PROGNOSTIC FACTORS IN RECTAL CANCER

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Identifying prognostic factors in rectal cancer is very valuable for choosing the method of treatment. Prognostic factors play an important role in making decision of margin of surgery, treating with pre- or postoperative radiochemotherapy. In last few years, apart from traditional clinical and histopathological factors, also genetic, biochemical and immunological factors there are taken in the consideration of the prognosis. In this study there has been used research records and publications from different clinical hospitals according to actual international literature.

Prognostic factors in rectal cancer might be divided into a few group:
1. Patient factors
2. Tumor factors
3. Concomitant tumor factors
4. Genetic and immunological factors
5. Factors associated with the treatment

The main **patient factors** which are actually taken as prognostic are:
- age
- gender
- family history of colorectal cancer
- general condition

Due to the aging of the general population, there has been a relative increase of elderly patients with rectal cancer. Prognosis depending on age is different for local recurrence rate and metastases from prognosis for 5-year survival. Metastases and local recurrence occurs less frequently in the elderly. Local recurrence rates decrease with age and it is respectively: 23% for age 15-64,18% for age 65-74,14% for age 75 and over. Different studies reported conflicting results of relationship between age and survival rate. 5-year survival seems to be similar in the three age groups, or a little better in the younger group. However, more favourable prognosis in younger patients is also connected with better general condition and it lowers the postoperative mortality rate, which is 1 % for patients younger than 60 years, than it steadily increases with age and for patients 80 years and older the operative risk is 10%. On the other hand, the youngest group with colorectal cancer includes patients with hereditary tumors, in which the risk of local recurrence and secondary tumors might reach even 80%. The 5-year survival in this group is only 41% for patients younger than 60 years, compared with 70% for patients with a negative family history.

Gender is thought to be the most independent patient predictor of recurrence and tumor-related mortality. Male patients have a worse prognosis compared with female patients. In stage I rec-

tal cancer, male patients have a recurrence rate of 15%, which is greater than the 5% recurrence rate of females. The 5-year survival of male patients in this stage is only 85% compared 98% survival rate for female patients. There was some speculations that outcome differences between male and female patients might be related to the extend of lateral clearance, because wide lateral margins are more difficult to obtain in the male pelvis. However, differences have been still present between male and female patients group with similar lateral and distant resection margin and similar numbers of recovered lymph nodes. More recently male gender has been shown to be an independent adverse prognostic factor also in patients with stages II and **in** rectal cancer.
A general condition is rather subjective factor. Mainly state of nutrition, anemia, coexisting diseases and liver function are considered. The liver function tests are thought as the most objective and significant of these factors. The abnormal liver function tests correlate with a short survival after surgery (examinated groups included patients with liver metastases).

The **tumor prognostic factors** are:
- **T** stage;
- Dukes' stage;
- tumor location;
- tumor mobility;
- size and depth of invasion;
- type of exenteration;
- presence of tumor ulceration;
- intratumoral blood vessel invasion (BVI);
- intratumoral lymphatic vessel invasion;
- neural invasion;
- histologic differentiation.

T stage and Dukes' stage remain basic factors in making decision of treatment. The table 1 shows correlation of T N M stage of colorectal cancer with Dukes' classification.

	T N M stage	Dukes' stage
Tis NO MO T1 NO MO T2 NO MO	I	A
T3 NO MO T4 NO MO Every T Nx MO	II Not staged	B
Every T N1 MO Every T N2-3 MO	III	C
EveryT, every N, M1	IV	D

Nx - regional lymph nodes cannot be assesed

T N M stage is the strongest predictor of clinical outcome and it is confirmed as a factor with the strongest independent effect on survival. Survival rate is respectively: 77-84% for stage I, 56.1% for stage II, 34.8% for stage III, 0.0% for stage IV and 57% for not staged tumors. Approximately 25% of rectal cancer patients present with stage I disease. The rate of local recurrence in these patients is 7% for Tl and 12% for T2, but it increases even to 48%, when other risk factors like male gender; blood vessel invasion and poor differentiation coexist. Adjuvant chemotherapy plus pelvic radiation has evolved as a standard of care for rectal cancer patients with stage II or III disease. It is not recommended for stage I rectal cancer, except the group of high-risk patients in which adjuvant therapy reduced the rate of recurrence and lead to an improved survival.
Tumor location is valuable prognostic factors in primary rectal cancer. Patients with proximal rectal cancers (>6 cm from the anal verge) have lower recurrence rate and better survival prognosis than patients with tumors of the distal rectum (< 6 cm from anal verge). Some authors suggest that an anterior tumor location has a significantly higher survival rate than other positions. Two-thirds of anterior tumors are of pathologically favorable Dukes' stages. However, the majority of studies provide that the posterior-located tumors, as infiltrating mesorectum instead of other organs, give better possibility of total excision. So that, in patients with posterior-located tumors the risk of recurrence is lower, and prognosis of survival is better.
Tumor mobility remains a dominant prognostic factor in patient selection and choice of surgery.
Size of the tumor is defined by its largest diameter more or less than 40 mm. This factor is significant in stage I disease only. Survival rate is 50.1% for 40 mm or less and 43% for more than 40-mm tumor diameter.
Rectal tumors with the infiltrating type of growth have a significantly worse prognosis than those with the expanding type. Expanding tumors have a well-delineated and circumscribed border of growth, while infiltrating tumors have cluster or single cells leaving the tumor mass and spreading into the bowel wall. Infiltrating tumors present more often blood vessel invasion and have much higher risk of recurrence and metastases. Better survival rate in patients with the expanding tumors (63.6% compared with 25.1% in infiltrating tumors) might be connected with the earlier diagnosis because of bleeding from rectum, which is a symptom often associated with these tumors.
The recurrence rate is a little higher in patients with tumor ulceration (15% compared with 10% for non ulcer tumors). Survival is similar for both tumor types.
Patients with either intratumoral vascular or lymph vessel invasion have a worse survival prognosis. Blood vessel invasion (BVI) is an independent predictor of recurrence and tumor related mortality in stage I disease. Male patients with BVI have a rapid rate of recurrence with almost 100% recurring by 24 months. Survival rate in all patients at stage I with BVI is 66%, compared with 80% in patients without BVI. In male patients with BVI mortality is 80% by 36 months. In patients with more advanced rectal cancer vascular or lymph vessel invasion is associated with an increased incidence of hepatic metastasis.
Pattern of tumor differentiation is usually described using two main features: glandular configuration at the histological level and nuclear polarity at the epithelial cell level. Tumors are described as well, moderately and poor differentiated. In poorly differentiated and undifferentiated tumors, glandular configuration and nuclear polarity are almost completely lost. Survival rate is strictly correlated with tumor differentiation and it is 72% for well, 47.5% for moderately and 25.4% for poorly differentiation tumors. Another histological factors of prognostic value are lymphocytic infiltration and extent of fibrosis. Survival rate is significantly higher in patients with extensive lymphocytic infiltration and little fibrosis in tumor. D N A ploidy and S-phase fraction can be measured easily on an intraluminal biopsy specimen before therapy is instituted. S-phase fraction (the percentage of cells in the S phase) determines the tumor proliferative activity. S-phase fraction is a statistically significant predictor of survival, especially in Dukesi C patients. Patients with S-phase fraction 10% or greater have 17 time greater chance of dying of rectal cancer, than patients with S-phase fraction less than 10%. On the other hand, tumors with a low S-phase fraction exhibit a higher local recurrence rate. This has been postulated to result from the relative resistance to radiotherapy of slowly proliferating cells.

The main **concomitant tumor factors,** which influence prognosis are:
- extrabowel skipped cancer infiltration
- lymph nodes metastasis
- liver metastasis
- synchronous primary or secondary tumors

During a pathologic examination, cancer nodules, and not lymph node metastases are often seen in the fatty tissue outside the rectum. This type of cancer spread is called extrabowel skipped cancer infiltration (ex) and indicates the aggressive biologic activity of rectal cancer. The overall recurrence rates after curative surgery are 58% for ex(+) group compared with 24.0% for ex(-) group. The ex(+) group exhibited a significantly worse survival. Therefore an extended dissection, postoperative adjuvant therapy seems to be necessary for patients with ex.
Lymph nodes metastases correlated with a short survival. Presence of lymph node metastases is included in T N M classification. Recent studies indicate that an accurate search for metastases in lymph nodes smaller than 5 mm in diameter seems to be important for staging. Researches demonstrated metastatic involvement in 50-78% lymph nodes measuring less than 5 mm in diameter. The use of monoclonal antibodies against cytokeratin in detecting occult microembolic metastases in lymph nodes of Dukes' stage B patients may improve the accuracy of pathologic staging. Presence of cytokeratin positive cells in the lymph nodes correlated with a poorer prognosis and it is indication for aggressive adjuvant therapy.
Liver metastasis is a poor prognostic factor. The mean survival time is 8.5 months for all patients. Prognosis is even worse in case of bilateral hepatic involvement, multiple tumors, abnormal liver function tests and other distant metastases.
In case of synchronous secondary tumors prognosis is very poor. Synchronous primary tumors might indicate hereditary character of disease.

New treatment strategies need to be coordinated with evolving knowledge about **genetic and immunological factors** connected with rectal cancer. There are:
- c-Ki-ras mutations
- C-myc mutations
- A P C gene mutations
- expression of C D44 variants 6 and 8-10
- nuclear p53 overexpression
- DCC-protein expression
- preoperative carcinoembryonic antigen level

c-Ki-ras and C-myc mutations have been implicated in tumor initiation and progression. A P C gene, p53 and D C C are also tumor suppressor genes implicated in rectal tumor carcinogenesis.
The relation between phenotypic expression in patients with familial adenomatous polyposis (FAP) and the site of mutations in the A P C (adenomatous polyposis coli) gene was examined. Germline mutations in the A P C gene cause FAP. Patients with severe polyposis have an increased rectal cancer risk. Present data support an association between severe polyposis phenotype and mutations at A P C gene codons 1309 and 1328. For other mutations phenotype is more variable. The prognosis in patients with these mutations is poor. Rectal cancer in these patients has a predisposition for local recurrence. Total proctocolectomy with end ileostomy should be performed in case of colorectal cancer in these patients.
C D44 variants 6 and 8-10 have been known as the useful marker of tumor progression. About 50% rectal tumors are positive for C D44 v.6 and v.8-10. There is significant correlation between C D44 immunoreactivity and both lymph node and hematogenous metastases and high recurrence rate. Survival rate is significantly lower in C D44 v.6 and v.8-10 positive cancer. Therefore C D44 v.6 and v.8-10 may be a biological prognostic markers.
Nuclear p53 protein is closely related to the development of postoperative recurrences of rectal cancer and has higher predictive value than standard pathological variables. Positive overexpression is more frequent in tumors with blood vessel invasion, p-53 - positive tumors show a higher likelihood of relapse and lower survival. The tumor-suppressor gene p53 encodes a transcription factor that plays a critical role in the induction of G1 cell cycle arrest and apoptosis after D N A damage. The rate of apoptosis is strictly correlated with the therapeutic effect of hypertermochemoradiotherapy. This effect occurs through apoptosis. This combined therapy can induce an additive or synergistic anti-tumor effect in rectal cancers with wild-type p53 as well as in those with mutated p53 through papooses, offering new therapeutic opportunities and a better prognosis.
D C C protein, for which a gene is located on chromosome 18q has recently been reported to have a prognostic value in colorectal cancer in predicting metachronous distant metastases after treatment. Expression of D C C protein was assessed in tissues from patients who developed distant metastases but no local recurrence. Nonexpression of D C C protein has an negative influence on survival for all tumor stages. In stage **II** cancers the negative predictive value was 88%. So, D C C is a useful prognostic marker in patients with rectal carcinomas for survival and occurrence of metachronous metastases.
High preoperative carcinoembryonic antigen level correlated with local recurrences, distant metastases and low survival rate

In prognosis of rectal cancer also **factors associated with treatment** are considered, such as:
- the number of lymph nodes found in resected specimens
- circumferential margin involvement
- postoperative septic complications
- adjuvant pre- and postoperative therapy

In patients without involved lymph nodes the long-term survival and local recurrence rates are significantly better when more than 10 lymph nodes are present in resected specimens. When fewer than 10 nodes are found, whatever the cause, adjuvant radiotherapy has to be considered, especially in patients having infiltrating T3 tumors.
Circumferential margin involvement is more an indicator of advance disease than inadequate local surgery. Both disease-free survival and mortality are related to margin involvement. Recurrent disease has been seen in 50% of the patients with a positive margin.
The actual survival rate of patients with major septic complications (like anastomotic dehiscence, peritoneal abscess) is significantly lower than that in noncomplicated cases. No statisical difference is observed in the survival of patients with minor septic complications (wall abscess).
Adjuvant pre- or postoperative chemoradiotherapy improve survival in **II** and **III** stage disease and in high-risk patients at I stage.

Conclusion
In patient selection and choice of treatment many prognostic factors should be considered simultaneously. Both recurrence rate and survival rate depend on many factors connected with each other. With the Cox model the following prognostic index (PI) was formulated:
PI = 1.37 x (gender)... 2.05 x (age)... 0.06 x (tumor status) + 1.85 x (type of exenteration)
-1.46 x (treatment)... 2.91 x (chemotherapy) + 2.83 x (S-phase fraction)
1.34 x (D N A ploidy)
When the parameter values are:
gender: 0 for male; 1 for female
age: 0 for <54 years; 1 for >54 years
tumor status: 0 for primary; 1 for recurrent
type of exenteration: 0 for posterior; 1 for anterior or total
treatment: 0 for other; 1 for irradiation and surgery:
chemotherapy: 0 for other; 1 for chemotherapy and surgery and radiation
S-phase: 0 for 9%; 1 for 10% or more
D N A ploidy: 0 for diploid; 1 for aneuploid.
According to PI, low-risk patients (PI of less than 1.37) have a 5-year survival rate of 68%, whereas high-risk patients (PI of 1.37 or more) have a survival rate of 24% only.

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