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APPENDIX: PARTICIPATING CENTRES AND PRINCIPAL CO-OPERATING CLINICAL ONCOLOGISTS

The Beatson Oncology Centre, Glasgow (Professor A. Barrett, Dr Canney, Dr MacBeth, Dr Robertson, Dr R.P. Symonds and Dr H. Yosef). Mount Vernon Centre, Northwood (Professor S. Dische and Dr M.I. Saunders). St Mary's Hospital, Portsmouth (Dr V. Svoboda). The Royal Infirmary, Bristol (Dr H. Newman). Mersey Regional Centre, Clatterbridge (Dr B. Cottier). The General Hospital, Nottingham (Dr D. Morgan). The Cookridge Hospital, Leeds (Dr I. Rothwell). The Royal Marsden Hospital, London (Dr J. Henk). Weston Park Hospital, Sheffield (Dr M. Whipp). The Velindre Hospital, Cardiff (Dr C. Gaffney). The Radiologische Klinik, Dresden (Dr T. Hermann). University Hospital, Umea (Dr B. Littbrand).

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Adjuvant Treatment in the Curative Management of Rectal Cancer: a Critical Review of the Results of Clinical Randomised Trials

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A critical analysis of the results of randomised studies on adjuvant rectal cancer led to a different interpretation than given by the 1990 National Institutes of Health (NIH) conference which concluded that combined postoperative chemotherapy and radiotherapy resulted in increased local control and survival in stage II and III patients. We think there is not as yet indisputable evidence for the use of such combination postoperatively. Furthermore, this approach resulted in increased toxicity and was only consistent with moderate compliance. Conversely, preoperative radiotherapy, which was not even mentioned in the conclusions and recommendations of the NIH consensus conference, definitely increases local control and should now be proposed as standard initial treatment in T3T4 resectable rectal cancer. Moreover, preoperative concomitant chemotherapy is an attractive area for clinical trials.
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INTRODUCTION

THE OUTCOME of resectable rectal cancer treated with surgery alone is associated in some groups of patients with a high risk of local failure (LF) and distant metastasis (DM) [1–3]. Due to the extreme disability caused by LF, a gain in local pelvic control represents a major end-point of adjuvant treatments. Adjuvant radiotherapy has been shown to decrease LF without any effect on survival. Lately, studies have suggested an improved survival in high risk patients when chemotherapy and irradiation were used in combination postoperatively [4, 5]. In 1989, a U.S. National Institutes of Health (NIH) Consensus Conference stated that postoperative pelvic irradiation and chemotherapy should be regarded as standard treatment for stage II and III rectal cancer patients [6]. The aim of this review is to analyse the published results of randomised adjuvant trials, which in part enabled the consensus conference analysis, to discuss its conclusions and finally to suggest some areas for clinical research in this disease.

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RESULTS WITH SURGERY ALONE

After curative resection, the prognosis of rectal cancer is correlated with the depth of tumoral extension through the bowel wall, the nodal involvement and the number of involved nodes [1–3]. The 5-year survival ranges from 44 to 76% in stage B2 Astler-Coller's patients, and drops to 10–40% when regional nodes are involved [2, 7, 8]. In all stages, local recurrence is a major reason for failure as a consequence of the mode of spread of the tumour, with direct invasion of the extra-peritoneal fat and of the neighbouring structures. Other difficulties include surgical access to the deep pelvis and the surgeon's ability to clear the mesorectal fat [9, 10]. Inadequate surgical clearance of the radial margin appears to be the first cause of LF in rectal cancer [11, 12]. LF rate ranges from 5% in a few selected series to 40% in most reports [2, 9, 13]. In randomised trials on adjuvant treatments, the control group with surgery alone is associated with a 23–44% 2 to 5-year LF rate in Astler-Coller's B and C patients (Tables 1–3). These data are in accordance with those reported in the Gastrointestinal Tumour Registry of Côte-d'Or in France [14]. The 5-year LF rate may reach the astonishing figure of 75% when using proper pathological staging reflecting the degree of extension beyond the wall and when giving an actuarial estimate of the risk instead of crude figures [11]. The risk of DM is also strongly correlated with the locoregional extension of the disease [1–3].

Table 1. Resected Duke's B and C rectal cancer. Randomised trials of postoperative irradiation versus surgery

Study	XRT dose/fraction/time	No. of patients XRT	No. of patients Control	Follow-up (months)	LF rate (%) XRT	LF rate (%) Control	5-year survival rate (%) XRT	5-year survival rate (%) Control
Denmark [15, 16]	50Gy/25F/7W (2W rest after 30Gy)	244	250	24	B11 C20	11 25	NA	
GITSG [4, 19, 20] 71–75	40Gy/20F/4W or 48Gy/27F/51/2W	50	58	94	20	24	52	43
NSABP RO1 [18]	46-47Gy/27F/5W (±6Gy boost)	184	184	64	16	25	41	43
Netherlands [17]	50Gy/25F/5W	88	84	NA	24	33	45	57

NA = not available. W = weeks.

Table 2. Randomised trials of combined irradiation and chemotherapy

Study	Scheme	No. of patients	Follow-up (months)	LF rate (%)	DM rate (%)	5-year survival rate (%)
Pre-op EORTC 40741 [21]	XRT = 34.5Gy/15F/3W	121		15		59
	versus		62		NA	
	XRT + C-5-FU* (34.5Gy)	126		15		46
Post-op GITSG 71–75 [4, 19, 20]	Surgery versus	58		24	34	42
	XRT = 40Gy/20F/4W or 44Gy/27F/5.5W + C-5-FU* + 5-FU-semustine (eight courses)	46	94	11	26	59 $P = 0.005$
NCCTG 79–4751 [5]	XRT = 50.4Gy/28F/51/2W	100		25	46	47
	versus		84	$P = 0.01$	$P = 0.01$	$P = 0.02$
	XRT (50.4Gy) + C-5-FU* + 5-FU-semustine (two courses)	104		13.5	28.8	57

Concurrent 5-FU. NA = not available. W = weeks.

Table 3. Clinically resectable recto-(sigmoid) cancer. Randomised trials of pre-operative irradiation alone versus surgery

Study	XRT dose/fraction/time	No. of Patients XRT	No. of Patients Control	Follow-up (months)	LR rate (%) XRT	LR rate (%) Control	5-year survival rate (%) XRT	5-year survival rate (%) Control
≤ 20 Gy pelvic volume								
Memorial [27]	20 Gy/8F/2W	376	414	60	NA		67	65
PMH [26]	5 Gy/1F	60	65	60	NA		35	35
VASAG I [24]	20 Gy/10F/2W	347	353	60	29*	36*	35§	29§
MRC [25]	5 Gy/1F	277	275	48	45†	44†	41.7	38
	20 Gy/10F/2W	272			48†		40	
≥25 Gy pelvic + para-aortic nodes volume								
VASAG II [30]	31.5 Gy/18F/31/2W	180	181	45	NA		43.3	46.5
Norway [28]	31.5 Gy/18F/31/2W	155	145	54	13.7	NS† 21.1	56.7	57.5
Stockholm [31]	25 Gy/5F/1W	424	425	53	11	$P < 0.01$ 24	42	42
EORTC 40761 [29]	34.5 Gy/15F/3W	166	175	74	15	$P = 0.03$ 30†	51.6	49

* Autopsied group; † actuarial rate; ‡ XRT significantly delayed LF (see text); § determinate survival, NA = not available.

RESULTS WITH ADJUVANT TREATMENT

Postoperative radiotherapy (with or without chemotherapy)

Postoperative pelvic irradiation has been compared to surgery alone in four multicentric randomised trials for Duke's B or C selected patients (Table 1).

In the Danish trial with 494 patients entered [15, 16], a 50 Gy dose was delivered using a three-fields technique, over a 7-week period with a 2-week interval after 30 Gy. Of the 244 patients allocated to radiation, 20 did not receive the full dose and 11 treatments were stopped because of acute intestinal complications. 25 patients had to be reoperated for paralytic ileus or intestinal perforation. Radiotherapy was responsible for 3 toxic deaths.

172 patients were entered into a Dutch trial [17]. A 50 Gy dose was planned over 5 weeks using a three or four-fields technique. Among the 88 patients allocated to the radiotherapy arm, 14 were not irradiated and 10 received only a 40 Gy dose due to acute intestinal complications. Late severe ileitis was observed in 2 patients resulting in 1 toxic death.

The NSABP conducted a three-arm trial (RO1 trial) in which postoperative irradiation or chemotherapy were compared with surgery alone [18]. 184 patients were entered in the radiotherapy arm. The planned pelvic dose was 46–47 Gy delivered in 5.5 weeks using AP-PA fields only. Among the 158 patients who began radiation, four treatments had to be stopped for metastasis or patient refusal. Acute toxicities were not reported in detail, however, there were no toxic deaths.

The GITSG conducted a four-arm postoperative trial in which irradiation, chemotherapy, or a combination of both were compared to surgery alone [4, 19, 20]. 50 patients were entered in the irradiation arm and were allocated to receive a 40–48 Gy dose in 4.5–5.5 weeks using AP-PA fields; 25 received a dose lower than 42 Gy. Severe gastrointestinal acute toxicities were observed in 16%.

None of the above trials showed a significant effect on local pelvic control or on survival using postoperative irradiation alone. Moreover, 12–27% of the patients did not receive the planned dose and lethal late treatment-related complications occurred in 1–3%.

Postoperative systemic chemotherapy was tested in comparison with surgery in two trials (Table 4): 48 patients entered the chemotherapy arm of the GITSG trial. 9 did not complete the programme: 5 refused and 4 suffered acute toxicity. 1 patient developed a leukaemia several years after the treatment. Among 187 patients entered in the NSABP chemotherapy arm, 154 began the treatment. Grade 2 acute haematological, vomiting or diarrhoea toxicities were observed, respectively, in 35, 60 and 45%. There was no late myeloproliferative disorder. The disease-free survival was significantly increased in the NSABP chemotherapy arm. Subgroup analysis showed that the survival benefit mostly occurred in males under 65 years of age. The compliance to treatment was 58 and 80%, respectively, in these two trials.

Combined treatment has been tested in three multicentre trials (Table 2). Concurrent fluorouracil (5-FU) with pre-operative irradiation was tested against pre-operative irradiation alone by the EORTC Gastro intestinal Group [21]. 34.5 Gy were delivered over 3 weeks using AP-PA fields extended up to L2. 5-FU was given during the first 4 days of irradiation. Severe acute reactions occurred in 3/168 patients of the control arm versus 6/171 in the combined modality arm, resulting in 2 pre-operative toxic deaths. The overall survival remained unchanged.

Adjuvant irradiation combined with chemotherapy has been tested postoperatively in comparison with surgery in only one trial. 46 patients entered the combined arm of the GITSG trial where 5-FU was administered during the first and last week of irradiation. Then, eight courses of 5-FU-semustine were added. Severe acute toxicities increased significantly up to 61% with 2 toxic deaths. After a follow-up of more than 5 years, the combined treatment seemed to significantly increase the overall survival. However, only 65% of the patients completed the chemotherapy programme, the major reason for non-compliance being patient refusal to pursue the treatment.

Postoperative pelvic irradiation with concurrent 5-FU delivered during the first and last week of irradiation, combined with systemic chemotherapy, one course before and one course after irradiation (5-FU-semustine), was compared with postoperative irradiation in the NCCTG trial [5]. Of 204 patients, only 5 were ineligible. Acute diarrhoea and haematological toxicities were increased by concurrent 5-FU. 17% of the patients did not receive the postirradiation chemotherapy course due to persistent toxicities. Late complications, usually small bowel obstruction, occurred in 7% of the patients in each arm. Combined treatment significantly decreased LF and DM and increased survival.

Preliminary results of two studies conducted by the GITSG and NCCTG indicate that semustine is no longer essential for the efficacy of combined treatment [22, 23]. The combined postoperative treatment using pelvic irradiation, concurrent 5-FU and systemic chemotherapy for the first time appears to increase survival in high risk rectal cancer. However, it increases acute toxicities and also possibly, the late ones. Treatment compliance was 65–80%.

Pre-operative radiotherapy

Pre-operative irradiation alone was compared to surgery alone in eight randomised trials (Table 3). In the early studies [24–27],

Table 4. Resected Duke's B and C rectal cancer. Randomised trials of post operative chemotherapy versus surgery

Study	Scheme	No. of patients		Follow-up months	LF rate (%)		DM rate (%)		5-year survival rate (%)	
		CT	Control		CT	Control	CT	Control	CT	Control
GITSG 71–75 [4, 19]	5-FU–semustine eight courses	48	58	94	27	24	27	34	57	47
NSABP RO1 [18]	5-FU–semustine + vincristine eight courses	187	184	64	21	25	24	26	53	43
									$P = 0.05$	

low doses ranging from 5 to 20 Gy were delivered to the pelvis from a few hours to 6 weeks before surgery. Subgroup analysis showed a reduction in LF in Memorial and Vasag I trials, and a survival benefit in Vasag I. However, the well conducted three-armed MRC trial definitely ruled out any effect of single or fractionnated pre-operative low dose irradiation.

In subsequent studies, moderate doses from 25 to 34.5 Gy were delivered to the pelvic and para-aortic nodes 1–6 weeks before surgery [28–31]. In the Norway trial, both LF and DM were significantly delayed from 13.3 months in control to 27.1 months in the pre-operative radiotherapy arm. The short schedule with a high dose per-fraction (25 Gy-5 fr-1 week) used in the Stockholm study resulted in a better local control than with surgery alone. Results within a similar range were observed in the EORTC study delivering irradiation with a more protracted schedule (3 weeks). None of these trials showed an effect on survival. 90–97% of the patients were fully compliant to moderate irradiation dose despite the inconvenience of extended fields. An increased incidence of wound infection and a longer healing time after amputation was observed in the experimental arms.

Table 5 summarises the overall acute and late toxicities and also compliance from the randomised trials on adjuvant treatment in rectal cancer.

DISCUSSION

Radiotherapy is often considered as an important part of the treatment of rectal cancer due to its ability to reduce LF. The postoperative approach allows for accurate staging and the inclusion of high risk patients selected from pathological examination. However, it did not significantly decrease the LF rate in randomised trials using pelvic doses in the 40–50 Gy range. Whether an increase in dose beyond 50 Gy over a carefully selected volume could improve local control remains questionable, but is a valuable objective for future trials. However, in order to improve local control, the total dose should be in the 60–75 Gy range delivered over 6–8 weeks and it is unlikely that this will be feasible in a large proportion of patients treated with APR or AR due to the presence of small bowel and/or colorectal anastomosis in the treated volume. Boosting the presacral and mesorectal areas with intra-operative radiotherapy is an alternative. Again it is technically difficult and not consistent with standard management of rectal cancer.

Postoperative systemic chemotherapy has not been fully evaluated in rectal cancer. The 5-FU-semustine combination does not improve overall survival in studies including both colonic and rectal cancer [32]. Whether the addition of vincristine is responsible for the increase in disease-free survival of rectal cancer, as it has been claimed in the NSABP trial, remains debatable. Moreover, using chemotherapy without radiotherapy results in an unacceptably high LF rate. The ability of combined postoperative radiotherapy and chemotherapy to increase survival is based only on the GITSG trial. Its conclusions may be disputable with regard to its quality (11% ineligible rate), lack of power (227 patients scattered between four arms), and a possible recruitment bias (a 5-year inclusion duration with 15 participating centres). The absence of a surgery alone control arm is detrimental to the NCCTG study. Moreover, the respective effects of concurrent 5-FU with irradiation and additive systemic chemotherapy remains unclear.

Table 5. Acute, late toxicities and compliance in randomised adjuvant treatment on rectal cancer

	Acute toxicities (%)	Late toxicities (%)	Toxic death (%)	Compliance
Pre-op XRT	< 5	?	0	97
Post-op XRT	20	10	1–3	85
Post-op XRT + CT	61	7–15	5	70

Conversely, pre-operative irradiation using doses in the 25–35 Gy range with fraction sizes of 2.3–5 Gy per day would appear to increase the local control, and provide better local control figures than those reported for postoperative irradiation in a Swedish randomised trial [33]. Moreover, a better treatment compliance and lower acute and late toxicity rates offer strong arguments for preferring pre-operative radiotherapy to postoperative radiotherapy in randomised multicentre studies and as a standard treatment for rectal cancer.

In summary, our conclusions do not fully overlap with those of the U.S.-NIH consensus conference, which stated that postoperative as well as pre-operative irradiation demonstrated a definite efficacy in reducing LF and that combined treatment improves both local control and survival in stage II and III rectal cancer patients.

The logical conclusion of our analysis is to propose that pre-operative irradiation should be the standard treatment against which experimental regimes must be compared. The main criticism of pre-operative treatment is about a possible over-treatment of early disease (T1–T2 UICC 1987 staging system). However, assessment of local invasion can be improved by intraluminal ultrasound. The accuracy is 87–95%, the rate of under-staging being about 5%, and over-staging 5–15% [34].

NEW APPROACHES IN THE ADJUVANT SETTING

If we accept pre-operative irradiation as the standard approach for clinically T3 and potentially resectable T4 rectal cancer, the next step is to test combined chemo-irradiation before surgery. This will provide the opportunity for further improvements in irradiation technique (better control of the target volume, optimisation of dose/time fractionation parameters) and will allow treatment of microscopic distant disease at an earlier and, therefore, more sensitive stage. The combination of 5-FU and leucovorin (LV) delivered concurrently with irradiation is attractive. Experimentally the biochemical modulation of 5-FU by LV further increases the potential effect of 5-FU on ionising radiation [35]. Three consecutive phase II studies performed in the EORTC group of radiotherapy have investigated the optimal dose of 5-FU when given with low dose LV during the first and fifth weeks of pelvic irradiation in rectal cancer [36]. A 4-arm randomised trial will be soon activated by the EORTC cooperative group of radiotherapy and the Fondation Française de Cancérologie Digestive, comparing pre-operative radiotherapy with combined pre-operative chemo-radiotherapy and pre-operative radiotherapy plus postoperative chemotherapy to pre-operative chemo-radiotherapy plus postoperative chemotherapy.

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