer.

Fig 2A

Fig 2B

Figure 2: Kaplan-Meier curves of disease-free survival, according to the surgical management (A) and the depth of submucosal invasion (B)