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observed in only a fraction of these cases, its prognostic importance could be revealed by multicentric cooperation.

9. The centralization of operations into those hospitals where the best facilities are supplied to the teamwork seems inevitable in Hungary.

**The routine pathological assessment of colorectal carcinomas
-the role of pathologist in the multidisciplinary team**

Doctoral (Ph.D.) thesis

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1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-induced death in the developed industrial countries. The incidence and mortality follows an increasing course in Hungary and the highest in both gender among the European countries. 5000 colorectal cancer deaths and twice as many new cases are registered yearly in Hungary. Although pilot screening programmes has performed successfully in Budapest and in rural cities, but a centrally organized screening programme is still lacking. Most of the patients attends to surgery with advanced cancers, so our survival data lags behind the European countries – the ratio of five years survival is about 40 to 45%. Consequently it is vital for the patients to be treated by specialized colorectal multidisciplinary teams (MDTs). In the multidisciplinary approach of patients with colorectal cancer, the pathologist plays a role in two phases: the diagnostic phase and the postsurgical phase. The diagnostic role concerns mainly the confirmation of clinically suspected carcinoma. In the postsurgical the pathologist investigates the surgical planes of the specimen and gives all the prognostic factors that are needed for the postoperative adjuvant therapy.

II. Questions and objects

We tend to investigate all these prognostic factors that could be found in the guidelines for reporting colorectal cancer, decisive from the therapeutic point of view and applicable in all pathological departments independently from its size and technical facilities.

2.1. The investigation of the epidemiological characteristics of colorectal cancer in our region

The age, gender, location and stage distribution of CRC are influenced by the geographical conditions, cuisine, lifestyle, genetics and screening practices. As a result of screening, the incidence of the right sided colon cancers increased in the United States and Western European countries. According to the literature this process has not begun in Hungary yet.

We would like to draw the attention of the importance of screening through our epidemiological data.

2.2. The pathological investigation of surgical quality in rectal cancers

2.2.1. The surgical planes of the resected specimen after total mesorectal excision (TME)

The local recurrence after curative resections varied widely; the highest incidence has been reported after the conventional blunt dissection. In the recent years the local control and survival have improved with the introduction of total mesorectal excision technique. As the plane of excision strongly connected to the circumferential margin involvement - its pathological assessment is indispensable. The early publications dealing with the surgical quality appeared from 2002 and until now became the integral part of pathological guidelines. Our goal was the introduction of surgical plane assessment into the routine pathological practice in Hungary too through our experiences.

2.2.2. The pathological assessment of the resected specimens after abdominoperineal excision of the rectum (APER)

Although in the best centres the local recurrence rate has fallen under 10 % with the combination of TME plus chemotherapy but the rate of circumferential involvement and local recurrence rate still remained high in APERs. Dr. Halin applied a different approach to the APER operation. He excised the anus and levator muscles from below with the patient lying prone. This resulted a completely different resection specimen with more tissue removed and the surgical margin much farther away from the muscularis propria and the sphincters. The levator muscles are included in the specimen with their natural relationships

intact. The surgical planes of the modified APER technique i.e. the levator, sphincteric and submucosal planes were presented by professor Quirke in Basingstoke at the Pelicra Centre and in the Rectal Congress in St. Gallen in 2007. The updated guideline of The Royal College of Pathologists for reporting the colorectal cancers accepted the use of this system in the same year. As the surgical quality of the APERs in Hungary is unknown, we investigated the distribution of different planes and the rate of perforation after APER in different hospitals in our material.

2.3. The effect of preoperative neoadjuvant chemoradiotherapy (CRT)

Despite the improvement of operative techniques, local recurrence after radical surgery remains a major problem in the management of CRC patients. This led to the development of a variety of adjuvant treatments such as chemotherapy, radiotherapy, or a combination of both. As a consequence the advanced and formerly inoperable cancers could be operated with good results. The chemoradiosensitivity is different among the rectal cancers. While some of them reacts with total or nearly total regression - in which cases it is impossible or hard to find microscopic foci of tumor - other cases shows little or no regression. It is important to submit, that the most crucial factor is the circumferential margin involvement in these cases too, so the thorough pathological assessment of this feature is essential. The amount of regression seems prognostically important too. The presence of metastatic lymph node after preoperative neoadjuvant therapy is the sign of chemoradioresistance and the presence of metastatic disease in these patients is more likely. All the pathologists who reports colorectal specimens should be aware of the histological changes after CRT and the different grades of regression. With standardized pathological reporting, the assessment of tumor regression would be comparable between the different centres.

2.4. The factors influencing lymph node stage

In the therapeutic decision making, besides the local invasion the presence of lymph node metastasis is the most decisive feature. The number of processed lymph nodes, the mode of harvesting, the number of investigated planes according to the size of the lymph node, the use of sentinel technique or the immunohistochemistry to find micrometastasis are highly variable worldwide. The low number of lymph nodes result underestimating and has an adverse effect for the adjuvant treatment of the CRC patients. According to my personal experiences the pathologists blames the surgeons, for dissecting small amount of lymph node bearing peritoneal or mesorectal fat. The shortage of pathologists and the lack of time for proper processing are also frequently mentioned factors. In contrast the surgeons feels that the poor quality of the lymph node harvesting performed by the pathologists is responsible for the low

numbers. Our aim was to harvest all the palpable lymph node independently from their size from the resected specimens and to investigate those factors that can influence the lymph node stage. With a questionnaire we tried to analyse the opinion of Hungarian pathologists from the lymph node harvest in CRC specimens.

2.5. The detection of venous invasion in CRC

Venous invasion by tumor is an independent prognostic indicator both prognosis and risk of development of distant metastasis in CRC and in the absence of lymph node metastasis it warrants the use of chemotherapy. The vascular invasion is underrecognized in CRC using conventional haematoxylin and eosin (H+E) staining. The use of special stains aids the detection of this feature in the resected specimens. We investigated the usefulness of a cheap and practical elastic stain, the orcein and haematoxylin which rendered the elastic membranes of vascular walls easily detachable.

2.6. Differentiation between isolated tumor deposit and metastatic lymph nodes

In some cases, it is difficult to tell the nature of an isolated pericolic or mesorectal tumorous focus. It can represent a metastatic lymph node and vascular invasion as well. If we report them as metastatic lymph node than the N stage and if as vascular invasion than the T stage will be affected.

2.7. The organization of the multidisciplinary team (MDT)

Pathologists should report CRC in the context of a specialist team who cares for these patients. In Great Britain the key members include pathologist, surgeon(s), radiologist(s), medical and clinical oncologist and specialized nurses. Their training as a team is compulsory, centrally organized and taken place in Maudsley in the Pelican Centre. Some years ago the importance of the MDTs was not unequivocal in Hungary. It hadn't existed in 2000 in the County Hospital of Baranya, so the author organized it according to his experiences, which he gained as a TRAMPIS-PHARE grantee in the Western General Hospital and the Pathology Department of the Medical University of Edinburgh.

III. Material and methods

3.1. Epidemiological analysis

Our material was established by the resections of 968 CRC patients performed in the Surgery Departments of the County Hospital of Baranya, the City Hospitals of Mohács, Szegvár, Kőszd and Sárdos between 2000-2008. All the important pathological data were recorded continuously in Excel files.

3.2. The pathological investigation of surgical quality in rectal cancers

3.2.1. The surgical planes of the rectal specimen after total mesorectal excision (TME)

From 2003 as a total 749 rectal resections were investigated. Because of the distance between the surgical departments and the pathology all the resected specimens were sent to our laboratory in fixative. The specimens were fixed in unopened state in 10% formalin for 48 hours. The quality of surgery was reported according to the Quirke's protocol.

The plane of dissection, the quality of the mesorectum (the intactness of the mesorectal fascia, the weight of the mesorectal fat, the tears and cuts) were thoroughly studied before taking and serial slicing of the specimen. Digital photos were taken from both the intact surface before taking and after slicing for the documentation of the status of circumferential margin (CRM). The CRM was reported as involved when the advancing margin of the tumor reached the nonperitonealized edge of the resection margin or the distance was ≤ 1 mm.

3.2.2. The pathological assessment of the resected specimens after abdominoperitoneal excision of the rectum (APER)

From the 249 cases 64 (25.7%) of the tumors were treated by APER. In these cases in addition to the investigation of the mesorectum we studied the surgical planes of the lower third of the rectum according to the Quirke's protocol. It could be achieved retrospectively before 2006 through our digital photo-documentation, then it was performed prospectively.

3.2.3. The knowledge of surgical quality control technique among the Hungarian pathologists

We sent our questionnaire into every pathology department in Hungary to assess the knowledge of pathologists from method of surgical quality control after TME.

3.2.4. The investigation of the reasons of CRM involvement after TME surgery

The nonperitonealized edge of resected specimens were assessed between 2004-2007 according to the T and N stage, vascular invasion, peritoneal infiltration, perforation, the pattern of the infiltrating edge of tumor, the grade of regression after peroperative CRT, the surgical volume, the type of operation, the plane of TME/APR and gender.

3.3.1. The effect of preoperative CRT in the resected CRC specimens

From 2003 to 2007 84 (52 male, 32 female) cases of CRT treated CRC specimens were reported that represented 35% of our material. The patients were treated in the Oncotherapy Department of the Medical University of Pécs with internationally accepted neoadjuvant protocol and were operated on after 6 weeks of termination of CRT. 55 (65,5%) patients were operated with anterior resection and 29 (34,5%) with the abdominoperineal method. The regression grade was assessed according to the Wheeler grading system.

The majority of post-CRT effects (the presence of fibrosis, tumor cell free muscle lakes, calcifications, giant cells, irradiation vasculitis) could be reported on HE slides. In those cases where the cells showed the signs of oncocyte modification we performed immunohistochemical stains to investigate the possible neuroendocrine differentiation. In one cases the cells formed solid nests and mimiced histocytes. For this reason we performed ultrastructural investigation too.

3.3. The knowledge of regression grading among the Hungarian pathologists

We sent a questionnaire into every pathology department in Hungary to assess the knowledge regression grading among the pathologists.

3.4. The pathological investigation of lymph node stage

3.4.1. Lymph node dissection in our practice from 1999 to 2007

The lymph node harvest had been performed manually, without cleaning solutions. The mesocolic or mesorectal fat was serially sliced, palpated and all the lymph node were collected. The highest (epineal) node was blocked separately.

3.4.2. The opinion of Hungarian pathologists from the lymph node harvesting

We sent a questionnaire into every pathology department in Hungary and asked the opinion of pathologists from the average number of harvested lymph nodes, the effect of the surgeon, pathologist, the tumor and the host immunologic status on the number of nodes and the involvement of pathologist assistants to the lymph node harvesting.

3.5.1. The investigation of vascular invasion in CRC specimens

From January 2000 to February 2006 the vascular invasion was recorded on HE slides when tumor was present within an extraluminal endothelium-lined space that was either

surrounded by a rim of muscle or contained red blood cells. After this period we parallelly stained HE and elastic stains on consecutive sections from 6 blocks of tumor in each case.

With this method we were able to demonstrate the intra and extraluminal lymphovascular invasion in those cases, where the endothelial lining was destroyed by the tumor.

We performed immunohistochemistry in 10 cases to assess of its the usefulness in presenting the vascular endothelium of the invaded vessels.

3.6. Differentiation between isolated tumor deposit and metastatic lymph nodes

We followed the TNM 5th version in decision making, which classifies the tumor deposits as metastatic node if its diameter is $\geq 20\mu\text{m}$, and isolated deposit if the diameter is less.

Moreover we tried to differentiate between them with the help of elastic stain or CD31 immunohistochemistry.

3.7. The operation of CRC MDT in the County Hospital of Baranya

The CRC MDT worked on a weekly basis. As a general rule the MDT made decisions in every case preoperatively. The continuous quality feedback was provided among the members of the team.

IV. Results and discussion

4.1. The epidemiological characteristics of the CRCs in the material of the Baranya County Hospital between 2001-2007

Age distribution – less than 10 % of our cases occurred under 50 years old patient, the peak of incidence occurred in the 71-75 years old group. The distribution of sex showed a slight male predominance (53 % male v 47% female).

The site distribution of tumors showed a shift to the right side, which differed from the statistical data published in the Hungarian CRC Treatment Guideline, but was in close agreement with the data published by the Semmelweis University from the 1993-2004 period, where the 2/3 of the cases focused distally and the rest proximally.

The stage distribution of our material: 14,1% Dukes A, 37,2% Dukes B, 40,7% Dukes C and 6,6% histologically proven metastatic adenocarcinoma.

The average diameter of the tumors was 4,65 cm, which in agreement with the stage distribution showed the advanced nature of our material at the time of operation.

4.2. The surgical quality of the CRC resections

4.2.1. The characteristics of TME

The 43% ratio of mesorectal fascial plane between 2004-2007 is comparable with the international results, but the operations performed in the mesorectal propria plane were unacceptably high (44%). This was the main reason of the high (54,7%) CRM involvement in our material.

We observed a considerable difference in the surgical quality due to the surgical and departmental volume. In the two biggest hospitals, where most of the patients were operated on, the incomplete ratio was 34% and 37%, while in the smaller city hospitals it varied between 53,8 % and 100% respectively. It is noteworthy that continuous improvement of the surgical quality between 2003-2006 has stopped in 2007, when the ratio of incomplete resections has increased by 10%. We suppose that this ominous change was the result of the complex structural changing of the Hungarian health care system in this period.

4.2.2. The quality of APFRs

The surgical quality of APFRs was poor independently from the surgical or hospital volume. Resection in the levator plane have not occurred in our material. Although the resections that were performed in the sphincteric plane appeared, in most of our cases the submucosa

represented the plane of excision and in 25 out of 51 cases (49 %) the specimen was perforated.

4.2.3. The knowledge of surgical quality control technique among the Hungarian pathologists

Sixty five answers arrived to our nationwide questionnaire from three university departments, three leading special departments, ten county hospitals and eighteen city hospitals in 2005.

In the university, special and county departments 52% of the pathologists stated that they have a thorough knowledge from the method of surgical quality control, while the ratio was only 40% in the city hospitals. Ninety five percent of the pathologists thought that the surgical quality control should be the part of the pathology report and that it is acceptable for the surgeons.

As only half of the Hungarian pathologists have a proper knowledge from the surgical quality control in rectal resections we suggest that the next pathological guideline should introduce this method.

4.2.4. The reasons of the circumferential resection margin involvement

• Anatomical features - As a consequence of longer and narrower bony pelvis in men the visibility is poor and the little space for manipulation might result a higher CRM involvement. The CRM involvement showed a male predominance in our material (14% in males versus 8,7% in females).

• Tumoral characteristics - It is feasible that the more advanced tumors will cause CRM involvement through direct or vascular invasion, perineural infiltration or metastatic lymph nodes. We analyzed 42 CRM+ cases from 2004 to 2007, in which the T stage (93%), the lymph node metastasis (62%) and the vascular invasion (73,8%) were the most decisive factors. The perineural infiltration and perforation were less frequent. It is important to submit that the perforation mostly occurred at the anterior wall after preoperative CKI or APFR.

• Surgical volume: - The surgical and departmental volume is also important. According to professor Hermanek, every surgeon who performs CRC surgery should perform at least one radical operation per month. Although none of the surgeons in our region reached this level, most of the operations have performed by a small number of colleagues.

If we separated the surgeons performing more operations in bigger hospitals from those operating less in small city hospitals, the rate of CRM involvement was 19,7% versus 30,3% respectively.

• Type of operation: The difference was similar between the anterior resections (20,1%) and APFRs (31,8%). In comparison we present the data of the Dutch Trial, where the rate of

CRM involvement was 10.7% in anterior resections and 30.4% in ADPERs. The high CRM involvement could be changed by the modified ALPER technique of J. Hohn, whose CRM involvement was only 7% after 16 months follow-up in his first 28 operations.

The ratio of CRM involvement according to the plane of excision was the highest in the muscularis propria plane (54.7%) but for the frequent involvement in the mesorectal fascial plane (31%) we blamed other non-surgical reasons.

- **Radiological investigations:** The mesorectal fascia involvement by the tumor should be investigated by MRI. Unfortunately the availability for MRI investigations was very limited in the Damnyu County Hospital, therefore in most of our cases the investigations has performed with CT. This could be the reason of unacceptably high rate of CRM involvement in the mesorectal fascial plane.

- **The role of chemoradiotherapy:** The rate of CRM involvement was only 1.1% in the cases of complete or near complete regression and this represented about 40% of our material. Our data suggests that the preoperative CRT could have a positive effect on the prevention of CRM involvement in rectal carcinomas.

- **The role of pathologists:** The rate of CRM involvement also depends from the reporting pathologist. If he/she is not aware of the importance of CRM involvement on local recurrence, and does not search it on the serially sliced specimen, then this important feature will miss from the pathological report. Of course if it is lacking, the R classification will be useless.

4.3. The histological changes caused by preoperative CRT

The most consistent features of CKI were fibrosis, appearance of foreign type giant cells, tumor cell free muscle lakes and calcifications.

In 30 (35.7%) out of our 84 cases we observed oncocyte modification in the CKI treated carcinoma cells. The adenomatoid structures has been returned in 29 cases, but in one the tumor cells formed solid nests. In the latter case we performed immunohistochemical and ultrastructural investigations to prove the origin of these cells as they cytologically mimicked histiocytes. The focal cytokeratin staining and the presence of desmosomes proved their epithelial origin. The cytoplasmic enrichment of mitochondrions could resulted the oncocyte appearance of this tumor.

Neuraminidase differentiation have shown due to the chromogranin and synaptophysin staining in four cases (13%). There were no signs of such a differentiation in the preoperative unrecutted biopsy material.

4.3.1. The knowledge of regression grading among the Hungarian pathologists

In contrast with the knowledge of surgical quality control, the method of regression grade investigation was less well-known among the Hungarian pathologists. Only eleven (17%) colleagues stated (6 from university departments or special institutes and 5 from county hospitals), that he/she knows one of the regression grading systems. It was totally unknown among the colleagues working in the city hospitals and less than third of the pathologists working in the bigger institutes or university departments has some knowledge from this subject in 2005 in Hungary.

We suggest, that the next modification of the guideline for reporting CRC should contain one of the regression grading systems.

4.4. The change of lymph node count in our material

1999 was the last year when the reporting of CRCs was uncentralized. From november 2000 the author performed the cutup and reported every case. The average lymph node count has increased from 2.67 in 1999-2001 to 9 in the last two years.

4.4.1. The evaluation the questionnaire dealing with the lymph node stage reporting

The answers are difficult to interpret, as 52% of the answering pathologists stated that they satisfied with the harvested lymph node number, but if we asked them from the reasons of low number of yielded lymph nodes – only 23% of them remained satisfied and the remainder determined one or more reasons for it.

Most of the pathologists felt that mostly the surgeons are responsible for the low lymph node counts, secondly the patient and the tumor characteristics are the cause and only at last the pathologist him or herself.

Our experiences contradict to these opinions and prove the primary importance of the devotion of pathologist. Of course other factors – the quality of the resection, the technical conditions, the workload of pathologists and pathologist assistants are also play an important role.

The decreasing number of pathologists raise the necessity of training the pathological assistants to take part in lymph node harvesting. According to the answers from the pathologists we have to wait for it in Hungary, because it is not universally acceptable for them. The smaller is a pathology department, the higher is refusalment of this idea.

4.5. The investigation of vascular invasion in CRC specimens

The demonstration of vascular invasion has performed in two distinct period. From January 2001-February 2006 the vascular invasion was searched with HE stain only. From February 2006 after the authors visit in the St. Marks Hospital, London and Pelham Centre, Basingstoke the investigation has performed on six blocks of tumor with the routine use of

elastic (vucin-haematoxylin) stain, that reached double increase in the identification of vascular invasion.

We investigated the immunohistochemical demonstrability of vascular invasion with antibodies directed against endothelium (CD31, CD34), but according to our experiences the endothelial lining of the invaded vessels is frequently destroyed by the direct compression or cytotoxic effect of the carcinoma cells.

4.6. Differentiation between isolated tumor deposit and metastatic lymph nodes

An universally accepted concept for the discontinuous peritumoral foci is still lacking. In TNM5 according to the 3-mm rule an isolated tumor deposit was called a tumor positive lymph node if its diameter was >3 mm. In TNM6 there has been a further change to lymph node definitions and also to the definition of a further high-risk feature, venous invasion. TNM6 states, "smooth metastatic nodules in the perinecrotic or perirectal fat are considered as lymph node metastasis and will be counting in the N staging". The definition of venous invasion was also changed, the irregularly contoured metastatic nodules in peritumoral fat are considered vascular invasion.

According to our experience the foci exceeding 3 mm in diameter can contain more than one pattern of invasion. In these cases it seems impossible to tell whether it represents a metastatic lymph node or a vascular invasion. The early venous invasion prior to destructive invasion of the venous wall by the tumor is always smooth. On the other hand, the invasion and destruction of the lymph node capsule results a structure with irregular contour. In conclusion we agree with those who suggested the ignoring of TNM6 modifications.

4.7. The multidisciplinary team

According to the international experiences the advantages of the technical developments can be utilized with the well organized teamwork of experienced experts. In Great Britain the training for the MDTs is centrally organized, their structure and working order is clearly defined. Although the organization and operation of the MDTs is compulsory in Hungary too, but the composition of team members the working order is changing from centre to centre. The pathologists need clear definitions and requirements for reporting colorectal cancers in order to fulfil their role in the team of experts. We hope that our work will contribute to the spreading of clear definitions in colorectal cancer reporting and will help the work of MDTs in Hungary.

V. Novel findings and practical applications

1. According to our epidemiological data we experienced a right shift in the location of CRCs, which differs from the data of the current Hungarian guideline for treating colorectal cancers. This supports the opinion, that the screening process should comprise the entire length of the colon.
2. The improvements of surgery, radiology and oncology requires improvements in the histopathological practice as well. The pathology reports should comprise every prognostically relevant information.
3. Every member of the multidisciplinary team is an important prognostic factor. With continuous feedback the pathologist contributes to the high quality work of the team. As the description of the surgical quality control through the assessment of the resection planes is lacking from the current Hungarian guidelines for reporting and treating colorectal cancers, in the next version it should be replaced.
4. The ratio of operations that has been performed in mesenteric propria plane in TME and in submesocolic plane in APR was inacceptably high in our material. The introduction of the Hohen's technique would result a lower rate of circumferential involvement in APRs.
5. In the focal recurrence of rectal cancers the most decisive factor is the circumferential margin involvement, which is affected by the surgical quality, the method and quality of peroperative diagnostic investigations, the advanced T and N stage of disease and the presence of vascular invasion. The rate of circumferential involvement could be decreased by screening, better patient selection before operation, good quality surgery and preoperative chemotherapy.
6. The surgeons and the pathologists should do their best to retrieve as many lymph node as they can, but at least 12 on average in order to put the patient in the proper N stage. The use of fat solving solutions are redundant. The involvement of pathologist assistants into lymph node harvest may resolve the problems caused by the shortage of pathologists.
7. The use of elastic stain greatly helps the identification of vascular invasion, so we suggest its inclusion in the next guideline for reporting colorectal cancers and its routine use.
8. The oncocyte modification occurring after preoperative CRT can cause differential diagnostic problems. According to the literature and our ultrastructural experience it is caused by the mitochondrial enrichment of the tumor cells. Neuroendocrine differentiation can be