Risk factors in the recurrence of the colorectal cancer

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Traditionally, the clinical outcome of colorectal cancer patients may be predicted by pathological staging by either Dukes staging or the UICC-TNM system. However, some of Dukes stage A (approximately 10% of patients) and Dukes B patients (30-40%) will develop local recurrence or distant metastasis years after receiving standard surgical treatments. Therefore it is important to find some other indicators that can predict for recurrence so that we can screen for high-risk early-stage patients who may need preventive chemotherapy or other adjuvant therapy. The aim of this study is determination of risk factor for local recurrence in rectal cancer. In this study there has been used and summarized also research records and publications from different clinical hospitals according to actual international literature. Part of elements connected with patient, tumor and genetic and immunological factors remains independent on curative procedures. However better investigation these factors might affect on therapy, frequency of follow-up examinations, and help to detect recurrence at very early phase. Concomitant treatment factors are able to be moderate by surgeons and therapeutics. Therefore precise definition of risk factors might be helpful in decrease recurrence rate in patients with rectal cancer.

Key words: colorectal cancer, pathological staging

PATIENT AND TUMOR FACTORS

The main patient factors are: age, gender, family history of colorectal cancer and general patient condition. Gender is thought to be the most important and independent predictor of recurrence in rectal cancer. Male patients have a worse prognosis compared with female patients. Even in stage I rectal cancer male patients have triple higher recurrence rate than women (15% comparing with 5-7% respectively). Prognosis depending on age is more complicated. Local recurrence rates decrease with age and it is 23% for age 15-64, 18% for age 65-74, 14% for age 75 and over. Lower recurrence rate in elderly is partly determined by higher postoperative mortality rate (not cancer connected only) and lower participation in follow-up investigations. There is no correlation between general condition and frequency of recurrence in rectal cancer. The same concern of family history of colorectal cancer except patients with hereditary tumors (f.e. HNPCC, FAP) in which risk of local recurrence might reach even 80%. The concomitant tumor factors which are actually taken as risk for recurrence are: tumor status (staging, size, differentiation), localization and mobility, tumor ulceration and blood vessel invasion. T stage and Dukes stage remain basic factors in making decision of treatment. Local recurrence increase with T stage and it is respectively: 3-5% for T1, 12% for T2, 21% for T3 and 18% for T4 tumors. T4 tumors have lower recurrence rate because of worse survival and impossibility to surgical excision part of primary tumors. Tumor size is defined by its largest diameter more or less than 40 mm. This factor is significant in stage I disease only. Recurrence rate at this stage is 0.5% for 40 mm or less and 3% for more than 40 mm in diameter. Tumors are usually described as well, moderately and poor differentiated according to glandular configuration at histological level and nuclear polarity at the epithelial cell level. Risk of recurrence is strictly correlated with tumor differentiation and is less than 1% for well differentiated, 9% for moderately and 18% for poorly differentiated or undifferentiated tumors. Most of poorly differentiation tumors were of T2 or more T status during primary surgery and often presenting an ulceration, which is also connected with worse recurrence prognosis. S-phase fraction (the percentage of cells in the S-phase) determining the tumor proliferative activity can be measured on an intraluminal biopsy before therapy. Tumors with a low S-phase fraction exhibit a higher recurrence rate, which has been postulated to result from relative resistance to radiotherapy of slowly proliferating cells. The recurrence rate according to tumor ulceration is
little higher in patients with ulceration in tumor compared with non-ulcer tumors (15% vs. 10%), but it do not affect on survival. Tumor localization is also one of recurrence predictor. The risk of recurrence is the least for proximal tumors located more than 11 cm from anal verge and it is less than 5%. It increases to 7% for tumors located between 6 and 11 cm, and to 15% for tumors located less than 6 cm from anal verge. Tumor mobility remains a dominant factor in choice of surgery. The better tumor mobilization with lack of infiltration circumferential tissue decrease risk of residual cancer cells and local recurrence. Moreover worse mobilized tumors are usually at worse T stage and poorly differentiated3. Blood vessel invasion is an independent predictor of recurrence in stage 1 disease. Male patients with BVI have a rapid rate of recurrence with almost 100% recurring by 24 months, unless adjuvant therapy has not been advocated. In patients with more advanced tumors BVI often coexisted with lymph node metastases in mesorectum15.

**GENETIC AND IMMUNOLOGICAL FACTORS**

There are some genetic and immunological factors affecting to risk of local recurrence in rectal cancer, including: alteration in APC gene, CD 44 v 6 and v.8-10 presence on tumor cells. p53 overexpression, CEA level. Mutation of APC gene is present in rectal tumors is course of familial adenomatous polyposis. FAP tumors have very high recurrence rate of 42%. Therefore, patients with FAP require more often follow-up examination. Examinations should be proceed whole their life, not 5-years period after surgery only8. Immunological detection of CD44 variants 6 and 8-10 in rectal cancer tissue induces twice higher risk of local recurrence - 24%, than in CD44-negative tumors (10% recurrences)11. Nuclear p53 protein is closely related to the development of postoperative recurrences in rectal cancer. Positive overexpression is more frequent in tumors with blood vessel invasion. Otherwise the lack of p53 protein expression is associated with poor response to preoperative adjuvant therapy, because p53 plays critical role in the induction of apoptosis and the apoptosis rate is correlated with the therapeutic effect of chemo radiotherapy6. Elevated CEA level is connected with increase risk of recurrence from 3% to 13%. CEA level has been measured preoperatively and 2 and 4 weeks after surgery. Patients with preoperative normal CEA level have the lowest recurrence rate; most of them have T1 or T0 tumors. The highest risk of recurrence is in-group patients with persistent elevated CEA level in 4 weeks after tumor excision. High postoperative CEA level might suggest incomplete resection or metastatic micro foci presence15.

**CLINICAL FACTORS**

Among clinical factors affecting recurrence risk there are: preoperative obstruction, tumor perforation, surgery, adjuvant therapy. Coexistence of preoperative obstruction with high recurrence rate has been explained by large size of tumors, which cause obstruction. Other recurrence risk factors as tumor perforation or urgent surgery usually are associated with obstruction. Migration of carcinoid cells with transudate through intestinal wall has not been proved, but some authors suggest such possibility.4,14. Undoubtedly tumor cells dissemination occurs as a result of tumor perforation. This factor is not quite independent - if often coexists with other risk factors such as advanced carcinoma, tumor ulceration, urgent surgery, septic complications. Risk of local recurrence is increased to 30% both by preoperative tumor perforation and perforation caused by surgeon intraoperatively16.

**Importance of treatment for risk of recurrence**

Factors concomitant surgery, which has been investigated as influence recurrence are: type of resection, circumferential margin involvement, and number of lymph nodes in respected specimen, surgeon experience. Abdominoperoineal excision of the rectum has been the surgical treatment of choice for rectal cancer of the lower third of the rectum for decades. However subsequent to technical developments particularly stapling instruments, sphincter saving procedures such as low anterior resection superseded abdominoperoineal excision in the majority of rectal tumors. Complete lymphadenectomy with high ligature of the inferior mesenteric artery and total mesorectum excision are fundamental components of this approach. Within last years clinical investigations has demonstrated that cure rate were not compromised by these techniques. Conversely, sphincter saving resection offered similar recurrence rate and oncologic cure rates even superior to abdominoperoineal excision.

For example Lavry and Fazios study from 1997 showed 23% recurrences after APR and 28% after AR. Four years later, in Wibe and Rendedals examination the recurrence rate after AR decrease to 12% and was lower than after APR (17%)9,12,14. Circumferential margin involvement is more an indicator of advance disease than inadequate local surgery. Recurrent disease has been seen in 50% patients with margin involvement. In case of lack of carcinoid cells in margin recurrence rate is 22% for margin less than 1 mm, 8% for margin less than 5 mm, below 3% for margin 10 mm and more from tumor border7. Risk recurrence is significant lower when 10 and more lymph nodes in resected specimen have been found. 50-78% lymph node metastases are less than 5 mm in diameter and can be detected by using monoclonal antibodies against cytokeratin. Presence of cytokeratin positive cells in the lymph nodes correlated with a high risk or recurrence and it is indication for aggressive adjuvant therapy. There are several techniques that are important for recurrence rate. Of greatest apparent importance is the adequacy of mesorectal excision, distance from tumor margin detected by surgeon in situ, intraoperative local tumor spillage, en block resection technique, skill and extent of regional lymphadenectomy. In general, higher local control and lower recurrence rate has to be expected for specialized colorectal surgeons with at least 10-years experience9. Adjuvant pre- or postoperative chemo radiotherapy improves survival in II and III stage disease, but do not influence recurrence rate. Adjuvant therapy de-
crease risk of recurrence in high-risk patients at stage I disease.\textsuperscript{10,13}

**CONCLUSION**

Following factors increase risk of local recurrence: male gender age 60 T3-T4 tumor status tumor size 40 mm localization 6 cm from anal verge tumor ulceration low differentiation of cancer blood vessel invasion APC gene mutation CD 44 v.6 and v.8-10 positive tumors elevated preoperative CEA level tumor perforation circumferential margin 10 mm number of lymph node in resected specimen 10 inexperienced surgeon Patients presenting few risk factors should be finding as high-risk group for local recurrence. The adjuvant therapy and close follow-up in these patients is recommended. The average recurrence rate has decreased for last ten years from 23% to 15%. Finding high-risk patients, especially at early stage of disease may help to diminish this risk.

**REFERENCES**