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CLINICAL INVESTIGATION **Rectum**

DEFINITION AND DELINEATION OF THE CLINICAL TARGET VOLUME FOR RECTAL CANCER

Sarah Roels, M.D.,* Wim Duthoy, M.D.,§ Karin Haustermans, M.D., Ph.D.,* Freddy Penninckx, M.D., Ph.D.,† Vincent Vandecaveye, M.D.,‡ Tom Boterberg, M.D.,§ and Wilfried De Neve, M.D., Ph.D.§

Departments of *Radiotherapy, †Surgery, and ‡Radiology, University Hospital Gasthuisberg, Leuven, Belgium; and §Department of Radiotherapy, Ghent University Hospital, Ghent, Belgium

Purpose: Optimization of radiation techniques to maximize local tumor control and to minimize small bowel toxicity in locally advanced rectal cancer requires proper definition and delineation guidelines for the clinical target volume (CTV). The purpose of this investigation was to analyze reported data on the predominant locations and frequency of local recurrences and lymph node involvement in rectal cancer, to propose a definition of the CTV for rectal cancer and guidelines for its delineation.

Methods and Materials: Seven reports were analyzed to assess the incidence and predominant location of local recurrences in rectal cancer. The distribution of lymphatic spread was analyzed in another 10 reports to record the relative frequency and location of metastatic lymph nodes in rectal cancer, according to the stage and level of the primary tumor.

Results: The mesorectal, posterior, and inferior pelvic subsites are most at risk for local recurrences, whereas lymphatic tumor spread occurs mainly in three directions: upward into the inferior mesenteric nodes; lateral into the internal iliac lymph nodes; and, in a few cases, downward into the external iliac and inguinal lymph nodes. The risk for recurrence or lymph node involvement is related to the stage and the level of the primary lesion.

Conclusion: Based on a review of articles reporting on the incidence and predominant location of local recurrences and the distribution of lymphatic spread in rectal cancer, we defined guidelines for CTV delineation including the pelvic subsites and lymph node groups at risk for microscopic involvement. We propose to include the primary tumor, the mesorectal subsite, and the posterior pelvic subsite in the CTV in all patients. Moreover, the lateral lymph nodes are at high risk for microscopic involvement and should also be added in the CTV.

Radiotherapy, Clinical target volume, Rectal cancer.

INTRODUCTION

Since the introduction of total mesorectal excision (TME), a significant decrease in local recurrence rate has been observed in resectable rectal cancer (1). The use of radiotherapy, either pre- or postoperatively, decreases the local recurrence rate and improves survival in cases of locally advanced rectal cancer (2–4). Chemotherapy has been shown to enhance the efficacy of pelvic radiation (5). Although postoperative chemoradiation allows patient selection based on histopathologic tumor characteristics, recent data demonstrate the superiority of preoperative radiation (6). Moreover, preoperative radiation allows downsizing of low-seated rectal tumors, which may result in more sphincter preservation (6, 7). Furthermore, recent data of the EORTC 22921 trial demonstrate that the addition of chemotherapy to preoperative radiotherapy increases downsizing and downstaging in T3–4 resectable rectal cancer (8). Based on the results of prior and recent randomized trials (2, 8, 9), radiation therapy to a dose of 45 to 50 Gy in 1.8 to 2 Gy per fraction, combined with 5-fluorouracil (5FU) chemotherapy is currently the standard pre-operative schedule in T3/T4 (and/or $N+$) tumors in many European centers.

Although the introduction of modern treatment techniques such as TME and combined preoperative chemoradiation has strongly reduced local recurrence rates to $<10\%$ (8, 9), there is still room for improvement in treatment in high-risk patients (T3–T4, lymph node positive) (10). In these selected patients, progress may be achieved with

Reprint requests to: Karin Haustermans, M.D., Ph.D., Leuven Cancer Institute, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. Tel: (+32) 16-346902; Fax: (+32) 16-346901; E-mail: Karin.Haustermans@uzleuven.be

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higher preoperative doses with or without altering the fractionation of radiotherapy (11, 12), and integrating novel chemotherapeutic and molecular targeted agents with radiosensitizing properties. However, further dose escalation is limited because of normal tissue toxicity (13–15).

In radiotherapy, multiple beam set-up, customized blocking, and the use of a special open table top or belly board device, shifting the small bowel out of the treatment field can limit the volume of small bowel treated (15). In modern radiotherapy, the intensity of the beams can be modulated to obtain a conformal dose distribution around the target volume while sparing the surrounding organs at risk. In rectal cancer, intensity-modulated radiotherapy (IMRT) and intensity-modulated arc therapy (IMAT) can be used to spare the small bowel around which the clinical target volume (CTV) is located in a horseshoe shape (16). However, because these techniques introduce dose gradients close to the planning target volume (PTV) (Fig. 1), proper definition and delineation of the CTV is required to avoid underdosage of regions that could possibly harbor cancer cells. Few studies are published on guidelines to define and delineate the CTV in rectal cancer (17–21), and most only give recommendations for 2D treatment portals. In this article we analyze reported data on the predominant locations and frequency of local recurrences and lymph node involvement in rectal cancer to propose a definition of the CTV for rectal cancer and guidelines for its delineation.

METHODS AND MATERIALS

Literature search strategy

MEDLINE (http://www.pubmed.com) was searched for the terms (((rectum or rectal or colorect* or rectosigm* or sigmo*) and (cancer or adenocarcinoma or carcinoma or neoplasm*)) and ((recurrence or failure or relapse or recurrent) or (spread or node or lymph)) and (local or locoregional or regional or pelvic)-in title) up to September 2005 (* depicts a "wildcard"). This yielded 403 articles. A selection was made based on the titles, excluding all articles dealing with prostate cancer, diagnostic techniques for recurrent disease, treatment of recurrence, or follow-up strategies for rectal cancer. Only publications in English, French, or German were retained. After this first selection, 114 articles remained, of which the abstracts were read, and only those articles that were expected to give precise anatomic information about the location of the recurrence or pathologic lymph nodes (more detailed than "pelvic" or "local") were retained. This yielded 22 articles. From these 22 articles, the full text was retrieved, and of these 22 only four gave adequate information on the precise location of recurrence and a clear description of the number of patients at risk. By extensive cross-referencing, 18 articles were eventually kept (19, 22–38). Of these, 1 article was withdrawn from the final analysis because of less reliable information, based on CT findings only (19), compared to histologically proven data.

Definitions

In an attempt to compare the results of the remaining 17 articles, we defined the pelvic areas that seemed most at risk for local recurrence or lymph node spread, aiming at the "greatest common denominator" of all areas discussed in the individual articles.

Pelvic subsites

Five subsites were defined as the predominant areas at risk for local recurrence: the mesorectal subsite (MS), the posterior pelvic subsite (PPS), the lateral pelvic subsite (LPS), the inferior pelvic subsite (IPS), and the anterior pelvic subsite (APS).

- The MS encompasses the mesorectum, defined as the adipose tissue with lymphovascular and neural structures, encapsulated by a fascia, the so-called mesorectal fascia. The mesorectum is cylindrical, with cone-shaped tips in cranial and caudal direction, starting at the level of the sacral promontory at the origin of the superior rectal artery and ending at the level where the levator ani muscle inserts into the rectal wall.
- The PPS covers mainly the presacral space: a triangular area, enclosed posteriorly by the presacral fascia (Waldeyer's fascia) and anteriorly by the mesorectal fascia. This volume is clearly recognizable on magnetic resonance imaging (MRI), and con-

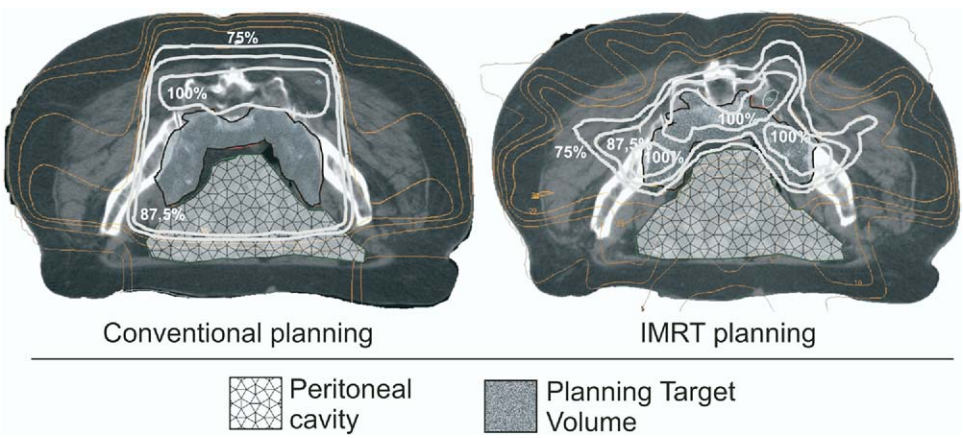

Fig. 1. Dose distribution in a transverse plane for a conventional plan (two lateral wedged beams and one posterior beam) (left), and an intensity-modulated radiotherapy (IMRT) plan (right). The ability to spare small bowel (16) with IMRT is clearly visible. Note that the conventional plan is more insensitive to the accuracy of delineation of the clinical target volume than the IMRT plan. In the latter approach, an erroneous clinical target volume definition will lead to underdosage of the target regions.

tains the median and lateral sacral vessels, the lymphatics of the presacral chains, the anterior branches of the sacral nerves, and the inferior hypogastric plexus (39).
- The LPS includes the area on the lateral aspect of the mesorectal fascia, including the lateral pelvic side walls.
- The IPS consists of the anal triangle of the perineum, containing the anal sphincter complex with the surrounding perianal and ischiorectal space.
- The APS contains all pelvic organs that are located ventrally from the MS.

The results in the different studies were obtained via retrospective analysis (23, 26, 34), follow-up series (22, 25, 33), and findings at planned second-look operations (24). Additional patient characteristics are summarized in Table 1.

Besides the recurrences in the different pelvic subsites, we also briefly discuss anastomotic recurrences.

Lymph node regions

To assess the risk of lymph node involvement, we analyzed all articles discussing the distribution and frequency of pathologic lymph nodes based on histopathologic examination at primary surgery (27–32, 35–38). Data on lymph node invasion are generally from Japanese studies, as extended pelvic lymphadenectomy evolved to become the standard treatment for low-lying rectal cancer in some centers in Japan (40, 41). Information on patient and tumor characteristics are reviewed in Table 2.

We defined five lymph node regions (LNR), as follows: the mesorectal lymph nodes (MLN), the upward lymph nodes (ULN), the lateral lymph nodes (LLN), the external iliac lymph nodes (ELN), and the inguinal lymph nodes (ILN).

Each LNR was chosen in accordance with the main lymphatic drainage pathways of the rectum. The MLN group is, similar to the MS, defined as the mesorectal tissue enclosed by the mesorectal fascia, containing the mesorectal nodes with their afferent and efferent vessels and the lymph nodes along the superior rectal artery. The ULN encompasses all lymphatic tissue along the inferior mesenteric artery. Lymphatic spread to the LLN is defined as involvement of the lymph nodes along the middle rectal, the obturator, and the internal iliac vessels. The lymph nodes along the external iliac artery and superficial inguinal lymph nodes are classified as ELN and ILN, respectively.

RESULTS

Pelvic subsites at risk for local recurrence

Table 3 shows the risk of local recurrence per pelvic subsite. For the IPS, the distribution of recurrences was further subdivided for patients who underwent abdominoperineal resection (APR).

Mesorectal subsite

Only two articles report on the incidence of recurrence in the mesorectal subsite (MS) in patients who underwent sphincter-saving surgery in the "pre-TME era" (26, 34). The introduction of TME as the actual standard surgical treatment has significantly reduced the risk for local recurrence in this subsite. However, the MS contains lymph nodes that are highly at risk for tumor involvement; therefore we will discuss this subsite in the section of the MLN.

Posterior pelvic subsite

For the posterior pelvic subsite (PPS), data on recurrences in the "presacral space" (22, 23), "posterior pelvis" (24, 34), or both (33) were considered. The results were merged, as most of the posterior relapses include presacral disease (21).

If all patients from the analyzed retrospective studies are considered (three studies, $n = 254$), 22% (57/254) of these patients had a recurrence in the PPS. Looking at all patients with recurrence ($n = 435$, five studies), 49% (211/435) had involvement of the PSS.

A recent publication reports on the location of recurrent rectal cancer in 123 patients with the help of a CT-based three-dimensional (3D) data file system. The investigators also found that local relapse was mainly situated in the posterior part of the pelvis (21).

Lateral pelvic subsite

The lateral pelvic subsite (LPS) represents the "lateral pelvic wall" in five studies and in one study only "lateral" is used, without specifying the exact location of this area (24). In our analysis, both names were considered as locations for recurrences in the LPS.

Six percent of all patients (42/722) in these series had invasion of the lateral pelvic subsite as a part of their disease relapse. When only considering patients with a local recurrence ($n = 469$), then 21% (97/469) had a relapse in the lateral pelvic subsite.

Inferior pelvic subsite

Information on inferior pelvic subsite (IPS) recurrence was found in four reports, including 1188 patients. All papers are retrospective analyses, and the overall risk of developing a recurrence in the IPS in these studies was about 4% (53/1188). In one study, the risk of IPS recurrence was calculated in relation to the tumor site, being 8% (18/234) for tumors located <6 cm from the anal margin, 3% (11/403) for tumors located between 6 cm and 11 cm from the anal margin, and nonexisting (0/284) for tumors ≥ 11 cm (25). When patients with an APR were considered (two studies, 189 patients), 11% (21/189) developed a recurrence in the IPS.

Furthermore, IPS involvement was seen in 12% (68/580) of all patients with a recurrence (five studies, 580 patients). Höcht *et al.* came to a similar conclusion, although no absolute numbers were reported in their publication (21).

These data clearly indicate that the IPS is especially at risk for local recurrence in those patients with a tumor ≤ 6 cm from the anal margin and in patients who have undergone APR.

Anterior pelvic subsite

Recurrences involving the vagina, bladder, prostate, seminal vesicles, urethra, or uterus were classified as anterior pelvic subsite (APS) recurrences. APS recurrences were found in 5% of the patients (63/1188). In patients with a pelvic recurrence, involvement of the APS was observed in 17% (104/626).

Table 1. Clinical characteristics of patients in articles that report on the location of local recurrences

Characteristic	First author (Ref.)						
	Gilbertsen (22)	Mendenhall (23)	Gunderson (24)	McDermott (25)	Killingback (26)	Hruby (33)	Wiig (34)
Patient *N*	89**	90	75	1008[‖]	532[#]	269[o]	46[o,1]
Tumor stage							
T1–2	ND	ND	ND	ND	ND	33	ND
T3	ND	ND	ND	ND	ND	198	ND
T4	ND	ND	ND	ND	ND	23	ND
N+	ND	ND	ND	ND	ND	140	ND
Dukes A	19	6	—	276	158	ND	ND
Dukes B	16	46	7	350	184	ND	ND
Dukes C	42	34	61	317	190	ND	ND
Other	12	4	—	65	—	15	ND
Tumor level							
Distance from AM	distal 10 cm: 89	0–7 cm: 40	0–5 cm: 28	<6 cm: 249	<7 cm: 126	ND	6–10 cm: 23
	ND	8–12 cm: 26	6–10 cm: 22	6–11 cm: 439	7–12 cm: 272	ND	11–15 cm: 18
	ND	>12 cm[†]: 23	>10 cm[††]: 15	11–18 cm: 305[¶]	>12 cm: 134	ND	>15 cm: 5
LR type							
Isolated LR/total LR	ND/47	24/41	25/52	107/191	17/41	150/269	46/46
Method of assessment of LR							
Autopsy	3	5	and/or (2)	ND	ND	—	—
Biopsy	and/or (25)	9		ND	21	155	—
Surgical exploration		—	46	ND	0	—	46[2]
Clinical examination	4	27	—	ND	20	114	46
Surgery type							
APR	89**	54	67	364	58	100	—
AR	—	28	ND	644	389	154	46
Other	—	7	—	—	85	15	—
TME (Y/N)	N	N	N	ND	N	ND	N
SSS	—	—	7	—	468	—	—
Time initial surgery	1940–1950	1959–1976	ND	1950–1983	1969–1993	1979–1997	1985–1994
Follow-up period months (median [range])	20 (3–76)	(60–252)	[§]	ND	82 (1–320)	ND	NA

Abbreviations: AM = anal margin; APR = abdominoperineal resection; AR = anterior resection; LR = local recurrence; N = number of patients in analysis; N+ = lymph node positive patients; NA = not applicable; ND = not determined; SSS = sphincter saving surgery; TME = total mesorectal excision (Yes/No).

[#] Only patients with sphincter saving procedures were evaluated for location of LR (468/532).

* Includes radiological examination in (22, 25, 33, 34).

[†] Within 20 cm.

[††] Unknown: 2.

[§] 2nd, 3rd, and 4th look operations at 6–12 months intervals after initial curative surgery until no disease was found or disease had spread beyond surgical control.

[‖] 934/1008 available for analysis of LR.

[¶] Unspecified: 15.

** Only patients that underwent APR were evaluated for location of LR (89/125).

[o] Only patients with LR.

[1] 46/100 patients that were operated for recurrent rectal cancer had primary low AR and were evaluated for location of LR.

[2] All 46 patients received radiotherapy followed by surgery for local recurrence.

Table 2. Clinical characteristics of patients in articles that report on the location of lymph node metastases

Characteristic	First author (Ref.)									
	Hojo (27)	Ueno (28)	Moriya (29)	Morikawa (30)	Hida (31)	Moreira (32)	Takahashi (35)	Steup (36)	Ueno (37)	Koda (38)
Patients N	389*	166[#†]	448[#]	171	182	95	745	605	237[#]	452[#‖]
Tumor stage										
T1–2	110	6	128	36	44	ND	245	86	—	70
T3	69	54	294	60	117	ND	170	148	224	133
T4	210	10	26	72	21	ND	349	281	13	62
Dukes-A	63	ND	88	ND	ND	23	ND	133	—	ND
Dukes-B	134	ND	142	ND	ND	24	ND	178	118	ND
Dukes-C	192	70[†]	218	ND	ND	48	ND	226	119	ND
Other	34	ND	—	3	ND	—	ND	69	—	ND
Tumor level										
Ra	148	—	—	68	72	—	298	133	—	—
Rb	241	70]	448]	65	70	95]	334	373	237	159
Rpr	—		—	—			—	99	—	106
Distance from AM	—	below pr	below pr	—	—	≤10 cm	—	—	<8 cm	ND
Size of tumor	<3 cm: 50	ND	ND	ND	ND	ND	ND	<3 cm: 120	53 mm (11–130)[§]	ND
	3–5 cm: 120	ND	ND	ND	ND	ND	ND	3–6 cm: 322	ND	ND
	>5 cm: 122	ND	ND	ND	ND	ND	ND	>6 cm: 163	ND	ND
	Other: 97	ND	ND	ND	ND	ND	ND	—	ND	ND
LMM N	220	52–17[††]	218–62[††]	98	104	10[††]	327	288	119	35[††]
Surgery type										
LLD	389**	70	322	171	182	95	745[¶]	605	237	265
SAL	389**	70	322	ND	ND	10	ND[¶]	605	237	265
APR	ND	41	211	ND	—	46	192	ND	117	ND
AR	ND	—	—	ND	LAR: 182	—	572	ND	ND	ND
TPE	ND	—	23	ND	ND	5	—	ND	6	ND
SSS	ND	5	198	ND	ND	44	ND	ND	114	ND
other	—	24	16	ND	ND	—	—	—	237 TME	97 TME - 355 CSx
Time year	1969–1980	1991–1995	1980–1994	1979–1986	1979–1986	1981–1991	1975–1995	1974–1990	1985–1999	1984–2000

Abbreviations: AM = anal margin; APR = abdominoperineal resection; AR = anterior resection; CSx = conventional surgery; LLD = lateral lymph node dissection; LNM = lymph node metastases; N = number of patients in analysis; ND = not determined; Ra = tumor located above peritoneal reflection (tumors in rectosigmoid are not included in (30, 31, 35); Rb = tumor located below peritoneal reflection; Rpr = tumor located at peritoneal reflection; SAL = systematic abdominopelvic lymphadenectomy/extended lateral lymph node dissection; SSS = sphincter saving surgery; TPE = total pelvic exteneration.

* 389/432 patients with SAL in analysis for location of LNM.

† Only Dukes-C with SAL in analysis for location of LNM.

†† Only lateral/disc lymph nodes - 5/17 were occult metastatic foci [28].

§ Median (range) tumor size.

‖ 265/452 with SAL in analysis for location of LNM.

¶ For some upper rectal cancers a dissection of the obturator space was replaced by a probe excision of LN.

** Wide resection with SAL - resection of primary tumor not further specified.

Only low seated and/or middle seated rectal tumors.

Table 3. Local recurrence per pelvic subsite

Pelvic subsite	Patient group	First author	Ref.	No. at risk (n)	No. rec. (n)	No. rec. in specified subsite (n)	Risk for rec. in specified subsite (%)	Involvement of subsite in R+ pts. (%)
PPS	All	Gilbertsen	22	89	32	14	16	44
		Mendenhall	23	90	40	18	20	45
		Gunderson	24	75	48	25	33	52
	Partial sum			**254**		**57**	**22**	
		Hruby	33	—	269	127	—	47
		Wiig	34	—	46	27	—	59
	Total sum				**435**	**211**		**49**
LPS	All	Gilbertsen	22	89	32	1	1	3
		Mendenhall	23	90	40	4	4	10
		Gunderson	24	75	46	13	17	27
		Killingback	26	468	34	24	5	70
	Partial sum			**722**		**42**	**6**	
		Hruby	33	—	269	30	—	11
		Wiig	34	—	46	25	—	54
	Total sum				**469**	**97**		**21**
IPS	All	Gilbertsen	22	89	32	5	6	16
		Mendenhall	23	90	40	4	4	10
		Gunderson	24	75	48	14	19	29
		McDermott	25	934	191	30	3	16
	Partial sum			**1188**		**53**	**4**	
		Hruby	33	—	269	15	—	6
	Total sum				**580**	**68**		**12**
	APR	Gilbertsen	22	89	—	5	6	—
		Hruby	33	100	—	16	16	—
	Partial sum			**189**		**21**	**11**	
APS	All	Gilbertsen	22	89	32	13	15	40
		Mendenhall	23	90	40	6	7	15
		Gunderson	24	75	46	21	28	44
		McDermott	25	934	191	23	2	12
	Partial sum			**1188**		**63**	**5**	
		Hruby	33	—	269	29	—	11
		Wiig	34	—	46	12	—	26
	Total sum				**626**	**104**		17

Abbreviations: APR = abdominoperineal resection; APS = anterior pelvic subsite; Involvement of subsite in R+ pts. = ratio of No. rec. in specified subsite over No. rec.; IPS = inferior pelvic subsite; LPS = lateral pelvic subsite; No. at risk = number of patients at risk for recurrence; No. rec. = number of patients with recurrence (in any subsite, unless specified); PPS = posterior pelvic subsite; Pts = patients; partial sum = refers to articles reporting the no. of patients at risk for recurrence (no. at risk); Ref. = reference; R+ pts. = No. rec. or all patients with recurrence (in any subsite, unless specified); Risk for rec. in specified subsite = ratio of No. rec. in specified subsite over No. at risk; total sum = refers to articles reporting the no. of patients with recurrence (no. rec.).

Anastomotic recurrences

Four articles report on the risk of anastomotic recurrences (as a percentage of locoregional sites involved), ranging between 10% and 21%, dependent on the definition of a true anastomotic recurrence (23, 25, 33, 34).

Lymph node regions at risk

In this study, 10 reports on lymphatic spread in patients with rectal cancer were analyzed to compute the relative frequency and location of metastatic lymph nodes in rectal cancer (27–32, 35–38). Table 4 shows the risk of lymph node involvement per LNR. The risk of lymph node invasion was analyzed according to T stage and level of the primary tumor. A separate analysis for high-seated and low-seated tumors was also made for ELN and ILN involvement.

Mesorectal lymph nodes

In 46% of all patients in the articles analyzed, at least 1 positive mesorectal lymph node (MLN) was found (615/1347). The MLN was involved in 87% of the patients with positive pelvic lymph nodes (615/706), showing the importance of this group. Morikawa *et al.* (30) provide detailed information on longitudinal mesorectal lymphatic spread. In the caudal direction, no lymphatic spread was found >4 cm away from the tumor. In the cranial direction, positive lymph nodes (in the mesorectum) were found ≤10 cm above the primary tumor (8%), whereas at >10 cm the risk was <2%.

Upward lymph nodes

In two articles, upward spread is defined along the superior rectal artery (SRA) and inferior mesenteric artery (IMA),

Table 4. Lymph node involvement per lymph node region

LNR	Patient group	References	No. at risk (*n*)	No. N+ (*n*)	No. N+ in specified LNR (*n*)	Risk for N+ in specified LNR (%)	Involvement of LNR in N+ pts (%)
MLN	All	27, 30, 31, 36	1347	706	615	46	87
ULN	All	27, 30, 31, 35, 36	2092	1033	578	28	56
LLN	All	27, 30, 31†, 32, 35, 36*	2187	1043	285	13	27
	T1-2	27, 28*, 29, 30, 35, 38*	595		28	5	
	T3	27–30, 35, 37*, 38	1004		142	14	
	T4	27–30, 35, 37, 38	742		112	15	
	HS/MiS	27, 30, 31, 35, 36, 38	924		42	5	
	LS	27, 28, 29–32‡, 35–38	2071		276	13	
ELN	All	36	605	285	25	4	9
	HS/MiS/AR	36	232		8	3	
	LS/APR	28, 36	443		22	5	
ILN	All	27, 36	994	505	8	1	2
	HS/MiS	27, 36	380		0	0	
	LS	27, 29‡, 36	832		10	1	

Abbreviations: APR = abdominoperineal resection; AR = anterior resection; ELN = external iliac lymph nodes; HS = high-seated = tumor located above the peritoneal reflection (PR); ILN = inguinal lymph nodes; Involvement of LNR in N+ patients = ratio of No. N+ in specified LNR over No. N+; LLN = lateral lymph nodes; LNR = lymph node region; LS = low-seated; MiS = middle seated = defined as located 1 cm above or 1 cm below the PR in [36] and as located between S2 and PR in [38]; MLN = mesorectal lymph nodes; No. N+ = number of patients with positive lymph nodes (in any LNR, unless specified); No. at risk = number of patients at risk for lymph node involvement; Pts = patients; Risk for N+ in specified LNR = ratio of No. N+ in specified LNR over No. at risk; ULN = upward lymph nodes.

* EIN are included in the LLN.

† LN along the common iliac artery are included in the LLN.

‡ LS includes tumors located at the PR (reported as one entity).

reported as one entity (27, 36). Other investigators only classify the lymph nodes along the IMA in this group (31, 35). In one study, upward spread is not further specified (30). Upward lymphatic spread seems to be the second most important path of lymphatic spread. Its incidence in a population of 2092 patients (five studies) was 28% (578/2135). Looking only at patients with positive lymph nodes in any site (five studies, $n = 1033$), 56% of these patients had lymph node metastases in the ULN (578/1033). Two articles make a distinction between positive lymph nodes along the peripheral IMA and the root of the IMA, the majority being located along the peripheral IMA (31, 36).

Lateral lymph nodes

The definition of LLN varies, going from lymph nodes along the internal iliac artery only (35), to nodes along the internal iliac artery, the middle rectal artery, and obturator artery (27, 29, 32), to even larger groups, including nodes along the common iliac artery (31) and the external iliac artery (28, 36–38). One article does not define lateral lymph node spread (30).

For all patients at risk (six studies, $n = 2187$), the incidence of lateral lymph node invasion was 13% (285/2187). When looking at the patients with positive lymph nodes, the risk doubled up to 27% (285/1043). The main clinical significance was seen in advanced and low-seated tumors. Six studies give detailed information on T stage, showing 5% positive LLN in T1-T2 tumors (28/595), 14% in T3 (142/1004), and 15% in T4 tumors (112/742). In high seated (HS) and middle-seated (MiS) tumors, the risk for positive LLN was 5% (42/924), whereas in tumors in the lower part of the rectum (LS), this risk was up to 13% (276/2071).

Steup *et al.* report on a relative large number of positive LN at the level of the obturator artery, the majority being related to tumors located below the peritoneal reflection (6%, 36/605) overall, and 9% (33/373) in low-seated tumors) (36).

External iliac lymph nodes and inguinal lymph nodes

Two articles report on external iliac lymph nodes (ELN). In these retrospective analyses, positive external iliac lymph nodes were found in 25 of 605 patients (4%) and in 25 of 285 (9%), when taking into account only those patients with positive lymph nodes. Most positive lymph nodes in this group originated from tumors located closer to the anal margin, resulting in a higher percentage for patients with low-seated tumors and/or patients who had undergone APR (5% for APR [22/443] vs. 3% for patients with an anterior resection and/or high or middle seated tumors [8/232]).

With regard to the inguinal lymph nodes (ILN), two articles provide data on 994 patients, showing only a 1% risk of positive inguinal lymph nodes (8/994). When looking at the data from Hojo *et al.* (27) and Steup *et al.* (36), all positive ILN were found in low-seated rectal tumors.

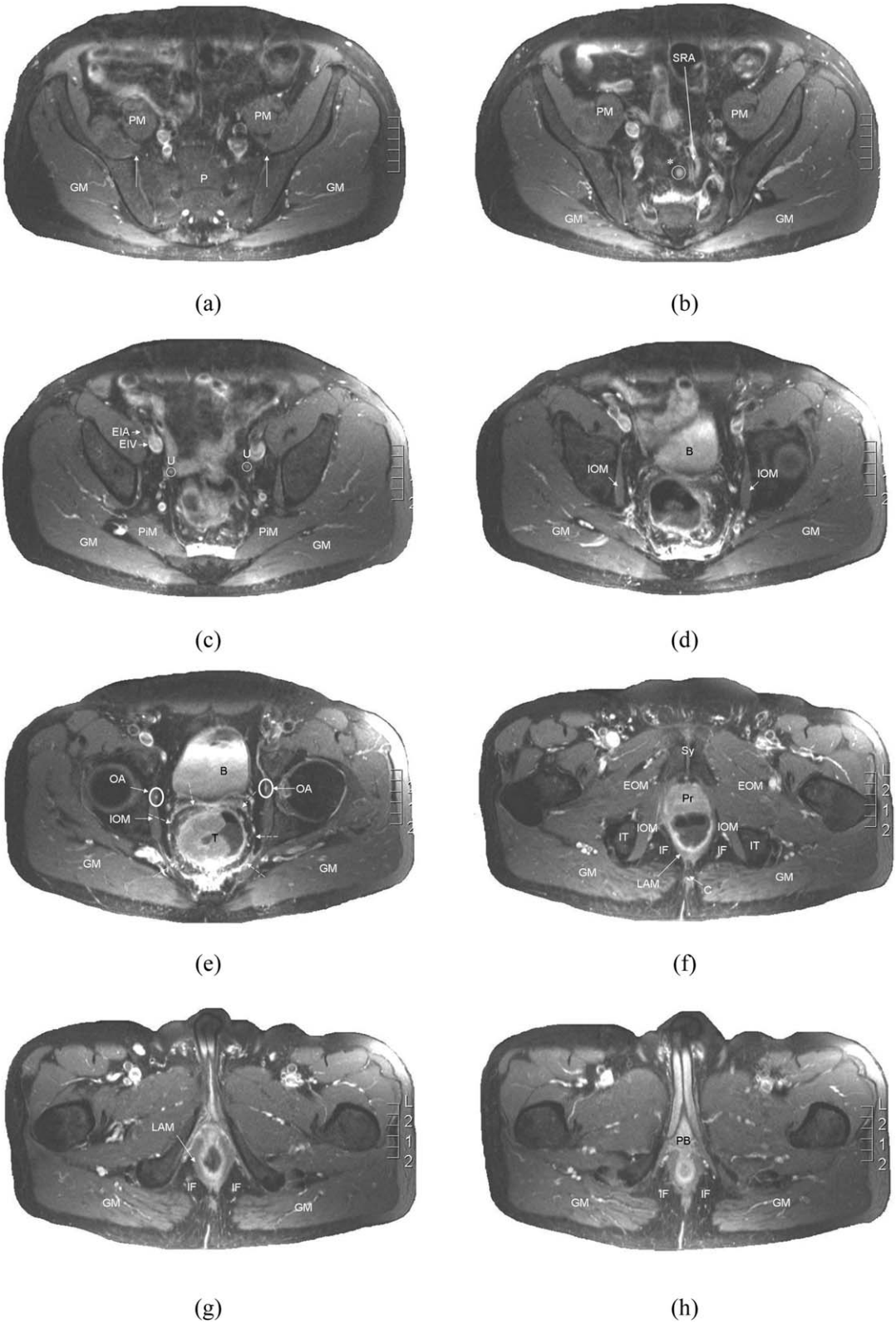

Fig. 2. (a–h) Transverse MR slices through the CTV from cranial (a) to caudal (h) direction. T1 fat-saturated turbo spin-echo images. *Abbreviations*: B = bladder; C = coccyx; EIA = external iliac artery; EIV external iliac vein; EOM = external obturator muscle; GM = major gluteal muscle; IF = ischiorectal fossa; IOM = internal obturator muscle; IT = ischial tuberosity; LAM = levator ani muscle; OA = obturator artery; P = promontory; PB = penile bulb; PiM = piriform muscle; PM = psoas muscle; Pr = prostate; Sy = pubic symphysis; SRA = superior rectal artery; T = tumor; U = ureter. The arrows in (a) indicate the sacroiliac joints. The asterisk in (b) shows a suspect lymph node along the SRA. The mesorectal fascia is best seen in (e) (dashed arrows).

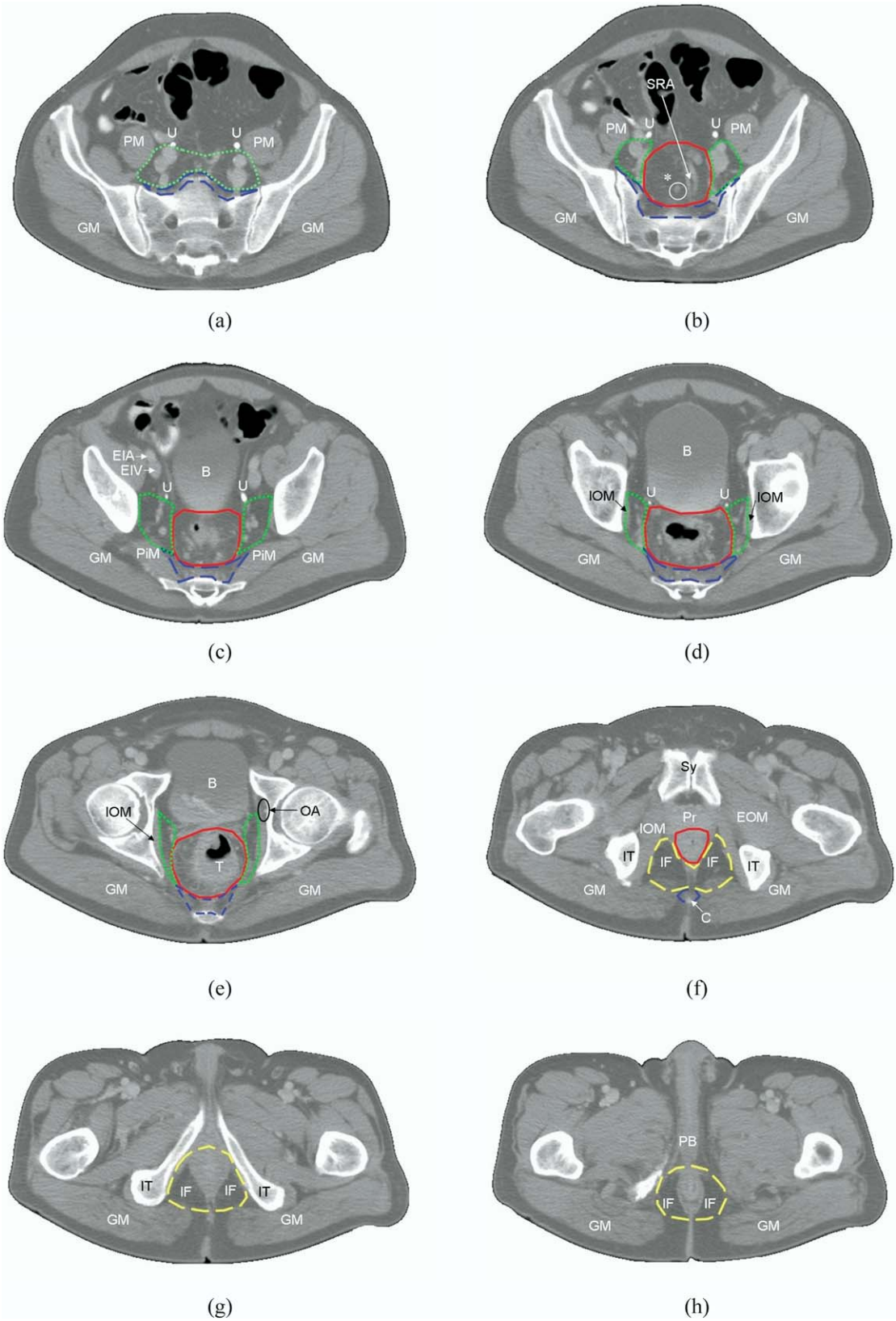

Fig. 3. Transverse computed tomographic slices through the levels corresponding to those in Fig. 2. *Abbreviations*: B = bladder; C = coccyx; EIA = external iliac artery; EIV external iliac vein; EOM = external obturator muscle; GM = major gluteal muscle; IF = ischiorectal fossa; IOM = internal obturator muscle; IT = ischial tuberosity; LAM = levator ani muscle; OA = obturator artery; P = promontory; PB = penile bulb; PiM = piriform muscle; PM = psoas muscle; Pr = prostate; Sy = pubic symphysis; SRA = superior rectal artery; T = tumor; U = ureter. The posterior pelvic subsite (PPS) is indicated by a blue/dark dashed line. The lymph node regions are outlined by a green/bright dotted line. The mesorectal subsite (MS) is delineated by a red/full dark line and the inferior pelvic subsite (IPS) by a yellow/bright dashed line. Asterisk in (b) shows a suspect lymph node along the superior rectal artery (SRA).

Delineation guidelines

Taking into account the results in Tables 3 and 4, we defined delineation guidelines for the CTV for rectal cancer patients, including the subsites and LNRs most at risk for microscopic disease (Figs. 2 and 3). To decide which subsite or LNR should be included into the CTV, an arbitrary limit was set to 10% overall risk for recurrence or lymph node involvement.

Several pelvic subsites partly cover LNRs and vice versa. Therefore, we describe only the most relevant subsites and LNRs.

Mesorectal subsite and mesorectal lymph nodes

As this area is highly at risk for lymphatic tumor spread, it must be included in the CTV. Its circumferential boundary (mesorectal fascia) is best visualized on MRI (Fig. 2e) and can sometimes be identified on CT scan. The surgeon dissects around this structure when performing a TME, and the pathologist requires an intact surface of the specimen for reporting a complete resection. The lower border is located at the level where the levator ani muscle inserts into the rectal wall. The upper border is situated at the peritoneal fold where the peritonealized rectum starts and bends anteriorly to form the recto-sigmoid. We propose to take the bifurcation of the IMA into the sigmoid artery and the upper rectal artery as the upper limit of the MS (42) (Figs. 2b, 3b). Anteriorly, the mesorectal fascia coincides with the Denonvillier fascia, bordered by the posterior wall of the prostate/seminal vesicles/bladder in men and the posterior vaginal wall/uterus in women (Figs. 2d to 2f, 3d to 3f). Below the dentate line, the mesorectal fascia matches the border of the levator ani muscle, which makes a funnel around the distal rectum (Fig. 2f, 2g). Above the dentate line, the piriform muscle bounds the fascia on both sides (Fig. 2c, 3c). Posteriorly, the MS lies alongside the PPS.

Posterior pelvic subsite

Parallel to the mesorectum, the posterior pelvic subsite (PPS) is at high risk, independent of tumor location and should therefore always be part of the CTV. The PPS corresponds mainly to the presacral space, a triangular, strongly curved volume that posteriorly faces the sacral concavity. Bounded anteriorly by the mesorectal fascia, it extends laterally toward the lateral borders of the sacrum where it encounters the posterior limit of the LLN (Fig. 3b to 3e). Its apex is directed caudally and corresponds to the coccyx (Fig. 3f), and the sacral promontory delineates its base (Fig. 2a, 3a). The anterior border that coincides with the posterior border of the mesorectal subsite is difficult to spot on CT images. Therefore, we propose to delineate this region by use of MRI or, if not available, take an arbitrary maximal margin of ± 1 cm ventrally from the sacral bone as anterior border, according to the results of a recent article on the anteroposterior width of the presacral space (43).

Inferior pelvic subsite

We suggest the inclusion of the inferior pelvic subsite (IPS) in the irradiated volume in the following instances: (*1*) when the surgeon aims at a sphincter-saving procedure and the tumor is located within $\pm$ 6 cm (depends on the center) from the anal margin, or (*2*) when the tumor invades the anal sphincter and an APR is necessary. This area includes the ischiorectal fossa and the internal and external anal sphincter (Fig. 2f to 2h, 3f to 3h), with the penile bulb/vestibular bulb as anterior border (Fig. 2h, 3h). The deeper part of the ischiorectal fossa, located above the transverse septum and bounded laterally by the internal obturator muscle and the ischium, is entirely at risk. We propose to extend this lateral border to the superficial/perianal part of the ischiorectal fossa, where no clear lateral anatomic border can be distinguished (Fig. 3h). The posterior border can be drawn at the level of the coccyx and the gluteal muscle. If the IPS is not at risk for subclinical disease (tumor is located $>$6 cm above the anal margin), the external and internal sphincter with the surrounding ischiorectal fossa, should not be included in the CTV.

Lymph node regions

As discussed above (Table 4), the LNRs at risk for microscopic disease depend on the level of the primary lesion. For tumors located in the upper part of the rectum (above the peritoneal reflection), the lymphatic spread is mainly in the upward direction along the inferior mesenteric nodes, whereas tumors in the middle and lower part of the rectum additionally drain in the lateral direction into the internal iliac nodes. Lesions that extend to the anal canal can spread to the ILN (20). If the primary tumor spreads beyond the mesorectal fascia and invades adjacent structures or organs, nodal drainage extends via the lymphatics of the involved organ (prostate, vagina, uterus, bladder). This includes the ELN if there is anterior organ involvement and the ILN if the lower third of the vagina is involved (20).

We propose to include the MLN and the LLN into the CTV for all patients. Taking into account the results of Steup *et al.* (36), the obturator nodes can be omitted if the lesion is located $>$10 cm above the anal margin, assuming that this level reflects the average position of the peritoneal fold (44). These guidelines are in correspondence with Arcangeli *et al.* (17). We did not find solid evidence to include the ELN in the target volume, except in these cases where anterior organ involvement is highly suspected. The LLN forms a triangular region with the internal iliac artery in the center and becomes enlarged caudally around its different visceral branches. The tip is located at the bifurcation of the common iliac arteries (Figs. 2a, 3a). Anteriorly, the ureter bounds this volume, whereas the posterior limit reaches the lateral edge of the sacroiliacal joint. Inferiorly, we propose to delineate this LNR till the level where the obturator artery enters the obturator canal (Figs. 2e, 3e). The lateral wall is lined superiorly by the psoas muscle and the ischium, followed by the medial surface of the piriform muscle, the internal obturator muscle and levator ani muscle

more caudally (Figs. 3a to 3f). The medial wall of the LLN region extends toward the plane of the mesorectal fascia. This area contains in the adipose tissue surrounding the internal iliac vessels most of their posterior parietal and visceral branches but also the lymphatic pathways of the middle main pelvic pathway, the proximal part of the posterior presacral pathway, the efferent pelvic nerves of the hypogastric plexus, and the origin of the sciatic nerve. To include the obturator nodes into the CTV, we suggest to expand the anterior border of the LLN toward the level of the obturator artery (Fig. 3e).

We defined upward lymph node spread along the IMA (39). It has been shown that para-aortic irradiation to elective doses does not improve the cure rate and is associated with greater toxicity (45). Therefore we propose to omit the nodes along the IMA from the CTV, while nodes along the SRA are regarded at risk for regional tumor extension and should be included in the CTV as part of the MLN (Fig. 3b).

DISCUSSION

In this article, delineation guidelines are defined after a detailed analysis of the literature, combining published data on the frequency and distribution of local recurrences and positive lymph nodes in patients with rectal cancer. These guidelines should help in the clinical implementation of conformal radiotherapy techniques, such as IMRT and IMAT, in rectal cancer.

The selected articles are sometimes difficult to compare because of diverse, incomplete, or even nonexisting definitions of pelvic subsites and LNRs, obscurity about the surgery performed (definition of curative surgery, the extension of lymphadenectomy (fields and lymph node groups included), the use of adjuvant therapies, number of patients in studies, collection of data (prospective, retrospective), definition of recurrences, assessment of recurrences (clinical, radiologic, histopathologic: biopsy- or autopsy-proven, or findings at second look operations), and differences in the method of recording: number of recurrences vs. number of patients with a recurrence per subsite. This problem is reflected in the heterogeneity of the data presented in Tables 3 and 4. Therefore, the information in these two tables must be regarded as an indicator for the exact incidence and distribution of local recurrences and pathologic lymph nodes. As a consequence, the guidelines should be considered as a starting point and need to be confirmed by prospective observations. Moreover, the description of the anatomic boundaries of the different subsites and lymph node regions for the delineation guidelines is based on the pelvic anatomy.

Pelvic subsites at risk

All articles on local recurrences (Table 3) report on the incidence and/or distribution of recurrences in the four pelvic subsites as described in this article, except the studies of McDermott *et al.* and Killingback *et al.*, in which the PPS either was not defined or was not clearly defined as a separate subsite (25, 26). In the first study, the investigators give information on additional subsites, such as "retroperitoneal," "operation site," "pelvis," and "other." Although some of these recurrences may be located in the posterior pelvic subsite, we did not have sufficient information on the exact location to categorize them in Table 3. The second study only reports one additional recurrence in the inguinal lymph nodes. Similar and different sites of recurrence were also described by Mendenhall *et al.* ("pelvis") and Gilbertsen ("aortic iliac") (22, 23). Hence the lack of information on the location of these additional pelvic areas of recurrence precludes an accurate estimate of the risk in certain pelvic subsites.

Although most patients have only one site of recurrence, some have two sites of noncontiguous involvement. This generally includes those patients with discrete perineal nodules in addition to pelvic recurrence after APR (33).

It should be noted that a distinction between a nodal and pelvic relapse is difficult to identify in clinical analysis and even in reoperative series some of the relapses coded as lateral or posterior were probably because of relapse within lymph nodes or replaced internal iliac nodes or presacral nodes rather than tumor bed relapse.

One article reports on the incidence of local disease recurrence as a component of disease recurrence (22), whereas Wiig *et al.* describe isolated recurrences only (34). The other studies record both local recurrence alone or in combination with distant relapse (23, 24–26, 33). We should, however, recognize that once a patient develops distant metastasis, the local disease status is often less carefully verified because of limited therapeutic relevance. Local recurrence in those patients will be discovered only by chance or in case of symptoms, except in the study of Gunderson and Sosin where initially planned single or multiple second look operations were performed (24) and in Killingback *et al.,* in which patients with distant metastases were kept under review until they were too ill to attend (26).

Recurrences in the MS are reported mostly before the introduction of TME. Various articles report on the importance of the mesorectum as a predominant subsite for local tumor spread, in both lateral and longitudinal directions. The value of the MS as a risk area for local recurrence comes mainly from TME studies (46, 47). Recently investigators in the Dutch TME trial investigated the pathologic properties of low rectal cancers in general and APRs, in particular within the Dutch Radiotherapy (RT) Plus Total Mesorectal Excision (TME) Trial (48). This study confirms the higher rate of CRM involvement, higher perforation rates, higher local recurrence rates, and poorer survival of low rectal cancer. Importantly, it shows that higher rates of local recurrence apply to APR because of increased occurrence of positive CRM. This was explained by the thinning of the mesorectum and the anatomy of the levators and sphincters at this site and the closeness of the CRM to the tumor. Therefore we believe that the MS should be covered by the CTV during preoperative radiotherapy.

Although difficult to discriminate from a MS recurrence

or IPS recurrence, anastomotic recurrences originate from contamination with cancer cells during operation, whereas mesorectal recurrences stem from remaining circumferential mesorectal tissue (in patients operated with a partial mesorectal excision or in the "pre-TME era"). The relative high incidence (21%) in some series, such as that of Hruby *et al.* (33) can be a reflection of a broader definition of a true anastomotic recurrence, but suggest that great care must be taken to avoid intraoperative soiling (33).

For the IPS, a subanalysis demonstrated a correlation between the type of surgery and the incidence of IPS recurrences. In the other analyzed subsites, correlations of patient or tumor characteristics with recurrence were scarce. The study of Hruby *et al.* found that T4 tumors, although they comprised only 9% of the initial T-stage tumors, were significantly correlated with anterior pelvic relapses. In addition, APR operations were strongly associated with perineal recurrences (Table 3). Wiig *et al.* (34) demonstrated no significant difference in site of recurrence in tumors located at or below 10 cm or above 10 cm from the anal margin.

Lymph node regions at risk

The relative high incidence of positive MLN in two studies (30, 31), is most likely caused by application of the modified clearing method, which enables the pathologist to detect more lymph nodes per patient than is possible with the conventional method. This modified clearing method permits more accurate assessment of the extend of lymph node metastases, but is complicated, laborious, and difficult to apply routinely (30).

Only one article classifies the lymph nodes along the SRA as MLN (31). Other articles consider the lymph nodes along the SRA and the IMA as one entity and classify these nodes under ULN (27, 36), apart from the MLN. Because the SRA is mainly located in the MS and distinction of the lymph nodes along the SRA from pararectal nodes is difficult, we propose to include the lymph nodes along the SRA and the pararectal lymph nodes in the MLN, whereas the ULN are located along the IMA. Takahashi *et al.* (35) consider the MLN as ULN, resulting in relative high numbers of positive ULN, compared with those in the other articles that define the MLN as a separate LNR.

We believe that it is unnecessary to extend the radiation field to include the lymph nodes along the IMA and the common iliac lymph nodes. Involvement of these LNR is regarded as metastatic disease, and the chances of cure remain very small even if these areas are aggressively treated (45).

The main clinical significance of lateral lymph node spread is seen in advanced-stage and low-seated tumors. It should be noted that most of the T3 and T4 tumors in this group are also low-seated tumors.

We found solid evidence of a higher incidence of lymph node involvement in the ELN only in low-seated tumors. Data on involvement of the ELN group in tumors that invade adjacent structures are scarce because of the inoperable state of these highly advanced lesions. Although some investigators state that the risk for ELN involvement is low for patients with T4 rectal cancer (49), it is generally believed that the CTV should include the ELN in tumors with anterior organ invasion and the ILN when the lower third of the vagina is involved, based on the lymphatic drainage pattern from those organs. The inclusion of the inguinal lymph nodes in the treatment field for tumors that extend into the anal canal has been advocated by some investigators (50–52), whereas others could not find evidence to justify routine elective groin irradiation (53). In this analysis, the three studies that report on ILN involvement in LS rectal cancer do not provide information on tumor invasion in the anal canal (27, 29, 36). Based on our clinical experience, we propose to include the ILN in the CTV when there is major tumor extension in the internal and external anal sphincter or when the lower third of the vagina is involved.

The level of the primary tumor is an important factor relative to the mode of spread in rectal cancer. Still, a large variation exists in the definition of low-seated, middle, and high-seated rectal tumors. The majority of the authors define the peritoneal reflection as the anatomic boundary between high- and low-seated tumors, based on a biologic barrier between lymphatic pathways. The location of the peritoneal reflection has been described in anatomy texts as 7.5 cm from the anal margin in men and 5.5 cm in women (54). The source of this information was not referenced but presumably stemmed from cadaveric dissections. Other investigators define a much larger distance of the anal margin to the peritoneal reflection (up to 12 cm anteriorly, 15 cm laterally, and 20 cm posteriorly), without specifying the methods of measurement (55). Some authors have proposed the anatomic reference of the second rectal valve as the location of the anterior peritoneal reflection (56). A recent study in 50 patients determined the length of the peritoneal reflection from the anal margin in male and female patients via simultaneous intraoperative proctoscopy and intra-abdominal visualization of the peritoneal reflection. The results from this study showed that the average length of the peritoneal reflection was greater than traditionally believed, and was not different between male and female patients. There also was a stepwise increase in length of the peritoneal reflection as one moved from anterior to lateral to posterior by 2- to 3-cm increments at each level.

CONCLUSION

Based on a review of articles reporting the incidence and predominant location of local recurrences and the distribution of lymphatic spread in rectal cancer, we defined guidelines for inclusion of the most critical pelvic subsites and LNR.

The CTV should encompass the tumor, the MS, and the PPS in all cases. The IPS is at risk if (*1*) the tumor is located within 6 cm from the anal margin and the surgeon aims at a sphincter-saving procedure, or (*2*) the tumor invades the anal sphincter and an APR is necessary.

We propose to include the MLN and the LLN into the CTV for all patients.

The obturator nodes should be included when the tumor is located <10 cm from the anal margin. The ELN should be part of the CTV only when anterior organ involvement is highly suspected and the ILN only when the tumor invades the lower third of the vagina or there is major tumor extension into the internal and external anal sphincter.

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