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Intra-operative irradiation (IORT) for primary advanced and recurrent rectal cancer: a need for randomised studies

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Abstract

The aim of this study was to determine the impact of intra-operative irradiation (IORT) combined with pre-operative external beam irradiation (EBRT) and surgical resection in patients with locally advanced primary or recurrent rectal cancer. 64 patients with locally advanced primary cancer and 104 with recurrence had EBRT (46–50 Gy) before surgery. 80 patients received IORT (median dose 15 Gy energy 12 MeV). 80 patients had R0 resections, 47 R1 and 41 R2 resections. More R1 resections were performed in the IORT group, more R0 and R2 resections in the non-IORT group. Median follow-up was around 22 months. 146 patients were resected, 22 had exploratory laparotomy. The cumulative overall survival was similar for both the IORT and non-IORT groups. 5-year survival for primary cancers was 48% versus 28% for recurrences. No R2 resections survived 3.5 years. 5-year-survival for R0 resections was nearly 60% and around 30% for R1 resections. The survival curves of the patients given and not given IORT treatment was not statistically different when R0, R1 and R2 resections were analysed separately. IORT did not seem to influence the local recurrence rate when R0 and R1 resections were analysed separately or in a multivariate analysis. The IORT and non-IORT groups were not identical with regard to type of cancer and R-stage. Still the lack of an identifiable impact of IORT suggests that there is a need for randomised studies of the IORT effect.

Keywords: IORT; Advanced rectal cancer; Survival; Local recurrence

1. Introduction

Rectal carcinoma is a frequent cancer type in many parts of the world. Unfortunately, isolated recurrences confined to the pelvis are a common problem after resection of locally advanced rectal carcinomas. Pre-operative external beam radiotherapy (EBRT) has been shown to reduce the local recurrence rate after operation for locally advanced rectal cancer [1–4]. The radiation dose required depends on the tumour burden. Thus the commonly applied irradiation doses will be more effective on microscopic than macroscopic cancer [5,6]. Higher radiation doses can be given to a tumour by combining EBRT with intra-operative radiotherapy (IORT). IORT is considered an ideal boost technique for increasing the dose within a restricted area without introducing significant toxicity, since radiosensitive structures such as small bowel and ureter can easily be kept out of the field. This technique has been found to improve the local control and survival in several studies on locally advanced primary or recurrent rectal cancers [6,7]. However, these studies all have historical control groups.

At our referral hospital we have performed IORT since 1990 as a supplement to EBRT for locally advanced primary and recurrent rectal cancer. Some patients have, for various reasons, not received IORT. We have compared the results in the groups given and not given IORT related to the R-stage of surgical resection in order to estimate the effect of IORT.

2. Patients and methods

Patients with locally advanced primary adenocarcinoma of the rectum or local recurrence of adenocarcinoma of the rectum were included in this study. The

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primary tumours were primarily irresectable and fixed to the neighbouring structures, evaluated either by digital examination or by a computed tomography (CT) scan. The local recurrences were also fixed to the surrounding structures in the vast majority of cases, but this was not a prerequisite for inclusion. All cases have been given multimodal treatment with radiotherapy and surgery. Patients with bony destruction or with metastases outside the pelvis were not included. Moreover, the ECOG performance status was 0–2 in eligible patients who had no medical contraindications to surgery or radiotherapy. Patients with previous radiotherapy to the pelvis were excluded.

Prior to inclusion, the patients were submitted to a CT scan of the pelvis, ultrasound of the liver, chest X-ray as well as digital and proctoscopic examination if possible. When infiltration in the ureter, bladder or prostate was suspected, cystoscopy and urography was performed. General blood chemistry and serum carcinoembryonic antigen (CEA) was measured in all patients.

Preoperative radiotherapy was usually given by a three-field technique with one posterior and two lateral portals. The superior and inferior borders of the treatment volume were the L5–S1 space and the perinaeum, respectively. Lateral borders of the posterior/anterior (PA) field were 1 cm outside the true bony pelvis. The posterior and anterior borders of the lateral fields were 1 cm behind the sacrum and the centre of the femoral heads, respectively. With massive tumour infiltration in the vagina, prostate or bladder or with suspicion of lymph node involvement anteriorly in the pelvis, a two-field technique was used. The patients were treated in the prone position and ideally had a full bladder. In general, a dose of 46 Gy with a daily fraction of 2 Gy was given to the total volume, but in later years an additional boost dose of 2 Gy twice was given to the tumour plus 2 cm of the margins (i.e. the clinical target volume, CTV). If a split course (2–3 weeks split) was necessary, due to skin or intestinal toxicity, this was compensated by additional fractions (usually two). Photon energies of 10–16 MV were used. No chemotherapy was given.

Evaluation was performed 4 weeks after end of preoperative external radiotherapy by the same procedures as before radiotherapy. If no contraindication to radical surgery and IORT was present (no disease outside the irradiation volume, except for a single liver or lung metastasis that could later be resected for cure), the patient underwent attempted radical surgery. The intention was to perform the operation 4–8 weeks after cessation of radiotherapy. This time interval was considered necessary to make the patient fit for surgery and to operate in an optimal period regarding oedema and fibrosis after radiotherapy. For various reasons the median time lag was longer than intended, 8 weeks, varying from 4 to 14 weeks. All major surgery was performed in the operating room. Five surgeons performed the operations, however the majority of operations were performed by the same surgeon. Frozen sections were taken according to the discretion of the surgeon. It was often difficult to decide the exact area of perirectal infiltration. In 14/47 (30%) R1 cases and 26/41 (63%) R2 cases IORT was not given. In contrast, 32/80 (40%) R0 cases received IORT.

If IORT was considered indicated (narrow margins, as determined macroscopically by the responsible surgeon, or microscopic or macroscopic residual disease, with no cancer outside an IORT field), an appropriate cone was selected by the oncologist and surgeon, the wound closed temporarily, and the patient transported to the radiotherapy room. Until February 1993 a hard-docking procedure was employed. Thereafter, a soft-docking optical-based procedure was used. The linear accelerator provided electron energies in the range 6–20 MeV. The electron energy was selected on the basis of depth of tissue to be irradiated (median 12 MeV, range 9–15). A dose of 15 Gy specified at the 90% isodose surface, was given if no macroscopic tumour tissue remained, and 17 (range 5–20) Gy was given if macroscopic tumour tissue was left. Cone sizes in the range of 40–90 mm, with bevels of 0, 30 or 40° were applied. The target volume for IORT was the area at highest risk, i.e. the area where the tumour was fixed to sacrum or lateral pelvic wall or where macroscopic or microscopic tumour tissue remained. After the IORT, surgery was finished in the radiotherapy room. Patients with disseminated disease were given standard 5-FU and leucovorin chemotherapy.

The resections were classified according to R-stage: R0, no microscopic cancer left; R1, microscopic cancer in the resection border; R2, macroscopic cancer left.

2.1. Follow-up

Patients were seen every 3 months the first 2 years and every 6 months thereafter for another 3 years. After 5 years the patients were seen on a yearly basis. At follow-up a clinical examination, CT scan of the pelvis, ultrasound of the liver, X-ray of the lungs and serum CEA determination were performed. If symptoms or sign of recurrence appeared, a biopsy for histology or cytology was performed if possible. A recurrence was considered local if it appeared inside the pelvis.

Survival was calculated from the time of the present surgery. Survival and disease-free survival curves were prepared with the Kaplan–Meier product-limit method, using the SPSS statistical software. Statistical differences between curves were calculated with the logrank test. Multivariate analysis was performed with a Cox proportional hazards model with survival and local relapse-free survival as endpoints.

Table 1
Patients characteristics and overall treatment

	IORT given *n* (%)	IORT not given *n* (%)	Total *n* (%)
No. patients treated	80 (48)	88 (52)	168 (100)
Age (years)			
Median (range)	64 (34–80)	68 (39–83)	
Sex			
Male	49 (61)	45 (51)	94 (56)
Female	31 (39)	43 (49)	74 (44)
Observation time (months)			
Median (range)	25 (1–86)	21 (1–76)	
Tumour			
Primary	20 (25)	44 (50)	64 (38)
Recurrent	60 (75)	44 (50)	104 (62)
Preoperative radiation dose (Gy)			
Median (range)	46 (40–56)	46 (50–64)	
Surgery			
R0 stage	32 (40)	48 (55)	80 (48)
R1 stage	33 (41)	14 (16)	47 (28)
R2 stage	15 (19)	26 (30)	41 (24)
Surgery + tumour combined			
R0 stage primary/recurrent	11/21	28/20	39/41
R1 stage primary/recurrent	7/26	9/5	16/31
R2 stage primary/recurrent	2/13	19/7	21/20

3. Results

Patient characteristics and irradiation treatment are given in Table 1. Following evaluation 4 weeks after radiotherapy 168 patients were submitted to surgery.

The sex distribution, median age and EBRT was similar in the groups given and not given IORT. The observation time was slightly longer in the IORT group, the longest being 86 months. The groups were not identical with regard to cancer and surgery. In the IORT group 25% of the patients had primary cancer versus 50% in the non-IORT group. Both R0 and R1 stage resections were approximately 40% in the IORT group versus approximately 55% and 16% in the group not given IORT.

The reasons for not giving IORT are stated in Table 2. A surgically considered adequate resection margin of a mobile tumour was the cause in 57% and extrapelvic lymph node or peritoneal metastases in 24%. In a few cases (2%) preoperative bleeding prevented the IORT treatment. In 5% of the total group of 168 patients the cancer was fixed to the large vessels in the pelvis and therefore considered technically inoperable. Various other causes were given in a few more cases.

3.1. Surgery

The surgical procedures performed are shown in Table 3. We have been reluctant to perform a low anterior resection in cases with a relatively high probability of local recurrence. Therefore, there are more resections of this kind in the group not given IORT. In cases with high risk of recurrence above the pelvic floor we have more recently performed Hartmann's procedure just above the anal canal. With a cancer adherent to the base of the bladder or prostate a cystectomy or cystoprostatectomy was performed. In one such patient with hyperplasia of the prostate we did a low anterior resection and radical prostatectomy with cystouretrostoma.

3.2. Complications

The major complications are given in Table 4. The only postoperative mortality (within one month of surgery) was a patient not given IORT during pelvic excenteration. He died suddenly 12 days after surgery with a clinical diagnosis of pulmonary embolus. Post-

Table 2
Reasons for not giving IORT

	No. of patients
Disseminated cancer	21 (24)
Preoperative bleeding	2 (2)
Fixed cancer	8 (9)
Unnecessary	50 (57)
Other reason	7 (8)
Total	88 (100)

Table 3
Surgical procedures

	No. of patients		
	IORT given *n* (%)	IORT not given *n* (%)	Total *n* (%)
	n = 80	*n* = 88	*n* = 168
Rectal procedure			
Abdominoperinaeal resection	33 (41)	19 (22)	52 (31)
Low anterior resection	7 (9)	25 (28)	32 (19)
Hartmann's procedure	13 (16)	14 (16)	27 (16)
Tumour resection	24 (30)	11 (14)	35 (21)
Exploratory laparotomy	3 (4)	19 (24)	22 (13)
Additional procedures			
Small bowel resection	20 (25)	13 (16)	33 (20)
Cystectomy	16 (20)	13 (16)	29 (17)
Bladder resection	3 (4)	2 (3)	5 (3)
Prostatectomy	16 (20)	9 (11)	25 (15)
Vesiculectomy	28 (35)	17 (21)	45 (27)
Hysterectomy	10 (13)	9 (11)	19 (11)
Vaginal resection	10 (13)	19 (24)	29 (17)

Table 4
Postoperative complications

	No. of patients		
	IORT given *n* (%)	IORT not given *n* (%)	Total *n* (%)
	(*n* = 80)	(*n* = 88)	(*n* = 168)
Mortality	0 (0)	1 (1)	1 (1)
Bowel leakage	3 (4)	8 (9)	11 (7)
Urinary leakage	4 (5)	4 (5)	8 (5)
Deep abscess	17 (21)	17 (19)	34 (20)
Septicaemia	4 (5)	3 (3)	7 (4)
Wound infection	2 (3)	8 (9)	10 (6)
Urinary infection	24 (30)	15 (17)	39 (23)
Pneumonia	4 (5)	4 (5)	8 (5)
Late perinaeal healing	7 (9)	6 (64)	13 (38)
Deep venous thrombosis	3 (4)	2 (2)	5 (3)
Pulmonary embolus	0 (0)	1 (1)	1 (1)

mortem examination was denied. Otherwise a number of major complications have appeared. None of these seem to be more frequent after IORT treatment with the exception of urinary infections.

3.3. Survival

The crude estimated 5-year survival rate was approximately 35% for both IORT and non-IORT groups (Fig. 1). Survival steadily declined from the time of operation and continued to do so after 5 years.

The 5-year survival was 48% for the primary cases versus 28% for patients with recurrences. This difference was not statistically significant (logrank 0.3667) (Fig. 2).

Not unexpectedly survival correlated with the stage of surgical resection (Fig. 3). After a R0 resection the estimated 5-year survival was nearly 60% versus approximately 30% for R1 resections. The 5-year survival of the combined R0–R1 stages (grossly resected) was nearly 50%. None of the R2 resections survived 3.5 years (logrank 0.0000).

In addition, for all three separate R-stages the survival curves were very similar for the IORT versus the non-IORT group (Figs. 4, 5, 6). Inclusion of R-stage, IORT and primary or recurrent cancer in a multivariate analysis did not show any significant effect of IORT on survival ($P = 0.99$).

3.4. Local recurrence

With regard to local recurrence there seems to be a difference between primary and recurrent cases as nearly 80% were recurrence-free at 5 years in the primary group versus 55% in the recurrent group (Fig. 7). However, the difference between the curves did not reach statistical significance (logrank 0.0941).

When the R-stages were analysed separately, the 5-year recurrence-free rate for patients with R0 stage in the IORT group was approximately 65% versus 85% in the non-IORT group (Fig. 8). This difference was not

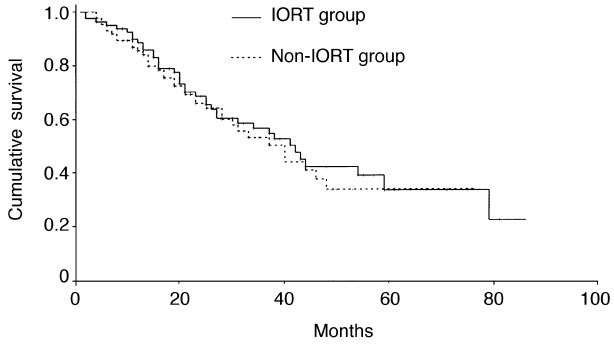

Fig. 1. Actuarial survival of 168 patients with primary locally advanced or locally recurrent rectal cancer with regard to IORT treatment. 80 patients in IORT (—), 88 patients in non-IORT group (·····).

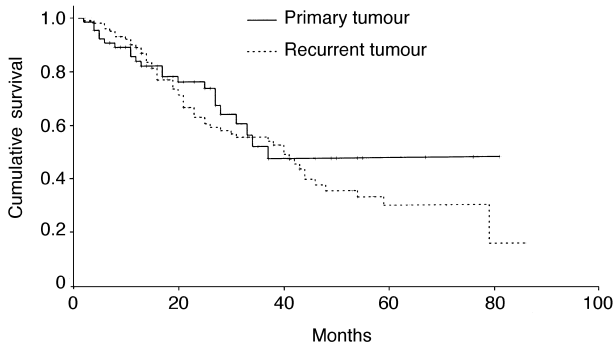

Fig. 2. Actuarial survival of 168 patients with regard to type of cancer. 64 patients with primary advanced (—), 104 patients with recurrent cancer (·····).

statistically significant (logrank 0.1396). In R1 stage patients, the recurrence curves were nearly identical for the two IORT groups with a 5-year local recurrence-free rate of approximately 55% (Fig. 9). Inclusion of R-stage, IORT and primary or recurrent cancer in a multivariate analysis showed a significantly lower local relapse in the non-IORT group ($P = 0.04$).

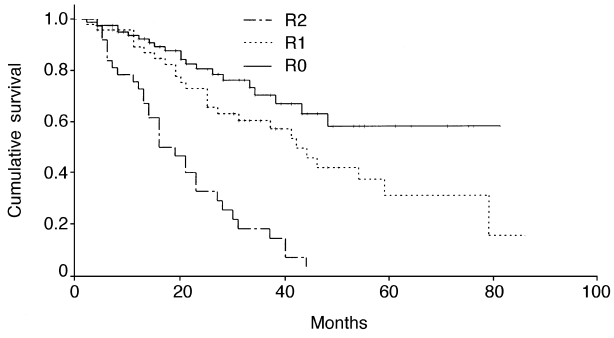

Fig. 3. Actuarial survival of 168 patients with regard to R-stage. 80 patients R0 (—), 47 patients R1 (·····), 41 patients R2 stage (–·–·–).

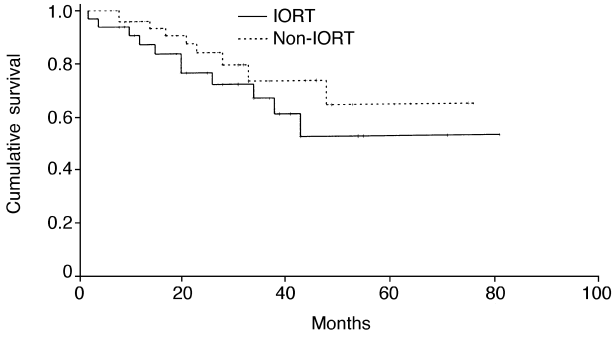

Fig. 4. Actuarial survival of 80 R0 stage patients with regard to IORT treatment. 32 patients in IORT (—), 48 patients in non-IORT group (·····).

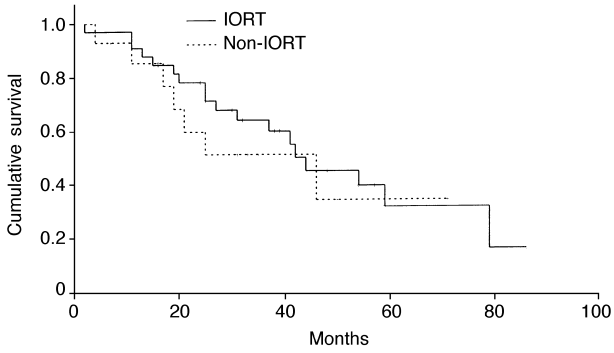

Fig. 5. Actuarial survival of 47 R1 stage patients with regard to IORT treatment. 33 patients in IORT group (—), 14 patients in non-IORT group (·····).

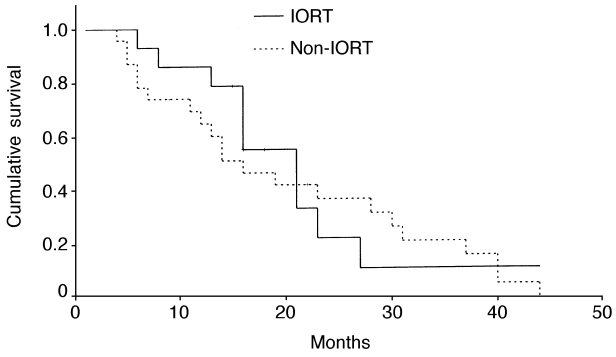

Fig. 6. Actuarial survival of 41 R2 stage patients with regard to IORT treatment. 15 patients in IORT group (—), 26 patients in non-IORT group (·····).

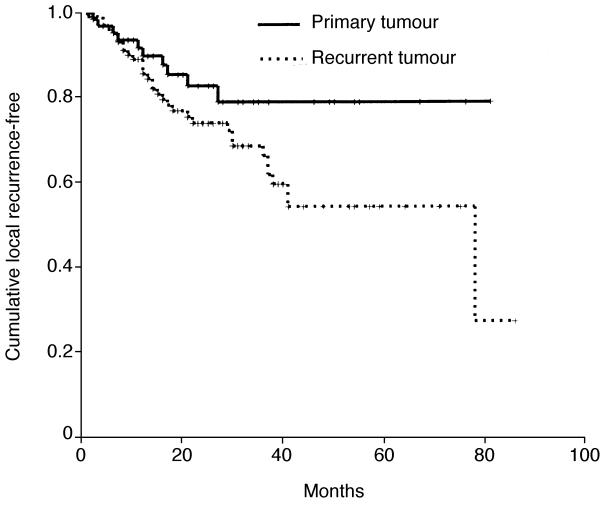

Fig. 7. Actuarial local control in 168 patients with regard to type of cancer. 64 patients with locally advanced primary (—), 104 patients with locally recurrent cancer (·····).

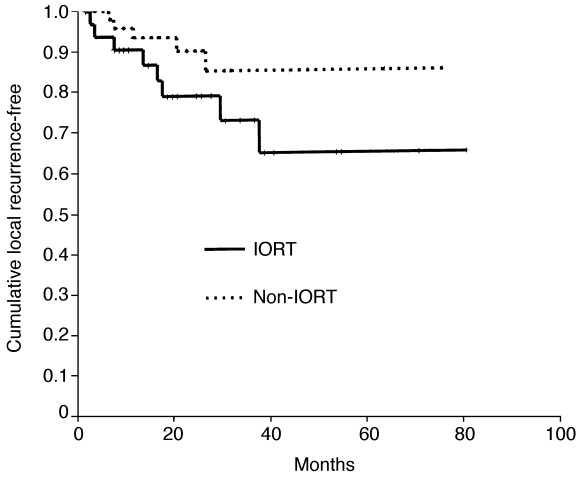

Fig. 8. Actuarial local control in 80 R0 stage patients with regard to IORT treatment. 32 patients in IORT (—), 48 patients in non-IORT group (·····).

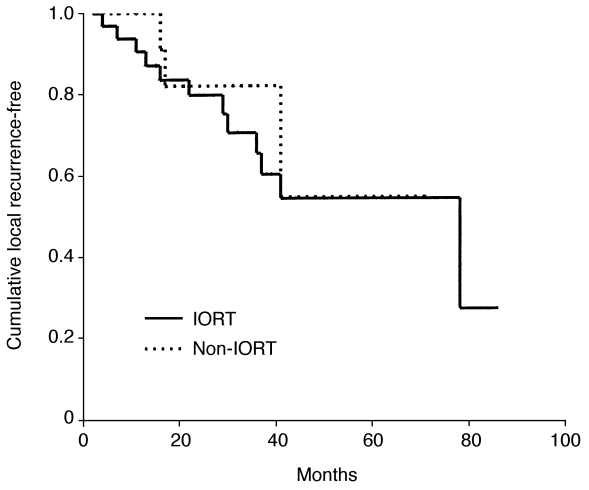

Fig. 9. Actuarial local control in 47 R1 stage patients with regard to IORT treatment. 33 patients in IORT (—), 14 patients in non-IORT group (·····).

4. Discussion

From a theoretical point of view it seems very likely that there will be a clinical beneficial effect of IORT — although single fraction irradiation is radiobiologically inferior to fractionate radiotherapy due to a reduced therapeutic ratio and lack of interfraction tumour re-oxygenation [8]. In view of the expected effect, major centres find it difficult to perform a randomised study on IORT treatment of rectal cancer. The procedure is also resource demanding and if effective might be applied in the majority of approximately 10% of cancers fixed at the time of diagnosis, as well as in recurrent cases. To our knowledge, randomised studies have only been performed in a small series of pancreatic cancer [9] and gastric cancer [10]. None of these studies have shown an effect on survival although there was possibly an effect on local recurrence. A randomised study on T3–T4 colorectal cancers has been started in France [11]. However to our knowledge, no results have been published from this study. It therefore seems important to establish whether the effect of IORT on rectal cancer is major, thereby causing randomisation to be an unethical task.

Several authors have claimed to show an effect of IORT on primary advanced and recurrent rectal cancers compared with historical controls [6,7,12,13]. Most of these papers originate from a few centres. In addition, the number of patients included in each group being compared is modest in many of the papers. It is also difficult to identify clearly the local extension of a 'locally advanced primary' or 'recurrent' rectal cancer. Thus, selection of patients may differ. The parameters presented, as well as the follow-up time, varied. These results may therefore not be easily compared.

In a previous report, we suggested that the effect of IORT on primary advanced or recurrent rectal cancer may not be a major one [14]. Several studies have shown that the effect of IORT depends on the amount of residual cancer tissue at irradiation [5,6,13,15]. The effect of IORT may therefore vary with the R-stage of the resection. Possibly the effect should be easiest to demonstrate in R1-resections with a relatively high expected local recurrence rate. After R2 resection where macroscopic cancer is left, the effect might be more difficult to evaluate.

In this study, no statistically significant difference in actuarian 5-year survival of the IORT and non-IORT groups either in the total group or R-stage subgroups was found. Thus the IORT and non-IORT groups should be roughly comparable even though the primary/recurrent ratio was 25/75% in the IORT group versus 50/50% in the non-IORT group. Inclusion of R-stage, IORT and primary or recurrent cancer in a Cox proportional hazards model showed no significant effect in favour of IORT on either survival or local recurrence. The present results therefore support our previous suggestion that the effect of IORT is not extensive.

In previous studies, the effect on survival of combined treatment including IORT has varied considerably. In primary advanced cases, the estimated 5-year survival has been reported as 43% in 42 rectal cancer patients [6], 53% in 15 patients [7] and 48% in 56 colorectal patients [15]. Thus our overall survival rate of 45% in 64 patients with or without IORT seems comparable with these reported IORT-treated groups. A recent study reports 65% actuarial 5-year disease-specific survival in 45 patients with R0 resections, 40% in 21 patients with R1 resections and 14% in R2 resections. In 66 patients with R0 resections who did not receive IORT the 5-year survival was 80% [16]. These results in IORT groups are similar to our mixed IORT/non-IORT groups with regard to R0–R1 resections though better than our R2 resections. In fact, their results did not indicate any effect of IORT on R0 resections either.

For recurrent cases, the estimated 5-year survival has been reported as 23% in 36 patients [7], 20% in 123 patients [17], 37% in 55 patients [18] and 58% in 33 patients with R0–R1 resections [12]. Our 5-year survival of 25% in 104 patients given or not given IORT is therefore within the reported figures for IORT-treated patients.

A recent study on a mixture of primary and recurrent cases only included 22 grossly resected patients [13]. Their estimated 5-year survival of 64% seems better than our nearly 50% of 127 patients. However, they included more primary rather than recurrent cases whilst our study included the opposite.

The local control after IORT in primary advanced cases has been given as 84% in 56 patients [15], 89% in 45 patients with R0 resections and 68% in 21 patients

with R1 resections, as well as 80% in 66 patients with R0 resections without IORT [16]. Our 5-year local control of primary advanced cancer with mixed IORT treatment of 78% seems comparable.

In recurrent cases with R0–R1 resections, local control at 5 years was 42% in 27 patients [18], and, with a median follow-up of 26 months, it was 64% in 33 patients [12]. Thus, with regard to local control, our patient group with and without IORT treatment and with a 5-year local control of 40% fared similarly to these reports on IORT-treated patients.

5. Conclusion

When comparing our R-stage IORT and non-IORT patients, with a mixture of primary and recurrent cases, to reports of the IORT-treated patients, our patients seem to do slightly worse than the reported primary advanced groups and slightly better than the reports on recurrent cancer.

Our results suggest that it will be ethical and that there is a need to perform randomised studies to evaluate properly the effect of IORT on primary advanced and recurrent rectal cancers. Our view is in accordance with that presented in a previous [7] and a recent publication [13].

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