Trakia Journal of Sciences, Vol. 12, Suppl. 1, pp 308-316, 2014

Available online at:
http://www.uni-sz.bg

ISSN 1313-7050 (print)
ISSN 1313-3551 (online)

INTENTIONALLY CURATIVE TREATMENT OF LOCALLY RECURRENT RECTAL CANCER: A SYSTEMATIC REVIEW

E. Enchev[1*], G. Minkov[2], D. Petrov[3], Y. Yovchev[2]

[1]Medical student, Medical Faculty, Trakia University, Stara Zagora, Bulgaria
[2]Department of Surgery – MHAT "Prof. Stoyan Kirkovich"AC, Stara Zagora, Bulgaria
[3]Department of Social Medicine and Healthcare Management, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

ABSTRACT

PURPOSE There is a lack of outcome data beyond local recurrence rates after primary treatment in rectal cancer, despite more information being necessary for clinical decision-making. We sought to determine patient selection, therapeutic modalities and outcomes of locally recurrent rectal cancer treated with curative intent.

METHODS We searched MEDLINE (1990–2010) using the medical subject headings "rectal neoplasms" and "neoplasm recurrence, local". Selection of cohort studies was based on the primary intention of treatment and availability of at least one outcome variable.

RESULTS 55 cohort studies comprising 3767 patients were included; 8 studies provided data on the rate of intentionally curative treatment from an unselected consecutive cohort of patients (481 of 1188 patients; 40%). Patients were symptomatic with pain in 50% (796 of 1607) of cases. Overall, 3088 of 3767 patients underwent resection. The R0 resection rate was 56% (1484 of 2637 patients. Overall postoperative mortality was 2.2% (57 of 2515 patients). Five-year survival was at least 25%, with an upper limit of 41% in 11 of 18 studies including at least 50 resections. We found a significant increase in reported survival rates over time ($r^2 = 0.214$, $p = 0.007$).

CONCLUSION More uniformity in treatment protocols and reporting on outcomes for locally recurrent rectal cancer is warranted. The observed improvement of reported survival rates in time is probably related to better patient selection and optimized multimodality treatment in specialized centers.

Key words: studies, local, recurrence, curative intent, rectum, neoplasm

INTRODUCTION

Substantial progress has been made in local control of rectal cancer in the past decades. First, anatomic consideration of the mesorectal fascia has led to the development of total mesorectal excision (TME). This surgical technique encompasses sharp dissection under direct vision resulting in resection of the rectum and mesorectum, ideally with an intact visceral pelvic fascia covering the resection specimen.

The TME technique has become widely accepted, as local recurrence rates declined from greater than 20% with conventional blunt dissection to 5%–10% with TME.[1] Second, the use of neoadjuvant therapy further reduced local recurrence rates, as shown in a meta-analysis of randomized controlled trials.[2] The local recurrence rate is the most relevant end point for interventional studies on neoadjuvant treatment in patients with rectal cancer, because survival is either not or only marginally improved.[2] However, there is a lack of adequate data beyond local recurrence rates, despite more information being necessary for clinical decision-making. Therefore, the aim of this systematic review was to analyze the recent literature on intentionally curative treatment of locally recurrent rectal cancer.

***Correspondence to**: *Emil Enchev, Faculty of Medicine, Trakia University, Stara Zagora, Bulgaria, 11 Armeiska str, e-mail:emil_19_89@abv.bg*

METHODS

We searched MEDLINE using the following medical subject headings: "rectal neoplasms" and "neoplasm recurrence, local." The search was carried out for the period 1990–2010 using the limits "humans" and "all adult: 19+ years." We reviewed all retrieved articles and systematically screened the reference lists of selected articles for additional studies of interest. The date of the most recent search was Oct. 1, 2010. Selection of cohort studies in patients with locally recurrent rectal cancer was based on the primary intention of treatment and availability of at least 1 outcome variable, either local control or survival. Multiple studies from the same institution were included only if there were different inclusion criteria based on patient characteristics or type of treatment and if there was no substantial overlap. We extracted the following data from the included papers (when provided): study period, selection criteria, treatment characteristics of primary rectal cancer, characteristics of local recurrence (symptom score S0–2), synchronous metastases, time interval from primary tumour to local recurrence, completeness of resection (R status), percentage of sacral resection, operative mortality, follow-up, crude distant metastasis and local control rate, actuarial local control and survival and median survival.

STATISTICAL ANALYSIS

We used descriptive statistics to determine overall results for evaluable studies. Analyses were performed using SPSS.

Therapy for primary rectal cancer

The median abdomino-perineal resection (APR) rate was 27% (range 0%–62%) in these studies. Local excision was specified as the primary surgical treatment in 13 studies; 2 of them[26,35] exclusively included patients who had undergone local excision, and the median local excision rate was 10% (range 6%–30%) in the remaining 11 studies.[4,7,17,20,25,29,34,40,44,45,47] Included patients had undergone EBRT as part of the primary treatment in a median of 28% (range 0%–100%) of cases in 43 studies **(Table 1).** Previous radiotherapy dose was specified in 10 studies,[4,7,9,12,19,27,28,41,55,57] with a total dose ranging from 10 to 110 Gy. The median percentage of patients who underwent chemotherapy as part of the treatment for the primary tumor was 37% (range 0%–100%) in 21 evaluable studies **(Table 1).**

Clinical presentation of local recurrence

Patients were asymptomatic (S0) when presenting with locally recurrent rectal cancer in 29% (571 of 2000) of cases in 27 studies **(Table 1).** Symptoms were classified according to presence of pain in 23 studies **(Table 1)**, and 50% (796 of 1607) of patients were symptomatic with pain (S2). Five studies[4, 14, 31, 33, 39] reporting on symptoms had a clinically relevant patient selection (sacral resection or intraluminal recurrence only). After exclusion of these studies, the rates of S0 and S2 clinical presentation were 30% (563 of 1884) and 47% (700 of 1491), respectively. The median interval between primary tumor and local recurrence ranged from 12 to 44 months in 40 studies **(Table 1),** with an overall maximum interval of 354 months, as reported by Das and colleagues.[57] Data on synchronous distant metastases were provided in 48 studies **(Table 1).** In 18 of these, there was no clinical sign of distant dissemination at the time of treatment for local recurrence. The proportion of patients in whom distant metastases were identified ranged from 2% to 41% in the other 30 studies, with a reported percentage below 10% in 14 of these studies **(Table 1)**. All distant metastases were resected with curative intent in 11 of these 30 studies (3%–16% of included patients), while selected patients received surgical treatment for distant disease in another 8 studies (2%–26% of included patients; **Table 1**).

Surgery for local recurrence

In the remaining 25 studies, the percentage of resection varied from 17% to 99%, with a resection rate above 70% in 15 of these 25 studies **(Table 2).** Differences in resection rates were mainly explained by the fact that patients with unresectable disease or intraoperatively detected distant disease were not excluded from the initial study population in some studies. The overall number of patients who underwent resection was 3088 of 3767 in the 55 selected studies. In the 51 studies specifying the duration of the study period, the median number of resections performed per year was 3.6 (range 0.8–19.6; **Table 2**). After excluding multicenter studies, only 12 centers performed at least 5 resections per year. The median reported R0 resection rate of 46 studies was 59% (range 14%–100%; **Table 2**). The overall calculated R0 resection rate was 56% (1484 of 2637 patients). A macroscopically complete resection (R0/R1) could be achieved in a median of 85% (range 31%–100%) of patients in 38 studies **(Table 2).** Part of the sacrum was included in the resection in all patients in 5 studies[12, 14, 33, 40, 51] and in no patients in another 17 studies **(Table 2).** In the remaining 20 studies reporting on sacral resection, the median rate was 13% (range 2%–73%; **Table 2**).

Table 1.*The surgical procedure for the initial tumor was described in 44 studies*

Table 1. Locally recurrent rectal cancer with curative intent: cohort selection, primary therapy and clinical presentation

Study	Year	Period yr	Selection		Ns	Primary therapy, %			Characteristics of local recurrence, %*					
			NI	Inclusion/exclusion		APR	RT	CT	S0	S1	S2	M1	M1res	Interval, mo*
Abuchaibo et al.[3]	1993	6.3	—	All IORT	27	—	26	37	0	30	70	0	0	—
Estes et al.[4]	1993	—	—	All exenterations	16	19	50	—	0	0	100	0	0	8
Gagliardi et al.[5]	1995	19	64	No irresectable, advanced M1	49	18	—	—	16	35	49	27	13	(13) (2–81)
Gunderson et al.[6]	1996	14.3	182	No prior RT, all IORT	123	—	0	24	—	—	—	8	6	—
Bussières et al.[7]	1996	—	—	All IORT	73	33	51	10	—	—	—	14	—	< 2 yr 54%
Knol et al.[8]	1997	15	292	Complete follow-up	280	44	—	—	15	21	64	41	0	(12) (3–96)
Bozzetti et al.[9]	1997	34	213	Suitable for reoperation	45	24	4	18	—	—	—	0	0	(13) (4–50)
Maetani et al.[10]	1998	18.1	59		59	61	—	—	—	—	—	20	15	—
Eble et al.[11]	1998	3.9	—	All IORT	31	—	—	19	—	—	81	—	—	—
Wanebo et al.[12]	1999	23	95	All sacral resection	53	55	100	—	—	—	—	4	4	< 12 mo 28%
Salo et al.[13]†	1999	9.9	194	No intestinal bypass	131	27	39	—	44	29	27	5	5	21
Zacheri et al.[14]	1999	9	—	All sacral resection	12	42	—	—	0	0	100	0	0	(41) (6–84)
Hashiguchi et al.[15]	1999	22.1	51		51	57	0	—	22	33	45	37	12	(32) (5–190)
Adachi et al.[16]	1999	11	21	No irresectable	9	22	0	—	56	33	11	0	0	35 (8–61)
Law et al.[17]	2000	10.7	47		47	30	—	—	—	—	—	—	—	18
Rödel et al.[18]	2000	3.9	35		35	17	0	17	—	—	—	9	9	(22) (4–112)
Lindel et al.[19]	2001	18.7	69	All IORT, no M1	49	28	13	—	—	—	—	0	0	(24) (4–123)
Lopez-Kostner et al.[20]	2001	13.9	117	No irresectable or M1	43	—	—	—	16	42	42	—	—	(20) (2–86)
Garcia-Aguilar et al.[21]	2001	11	87		87	28	32	32	—	—	—	0	0	25
Yamada et al.[22]	2001	16.9	83		83	53	0	—	—	—	—	0	0	(20) (11–31)
Bergamaschi et al.[23]	2001	23	91	No M1, all initial LAR	35	0	0	—	43	—	—	3	3	(16) (3–58)
Huguier et al.[24]	2001	30	60	All initial local excision	38	21	3	—	71	—	—	34	26	15 (9-x)
Shoup et al.[25]	2002	10.5	634	No irresectable, all IORT	100	16	50	—	—	—	—	—	—	21
Frisé et al.[26]	2002	12	—	All initial local excision	29	0	7	—	66	—	—	7	3	(26) (5–89)
Mohiuddin et al.[27]	2002	13	—	All prior RT	103	—	100	—	—	—	—	—	—	(19) (2–86)
Pezner et al.[28]	2002	10	—	All prior RT, all IORT	15	27	100	80	—	—	33	7	7	(25) (0–62)
Hahnloser et al.[29]‡	2003	15.5	429	No M1 after preoperative RT	304	29	—	—	23	23	54	0	0	(33) (2–175)
Saito et al.[30]	2003	14.3	—	No anastomotic recurrence	85	61	0	—	—	—	—	31	0	(22) (10–56)
Kakuda et al.[31]	2003	12.5	—	All exenteration	22	—	—	—	14	38	48	9	0	—
Balox et al.[32]	2004	15	—	No initial local excision	40	28	55	—	38	28	34	5	5	(17) (5–188)
Moriya et al.[33]	2004	18	163	All sacral resection	57	51	4	—	0	0	100	9	9	(23) (7–102)
Reerink et al.[34]	2004	9.6	50	No palliative intent	40	20	0	0	—	—	—	0	0	(17) (5–74)
Weiser et al.[35]	2005	33	—	All initial R0 local excision	50	0	44	—	49	—	—	16	16	(20) (4–70)
Vermaas et al.[36]	2005	18	117	Not fit enough, M1	92	25	—	—	—	—	31	2	—	(15) (2–186)
Boyle et al.[37]	2005	7	64		64	34	58	—	33	31	36	—	—	31
Henry et al.[38]	2005	15	90	19 no data on hydronephrosis	71	27	58	69	51	—	—	4	4	24
Rudmik et al.[39]	2005	9	—	All intraluminal recurrence	9	0	11	11	56	44	0	0	0	(21) (8–53)
Melton et al.[40]	2006	17	—	All sacral resection	29	45	93	76	—	—	—	10	10	(44) (15–294)
Valentini et al.[41]	2006	4.2	—	All prior RT	59	24	100	75	—	—	41	0	0	(27) (9–106)
Bedrosian et al.[42]	2006	10	134	No palliative intent (R2 or M1)	85	23	—	—	—	—	—	0	0	(22) (1–113)
Asoglu et al.[43]	2007	7	72	No irresectable or M1	50	34	100	—	0	48	52	0	0	(24) (4–113)
Palmer et al.[44]	2007	10	141	All surgical exploration	57	28	30	—	35	—	—	18	2	(16) (3–70)
Wells et al.[45]	2007	7.9	52		52	23	46	62	—	—	—	12	0	(21) (3–166)
Wiig et al.[46]	2008	13.3	204	No prior RT	150	27	0	—	37	—	—	5	0	(19) (3–161)
Heriot et al.[47]	2008	16.7	160		160	7	6	—	30	—	—	—	—	(23) (1–159)
Schurr et al.[48]	2008	—	72		72	28	76	69	—	—	—	27	13	42
Tanaka et al.[49]	2008	18	43		43	—	0	70	—	—	—	19	0	(26) (3–100)
Reidos et al.[50]	2008	11	—	All RT for recurrence	94	—	0	18	—	—	—	33	0	—
Sagar et al.[51]§	2009	6	—	All sacral resection	40	40	38	45	—	—	—	5	5	(35) (12–104)
Kusters et al.[52]	2009	13.9	209	No irresectable	170	31	51	—	25	35	40	0	0	(29) (3–283)
Fujii et al.[53]	2009	20	76	No R2 resection or M1	61	—	—	—	—	—	—	0	0	—
de Chaisemartin et al.[54]	2009	—	18	—	18	—	22	33	44	34	22	22	0	(14) (3–60)
Park et al.[55]	2009	7	—	No T1, M1 or local excision	62	48	19	100	—	—	—	0	0	29
Pacelli et al.[56]	2010	15.9	157	No irresectable or M1	58	17	33	59	50	21	29	0	0	—
Das et al.[57]	2010	4	—	All prior RT	50	—	100	—	—	—	—	26	0	(28) (5–354)¶
Total					3767									

APR = abdominoperineal resection; CT = adjuvant chemotherapy; Interval = mean (median) (range) time interval from primary tumour; IORT = intraoperative radiotherapy; M1 = distant metastasis either before or synchronous with local recurrence; M1res = resected distant metastasis; NI = initial population; Ns = study population after selection; RT = radiotherapy with or without concurrent chemotherapy, either pre- or postoperative; S0 = no symptoms; S1 = symptomatic without pain; S2 = symptomatic with pain.

*Unless otherwise indicated.

†24 and 3 patients also included by Shoup et al.[25] and Melton et al.[40] respectively.

‡Including 122 patients described by Gunderson et al.[6]

§7 patients already described by Boyle et al.[37]

¶Interval between RT treatments (7 patients previous RT for other cancer).

Table 2. *All patients from 30studies underwent resection of the pelvic recurrence*

Table 2. Locally recurrent rectal cancer with curative intent: therapy for local recurrence

	Characteristics of surgery for local recurrence						Perioperative treatment for local recurrence, %						
	Resection												
Study	No.	(%)	No./yr	R0, %	R0/R1, %	Sacral, %	Preop EBRT	ICRT	Postop EBRT	Total EBRT	Re-EBRT	CRT	CT
Abuchaibe et al.[3]	26	(96)	4.1	31	31	0	31	100	46	77	4	27	—
Estes et al.[4]	16	(100)	—	100	—	19	25	0	0	25	0	0	—
Gagliardi et al.[5]	49	(100)	2.6	27	51	—	2	0	61	63	—	0	—
Gunderson et al.[6]	122	(99)	8.5	14	47	—	84	100	23	98	0	75	2
Sussidrese et al.[7]	63*	(96)	—	—	67	0	25	100	16	41†	0	0	16
Knol et al.[8]	48	(17)	3.2	—	42	—	25	0	77	100	—	58	—
Boretti et al.[9]	45	(100)	1.3	47	—	0	0	0	38	38	0	11	—
Maetani et al.[10]	59	(100)	3.3	—	—	73	44	0	0	44	—	—	—
Ebie et al.[11]	31	(100)	7.9	45	74	0	71	100	29	100	—	71	—
Wanebo et al.[12]	53	(100)	2.3	85	100	100	0	0	0	0	0	—	—
Salo et al.[13]	103	(79)	10.4	69	82	3	21	40‡	28	49	0	—	—
Zacheri et al.[14]	12	(100)	1.3	100	100	100	33	0	0	33	—	8	—
Hashiguchi et al.[15]	51	(100)	2.3	24	53	—	41	53	43	75§	0	—	—
Adachi et al.[16]	9	(100)	0.8	78	78	11	0	0	0	0	0	0	—
Law et al.[17]	47	(100)	4.4	51	—	11	—	0	—	—	—	—	—
Rodel et al.[18]	26	(74)	6.7	65	100	12	100	0	0	100	0	100	66
Lindel et al.[19]	49	(100)	2.6	51	69	—	94†	100	3	97†	7	52	—
Lopez-Kostner et al.[20]	43	(100)	3.1	—	—	—	—	0	—	—	—	—	—
Garcia-Aguilar et al.[21]	51	(59)	4.6	82	—	—	0	0	0	0	0	—	0
Yamada et al.[22]	60	(72)	3.6	—	—	38	0	0	0	0	0	0	0
Bergamaschi et al.[23]	35	(100)	1.5	34	100	0	0	0	60	60	0	0	—
Huguier et al.[24]	38	(100)	1.3	—	—	—	0	16	79	79	0	32	8
Shoup et al.[25]	100	(100)	9.5	64	94	—	37	100	0	37	0	—	58
Frisel et al.[26]	29	(100)	2.4	72	83	0	41	0	17	59	0	0	—
Mohiuddin et al.[27]	34	(33)	2.6	—	—	0	100	0	0	100	100	100	—
Pomer et al.[28]	15	(100)	1.5	27	80	0	0	100	20	20	20	0	13
Hahnloser et al.[29]	304	(100)	19.6	45	54	—	0	43	80	80	—	55	—
Saito et al.[30]	57	(67)	4.0	75	—	37¶	40	0	0	40¶	0	0	0
Kakuda et al.[31]	22	(100)	1.8	55	77	4	—	32	—	—	—	—	—
Balick et al.[32]	40	(100)	2.7	40	100	20	10	0	25	33§	—	0	—
Moriya et al.[33]	57	(100)	3.2	84	100	100	40	16	0	40	0	—	—
Roorink et al.[34]	25	(63)	2.6	68	—	0	52	0	48	100	0	12	—
Wieser et al.[35]	49	(98)	1.5	96	100	12	29	26	14	42	—	42	49**
Vermaas et al.[36]	92	(100)	5.1	58	85	13	64	29	32	96	—	0	10
Boyle et al.[37]	57	(89)	8.1	42	86	12	42	0	0	42†	0	—	—
Henry et al.[38]	71	(100)	4.7	59	83	—	—	37‡	—	56	—	41	10
Rudmik et al.[39]	9	(100)	1.0	100	—	0	0	0	22	22	—	22	0
Melton et al.[40]	29	(100)	1.7	62	97	100	0	41	14	14	3	0	45
Valentini et al.[41]	39*	(66)	9.3*	54	62	0	100	0	0	100	100	100	77
Bedrosian et al.[42]	85	(100)	8.5	76	100	—	27	42	0	27	2	27	53**
Asoglu et al.[43]	36	(72)	5.1	67	100	0	0	0	0	0	0	0	—
Palmer et al.[44]	50*	(88)	5.0*	50	—	0	28	22	0	28	0	0	—
Wells et al.[45]	52*	(100)	6.6*	80	100	54	50	0	0	50	0	38	—
Wilg et al.[46]	139	(93)	10.5	47	89	4	100	—	0	100	0	11	—
Heriot et al.[47]	153*	(96)	9.2*	64	90	19	61	8	3	63†	6	44	0
Schurr et al.[48]	45	(63)	—	—	82	24	16	0	0	16	0	16	18**
Tanaka et al.[49]	35	(81)	1.9	77	—	0	—	0	—	—	0	—	—
Rades et al.[50]	46	(49)	4.2	52	85	—	0	0	100	100	0	67	67
Sagar et al.[51]	40	(100)	6.7	50	98	100	60	0	3	63	0	60	13
Kusters et al.[52]	170	(100)	12.2	55	—	25	85	91	0	85	42	62	—
Fujii et al.[53]	61	(100)	3.1	—	100	0	11	0	0	12	0	0	30††
de Chaisemartin et al.[54]	11	(61)	—	100	—	0	45	0	18	63	0	—	—
Park et al.[55]	38	(61)	5.4	61	—	11	39¶	0	0	39	—	39	—
Pocelli et al.[56]	44	(76)	2.8	57	80	2	79	50	0	79	—	79	44
Das et al.[57]	18	(36)	4.5	39	100	0	100	50	0	100	100	96	—
Total	3088												

CT = adjuvant systemic chemotherapy; CRT = concurrent chemotherapy during EBRT as percentage of total resections; EBRT = external beam radiotherapy; ICRT = intraoperative radiotherapy; Postop = postoperative; Preop = preoperative; re-EBRT = EBRT for both primary tumour and local recurrence; Sacral = abdominosacral resection.
*Multicentre study: Sussidrese 6 centres,[7] Valentini 12,[41] Palmer 9,[44] Wells 2,[45] Heriot 2.[47]
†Percentage of study population.
‡28 of 52 patients and 24 of 26 patients brachytherapy, respectively.
§5 and 1 patients both preoperative and postoperative EBRT, respectively.
¶Percentage of R0 resections.
**Including some patients with preoperative chemotherapy.
††Intraoperative hyperthermic intraperitoneal chemotherapy.

Perioperative treatment for local recurrence

External beam radiotherapy was uniformly performed either in the preoperative or in the postoperative setting for all patients in 9 studies, whereas no patients in 5 of the studies underwent EBRT. The rate of EBRT reported in 37 other studies ranged from 12% to 97% **(Table 2).** External beam radiotherapy was given preoperatively in 37 studies; in 20 of these, radiotherapy was uniformly applied in the preoperative setting **(Table 2).** Postoperative EBRT was described in 25 studies, and irradiation occurred exclusively in the postoperative setting in 8 of these 25 studies **(Table 2).** Radiotherapy dose was specified in 28 studies.[3-9, 11, 18, 19, 28, 29, 30, 33–37, 41, 44, 46, 47, 50–53, 56, 57] Without prior EBRT, the total dose was 40–60 Gy in most studies, with an overall range of 15–80 Gy. Conventional fractionation (1.8–2.0 Gy per fraction) was uniformly applied in 13 studies, [3, 6, 7, 9, 11, 18, 19, 28, 30, 36, 46, 50, 52] and selective use of a hypofractionated schedule (fractions of 5 Gy) was described in 2 studies.[34,44] In 3 studies,[27, 41, 57] all patients had undergone EBRT for the primary tumor; the median (and range) rates were 50.4 (30–55) Gy, 50.4 (30–74) Gy and 47 (25–70) Gy, respectively. Reirradiation schedules were as follows: 40.8 Gy in daily fractions of 1.2 Gy, median 34.8 (range 15–49.2) Gy in daily fractions of 1.2 or 1.8 Gy, and 39 Gy in fractions of 1.5 Gy twice daily, respectively.27,41,57 An additional 8 studies [3,19, 28, 40, 42, 47, 52, 56] described the use of re-EBRT, 7 of which specified the rate.[3, 19, 28, 40, 42, 47, 52] The radiotherapy schedule was specified in 3 of these studies,[28, 52, 56] with a total dose ranging from 23.4 to 30.6 Gy in daily fractions of 1.2 or 1.8 Gy. External beam radiotherapy was part of a chemoradiotherapy regimen, mostly fluorouracil-based, in 27 studies **(Table 2);** routine use of chemoradiotherapy was reported in only 3 studies.[18, 27, 41] Outcome after treatment with curative intent Postoperative mortality was 2.2% (57 of 2515 patients), across 46 studies, most of which defined postoperative mortality as in-hospital mortality or 30-day mortality; 2 studies[48, 52] defined it as 60-d and 90-d mortality, respectively. The observed crude rate of distant metastases during follow-up varied between 9% and 68%, with a median rate of 41% across 29 studies. The crude local control rate in patients who underwent R0 resection ranged between 29% and 100%; the rate was above 75% in 9 of 14 studies. The actuarial local control rate for R0 resection was more than 55% in 7 of 8 studies. The most consistently reported outcome parameter was 5-year survival, which ranged from 11% to 51%. Five-year survival was at least 25%, with an upper limit of 41%, in 11 of 18 studies including at least 50 resections.

DISCUSSION

In general, local recurrence is the reflection of an aggressive biological behaviour of the primary tumor as it is accompanied by synchronous distant disease in a high percentage of patients. In the Dutch TME trial, [58] 83 of 129 patients (63%) with local recurrence also had distant metastases. The Swedish Rectal Cancer Trial and Stockholm I trial reported distant disease in 66 of 143 patients (46%) and 86 of 156 patients (55%) with local recurrence, respectively.[59, 60] Our systematic review suggests that 40% of unselected consecutive patients with locally recurrent rectal cancer are candidates for intentionally curative treatment. Curative treatment of both local and distant recurrence is achievable in only a small subgroup of patients **(Table 1).** Probably such treatment should only be considered in patients with indolent tumor behavior based on a long disease-free interval (at least 2 yr.) from primary treatment. Overall, half of the patients were classified as having S2 clinical presentation (symptomatic with pain). Although these were selected patients who were candidates for intentionally curative treatment, this finding is concordant with an unselected cohort of 156 patients with locally recurrent rectal cancer from the Stockholm Rectal Cancer Study: the rates of S0, S1 and S2 clinical presentation were 13%, 33% and 54%, respectively. While distant disease is the determining factor for prognosis in most of these patients, local recurrence will generally affect quality of life.[61,62] Complete or partial initial relief of pain after radiotherapy alone or after multimodality treatment, including surgery, is reported in up to 83% of patients, although the rate of long-term pain-free survival is about 30%.[27,41,63] The 2 most important predictors of radical resection of local recurrence are previous anterior resection instead of APR and the absence of pain at the time of recurrence.[43,64,65] Intraluminal recurrences, especially after initial local excision, are separated from the bony pelvis and sacral nerves by remaining soft tissue, thereby not resulting in pain and enabling resection with adequate margins in almost all patients.[26,35,39] Given the worse outcome for local recurrence after prior APR, optimal primary

treatment of distal cancers is of utmost importance. The pelvis becomes narrower at the level of the levator ani. The extralevatoric APR with en bloc removal of the levator muscle in combination with downstaging by neoadjuvant therapy will improve local control in distal rectal cancers.[66,67] We found a wide variety in treatment protocols with regard to perioperative radiotherapy for locally recurrent rectal cancer reported in the studies we reviewed **(Table 2).**

There is no concluding evidence to determine the most optimal treatment strategy for locally recurrent rectal cancer. This is also related to the heterogeneity of the disease, as shown in the present review, based on type of primary surgery, previous radiotherapy, extent of recurrent disease (fixation grade, extension to pelvic sidewall) and the presence of symptoms or distant metastases. The available data do not enable pooling of data from several subgroups to compare different treatment approaches among different disease entities. However, there is increasing consensus that EBRT should be given preoperatively with concurrent chemotherapy, as demonstrated by papers published since 2006 **(Table 2).** This recommendation is based on the need for optimal preoperative downsizing and downstaging to maximize the chance of an R0 resection, which is the most important predictor for survival after treatment for locally recurrent rectal cancer.[68,69] The calculated overall R0 resection rate of 56% leads us to conclude that there is room for improvement. Better comparison of data can be achieved by determining outcomes for similar groups of patients (those who undergo R0 or R0/R1 resection) using standardized parameters, such as 3- and 5-year local control and overall survival. Missing follow-up data and inappropriate length of follow-up in most of the remaining studies reflect the low quality of available data on the treatment of locally recurrent rectal cancer. The use of EBRT for primary rectal cancer has increased during the past decades. Without previous radiotherapy, patients with locally recurrent rectal cancer can be optimally treated by full-dose (chemo) radiotherapy. In the Dutch TME trial, radiotherapy at a dose of 45 Gy or higher was applied in 42% of patients for local recurrence after TME alone, whereas the rate was only 4% for the preoperative radiotherapy group.[69] Long-term follow-up of the Swedish and Dutch rectal cancer trials showed that time from local recurrence to death was significantly shorter in the irradiation group than in patients who underwent surgery alone.[59, 69] Thus, radiotherapy does not affect systemic dissemination and, therefore, local recurrences after radiotherapy are more often concomitant with distant disease, leading to a worse prognosis from time of local recurrence. From these data, it can be concluded that radiotherapy for primary resectable rectal cancer mostly prevents potentially curable local recurrence.

CONCLUSION

If intentionally curative treatment in a patient with locally recurrent rectal cancer is considered by the multidisciplinary team, a standardized approach with optimal neoadjuvant treatment is indicated. Full-dose chemo-radiotherapy or an adapted schedule depending on previous EBRT maximizes the chance of an R0 resection, which is the most important prognostic factor. Surgery should be performed in specialized centers by an experienced surgeon. The distant metastasis rate during follow-up supports the use of adjuvant chemotherapy, although there is no conclusive evidence. Systemic chemotherapy preceding or following (re)irradiation in a neoadjuvant setting is probably worthwhile to explore in future studies given the systemic nature of the disease. Standardized reporting of actuarial local control and survival for predefined categories based on these data will improve available evidence.

REFERENCES

1. Peeters KC, van de Velde CJ. Surgical quality assurance in rectal cancer treatment: the key to improved outcome. Eur J Surg Oncol 2005; 31: 630-5.2. Wong RK, Tandan V, De Silva S, et al. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma.
2. Cochrane Database Syst Rev 2007; CD002102.
3. Abuchaibe O, Calvo FA, Azinovic I, et al. Intraoperative radiotherapy in locally advanced recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 1993; 26:859-67.
4. Estes NC, Thomas JH, Jewell WR, et al. Pelvic exenteration: a treatment for failed rectal cancer surgery. Am Surg 1993; 59:420-2.
5. Gagliardi G, Hawley PR, Hershman MJ, et al. Prognostic factors in surgery for local recurrence of rectal cancer. Br J Surg 1995; 82:1401-5.
6. Gunderson LL, Nelson H, Martenson JA, et al. Intraoperative electron and external beam irradiation with or without 5-

fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. Dis Colon Rectum 1996; 39:1379-95.
7. Bussières E, Gilly FN, Rouanet P, et al. Recurrences of rectal cancers: results of a multimodal approach with intraoperative radiation therapy. French Group of IORT. Intraoperative Radiation Therapy. Int J Radiat Oncol Biol Phys 1996; 34:49-56.
8. Knol HP, Hanssens PE, Rutten HJ, et al. Effect of radiation therapy alone or in combination with surgery and/or chemotherapy on tumor and symptom control of recurrent rectal cancer. Strahlenther Onkol 1997; 173:43-9.
9. Bozzetti F, Bertario L, Rossetti C, et al. Surgical treatment of locally recurrent rectal carcinoma. Dis Colon Rectum 1997; 40:1421-4.
10. Maetani S, Onodera H, Nishikawa T, et al. Significance of local recurrence of rectal cancer as a local or disseminated disease. Br J Surg 1998; 85:521-5.
11. Eble MJ, Lehnert T, Treiber M, et al. Moderate dose intraoperative and external beam radiotherapy for locally recurrent rectal carcinoma. Radiother Oncol 1998; 49:169-74.
12. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: technical considerations and outcomes. Dis Colon Rectum 1999; 42:1438-48.
13. Salo JC, Paty PB, Guillem J, et al. Surgical salvage of recurrent rectal carcinoma after curative resection: a 10-year experience. Ann Surg Oncol 1999; 6:171-7.
14. Zacherl J, Schiessel R, Windhager R, et al. Abdominosacral resection of recurrent rectal cancer in the sacrum. Dis Colon Rectum 1999; 42:1035-9.
15. Hashiguchi Y, Sekine T, Sakamoto H, et al. Intraoperative irradiation after surgery for locally recurrent rectal cancer. Dis Colon Rectum 1999; 42:886-93.
16. Adachi W, Nishio A, Watanabe H, et al. Reresection for local recurrence of rectal cancer. Surg Today 1999; 29:999-1003.
17. Law WL, Chu KW. Resection of local recurrence of rectal cancer: results. World J Surg 2000; 24:486-90.
18. Rödel C, Grabenbauer GG, Matzel KE, et al. Extensive surgery after high-dose preoperative chemoradiotherapy for locally advanced recurrent rectal cancer. Dis Colon Rectum 2000; 43:312-9.
19. Lindel K, Willett CG, Shellito PC, et al. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. Radiother Oncol 2001; 58:83-7.
20. Lopez-Kostner F, Fazio VW, and Vignali A, et al. Locally recurrent rectal cancer: predictors and success of salvage surgery. Dis Colon Rectum 2001; 44:173-8.
21. Garcia-Aguilar J, Cromwell JW, Marra C, et al. Treatment of locally recurrent rectal cancer. Dis Colon Rectum 2001; 44:1743-8.
22. Yamada K, Ishizawa T, Niwa K, et al. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. Br J Surg 2001; 88:988-93.
23. Bergamaschi R, Pessaux P, Burtin P, et al. Abdominoperineal resection for locally recurrent rectal cancer. Tech Coloproctol 2001; 5:97-102.
24. Huguier M, Houry S, Barrier A. Local recurrence of cancer of the rectum. Am J Surg 2001; 182:437-9.
25. Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. Dis Colon Rectum 2002; 45:585-92.
26. Friel CM, Cromwell JW, Marra C, et al. Salvage radical surgery after failed local excision for early rectal cancer. Dis Colon Rectum 2002; 45: 875-9.
27. Mohiuddin M, Marks G, Marks J. Long-term results of reirradiation for patients with recurrent rectal carcinoma. Cancer 2002; 95:1144-50.
28. Pezner RD, Chu DZ, Ellenhorn JD. Intraoperative radiation therapy for patients with recurrent rectal and sigmoid colon cancer in previously irradiated fields. Radiother Oncol 2002; 64:47-52.
29. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. Ann Surg 2003; 237:502-8.
30. Saito N, Koda K, Takiguchi N, et al. Curative surgery for local pelvic recurrence of rectal cancer. Dig Surg 2003; 20:192-9.
31. Kakuda JT, Lamont JP, Chu DZ, et al. The role of pelvic exenteration in the management of recurrent rectal cancer. Am J Surg 2003; 186:660-4.
32. Bakx R, van Tinteren H, van Lanschot JJ, et al. Surgical treatment of locally recurrent

rectal cancer. Eur J Surg Oncol 2004; 30:857-63.
33. Moriya Y, Akasu T, Fujita S, et al. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer in the pelvis. Dis Colon Rectum 2004; 47:2047-53.
34. Reerink O, Mulder NH, Botke G, et al. Treatment of locally recurrent rectal cancer, results and prognostic factors. Eur J Surg Oncol 2004; 30:954-8.
35. Weiser MR, Landmann RG, Wong WD, et al. Surgical salvage of recurrent rectal cancer after transanal excision. Dis Colon Rectum 2005; 48:1169-75.
36. Vermaas M, Ferenschild FT, Nuyttens JJ, et al. Preoperative radiotherapy improves outcome in recurrent rectal cancer. Dis Colon Rectum 2005; 48:918-28.
37. Boyle KM, Sagar PM, Chalmers AG, et al. Surgery for locally recurrent rectal cancer. Dis Colon Rectum 2005; 48:929-37.
38. Henry LR, Sigurdson E, Ross E, et al. Hydronephrosis does not preclude curative resection of pelvic recurrences after colorectal surgery. Ann Surg Oncol 2005; 12:786-92.
39. Rudmik LR, Buie WD, Heine JA. Reoperation for intraluminal rectal cancer recurrence. Dis Colon Rectum 2005; 48:1752-4.
40. Melton GB, Paty PB, Boland PJ, et al. Sacral resection for recurrent rectal cancer: analysis of morbidity and treatment results. Dis Colon Rectum 2006; 49:1099-107.
41. Valentini V, Morganti AG, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: a multicentric phase II study. Int J Radiat Oncol Biol Phys 2006; 64:1129-39.
42. Bedrosian I, Giacco G, Pederson L, et al. Outcome after curative resection for locally recurrent rectal cancer. Dis Colon Rectum 2006; 49:175-82.
43. Asoglu O, Karanlik H, Muslumanoglu M, et al. Prognostic and predictive factors after surgical treatment for locally recurrent rectal cancer: a single institute experience. Eur J Surg Oncol 2007; 33:1199-206.
44. Palmer G, Martling A, Cedermark B, et al. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. Ann Surg Oncol 2007; 14:447-54.
45. Wells BJ, Stotland P, Ko MA, et al. Results of an aggressive approach to resection of locally recurrent rectal cancer. Ann Surg Oncol 2007; 14:390-5.
46. Wiig JN, Larsen SG, Dueland S, et al. Preoperative irradiation and surgery for local recurrence of rectal and rectosigmoid cancer. Prognostic factors with regard to survival and further local recurrence. Colorectal Dis 2008; 10:48-57.
47. Heriot AG, Byrne CM, Lee P, et al. Extended radical resection: the choice for locally recurrent rectal cancer. Dis Colon Rectum 2008; 51: 284-91.
48. Schurr P, Lentz E, Block S, et al. Radical redo surgery for local rectal cancer recurrence improves overall survival: a single center experience. J Gastrointest Surg 2008; 12:1232-8.
49. Tanaka K, Noura S, Ohue M, et al. Doubling time of carcinoembryonic antigen is a significant prognostic factor after the surgical resection of locally recurrent rectal cancer. Dig Surg 2008; 25:319-24.
50. Rades D, Kuhn H, Schultze J, et al. Prognostic factors affecting locally recurrent rectal cancer and clinical significance of hemoglobin. Int J Radiat Oncol Biol Phys 2008; 70:1087-93.
51. Sagar PM, Gonsalves S, Heath RM, et al. Composite abdominosacral resection for recurrent rectal cancer. Br J Surg 2009; 96:191-6.
52. Kusters M, Dresen RC, Martijn H, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys 2009; 75:1444-9.
53. Fujii S, Shimada H, Yamagishi S, et al. Surgical strategy for local recurrence after resection of rectal cancer. Hepatogastroenterology 2009; 56:667-71.
54. de Chaisemartin C, Penna C, Goere D, et al. Presentation and prognosis of local recurrence after total mesorectal excision. Colorectal Dis 2009; 11:60-6.
55. Park JK, Kim YW, Hur H, et al. Prognostic factors affecting oncologic outcomes in patients with locally recurrent rectal cancer: impact of patterns of pelvic recurrence on curative resection. Langenbecks Arch Surg 2009; 394:71-7.
56. Pacelli F, Tortorelli AP, Rosa F, et al. Locally recurrent rectal cancer: prognostic factors and long-term outcomes of

multimodal therapy. Ann Surg Oncol 2010; 17:152-62.
57. Das P, Delclos ME, Skibber JM, et al. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. Int J Radiat Oncol Biol Phys 2010; 77:60-5.
58. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007; 246:693-701.
59. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005; 23:5644-50.
60. Holm T, Cedermark B, Rutqvist LE. Local recurrence of rectal adenocarcinoma after 'curative' surgery with and without preoperative radiotherapy. Br J Surg 1994; 81:452-5.
61. Frykholm GJ, Pahlman L, Glimelius B. Treatment of local recurrences of rectal carcinoma. Radiother Oncol 1995; 34:185-94.
62. Meagher AP, Ward RL. Current evidence does not support routine adjuvant radiotherapy for rectal cancer. ANZ J Surg 2002; 72:835-40.
63. Miner TJ, Jaques DP, Paty PB, et al. Symptom control in patients with locally recurrent rectal cancer. Ann Surg Oncol 2003; 10:72-9.
64. Dresen RC, Peters EE, Rutten HJ, et al. Local recurrence in rectal cancer can be predicted by histopathological factors. Eur J Surg Oncol 2009; 35:1071-7.
65. Huguier M, Houry S. Treatment of local recurrence of rectal cancer. Am J Surg 1998; 175:288-92.
66. den Dulk M, Marijnen CA, Putter H, et al. Risk factors for adverse outcome in patients with rectal cancer treated with an abdominoperineal resection in the total mesorectal excision trial. Ann Surg 2007; 246:83-90.
67. West NP, Anderin C, Smith KJ, et al. Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. Br J Surg 2010; 97:588-99.
68. Caricato M, Borzomati D, Ausania F, et al. Prognostic factors after surgery for locally recurrent rectal cancer: an overview. Eur J Surg Oncol 2006; 32:126-32.
69. van den Brink M, Stiggelbout AM, van den Hout WB, et al. Clinical nature and prognosis of locally recurrent rectal cancer after total mesorectal excision with or without preoperative radiotherapy. J Clin Oncol 2004; 22:3958-64.