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Pathological evidence in support of total mesorectal excision in the management of rectal cancer

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Rezumat

Suportul histopatologic al exciziei totale de mezorect în terapia cancerului de rect

Introducere: Recidiva locală după rezecția convecțională a rectului, efectuată pentru cancer este obişnuită. În studiile prospective randomizate s-a arătat că iradierea preoperatorie injumătățeşte acest risc.
Scop: Acest studiu multicentric are ca obiectiv estimarea necesității exciziei totale a mezorectului în cancerul de rect.
Material şi metodă: Au fost studiate piesele de rezecție după rezecții curative conținând țesutul mezorectal excizat complet, la 50 de pacienți cu adenocarcinoame ale rectului situate până la 12 cm de la linia anocutanată. Piesa rezecată a fost examinată de unu sau doi anatomopatologi. Au fost examinate 50 de piese de mezorect excizate în cursul rezecțiilor de rect canceroase. 38 de piese de mezorect excizate au aparținut rezecțiilor anterioare joase şi 12 rezecțiilor abdomino-perineale. "Vindecarea" a fost definită prin absența bolii metastatice, la nivelul întergului țesut tumoral extirpat, cu margini proximale şi distale negative. Excizia totală de mezorect s-a efectuat după tehnica descrisă de Heald şi colab.. Mezorectul a fost evaluat pentru noduli limfatici şi depozite tumorale în trei zone: în tumoră, în mezorectul proximal şi în cel distal.
Rezultate: Şase pacienți au prezentat leziuni în stadiul Dukes A. Din 21 de pacienți cu tumori Dukes B, cinci au prezentat focare mici de adenocarcinom în mezorect, fără evidențiere de metastaze în limfonoduli. Leziunile Dukes C au fost mult mai heterogene, însă 12 din 23 de pacienți au avut depozite distincte în mezorect, în paralel cu invazia limfatică a mezorectului. Invazia circulară a marginilor a fost rară, însă la 17 din 44 de pacienți cu tumori pT3 au prezentat depozite tumorale în mezorect şi 23 din 44 au prezentat invazia ganglionilor limfatici din mezorect. Nici un pacient cu tumoră pT2 nu a prezentat invazia mezorectului. Lipsa exciziei complete a mezorectului a reprezentat un potențial pentru boala reziduală microscopică sau macroscopică, ceea ce predispune teoretic la eşecul local.
Concluzii: Excizia totală de mezorect este necesară pentru a evita evaluarea anatomopatologică incompletă a mezorectului şi încadrarea într-un stadiu inferior al cancerului de rect.

Cuvinte cheie: mezorect, excizia totală de mezorect, cancer de rect

Abstract
Background: Pelvic recurrence following conventional rectal resection for cancer is common. Preoperative iradiation has been shown in prospective randomized studies to halve this risk.
Aim: This multiinstitutional study aimed to assess the necesity of total mesorectal excision in rectal cancer.
Patients and method: Pathological resections from 50 consecutive patients with adenocarcinoma of the rectum within 12 cm of the anal verge who underwent currative resection incorporating total mesorectal excision were examined. The resection specimen was examined by one of two pathologists. Some 50

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total mesorectal excision specimens were examined following rectal excision for cancer. Some 38 had total mesorectal excision as a component of a low anterior resection and 12 with abdomino-perineal resection. "Cure" was defined as absence of metastatic disease and the excision of entire macroscopic tumor tissue with negative proximal and distal borders. TME was performed as described by Heald et al. The mesorectum was evaluated for lymph nodes and tumor deposists in three areas: deep to the tumor, in the proximal mesorectum and in the distal mesorectum.
Results: Six patients had Dukes A lesions. Of 21 patients with Dukes B tumors, five had discrete foci of adenocarcinoma in the mesorectum, with no evidence of lymph node metastasis. Dukes C lesions were more heterogeneous, but 12 out of 23 patients had distinct mesorectal deposists in addition to mesorectal node involvement. Circumferential margin involvement was rare, but mesorectal tumor deposits were present in 17 of 44 patients with pT3 tumors, and 23 of 44 had mesorectal nodal involvement. No patient with a pT2 tumor had mesorectal involvement. Failure to excise the mesorectum completely has the potential to leave gross or microscopic residual disease that may in theory predispose to local failure.
Conclusion: Total mesorectal excision is necessary to avoid incomplete pathological evaluation of the mesorectum and understaging of rectal cancer.

Key words: mesorectum, total mesorectal excision, rectal cancer

Introduction

Pelvic recurrence following conventional rectal resection for cancer is common, with a worldwide incidence of approximately 30 per cent for tumors that have penetrated the rectal wall (pT3), irrespective of nodal status (1,2,3,4,5). Preoperative irradiation with or without chemotherapy has been shown in prospective randomized studies to have survival benefit (6,7,8, 9). Although the high local failure rates can be significantly improved upon with adjuvant therapy, there is increasing opinion that many local recurrences are due to incomplete excision of the mesorectum or breach of the mesorectum during rectal resection (10,11,12,13). The rectum and mesorectum, enveloped by the visceral layer of the pelvic fascia, is a distinct anatomical unit within the pelvis, wherein virtually all regional spread of disease is found (14). Total mesorectal excision (TME) accomplished by sharp dissection under direct vision along a plain that separates the parietal from the visceral layers of the pelvic fascia, completely excises this unit (15,16,17,18). Conventional resection is usually performed by blunt dissection along the visceral plan of pelvic fascia, where violation of the mesorectum is probably a common event. Moreover, surgeons seeking 2-3 cm of distal mural clearance may breach the mesorectum just below the tumor and leave behind the distal mesorectum (18). Heald et al. (10) in 1982 first reported a case of mesorectal deposits in the distal mesorectum and cautioned that failure to perform TME may predispose to local failure. This contention was supported in 1993 when Heald and coworkers, reported an overall 5 years local failure rate of 5 per cent in 135 patients with pT3 rectal tumors who had undergone TME in combination with rectal excision (19).

TME has been the standard operation of the present authors for rectal cancer for approximately 10 years, with a pelvic recurrence rate 6 per cent. Over the past 5 years TME has been combined with a detailed assessment of the mesorectum in all cases.

Patients and methods

Pathological resections from 50 consecutive patients with biopsy proven adenocarcinoma of the rectum within 12 cm of the anal verge who underwent currative resection incorporating TME were examined. Experience in teaching TME has founded on dissection of the plain between the seminal vesicle and the anterior surface of Denonvilliers fascia *(Fig. 1)*.

Operative anatomy reveals Denonvilliers' fascia as a trapezoidal "apron" of thickened anterior surface of the mesorectal envelope in the same craniocaudal plain as the peritoneal cul de sac above and fusing with the back of the prostatic capsule and perineal body *(Fig. 2)*.

Denonvilliers' fascia has identifiable left and right edge, which are perilously close to the converging neurovascular bundles *(Fig. 3)*.

Some 38 had TME as a component of a low anterior resection and 12 with abdomino-perineal resection. "Cure" was defined as absence of metastatic disease and the excision

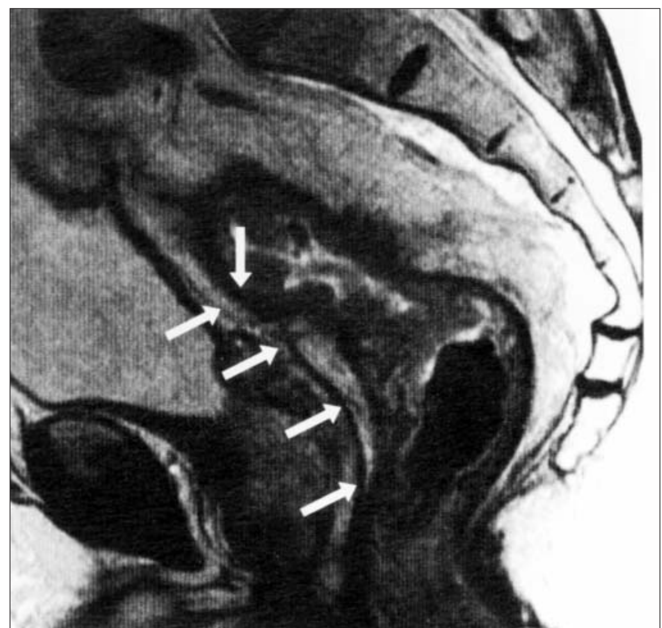

Figure 1. *Magnetic resonance image demonstrate Denonvilliers fascia*

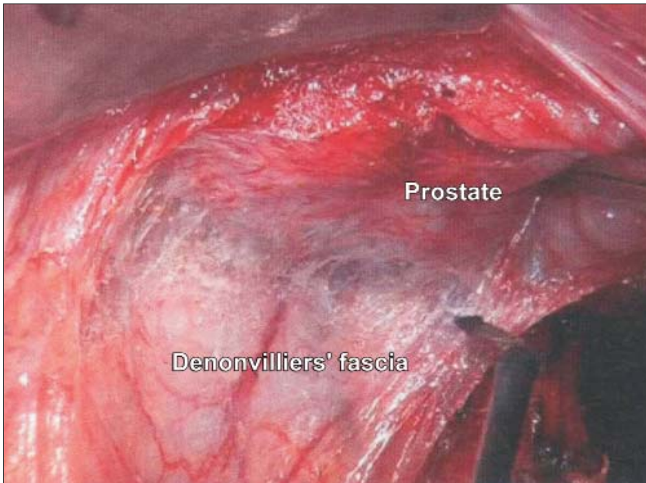

Figure 2. *The limits of mesorectum*

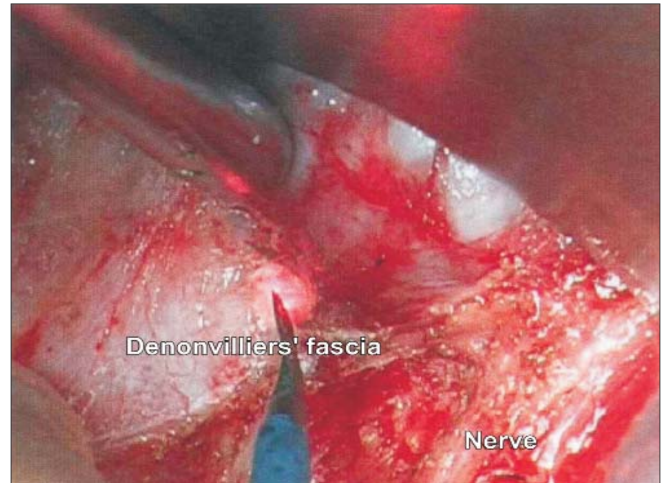

Figure 3. *The limits of mesorectum*

of entire macroscopic tumor tissue with negative proximal and distal borders. TME was performed as described by Heald et al. (11).

The resection specimen was examined by one of two pathologists. Serial transverse sections were made at 5 mm intervals through the tumor, bowel wall and mesorectum in continuity, as described by Quirre et al. (20). The presence of vascular lymphatic and perineural invasion was recorded. Proximal and distal margins were inspected.

The mesorectum was evaluated for lymph nodes and tumor deposists in three areas: deep to the tumor, in the proximal mesorectum and in the distal mesorectum *(Fig. 4)*.

Mesorectal deposits were defined as discrete foci of adenocarcinoma, discontinious from the primary tumor with no evidence of nodal tissue. Sections were also examined microscopically for circumferential resection margins involvement.

All specimens were assigned a Dukes and tumor node metastasis (TNM) stage (21,22,23).

Statistical significance was determined by x^2 analysis with Yate's correction.

Results

Dukes and pTNM staging is shown in *Table 1*.

Mr ± devotes the presence or absence of apparent non-nodal foci of adenocarcinoma (mesorectal deposits) within the mesorectum.

Dukes C lesions were more heterogeneous, but 12 out of 23 patients had mesorectal deposits in addition to mesorectal node involvement. Six patients had Dukes A lesions. Of 21 patients with Dukes B tumors five had foci of adenocarcinoma in mesorectum, with no evidence of lymph node metastasis. From all specimens two (4%) showed circumferential margin involvement microscopically, both in patients with extensive mesorectal nodal and extra-nodal disease.

Of six patients with pT2 tumor, no involved mesorectal

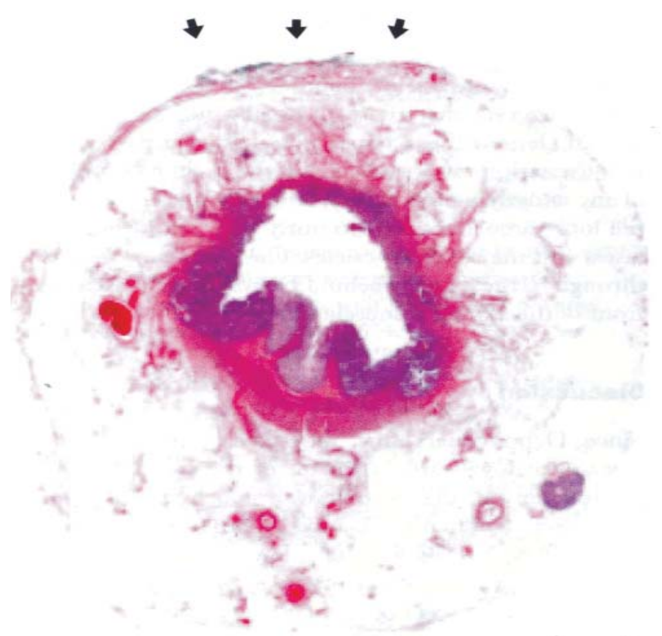

Figure 4. *Histological whole mount section (haematoxylin and eozine stain)*

Table 1. *Pathological characteristics according to Dukes and tumor node metastasis classification*

TN	No. of patients	Dukes stage
T2N0	6	A
T3N0(Mr-)	16	B
T3N0(Mr+)	5	B
T3N1(Mr-)	10	C
T3N1(Mr+)	3	C
T3N2(Mr-)	1	C
T4N2(Mr+)	9	C

nodes or deposits were retrived. 28 of 44 patients with pT3 lesions had involved nodes or deposits ($p<0.05$).

The number of patients with involved deep, proximal or distal mesorectal nodes or deposits is shown in *Table 2*.

In the majority of cases mesorectal involvement was present deep to the tumor. In 12 patients the distal mesorectum was involved. In five of these 12 cases mesorectal involvement was more than 2 cm below the distant rectal tumor. In five cases overall, mesorectal deposits were identified in the absence of mesorectal node involvement.

The correlation between mesorectal node involvement with nodes or deposits in patients with pT3 tumors and maximum tumor dimensions, tumor thickness, borders, lymphatic or vascular or perineural invasion is shown in *Table 3*.

There was a significant association between mesorectal involvement and maximum tumor diameter greater than 5cm, infiltrating borders, and vascular, lymphatic and perineal invasion. Tumor thickness did not correlate with mesorectal involvement.

Table 2. *Incidence of involvement of mesorectal nods and deposits in the mesorectum proximal, deep and distal to the tumor in 44 patients with pT3 tumors*

	Node positive	Deposit positive
Proximal	16	9
Deep	21	16
Distal	9	6

Table 3. *Correlation between variables in 44 patients with pT3 tumors*

	Mesorectal nodes or deposits			
	Involved n=28	Tumor free n=16	x^2	P
Vascular invasion				
Present	13	0	8.4	<0,01
Absent	15	16		
Lymphatic invasion				
Present	12	0	7.4	<0,01
Absent	16	16		
Perineural invasion				
Present	11	0	6.4	<0,02
Absent	17	16		
Tumor Borders				
Infiltrating	20	5	5.1	<0,05
Pushing	8	11		
Maximum diameter (cm)				
>5	20	5	5.1	<0,05
<5	8	11		
Tumor thickness (cm)				
>1.5	17	5	2.4	0,1
<1.5	11	11		

Discussions

The local control of malignant solid neoplasms is based on the removal of the primary tumor and its vascular and lymphatic drainage. In the recent years, the surgical technique has emerged as a crucial factor for local recurrence, ever since the popularization of total mesorectal excision (TME), a concept introduced by Heald et al.

There is increasing evidence that a detailed pathological evaluation of the mesorectum, rarely reported and probably rarely performed, is worthwhile and can be used as an audit tool.

First, it may predict local recurrence: using sequential transverse whole–mount sections of the tumor and mesorectum. Quirre et al. (20) reported in 1986 that local failure in patients undergoing conventional rectal resection was related to microscopic spread beyond the circumferential resection margin: 85% of patients with circumferential margin involvement developed local recurrence, compared to 3% of those with negative margins. From the same group (23) 23 of 58 patients (40%) with circumferential margin involvement developed a local recurrence compared to 9 of 115 (8%) with clear margins.

Heald and al (10) cautioned that distal mesorectal lymphatic spread, contrary to previous reports (24), may exceed mural spread and that transecting the mesorectum 2 cm below the tumor may leave residual disease.

Scott et al (25), Jesus et al (26) recent confirmed that distal mesorectal spread often exceeds intramural spread, and reported the presence of the tumor in the distal mesorectum in 4 patients out of 20 who underwent TME.

Finally, mesorectal analysis may reveal findings of independent prognostic significance: Cawthorn et al (28) demonstrated that mesorectal invasion (greater than 4 mm) was associated with a significantly decreased survival in patients with minimal (less than 4 mm) mesorectal spread.

The prognostic significance of foci of tumor deposits within the mesorectum is controversial. It is possible that they represent completely replaced lymph nodes. Hale et al (32) studied the prognostic value of circumferential margin involvement in a series of 153 rectal cancer patients treated with mesorectal excision with curative intent by a single surgeon. Disease-free survival and overall survival were significantly lower in patients with positive margins, but the local recurrence rate was not different between groups.

More recently, Nagtegaal et al (31) have shown that the involvement of the circumferential resection margin is a strong predictor for local recurrence after TME. A disease-free margin of less than 2 mm was associated with a statistically significant increase in the risk of local recurrence compared to wider margins (16,0% vs. 5,8%). In fact margins of 1mm or less were positively associated with a higher risk of distant metastases (37,6% vs. 12,7%) and shortened survival.

Furthermore, the prognostic value of circumferential resection margin involvement is independent of the TNM classification. All these reports have confirmed the importance of excising the rectum outside its fascia propria for preventing local tumor recurrence. The Leeds study (23) showed that 25% of patients (35 of 141) undergoing conventional resection had

a circumferential margin, whereas this was evident in only 4% of patients (2 of 50) in the present TME series.

Although intramural involvement rarely extends distally beyond 2 cm, enabling “close-shave” sphincter-saving resections with respect to mural clearance (28,29,30), the distal mesorectum in the present series was involved by lymph nodes in 9 of 44 patients with T3 tumors and by foci of adenocarcinoma in 6 of 44.

The control arm of the Dutch study (33) on preoperative radiotherapy combined with TME for resectable rectal cancer contains the only prospective data on the local recurrence after TME. In that series the local recurrence rate after a median follow-up of more than 2 years was 8,2%, 0,7% for stage I, 5,7% for stage II and 15% for stage III.

The quality of life after radical proctectomy with TME is impaired by the routine formation of a temporary nonfunctioning stoma (34).

Discontinuous mesorectal deposits have previously been described between 2 and 4 cm below the main tumor mass (10). This has been confirmed in the present study and in one case a deposit was present 5cm below the main tumor mass.

This data supports the rationale for TME and low anastomosis for rectal tumors below the peritoneal reflection, including high mid-rectal tumors, despite the greater potential for perioperative complications and risk of functional problems. (35,36,37,38)

The authors consider that failure to make detailed pathological assessment of the mesorectum may overlook nodes or deposits and understage the disease, and that failure to perform TME may potentially leave residual disease in the distal mesorectum or at the circumferential margin and predispose to pelvic recurrence.

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