Original article

Combined therapy: surgery and intraoperative HDR brachytherapy for locally advanced and recurrent rectal cancer. Practical experience of Brachytherapy Department in Warsaw

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Abstract

Purpose: Patients with locally advanced and recurrent rectal cancer have a dismal prognosis. The aim of proposed combined therapy – surgery and intraoperative brachytherapy, is to improve results of already applied methods and to define optimal group of patients for this treatment. We introduce practical experience of Brachytherapy Department in Cancer Centre – Institute in Warsaw.

Material and methods: Patients with primary T4NxM0 rectal cancer and isolated local pelvic recurrence were qualified for therapy. Between January 2005 and September 2008, 13 patients were included: 4 with primary cancer and 9 with recurrence, median age of 56. After surgical resection intraoperative radiotherapy was delivered with boost of high dose rate brachytherapy of 20Gy dose to the tumor bed.

Results: Primary point of the study is to evaluate impact of applied therapy on local control (LC), overall survival (OS) and disease free survival (DFS). Median follow-up is 16 months. Four of the patients died and 3 survivors are disease-free. There was no case of perioperative mortality.

Conclusions: A multimodality approach, using surgical resection with intra operative brachytherapy improves local control as well as patients survival in comparison with historical treatment group. Combined therapy is related to high morbidity, but low mortality. The preliminary observations seem to correspond with other authors data.

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Key words: locally advanced rectal cancer, recurrent rectal cancer, intraoperative radiotherapy, HDR brachytherapy.

Purpose

In Poland, colon neoplasm comes second in ranking of mortality and morbidity caused by malignancies. Rectal and sigmoid cancer stands for about 70% of colon cancer [1]. In 2003 in Poland 5457 patients were diagnosed with rectal and recto-sigmoid cancer, and 2435 deaths were noted [2]. In primary rectal cancer approximate 10% is in tumor stage T4 [3], and within this group (if surgical resection is possible) recurrence rate exceeds 50%.

Among all patients with rectal cancer treated radically with cure intend (surgery and/or teleradiotherapy and/or chemotherapy), the total 3 to 35% would experience local recurrence. Between 50 to 80% of recurrences reveal itself within two years after surgery, where primary advanced staging of the tumor is the main risk factor. It is estimated that about 30-50% of patients with recurrent rectal cancer die of local complications resulting from that recurrence, and about 15% die without distant metastases. Even up to 50% of patients with early diagnosed local relapse is free from distant metastases [4, 5].

Conventional treatment of locally advanced, non resectable rectal cancer and local relapse is highly unsatisfactory. Mean survival value of both groups, without treatment, is only 7-8 months. There is no standard procedure in these clinically difficult cases. Surgical resection is only possible in 5 to 20% of cases and usually restricted to cases with anastomotic recurrence. Most oncologic institutions apply palliative therapy. However, palliative chemotherapy is not able to reach 5-years overall survival rate higher than 5%. Palliative radio and chemotherapy results in 10 to 17 months of mean survival time according to literature data [6]. Additionally, palliative electron beam radiation (EBRT) is often limited or not considered in previously irradiated tumor, because of high toxicity and adjoining of critical organs in irradiated field. Acceptable local control was achieved only when postoperative radiation of 60 Gy or higher was applied.

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Intraoperative radiotherapy allows displacement of the radiosensitive structures from the tumor bed during the procedure, reducing the risk of radiation damage to normal tissues and therefore delivering large fraction of radiation directly to the area at risk.

Combined therapy: surgery with intraoperative radiotherapy (IORT) provides the possibility of treatment with cure intent. Radiotherapy in certain stages of rectal cancer proves to be beneficial. Preoperative short term EBRT in doses of 25 Gy is associated with enhanced local control, whereas long term EBRT in doses range 45-50 Gy in advanced tumors allows downsizing the tumor mass in 50-75%, and often enables surgical resection [3]. Therefore, one can assume positive impact of IORT. The IORT has been used worldwide already for 30 years. Generally, two techniques of IORT are in use: large single electron beam dose delivered from a linear accelerator, applied in teleradiotherapy (intra operative electron beam radiotherapy – IOEBRT), and intraoperative high dose rate brachytherapy (IOHDR). In very rare cases of rectal cancer, other methods of treatment are used such as: perioperative brachytherapy in fractionated doses and low dose rate brachytherapy (LDR) with 125-Iodine seeds implantation [7,8]. However, the character of these two techniques is marginal for the reason of transposition of implants or catheters, cost effectiveness and radiation security.

Nowadays, IORT is performed in different neoplasm's localizations. It seems that the use of IORT in sarcomas and pancreas cancer decreases local relapse, however its impact on survival rate is indistinct [9-11]. In pancreas and papillae Vateri in non resectable neoplasms, the palliative impact of radiotherapy is noticeable – it decreases pain symptoms, prolongs asymptomatic survival and visibly reduces tumor mass. IORT application in gastric cancer [12] in stage T3-4N+ with additional preoperative radiotherapy improves overall survival rate in comparison with surgical resection alone.

Comparing the IORT technique (in theory advantages of IOEBRT) with IOHDR, the depth of radiation is more than 1 cm and short time of radiation (less than 10 min) [13]. On the other hand, deeper radiation could be the cause of additional complications due to critical organs. However, in spite of different types and shapes of applicator's cones, sometimes it is difficult to reach the area of interest in pelvis with IOEBRT system, especially when the tumor lies internally (10% of such cases), IOEBRT is not available for treatment. In IOHDR flab, a flexible template easily conforms the different shapes and enables irradiation of any site of pelvis. There are few publications available about providing IOHDR in rectal cancer (only a small number of centers published their clinical practice, where 74 patients is the most numerous group [13-16], although results appear to be comparable to IOEBRT technique). Below we introduce clinical experience of our Centre, but because of small amount of patients – 13, we were not able to produce any statistical analysis – it's a preliminary report of planned study.

Material

Since January 2005, in Brachytherapy Department of Cancer Centre – Institute in Warsaw, a combined treatment was performed in a group of 13 patients with rectal cancer. For this integrated therapy patients with primary locally advanced rectal cancer in stage cT4NxM0 and with isolated pelvic recurrence were qualified. The evaluation of patients was based on physical examination, chest X-ray, computer tomography or magnetic resonance of abdomen and minor pelvis. Whenever needed, vaginal ultrasound examination was performed and tumor biopsy if possible.

Primary advanced tumor was detected in 4 cases, while in 9 cases – pelvic recurrence. The group consists of 6 males and 7 females, median age 56 years (range 23-75). One patient was diagnosed with recurrence of anorectal cancer (histologically – adenosquamosus), and others with adenocarcinoma, mainly histological G2 degree.

Because of local relapses, some patients received previous treatment: 4 were irradiated and 2 of them received postoperative EBRT in doses 50.4 Gy; one patient with anorectal cancer obtained radical radio and chemotherapy according to scheme: 30.6 Gy on pelvic area and additional 24 Gy on anal tumor; one patient received preoperative radiation of 25 Gy dose. Present neoplasm's recurrences were confirmed in two patients. Median time of treatment from primary tumor to relapse was 32 months.

Method

Combined therapy is performed in a specially dedicated operating room with appropriate shielding for Ir-192 source. The procedure starts with surgical resection of the tumor in maximal possible dimension. Planned surgery include: frontal rectal resections, abdominal and perineal resections, extirpations of uterine and adnexa and total exenterations. During the surgery, if necessary, specimens are taken to a frozen section in order to conform the neoplasm's infiltration to tumor bed and to define margins of extra infiltration. Because the efficiency of irradiation is conditioned by oxygenation of tissues, brachytherapy could be provided at the same time according to satisfactory hemoglobin level in blood – permissible 9 mg%. If value of hemoglobin is below 9 mg%, IOHDR is delayed till general condition of the patient is stabilized and hematologic parameters are equalized. In this case it was two-stage treatment procedure. Tumor bed was secured by metal clips around the target surface in order to expose the irradiating area, followed by radiograms and CT scans. Flexible intra operative applicator FLAP was adjusted into the target surface (HAM applicator: Harrison-Anderson-Mick applicator; Fig. 1). Position of the FLAP was stabilized by filling the pelvis with gauze pads, and, as a result, pressing the applicator against the area at risk (Fig. 2). Packing was performed to distance critical organs, like urine bladder, bowel, and especially all anastomoses from the area at risk. The HAM applicator is a 10 mm thick pad, made of flexible silicon with 1 cm spaced parallel tubes running through the template, which guides radiation source from HDR remote after-loader via connecting tubes. Prior to actual connection, a radiograph or CT scan with imitation of sources in the catheters was used to verify the position of the applicator, and to calculate proper scheme for radiotherapy.

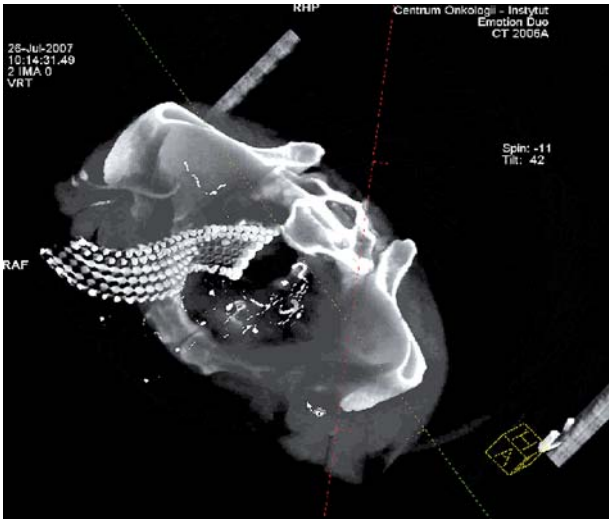

Fig. 1. Flexible HAM applicator (six channels) adjusted to the right pelvic wall in area at risk – 3-D reconstruction

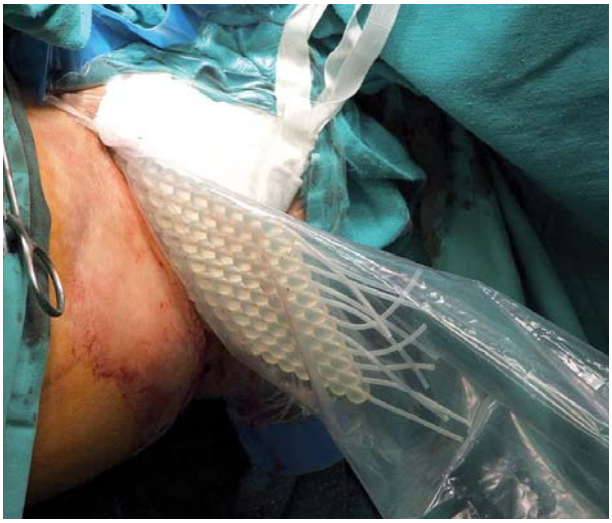

Fig. 2. 11-channel (1 cm spaced parallel tubes) applicator stabilized to right pelvic wall by gauze pads

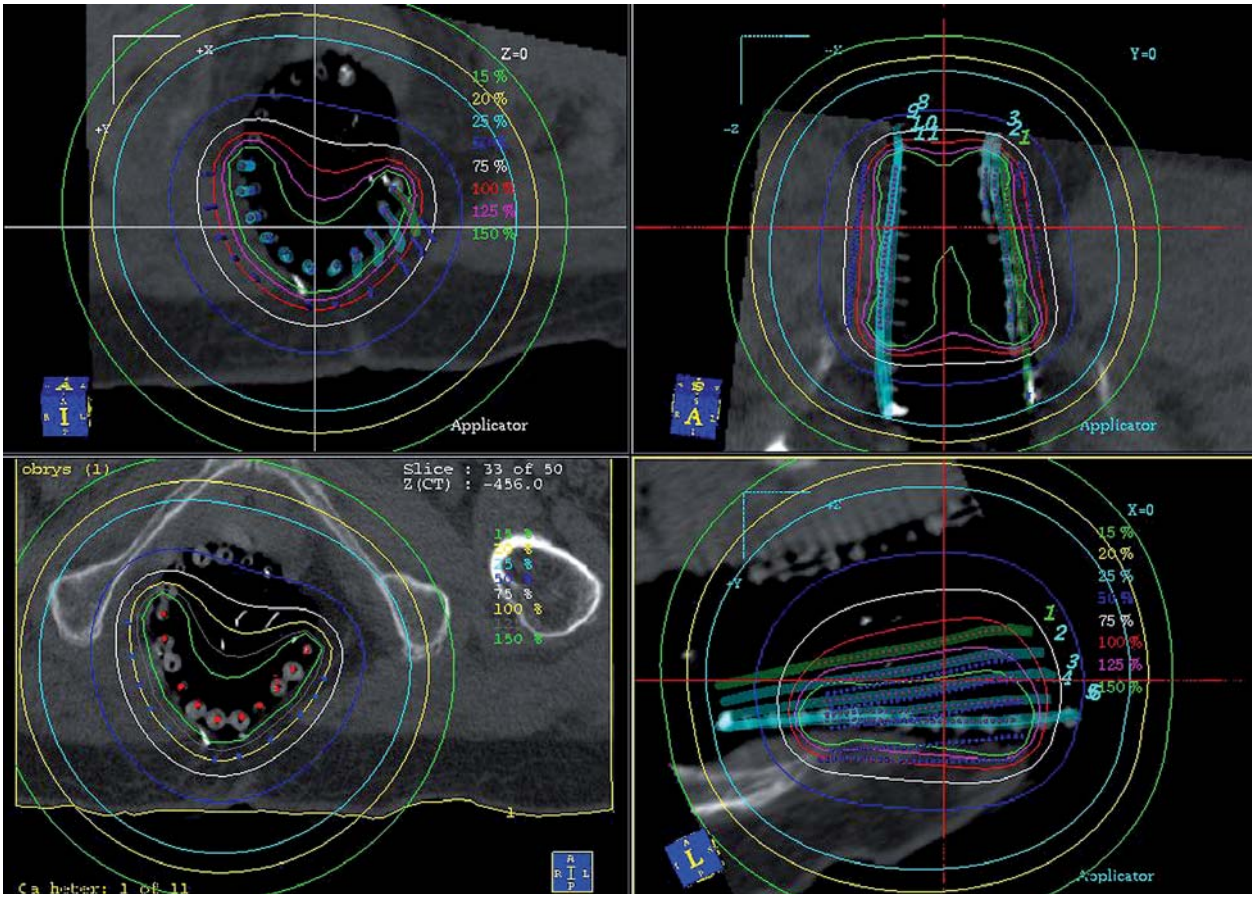

Fig. 3. Schedule of isodoses – dose of 20 Gy was calculated at 10 mm from the applicator surface

Microselectron HDR of Nucletron® was used for irradiation. It's a remote after-loading system in high dose rate brachytherapy using single source of Ir-192. System include: HDR device with Ir-192 source, additional security switch, door's detectors and TV camera in the operating room. Second room consists: control panel, printer, connection box and a special device that is linked to planning system PLATO. Microselectron HDR contains small radiation source (diameter 0.9 mm) placed in a flexible guide tube, that allows to reach different localizations. System of source shifting (from nearest programmed position, with a shift pitch of 2.5, 5 or 10 mm)

guarantees high precision of source positioning, and computer controlled time of radiation with 0.1 sec accuracy. Radiation is possible in maximum of 18 applicator's catheters, connected to 18 channels in HDR. Dosage distribution is controlled by a stoppage of precise positioning in each programmed catheters of applicator. System is equipped with number of safety devices and security programs, protecting patients and medical staff.

A single dose of 20 Gy boost was delivered at 1 cm distance from the applicator surface (Fig. 3). In one case, because of R0 resection and previously delivered EBRT, the dose of 10 Gy was applied. Till the end of 2006, treatment planning was performed on the basis of radiograms; nowadays CT scans – computer tomography installed in the operating room is used for this procedure. The size of radiation section and current activity of the emission source have an effect on radiation time. After irradiation, applicator was removed and after hemostasis, abdomen was closed in regular way.

Patients with primary cancer underwent 3 abdominoperineal resections and 1 exenteration posterior. In recurrent cancer – 2 anterior resections, 3 anterior resections with extirpation uteri with adnexes and 4 total exenterations were performed. In 3 cases segmental resection of the ureter was necessary, in 2 – segmental small bowel resection and in 1 case – right hemicolectomy. One female with recurrence had 2 single metastases in omentum major (attached to pelvis) that were removed simultaneously during surgery. The range of operations based on postoperative histopathological examination was as follow:

- in recurrence group of 9 patients: 7 R2, 1 R1, 1 R0 (with narrow margin < 2 mm),
- in T4 primary tumors: 1 R2, 1 R1, 2 R0 (one with narrow margin < 2 mm) (Fig. 4).

IOHDR and surgical resection were performed in operation room dedicated to this procedure. 12 patients received IOHDR in dose 20 Gy, 1 female received dose 10 Gy (previous radiation, resection R0 with narrow margin 2-3 mm). The actual irradiation time ranged from 16.6 min to 150.6 min (median time: 58.5 min). However, the complete time of brachytherapeutic procedure including treatment planning was much longer (according to literature data usually it is 2-3 times longer than radiation time, which was also observed in our Department). Radiation surface ranged from 45 cm^2 to 225 cm^2 (median, 88 cm^2). Anesthesia time (surgery + IOHDR time) lasted from 5 h to 12.5 h (median time 7 h). In 6 out of 13 patients, due to excessive blood loss, two-stage procedure was conducted (IOHDR wasn't performed in case of hemoglobin level less then 9 mg/dl). In these cases first stage of treatment (surgery) lasted from 3 to 5.5 hours. Number of necessary erythrocyte blood mass transfusions intra operative or postoperative varied from 0 to 14 units of ME (median: 5.5 units of ME).

In each case we considered pre- or postoperative additional teleradiotherapy or chemotherapy. Preoperative radiotherapy in total dose of 25 Gy (5 x 5 Gy) was performed in 2 patients with primary tumor and in 1 case of local relapse, preoperative radiotherapy in dose of 50 Gy, in fractions of 1.8 Gy was performed in 1 primary cancer. In case of 1 recurrence, postoperative radiotherapy was performed in dose 50 Gy. 5 patients received postoperative chemotherapy: in 3 cases 5-FU + LV, 1 patient chemotherapy Folfiri (Campto, 5-FU, LV) and 1 patient according to FOLFOX program (oxaliplatinum, LV, 5-FU).

Results

Hospital stay ranged from 7 to 59 days (median 18 days), the longest duration was in case of patient with total parenteral nutrition, resulting from short bowel syndrome due to previous resections of the bowel and complications. 2 patients had abscess in laparotomy wound. 3 patients experienced perineal wound dehiscence, in 2 cases late radio-induced reaction with necrotic changes, treated conservatively (they required long-term ambulatory treatment). One patient with intraoperative injury of vena iliaca communis experienced post – surgery thrombosis and was treated conservatively with success. 2 patients had ureteral fistula, treated with providing nephrostomy. One patient had temporary obstruction that required readmission to hospital for conservative treatment. Neuropathy was observed in 3 patients, in one case – severe with temporary paraplegia, unable to walk for a month.

The mean follow-up time was 16 months (range 1-28 months). 4 patients died because of cancer progression – 3 of them were patients with recurrence, all after R2 resection; 2 died because of metastases, without local relapse after IOHDR – 6 and 16 months after combined treatment and 1 died of relapse in irradiation field

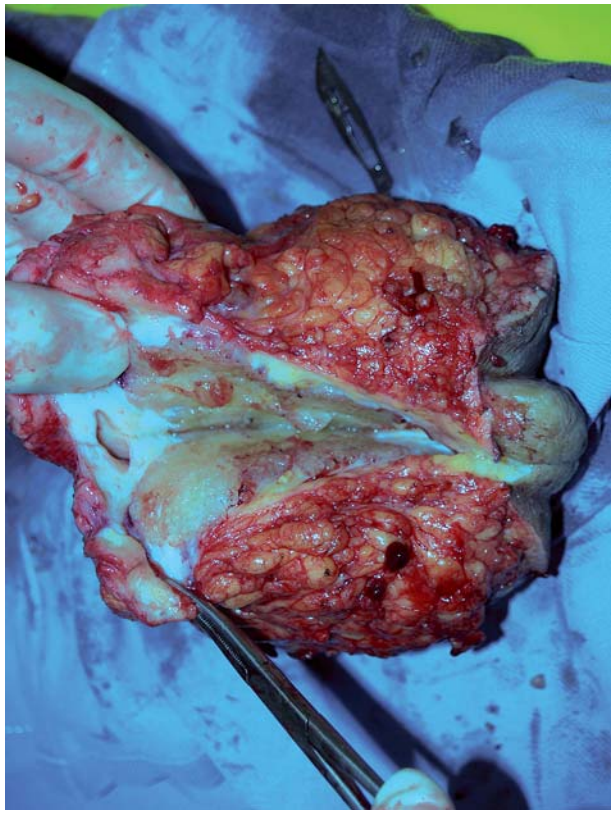

Fig. 4. Perineal recurrent tumor – type of resection R1

– 13 months after IOHDR. One death concerned a person with primary rectal cancer caused by liver metastases – 28 months after surgery (metastases after 8 months, local relapse after 26 months).

Among living patients: 3 cases (1 with primary cancer) – without sighs of disease progression with median follow-up 8 months); in group with recurrences: 1 patient has local relapse after IOHDR (after 4 months as the only one localization of the cancer); 4 patients have distant metastases (after 4, 6, 10 and 10 months, without pelvis recurrence); in group with primary advanced neoplasm: 1 case with isolated local relapse after IOHDR.

Discussion

Surgery in advanced rectal cancer and local recurrence is an enormous challenge that often requires multivisceral resections. The extent of performed operations (anterior resection – 46%, abdominoperineal resection – 23%, exenteration – 31%) corresponds with literature data [15, 17, 18]. In case of local recurrence, the main focus of attention is necessity of exenteration – in our group, all this kind of surgical procedures concern patients with recurrence.

According to literature data, among patients qualified to combined treatment, about 12,5% of cases with primary tumors and 30% with pelvis recurrence are disqualified during laparotomy, due to metastases statement. Because of distant metastases, 15% of cases in our data were withdrawn from this procedure. In next 15% of cases, IOHDR was not performed, because of wide margin of healthy tissues around the tumor, verified in frozen sections.

Time of the entire procedure was rather long with median time of 420 min. However, it doesn't differ from data of other authors (345-510 min), in spite of small amount of performed procedures in our Department [15, 17, 18]. Blood loss was estimated at median number of 5.5 of necessary erythrocyte mass transfusions and is also similar to other clinical experiences (1400-4100 ml). Dose of 20 Gy is the most frequently applied dose in our Department and is the highest well-tolerated dosage determined experimentally [19-21]. Most centers usually use doses ranging 10-20 Gy and because of high toxicity, doses above 20 Gy are applied in extremely rare cases.

There are only few centers using IOHDR treatment and, when discussing about the results of intraoperative radiotherapy, the IOEBRT therapy needs to be also included. The results achieved by these two methods seems to be comparable according to publication of Arthur James Cancer Hospital and Comprehensive Cancer Centre, The Ohio State University, where three methods of intraoperative radiotherapy (IOEBRT, IOHDR, I-125 seeds) are applied. The findings presents Martinez-Monge [8]. This centre has its own therapeutic schema for different types of intra operative radiotherapy: implantation of I-125 seeds is used for macroscopic left infiltration, for microscopic infiltration within easy to reach surface – IOEBRT, for difficult to reach areas – IOHDR.

Treatment results from others centers are expressed in percentage of survival without recurrence (LC-local control), disease free survival (DFS) and overall survival (OS), and the findings are better in primary T3-4NxM0 rectal cancer than in recurrences. However, qualification of IORT is not homogeneous – some authors qualify only T4 tumors, while others include also T3N+. The 2-yr period of LC for primary cancer [13, 15, 17, 22-26] ranged from 81% to 97%; 5-yr period: LC- 65-93%. Radicality of resection is the most important factor to influence the LC. In group R0, 5-yr period of LC (72-94%), results are statistically much better than in R1/R2 group (38-77%). In publications concerning recurrent cancer [5, 13-16, 18, 27-30], 2-yr LC ranged from 43 to 60%. Also here, the most important factor was the involvement of surgical margin by neoplasm's infiltration. Furthermore, 2- or 3-yr LC in R0 group ranged 79-89%, in R1/R2 group – 19-45%, whereas 5-yr LC for R0 resections was 43-56% and for R1/R2 – 17-26%. Most authors of scientific publications doesn't consider certain factors such as age, gender, type of surgery, time from primary treatment to relapse, or grading, to have an impact on LC. Some authors show positive effect of preoperative radiotherapy on metastases-free lymph nodes before combined procedure.

The impact of combined treatment on survival in our group of patients is hard to interpret at this moment, on account of short follow-up and small number of patients. However, according to other publications for primary tumors [13, 15, 17, 22-26], 2- or 3-yr period of OS ranged from 61 to 89%, while 5-yr ranged from 49 to 79%. In OS, the most frequent independent prognostic factor was resection status; others mentioned by some authors were: staging, grading, adjuvant preoperative radiotherapy and metastases in lymph nodes. In group R0 5-yr OS ranged 66-74% and in R1/R2 group 38-55%. In recurrent cases [5, 13-16, 18, 27-30], OS was significantly decreased: 2- or 3-yr OS range 29-75% and 5-yr OS 0-30%. In recurrence group of patients, the most significant and frequent prognostic factors were: resection status, volume of target area, preoperative pain, usually associated with nerves filtration and lack of adjuvant radio-chemotherapy (rarely mentioned). In group R0 5-yr OS ranged from 36 to 74% (median survival time 34-43 months), in group R1/R2 from 11 to 52%, usually better for R1 than for R2 group (median time survival 9-24 months, 9 months for R2).

Likewise, in case of DFS, the most frequent impact was noted in: R0 resection vs. R1/R2, preoperative radiotherapy, neuropathic symptoms, rarely adjuvant chemotherapy. Other factors were insignificant or not analyzed. 2- or 3-yr DFS in primary tumors were 22-47%, but in group R1/R2 – 0-38%. In recurrence group 2- or 3-yr DFS ranged from 22 to 47%, while in 5-yr 13-23%. However, in R1/R2 resection status 2- or 5-yr DFS did not exceed 11%.

In few articles, patients treated with IORT and other treatment methods (surgery, surgery and/or EBRT and/or chemotherapy) were compared directly [3, 17, 23, 24, 28, 30, 31]. Most authors show advantages of applying IOHDR and IOEBRT therapy in rectal cancer. Moreover, especially distinct impact was visible on LC and OS. The effect of frequency and time on distant metastases remains still unclear. Although, there are no randomized examinations in literature, so results are based on single or multivariate (less frequent) statistical analysis.

Table 1. Potential complications in treatment of patients with combined surgery and IORT

Compli-cations (%)	Morbidity	Peri-operative mortality	Wound complication	Ureteral fistula/ obstruction	Neuro-pathy	Bowel fistula	Intra-peritoneal abscess	Bowel obstruction
Literature data	30-84	0-7	6-46	2-23	8-32	0-21	4-24	0-23
Own serie	69	0	38	15	23	7,5	0	15

In spite of small amount of patients, the obtained results seem to be similar to the most of the findings of other authors. Longer survival is noted in primary rectal cancer group. Intraoperative radiotherapy allows to obtain higher percentage of local tumor control. The proposed method prolongs overall survival time in comparison to historical group. The impact of time factor on metastases appearance is uncertain. Because of high rate of R1/R2 resections (77%), the most important aspect is resection status that is connected to poor prognosis of advanced cases qualified for this treatment. It's worth to mention the fact that results of LC, OS and DFS, publicized by different centers, differ in R0 resection from R1/R2, and they need to be interpret separately. In some publications the rate of R0 operations is as high as 91% (e.g. Krempien [22]), what can be deceiving if handling summarily. In case of several patients qualified initially for combined treatment, IOHDR was not performed because of satisfactory wide margins after resection (R0 > 2-3 mm). In our team we assume that combined treatment is directed to patients with doubtful radical resection of tumor.

Frequency of early and late complications in literature data [5, 8, 13-16, 22, 23, 27] range from 30 to 84%. Perioperative mortality is low. Within the most often cited complications (Table 1) are: wound complications/wound dehiscence, ureteral fistulas or obstruction and neuropathy. Rate of bowel fistulas or anastomosis dehiscence vary from 0 to 21%, rate of intraperitoneal abscess: 4-24%. These above mentioned two complications are comparable in group of patients treated only surgically. In our group of patients, problems with wound healing were, with one exception, with perineal wounds, in 2 cases with late radio-induced toxicity. These two patients required ambulatory medical attention for many months. This complications cause worse quality of live and it occurs in group of patients that received additional preoperative radiotherapy – it's a group of patients (resection abdominoperineal, preoperative radiotherapy) that most likely require lower dose of IORT.

Some part of complications is clearly IOHDR-related. The most common type of radiation toxicity are: wound complication with late radio-induced reaction, obstruction and ureteral fistulas, peripheral nerve damage. However, sometimes it is difficult to specify IORT-related complications. Theoretical radiotherapy's influence on increased rate of bowel or ureteral anastomotic fistulas, based on some publications comparing different methods [5, 23, 30], is not confirmed.

Type and rate of complications obtained in our series, compares quite well with already published series (Table 1). Rate of complications, include severe ones that require invasive interventions, is fairly high. However, in consideration of relatively low mortality (in 13 patients no treatment-related perioperative death occurred) and the fact that uncontrolled tumor growth entails deterioration of live quality and often forces into palliative invasive interventions (e.g. bringing a stoma, nephrostomy puncture, nerve anaesthetic), this high rate seems to be acceptable.

Conclusions

Combined treatment: surgery and intraoperative brachytherapy is a promising option for selected group of patients with primary locally advanced and isolated pelvic recurrent rectal cancer. Additional IOHDR may increase local control and overall survival time in these groups, but it seems to have no effect of time factor on metastases appearance. Cancer-related deaths are most often related to disseminated disease, which suggests the need for additional systemic therapy. The fact that local recurrence have major negative impact on patient's quality of live as well as significant percentage of patients die of local tumor progression, justifies an aggressive multimodality treatment to improve local palliation and in some cases, to provide permanent cure. The preliminary data is encouraging, however, additional studies are necessary to confirm the advantage of intraoperative radiotherapy over conventional treatment.

References

1. Nowacki M. Nowotwory jelita grubego. Centrum Onkologii – Instytut im. M. Skłodowskiej-Curie, Warszawa 1996 [Polish].
2. Wojciechowska U, Didkowska J, Tarkowski W et al. Nowotwory złośliwe w Polsce w 2003 roku. Centrum Onkologii – Instytut im. M. Skłodowskiej-Curie, Warszawa 2005 [Polish].
3. Kim HK, Jessup JM, Beard CJ et al. Locally advanced rectal carcinoma: pelvic control and morbidity following preoperative radiation therapy, resection, and intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 1997; 38: 777-783.
4. Heriot AG, Tekkis PP, Darzi A et al. Surgery for local recurrence of rectal cancer. *Colorectal Disease* 2005; 8: 733-747.
5. Wiig J, Tveit K, Poulsen J et al. Preoperative irradiation and surgery for recurrent rectal cancer. Will intraoperative radiotherapy (IORT) be of additional benefit? A prospective study. *Radioth Oncol* 2002; 62: 207-213.
6. Yoshihiro M. Treatment strategy for Locally Rectal Cancer. *Jpn J Clin Oncol* 2006; 36: 127-131.
7. Martinez-Monge R, Nag S, Martin E et al. 125-Iodine brachytherapy for colorectal adenocarcinoma reccurent in the pelvis and paraaortics. *Int J Radiat Oncol Biol Phys* 1998; 42: 545-550.
8. Martinez-Monge R, Nag S, Martin E et al. Three Different Intraoperative Radiation Modalities (Electron Beam, High-Dose-Rate Brachytherapy, and Iodine-125 Brachytherapy)

in the Adjuvant Treatment of Patients with Reccurent Colorectal Adenocarcinoma. *Cancer* 1999; 86: 236-247.
9. Makarewicz R. Brachyterapia HDR. *Via Medica*, Gdańsk 2004 [Polish].
10. Dziewirski W, Rutkowski P, Nowecki Z et al. Surgery combined with intraoperative brachytherapy in the treatment of retroperitoneal sarcomas. *Ann Surg Oncol* 2006; 13: 245-52.
11. Calvo FA, Merino RM, Orecchia R. Intraoperative radiation therapy. Part 2. Clinical results. *Oncology/Hematology* 2006; 59: 116-127.
12. Skoropad VY, Berdov BA, Mardynski YS et al. A prospective, randomized trial of pre-operative and intraoperative radiotherapy versus surgery alone in resectable gastric cancer. *Eur J Surg Oncol* 2000; 26: 773-779.
13. Nuyttens JJ, Kolkman-Deuroloo I-K, Vermaas M et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or reccurent rectal cancer. *Int J Radiat Oncol Biol Phys* 2004; 58: 106-112.
14. Alektiar KM, Zelefsky MJ, Paty PB et al. High-dose-rate intraoperative brachyterapy for reccurent colorectal cancer. *Int J Radiat Oncol Biol Phys* 2000; 48: 219-226.
15. Harrison LB, Minsky BD, Enker WE et al. High dose rate intraoperative radiation therapy (HDR-IORT) as part of the management strategy for locally advanced primary and recurrent rectal cancer. *Int J Radiat Oncol Biol Phys* 1998; 42: 325-330.
16. Nag S, Martinez-Monge R, Mills J et al. Intraoperative high dose rate brachyterapy in recurrent or metastatic colorectal carcinoma. *Ann Surg Oncol* 1998; 1: 16-22.
17. Ferenschild FT, Vermaas M, Nuyttens JJ et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. *Dis Colon Rectum* 2006; 49: 1257-1265.
18. Mannaerts G, Martijn H, Crommelin M et al. Intraoperative electron beam radiation therapy for locally recurrent rectal carcinoma. *Int J Radiat Oncol Biol Phys* 1999; 45: 297-308.
19. Sindelar WF. Experimental and clinical studies of intraoperative radiation therapy. *Current Problems in Cancer* 1994; 8-9: 253-289.
20. Sindelar WF, Tepper JE, Kinsella TJ et al. Late effects of intraoperative therapy on retroperitoneal tissues, intestine and bile duct in a large animal model. *Int J Radiat Oncol Biol Phys* 1994; 29: 781-788.
21. Willet Ch. Intraoperative radiation therapy. *Int J Clin Oncol* 2001; 6: 209-214.
22. Krempien R, Roeder F, Oertel S et al. Long-term results of intraoperative presacral electron boost radiotherapy (IOERT) in combination with total mesorectal excision (TME) and chemoradiation in patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2006; 66: 1143-1151.
23. Sadahiro S, Suzuki T, Ishikawa K et al. Preoperative radio/chemo-radiotherapy in combination with intraoperative radiotherapy for T3-4Nx rectal cancer. *EJSO* 2004; 30: 750-758.
24. Ratto C, Valentini V, Morganti A et al. Combined-Modality therapy in locally advanced primary rectal cancer. *Dis Colon Rectum* 2003; 46: 59-67.
25. Mannaerts G, Martijn H, Crommelin M et al. Feasibility and first results of multimodality treatment, combining EBRT, extensive surgery and IOERT in locally advanced primary rectal cancer. *Int J Radiat Oncol Biol Phys* 2000; 47: 425-433.
26. Gunderson LL, Nelson H, Martenson JA et al. Locally advanced primary colorectal cancer: Intraoperative electron and external beam irradiation +/- 5-FU. *Int J Radiat Oncol Biol Phys* 1997; 37: 601-614.
27. Pezner R, Chu D, Ellenhorn J. Intraoperative radiation therapy for patiets with recurrent rectal and sigmoid colon cancer in previously irradiated fields. *Radioth Oncol* 2002; 64; 47-52.
28. Suzuki K, Gunderson LL, Devine RM et al. Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. *Cancer* 1995; 75: 939-952.
29. Haddock MG, Gunderson LL, Nelson H et al. Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. *Int J Radiat Oncol Biol Phys* 2001; 49: 1267-1274.
30. Hashiguchi Y, Sekine T, Sakamoto H et al. Intraoperative irradiation after surgery for locally recurrent rectal cancer. *Dis Colon Rectum* 1999: 42: 886-893.
31. Mannaerts G, Rutten H, Martijn H et al. Comparison of Intraoperative Radiation Therapy-Containing Multimodality Treatment with Historical Treatment Modalities for Locally Reccurent Rectal Cancer. *Dis Colon Rectum* 2001; 44: 1749-1758.