

ORIGINAL ARTICLE

Frequency of Morphologic Prognostic Factors in Surgically Treated Colorectal Cancer

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SUMMARY

Introduction. Colorectal cancer is one of the most frequent malignant tumours worldwide. In Latvia, the incidence and mortality from colorectal cancer has increased over the past five years. Surgery is the mainstay of colorectal cancer treatment. However, the prognosis of an individual patient after the operation depends on many factors. Here, we report the prognostically important morphologic factors in potentially radically operated colorectal cancer patients in order to create the "morphologic prognostic portrait" - the basic morphologic characteristics of colorectal cancer in Latvian patients. Such data could be helpful in prognostic estimates.

Aim of the study was to describe the local tumour spread by pT, to evaluate the occurrence of certain morphologic prognostic factors and to assess lymph node involvement in potentially radically operated colorectal cancer patients.

Material and methods. In a retrospective study, 173 consecutive patients who underwent a potentially radical operation in a single university hospital within the year 2012 were identified by archive search. The pathology reports that have been created by protocol approach and diagnostic microscopy slides were reanalysed. Tumour morphology and pTN parameters were assessed according to the World Health Organization and the American Joint Committee on Cancer classifications.

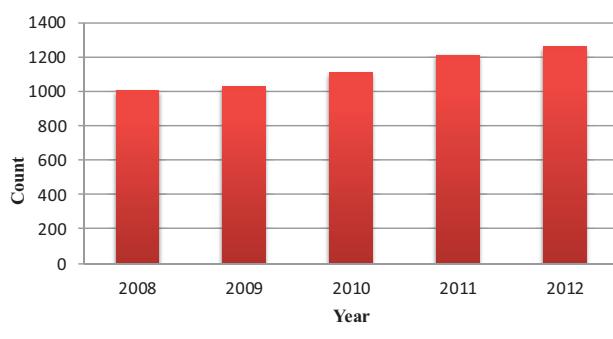
Results. The study included 98 women (56.6%) and 75 men (43.4%). The mean age of patients was 68.5 years [95% confidence interval: 66.9 – 70.1]. Only 4.6% [2.4 – 8.9] of patients were younger than 50 years. The most frequent histological tumour types were colorectal adenocarcinoma in 86.7% [80.8 – 90.9] patients and mucinous carcinoma in 9.2% [5.7 – 14.5] of patients. Evaluating the pT parameter, pT3 was found in 43.2% [36.1 – 50.6] and pT4 in 39.8% [32.8 – 47.2] of cases. Lymphatic invasion was found in 35.1% [25.3 – 46.2] of pT3 and 75.4% [64.0 – 84.0] of pT4 cases; $p < 0.001$. Perineural cancer invasion in pT3 and pT4 tumours was found in 29.9% [20.8 – 40.9] and 69.6% [57.9 – 79.2], respectively; $p < 0.001$.

Conclusions. Colorectal cancer affects both genders with equal frequency. The tumour is mostly diagnosed after the age of 60 years. Adenocarcinoma is the predominant colorectal cancer type in radically operated patients. Perineural and lymphatic invasion in pT4 tumours is statistically significantly more frequent than in less advanced tumours and thus may be pathogenetically linked to wide local tumour spread.

Key words: colorectal cancer, morphology, prognostic factors, synchronous colorectal cancer

INTRODUCTION

Colorectal cancer is one of the most frequent malignant tumours worldwide. In Latvia the incidence and mortality from colorectal cancer has increased (Figure 1) over the past five years. According to the Centre for Disease Prevention and Control of Latvia, there were 1233 new colorectal cancer cases in Latvia in 2012. Among these cases, the largest proportion of patients was diagnosed in the third and fourth stage, characterised by cancer spread beyond the primary tumour (data by the Centre for Disease Prevention and Control of Latvia). For colorectal cancer, the known unfavorable prognostic factors comprise marked local spread of the tumour, metastatic involvement of the lymph nodes, the development of perforation, presence of residual adenoma, and invasion in the perineural space and blood or lymphatic vessels [Marzouk and Schofield, 2011; Walsh and Carey, 2013]. Presence of synchronous second colorectal carcinoma has been analysed as a prognostic factor as well [Cunliffe *et al.*, 1984; Takeuchi *et al.*, 1997].



New colorectal carcinoma cases, 2008 - 2012

Fig. 1. The number of newly diagnosed colorectal carcinoma cases in Latvia per year.

Data: the Centre for Disease Prevention and Control of Latvia

AIM OF THE STUDY

The aim of this study was to describe the local tumour spread by pT, the frequency of certain morphologic prognostic factors and to assess lymph node involvement in radically operated colorectal cancer patients from Latvia.

MATERIAL AND METHODS

In a retrospective study, 173 consecutive patients who underwent potentially radical surgical treatment of colorectal cancer in a single university hospital within 2012 (January 1st–December 31st, 2012) were identified by archive search. The corresponding pathology reports and diagnostic microscopy slides were retrieved. Within the present study, potentially radical operations were defined as major colonic and rectal resections, namely, partial, subtotal or total colectomy, anterior rectal resection, Hartmann operation, rectosigmoidectomy and rectal extirpation [Bhangu *et al.*, 2013]. The data on neoadjuvant chemotherapy were assessed by medical records. The tumour morphology and pTN parameters were evaluated according to the classifications and criteria as defined by World Health Organization and the American Joint Committee on Cancer [Hamilton and Aaltonen, 2010; Edge *et al.*, 2010]. The presence of perforation and synchronous second colorectal carcinoma was analysed by pathology reports. Tumour perforation was defined as a defect in the bowel wall through the tumour [Swamy, 2010]. The presence of residual adenoma, perineural and intraneuronal invasion and involvement of lymphatic vessels and veins in the process were analysed in the retrieved diagnostic pathology slides [Fleming *et al.*, 2012]. As the current recommendations highlight the importance of a sufficient number of lymph nodes found for adequate staging of colorectal cancer [Compton *et al.*, 2000; Kuijpers *et al.*, 2013], the total number of retrieved lymph nodes was also assessed. The slides were routinely stained with hematoxylin and eosin. Additional immunohistochemical investigation was performed upon necessity if the tumour histogenesis was otherwise unclear. Descriptive statistical analysis was performed. The descriptive data were expressed as mean ± standard deviation (SD), median with interquartile range or frequency. To detect statistically significant differences, the 95% confidence interval (CI) was calculated by CIA software (Altman *et al.*, 2000) and the findings were further confirmed by the χ^2 test regarding frequency and two sample t-test regarding the mean values. Differences were considered statistically significant, if p value was less than 0.05.

RESULTS

The study included 173 patients: 98 women (56.6%) and 75 men (43.4%). The mean age of patients was $68.5 \pm SD 10.6$ years [95% CI: 66.9 – 70.1], ranging from 41 to 97 years. Only 8 patients were younger than 50 years, comprising 4.6% [2.4 – 8.9] of the study group (Figure 2). No statistically significant difference was found regarding the mean age of women estimated as $69.7 \pm$

$SD 10.4$ years [67.7 – 71.8] and men estimated as $67.0 \pm SD 10.6$ [64.5 – 69.4]. The lack of statistical difference was confirmed by $p = 0.811$.

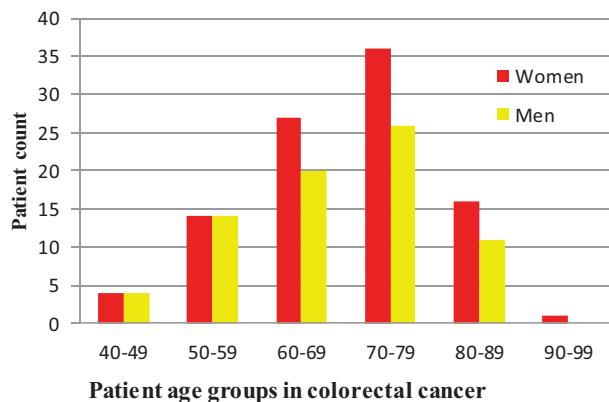


Fig. 2. The age and gender distribution of the studied surgically treated colorectal carcinoma cases

Colorectal adenocarcinoma was found in 86.7% [80.8 – 90.9] of patients with colon cancer. Mucinous carcinoma was found in 9.2% [5.7 – 14.5] cases. There were single cases of medullary and undifferentiated carcinoma as well as few cases of primary signet ring cell carcinoma of the large bowel and moderately differentiated (G2) neuroendocrine tumour (Table 1, Figure 3).

Table 1. Histological type of colorectal tumour by gender

Tumour type	Number	Frequency, % [95% CI]	Women	Men
Adeno-carcinoma	150	86.7 [80.8 – 90.9]	84	66
Mucinous carcinoma	16	9.2 [5.7 – 14.5]	9	7
Signet ring cell carcinoma	3	1.7 [0.5 – 4.9]	2	1
Neuro-endocrine tumour	2	1.2 [0.3 – 4.1]	2	0
Medullary carcinoma	1	0.6 [0.1 – 3.2]	0	1
Undifferentiated carcinoma	1	0.6 [0.1 – 3.2]	1	0

Abbreviation in the Table: CI, confidence interval

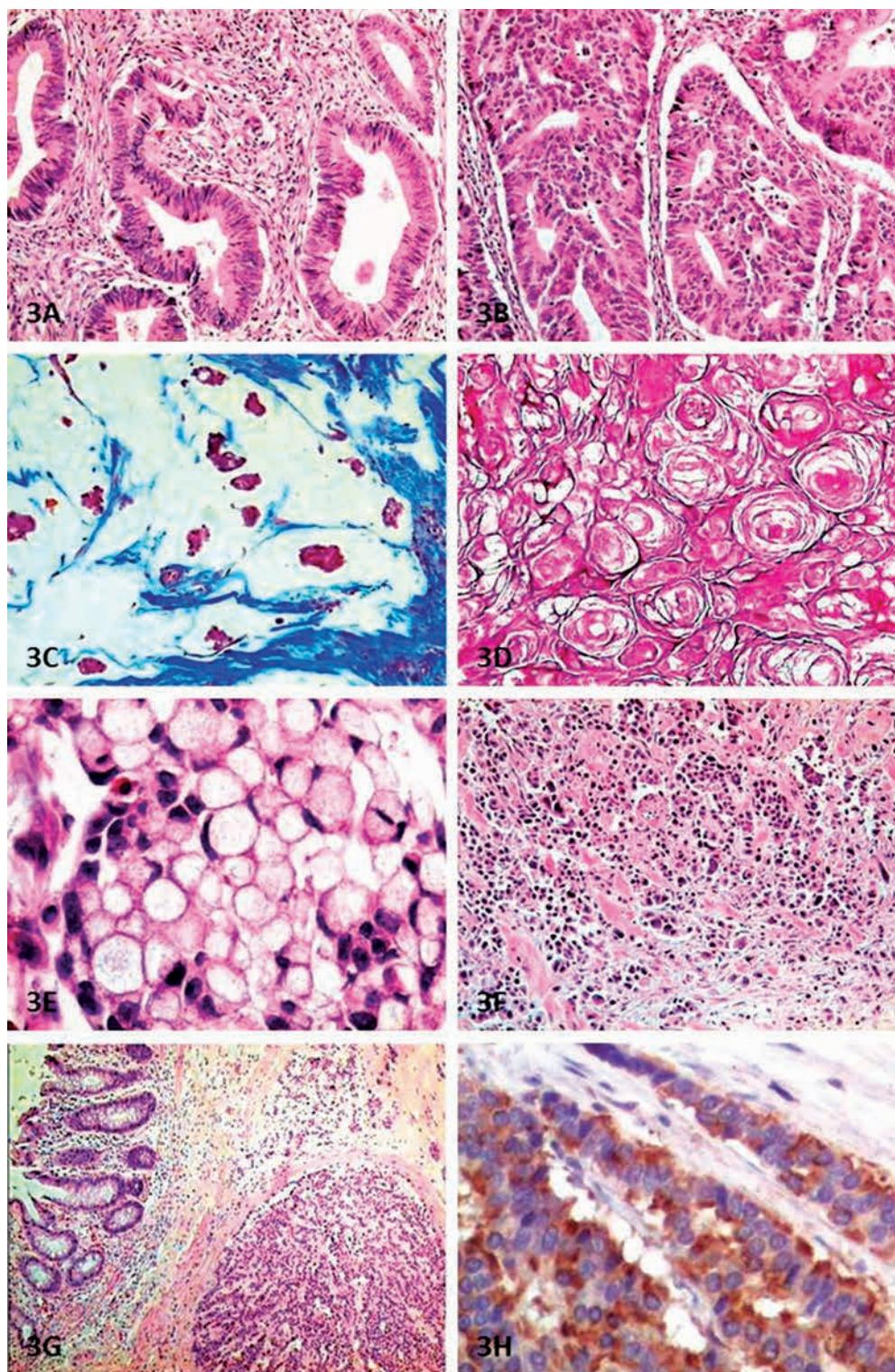


Fig. 3. The histological types of colorectal carcinoma. 3A-B, adenocarcinoma. Note low-grade architecture in 3A and high-grade in 3B; 3C-D, mucinous carcinoma. Note mucus lakes in both 3C and 3D as well as slight fibrosis in 3C; 3E, signet ring cell carcinoma; 3F, undifferentiated carcinoma; 3G-H, neuroendocrine tumour. Note the characteristic architecture in 3G and cytoplasmic expression of synaptophysin in 3H. 3A, B, E, F, G: haematoxylin-eosin; 3C, Masson's trichrome; 3D, PAS; 3H, immunoperoxidase. Original magnification: 3A, B, C, D, F, G: 100x; 3E and H: 400x.

Evaluating the anatomic localization of the tumour and the related type of the operations, it was found that radical surgery in relation to colorectal cancer was performed mostly on the left part of the bowel, representing 76.9% [70.1 – 82.5] of cases. The most frequent single localization of colorectal cancer was the rectum, where the tumour was detected in 39.3% [32.3 – 46.7] of cases (Table 2). Few patients affected by rectal cancer underwent neoadjuvant treatment: 7.4% [2.8 – 16.5].

Table 2. The anatomic localisation of surgically treated colorectal carcinoma

Site	Number of cases	Frequency, %	95% CI of the frequency
Caecum	11	6.3	3.6 – 11.0
Ascending colon	22	12.7	8.5 – 18.5
Transverse colon	20	11.6	7.6 – 17.2
Descending colon	7	4.1	1.9 – 8.1
Sigmoid colon	45	26.0	20.1 – 33.0
Rectum	68	39.3	32.3 – 46.7

Abbreviation in the Table: CI, confidence interval

Left-sided colorectal adenocarcinoma accounted for 117 cases or 87.9% [81.3 – 92.5] of left side operations. Mucinous colorectal carcinoma was found in 9.0% [5.2 – 15.1] of all left side operations. There were 62 cases of rectal adenocarcinoma, corresponding to 41.3% [33.8 – 49.3] of the total number of adenocarcinomas. In sigmoid colon, adenocarcinomas were found in 26.0% [19.6 – 33.6] of cases. Mucinous carcinoma of the sigmoid colon represented 37.5% [18.5 – 61.4] of all mucinous cancer cases (Table 3).

Table 3. Histological type of tumour by anatomic localisation site

Localisation	Number of cases					
	Adeno-carcinoma	Muci-nous carci-noma	Signet ring cell carci-noma	Medul-lary carci-noma	Neuro-endo-crine tumour	Undif-feren-tiated carci-noma
Caecum	8	2	0	0	1	0
Ascending colon	19	2	0	0	0	1
Trans-ver-sive colon	15	2	2	1	0	0

Descending colon	7	0	0	0	0	0
Sigmoid colon	39	6	0	0	0	0
Rectum	62	4	1	0	1	0

Evaluating the T parameter, pT3 carcinoma represented 43.2% [36.1 – 50.6], and pT4 – 39.8% [32.8 – 47.2] of all cases (Figure 4). Among the pT3 cases, 77.9% [67.5 – 85.7] were localised in left side, but among pT4 – 75.4% [64.0 – 84.0] cases were left-sided paralleling the general distribution of colorectal carcinoma (Table 4).

Table 4. pT parameter distribution of colorectal carcinoma by the affected side of large bowel

pT	Number of cases					
	Right side			Left side		
	Count	Frequency, %	95% CI	Count	Frequency, %	95% CI
pT1	3	7.5	1.9 – 20.6	4	3.0	0.9 – 7.7
pT2	3	7.5	1.9 – 20.6	17	12.8	8.0 – 19.6
pT3	17	42.5	28.5 – 57.8	60	45.1	36.9 – 53.6
pT4	17	42.5	28.5 – 57.8	52	39.1	31.2 – 47.6
Total	40			133		

Abbreviation in the Table: CI, confidence interval of the frequency

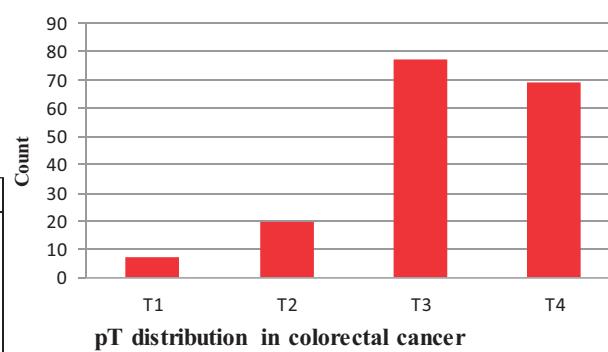


Fig. 4. pT distribution in surgically treated colorectal carcinoma

The number of identified lymph nodes ranged from 1 to 33. The median value was 11, interquartile range 8. The mean number of investigated lymph nodes per patient was $11.8 \pm SD 6.4$ [10.8 – 12.8]. In 80 cases (46.2%), the number of identified lymph nodes reached or exceeded 12 while in 45 (26.0%) cases the number of

retrieved lymph nodes found was 8 to 11. No metastasis in regional lymph nodes (pN0) was detected in 49.1% [41.8 – 56.5] of cases. The pN1 spread (1 – 3 metastases in regional lymph nodes) was identified in 27.8% [21.6 – 34.8] patients. If more than 12 lymph nodes were retrieved, pN1 was detected in 28.7% [19.9 – 39.5] of cases and pN2 in 22.5% [14.7 – 32.8] of cases. In patients with 8 to 11 identified lymph nodes, pN1 was found in 24.4% [14.2 – 38.7] and pN2 in 20.0% [10.9 – 33.8] of cases. Comparing the pN distribution (pN0 versus pN1 versus pN2) between the patients with less than 8 retrieved lymph nodes, 8 – 11 or at least 12 identified lymph nodes, there were no statistically significant difference as shown by χ^2 test, resulting in $p = 0.917$. Perforation, defined as a complete defect in bowel wall through the tumour, was observed in 11 cases, corresponding to 6.4% [3.6 – 11.0] of the total number of cases. The pT4 tumours were responsible for 63.6% [35.4 – 84.8] of all tumour perforation cases. Perforation was seen in 10.1% [4.9 – 19.2] of pT4 cases (Table 5).

Table 5. Frequency of colorectal carcinoma perforation by the pT characteristics

Parameter	Number of perforated cases	Total case count by pT	Frequency of perforation, % [95% confidence interval]
pT1	0	7	0.0 [0.0 – 40.4]
pT2	2	20	10.0 [2.8 – 30.1]
pT3	2	77	2.6 [0.7 – 8.9]
pT4	7	69	10.1 [5.0 – 19.5]

Synchronous second colorectal carcinoma was identified in 17 cases or 9.8% [6.2 – 15.2]. The other cancer was mostly associated with pT4 cases, namely, it was revealed in 9 patients constituting 13.0% [7.0 – 22.9] of all pT4 cases. Among the patients with synchronous other carcinoma, lymph node metastases (pN1 and pN2) were detected in 9 cases, accounting for 52.9% [31.0 – 73.8] of the patients affected by synchronous second carcinoma and 10.5% [5.6 – 18.7] of the total number of cases displaying lymph node metastases. Residual adenomas in our study were detected in 19.1% [13.9 – 25.6] of cases, mostly in patients with pT3 and pT4 characteristics of local spread (Table 6).

Table 6. Frequency of residual adenoma by pT in colorectal cancer

Parameter	Number of cases exhibiting residual adenoma	Frequency, % [95% confidence interval]
pT1	3	42.9 [15.8 – 75.0]
pT2	6	30.0 [14.5 – 51.9]
pT3	15	19.5 [12.2 – 29.7]
pT4	9	13.0 [7.0 – 23.0]

In the whole study group, tumour invasion in lymphatic vessels was found in 82 cases or 47.4% [40.1 – 54.8]

of patients. There was no lymphatic invasion in pT1 tumours: 0% [0 – 35.4]. Regarding pT2 carcinomas, such invasion was found in 3 cases, corresponding to 15.0% [5.2 – 36.0] of pT2 cases. Evaluating the lymphatic invasion in pT3 and pT4 tumors, it was present in 35.1% [25.3 – 46.2] of pT3 and 75.4% [64.0 – 84.0] of pT4 cases. The statistical significance of the observed difference was confirmed by $p < 0.001$. Invasion into veins was observed in 29.0% [19.6 – 40.6] of pT4 cases, but intraneuronal growth – in 47.8% [36.5 – 59.4] of pT4 carcinomas. Both findings were significantly more frequent than in pT3, $p = 0.002$. Perineural cancer invasion in pT3 and pT4 tumours were found in 29.9% [20.8 – 40.9] and 69.6% [57.9 – 79.2], respectively (Table 7). The statistical significance of the observed difference was again confirmed by $p < 0.001$.

Table 7. Manifestations of invasive growth in pT3 and pT4 colorectal carcinoma

Parameter	Frequency, % [95% confidence interval]			
	Lymphatic invasion	Venous invasion	Perineural invasion	Intraneuronal invasion
pT3	35.1 [25.3 – 46.2]	9.1 [4.5 – 17.6]	29.9 [20.8 – 40.9]	14.3 [8.2 – 23.8]
pT4	75.4 [64.0 – 84.0]	29.0 [19.6 – 40.6]	69.6 [57.9 – 79.2]	47.8 [36.5 – 59.4]

DISCUSSION

Colorectal cancer as the one of the leading cause of death in the world speaks neither women nor men. In the present study, occurrence in both genders was observed as well. In our study, only 4.6% of patients were younger than 50 years. Hypothetically, younger patients can more frequently present with unresectable tumour [Berut *et al.*, 2013], and such cases undergoing palliative treatment only would be excluded from the present study focusing on major surgical resections. By literature data, younger patients have higher frequency of American Joint Committee on Cancer stage III carcinomas exhibiting vascular and perineural invasion [Ghazi *et al.*, 2012]. In Latvia, many patients are diagnosed after the age of 50 years, therefore screening for colorectal cancer, beginning from the age of 50 years, would have high diagnostic yield.

In our study, significant fraction of mucinous colorectal carcinoma was localised in left side of large bowel, while in other studies mucinous carcinoma has been localised mostly in right side of colon [Nawa *et al.*, 2008]. Considering the known association between mucinous differentiation and molecular types in colorectal cancer [Umar *et al.*, 2004], different distribution of these types can be suspected in Latvia. Such differences hypothetically can be attributable both to risk factor distribution and genetic predisposition. Obviously, larger studies are necessary to solve this issue. This study did not focus to study the genetic predisposition. Only 40 cases in our study were right-sided tumours, which in literature are associated with positive family history [Pomz de Leon *et al.*, 1990]. The low rate of young patients also

is not suggestive of frequent hereditary predisposition. However, this finding is by no means exclusive as hereditary cancers can also develop in aged patients [Vanags *et al.*, 2010]. The pT4 tumours have a tendency to more frequent perforation. It could be associated with tumour spread through all layers of the bowel wall. However, tumour necrosis and inflammation should be analyzed in association of perforation in further studies, because, as our study showed, perforation was not limited by pT4, where tumour has spread further than *lamina muscularis propria* and has reached bowel surface. Surgically induced perforation at the tumour site can also develop. To discriminate such event from the true tumour perforation, clarification from surgeons can be helpful [Fleming *et al.*, 2012].

Patients affected by pT4 cancer in our study in 13% of all cases had synchronous second carcinoma. There are published data that patients with synchronous colorectal carcinomas have also higher incidence of benign polyps [Abe *et al.*, 2006].

By recent estimates, perineural invasion can have similar prognostic role as lymphovascular invasion [Compton *et al.*, 2012; Gagliardi *et al.*, 2013]. Our study showed that 69.6% pT4 tumours had perineural and 75.4% lymphatic invasion, while invasion in vessels were found only in 29.0% of pT4 cases. Notably, the perineural, lymphatic and vascular invasion was statistically significantly more frequent in pT4 carcinomas suggesting inherent higher invasive capacity in these advanced tumours.

The mostly accepted guidelines for colorectal carcinoma investigation suggest that at least 12 lymph nodes must be retrieved. However, variations exist between different countries [Compton *et al.*, 2000; Kuijpers *et al.*, 2013]. In our study, at least 12 lymph nodes were identified in 46.2% of patients, while in 26.0% cases the number of retrieved lymph nodes was 8 to 11 and in 27.8% - less than 8 lymph nodes were identified. This is in accordance with Zhang *et al.*, recently reporting that only 27.9% of colorectal patients had at least 12 examined lymph nodes [Zhang *et al.*, 2013]. In addition, many authors have noted that the target number of 12 retrieved lymph nodes is not always possible to reach even in USA and European clinics [Li Destri *et al.*, 2014]. In northwest of England, at least 12 lymph nodes have been identified in less than 50% of resected colorectal cancer materials [Mitchell *et al.*, 2009]. Similarly, Johnson *et al.* reported that 12 lymph nodes have been retrieved only in 55.3% of colorectal surgery materials including any removed lymph nodes [Johnson *et al.*, 2010]. The Dutch Surgical Colorectal Audit recognised that at least 10 lymph nodes have been examined in 73% of colon cancers and 58% of rectal cancers [Kuijpers *et al.*, 2013]. The median value of identified lymph nodes in our study was 11. In United States, the median number of retrieved lymph nodes has increased from 12 in the year 2004 to 17 in 2010 [Budde *et al.*, 2014]. Thus, our study has identified a clear potential for improvement. However, it must be also emphasised that in USA the growing number of retrieved lymph nodes has not been accompanied by higher frequency of stage III disease [Budde *et al.*, 2014].

Treatment can significantly influence the lymph node yield, especially in rectal tumours [Morcos *et al.*, 2010; Marks *et al.*, 2010]. However, this confounder was rarely observed in the present study. In contrast, the lymph node yield is significantly influenced by the location of tumour. The highest lymph node yield is reported in right-sided cases, exceeding the mean number of identified lymph nodes in left-sided and rectal cancers [Ahmadi *et al.*, 2014]. Our group is characterised by the predominance of left-sided cancers. In addition, most of patients were elderly. Aging can result in diminished activity of immune system [Stocchi *et al.*, 2011], morphologically paralleling lymph node involution [Shia *et al.*, 2012]. It has been suggested that the mean lymph node yield decreases by 1 for every 7 years advancement of age [Ahmadi *et al.*, 2014] or by 9% for every 10 years of age [Chou *et al.*, 2010]. To improve the assessment of tumour dissemination via lymphatic route, it has been suggested to evaluate the lymph node ratio, i.e. the ratio between the number of metastatic and examined lymph nodes [Costi *et al.*, 2014] or the log odds of positive lymph nodes [Arslan *et al.*, 2014]. Stage migration phenomenon has been recognized in colon carcinoma implying that lower tumour stages have been identified, e.g., in patients undergoing treatment in non-teaching hospitals or in hospitals where lymph nodes were retrieved by less experienced clinicians. However, even under these circumstances there were no interinstitutional differences in recurrence according to tumour stage [Ueno *et al.*, 2014]. Thus, our data display the actual problems and challenges in colorectal cancer surgery.

CONCLUSIONS

1. Colorectal cancer occurs with equal frequency in both sexes, often after the age of 60. Colorectal cancer screening would have high efficiency if started at the age of 50 years.
2. Among radically operated colorectal cancers, adenocarcinoma is the predominant histological type. Rectum is the most frequently affected anatomic localisation. Frequent localisation of mucinous colorectal carcinoma in left side of the intestine was found. However, wider studies are desirable.
3. The pT4 tumours have a tendency to increased frequency of perforation. It could be associated with but not limited by transmural tumour spread.
4. The pT4 colorectal cancer is characterized by invasion of lymphatic vessels, perineural and intraneuronal invasion. Perineural and lymphatic invasion in pT4 tumours was statistically significantly more frequent than in less advanced cancers and can be pathogenetically associated with wide local tumour spread.

Conflict of interest: None

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