cal surgery can be doubtful due to difficulties in dissection. This is especially true for men, when the tumour is growing anteriorly. Therefore all patients, despite the size of the tumour, should have pre-operative radiotherapy if it is known in advance that the patient will have an abdominoperineal excision.

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THE DEVELOPMENT of a locoregional recurrence of a rectal carcinoma has a substantial influence on the overall prognosis [1–5]. An earlier analysis involving our own patients showed that, following an RO resection (and leaving out consideration of all other criteria), the 5-year survival rate for patients with no local recurrence was 85%. Otherwise, the 5-year survival rate was only 23% [6]. It has also been shown that, as the global local recurrence rate over the last three decades has declined from more than 40% to just under 10% today, so the 5-year survival rate has increased from 50 to 71% [7]. A review of the results reported in the literature also confirms this direct association [8–14] as does the evaluation of the German Study Group Colorectal Carcinoma (SGCRC) with respect to the individual surgeon (Figure 1). Finally, in a multivariate analysis based on data of the SGCRC, curative

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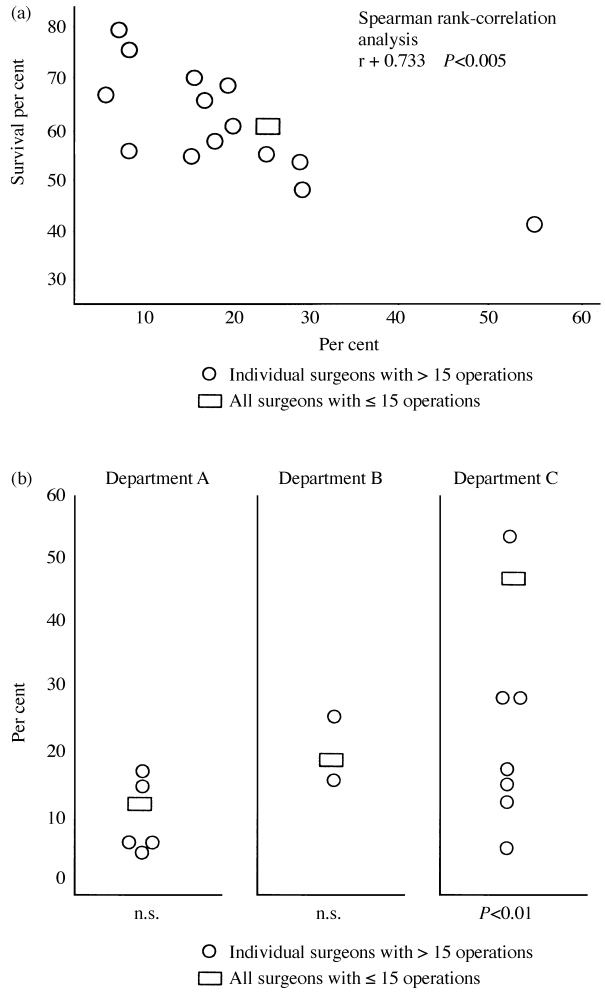

Figure 1. (a) Correlation between locoregional recurrence rate and observed 5-year survival. (b) Locoregional recurrence rate in relation to departments and surgeons.

resection (M0, R0) was shown to be an independent prognostic factor for the development of locoregional recurrence, with an odds ratio of 12.09 [15].

Against this background, the target criterion for evaluating the effect of radiochemotherapy is primarily the incidence of local recurrent disease following curative surgery of a rectal carcinoma. However, irrespective of this, patients with no local recurrent disease, that is, after apparently optimal surgical treatment, develop distant metastases—depending on UICC stage—with an incidence of between 8% (stage I) and 40% (stage III) [7]. Such metastases also have a substantial effect on the prognosis.

In this regard, two facts point to the limitations of surgery. Firstly, the development of locoregional recurrent disease has no significant influence on distant metastasis. Thus, of the patients with no local recurrence, 80% did not develop metastases within 10 years following the operation, nor do 68% of those with a local recurrence ($P = 0.44$) [7]. Secondly, the corresponding distant metastasis rates have remained constant for decades despite improvements in surgical techniques and the resulting decrease in local recurrence rates [7]. Thus, attempts to improve overall prognosis of rectal carcinoma have primarily focused on reducing local recurrence rates, and in particular, the use of adjuvant radiotherapy has been investigated, in part in combination with chemotherapy.

The second approach aims to reduce the rate of distant metastasis with the aid of chemotherapy applied for longer than the duration of radiotherapy. While initial reports indicate such a possible effect in combination with pre-operative irradiation, the extent of this effect still remains uncertain. Thus, Krook was able to show that using additional chemotherapy, a significant ($P = 0.011$) reduction in the distant metastasis rate from 46 to 28.8% as compared with irradiation alone, was achieved [16].

VARIABILITY OF THE RESULTS OF SURGERY IN TERMS OF LOCOREGIONAL RECURRENCE

In recent years, several publications have drawn attention to the prognostic effect of the individual surgeon on the incidence of locoregional recurrent disease [17–20]. In Germany the results of the SGCRC showed that, in the case of a locoregional recurrence, the institution itself is the most important prognostic factor [2, 15]. Individually, there were considerable differences between the 7 participating institutions in terms of locoregional recurrence rate. In this study, fewer than 15% of all the patients enrolled were treated adjuvantly with chemotherapy and/or radiotherapy.

Independently of controlled studies, experience also shows not only that differences in the results of treatment occur globally between institutions, but also that the surgeon himself represents a prognostic factor. Here, too, the SGCRC also confirmed a significant influence of the individual surgeon on the rate of locoregional recurrence [2, 15]. This study also revealed that some surgeons are capable, by surgical measures alone, of achieving global local recurrence rates of substantially under 10% (Figure 1b). Independently of this, surgeons with very low local recurrence rates have shown that, in the case of a carcinoma affecting the lower two-thirds of the rectum, complete excision of the mesorectum is required. For carcinomas of the upper third, an aboral margin of at least 5 cm with transverse divisioning of the mesorectum at the same level—care being taken to avoid coning—is needed [3, 7, 11, 21]. The basis for these requirements have been documented by relevant pathohistological investigations [4, 5].

These technical surgical requirements have become incorporated into guidelines. Since, however, their proper implementation can be indirectly documented only by a knowledge of the long-term results, when studies are performed the required surgical measures must be defined and in addition the surgeon, or at least the participating institution, stratified for randomisation.

WHAT HAVE THE STUDIES ON ADJUVANT RADIOTHERAPY ACTUALLY SHOWN US?

The prospective randomised studies on adjuvant radiotherapy published in recent years and including a surgery-alone treatment arm are listed in Table 1. They can be divided into two groups: those studies with locoregional recurrence rates in the surgery alone arm of between 15–29%—with a mean of 23%—this being reduced by adjuvant radiochemotherapy to around 14%; and those with local recurrence rates in the surgery alone arm of more than 30%, with a mean of 37%, this figure being reduced by adjuvant therapy to 29%. In none of the studies involving multimodal treat-

Table 1. *The role of local recurrence in randomised controlled trials using adjuvant and neoadjuvant therapy in rectal cancer*

Reference	Year	Group	Treatment arms	Local recurrences (%)	5-Year overall survival (%)
Local recurrence rates between 15 and 29% in the surgical control arm					
Stearns [38]	1980		Surgery only	17	58
			neoadjuvant RT 20 Gy	11	57
Balslev and colleagues [29]	1986 1979–1985	Denmark	Surgery only adjuvant RT 50 Gy	18 16 n.s.	n.a. n.a. no significant survival benefit
Cedermark [39]	1994 1987–1993	Stockholm II	Surgery only neoadjuvant RT 25 Gy	21 10	n.a. n.a.
GITSG [9]	1985 1975–1980	GITSG	Surgery only adjuvant RT 40-48 Gy adjuvant CT 5FU(bolus)/ mCCNU adjuvant RCT	24 20 27 10.8	46 52 n.s. 56 n.s. 59 n.s
Fisher and colleagues [8]	1988 1977–1986	NSABP R-01	Surgery only adjuvant RT 46-47 Gy adjuvant CT bolus-MOF	25 16 $P=0.06$ n.a.	43 41 n.s. 53 $P=0.05$
Krook and colleagues [16]	1991 1980–1986	NCCTG	RT 45-50.4 Gy adjuvant RCT 5FU(bolus)/ mCCNU	25 13.5 $P=0.36$	47 (32 after 7 y) 56 (52 after 7 y) $P=0.025$
Dahl and colleagues [40]	1990 1976–1975	Norway	Surgery only neoadjuvant RT 31.5 Gy	26 (R0: 23) 17 (R0: 14)	57 (R0: 64) 58 (R0: 61)
Swedish RCT [41, 42]	1995–1997 1987–1990	Sweden	Surgery only neoadjuvant RT 25 Gy	27 (R0: 20%) 11 (R0: 7%) $P<0.001$ (R0: $P<0.001$)	58 48 $P=0.004$
Cedermark and colleagues [43]	1995 1980–1987	Stockholm I	Surgery only neoadjuvant RT 25 Gy	28 (R0: 30) 14 (R0: 16) $P<0.01$ R0: $P<0.01$	n.a. n.a. no significant survival benefit
Local recurrence rates of more than 30% in the surgical control arm					
Gérard and colleagues [44]	1988 1976–1981	EORTC	Surgery only neoadjuvant RT 34.5 Gy	30 15 $P=0.003$	60 (R0: 59) 62 (R0: 69, $P=0.08$)
MRC [36]	1996 1984–1989	MRC	Surgery alone adjuvant RT 40 Gy	33 20 $P=0.001$	46 52 n.s.
Arnaud and colleagues [30]	1997 1981–1986	EORTC	Surgery only adjuvant RT 46 Gy	34 29.8 n.s.	
MRC [10]	1984 1975–1978	MRC	Surgery only neoadjuvant RT 5 or 20 Gy	43 45 or 47	38 42 or 40
MRC [45]	1996 1981–1989	MRC	Surgery only neoadjuvant RT 40 Gy	46 35	n.a. n.a.

n.a., not available; n.s., not significant; MOF; 5-FU + mCCNU + vincristine.

ment of rectal carcinoma was a local recurrence rate of less than 15% achieved by surgery alone.

Thus, all these figures are substantially above those obtained by a number of surgeons using surgical treatment alone [3, 7, 11, 21–23]. A number of years ago, we pointed out that, although it has been documented that adjuvant radiochemotherapy is capable of reducing the local recurrence rate, the question still remained as to whether this continues to be true for a global local recurrence rate of less than 15% [24].

CRITICAL CONSIDERATION OF PREVIOUS STUDIES ON MULTIMODAL TREATMENT OF RECTAL CARCINOMA

A basic question is whether radiotherapy should be applied pre-operatively or postoperatively, either alone or in combination with chemotherapy. In addition, questions relating to radiation dose, application mode, irradiation technique, the selection of chemotherapeutic agents and their combination and doses and the timing of radiotherapy and chemotherapy, still remain to be answered. We have focused on the basic information provided by the most important studies, together with their possible weaknesses, with the aim of identifying promising new approaches against the background of optimal surgical treatment.

Postoperative radio-(chemo-) therapy

Initial non-randomised phase II studies on postoperative radiotherapy [25–28] have, in comparison with a historical control group, revealed a relative decrease in the local recurrence rate of approximately 20% and—according to Tepper—even of 50%. Despite limitations, i.e. the absence of surgical quality control in some studies [25] or the unacceptably high local recurrence rates of up to 49 and 57%, respectively [26, 27], the results reported did provide encouragement for prospective, randomised studies with postoperative radiotherapy alone [8, 9, 29] or combined radiochemotherapy [9, 10, 16, 30–33] and led to the NHI recommendation [34]. In contrast, the ineffectiveness of postoperative radiotherapy alone was definitively demonstrated by GITSG, the NSABP R01, the EORTC study and by Balslev [8, 9, 29, 30].

These results were also confirmed by the only study directly comparing pre-operative with postoperative radiotherapy, which also showed the advantages of neoadjuvant treatment, with asignificantly lower local recurrence rate (12 versus 21%, $P = 0.02$) and lower morbidity and identical postoperative mortality [35].

Different results have been reported in the recently published study by the MRC showing significant ($P = 0.001$) reduction in local recurrence rate from 33% to 20%, but no effects on survival [36]. However, the still too high locoregional recurrence rate with an almost identical 'historical' high ratio of abdomino-perineal excisions to anterior resections, and also the lack of differentiation between patients with curative and those with non-curative operations, raises considerable doubts as to the value of this study.

Thus, the statistically significant advantages—more apparent than real—of a postoperative combined radiochemotherapy, must not be allowed to obscure a number of serious shortcomings in the studies. In general, of course, differences in study design with differing presentation of the data and varying, usually short, follow-up periods, makes a comparative evaluation difficult. Precise information on survival, incidence of recurrence, that is, 5-year survival rates, disease-free survival, 5-year local and distant metastasis rates, are only rarely given. The sensible recommendation by Marsh [37], to indicate local recurrence rates both alone and together with distant metastasis rates for the patients overall, as well as separately for those undergoing curative surgery, was never followed. As a result, it is only with difficulty that conclusions can be drawn—and then only indirectly—as to what constitutes optimal adjuvant measures.

The main criticism is the already mentioned obviously poor quality of the surgical procedure, together with the often complete absence of any quality control by the failure to incorporate a surgery-alone arm [16, 32]. Moreover, the percentage of abdomino-perineal excisions in comparison with anterior resections in all the studies mentioned is, with an average of 53 and 47% [8, 9, 29–31, 36] still almost as high as in the 1960s and 1970s, which contrasts strongly with the current situation (Erlangen, 1979–1985, 39 versus 62%; 1996, 20 versus 80% [6]). A similar criticism also applies to the surgical quality of the studies on pre-operative adjuvant treatment, the corresponding ratio being 72 versus 28% [40, 44–47].

From the radiotherapeutic point of view, we merely wish to note that the postoperative time interval to the start of adjuvant radiotherapy was, in principle, too long and, in addition, in the event of postoperative problems, may be longer, to the detriment of the patient Accordingly, postoperative irradiation is in effect, rarely initiated earlier than 30 [29]—and often 50 and sometimes more than 80 days after surgery [9, 31]. For tumour-biological reasons, such a delay is unfavourable.

Last but not least, the rate of side-effects, in particular the documented late complications, especially the risk of small bowel obstruction, is higher with postoperative radiotherapy [29, 35, 48]. The reason for this is certainly the fact that the small bowel, which after abdomino-perineal excision of the rectum falls into the pelvis, is also irradiated [49]. The situation might possibly be improved by optimising the radiotherapy technique and intra-operative introduction of a net to prevent the descent of the small bowel.

With respect to early complications, in the case of preoperative treatment, an elevated wound infection rate has been described after abdomino-perineal excision of the rectum [46, 50, 51]. An effect on the anastomotic leak rate, however, was excluded [35, 44, 46, 50–52]. Not only in the sole study directly comparing pre- and postoperative irradiation [35, 50] but also in other trials, it was reported that preoperative treatment is better tolerated and more frequently applied in full [8, 9, 31, 44, 46, 51, 52].

Using modern radiotherapeutic techniques applied preoperatively, Påhlman [35, 50] observed a reduction in the previously reported mortality rates, in particular among older patients [46, 52], to almost zero.

Thus, it is not only theoretical advantages such as a more efficient dose–tumour volume ratio and a reduction in tumour cell spread beyond the target volume [53], together with a suspected increase in hypoxy-related resistance to postoperative radiotherapy [54], that militate in favour of neoadjuvant treatment.

Pre-operative radio-(chemo-) therapy

Only when the initially inadequate doses [10, 55–57] were increased did randomised studies report improvements in the local recurrence rate [40, 46, 47]. A small, but non-significant survival benefit was shown only by the EORTC study [44]. An increase in postoperative mortality—although only in over 70-year-old patients—due to elevated individual doses of 5.1 Gy coupled with an inadequate radiotherapeutic technique, was reported only in the Stockholm I study [43]. Using an improved application involving the four-field technique and the same total and individual doses, Påhlman reported no increase in mortality irrespective of age [35, 50]. These data were successfully incorporated directly into the Stockholm II study [39], in which the overall local recurrence rate was significantly reduced from 21 to 10%. This was coupled with a significant prolongation of overall survival ($P < 0.05$) and a reduction in distant metastasis (13% as compared with 19%; $P = 0.024$) [39]. The latest publications from the Swedish Rectal Cancer trial also reported a highly significant ($P = 0.004$) improvement in the 5-year survival to 54%, following adjuvant irradiation, as compared with 48% after surgery alone [41].

The question of whether the benefits of pre-operative irradiation can actually be optimised by simultaneous chemotherapy has not yet been answered. Initial, uncontrolled, clinical experience with the combined use of 5-fluorouracil (5-FU) at the University of Texas, has been highly satisfactory [57, 58]. The only controlled randomised study was carried out by the EORTC and produced disappointing results [59]. Although the local recurrence rate was 15%, the survival rate was lower following radiochemotherapy, as a result of peri-operative and immediately postoperative mortality. However, this study employed a suboptimal overall dose and an inadequate application technique, as well as an unfavourable 5-FU bolus administration. Furthermore, a surgery-alone arm was again lacking.

The initial considerable reservations concerning the possibility of increased postoperative morbidity have, gratifyingly, not been confirmed. An increase in the anastomosis insufficiency rate was never observed. Merely the incidence of perineal wound infection after abdomino-perineal excision of the rectum following pre-operative adjuvant treatment was increased [39, 43, 46]. In our own experience, this complication can be avoided by primary packing of the pelvic wound and leaving it open.

CONCLUSIONS

The studies so far published on pre-operative or post-operative radio-(chemo-) therapy have been carried out without any adequate definition of the surgical procedure and without appropriate quality control. In none of the cases were explicit details given of the procedure applied, together with the criteria to be met with respect to indication, safety margins, excision of mesorectum, lymph node dissection and the actual postoperative situation, for example, margins of clearance achieved and the number of lymph nodes removed. Merely on the basis of the—usually less than accurate—information on local recurrence rates is it possible to estimate the quality of surgery. This is most likely to be achieved by the use of a surgery-alone control arm. However, it must be noted that the local recurrence rates were all unacceptably high—not merely in the groups receiving surgery alone.

The question therefore still remains to be answered of whether, in the light of the currently achievable global local recurrence rates of less than 10% by surgery alone, a further improvement can—as we and others hope—be obtained by adjuvant radiochemotherapy. Our aim must be to support this hypothesis in carrying out further trials. The question then arises as to what constitutes appropriate approaches to the problem. Principally, it has been shown that, assuming proper application, postoperative radiotherapy alone is superior to a combination of postoperative radiochemotherapy and that pre-operative therapy is superior to post-operative treatment.

Currently we are participating in a multicentre study in which a therapy arm comprising surgery followed by radiochemotherapy in accordance with the 1991 NCI recommendation is compared with a second arm involving neoadjuvant radiochemotherapy, surgery and postoperative maintenance therapy. This involves a pre-operative 5-week course of irradiation (50.4 Gy in 28 fractions) combined with 2 cycles of continuous 5-FU infusion and 4 courses of postoperative maintenance drug treatment.

However, we failed to gain support for the incorporation into the study of a control arm comprising surgery alone, since the Review Committee of the German Cancer Society at that time, were of the opinion that this would be unethical—although the points of criticism we advanced then still continue to document the need for a surgical control arm. Admittedly, only institutions achieving a global local recurrence rate of less than 15% were accepted for participation in the study. In addition, stratification of all the surgeons involved has been provided for.

Summarising, it must be said that, in particular, adjuvant radiochemotherapy can reduce the local recurrence rates. Our major criticism is directed against the fact that almost all studies so far lack any adequate quality control of surgical treatment, and that the surgical control arm, when employed, shows unacceptably high local recurrence rates. A considerable number of surgeons are presently capable of achieving global local recurrence rates of 10% and even considerably less, in the absence of adjuvant therapeutic modalities. In none of the study results so far published has a surgical control arm with such local recurrence rates been presented. Thus, the question has yet to be answered as to whether in this situation, adjuvant radiochemotherapy is at all capable of achieving any further improvement. This means that studies investigating this question are urgently required. The protocols of such trials, however, need to stratify the institutions as well as the individual surgeons.

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