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Tumor Infiltrating Lymphocytes as Prognostic Factor of Early Recurrence and Poor Prognosis of Colorectal Cancer After Radical Surgical Treatment

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1. Introduction

Sixty percent of patients with colorectal cancer (CRC) are afflicted with distant metastases (liver or lung metastatic process) or a local relapse of malignancy (Bird et al., 2006). The possibilities of surgical and oncological treatment of this disease offer us a large spectrum of treatments including the combination of surgical procedures and consecutive oncological treatments. In the case of radical surgical therapy we can consider the curative access. The main medical problem of CRC is the high rate of recurrences after radically performed surgical therapy. The operability of recurrence is only about 30% in the case of local relapse and 20% in the case of distant metastases (Coleman et al., 2008; Kobayashi et al., 2007). The second dominant problem is the early recurrence of CRC after radical surgical treatment, when the patients undergo a difficult and exhausting procedure with a high risk of perioperative complications without any significant differences in overall survival against modern palliative therapy (Van den Eynde & Hendlisz, 2009).

Contemporary clinical and histopathological prognostic factors (staging, grading, etc.) used for the detection of patients with a high risk of relapse and a short overall survival rate and for the indication of adjuvant oncological treatment after radical surgery are not sufficient. Tumor infiltrating lymphocytes (TIL) were described as a good prognostic factor for patients with a high risk of relapse. They are critical indicators of efficient antitumor immunological response. Their number, type and morphology of TIL cells determine resulting tumor prognosis (Atreya & Neurath, 2008; Galon et al., 2006). They could be connected also with the suppression of micrometastatical disease after radical surgery (Gajewski et al., 2006; Pages et al., 2005). We can recognize either the type of immune cells or distinguish their morphological aspects (infiltration of any part of tumor or surrounding of tumor or tributary lymph nodes) (Talmadge et al., 2007).

We detail only short overview of their types and function. We recommend the readers with deeper interest in these problems to find comprehensive reviews in the cited papers (Jochems et al., 2011; Ohtani 2007). From this view we find CD8+ and CD4+ T lymphocytes (Fig. 1a & Fig. 1b), natural killer cells (Fig. 1c), dendritic cells (Fig. 1d), macrophages, etc. The exact function of these cells is under current discussion. We only know that they play main role in controlling tumor development and growth. CD8+ T lymphocytes within cancer cell nests of colorectal cancer have significant impact on the survival of patients. They contain the cytolytic enzyme granzyme-B. In case of increased proliferating activity of CD8+ T lymphocytes we observe their activated and cytotoxic phenotype that is significantly associated with the absence of early metastatic events (vascular emboli, lymphatic invasion or perineural invasion of tumor cells) and with a decreased rate of cancer recurrence (Atreya & Neurath, 2008, Pages et al., 2010). A high density of memory T lymphocytes within colorectal cancer tissue was more frequently observed in patients without early detectable signs of metastatic events and was associated with both improved disease free interval (DFI) and prolonged overall survival (OS) (Galon et al., 2006; Pages et al., 2005).

Natural killer cells (NK cells) mediate an effective lysis of cancer cells but the mechanism of detection of cancer cells is different from CD8+ T lymphocytes (Cooper et al., 2009). NK cells are mainly involved in the innate immune response and do not recognize specific tumor associated antigen on the surface of cancer cells as CD8+ T lymphocytes. NK cells lyse the cancer cells that are opsonized by surface antibody. NK cells also respond to other signals as cytokines produced by antigen presenting cells, which allow them to mediate early host responses against pathogen (Moretta et al., 2006). Decreased preoperative number of NK cells was associated with increased frequency of postoperative recurrence of colorectal cancer (Atreya & Neurath, 2008; Cooper et al., 2001). Their crucial role in the elimination of haematological malignancies, primary and secondary tumors has been recognized (Lucas et al., 2007; Ljunggren & Malmberg, 2007, Stojanovic & Cerwenka, 2011). In the last year there are some signs that NK-cells have the capacity for memory-like responses, a property that was previously thought to be limited to adaptive immunity, but in this view the discussion still continues (Cooper et al., 2009).

Dendritic cells are considered to be most potent antigen presenting cells. They play key role in activation, stimulation and recruitment of T lymphocytes. They can also induce antigen-specific unresponsiveness or immune tolerance. Immature dendritic cells enter tumor tissue, uptake and process its antigens. Then after they migrate to lymph nodes, undergo maturation and interact with T-lymphocytes that are able to recognize presented antigen and so T-lymphocytes play effector role of this tumor-specific immunity (Atreya & Neurath, 2008; Pages et al., 2005; Sandel et al., 2005; Steinman et al., 2003).

Macrophages are important producers of different factors that have function during tumor progression and also during tumor progression control. Their function is not fully understand, but it was described that the number of tumor infiltrating macrophages correlates with overall survival of colorectal cancer patients (Atreya & Neurath, 2008; Pollard, 2004; Forssell et al., 2007). It seems that several types of tumor infiltrating macrophages influence the balance between pro- and anti-tumor properties of immune system (Forssell et al., 2007).

From the morphologic view we can observe TIL in the specific portions of tumor and so we detect lymphocytic infiltration intratumoral (ITL – intratumoral lymphocytes) (Fig.

2a),intrastromal (ISL – intrastromal lymphocytes) (Fig. 2b), peritumoral (PTL – peritumoral lymphocytes) (Fig. 2c) and Crohn-like reaction (Crohn-like PTL)(Fig. 2d). We can also describe reactive histological changes in tributary lymph nodes (LN reactions). It means follicular hyperplasia (LN-FH) (Fig. 3a.), sinus histiocytosis (LN-SH) (Fig. 3b.) and the presence of granulomas (LN-GR) (Fig. 3c) (Ogino et al, 2009; Pages et al., 2005).

The aim of this study was to analyze the relationship of contemporary clinical and histopathological factors and TIL to determine patients with a high risk of poor overall survival and tendency to early recurrence of malignancy with shortened disease free interval (DFI) after radical surgery for CRC.
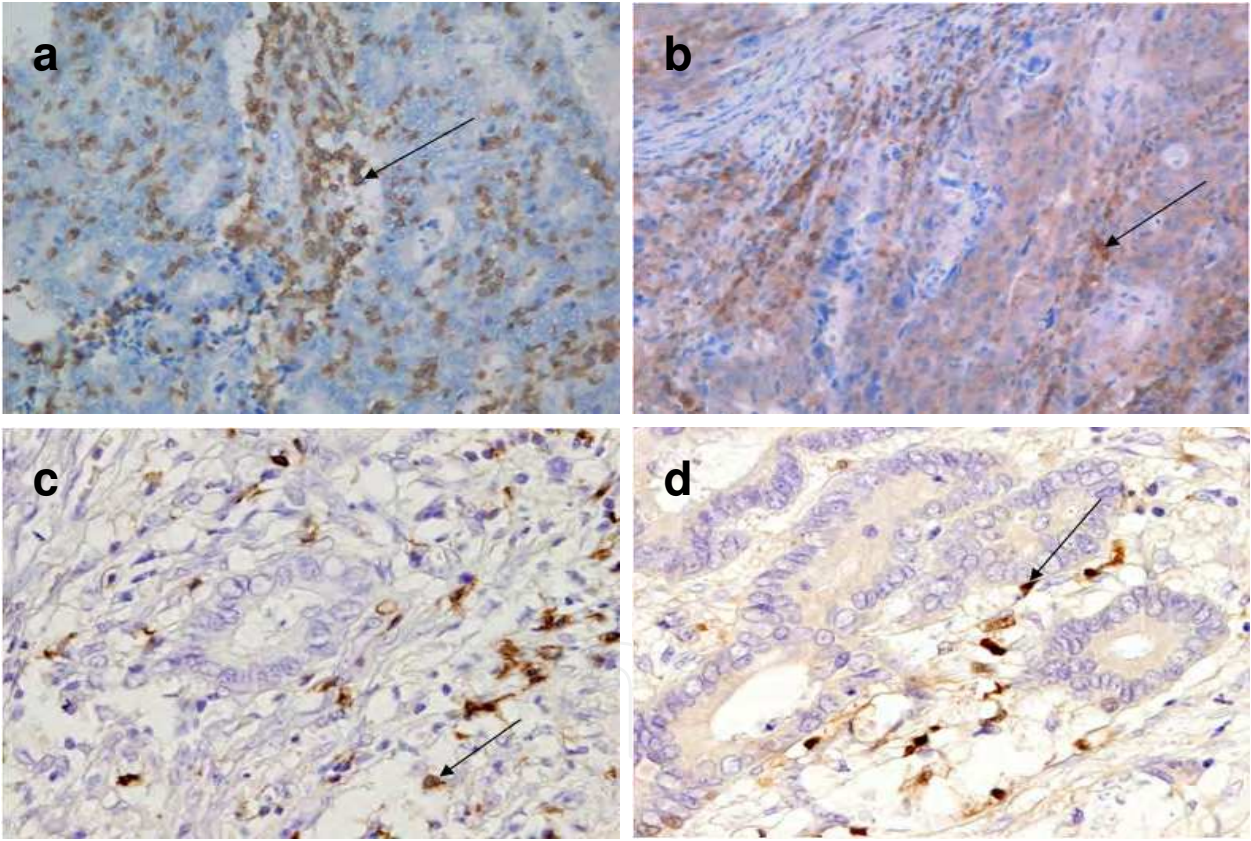

Fig. 1. Examples of tumor infiltration by immune cells: a) CD8+ T lymphocytes; b) CD4+ T lymphocytes; c) Natural killer cell (CD 57 staining) and d) Dendritic cells (S 100 staining).
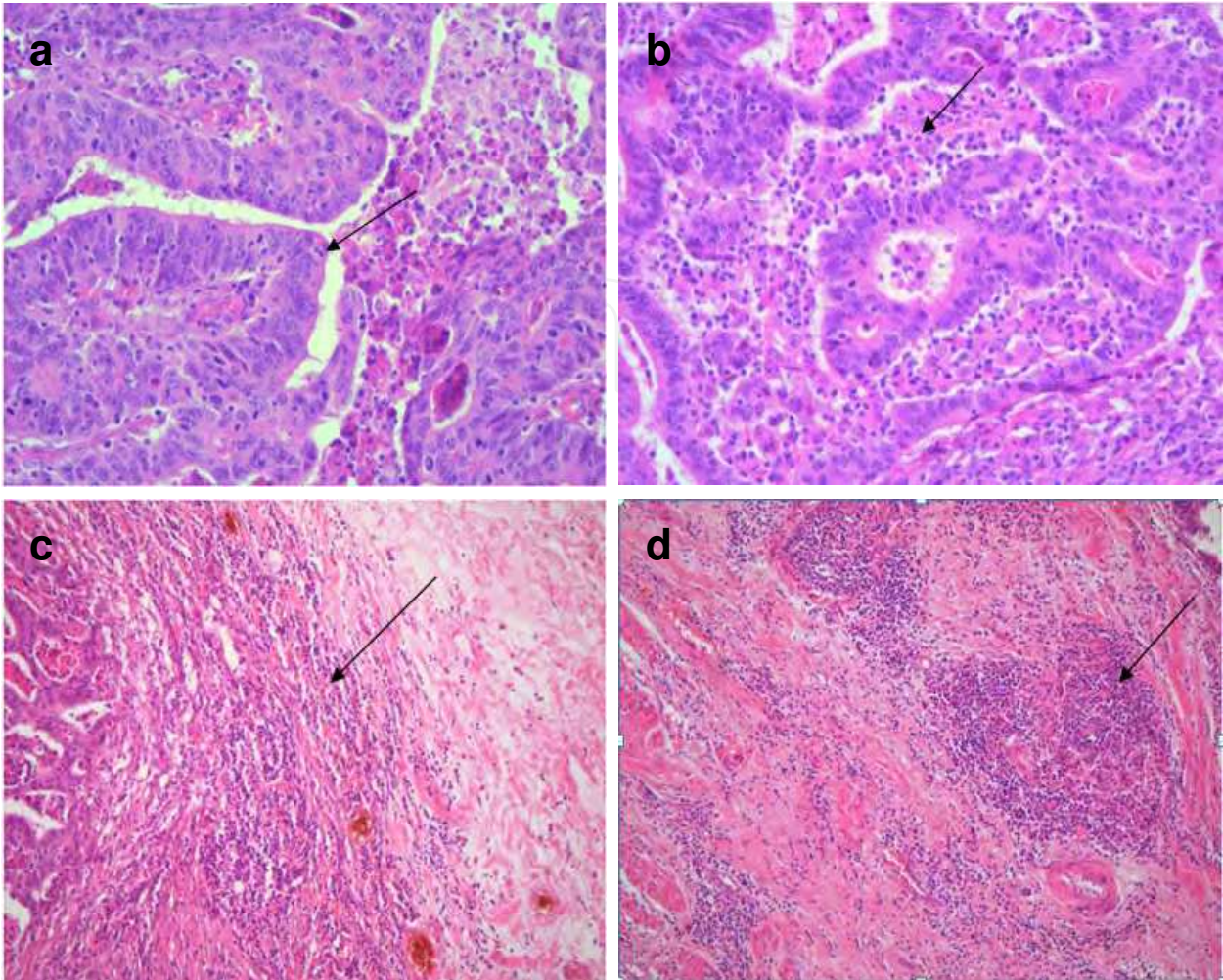
Fig. 2. Different localisation of TIL within the tumor tissue: a) intratumoral lymphocytes; b) intrastromal lymphocytes; c) peritumoral lymphocytes and d) Crohn-like peritumoral lymphocytes. All sections stained with hematoxylin-eosin.
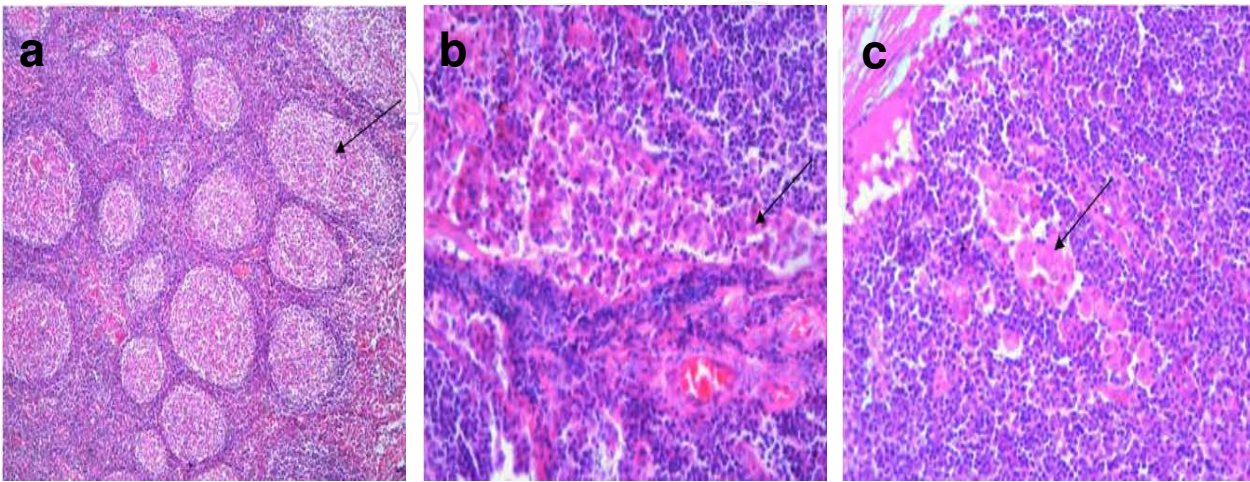

Fig. 3. Reactive histological changes in tributary lymph nodes: a) follicular hyperplasia; b) sinus histiocytosis and c) presence of granulomas. All sections stained with hematoxylin-eosin.

2. Methods

We analyzed 150 patients who underwent radical surgical procedure for CRC between the years 2004-2007 at the Department of Surgery, Medical School and Teaching Hospital in Pilsen, Charles University in Prague. We selected only patients who were operated on electively – our aim was to decrease the risk of inflammation that is often connected with the acute operation of CRC and does not depend on the immune reaction against a tumor but could be evoked by the distension of the bowel. We also excluded patients who had risk of understaging (for example low number of analysed lymph nodes) and patients with a synchronous metastatic process. The inclusion standard was also the entire follow-up of patients during the whole postoperative period to increase the number of patients with a diagnosed early recurrence of CRC.

The following clinical parameters were statistically analysed in relation to the disease free interval (DFI) and the overall survival (OS): staging, grading, preoperative leukocytosis, type of surgical procedure (radical vs. palliative), postoperative complications and postoperative oncological treatment.

2.1 Histology

We examined three different sections of each tumor and also sections of all found lymph nodes. Tissue for light microscopy was fixed in 4% formaldehyde and embedded in paraffin using routine procedures. Five micrometer-thick sections were cut from the tissue blocks and stained with hematoxylin-eosin.

The type and grade of all tumors were determined according to WHO 2000 guidelines. The stage of tumors was established according to UICC 2002 guidelines. We evaluated endovascular (VI), endolymphatic (LI) and perineural infiltration (PI) by cancer cells (0 – none, 1 – yes). Lymphocytic infiltration was detected as intratumoral (ITL – intratumoral lymphocytes), intrastromal (ISL – intrastromal lymphocytes), peritumoral (PTL – peritumoral lymphocytes) and Crohn-like reaction (Crohn-like PTL), and scaled as none (0), mild (1), moderate (2) and severe (3). Reactive histological changes in lymph nodes (LN reactions) were detected as follicular hyperplasia (LN-FH), sinus histiocytosis (LN-SH) and the presence of granulomas (LN-GR), and all these parameters were quantified in the same manner as lymphocytic infiltration.

2.2 Immunohistochemistry

For immunohistochemical investigations the following primary antibodies were used: CD4 (clone 4B12, 1:50, Vector Laboratories, Burlingame, CA, USA) and CD8 (clone C8/144B, 1:50, Dako, Glostrup, Denmark). Microwave pretreatment was used in both cases. The primary antibodies were visualized using the supersensitive streptavidin-biotin-peroxidase complex (Biogenex, San Ramon, CA). Appropriate positive and negative control slides were employed. The density of intratumoral infiltration by lymphocytes was evaluated in five High power microscopical fields (HPF) and expressed as the number of immunopositive cells per HPF.

2.3 Statistical evaluation

Statistical analysis was processed by the statistical software Statistica 9.0. The mean, median, standard deviation (SD), minimum, maximum, quartiles, frequencies and other basic statistical measurements were computed in given groups and subgroups of patients corresponding to studied clinical and histopathological parameters.

The relationships between the variables were described by Spearman rank correlation coefficients.

The analyses of Overall survival (OS) and Disease free interval (DFI) were performed by Kaplan-Meier´s survival functions. The influence of given covariates (clinical and histopathological factors) was tested by the Log-Rank test and Wilcoxon test. The Cox regression hazard model, hazard ratio (HR) and 95% confidence interval (CI) for HR were computed for the evaluation of given clinical and histopathological factors to OS or DFI. Multivariate analysis was performed by the use of classification and regression trees (CART). The Cox regression hazard model (stepwise regression) was applied to find the predictors in CART.

3. Results

The statistical analysis of the studied cohort of patients after surgical treatment for colorectal cancer demonstrated an acceptable distribution of basic statistical description parameters (gender ratio 93:57 (male vs. female)). 1, 3 and 5 years overall survival was 92.2%, 76.5% and 70.2% and 1, 3 and 5 year DFI was 85.3%, 64.3% and 49.4%.

The Spearman rank correlation coefficient did not prove any stronger correlation than a moderate correlation at endolymphatic invasion (LI) and lymph node infiltration by metastatic process (Spearman rank correlation coefficient 0.56, p<0,05). All the other studied factors were independent factors or factors with a low correlation.

Statistical analysis proved lymph node infiltration by metastatic process as statistically significant for the prognosis of overall survival (p<0.05) and N2 status of lymph nodes increased the risk of shorter overall survival 9.3x (Fig. 4.).
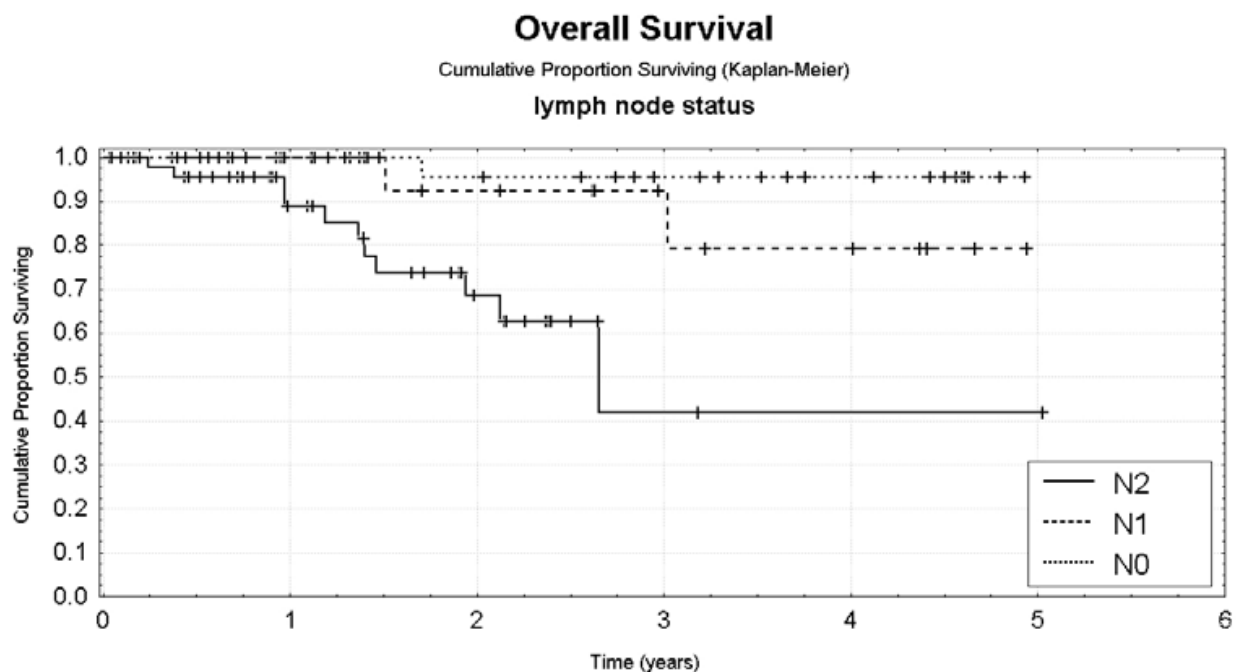

Fig. 4. Statistical analysis proved the lymph node infiltration by a metastatic process as statistically significant for the prognosis of overall survival (p<0.05), and the N2 status of lymph nodes increased the risk of a shorter overall survival 9.3x.

Endovascular infiltration (VI) was proved as a negative prognostic factor of shorter overall survival (Fig.5.). Patients with positive histopathological findings of VI have 3.1x increased risk for shorter overall survival. The presence of peritumoral lymphocytes (PTL) (Fig.6.) and of Crohn-like PTL (Fig.7.) was proved as a positive prognostic factor of OS. Patients with a positive histopathological finding of PTL and Crohn-like PTL have a decreased risk for shorter overall survival (2.3x and 2.3x respectively). Lymph node follicular hyperplasia (LN-FH) was verified as a positive prognostic factor for longer overall survival (Fig.8.). The statistical significance of LN-FH increased also with the raised density of infiltration. LN-FH positivity decreased the risk of shorter overall survival 3.3times.

The severity of CD8+ lymphocytic infiltration was proved by the Cox regression hazard model as a positive prognostic factor enlarging overall survival (cut off 30 cells/HPF). The severity of CD4+ lymphocytic infiltration was proved as a significant factor for the prognosis of overall survival (cut off 4cells/HPF) with 2.5x increased hazard ratio in patients over the cut off (Fig.9.). Statistical analysis did not confirm the statistical significance of CD8/CD4 ratio.
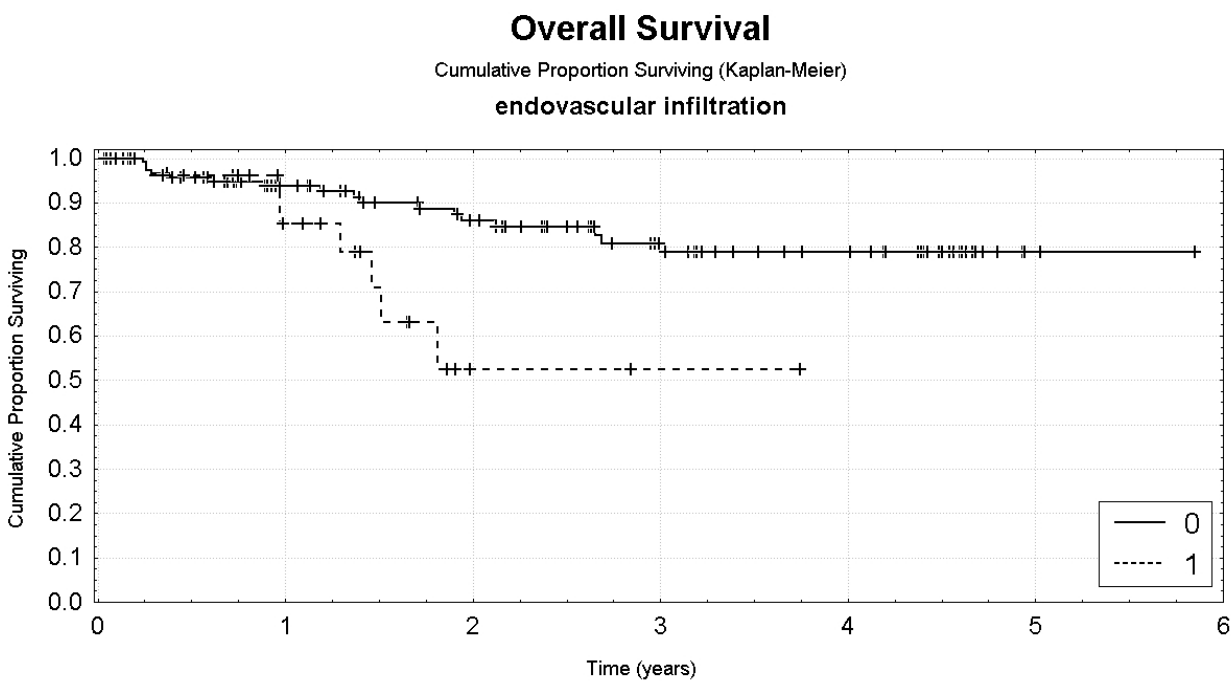

Fig. 5. Endovascular infiltration by cancer cells (VI) was proved as a statistically significant factor for the prognosis of overall survival (p<0.05). The patients with a positive histopathological finding of VI have 3.1x higher risk ratio for shorter overall survival.

Overall Survival

Cumulative Proportion Surviving (Kaplan-Meier)
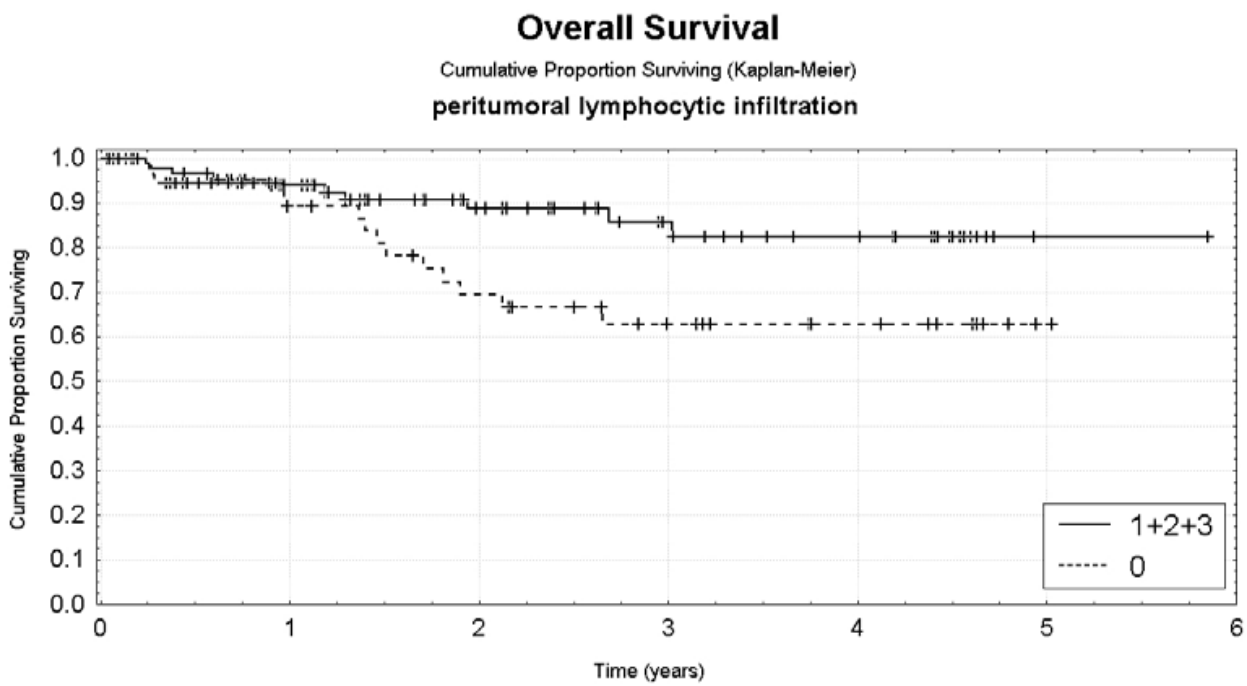
peritumoral lymphocytic infiltration

Fig. 6. Presence of peritumoral lymphocytes (PTL) was proved as a statistically significant positive factor for the prognosis of overall survival ($p<0.05$). The patients with a positive histopathological finding of PTL have 2.3x lower risk ratio for a shorter overall survival.

Overall Survival

Cumulative Proportion Surviving (Kaplan-Meier)

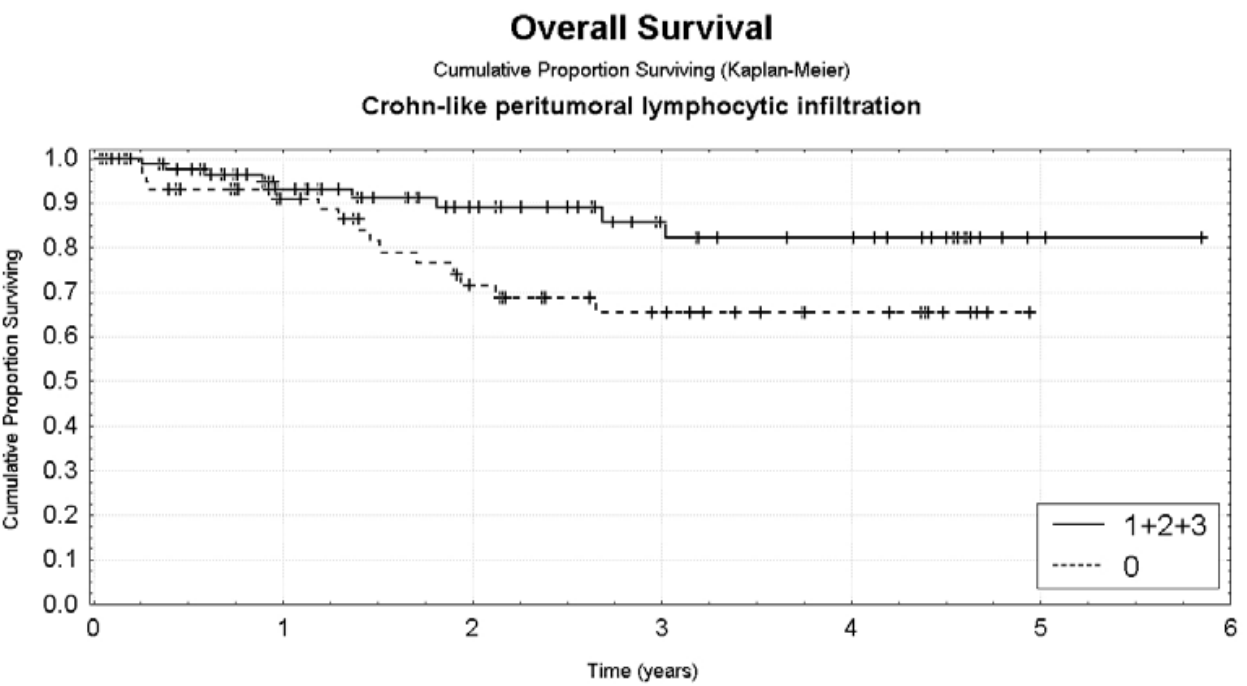**Crohn-like peritumoral lymphocytic infiltration**

Fig. 7. Presence of Crohn-like PTL was proved as a statistically significant positive factor for the prognosis of overall survival ($p<0.05$). The patients with a positive histopathological finding of PTL have 2.3x lower risk ratio for a shorter overall survival.
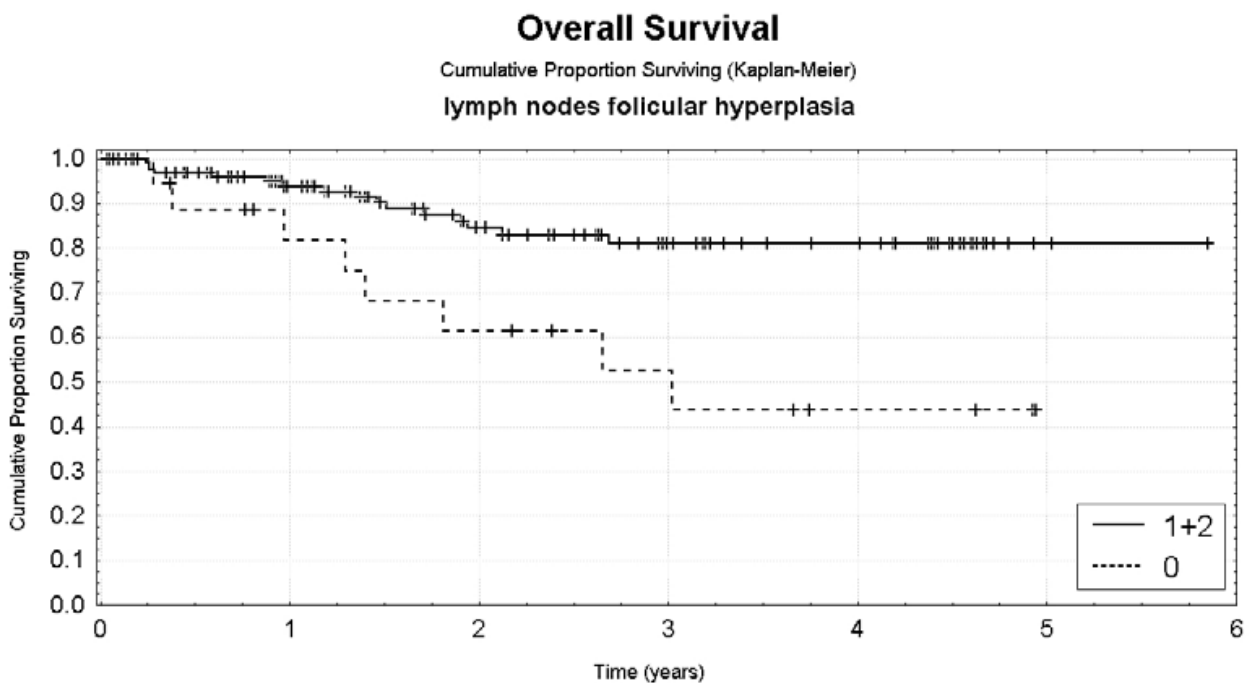
Overall Survival

Cumulative Proportion Surviving (Kaplan-Meier)

lymph nodes follicular hyperplasia

Fig. 8. Lymph node follicular hyperplasia (LN-FH) was verified as a positive prognostic factor for a longer overall survival (p<0.05). The statistical significance of LN-FH increased also with the raised density of infiltration. LN-FH positivity decreased the risk of a shorter overall survival 3.3x.

Overall Survival

Cumulative Proportion Surviving (Kaplan-Meier)
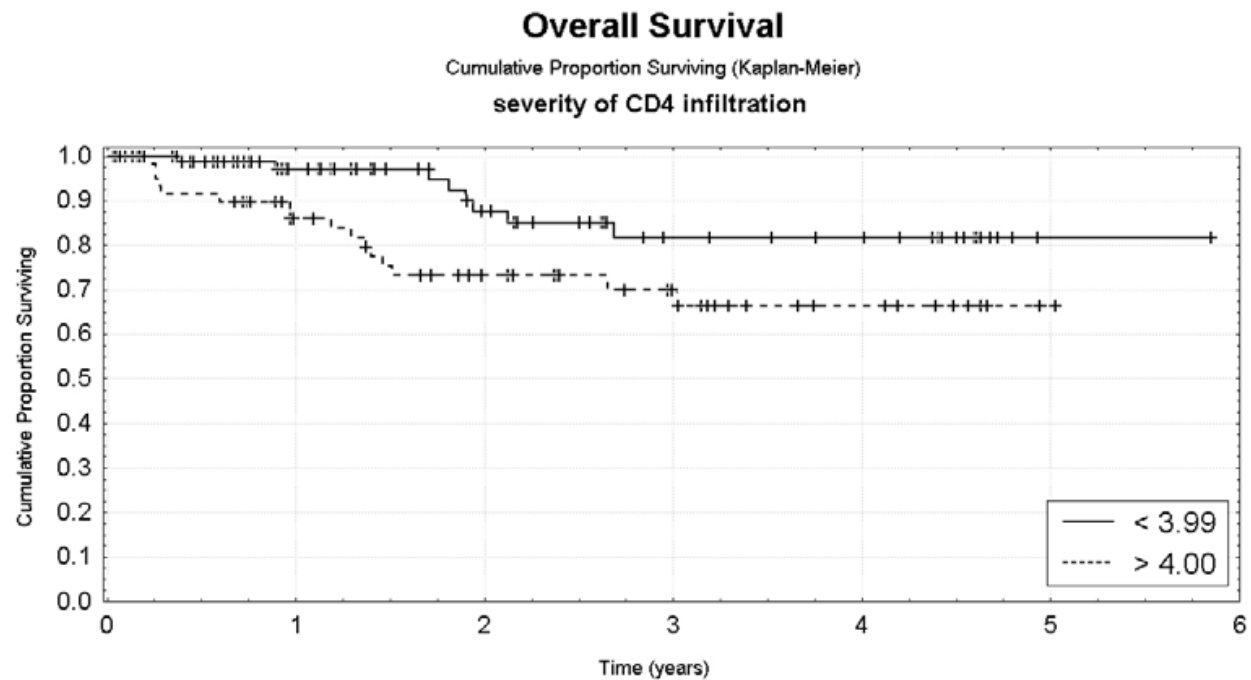
severity of CD4 infiltration

Fig. 9. Severity of CD4+ lymphocytic intratumoral infiltration was proved as a significant factor for the prognosis of overall survival (cut off 4cells/HPF) with a 2.5x increased hazard ratio in patients over the cut off (p<0.05).

The Multivariate Cox Regression Hazard Model proved the combination of the severity of lymph node infiltration by metastatic process and LN-FH as the best prognostic factors for the prediction of the risk of shorter overall survival. This situation is demonstrated in the Classification and Regression Tree (CART)(p<0.05) (Fig.10.). All other studied parameters were not proved as statistically significant for the prognosis of overall survival.

Classification and Regression Tree
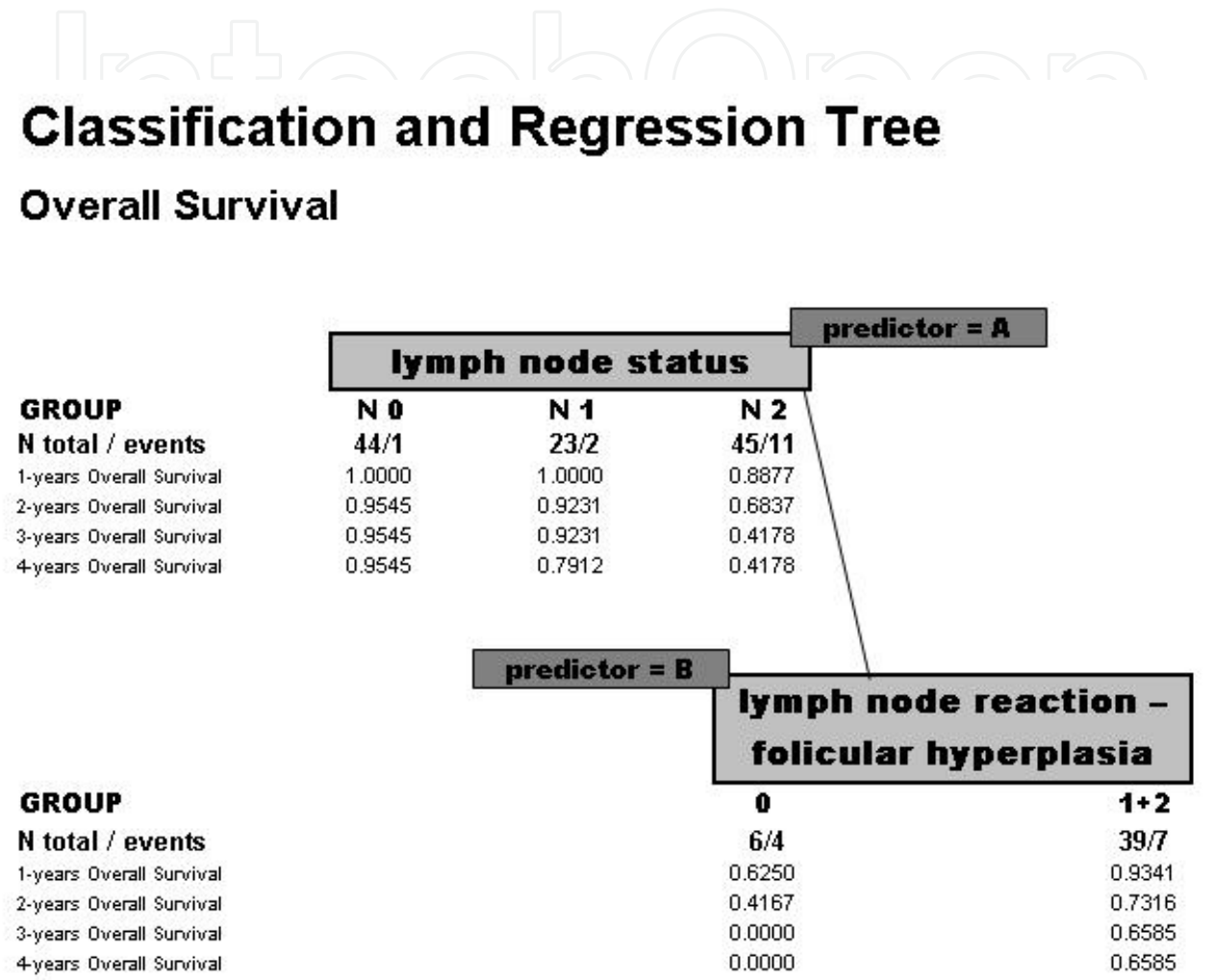
Overall Survival

Fig. 10. Multivariate Cox Regression Hazard Model proved the combination of the severity of lymph node infiltration by a metastatic process and LN-FH as the best prognostic factors for the prediction of risk of a shorter overall survival (p<0.05). This situation is demonstrated in the Classification and Regression Tree (CART).

Perineural infiltration (PI) was proved as a negative prognostic factor of an earlier recurrence (Fig.11.). Patients with a positive histopathological finding of PI have 3.8x increased risk for shorter DFI.

The severity of CD8+ lymphocytic infiltration was proved by the Cox regression hazard model as a positive prognostic factor enlarging DFI (cut off 30cells/HPF) (Fig.12.). Patients over the cut off have 2.2x increased risk of an early recurrence. The severity of CD4+ lymphocytic infiltration was not proved as a significant factor for the prognosis of DFI. Statistical analysis did not confirm the statistical significance of the CD8/CD4 ratio.
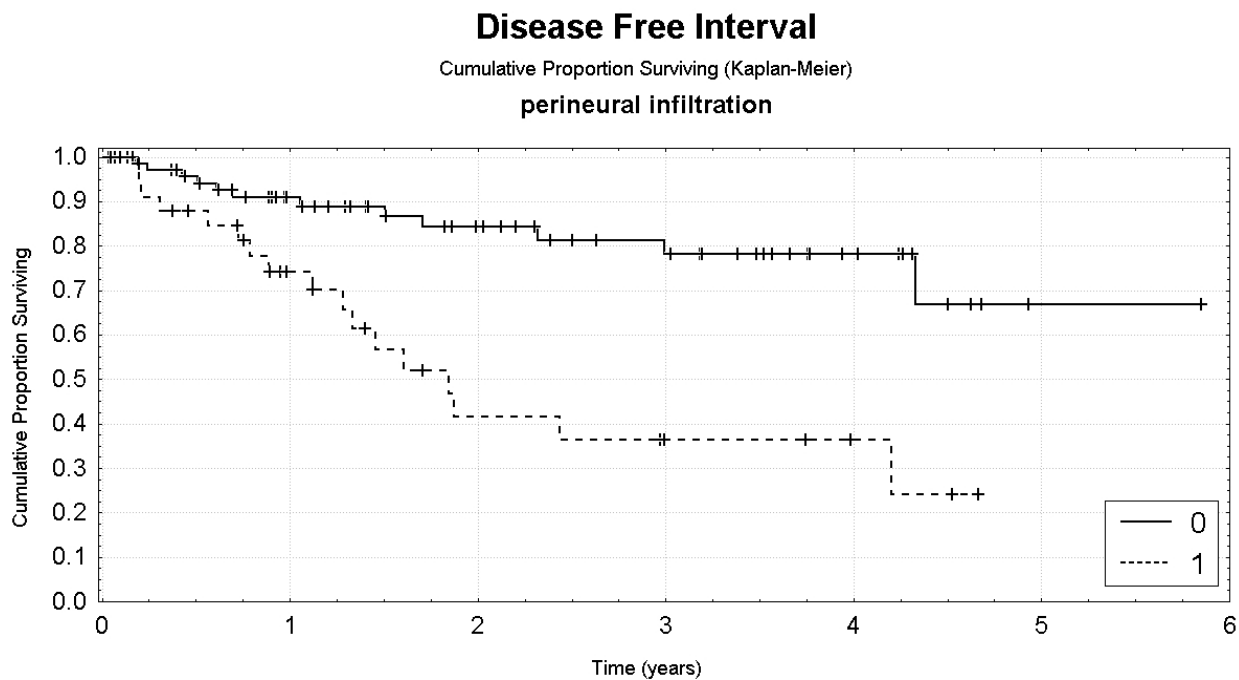
Disease Free Interval

Cumulative Proportion Surviving (Kaplan-Meier)

perineural infiltration

Fig. 11. Perineural infiltration (PI) was proved as a negative prognostic factor of an earlier recurrence (p<0.05). Patients with a positive histopathological finding of PI have a 3.8x increased risk for shorter DFI.

Statistical analysis proved lymph node infiltration by a metastatic process as statistically significant for the prognosis of DFI and N2 status of lymph nodes increased the risk of shorter DFI 5x (Fig. 13.).

Disease Free Interval

Cumulative Proportion Surviving (Kaplan-Meier)
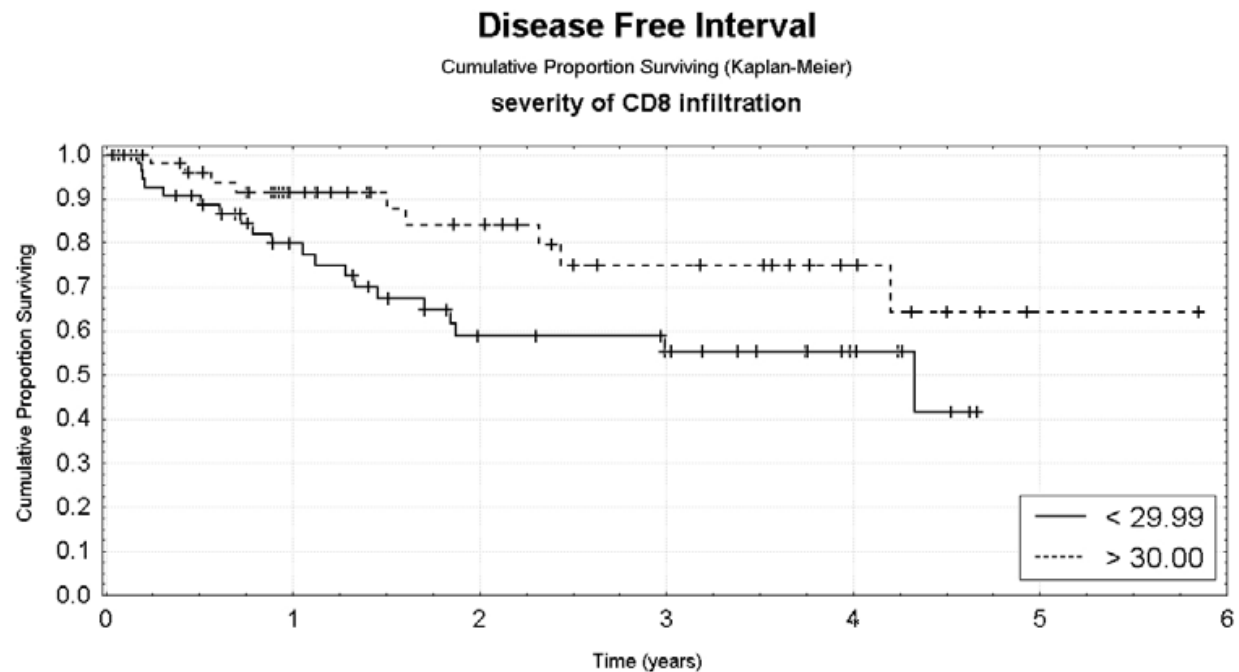
severity of CD8 infiltration

Fig. 12. Severity of CD8+ lymphocytic intratumoral infiltration was proved as a positive prognostic factor enlarging DFI (cut off 30 cells/HPF) by the Cox regression hazard model (p<0.05). Patients over the cut off have a 2.2x increased risk of an early recurrence.

Disease Free Interval

Cumulative Proportion Surviving (Kaplan-Meier)
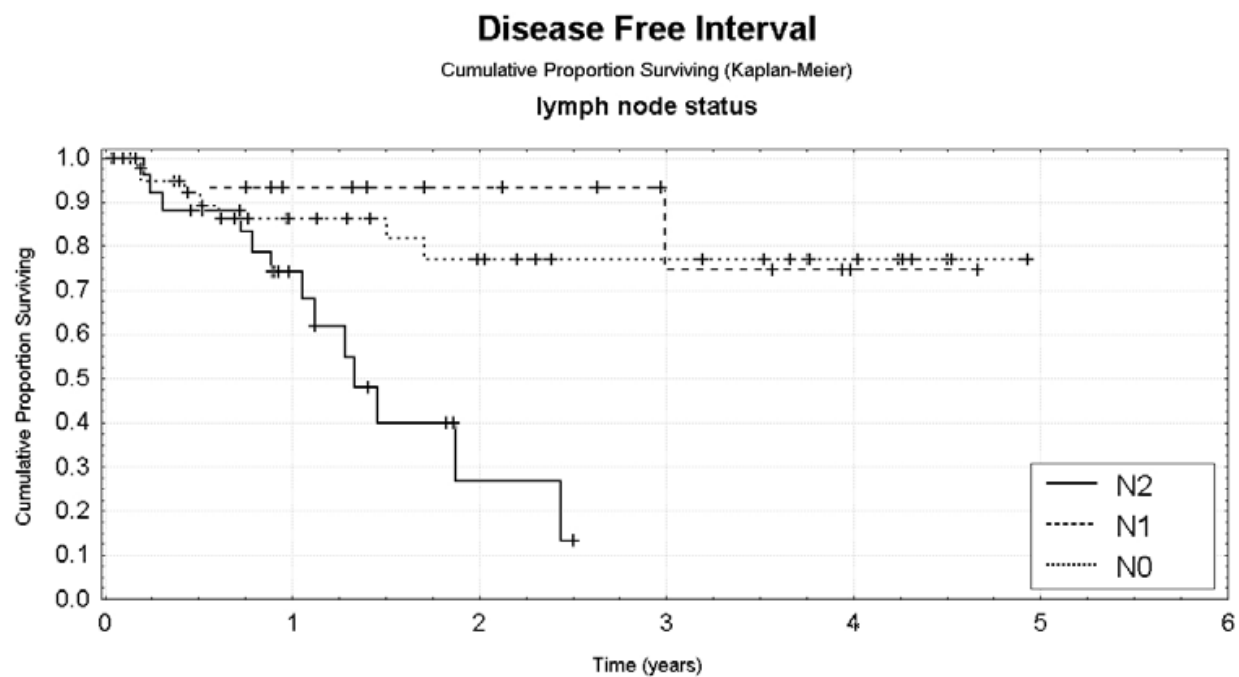
lymph node status

Fig. 13. Statistical analysis proved lymph node infiltration by a metastatic process as statistically significant for the prognosis of DFI, and a N2 status of lymph nodes 5x increased the risk of a shorter DFI ($p<0.05$).

The Multivariate Cox Regression Hazard Model proved the combination of the severity of the lymph node infiltration by a metastatic process and the severity of CD8 positivity of infiltrating lymphocytes as the best prognostic factors for the prediction of risk of early recurrence ($p<0.05$). This situation is demonstrated in the Classification and Regression Tree (CART) (Fig. 14). All other studied parameters were not proved as statistically significant for the prognosis of DFI.

4. Discussion

The role of the adaptive immunological response in controlling the growth and relapse of CRC remains controversial and contemporary studies have not answered all the questions about the prognosis of patients after radical surgical treatment of CRC (Galon et al., 2006; Ohtani, 2007; Van den Eynde & Hendlisz, 2009). We analysed our large cohort of patients of CRC with consideration to detect the negative and also positive prognostic factors of early recurrence of the disease and the poor overall survival after radical surgery. It was stimulated by the unsatisfactory situation and some dilemmas in the indication of surgical and oncological treatment, when early recurrence depreciates our effort to radical surgery with a high risk of complications and the long time of the decreased quality of life of our patients.

In the presented clinico-pathological study we demonstrated that lymph node infiltration by a metastatic process, N2 status of lymph nodes, VI, and extent of CD4+ lymphocytic intratumoral infiltration as negative prognostic factors of OS. In contrary PTL, Crohn-like PTL, LN-FH, and severity of CD8+ lymphocytic intratumoral infiltration were proved as positive prognostic factors of the overall survival.

Classification and Regression Tree

Disease Free Interval

lymph node status			predictor = A
GROUP	**N 0**	**N 1**	**N 2**
N total / events	43/7	15/2	26/13
1-years DFI	0.8617	0.9333	0.7411
2-years DFI	0.7710	0.9333	0.2668
3-years DFI	0.7710	0.7467	-
4-years DFI	0.7710	0.7467	-

predictor = B

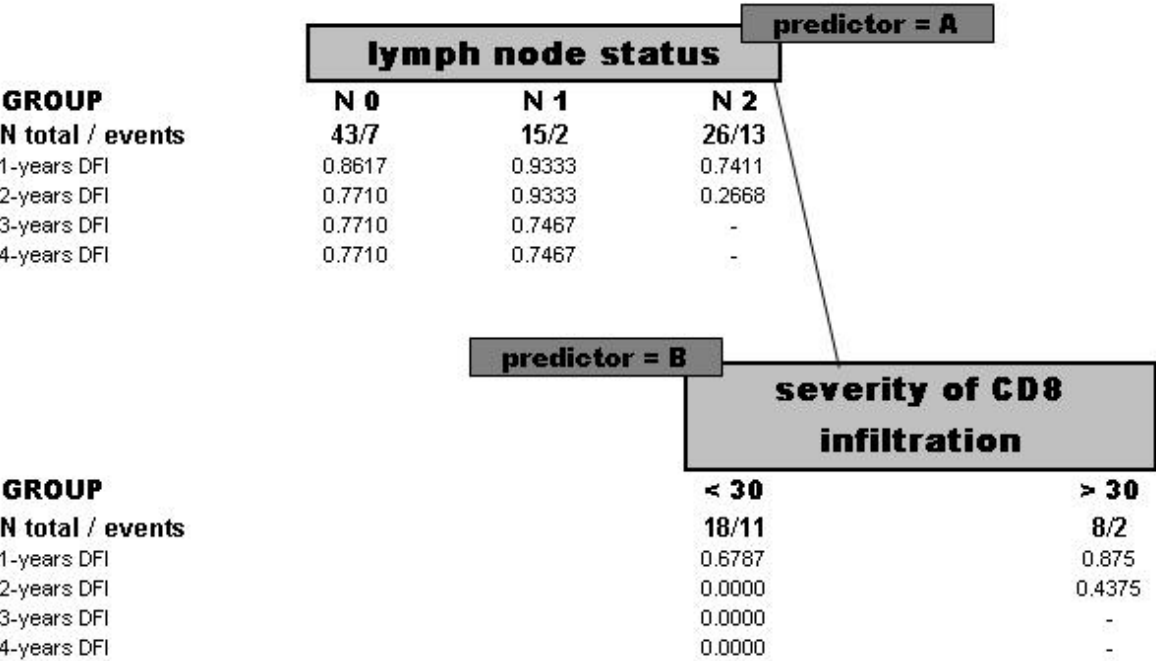|	**severity of CD8 infiltration**	
GROUP	**< 30**	**> 30**
N total / events	18/11	8/2
1-years DFI	0.6787	0.875
2-years DFI	0.0000	0.4375
3-years DFI	0.0000	-
4-years DFI	0.0000	-

Fig. 14. Multivariate Cox Regression Hazard Model proved the combination of the severity of lymph node infiltration by a metastatic process and the severity of CD8 positivity as the best prognostic factors for the prediction of risk of an early recurrence (p<0.05). This situation is demonstrated in the Classification and Regression Tree (CART).

The combination of the severity of the lymph node infiltration by a metastatic process and LN-FH were proved as the best prognostic factors for the prediction of risk of a shorter overall survival by the Multivariate Cox Regression Hazard Model.

We also demonstrated PI, lymph node metastatic infiltration and the N2 status of lymph nodes as negative prognostic factors of an earlier recurrence, and the severity of CD8+ lymphocytic intratumoral infiltration as a positive prognostic factor enlarging DFI. The combination of the severity of the lymph node infiltration by a metastatic process and the severity of CD8+ lymphocytic intratumoral infiltration were proved as the best prognostic factors for the prediction of the risk of an early recurrence by the Multivariate Cox Regression Hazard Model.

Our results support the hypothesis that the adaptive immunological response in tumor tissue and its reaction in regional lymph nodes can influence the behavior of CRC and so affect the prognosis of patients (Atreya & Neurath, 2008; Galon et al., 2006). CD4 and CD8 positivity of ITL was demonstrated as a key histopathological sign of tumor-specific immune response that could reflect the contemporary clinical situation and a tendency to relapse (CD4+) or the larger overall survival (CD8+) (Chiba et al. 2004; Koch et al., 2006, Pages et al., 2010).

We assessed several types of tumor infiltrating lymphocytes and clearly identified their relationships to relapse and the overall survival as positive or negative prognostic factors in contrary to previous publications that evaluated only the infiltration of the tumor but not the quality and type of infiltration (Ogino et al., 2009).

Tumor infiltration by lymphocytes seems to be a promising prognostic factor reflecting the risk of patients to early recurrence or poor overall survival. Future work has to be focused on the molecular-biological background of tumor infiltration by lymphocytes to understand their pathophysiological functions (Pages et al., 2005, Zbar, 2004).

5. Conclusion

Tumor infiltrating lymphocytes seem to be promising prognostic factors that could find their use in colorectal surgery and consecutive oncological treatment as an indicator of the type or combinations of therapies reflecting the risk of patients to early recurrence or poor overall survival. The TIL status corresponds to immune control of cancer progression.
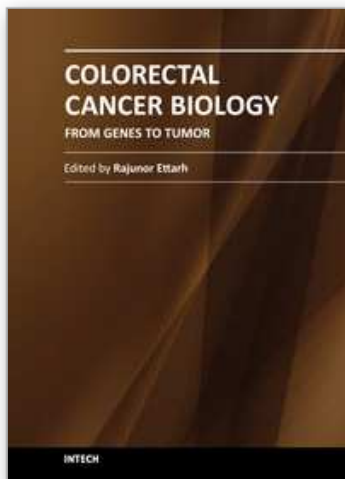
6. Acknowledgment

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Colorectal Cancer Biology - From Genes to Tumor

Edited by Dr. Rajunor Ettarh

Colorectal cancer is a common disease, affecting millions worldwide and represents a global health problem. Effective therapeutic solutions and control measures for the disease will come from the collective research efforts of clinicians and scientists worldwide. This book presents the current status of the strides being made to understand the fundamental scientific basis of colorectal cancer. It provides contributions from scientists, clinicians and investigators from 20 different countries. The four sections of this volume examine the evidence and data in relation to genes and various polymorphisms, tumor microenvironment and infections associated with colorectal cancer. An increasingly better appreciation of the complex inter-connected basic biology of colorectal cancer will translate into effective measures for management and treatment of the disease. Research scientists and investigators as well as clinicians searching for a good understanding of the disease will find this book useful.

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