SUMMARY

The prognostic value of the expression of e-cadherin, β-catenin, vimentin and tumor budding in the rectal cancer and its relationship with selected clinical and pathological factors

Introduction

Rectal cancer still remains a great epidemiological issue in high – developed countries. It is the third greatest cause of neoplasms in male patients and the second largest in female patients worldwide. At the beginning of the 21st century in Poland a very dynamic increase of incidence of rectal cancer was observed. The mortality rate, as a result of rectal cancer, is still higher in Poland comparing to the other European Union countries. Although, the differences decreases each year, consecutively.

The treatment of colon cancer is complex and interdisciplinary. Introduction of total mesorectal excision in surgical armamentarium caused improvement in 5-year overall survival rates and local control. Preoperative hypofractionated radiotherapy (5x500 cGy) with surgical procedure within one week after the ending of irradiation is associated with better local control compared to surgery alone. The irradiation according to these schemes is the preferred one if downsizing of the tumor is not necessary.

The main cause of death in rectal cancer is dissemination. The differences in treatment results among patients in the same stage of disease are observed. The approved clinical and pathological risk factors for recurrence do not allow for precise identification of patients with rectal cancer to proper treatment. There is still a need for searching for new additional factors such as *tumor budding* with the expression of e-cadherin, β-catenin and vimentin, that can provide better prognostic information.

Objective

The main objective of study was to evaluate the probability of the overall observed survival, disease free survival, distant metastasis and local recurrence free survival in patients with advanced rectal cancer depending on *tumor budding*, the expression of e-cadherin, β-catenin and vimentin.

It has been assumed that the main objective will be achieved accomplishing the following detailed targets:

1. Assessment of the rate of incidence of *tumor budding* with the assessment of the expression of e-cadherin, β-catenin and vimentin in the invasive tumor front.

2. Assessment of the impact of *tumor budding* on overall observed survival, disease free survival, distant metastasis and local recurrence free survival.

3. Assessment the expression of e-cadherin, β-catenin and vimentin on the overall observed survival, disease free survival, distant metastasis and local recurrence free survival.

4. Assessment of the relations between the analyzed clinical and pathological factors and *tumor budding*, expression of e-cadherin, β-catenin and vimentin.

5. Assessment of the impact of analyzed clinical and pathological factors on the overall observed survival, disease free survival, distant metastasis and local recurrence free survival.

6. Assessment of the usefulness of the selected clinical and pathological factors in predicting the risk of death and relapse in patients treated for advanced rectal cancer.

Material and methods

The study is retrospective. The approval of Bioethic Committee of Collegium Medicum Jan Kochanowski's University was obtained (39/2020).

The material for the study comprised the clinical data of 132 patients with confirmed rectal cancer. The whole diagnostic process and treatment procedures were conducted in Holy Cross Cancer Center in Kielce, Poland in the years 2000 – 2014. The analysis was based on the patient's medical records. Observation was closed on 28.22.2018. Paraffin blocks of tissue removed during surgical procedures were analyzed. The paraffin blocks of tissues have been found in the archives of the Cancer Pathology Department of the Holy Cross Cancer Center, where all pathological examinations were performed (the presence of *tumor budding*, the expression of e-cadherin, β-catenin and vimentin).

The following factors have been analyzed:

1. Factors depending on the patient and disease: age, sex, size and localization of the tumor, symptoms, stage of the disease, the degree of cancer malignancy, perineural invasion, lymphovascular space invasion, extracapsular lymph node invasion, the type of tumor growth in the invasive tumor front, presence of

tumor budding, expression of e-cadherin, β-catenin and vimentin, pathological response to preoperative radiotherapy.

2. Factors depending on the diagnosis and the treatment: the assessment of the tumor mobility to surrounding tissues during per rectal examination, the irradiation technique, type of surgical procedure, time between the ending of irradiation to surgical procedure, the presence of surgical intraoperative and postoperative complication, the assessment of surgical margins, the implementation of chemotherapy.

Results

The presented material comprises a group of 132 patients treated for advanced rectal cancer over the period of over 14 years in Holy Cross Cancer Center.

The conducted analysis showed no significant influence in regards to *tumor budding*, expression of e-cadherin, β-catenin and vimentin on overall survival, disease free survival, distant metastasis and local recurrence free survival. However there was negative, statistically nonsignificant influence on survival probabilities.

The conducted analysis showed statistically significant relationship between the expression of nuclear β-catenin and the decreased expression of e-cadherin in *tumor budding* which is a typical phenomenon.

The multivariate analysis showed statistically significant impact of presence of nuclear β-catenin on the risk of death, relapse, dissemination and local recurrence. This type of expression caused 3 times greater risk of death.

The factors that had a significant impact on overall survival, disease free survival, distant metastasis and local recurrence free survival included: disease stage, lymph node metastasis, extracapsular lymph node invasion, perineural invasion, radial margin invasion and surgical margin invasion.

The only factor that had the negative influence on locoregional control was the invasion of radial margin.

The conducted analysis revealed statistically significant relationship between the *tumor budding* and higher stage of the disease, lymph node metastasis, extracapsular lymph node invasion, perineural invasion, infiltrative tumor type growth.

The analysis confirmed a significant effect on the risk of death, relapse, dissemination, local recurrence in the case of the radial margin invasion and expression

of nuclear β-catenin. The most important factor for predicting the risk of the abovementioned events was radial margin invasion. It increased the risk of death 5 times, recurrence and dissemination 3 times and local recurrence 5 times.

Conclusions

1. No significant influence of *tumor budding*, the expression of e-cadherin, β-catenin and vimentin on overall observed survival, disease free survival, distant metastasis and local recurrence free survival time was observed.

2. The presence of *tumor budding* showed a connection with clinical and pathological factors such as: higher stage of the disease, lymph node metastasis, extracapsular lymph node invasion, perineural invasion, infiltrative tumor type growth.

3. The analysis showed the statistically significant relationship between the expression of nuclear β-catenin and decreased expression of e-cadherin in *tumor budding*.

4. Clinical and pathological factors which had an adverse impact on overall survival, disease free survival, distant metastasis and local recurrence free survival were: disease stage, lymph node metastasis, extracapsular lymph node invasion, perineural invasion, radial margin invasion and surgical margin invasion.

5. The only factor which had an adverse impact on local recurrence free survival was radial margin invasion.

6. Based on the conducted analysis the usefulness of clinical and pathological factors such as expression of nuclear β-catenin, radial margin invasion and extracapsular lymph node invasion, in predicting the risk of death, expression of nuclear β-catenin, radial margin invasion and lymph node metastasis in predicting the risk of relapse and dissemination and expression of nuclear β-catenin, radial margin invasion and disease stage in predicting local recurrence in patients with rectal cancer, was confirmed.

Keywords: rectal cancer, preoperative radiotherapy, tumor budding, e-cadherin, β- catenin, vimentin.