Recurrence of the disease represents the major problem in patients who undergo "curative" resection for rectal cancer, with published rate ranging from 3 to 50%. Most relapses occur within the first two years of follow-up. Depending on the site of the recurrence, it can be local or distant. It also can be solitary or diffuse. In terms of potential surgical cure the best results are achieved with solitary, localized metastases. The most common sites of the solitary metastases are pelvis, liver and lung, with a fairly even distribution among these three sites. Other sites of the localized metastases can be peritoneum, lymph nodes, brain, bone, abdominal wall, ureter and kidney. These sites are less common, but not so amenable to resection. Local recurrence varies depending on the original type of surgery. It can be stated that surgical technique directly influences local recurrence rate in patients with rectal cancer. According to the results from a number of different authors 5-year survival rate after re-resection is 2-13% of all patients with locally recurrent cancer, both alone and associated with distant metastases. Absolute contraindications for salvage surgery are: "frozen pelvis", aneuploid tumors and those with mucinous component, clinical or CT evidence of invasion of the pelvic nerves, lymphatics or veins, or ureter bilaterally. Also, evidence of involvement of the lateral pelvic sidewalls and/or upper sacral marrow, and/or S2 is an absolute contraindication for surgery. Thus, main goals of this type of surgery are respectively: palliation of symptoms, a good quality of life and, if possible, cure with low treatment-related complication rates.

Key words: local recurrence, rectal cancer, salvage surgery

THE DEFINITION OF LOCAL RECURRENCE:
The definition of local recurrence is clinical, radiological or pathological evidence of recurrent rectal carcinoma in the soft or bony tissues of the pelvis, with exception of the ovaries, including patients with isolated local recurrence as well as those with local recurrence in association with distant metastases.

Some authors define recurrence as a re-growth of the adenocarcinoma at the resection site at least three months following radical resection, either as isolated local disease or in addition to distant metastases.

In this chapter the focus of our interest will be the recurrent disease localized inside the minor pelvis, which presents the most difficult and dangerous to cure, most often late complication of the surgery for rectal cancer.

INFLUENTIAL FACTORS IN GENESIS OF LOCAL RECURRENCE

Local recurrence has different features, depending on several factors: tumor characteristics, patient constitution and surgeons knowledge and ability.

Tumor characteristics, well known to influence the risk of local recurrence, are: location, size, mobility and gross appearance - those are the first and easiest to be assessed.

Patient constitution has two groups of risk factors. The first group makes surgery technically more difficult - narrow "male" pelvis, obese patients; it's also noted that irresectability is earlier suspected or diagnosed in male patients. The second group contains factors with negative influence on immunological status of the host - all types of immunodeficiency disorders (AIDS for example), some other systemic disorders, elderly patients, other non-related serious health conditions.

Surgeon, also, plays an important role in genesis of local recurrence. Surgery for rectal cancer is difficult one, and the surgeon and the entire team of the institution, where the patient is treated, influence its results. Results of Stockholm trial and similar studies, showed that high...
volume surgeons in high volume hospitals had significantly lower percentage of local recurrence (in Stockholm trial, local recurrence rate was 4% versus 10% when comparing high and low-volume surgeons, respectively). Also, surgeons who underwent certain basic training more frequently performed TME, sphincter saving operations and sent patients to preoperative radiotherapy.

INITIAL TREATMENT OF RECTAL CANCER

Local recurrence has different characteristics depending on the original type of "curative" surgery. Furthermore, surgical technique directly influences the local recurrence rate in patients with potentially curable disease.

Main surgical modalities in the treatment of rectal cancer depending on the number of various factors are: anterior resection (AR), abdominoperineal resection (APR), local excision, and sometimes, Hartmann’s procedure.

Regardless of the type of "radical" procedure, some basic, well established rules of rectal cancer surgery are to be followed: total mesorectal excision (TME), distal clearance, high ligation of IMA, excision of the lymphovascular "baring" segment, preservation of the vegetative pelvic nerves. Along with these rules we will address another important factor for prediction of local recurrence - circumferential margin of resection (CRM).

Total mesorectal excision (TME) is well-established "gold standard" of rectal cancer surgery, and it includes a meticulous sharp dissection of the avascular "holy" plane between visceral mesorectal fascia and endopelvic fascia under direct vision.

Distal clearance has been the subject of different discussions and speculations in the last few decades, concerning the radicality of the procedure. There is no question that the "5 cm rule" is, only, history fact now. The works of Madsen and Williams showed that, distally, tumor spreads rarely, thus making sphincter saving procedures possible, provided there were no technical limitations. Even low intersphinteric resections showed no increase in local recurrence, when compared to APR.

CRM is the most important predictive factor in genesis of local recurrence. Tumor involvement of CRM in rectal cancer is the only pathologic variable that independently influences both survival and local recurrence. The tumor that has lateral clearance less than 1 mm has much greater probability of recurring (3.5 times greater risk). It also doubles the risk of death. The accuracy of CRM status in predicting the likelihood of local recurrence is 75%. The percentage of local recurrence was 38.2% versus 10% when comparing involved and uninvolved CRM margins, respectively. 5-year survival was also influenced by CRM (72% vs. 29% when compared uninvolved and involved CRM).

Local recurrence in patients who underwent AR can be anastomotic or localized elsewhere in the pelvis. Anastomotic recurrence rarely originates from the mucosal suture line, as it may appear logical, but it originates from the wall of the bowel and is often perianastomotic. "Good" aspect of this type of recurrence is that, in contrary to APR, it provides more options for the follow-up (digital, endoscopical examination, biopsy if necessary and it can become symptomatic earlier). The reasons for the local recurrence in this type of operation can be found in biology of the tumor, the stage of the disease and in technical aspects of surgical procedure. The stage of the disease is, perhaps, the most illustrative: stage I of the disease has 5-year recurrence rate of around 10%, stage II, approximately 24% and stage III about 41%

Some authors report much better results of salvage surgery in the group of patients treated in other institutions, where well-known oncological principles (TME) of the surgery of the rectum were not completely conducted. This was explained with the longer period of time needed for tumor to infiltrate the surrounding structures, in the case of incomplete mesorectal excision. (Figure 1).
infiltration of these structures makes any attempt of salvage surgery much more difficult, and sometimes impossible. Nevertheless, symptoms of the recurrent tumor within the pelvis after the initial operation with incomplete TME occur much faster, than in those with TME.13,19,24

Salvage surgery after APR is always more difficult, and the percentage of local recurrence is much higher.21,25 Curative salvage surgery is possible in significantly lower number of cases. There are several factors that contribute to this. Usually, patients who undergo this type of operation have larger tumors in more advanced stage. Furthermore, surgical manipulations are much more limited in attempted salvage surgery, normal anatomy is much more violated. Also, follow up of these patients is much more difficult. Physical examination is not easily feasible. In women vaginal examination (especially endovaginal endosonography) is often very useful, in detecting the local recurrence, in men the only mean of follow up are radiological methods (CT, NMR, PET scan). Figure 2) Also, asymptomatic period in these patients is much longer (no apparent bleeding or obstruction).

Salvage surgery after local excision is not uncommon. Different studies report a rate of salvage surgery that ranges from 22 to 100 %.22,23,24 For patients in stage I of the disease, local excision, in recent years, has increasingly become the therapy of choice. T1 and T2 tumor can be treated with local excision but in certain strictly defined indications. T2 tumors have much greater risk of local lymph node involvement, thus are much more amenable to locoregional recurrence, and are reserved for patients, that are not in condition to undergo "radical" treatment. Despite all precautions, estimated 5-year local recurrence rate is around 28% compared to much lower percentage after anterior resection in the same stage of the disease. Immediate salvage surgery is mandatory if histopathology results are unfavorable. Poor prognostic factors in pathohistology report are: tumor invasion of muscularis propria, positive margins of resection, poor differentiation, lymphovascular invasion. The results after immediate salvage surgery are much better, than in surgery for already existing local recurrence.26,27

If pathology result is favorable, close follow-up is mandatory (every two months for 3-4 years, occasional endorectal ultrasound (ERUS)).

It should be noted, however, that results after this type of salvage surgery are less favorable than after initial "radical" surgery.27

Though salvage surgery may appear futile, around 50 % of patients with local recurrence have a solitary tumor inside the pelvis, and they are candidates for "second look" procedure. However, the number of patients that can be resected for cure is less than 50 % (between 30 and 40 %) and median survival of these patients varies from 21 to 36 months.28,29,30

Preoperative radiotherapy (PRT) is very important in treatment of distant rectal cancer. After PRT, combined with TME, percentage of local recurrence rate is significantly lower. In the Dutch trial,51 excellent results were achieved, concerning local recurrence. After TME alone, 2-year local recurrence rate was 8.2 %, and after TME combined with PRT, 2-year local recurrence rate was 2.4%. However, a number of studies,32 showed that survival after local recurrence in patients treated with PRT was reduced. It is explained with the fact that local recur-
rences after PRT may be treated less aggressively, because maximal dose radiotherapy is no longer possible as part of multimodality treatment. It is also stated that the recurrences occurring after PRT are frequently associated with distant metastases.

**FOLLOW-UP**

As mentioned at the beginning of this text, close follow-up is mandatory for patients who underwent surgery with curative intent.

Other very important factors that should closely be monitored during the follow-up are metachronous tumors, other malignancies and distant metastases. Metachronous tumors and other premalignant lesions should be mentioned here because their early detection offers a chance of a cure.

Patients with rectal and colon cancer are also amenable to other malignancies (breast, gynecological, lung) and investigations to discover those should be also included in the follow-up.

Once more we should highlight several factor, very important for good and reliable follow-up. The most important factors that can stratify risk group of these patients are: stage of the disease, as mentioned, invasion into adjacent structures, tumor fixation and grading, mucinous component of a tumor and adjuvant treatment. Another factor, very important, but difficult to ascertain is surgeon.

Close follow-up of patients should be maintained for three, not two years. In order to rationally distribute the resources, patient should be divided into three risk groups and followed accordingly.

**DIAGNOSIS OF LOCAL RECURRENCE**

The early detection of local recurrence is one of the main goals of follow-up.

Most relapses, when discovered, are either locally extensive or widespread disseminated; occur, as mentioned, within a 2-year period from initial "curative" operation. However, a small number of patients are in good general shape, with a surgically resectable recurrence, offering a chance for potentially curative resection.

Early detection of the local recurrence can be achieved by a combination of history, physical examination, CEA and Ca 19-9 measurements, endoscopy and imaging (CT, NMR, FGD-PET scan, ERUS). In any clinical situation, there is frequently a single test that gives the physician the first hint of recurrent cancer.

Usual symptoms of a recurrent tumor are: pelvic pain (sometimes with radiation to lower extremities), rectal bleeding and change in bowel habits. For easier classification and assessment of treatment and prognosis, we can divide patients into groups, according to symptoms as S0- asymptomatic, S1 symptomatic, without pain, S2 symptomatic with pain.

It must be noted that a significant number of patients (around 50 %) appear to be asymptomatic, despite evident recurrent tumor; certainly, if a patient complaints of a number of nonspecific symptoms, the physician’s index of suspicion should increase.

Physical examination can reveal a palpable mass within a minor pelvis; Digital examination may be very useful in detecting recurrence, which may be amenable to further surgery.

A review of symptoms and physical examination can reveal the recurrence in 21 % of cases.

Also, CEA level should be monitored regularly and its significant rise can lead to further investigations in early detection of local recurrence. The ability to predict recurrence when the serum CEA is elevated preoperatively (the sensitivity of a test) ranges from 43% to 98%, and the ability to predict that recurrence will not occur if the preoperative serum CEA is normal (the specificity of a test) is higher (range 70% to 90%) as reported an accuracy for CEA estimation of 84 % if the upper limit was set at 7.5 ng/ml. Other authors defined an abnormal CEA assay as three progressively rising CEA values over postoperative baseline with at least one value over 10 ng/ml. Computed tomography (CT) may provide useful anatomic information when evaluating hepatic metastases, but has limited accuracy in predicting resectability for cure because of its failure to detect other small lesions in the liver, or metastases elsewhere in the body. Also, the evaluation of CT scans should be taken with caution, because of a significant percentage of false-positive results in detecting recurrent disease, especially in the liver and the pelvis.

Magnetic resonance imaging (MRI) may be more sensitive than CT in detecting direct invasion of the sacrum in the patients with pelvic tumor recurrence, but both CT and MRI are not so successful in differentiating pelvic recurrence form postoperative fibrosis.

Fluoro-deoxy-glucose positron emission tomography (FDG-PET scan) is a relatively new, very useful, procedure that exploits the increased rate of glycolysis in tumor cells. (Figure 3) It can successfully distinguish scar, from tumor tissue, which can prevent an unnecessary "second look" surgery. Schiepers et al. compared CT and FDG-PET in the evaluation of 74 patients for recurrent colorectal cancer and found that specificity and sensitivity of FDG-PET to be much better (98% and 92%) than those of CT (60% and 72%).

A number of other diagnostic methods are available, and in some cases of crucial importance in deciding whether the patient is a candidate for curative procedure: barium enema, full lung tomography, intravenous pyelography (IVP), liver, spleen and bone scintigraphy.

Some new diagnostic tools are being evaluated, for example- Carcinoembryonic antigen radioimmunodetection of colorectal cancer recurrence. It is a method compatible to CT scan and potentially can help in avoiding more invasive diagnostic methods. Lechner et al. report an overall accuracy of 91.6% in detecting recurrent colorectal cancer, which is superior to the results that could be obtained by the means of CT scan and/or endoscopy. Also, immunoscintigraphy detected more lesions in extra-hepatic areas, compared to CT scan.
In ideal circumstances a diagnostic laparoscopy could provide highly accurate information, and help in avoiding further more invasive surgery. However, aside from its invasive nature, sometimes it is very difficult to explore all areas of interest, without excessive manipulation.

When all other, non-invasive diagnostic methods fail to confirm the existence of highly suspectable recurrent tumor, "second look" surgery is indicated.

**SURGICAL TREATMENT OF RECURRENT DISEASE**

Local recurrence of rectal carcinoma is a great challenge for a surgeon. Contrary to the majority of other locally recurrent tumors in the digestive system, it’s possible to radically remove locally recurrent rectal cancer.

Based on results from a number of different authors,5-year survival after re-resection is 2-13 % of all patients with locally recurrent cancer, both alone and associated with distant metastases, we can say that the goals of this kind of surgery are respectively: palliation of symptoms, a good quality of life and, if possible, cure with low treatment-related complication rate.

The ideal goal of salvage surgery is to accomplish en bloc R0 resection, if it’s technically feasible and safe. Palliation can also be a very important goal of re-resection, preferably without extensive surgical procedures, unless disabling complications of sepsis or bleeding are an issue.

The decision for salvage surgery should be brought on the basis of:

- Patients general health—the patient should be fit enough for potentially extensive surgery.
- Necessary surgical expertise should also be available for these operations, which should be undertaken in the specialized centers were a multidisciplinary team is available.53

The most important moment in this problem is to decide when not to operate. The first and most obvious contraindication for surgery is "frozen pelvis", the condition where recurrent tumor involves all structures of the minor pelvis, including the pelvic walls.

In addition, aneuploid tumors and those with mucinous component have negative impact on survival53.

The next contraindication is clinical or CT evidence of invasion of the pelvic nerves, lymphatics or veins, or ureter bilaterally (as indicated by the presence of sciatic pattern of pain, unilateral swelling of the lower limb and bilateral hydronephrosis, respectively). Also, evidence of involvement of the lateral pelvic sidewalls and/or upper sacral marrow, and/or S2 is an absolute contraindication for surgery.53

In order to easier evaluate the impact of fixation of the tumor for the surrounding structures, recurrent tumors were classified as: F0 non-fixed, F1 fixed to the one side, F2 two sides, and F3 three or more sides.53 Afterwards, the pathohistological report gives us more data: grade, stage and the potential presence of lymphatic, venous or perineural invasion.

Every surgical procedure begins with an explorative laparotomy. Peritoneal seeding, unexpected liver metastases and invasion of para-aortic lymph nodes are, in general, contraindications for continuing with a procedure. It is recommended to avoid injury of critical structures before the decision on resectability.

Pelvic recurrences are usually amenable to resection if they are strictly anterior or posterior. Lateral sidewall involvement diminishes a chance for R0 resection, as well as involvement of two pelvic walls simultaneously (fixation degree F2). Recurrent tumor that occurs below S2 level is amenable to resection by distal sacrectomy; unfortunately, the existence of tumor in this location usually excludes R0 resection. Similarly, unilateral tumor involvement of blood vessels distal to the aorta may be resectable, bilateral affection of these structures with the recurrent tumor is a contraindication for radical resection. When prostate or base of the bladder are minimally adherent to the recurrent tumor, and have good function it’s preferable to attempt combined external-beam radio therapy (EBRT) with infusional 5-FU, followed by organ preserving resection and intra-operative radio therapy (IORT). The alternative to this is pelvic exenteration. In cases of more advanced disease and the existence of severe postoperative and postirradiational adhesions, can’t be avoided.

Another downside of surgery for recurrent rectal tumor is the problem of intestinal continuity. It’s rarely possible or reasonable to create another anastomosis in that kind of surroundings which is at high risk of another relapse. In some series of patients treated for local recurrence even 93 % of them ended up with permanent colostomy. Nevertheless, sometimes, in highly motivated patients with favorable local findings (mucosal anastomotic recurrence), it’s possible to perform a low coloanal anastomosis. To perform a low anterior resection with anastomosis, in these situations, moderate doses of preoperative EBRT and chemotherapy are needed. Unfortunately, usually, a previous low AR is being converted to an APR, and previous APR to an abdominosacral resection or pelvic exenteration.

If at the end of resection it is decided that postoperative EBRT in needed, vascular clips should be placed in the area of peritumoral fibrosis or residual tumor tissue.53

Extensive procedures employed in treatment of local recurrence carry significant risk. Patients suffer significant blood loss, morbidity, mortality, longer hospital stay and operative time. Postoperative complications also occur: infectious disease (sepsis, intrabdominal abscess, enteric fistula, wound infection), urinary disease (fistulous communications with other organs, stenosis, anastomotic leak), and bowel obstruction.58 The incidence of complications after abdominosacral resection, for example, according to some authors, is higher than 80%. The commonest are: perineal wound complication (48%) and urinary retention/incontinence, followed by peritonitis, pneumonia, pyelonephritis, and different fistulous communications, respectively.59

Mortality rate after these complicated procedures are less than 5%.63
NON-SURGICAL TREATMENT OF LOCAL RECURRENCE

Although, the surgery plays the major role in therapy for recurrent local disease, other modalities of therapy should be considered. Maintenance of chemotherapy as a component of aggressive treatment approach is recommended, because a local relapse is a prelude of distant metastases in about 50% of cases.

Radiotherapy in all of its modalities deserves an important place. Reduction of pain and bleeding was achieved in majority of patients, whereas a response to other pelvic symptoms was not apparent. Unfortunately, the duration of effective palliation is achieved for only about one third of remaining life span of the patient.

Also, complications of this mode of therapy are not to be disregarded.

In conclusion, EBRT and IORT when combined only with R0 resection improve results of therapy.

PROGNOSTIC FACTORS

It is interesting to review all factors mentioned (operative, operative and post operative) and establish their influence on postsalvage survival rates.

Patients age, gender and the initial stage of primary tumor do not appear to change postresection survival rate. Prior APR, presentation with pain, elevated CEA levels and unresectable disease are adverse factors. Completeness of resection strongly influences survival, which is significantly shorter in R2, than in R0 and R1 cases. R0 resection is, of course, in correlation with the best results.

Patients with prior APR have significantly worse prognosis than those with AR. They more frequently present with pain, elevated CEA levels, and experience longer period between primary and salvage operation. Longer period is explained with no possibility for digital examination, sigmoidoscopy, or changes in bowel habits. Reported resectability rate after APR is 60% and after AR is 86%. But on the positive side, in case of resectable disease, there is no statistically significant difference in post-salvage survival rates between APR and AR, though results after AR tend to be better. As mentioned, the best results in salvage surgery are achieved after local excision when the indication for operation is unfavorable pathohistological report.

In other cases, the most favorable outcome is achieved with patients who had recurrent disease within the bowel wall.

Many attempts have been made to determine the value of prognostic predictors, for patients planned for curative salvage surgery (St. Marks group, Mayo Clinic group). So far, no consensus was made. The only predictive factor, for now, that appears to be valuable is the tumor diameter larger than 3 cm, and tumor fixation degree 2. However, it can be useful to follow the recommended tests, CEA level of 9 ng/ml, if reached in non-smoker, laparotomy is indicated even if all other tests are negative.

CONCLUSION:

Surgical treatment of locally recurrent rectal carcinoma after initial curative surgery is not always curative, but can provide good palliation of severe pain, bleeding, perforation, obstruction and sepsis. These procedures can be carried out with minimal mortality rates (0.8%) and can benefit in long-time survival benefits. More than 50% of patients could undergo a curative (R0) resection. It requires careful consideration of several most important factors: procedures must be carried out by an experienced, high volume surgeon, with a considerable expertise in this field, patients together with the type of salvage procedure must be selected carefully, considering all factors listed above. Procedures should be carried out in high volume hospitals.

Meticulous follow-up and early detection of recurrence are conditions for curative salvage surgery. Advanced stages of disease may not always be a contraindication for operative treatment, providing a good surgical strategy and tactics.

Multidisciplinary approach and teamwork are ultimate conditions for success. Besides surgery, which is a dominant method of treatment other modalities of therapy, namely hemio and radiotherapy, should be included.

SUMMARY


Ključne reči:
REFERENCES:


