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Original research article

Gender-related significance of time interval between radiotherapy and surgery in hypofractionated preoperative radiotherapy for rectal cancer patients' survival

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ARTICLE INFO

Article history:
Received 17 June 2015
Received in revised form
30 October 2015
Accepted 21 January 2016
Available online 20 February 2016

Keywords:
Rectal cancer
Break in the treatment
Preoperative radiotherapy
Patients' survival
Overall treatment time

ABSTRACT

Aim and background: An optimal break between radiotherapy (RT) and surgery in short-course of RT (SCRT) for locally advanced rectal cancer is not clearly established.

The aim of the study was to investigate the influence of the break in the preoperative SCRT and overall treatment time (OTT) for locally advanced rectal cancer patients (whole group and male/female subgroups) on patients overall survival (OS), recurrence-free survival (RFS), metastasis-free survival (MFS).

Materials and methods: 131 patients were treated with SCRT (5 Gy/5 days), followed by surgery 3–53 days later. Break was calculated as the time interval between the end of irradiation to surgery and OTT as time interval from the beginning of RT to surgery.

Results: Mean break was 21.5 (range 3–53.0) days and mean OTT was 26.5 (range 7–58.0) days. In univariate analysis, a break longer than 15 days and OTT >23 days were negative prognostic factors for OS for all patients, and particularly for the male patients' subgroup. RFS was non-significantly higher ($P = 0.066$) for patients treated with a break ≤15 days and OTT ≤23 days ($P = 0.099$), irrespectively of patients' sex. Patients treated with a break longer than 15 days and OTT >23 days had non-significantly lower level of MFS than those treated with a shorter break ($P = 0.269$) and OTT ≤23 days ($P = 0.498$).

Conclusion: In SCRT, a break in the treatment longer than 15 days, especially in the male patients subgroup, should be avoided, because it negatively affects patients' survival.

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http://dx.doi.org/10.1016/j.rpor.2016.01.004

1. Background

Currently, there is no consensus on the definition of early rectal cancer, and the optimal treatment for non-advanced rectal cancer remains a topic of debate.[1] Two modalities of preoperative radiotherapy (RT) have been used in treating localized (T2-4 and N0 M0, locally resectable) rectal carcinoma: either short course RT (SCRT) with 5×5 Gy followed by immediate surgery or long course radio-chemotherapy with 50.4 Gy in 25–28 fractions with surgery after a 4–8 weeks' break.[2] The Stockholm III study addressed the question of the optimum interval between RT and surgery and compared the complication rate after SCRT and surgery given in one of the three schedules: SCRT with 25 Gy in 5-Gy fractions followed by surgery within 1 week, SCRT with 25 Gy in 5-Gy fractions followed by surgery 4–8 weeks later, or longer-course RT (25×2-Gy fractions) followed by surgery 4–8 weeks later. The study showed that SCRT and immediate surgery tended to be associated with more postoperative complications than the other schedules, and the authors suggest that surgery may be performed either within 5 days after the initiation of SCRT or 4 weeks afterwards.[3]

In radiotherapy, it is obvious that overall treatment time (OTT), that is the time interval from the beginning of RT to surgery is an important factor influencing the efficacy of RT.[4] Therefore, in treatment comprising SCRT, OTT might have an influence on patients' survival, as the accelerated repopulation of tumor clonogenic cells surviving irradiation is considered to be the reason for reduced local control when treatment time is prolonged without dose compensation.[5]

In our earlier study,[6] we suggested that in rectal cancer treated with SCRT and delayed surgery (longer than 15 days after RT), correlation between pretreatment Ki-67, Ku70, and BCL-2 proteins expression and pTNM (at surgery) might indicate tumor progression during the break.

2. Aim

The aim of the study was to check how break in the treatment and OTT may influence patient's survival. The results may provide the answer to the question whether in SCRT longer breaks in the treatment can be used.

3. Materials and methods

3.1. Patients

One-hundred and thirty-one patients with rectal carcinoma who underwent preoperative radiation between November 2003 and January 2006 were included in the study. Patients were qualified either for SCRT (5 Gy/5 days) and surgery about 1 week after RT or for SCRT and a 4-week interval before surgery. Because the interval between RT and surgery appeared to be longer than planned, a mean break in the treatment lasted from 3 to 53 days. Inclusion and exclusion criteria and detailed information on irradiation and surgery were given earlier.[7] Postoperative chemotherapy (CHT; fluorouracyl and levamisole) was given to 39 (29.8%) patients (29 males and 10 females). Tumors were classified according to the World Health Organization classification of intestinal carcinoma[8] and staged according to the AJCC TNM 2002 classification.[9] The protocol was approved by the local Ethical Committee of the Regional Medical Chamber in Cracow and each patient had given their written consent.

3.2. BED calculations

3.2.1. Defining parameters chosen

Biologically effective dose for tumor and early reactive tissues (BED_{10}) were calculated according the following formula[10]:

$$BED_{10} = nd(1 + d/\alpha/\beta) \quad (1)$$

where for $\alpha/\beta = 10$ Gy, d is the dose fraction and $n \times d$ is the total dose. For the calculation of biologically effective doses for late reacting tissues (BED_3), in the BED formula for $\alpha/\beta - 3$ Gy was used.

The normalized total dose (NTD), i.e. the dose given in standard fractionation using the dose per fraction of 2 Gy, which has the same effect (survival fraction) as the dose given with nonstandard dose per fraction (d), was calculated from the following equation:

$$NTD = D(\alpha/\beta + d)/(\alpha/\beta + 2),$$

where D denotes total physical dose given with a fraction size of d Gy.

3.3. Statistical methods

Statistical analysis was performed with STATISTICA vs.9. For determination of mean values for variables and standard errors of means (SE), descriptive statistics were used. Intergroup differences in the mean values were tested with one-way ANOVA test or Student's t-test. Associations between investigated categorical parameters and clinicopathological variables were evaluated by Pearson's Chi^2 test. Differences were considered significant at P value of <0.05. The survival function was estimated using the Kaplan–Meier method.[11] The difference in survival rates between groups was assessed by the log-rank test. Break between RT and surgery was calculated as the interval between the last day of RT to surgery. Survival was measured from surgery to death or last follow-up. In univariate analysis, 15 days for break between RT and surgery, and median OTT of 23 days were the first significant time-points in log-rank test, and therefore were used as cut-off points.

4. Results

A total of 131 patients were included in the study. Mean break in the treatment was 21.5 (range 3–53.0) days and mean OTT was 26,5 (range 7–58.0) days. There were 87 males and 44 females with a mean age for the entire group of 61.2 (range 30–82) years (Table 1). At the time of recruitment, no statistical differences between the two groups were found for prognostic factors such as age, tumor stage or histological grade, interval between RT and surgery, and type of surgery,

Table 1 – A comparison of clinicopathological and treatment characteristics for male and female rectal cancer patients treated with SCRT and short or long break before surgery.

Characteristics	N	Sex		P-value	Break		P-value
		Men	Women		≤15 days	>15 days	
Mean age	131	87[a]	44	P = 0.861	61	70	P = 0.419
(range) (years)		61.3 (30–77)	61.0 (43–82)		60.4 (30–82)	61.9 (43–77)	
Clinical stage (AJCC) TNM							
I	33	24 (27.6%)[b]	9 (24.0%)		13 (21.3%)	20 (28.6%)	
II	80	54 (62.1%)	26 (59.1%)	P = 0.130	39 (63.9%)	41 (58.6%)	P = 0.631
III	18	9 (10.3%)	9 (20.4%)		9 (14.8%)	9 (12.8%)	
Clinical tumor category							
cT2	34	25 (28.7)	9 (20.5%)		14 (23.0%)	20 (28.6%)	
cT3	90	59 (67.8)	31 (70.4%)	P = 0.280	44 (72.1%)	46 (65.7%)	P = 0.729
cT4	7	3 (3.4%)	4 (9.1%)		3 (4.9%)	4 (5.7%)	
Clinical node category							
cN0	113	78 (89.7%)	35 (79.5%)		52 (85.2%)	61 (87.2%)	
cN1	17	9 (10.3%)	8 (18.2%)	P = 0.157	9 (14.8%)	8 (11.4%)	P = 0.559
cN2	1	0 (0.0%)	1 (2.3%)		0 (0.0%)	1 (1.4%)	
Pathological stage (AJCC) pTNM							
0	6	4 (4.6%)	2 (4.5%)		0 (0.0%)	6 (8.6%)	
1	56	40 (46.0%)	16 (36.4%)		27 (44.3%)	29 (41.4%)	
2	21	11 (12.6%)	10 (22.7%)	P = 0.591	13 (21.3%)	8 (11.4%)	P = 0.069
3	43	29 (33.3%)	14 (31.8%)		20 (32.8%)	23 (32.9%)	
4	5	3 (3.4%)	2 (4.5%)		1 (1.6%)	4 (5.7%)	
Pathological tumor category							
pT0	6	4 (4.6%)	2 (4.5%)		0 (0.0%)	6 (8.6%)	
pT1	10	6 (6.9%)	4 (9.1%)		4 (6.6%)	6 (8.6%)	
pT2	50	38 (43.7%)	12 (27.3%)	P = 0.041	25 (41.0%)	25 (35.7%)	P = 0.212
pT3	57	31 (35.6%)	26 (59.1%)		28 (45.9%)	29 (41.4%)	
pT4	8	8 (9.2%)	0 (0.0%)		4 (6.5%)	4 (5.7%)	
Pathological node category							
pN0	84	56 (64.4%)	28 (63.6%)		41 (67.2%)	43 (61.4%)	
pN1	22	16 (18.4%)	6 (13.7%)	P = 0.652	8 (13.1%)	14 (20.0%)	P = 0.574
pN2	25	15 (17.2%)	10 (22.7%)		12 (19,7%)	13 (18.6%)	
Histological grade							
G1	33	19 (21.8%)	14 (33.3%)		10 (16.4%)	23 (33.8%)	
G2	93	66 (75.9%)	27 (64.3%)	P = 0.203	48 (78.7%)	45 (66.2%)	P = 0.020
G3	3	2 (2.3%)	1 (2.4%)		3 (4.9%)	0 (0.0%)	
OTT (days)	131	87	44	P = 0.246	61	70	–
Mean (range)		25.6 (8.0–50.0)	28.3 (7.0–58.0)		14.4 (7.0–20.0)	37.0 (21.0–58.0)	
Interval between RT and surgery (days) Mean (range)	131	87 20.6 (3.0–45.0)	44 23.3 (3.0–53.0)	P = 0.242	61 9.4 (3.0–15.0)	70 32.0 (16.0–53.0)	–
Type of surgery							
Abdominoperineal excision	55	41 (47.1%)	14 (31.8%)	P = 0.094	27 (44.3%)	28 (40.0%)	P = 0.622
Anterior resection	76	46 (52.9%)	30 (68.2%)		34 (55.7%)	42 (60.0%)	
Patients' survival (months) Mean (range)	131	87 53.4 (4.3–142.0)	44 49.8 (1.9–105.0)	P = 0.419	61 56.5 (4.3–142.0)	70 48.4 (1.9–100.0)	P = 0.058
Time to recurrence (months) Mean (range)	18	10 22.4 (8.5–49.0)	8 16.2 (7.0–30.0)	P = 0.263	5 21.0 (7.0–49.0)	13 19.1 (8.5–33.0)	P = 0.757
Time to metastasis (months) Mean (range)	26	16 15.1 (1.0–36.0)	10 22.3 (3.0–43.0)	P = 0.408	10 21.9 (4.0–36.0)	16 15.4 (1.0–43.0)	P = 0.183

[a] Number of cases.
[b] Percentage of cases within the subgroups.

except pathological tumor category (Table 1). In clinicopathological characteristics of the investigated group, only the grade differed between subgroups treated with the SCRT with a short and long break (Table 1).

Before RT, in 18 (13.7%) out of 131 patients nodule involvement was found clinically (cN stage) and the percentage was similar in patients treated with a break shorter or longer than 15 days (14.8% vs. 12.8%) (Table 1). When pN stage was

Table 2 – The association between the interval between radiotherapy and surgery and number of involved nodules in rectal cancer patients or incidence of local recurrence and metastases.

Interval between RT and surgery	cN stage		pN stage		Local recurrence	Metastases
	cN0	cN1-2	pN0	N1-2		
≤7 days	21[c]	1 (4.5%)[a]	14	8 (36.4%)	3[c] ((16.7%)[b]	6 (23.1%)
8–15 days	31	8 (20.5%)	27	12 (30.8%)	2 (11.1%)	4 (15.4%)
16–30 days	14	3 (17.6%)	9	8 (47.0%)	2 (11.1%)	3 (11.5%)
31–40 days	42	6 (12.5%)	29	19 (39.6%)	11 (61.1%)	12 (46.1%)
>40 days	5	0	5	0	0	1 (3.8%)
All	113	18 (13.7%)	84	47 (35.9%)	18 (100%)	26 (100%)

[a] Percentage of involved nodules in a row.
[b] Percentage of cases in the group.
[c] Number of cases.

assessed at surgery, nodule involvement was indicated in 47 (35.9%) patients. Percentage of involved nodules (32.8%) in patients treated with a break ≤15 days did not differ from the incidence (38.6%) measured in patients treated with a break longer than 15 days (Table 2).

Local recurrence (LR) rate in the entire patient group was 13.7% (18/131) and occurred after a mean period of 19.7 ± 2.5 months after surgery. The incidence of LR found in patients treated with SCRT with a short break was lower 5/18 (27.8%) than those indicated in patients treated with a longer break – 13/18 (72.2) (Table 2). Metastases occurred in 26 (19.8%) patients: 19 (73.1%) in the liver, four (15.4%) in the lungs, one (3.8%) in the cerebellum and two (7.7%) in the nodules in mean time of 17.9 ± 2.3 months after surgery. In patients treated with SCRT with a break ≤15 days, 38.5% (10/26) metastases were indicated whereas in patients treated with a longer break, 61.5% (16/26) metastases were found (Table 2).

4.1. *BED calculations*

The mean interval from RT to surgery (break) was 21.5 days (3.0–53.0). OTT ranged from 7 to 58 days, and the mean interval was 26.5 days. BED_{10} was calculated according to formula (1):

$$\text{Standard } BED_{10} = n \times d(1 + d/10) = 5 \times 5(1 + 5/10) = 37.5 \text{ Gy.}$$

The biological equivalent of SCRT for conventionally fractionated RT would be:

Normalized total dose in 2 Gy fractions:

$$NTD = D \times \left[\frac{(\alpha/\beta + dx)}{(\alpha/\beta + 2 \text{ Gy})} \right] = 31.2 \text{ Gy}$$

For SCRT (5 × 5 Gy) BED_{10} is equal to 37.5 Gy, and NTD equals 31.2 Gy.

BED_3 for late effects ($\alpha/\beta = 3$ Gy) is equal to $5 \times 5 (1 + 5/3) = 66.7$ Gy.

4.2. *Overall survival*

Within more than 10-year follow-up, 96 (73.3%) out of 131 patients were still alive and 35 (26.7%) died from recurrence or metastasis. The overall median duration of follow-up time was 52.1 (range 1.9–142) months, and was similar between genders. There were no gender differences in the death rate within follow-up, 27.2% (12/44) females, and 26.4% (23/87) males died. Patients with lower clinical tumor advancement ($P = 0.029$), lower grade ($P = 0.000$) and pTNM ($P = 0.000$) survived significantly better. There was no difference in OS between genders (log rank $P = 0.771$). Patients who had a break between RT and surgery longer than 15 days survived significantly shorter periods than those treated with a break ≤15 days ($P = 0.028$) (Fig. 1a). This was true for the male subgroup ($P = 0.018$, Fig. 1b) but not for the female subgroup ($P = 0.770$, Fig. 1c). Patients treated with 3–7 days break survived also better, compared to the rest, but due to the low number of patients, P value for the log-rank test was non-significant. Also OTT was a significant prognostic factor in the whole patient group ($P = 0.010$, Fig. 2a), and in the male subgroup ($P = 0.023$, Fig. 2b). For male patients treated with a break ≤15 days, and OTT ≤23 days, the probability of OS was about 50% higher than for those treated with a break >15 days and OTT >23 days (Figs. 1b and 2b). However, in the female subgroup, the break size or OTT had no significant influence on survival (Figs. 1c and 2c). Adjuvant chemotherapy had no significant influence on patients' survival. Only in patient treated with a break lower than 15 days, CHT improved OS for about 5–7%, irrespective of patient gender.

In univariate analysis, a break between RT and surgery shorter than 15 days and OTT ≤23 days were factors affecting overall survival. These parameters, however, had less impact on the recurrence and metastasis rates. Recurrence-free survival was non-significantly higher ($P = 0.066$) for patients treated with a break shorter than 15 days and OTT ≤23 days ($P = 0.099$), irrespective of patients' sex. Patients treated with a break longer than 15 days and OTT >23 days had a non-significantly lower level of metastasis-free survival than those treated with a shorter break ($P = 0.269$) and OTT ≤23 days ($P = 0.498$).

5. Discussion

The presented results were based on a group of 131 patients treated with SCRT with a break before surgery ranging from 3 to 53 days. We showed that, besides the well known negative clinicopathological prognostic factors, such as high tumor grade and pTNM, a break between RT and surgery longer than >15 days and OTT longer than 23 days were negative prognostic factors for patients' overall survival. This is not surprising, because both these parameters are related, as in OTT break before surgery is included. We indicated gender-related

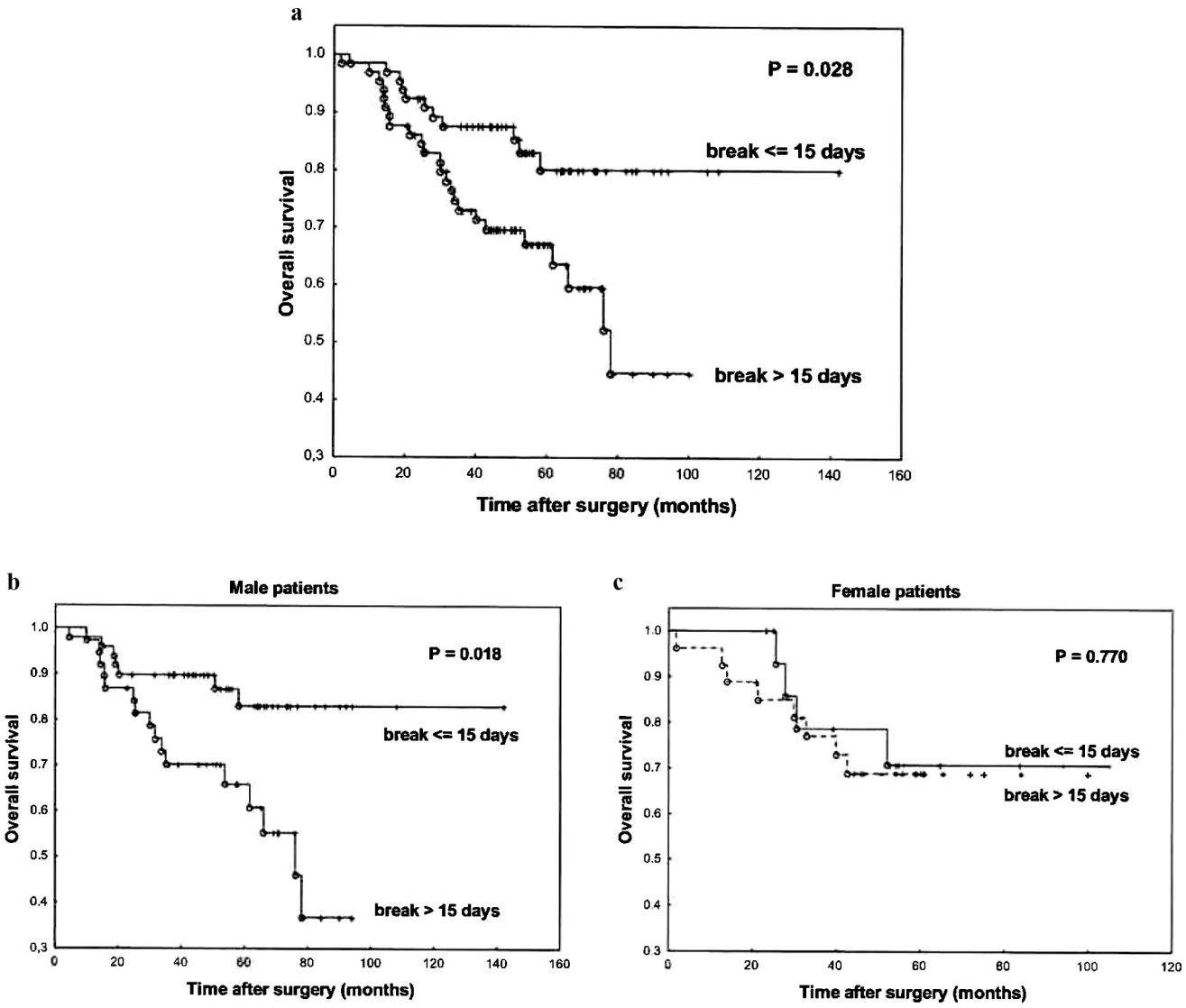

Fig. 1 – Influence of interval between radiotherapy (RT) and surgery (break ≤ 15 days) on overall survival of whole group (a), male (b), and female subgroup (c) of rectal cancer patients.

difference in OS based on a break length and OTT. Male patients receiving treatment with a short break (≤15 days) showed significantly higher (about 50%) 10-year OS than those treated with a break >15 days. Despite a higher tumor grade indicated in patients treated with a short break, they have a higher OS. However, the difference in survival was not observed in women.

BED_{10} calculated by us (without time factor) was equal to 37.5 Gy. Actually, hypofractionated SCRT (5 × 5 Gy) regimen is biologically equivalent to a conventionally fractionated dose of 31.2 Gy for tumor. This dose is lower than suggested by Pettersson et al.[3] for curative treatment (equivalent dose 25 × 2 Gy, BED_{10} = 60 Gy, formula (1)). Therefore, the 5 × 5 Gy schedule represents a relatively low BED_{10} dose which should be used for locally advanced disease and with short break (3–7 days) treatments rather than large disease volumes and a long interval before surgery.[2]

BED_{10} was the same for all patients as RT schedule was the same for each patient. SCRT with a large daily fractionation (5 × 5 Gy) should not be affected by repopulation, if surgery occurs about a week after RT. However, if a long break before surgery is applied, it could raise some concerns regarding lowering the effectiveness of prescribed dose and the probability of developing local recurrence and metastases, and negative influence on patients' survival. The hazard of accelerated tumor clonogen repopulation during radiotherapy is a well known phenomenon,[4] and in the case of rectal cancer, it was observed from 28 days after hypofractionated RT as a consequence of cell depopulation.[12]

Suwinski et al.[13] showed that subclinical pelvic deposits of rectal cancer grow rapidly during preoperative radiation therapy and stated that low doses only offer a clinically relevant reduction in risk of pelvic relapses, if the overall radiation treatment time is short.

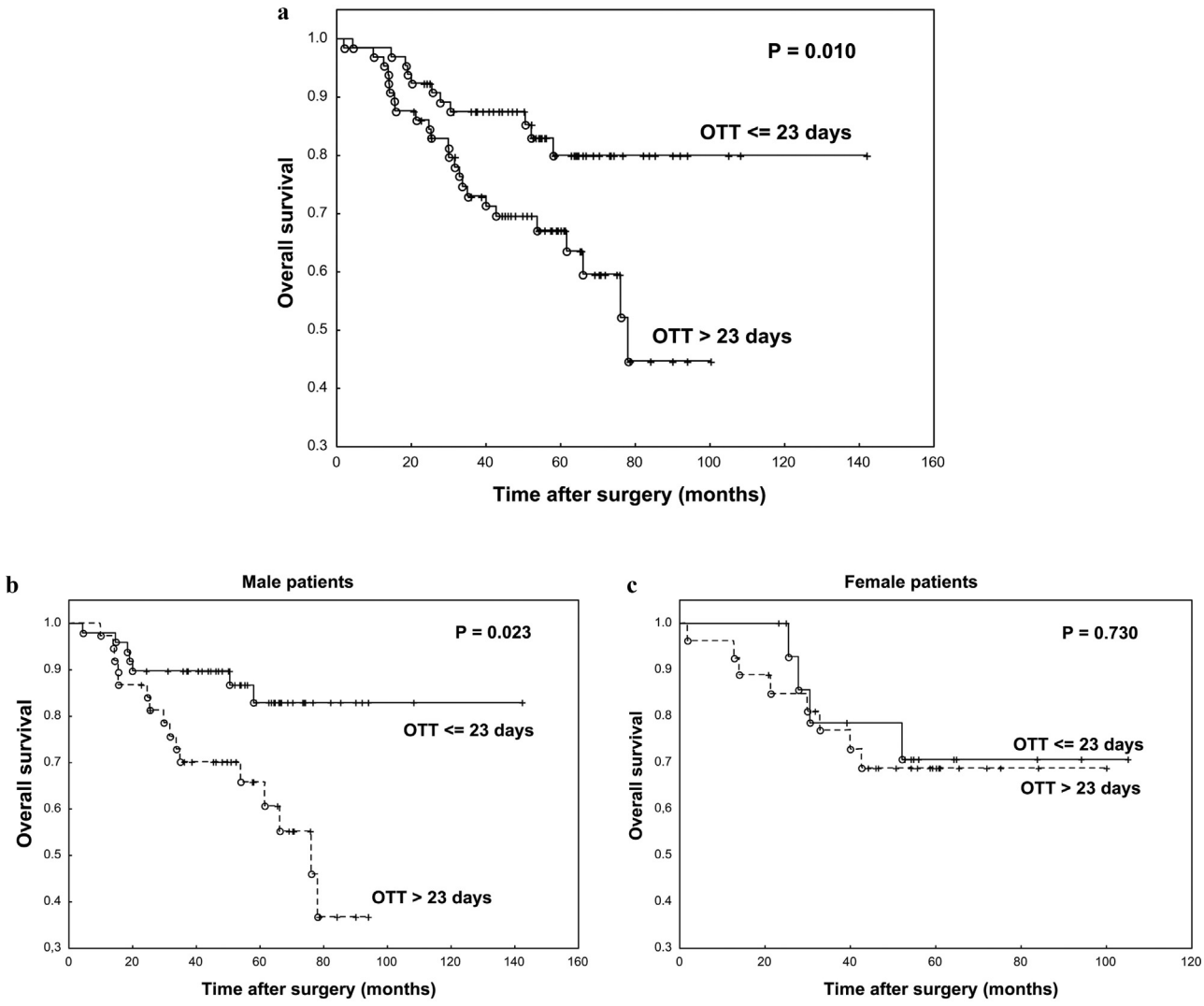

Fig. 2 – The relationship between OTT and overall survival for all (a), male (b), and female subgroup (c) of rectal cancer patients. Cut-off point, mean OTT of 23 days.

The Swedish Rectal Cancer Trial[14] demonstrated that SCRT with surgery within a week after RT reduced the risk of local recurrences by half in the treatment of curative rectal cancer patients. We show, however, that if the interval between RT and surgery is longer, this has a negative impact on patients' survival and the incidence of local recurrences and metastases. Therefore, unnecessary breaks in treatment should be avoided, or if unavoidable, should be compensated for by increased treatment intensity after the break.[5] This is important, because recurrence time distributions after surgery resemble those after radiotherapy, which suggests that tumor cells residual after surgery also accelerate their growth rate.[15]

In our patients' group, gender-related differences in tumor repopulation,[12] pathological tumor response[6] and present significance of break in the treatment and OTT were indicated. It may be that the tumor biology or/and tumor microenvironment in male patients is responsible for this difference. Whether female gender is associated with improved survival in rectal cancer remains under investigation. Although epidemiologic studies suggest that women present a more advanced stage of disease, female gender is a predictor for improved survival in a number of studies.[16,17] Therefore, identifying favorable factors for survival, such as short treatment time in the male subgroup, characterized by better prognosis is particularly important.

6. Conclusions

Break between RT and surgery longer than 15 days, or OTT longer than 23 days are negative prognostic factors for overall survival for all, and particularly male rectal cancer patients'.

Conflict of interest

None declared.

Financial disclosure

This work was supported by grant of the State Committee for Scientific Research No. PBZ-KBN-091/P05/2003.

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