Laparoscopic surgery of colorectal cancer - the significance of lymphatic spread and the role of sentinel node biopsy in the minimally invasive surgical management of colorectal tumours

PhD Thesis

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I. Introduction

In developed countries - including Hungary - CRC is the most common cause of cancer death among non-smokers and the second most common among smokers. About 5000 patients die annually due to colorectal cancer indicating high morbidity and mortality in present day Europe. There are no exact data available on the incidence of colorectal cancer but according to certain studies 7500-8000 new diseases can be counted with each year.

There is more consistency in the literature regarding the minimum number of lymph nodes to be removed during the surgical intervention and to be examined during histological processing; however, there are diverse pieces of information when it comes to micrometastases and sentinel lymph nodes. The detection of micrometastases is lengthier and more expensive, nevertheless according to certain literature data their study may trigger upstaging by as much as 30%, thus modifying the prognosis of the disease. The role of the sentinel lymph nodes is controversial, and there is still no recommendation and evidence for their assessment and some literature data suggest it is not beneficial or applicable in colorectal tumours. Unsurprisingly there are opposite opinions as well thus - beside other procedures - sentinel lymph node biopsy may become reliable also in colon and rectum surgery and as the histological processing and detectability of tumour cells are also developing even a very small amount of tumour can be identified in the regional lymph nodes.

The treatment of colorectal tumours is primarily surgical: without surgery the disease cannot be cured. The successful operation performed to established professional standards essentially determines the short and long-term results. The surgeon is an independent prognostic factor for the outcome after CRC. Alongside traditional open procedures the laparoscopic method is becoming more and more widespread providing many advantages for the patient without oncological compromise due to its minimally invasive nature. Possessing supportive data the aim of our study was to analyse the long-term oncological results of laparoscopic colorectal surgeries and to compare laparoscopic and open procedures. We intended to study the practicability of sentinel lymph node localisation of colorectal tumours in daily clinical practice, especially regarding laparoscopic surgery. An answer was sought whether tumour marking with patent blue dye and the sentinel lymph node identified by this technique determines the level of lymphadenectomy and thus the feasibility of a less extensive gut resection. Our aim was to define if a marker lymph node could be pinpointed by this method and able to be used in the surgical practice to determine the surgical resection and the level of lymphadenectomy.

II. Case–matched comparison of short and middle term survival after laparoscopic versus open rectal and rectosigmoid cancer surgery

II.1. Introduction
The aim of our study was to compare survival data - as the most important quality indicator - following 100 open and 100 laparoscopic rectal and rectosigmoid resections for tumours of matching stage in order to be able to support – or refute – the laparoscopic approach depending on results.

II 2. Materials and methods
Only elective and curative resections (i.e. absence of distant metastases) were selected into each group to ascertain homogeneity and match for tumour stage. 100 successive open rectal and rectosigmoid resections were compared with 100 similar laparoscopic procedures between 1st February 2005 and 31st December 2009 performed at the Department of General Surgery, Borsod-Abaúj-Zemplén County and University Teaching Hospital. We eliminated

selection bias by analysing successive procedures the investigation period being solely determined by achieving the desired number of cases.

A retrospective analysis was carried out and the patients were subsequently followed up until 30th April 2012. We included all cancers from the anus to 22cms using UICC (2003) classification. Clinical data were prospectively collected the primary endpoint being average survival in the two groups secondary endpoints being stage specific survival, incidence of loco-regional recurrence and distant metastases. We also recorded intra- and postoperative complications, operating time, onco-pathological specimen quality and length of stay. Median follow up in the open group was 39.8 months (minimum 36 months) and 41.6 months (min. 24 months) in the laparoscopic group.

II. 3. Results

Patient demographics were comparable in the two groups: mean age in the laparoscopic (LX) group was 63 years (range: 32-83) and 65 years (31-80) in the open (O) group. The LX group constituted 31 female and 69 male patients the O group of 27 and 73, respectively. There were 43 cases of Dukes A tumour in the LX group and 34 in the O group; Dukes B were 23 to 31 and Dukes C 34 to 35. In the laparoscopic group 40% of the patients underwent neoadjuvant treatment; in open group this rate was 57%. In both groups 60% of the patients underwent adjuvant therapies. The differences are not significant. (Table I).

Procedures n=200	LX n=100	O n=100	p (Chi-square)
Mean age	63(32-83) years	65(31-80) years	ns
Male n=142	n=69	n=73	ns
Female n=58	n=31	n=27	ns
Dukes A n=77	n=43	n=34	ns
Dukes B n=54	n=23	n=31	ns
Dukes C n=69	n=34	n=35	ns
Neoadjuvant therapy n=97	n=40	n=57	ns
Adjuvant therapy n=120	n=60	n=60	ns

Table I. Demographical data

Table II details intraoperative complications highlighting tumour breach that would have serious impact on outcome due to dissemination of cancer cells: this occurred in 4 cases in the LX and in 7 cases in the O group. Positive air test was found in 1 case in the LX and in 3 cases in the O group - in such events protective defunctioning loop ileostomy was routinely formed. Blood supply insufficiency to the proximal bowel end was identified in 1 and 3 cases, respectively.

Intraoperative complications n=27	LX n=10	Open n=17	Fisher's exact test ns (p=0.107)
Tumour breach n=11	n=4	n=7	ns
Positive air test n=4	n=1	n=3	ns
Proximal bowel perfusion insufficiency n=4	n=1	n=3	ns
Vaginal injury n=1	n=1	n=0	ns
Instrumental bowel injury (Babcock tissue holder) n=3	n=3	n=0	ns
Stapler failure n=2	n=0	n=2	ns
Splenic injury n=1	n=0	n=1 (required tissue glue only)	ns
Involved resection margin n=1	n=0	n=1 (subsequent APR performed)	ns

Table II. Surgical data - Intraoperative complications

Type of operations are listed in Table III: there were no significant differences between the two groups. Defunctioning ileostomy was fashioned in 12 cases in the LX group and in 22 cases in the O group.

Operation type: n=200	Laparoscopic n=100	Open n=100	
Rectosigmoid resection n=115	n=60	n=55	Chi - square test p=0.18, ns
Rectosigmoid resection with ileostomy n=34	n=12	n=22	
Abdomino-perineal resection n=47	n=27	n=20	
Colectomy+rectal resection n=2	n=1	n=1	
Proctocolectomy n=2	n=0	n=2	

Table III. Surgical data – Type of procedure

We compared several other variables using Mann-Whitney test but neither the length of the resection specimen nor the distance of the proximal and distal resection margins showed significant differences. No significant difference was found in the number of total and positive lymph node count, either. Operating time and length of stay were also compared between the two groups and it was found that patients in the LX group spent significantly shorter time in hospital (Table IV). Although no significant difference was found in operating times an interesting observation was made based on the histograms: 180 minutes was a major threshold beyond which laparoscopic procedures rarely extended (Figure 1). This prompted a comparison of operations lasting less and more than 3 hours in the two groups and with Fisher's exact test a significant difference was found (p=0.054) (Table IV).

	Laparoscopic surgery	Open surgery	Mann-Whitney
Specimen length (mean cm)	21,15	24,20	ns
Distal resection margin (mean cm)	3,83	3,64	ns
Proximal resection margin (mean cm)	14,06	16,45	ns
Mean number of examined (removed) lymph nodes	7,33	7,07	ns
Number of positive lymph nodes (mean)	1,2	1,26	ns
Hospital stay (mean days)	9,7	12,4	<0,001
Operating time (mean minutes)	165	171,7	ns

Table IV. Comparing specimen length, proximal and distal resection margins, total number of lymph nodes and number of positive lymph nodes hospital stay and operating time between open and laparoscopic group with Mann-Whitney test
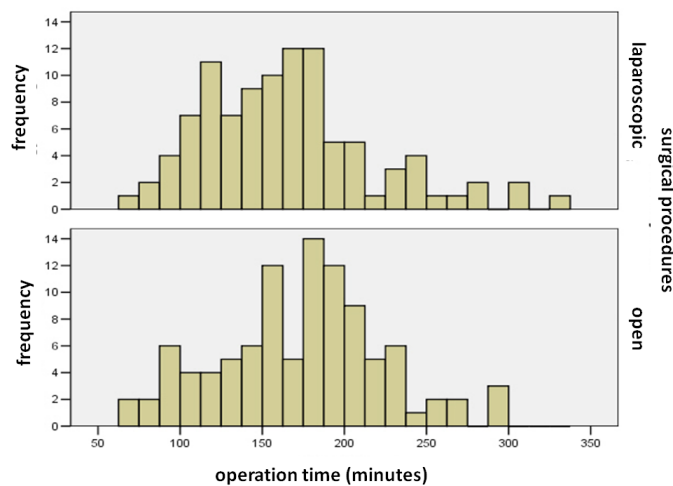
Figure 1. Operating times

Noteworthy of postoperative complications is the incidence of anastomotic leak that was detected in 2 patients in the LX group and in 5 in the O group (statistically non-significant difference). Neither was significant the difference found in the incidence of surgical site infection (5 in the LX group and 9 in the O group). Postoperative bleeding requiring reoperation did not occur at all. The incidence of incisional herniae diagnosed during the follow up period was, however, significantly different with 4 cases in the LX and 18 in the O group (p=0,001). During the follow up period (LX group 41.6 months, O group 39.8 months) we found similar disease recurrence and survival data: loco-regional recurrence was found in 1 case in the LX and in 4 cases in the O group; distant metastases occurred in 20 and 22 cases. 13 patients died from rectal cancer recurrence during follow-up in the LX and 19 in the O group. The mean 3-year survival was 76% in the LX and 69% in the O group. Recurrence rate and 3 year survival rate after the two types of surgeries also were analyzed separately in the different Dukes grades, as well as summarized. We performed the analysis using the Kaplan-Meier method. When examining the different Dukes grades separately we did not find significant differences between laparoscopy and laparotomy, except in Dukes C cancers where survival intervals were better in the laparoscopic group the difference being statistically non-significant (p=0.24) (Figure 2).
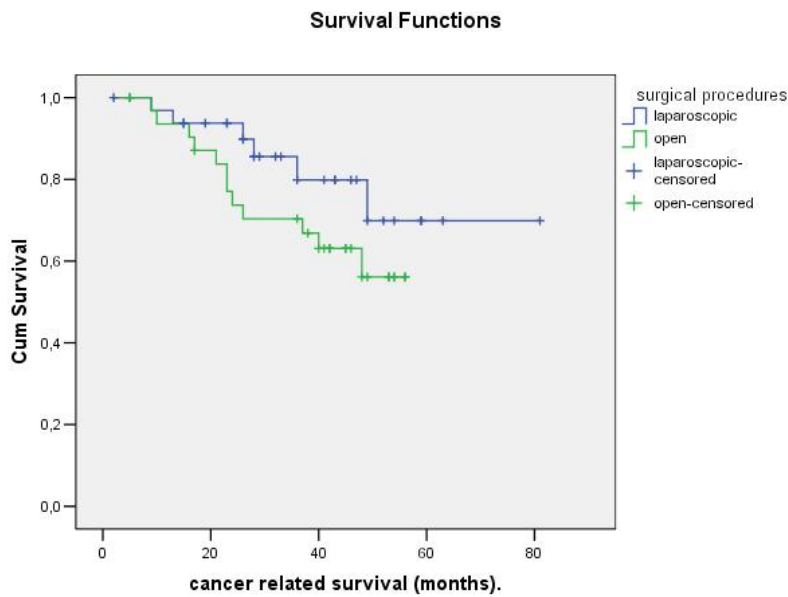
Figure 2. Kaplan-Meier graph for the Dukes C stage

Similarly, whereas the recurrence intervals for the three Dukes stages did not differ significantly in the LX group the same cannot be said for the O group where Dukes C tumours are associated with a much shorter recurrence interval (Figure 3). Kaplan-Meier's significance, Logrank's test: p<0.001.
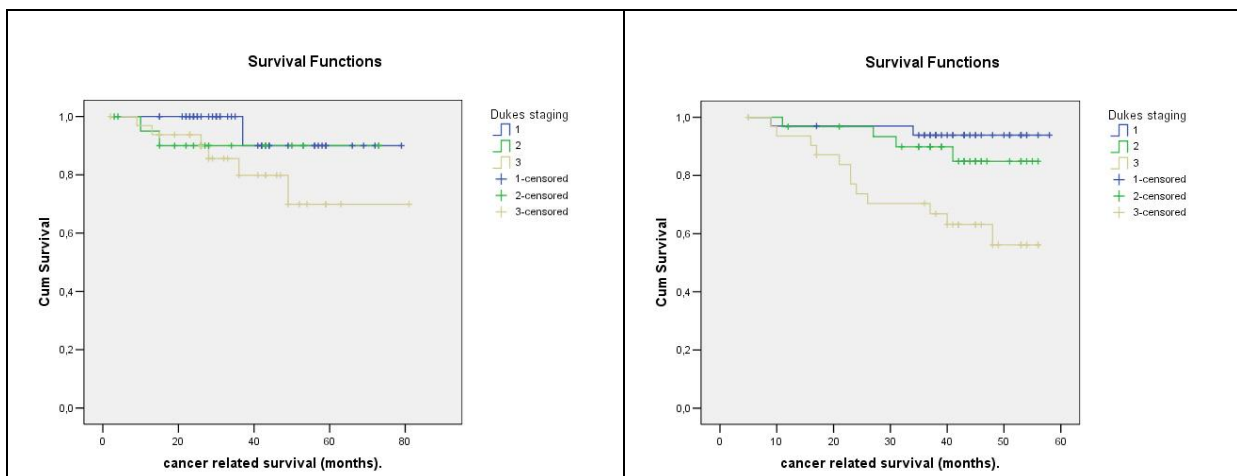

Figure 3. Kaplan-Meier graphs on the incidence of cancer recurrence in the LX and O group.

II. 4. Discussion

The currently existing golden rules (Turnbull principles) of colorectal cancer surgery, namely bowel segment isolation, no-touch manipulation, high ligation of blood vessels and lymphatic dissection can all be fully applied in laparoscopic surgery as well. Among our groups morbidity associated with laparoscopic procedures was 11% and mortality 2%; with open procedures the relevant figures were 22% and 3% (non-significant difference) in line with literature data. Anastomotic insufficiency is another key measure and a host of studies address this issue reporting incidences between 0 and 27%. Based on literature data the figures are comparable for laparoscopic and open procedures; our cohort showed 2% in the LX group and 5% on the O group (p=0.20, n.s). Certain literature data prove there is no evidence of

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oncological compromise when investigating the pathological quality of resection specimen or recurrence or survival rates associated with open and laparoscopic resections of middle and lower third rectal cancers following neoadjuvant treatment; the only downsides were longer operating times. We, on the contrary, identified shorter laparoscopic procedure times and when presenting them in histogram form we showed that the majority were completed within 3 hours. For this reason we compared procedures taking less than 3 hours in the two groups and found statistically significant difference in favour of the laparoscopic technique (p=0.045). The occurrence of intraoperative complications was negligible and statistically non-significant in either of the groups (LX=10%, O=17%); none were major, unmanageable or fatal this once again correlating with 5-20% quoted in the literature. With respect to incisional hernia incidence our data indicated significantly better outcomes in the LX group (p=0.001) and studies also report other advantages like reduced rates of surgical site infection, anastomotic strictures, ileus and intraabdominal adhesions with laparoscopy. Good quality indicators of onco-surgical radicality are intact fascia propria recti and resected lymph node count in the specimen. The minimum standard for the latter is 12 but this is often difficult to achieve following chemo-radiotherapy. Pathology also plays an important role in quality assurance and quality of circumferential resection margin is a very important oncological parameter. In our material only 2 laparoscopic cases had involved resection margins against 3 cases in the open group (all having been T4 tumours after chemo-radiotherapy) giving a 98% clear margin and curative laparoscopic surgery rate. Similar to literature data we found no significant difference between the laparoscopic and open group for lymph node count or resection margin (LX group = avg. 7.33 nodes, median 3.83cm distal margin; O group = 7.07 and 3.64, respectively). Our local recurrence rates were 1% after laparoscopic and 4% after open procedures underlining the literature statement that laparoscopic resections have acceptable and comparable recurrence rates ranging from 3 to 7.6%. In our study laparoscopic rectal and rectosigmoid operations proved to be safe and to provide definite benefits to patients. Our 3 year survival figures were 76% in the LX and 69% in the O group - the difference being non-significant - and are in line with literature data for both laparoscopic and open operations.

In our study we found that laparoscopy used to treat rectal and rectosigmoid cancer is safe and provides measurable benefits for patients. Among our patients 3 year survival was 76% in the laparoscopy group and 69% in the laparotomy group the difference not significant. Results from our study are similar to literature data both after laparoscopy and after laparotomy.

III. Comparison of the open and laparoscopic procedures in lower and middle third rectum tumours after neoadjuvant treatment

III.1. Introduction

The viability of laparoscopic colon tumour surgery is supported by several level I/a evidence. Excellent early and late results have been published regarding the laparoscopic surgery of sigmoid and upper third rectum tumours; however, this level of literature resolution is rare in the surgery of rectum tumours following chemo-radiotherapy. The laparoscopic surgery of rectum tumours may be a greater challenge for the surgeon as the TME and the sparing of the autonomous nerves may be more difficult to achieve but lead to better functional and oncological results. Our aim was to study and to compare the open and laparoscopic treatment of lower and middle third rectum tumours after chemo-radiotherapy. We examined and analysed quality of the surgeries, the pathologic characteristics of the specimen, features of the perioperative period as well as survival data and recurrence of the disease.

III.2. Materials and methods

Between 1st January 2006 and 31st December 2011, 378 patients underwent surgery for lower and middle third rectum tumours. 182 of these patients did not receive neoadjuvant treatment and in 24 cases only exploration or stoma formation occurred. 62/378 patients had distant metastases and 15 had synchronous tumours as well. In their history 12 patients had a previous tumour. 196 of the 378 patients received neoadjuvant treatment; of these 12 was lost to follow up, therefore data for 184 patients were analysed. Patients with tumours located within 10 cm of the anal canal were included. The mean follow-up time was 31 months (1-73 months).

III.3. Results

Of the 184 patients, 132 were male and 52 female. The mean age was 62 years; the youngest was 32 while the oldest was 85. The general health and the surgical risk of patients were similar in the two groups compared by ASA classification. The laparoscopic and the open group were comparable but the ratio of ASA III patients was slightly higher (chi square test p=0.37, not significant) amongst those whose procedure had to be converted from laparoscopic to open their co-morbid status likely to have played a role in the decision for conversion. The body mass index of the patients was also analysed and found to be similar in the two groups.

67 patients received laparoscopic operation and in 15 cases conversion occurred. Open operation was performed on 117 patients. Out of the 184 resections 39 occurred without ileostomy: 11 of these were laparoscopic and 3 required conversion; the other 28 patients had open operations. Resection with defunctioning ileostomy was performed in 70 patients of whom 36 had laparoscopic and 11 were converted; 34 patients received open operations. 38.6% (71) of the patients had total abdominoperineal rectum resection. Laparoscopic total rectum resection was performed in 20 cases - one of these converted - while 51 patients received open operations. Hartmann`s resection was performed in 2 cases and open proctocolectomy in 1 patient. We were forced to make conversion in 15 patients, in almost half of these cases due to a large tumour occupying the pelvis. In 1 case each splenic injury, vaginal injury, vesicular injury, identification difficulty of the descending blood supply and the insufficiency of the Riolani arch lead to the conversion. There were more reoperations in the open group than in the laparoscopic, however, the difference was not significant.

The oncological adequacy of the surgical intervention was examined from several points of view. The high or low ligation of the inferior mesenteric artery (IMA) was analysed based on the operation notes. Using the chi square test (p=0.002) the proportion of high and low ligation of the IMA is significantly different in certain types of surgery: while high ligation is more frequent in laparoscopic surgery in open procedures low ligation is more typical.

The most important measure of oncologically adequate surgery is the precise execution of TME in lower and middle third rectum tumours which is indicated by the intact fascia propria recti. Since the quality of the TME was not included in the histological findings we could only assess this by retrospective analysis of the notes, hence the quality of TME was measured on the basis of the opinion of the operating surgeon. The clear disadvantage here is full subjectivity, however other data were unavailable.

Regarding disease recurrence and survival the soundness or the involvement of the circumferential resection margin (CRM) is also extremely important. There was no significant difference between the three groups in this respect (chi square test, p=0.94). The macroscopic pathological features of the `pre-treated` low and middle third rectum tumours were analysed for each surgical group and classified by Dukes stages. The three surgical groups did not differ significantly regarding the distribution of the stages (chi square test, p=0.3). Applying Mann-Whitney test no significant difference was found between tumour sizes: the mean

tumour size in the laparoscopic group was 2.9 cm (0.5-7 cm), 3.2 cm (0-10 cm) in the open group and 3 cm (0-6 cm) for cases needing conversion. The removed specimen were also compared for distal resection margin and overall length of specimen and no significant difference was established between the open and the laparoscopic group.

The number of removed lymph nodes and the ratio of positive to total nodes were also recorded with no statistically significant difference found between the laparoscopic and the open group. The graphical representation of these data is shown in Figures 4 and 5.
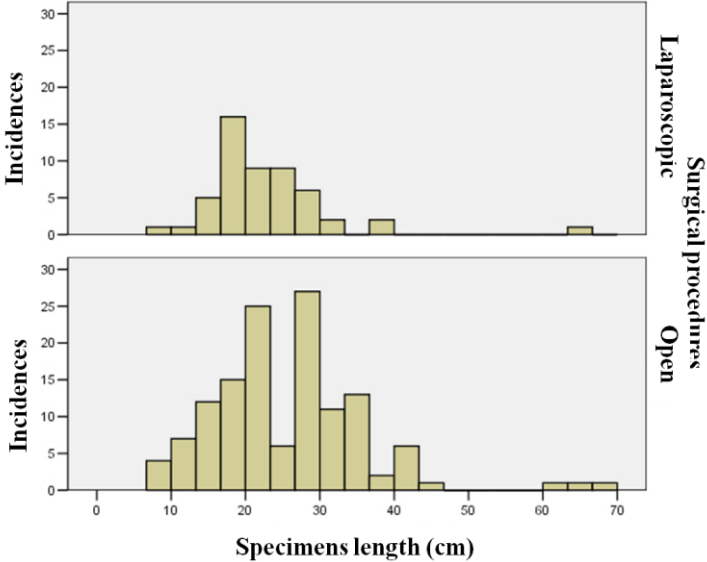
Figure 4. Comparison of the specimen length in the laparoscopic and open groups.
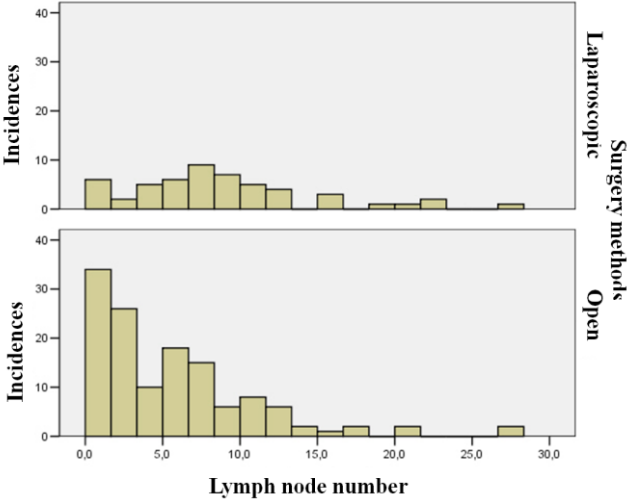

Figure 5. Numerical distribution of the removed lymph nodes in the two groups.

Studying the perineural invasion of tumours - which is also an important prognostic factor – significant differences were found in the three surgery groups (chi square test, p=0.01).

Also significant (chi square test, p=0.04) was the difference between transfusion demand: during the perioperative period one patient received 2 units of red blood cell concentrate (RBC) in the laparoscopic group, while in the open group 20 patients were given a total of 55 units RBC. Additionally, 15 units fresh frozen plasma (FFP) were also given to those in the open surgery group.

The open group was found disadvantaged for postoperative complications. More pyrexia and surgical site complications were observed presumably due to the extensive abdominal

dissection. Additionally, more urinary disorders were found due to the more traumatic technique and interestingly, despite the distension of the abdominal cavity less cardiac complications were noted in the laparoscopic group.

Surgery times were similar in the laparoscopic, the converted and the open group; there was no significant difference. There was no significant difference in the number of postoperative deaths, either. The cause of the 6 surgical deaths in the open group was sepsis in 3 cases due to anastomotic insufficiency with two cardiac failures and one stroke.

The mean follow-up time was 31 months (1-73 months). Recurrence rates were 17% in the laparoscopic and 22.7% in the open/converted group and although cancer deaths were higher in the open group the difference was statistically not significant.

Interpreting recurrence rates by Kaplan-Meier procedure no significant difference was found between the two groups. The Logrank test showed p=0.559 (Figure 6).
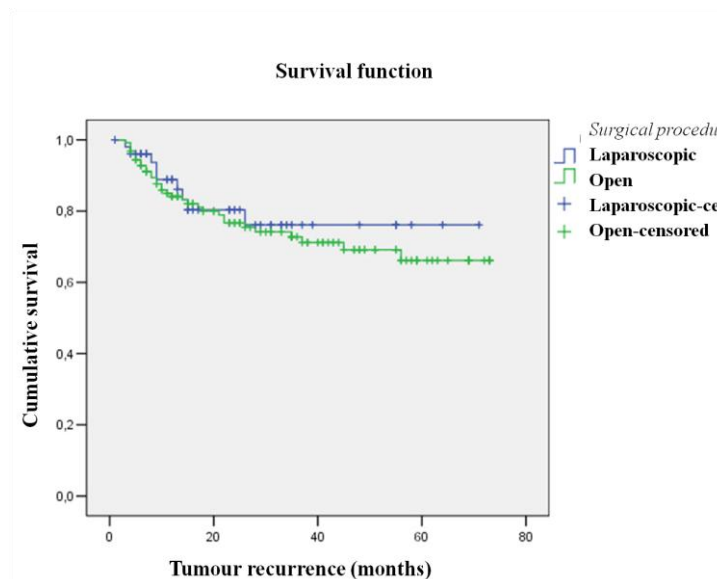

Figure 6. The Kaplan-Meier graph showing the recurrence of the disease. The Logrank test showed p=0.559.

Interpreting survival data by Kaplan-Meier procedure no significant difference was found between the laparoscopic and the open groups. The Logrank test showed p=0.611 (Figure 7).
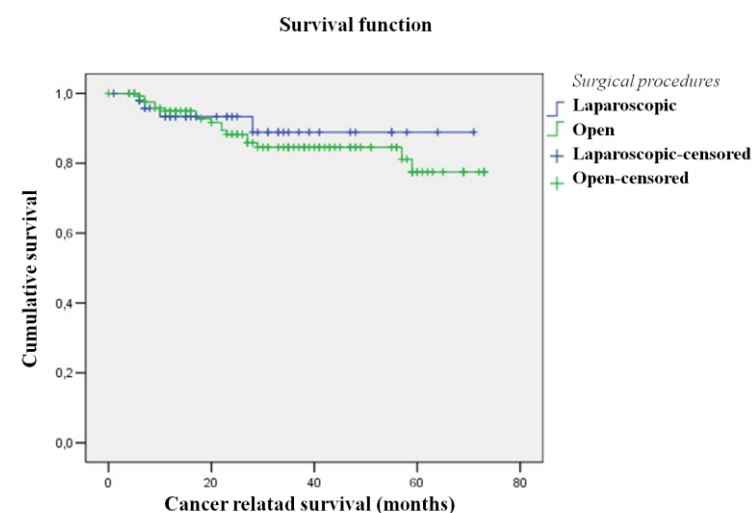
Figure 7. The Kaplan-Meier graph showing the cancer related survival in the two groups. The Logrank test showed p=0.611.

The incidence of incisional (abdominal wall) hernia was compared in the two groups. Using Fisher's exact test no significant difference was shown. In case of the 52 followed up laparoscopic patients 1 hernia was noted (1.9%) while jointly investigating the open and the converted patient group 7 hernias were detected (5.6%) the difference not significant (chi square test, p=0.26).

V.4. Discussion

67 laparoscopic low and middle third rectum tumours were included in our studies performed by 2 surgeons. There was no patient selection that may explain the relatively high conversion rate of 22.4%. The main reason for conversion was large tumour size obstructing access by laparoscopic instruments. Unfortunately, the majority of our patients were diagnosed in the advanced T3 and T4 stages. Despite a non-selected group of patients the laparoscopic results are still acceptable as demonstrated by comparable Dukes stages and ASA grades the BMI of patients not showing a significant difference either. When compared between the laparoscopic and other groups the length of the removed specimen and tumour sizes were also similar. The execution of full TME is extremely important and – based on surgeons` own accounts - occurred in almost 90 % of cases as expected. The final evaluation of the TME is the task of the pathologist, however, and its objective description by M.E.R.C.U.R.Y standard was unavailable in the histological report, hence we were forced to rely on the operation notes and the photographic documentation of the unfixed specimen. For this reason our data can be considered not representative regarding the quality of the TME. When estimating recurrence risk of the disease the involvement of the circumferential resection margin (CRM) is an extremely important factor and this was seldom positive. In the laparoscopic group, a higher lymph node count was able to be achieved. The principle of central ligation of IMA prevailed in slightly higher numbers in the laparoscopic group the reason being dissection from medial to lateral as following central ligature of the vessels the dissection along the Toldt fascia in an avascular plain facilitates the sparing of the hypogastric plexus, the ureter and the gonadal vessels. In summary, the oncological quality of laparoscopic resections is adequate similarly to that of open procedures. Intraoperative complication rates were similar, but postoperatively there was a significant difference in transfusion demand in favour of laparoscopic procedures and in accordance with literature data much less surgical site infections and febrile states were observed. Historically 10% of laparotomies result in incisional hernia and in case of infection this number can be exponentially higher. The number of postoperative hernias was lower in the laparoscopic group, however, it did not show a significant difference from the open or conversion group. The operating times and length of hospital stay were comparable, what is more, the duration of laparoscopic surgeries was shorter which can be explained by the higher level of expertise of the surgeons performing these operations (the mean length of laparoscopic procedures was 164, while that of the open ones was 184 minutes). Length of stay was also similar since in the majority of the cases defunctioning ileostomy was performed according to literature recommendations and its initial maintenance and stoma therapy requires time. During follow-up there was no significant difference either in recurrence rates or in disease free survival although the figures were always more favourable in the laparoscopic group (recurrence rates were 17.3% in the laparoscopic and 22.72% in the open plus converted group). During the follow-up period 7.69% died from cancer recurrence in the laparoscopic and 15.15% in the open group. Based on all these, beside its short-term advantages laparoscopic surgery is oncologically safe to treat rectum tumours following chemo-radiotherapy.

IV. Relevance of sentinel node technique in the laparoscopic and open surgical management of colorectal tumours

IV.1. Introduction
The most important prognostic indicator of potentially curable (i.e. removable by R0 resection) colorectal cancers is regional lymph node status. Sentinel lymph node localisation aims to determine nodal status intraoperatively which is good and current practice in the surgical treatment of melanoma and breast cancer; its role in colorectal surgery is at present controversial and contemporary literature takes a stance against it. In cases of breast cancer and melanoma the advantage of the sentinel technique is unambiguous and helps prevent limb lymphoedema. We sought to find answer to the question whether sentinel node localisation can be achieved in unselected patients with a variety of conditions during our daily work, whether the sentinel technique has a role in colorectal surgery and whether it has an impact on the surgical procedure and later on the fate of the patient especially in laparoscopic resections where cosmetic results are also of considerable significance.

IV.2. Patients and method
Sentinel lymph node marking was performed intraoperatively in 188 unselected colorectal patients undergoing either open or laparoscopic procedures. The study was conducted between 1st October 2009 and 1st July 2012. In the end only 180 patients were considered as in 7 cases benign polyps and in one case diverticulitis was diagnosed on final histology. At the start of the procedure 1ml of blue dye was injected subserously on the antimesenterial side immediately distal to the tumour. After photo documentation of the unfixed specimen at the end of surgery the lymph node dyed most intensively blue and closest to the tumour was isolated and named surgical sentinel node. In case of formalin fixed specimen the pathologist identified the node dyed most intensively blue and closest to the tumour during the histological processing to be the pathological sentinel node making the technique of marking more accurate because if surgically no sentinel node was found the pathologist would have still been able to find one. In case of node negative cases the sentinel nodes were examined for micrometastases by pan-CK immunohistochemistry.

IV.3.Results
The mean age of patients was 66 years the youngest being 32 while the oldest 85 years old. 132 male and 56 female patients were subject to surgery. Laparoscopic surgery was performed in 95 (50.5%) and open surgery in 93 (49.5%) cases. Conversion took place in 20 cases (21%). Of the 188 operations histology revealed benign changes in 8 cases. The Dukes staging of the remaining 180 patients were the following: among the 90 laparoscopic cases were 20 Dukes A, 30 Dukes B and 40 Dukes C and among the 90 patients in the open group 7 Dukes A, 41 Dukes B, 32 Dukes C and 10 Dukes D. In the laparoscopic group postoperative complications were found only in the converted cases, one surgical site infection and one postoperative peritonitis. In the open group 2 reoperations occurred due to anastomotic insufficiency and one due to peritonitis. In the open group 5 surgical site infections were found and one rectovaginal fistula was detected. At the beginning of our investigation only `in vivo` sentinel lymph node marking and isolation was performed and the data from 85 patients were analysed: it became clear that the technique cannot be utilised in surgical practice as the dyed lymph node was hard to identify in vivo in patients with high BMI and even when it was easy to detect, in some cases nodes infiltrated by tumour could be detected adjacent to negative sentinel nodes in the vicinity of the cancer. The same problems were experienced during the preparation of the unfixed specimen. The staining ratio was 100%. Of the 85 patients 37 node positive and 48 node negative cases were described. In 72 cases sentinel

node negativity was found and among these peritumoral lymph node positivity was detected in 24 cases (false negative ratio=33.3%).

In this group in case of the 19 T1 or T2 stage tumours no sentinel node positivity was found yet final histology revealed peritumoral lymph node positivity in 3 cases of T2 tumours (false negative ratio of 15.78% even in the early stages). Sentinel lymph node positivity was detected in 13 cases. Two of them were micrometastases yet even in these cases other positive peritumoral nodes were found. All of the 13 sentinel node positive patients were in tumour stages T3 or T4 and beside the sentinel other peritumoral lymph node positivity was also found by the pathologist (no false positive event). Our results showed that the fate of the patient cannot be based on the sentinel node technique alone. It was concluded that of the 85 cases when only sentinel node status identification was performed the final histology revealed node positivity in 35 cases and of these the sentinel node was also positive in 13 cases and negative in 22, therefore an extremely high false negative ratio was obtained. In the presence of such high false negative ratio it could be stated that sentinel node biopsy alone was unable to replace the extended node dissection and it had no predictive or prognostic role. However, interesting results were obtained if further lymph node blocks were examined. The second half of the investigation was to study the distal marker lymph node at the convergence of the veins and the proximal marker lymph nodes at the end of the vein shaft and the following results were obtained: of the 95 patients positivity in the distal marker lymph node was found in 13 cases and among these the sentinel lymph nodes were positive only in 6 cases but with involved nodes peritumorally in other clusters. Therefore, of the 36 lymph node positive cases, there were 13 distal marker positivities. If the more central lymph node level i.e. the proximal marker of these 13 cases were examined we found that in 4 cases the proximal marker was also positive and in 9 cases it was negative. This meant that applying the principle of central ligation in the case of 95 patients 4 (4.2%) benefited from extended dissection; it would have been enough to perform the dissection to the level of the distal marker lymph node in 91/95 cases (95.8%). This was not the surgical sentinel lymph node closest to the tumour and dyed intensively blue, but the marker lymph node located at the convergence of the veins. If the frozen section histology of this lymph node was examined during surgery and found to be negative the node dissection would not have to be continued centrally. When the tumour stages of the 4 patients with proximal marker node positivity were looked at all were T3 stage and based on tumour characteristics a curative surgery could have been achieved by extended lymph node dissection, however, two of these patients had liver metastasis as well, hence they were operated on in a more advanced tumour stage. Based on all of the above it can be stated that the prognostic role of the distal marker lymph node is unambiguous and if it is positive the node dissection should be extended towards the central ligature of the veins. However, if positivity can be detected also here this suggests an extremely poor prognosis. It was a very important observation that no jumping metastasis was found in these lymph node chains and if the proximal was positive, the distal proved to be positive in each case as well. During the distal marker node dissection and subsequent frozen section examination performed intraoperatively the negativity proved to be true permitting an operation without central ligature and therefore resection at the level of the distal marker node. Other than the method allowing to determine the extent of the lymph node dissection it is also allowing the pathologist to examine more lymph nodes, therefore promoting its prognostic role; similarly, if there are not enough lymph nodes examined in T1 and T2 tumours patients may receive toxic chemotherapy which in the presence of sufficient lymph nodes can be avoided. If rectum tumours were excluded from our material (chemo-radiotherapy was given in 39 cases and for these the adequate number of lymph nodes could not be guaranteed) and the marked patients were compared with the same number of non-marked patients with colon cancer the mean lymph node count for the former was 23.5 (11 to 65) and for the latter 13.17 (5 to 25): the

difference is significant and based on these it can be stated that lymph node marking may help the pathologist.

IV.4. Discussion

The lymph node marking technique performed by us, namely the ex vivo examination of surgical sentinel node and marker lymph nodes, may be a prognostic indicator and the blue dyed lymph nodes may simplify the assessment of sufficient amount lymph nodes in the formalin fixed (and therefore usually shrunk and distorted) specimen for the pathologist. From our material it was found that the lymph nodes dyed blue in the course of sentinel marking helped the pathologist and thus significantly more lymph nodes could be processed. Marker lymph node is defined as the blue dyed lymph node located the greatest distance from the tumour and is marked at the convergence of the veins. Searching for the marked distal marker lymph node is technically easier, even intraoperatively, since in the majority of the cases, the fat tissue of the mesocolon is tapered here. If the intraoperative frozen section of this lymph node was negative a smaller resection would be performed especially in the case of older and obese patients with comorbidity. The proximal marker lymph node may also be a prognostic indicator. In case the intraoperative frozen section of the proximal marker node was negative the central ligature of the vein supplying the relevant section of the colon may be ignored. The blue dyed lymph nodes also help the pathologist to identify them, therefore a higher number of nodes are assessed and reported on that may also influence postoperative treatment. Owing to the lymph node marking, the intraoperative examination of the marker lymph node, if negative, allows a smaller resection without oncological compromises, thus, central venous ligature is not necessary and a safer colonic anastomosis can be fashioned between gut ends with more reliable blood supply. The examination of the marker lymph node beyond the sentinel lymph node provides additional data for prognosis and adjuvant therapy. The method is safe and there is no difference in applicability in the open and the laparoscopic technique. The possibility of accidental intraoperative tumour spread during marking may be the subject of further investigations.

V. Summary of the new findings

1. Laparoscopic surgery of rectum and rectosigmoid cancers is oncologically safe and offers short- and long-term advantages for the patient. Compared with open operations survival proves to be slightly improved, however, the differences are not significant. The short-term advantages of laparoscopic rectum surgery are less surgical site complications, cosmetic advantages and significantly reduced postoperative incisional hernia rates. In more advanced tumour stages favourable longer-term survival can be achieved. Due to its technical characteristics more accurate haemostasis can be achieved thus transfusion demand is less this also providing more favourable outcomes to the patient.

2. Laparoscopic surgery of the rectum tumours following chemo-radiotherapy is safe, there is no oncological compromise and additionally, we recommend it to working groups having expertise in laparoscopic colorectal surgery due to its short-term advantages.

3. The examination of intraoperatively blue dye marked and subsequently most intensively blue sentinel lymph node in the vicinity of the tumour is not reliable to indicate less extensive bowel resection, since in some cases non-dyed but involved nodes can be detected adjacent to the negative sentinel node. The reason for this is probably the obstruction of lymph vessels due to which lymph may flow in a different direction.

4. The role of the intraoperative assessment of the so called marker lymph nodes may be significant, of which the distal marker node being closer to the tumour may indicate less

extensive resection or more distal ligature of blood vessels. The proximal marker lymph node being further away from the tumour may have prognostic significance.

5. In formalin-fixed specimen owing to the lymph node marking the lymph nodes may become easier for the pathologist to identify, therefore, significantly more lymph nodes may become subject to processing that may also enhance their prognostic value and impact on the postoperative treatment plan.

6. The procedure does not add further burden to the patient, it is low risk and is cheap and simple. The possibility of accidental intraoperative tumour spread during marking may be the subject of further investigations.

VI. Acknowledgements

VII. Publications and presentations

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